ISSN 1948-9366 (online)

World Journal of

Gastrointestinal Surgery

World J Gastrointest Surg 2023 April 27; 15(4): 495-744

Published by Baishideng Publishing Group Inc

World Journal of Gastrointestinal Surgery

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Editorial Board Member of *World Journal of Gastrointestinal Surgery*, Sami Akbulut, MD, PhD, Full Professor, Department of Surgery and Liver Transplant Institute, Inonu University Faculty of Medicine, Malatya 44280, Turkey. akbulutsami@gmail.com

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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 National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 Edition of Journal Citation Reports® cites the 2021 impact factor (IF) for *WJGS* as 2.505; IF without journal self cites: 2.473; 5-year IF: 3.099; Journal Citation Indicator: 0.49; Ranking: 104 among 211 journals in surgery; Quartile category: Q2; Ranking: 81 among 93 journals in gastroenterology and hepatology; and Quartile category: Q4.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Gastrointestinal Surgery

ISSN
ISSN 1948-9366 (online)

LAUNCH DATE
November 30, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Peter Schemmer

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

PUBLICATION DATE
April 27, 2023

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World J Gastrointest Surg 2023 April 27; 15(4): 495-519

DOI: 10.4240/wjgs.v15.i4.495

ISSN 1948-9366 (online)

REVIEW

Current and emerging therapeutic approaches for colorectal cancer: A comprehensive review

Anil Kumar, Vipasha Gautam, Arushi Sandhu, Kajal Rawat, Antika Sharma, Lekha Saha

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): 0
Grade C (Good): C, C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Luo W, China; Wang LH, China

Received: October 21, 2022
Peer-review started: October 21, 2022
First decision: January 3, 2023
Revised: January 11, 2023
Accepted: March 3, 2023
Article in press: March 3, 2023
Published online: April 27, 2023

Anil Kumar, Vipasha Gautam, Arushi Sandhu, Kajal Rawat, Antika Sharma, Lekha Saha, Department of Pharmacology, Post Graduate Institute of Medical Education and Research, Chandigarh 160012, India

Corresponding author: Lekha Saha, MBBS, MD, MNAMS, Full Professor, Department of Pharmacology, Post Graduate Institute of Medical Education and Research, Research Block B, Chandigarh 160012, India. lekhasaha@rediffmail.com

Abstract

Colorectal cancer (CRC) affects 1 in 23 males and 1 in 25 females, making it the third most common cancer. With roughly 608000 deaths worldwide, CRC accounts for 8% of all cancer-related deaths, making it the second most common cause of death due to cancer. Standard and conventional CRC treatments include surgical expurgation for resectable CRC and radiotherapy, chemotherapy, immunotherapy, and their combinational regimen for non-resectable CRC. Despite these tactics, nearly half of patients develop incurable recurring CRC. Cancer cells resist the effects of chemotherapeutic drugs in a variety of ways, including drug inactivation, drug influx and efflux modifications, and ATP-binding cassette transporter overexpression. These constraints necessitate the development of new target-specific therapeutic strategies. Emerging therapeutic approaches, such as targeted immune boosting therapies, non-coding RNA-based therapies, probiotics, natural products, oncolytic viral therapies, and biomarker-driven therapies, have shown promising results in preclinical and clinical studies. We tethered the entire evolutionary trends in the development of CRC treatments in this review and discussed the potential of new therapies and how they might be used in conjunction with conventional treatments as well as their advantages and drawbacks as future medicines.

Key Words: Colorectal cancer; Chemotherapy; Immunotherapy; RNA interference; Probiotics; Oncolytic viral therapy

Core Tip: This review highlights some of the latest colorectal cancer treatment approaches that have the potential to soon translate into standard care. A vast literature of patient data has revealed that conventional therapies are non-specific and have numerous secondary complications. Additionally, patients develop resistance to conventional chemotherapies. There is a need to develop new target-specific arrows in the cancer-fighting quiver.

Citation: Kumar A, Gautam V, Sandhu A, Rawat K, Sharma A, Saha L. Current and emerging therapeutic approaches for colorectal cancer: A comprehensive review. *World J Gastrointest Surg* 2023; 15(4): 495-519
URL: https://www.wjgnet.com/1948-9366/full/v15/i4/495.htm
DOI: https://dx.doi.org/10.4240/wjgs.v15.i4.495

INTRODUCTION

Starting from the industrial revolution, the scientific world has evolved progressively. After reaching the 21st century, certain diseases need novel therapeutic moieties for their cure, and colorectal cancer (CRC) is one of them. CRC is the third most prevalent cancer globally (6.1%) after lung cancer (11.6%) and breast cancer in females (11.6%) and prostate cancer in males (7.1%)[1]. It ranks second among all cancer in terms of mortality, accounting for 9.2% of all cases (9% male and 8% female)[1]. Estimates have shown that by the year 2035, there will be an increment in the cases of colon and rectal cancer by 71.5% and 60.0%, respectively[2]. This rapid disease progression has led to an economic burden on the countries and requires a major part of gross domestic product expenditure on public health.

The primary therapy for resectable CRC is surgical removal, and in non-resectable CRC, standard therapies include chemotherapy, radiotherapy, and immunotherapy. However, these therapies have certain drawbacks, such as being non-specific and cytotoxic to normal cells, which leads to secondary complications[3]. Depending upon the confinement and progression of the CRC, these therapies can be utilized in combinations. However, even with combinational therapies, more than half of patients relapse into acquired multidrug resistance CRC[4]. According to 2021 statistics, despite significant advancements in CRC screening, surgical resection, and adjuvant treatment, the death rate for CRC patients is still relatively high[1]. Therefore, there is a need to develop novel CRC therapies that render resistant tumors more sensitive to chemotherapeutic drugs.

Immune checkpoint inhibitors (ICIs), chimeric antigen receptor (CAR) T cell therapy, T cell receptor (TCR) alterations, and cytokine therapy have recently emerged as effective treatments for CRC. Also recent research on the use of probiotics[5], RNA-based therapies [small interfering RNA (siRNA), microRNA (miRNA), and RNA aptamer][6], oncolytic viral therapies[7], and natural products[8] in the treatment of CRC have yielded promising results. However, the survival rate of patients at an advanced stage remains a major problem. Scientists are working hard to understand the pathophysiology of CRC to have a better approach for treatment while enhancing current treatments like radiation therapy, targeted therapy, endoscopic resection, chemotherapy, and immunotherapy.

An individualized standard chemotherapeutic regimen is prescribed to a patient based on certain factors such as overall health profile, co-medication, comorbidities, patient compliance, psychosocial factors, results of prior resection, adjuvant therapy, route of administration, logistical support, consideration of side effect profiles, the biology of the tumor, the main location of the tumor, the presence of *RAS* and *BRAF* mutations, or microsatellite instability. Considering these factors, patients are divided into risk groups with varying treatment strategies. Since colon cancers and rectal cancers are different, multidisciplinary and distinct approaches must be taken depending on the staging information before treatment[9]. This review traced the evolutionary development of many standard CRC treatments and recent promising therapeutic approaches. We also reviewed the benefits and hurdles that still need to be overcome in treating CRC.

THERAPEUTIC APPROACHES

Local approaches

Radiation therapy: Neoadjuvant therapy, including radiotherapy and chemotherapy when used alone or in combination, has been recommended in rectal cancer and has effectively reduced tumor burden for intermediate and advanced stage cancer. The primary objective of radiotherapy is to decrease the risk of local recurrence and improve overall survival. However, evidence suggests that preoperative radiotherapy is more effective than postoperative therapy in reducing local recurrence, but it does not improve overall survival[10]. With two available adjuvant radiotherapies, short-course radiotherapy (RT) and long-course RT, there was always a question of which one was better. Higher rates of acute

toxicity are observed with long-course RT than with short-course RT, but late side effect incidence rates do not show significant differences[11]. Radiation and adjuvant radiation therapy are better options for treating stage II and III CRC. However, radiation therapies have some plausible long-term toxicity impacts on vital organs.

New delivery methods, such as intensity-modulated RT (IMRT), have been widely adopted in clinical practice and have demonstrated potential benefits with decreased toxicity for patients with rectal cancer by lowering the radiation dose[12]. IMRT employs linear accelerators to safely deliver precise radiation to a tumor while reducing the exposure to nearby healthy tissue. With IMRT, radiation dosages to adjacent healthy organs can be limited while still being delivered at high doses to the tumor and nearby lymph nodes. By adjusting the dose in this way to avoid normal, unaffected tissues, it can lessen adverse effects and potentially improve the toxicity profile. Additionally, the use of IMRT for rectal cancer may help to speed up the time to surgery, promote better postoperative recovery, and enhance the tolerability of adjuvant chemotherapy[13]. IMRT may help reduce treatment interruptions, emergency department visits, and hospitalizations compared to 3-dimensional conformal radiation therapy[14]. In a United Kingdom study of radiotherapy facilities, 68% of respondents reported using IMRT for all rectal cancer patients[15]. In the future, more clinical data will be needed to support the use of IMRT for rectal cancer, which could encourage doctors to incorporate IMRT planning into preoperative chemoradiotherapy for rectal cancer.

Systemic approach

Chemotherapy: The ultimate treatment for locoregional CRC is surgical resection. Advances in primary and secondary treatments have improved the survival time in CRC. Notably, in some circumstances, chemotherapy or radiotherapy may be used as neoadjuvant or adjuvant treatments before or after surgery in order to significantly reduce and cure the tumor. Of note, chemotherapy is used to either eliminate cancer cells or stop them from proliferating. Cytotoxic drugs approved for CRC slow down disease progression and increase an individual's lifespan. The medications approved are fluoropyrimidines, irinotecan, oxaliplatin, tri-fluridine-tipiracil, capecitabine, and 5-fluorouracil (5-FU), most commonly used as a chemotherapeutic agent for curing CRC.

Adjuvant fluoropyrimidine-based chemotherapy after surgery for CRC has been a standard treatment due to their ability to reduce the recurrence of the tumor and increase the survival as shown in trial by Moertel *et al*[16]. Leucovorin (LV, folinic acid), a chemoprotectant, potentiates the activity of 5-FU by forming a stable complex and preventing its adverse effects[17]. The fluorouracil + L-folinic acid (FU/LV) regimen given daily for 5 d in 6 cycles resulted in a 15% reduced risk of death at 5 years[18,19]. All 5-FU-based regimens must include LV as it has been demonstrated to improve patient survival and tumor response rate (RR) when combined with 5-FU[20]. Despite being one of the safest chemotherapeutic agents, 5-FU has side effects for some CRC patients, including fever, mucositis, stomatitis, leukopenia, and thrombocytopenia[21]. Cerebellar ataxia and other neurological diseases also affect 1% of patients[22].

Another imperative drug used is capecitabine, a prodrug of 5-FU. Its bioavailability is virtually 100%, and Cmax and area under the curve increase linearly with dosage. In patients with metastatic CRC, two phase III randomized studies compared capecitabine as a single drug to the typical 5-FU/LV therapy combination, and the RR in both studies were as efficient as 5-FU/LV[23].

Topoisomerase I inhibitor irinotecan and oxaliplatin were added to the 5-FU regimen as part of a cytotoxic combination therapy for metastatic colorectal cancer (mCRC) to enhance its efficacy. Oxaliplatin is a diaminocyclohexane platinum complex that has the potential to generate DNA adducts and interferes with the mechanism of DNA repair, thereby leading to a cytotoxic effect in CRC[22]. Patient survival improved due to the inclusion of oxaliplatin or irinotecan in the 5-FU regimen but at the same time has increased the toxicity levels. In the first-line treatment of mCRC, 5-FU/LV is coupled with oxaliplatin (FOLFOX), irinotecan (FOLFIRI), and both oxaliplatin and irinotecan (FOLFOXIRI). The combination therapies FOLFOX, FOLFIRI, and FOLFOXIRI have established themselves as effective cytotoxic regimens, with an average improvement in survival of about 2 years. According to the Gruppo Oncologico dell'Italia Meridionale trial, overall survival (OS) rates for FOLFIRI and FOLFOX were 14 mo and 15 mo, respectively. The GERCOR trial found that OS was 21.5 mo for patients who received FOLFOX first followed by FOLFIRI and 20.6 mo for those who received FOLFIRI first followed by FOLFOX. Trifluridine-tipiracil, a fluoropyrimidine, contains tipiracil hydrochloride, which prevents the degradation of trifluridine. The incorporation of trifluridine into DNA is the primary mechanism of action. Compared to the best supportive care alone, the prospective randomized clinical phase III trial RECOURSE found that it significantly increased median OS[24].

Tyrosine kinase signaling pathways typically prevent unchecked cell growth or boost sensitivity to trigger apoptosis. These signaling pathways are often genetically or epigenetically dysregulated in cancer cells, offering them a selective advantage. The human genome contains about 500 protein kinase genes, which constitute about 2% of all human genes. The structures of over 280 human protein kinases have been determined[25]. Regorafenib is a Food and Drug Administration (FDA)-approved tyrosine kinase inhibitor that targets numerous targets, including vascular endothelial growth factor (VEGF) receptor (VEGFR), platelet-derived growth factor, fibroblast growth factor, and BRAF in mCRC due to its better median OS and progression-free survival (PFS) in the phase III CORRECT trial[26] and the

CONCUR trial[27]. Other promising tyrosine kinase inhibitors are listed in Table 1 with their specific target.

Neoadjuvant chemotherapy (NACT) is an emerging field in cancer. It is mainly used to treat solid tumor malignancies such as gastric, esophageal, and rectal cancers[28], but its efficacy has not been fully explored in cases of CRC. Utilization of NACT before surgery can result in better outcomes in CRC patients with liver metastases. As a result, NACT is being investigated in primary rectal and colon cancers as a potential method to reduce the size of the tumor, enable a curative resection, and mitigate the chance of metastases. A potential benefit of NACT was reported in a trial on patients with stage III colon cancer, in which they received preoperative capecitabine + oxaliplatin (CAPOX) followed by adjuvant therapy (CAPOX) after resection. Tumor volume was reduced by 69.5%, without any progression of disease during therapy, and OS was 100%[29]. A similar protocol with an addition of 5-FU in some cases[30] resulted in the majority of patients experiencing a reduction in tumor volume of 62.5%. This finding was the basis of an ongoing randomized phase II study of neoadjuvant CAPOX in locally advanced colon cancer.

Based on the efficacy of FOLFOXIRI established in mCRC, the same triplet therapy was utilized as NACT in patients with stage IIIB colon cancer, followed by resection and then adjuvant therapy of either FOLFOXIRI or CAPOX. This trial documented a reduction in tumor in 91.3% of patients with toxicities of grade 3-4. At the end of trial, only 52.2% of patients were left with OS of 95.7% and 2-year recurrence rate of 26.1%[31]. There are several other proposed and ongoing randomized phase II and III clinical trials taking place utilizing NACT such as CAPOX, FOLFOX, ipilimumab + nivolumab ± celecoxib and many more[32]. Despite the controversial role of targeted agents in other cancers, these could be considered as a potential weapons in CRC, enhancing the efficacy of neoadjuvant therapy[33]. Treatment with bevacizumab and chemotherapy before surgery in CRC patients with liver metastases has been found to increase the survival in several phase II trials[34]. The efficacy of targeted neoadjuvant therapy requires studies involving larger population. Therefore, definite conclusions cannot be drawn from trials involving small population size, demanding further investigations.

Presently, progress in the adjuvant therapy following resection has taken a pause. A shift has been taken towards the utilization of NACT in both colon and rectal cancers instead. Large, randomized clinical trials are being conducted worldwide to investigate various strategies used for safe and accurate administration of treatment. However, certain parameters like standardization of regimen combination, standard intensity, and duration of therapy, postoperative settings, *etc* are still undefined because of lack of long-term oncological results of randomized phase II and phase III studies, warranting further investigation.

Target-specific approaches

Immunotherapy as a promising candidate for CRC treatment: Following early breakthroughs in the treatment of melanoma, immunotherapy has been quickly established as a prominent therapeutic strategy for a variety of solid tumors[35,36], including CRC. Cancer immunotherapy conquers the issue of specificity, which is a severe issue of chemotherapy, radiotherapy, and other approaches. Figure 1 illustrates all currently available and emerging immunotherapies for CRC. The cancer immunotherapy area has shown potential in treating a variety of solid tumors, with a growing number of FDA-approved monoclonal antibodies and single and combinational immunotherapeutic medicines throughout time [37].

Anti-epidermal growth factor/receptor antibodies: The epidermal growth factor receptor (EGFR) signaling pathway is a complicated and closely controlled process that plays a role in proper cell development, proliferation, and survival. When this pathway malfunctions and continues unregulated, neoplastic cells can grow, proliferate, survive, and spread. With encouraging preclinical results, cetuximab, the first monoclonal antibody targeting EGFR, was introduced. Cetuximab is a chimeric immunoglobulin G (IgG) antibody that causes EGFR internalization and destruction[38]. According to the BOND trial, which supported the FDA's 2004 approval of cetuximab for treating mCRC, cetuximab showed considerable promise in improving PFS and OS in patients with a low response to single-agent IRI therapy[39]. Cetuximab, in combination with other chemotherapies, showed encouraging outcomes as well. The phase III CRYSTAL trial found that the combination of cetuximab and the FOLFIRI regimen had better progression control than FOLFIRI alone [8.9 mo *vs* 8.0 mo, hazard ratio (HR): 0.85, $P = 0.048$] [40]. However, being a chimeric antibody, cetuximab may ultimately result in immunogenic responses.

To minimize the immunogenic responses, the fully humanized antibody panitumumab was developed. Panitumumab, unlike cetuximab, does not cause antibody-dependent cell-mediated cytotoxicity[41]. In the PRIME trial, the combination regimen of FOLFOX plus panitumumab outperformed FOLFOX alone in terms of PFS (10.0 mo *vs* 8.6 mo, HR: 0.80, $P = 0.01$) and OS (23.9 mo *vs* 19.7 mo, HR: 0.88, $P = 0.17$), with further evidence of significance in the updated survival analysis (HR: 0.83, $P = 0.003$) in patients with mCRC[42,43].

Humanized antibodies are also a bit immunogenic compared to human antibodies. Necitumumab is a completely human monoclonal antibody approved by the FDA for advanced squamous non-small cell lung cancer. Necitumumab plus modified FOLFOX6 was studied in a phase II study for the first-line treatment of locally advanced or mCRC[44]. PFS and OS were 22.5 mo (11.0-30.0) and 10.0 mo (7.0-12.0),

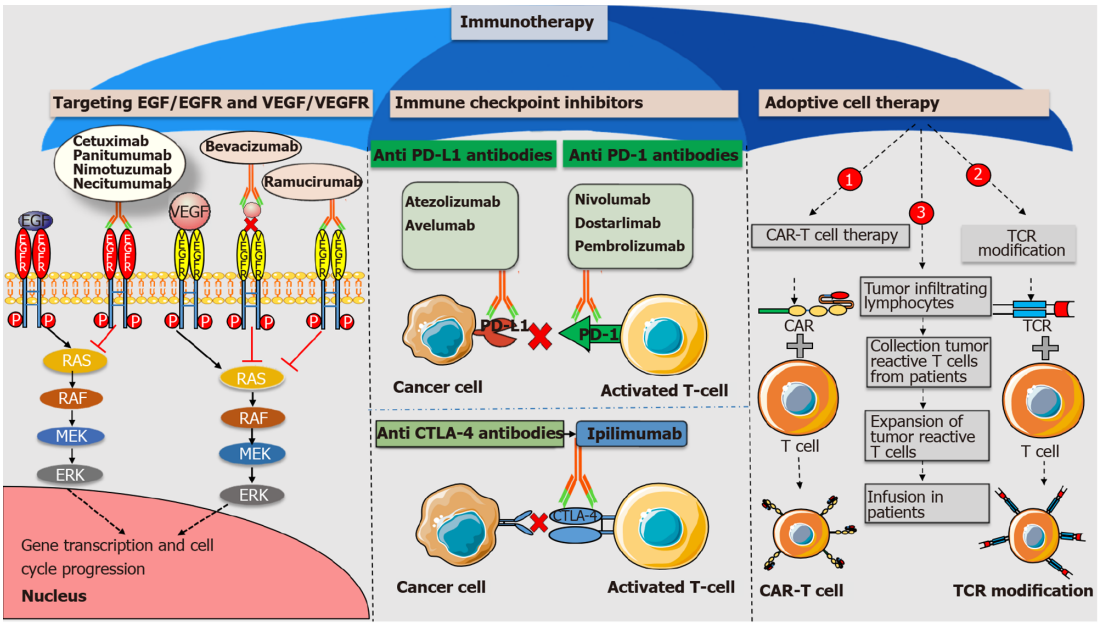
Table 1 Tyrosine kinase inhibitors, plant based drugs, and selected target specific agents against colorectal cancer

Agent	Type of agent	Target/mechanism	FDA approval date/trial number/status	Sources/interventions	Results
Sunitinib	TKI	VEGFR1-3	NCT00457691. Completed	Phase II study: FOLFIRI and sunitinib for mCRC	Sunitinib did not add to the antitumor activity of FOLFIRI
Axitinib	TKI	VEGFR1-3	NCT00460603. Completed	Phase II study: axitinib and/or bevacizumab with modified FOLFOX-6 as first-line therapy for mCRC	Neither the addition of continuous axitinib nor the axitinib/bevacizumab combination to FOLFOX-6 improved ORR, PFS, or OS compared with bevacizumab as first-line treatment of mCRC
Sorafenib	Kinase inhibitor	VEGFR	NCT00326495. Completed	Phase II study: cetuximab and sorafenib for the treatment of *KRAS*-mutated mCRC	No objective responses were observed
Regorafenib	Multikinase inhibitor	VEGFR1-3, TIE2, KIT, RET, RAF, PDGFR-B, FGFR	September 27, 2012	Approved for ACRC, mCRC	-
Encorafenib	Kinase inhibitor	*BRAF*-V600E as well as wildtype *BRAF* and *CRAF*	April 8, 2020	Approved for mCRC	-
Simtuzumab	Monoclonal antibody	LOXL2	NCT01479465. Completed	Phase II study: efficacy of simtuzumab with FOLFIRI as second line treatment in CRC	The addition of simtuzumab to FOLFIRI did not improve clinical outcomes in patients with metastatic *KRAS*-mutant CRC
Lenvatinib	TKI of VEGFR	VEGFR1-3, KIT, RET, PDGFR-alpha, FGFR	NCT04776148. Ongoing	Phase III study ongoing: lenvatinib in combination with pembrolizumab for mCRC	Ongoing
Tivozanib	TKI of VEGFR	VEGFR1-3	NCT01058655. Completed	Phase II study: everolimus (RAD001) and tivozanib (AV-951) in patients with refractory or mCRC	The oral combination of tivozanib and everolimus was well tolerated, with stable disease achieved in 50% of patients with refractory or mCRC
Tipifarnib	Farnesyltransferase inhibitor	Farnesyltransferase	NCT00005833. Completed	Phase II trial study: R-115777 given as a single agent	Ineffective in patients with mCRC
D-1553	Small molecule KRasG12C inhibitor	*KRAS* G12C	NCT04585035. Ongoing	Phase I study using D-1553 in CRC with *KRAS* G12C mutation	Ongoing
Aflibercept	Recombinant fusion protein	VEGF-A and VEGF-B, PGF	NCT02181556. Completed	Phase II study: aflibercept in combination with FOLFIRI as first-line chemotherapy in patients with mCRC	Although the primary objective was not met, first-line FOLFIRI + aflibercept for mCRC resulted in median PFS and OS close to those reported with traditional doublet and targeted therapies
Berberine	Alkaloid	Anti-proliferation, cell cycle arrest	*In vitro* study	Plant/berberine	Berberine inhibited telomerase activity and induced cell cycle arrest and telomere erosion in colorectal cancer cell Line, HCT 116[149]
Piper nigrum ethanolic extract	Alkaloid	Antioxidative activity	*In vitro* study	Plant/EEPN	Time- and dose-dependent increase in the cytotoxic efficacy of 50% EEPN against colorectal carcinoma cell lines were noted[150]
Fucoidan	Polysaccharide	Inhibit growth and angiogenesis	*In vitro* study	Brown seaweed/combination of fucoidan with vitamin C	The combination of fucoidan with vitamin C showed significant inhibitory effects

					on HCT-116 colon cell viability[151]
Curcumin	Polyphenol	Apoptosis, antiangiogenesis, and cell cycle arrest	NCT02439385. Completed	Plant/phase II study: bevacizumab/FOLFIRI with ginsenoside-modifies nanostructured lipid carrier containing curcumin (G-NLC) in patients with mCRC	Bevacizumab/FOLFIRI with G-NLC increased long-term survival. Further randomized control studies are needed
			NCT01490996. Completed	Phase I/II study: curcumin combined with FOLFOX	Curcumin with FOLFOX was safe and tolerable. The HR for PFS and OS was 0.57 and 0.34, respectively
Gingerol	Polyphenol	Antioxidative and anti-inflammatory	NCT01344538. Completed	Plants/phase II randomized control trial. Ginger for CRC prevention	Result suggested ginger may reduce proliferation and increase apoptosis
EPA	Polyunsaturated fatty acids	Inhibit angiogenic factors	NCT00398333. Terminated	Marine microalgae/phase IV	Due to small sample size further investigation needed
EGCG	Polyphenol	Apoptosis	NCT02891538. Ongoing	Plants/early phase 1 study: EGCG in CRC patients	Ongoing
PSK	Polysaccharide	Apoptosis and antiproliferative	NCT00497107. NA	Fungi/phase III study: oral tegafur/uracil plus PSK	Results suggested that there was reduction in recurrence and mortality by 43.6% and 40.2%, respectively in stage I and stage II
Resveratrol	Polyphenol	Apoptosis and antiproliferative	NCT00920803. Completed	Plants/phase I study: resveratrol for resectable CRC	Resveratrol was effective in treating CRC by modulating the Wnt pathway
Topotecan	Alkaloid	Antiproliferative	EORTC	Plants/phase II study: oral topotecan	Topotecan administered as a five times daily regimen has only minor activity as a single-agent therapy in colorectal cancer
Metformin	Alkaloid	Antiproliferative and antimetastatic	NCT03047837. NA	Plants/phase II study: using aspirin and metformin in stage I-II CRC	Result suggested that the given intervention delayed recurrence and improved prognosis
Everolimus	Macrolide	Antiproliferative and antimetastatic	NCT01387880. Completed	Bacterial/phase II study: irinotecan, cetuximab, and everolimus to patients with mCRC	Everolimus showed promising effects on CRC prognosis
			NCT01058655. Completed	Phase II study: tivozanib and everolimus for patients with refractory mCRC	Oral combination of tivozanib and everolimus was well tolerated in 50% of the patient
Andrographolide	Diterpenoid	Apoptosis, antiproliferative, and cell cycle arrest	*In vitro* study	*In vitro* study using 5-FU with andrographolide	Andrographolide enhanced 5-FU induced antitumor effect in CRC *via* inhibition of the c-MET pathway[152]
Silymarin	Flavnoid	Apoptosis, antiproliferative	NCT03130634. Completed	Plants/phase IV study using silymarin in patients treated with first-line treatment FOLFIRI	Silymarin is a potential supplement for reducing toxicities in mCRC patients undergoing FOLFIRI plus bevacizumab first-line treatment
MMC	Hyleneimines	Antiproliferative	NCT00643877. NA	Streptomyces/phase III study using PHARC with oxaliplatin, MMC FUDR	Addition of PHRAC improved DFS in patients with stage II and stage III CRC
			NCT03073694. Ongoing	Phase II study using MMC and melphalan	Ongoing

5-FU: 5-fluorouracil; ACRC: Advanced colorectal cancer; *BRAF*-V600E: BRAF protein coding gene; CRC: Colorectal cancer; DFS: Disease-free survival; EEPN: Ethanolic extract of *Piper nigrum*; EGCG: Epigallocatechin gallate; EORTC: European Organization for Research and Treatment of Cancer; EPA: Eicosapentaenoic acid; FDA: Food and Drug Administration; FGFR: Fibroblast growth factor receptor; FOLFIRI: 5-flurouracil, leucovorin, and irinotecan; FOLFOX-6: 5-flurouracil, leucovorin, and oxaliplatin-6; FUDR: Fluorodeoxyuridine; G-NLC: Genistein-nanostructured lipid carriers; HR: Hazard ratio; KIT: Proto-oncogene receptor tyrosine kinase; LOXL2: Lysyl oxidase-like 2; mCRC: Metastatic colorectal cancer; MMC: Mitomycin C; NA: Not available;

ORR: Objective response rate; OS: Overall survival; PDGFR-B: Platelet-derived growth factor receptor B; PFS: Progression-free survival; PGF: Placental growth factor; PHARC: Preoperative hepatic and regional atrial chemotherapy; PSK: Polysaccharide krestin; RAF: Rapidly activated fibrosarcoma; RET: Ret proto-oncogene; TIE2: Tyrosine kinase with immunoglobin and epidermal growth factor 2; TKI: Tyrosine kinase inhibitor; VEGFR1-3: Vascular endothelial growth factor 1-3.



DOI: 10.4240/wjgs.v15.i4.495

Figure 1 Immunotherapeutic approaches against colorectal cancer. Antiangiogenic monoclonal antibodies like cetuximab, panitumumab, nimotuzumab, and necitumumab target epidermal growth factor (EGF) receptor (EGFR). Antiangiogenic monoclonal antibodies such as bevacizumab and ramucirumab target vascular EGF and its receptor, respectively. All antiangiogenic monoclonal antibodies downregulate the RAS-RAF-MEK-ERK pathway and prevent the transcription of genes involved in cell cycle progression. Immune checkpoint inhibitors (ICIs) like atezolizumab and avelumab target programmed cell death ligand 1 (PD-L1). ICIs like nivolumab, dostarlimab, and pembrolizumab target programmed cell death protein 1 (PD-1). The ICI ipilimumab targets cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4). ICIs act as immune brakes that prevent checkpoint proteins from interacting with their companion proteins, thus boosting T cell effector activity. T cell boosting therapy, like adoptive cell therapy, includes chimeric antigen receptor T cell therapy (CAR-T), T cell receptor modification (TCR), and tumor infiltrating lymphocyte boost T cell activity to combat cancer cell growth. VEGF: Vascular epidermal growth factor; VEGFR: Vascular epidermal growth factor receptor.

respectively. First-line necitumumab modified FOLFOX6 effectively treated locally advanced or mCRC with manageable side effects; further research on the effect of necitumumab on RAS-associated mutation is necessary. Humanized anti-EGFR antibodies, such as nimotuzumab, have a better safety record than most anti-EGFR antibodies.

In clinical practice, there were no discernible differences in the objective RR, disease control rate, PFS, or median survival between chemotherapy plus nimotuzumab and chemotherapy alone in patients with advanced CRC, indicating that these treatments were equally effective for treating the disease[45]. Both cetuximab and panitumumab are FDA-approved first-line treatments for CRC. Anti-EGFR medicines may be a low priority for second-line or beyond CRC treatment because cetuximab and panitumumab failed to achieve statistically superior PFS or OS for patients with CRC in multiple studies[46,47].

Anti-VEGF/VEGFR antibodies: Angiogenesis is required for tumor invasion and metastasis to progress beyond the size of a few centimeters. In CRC and other malignancies, VEGF is the most important angiogenic factor. As a result, multiple studies examining VEGF expression in CRC patients have been conducted, and several therapeutic drugs targeting the VEGF pathway have been tested. Bevacizumab, an antiangiogenic antibody, has proven to be more effective than chemotherapy when combined with IRI, 5-FU, and LV plus placebo in phase II and III AVF2107 studies based on antiangiogenic therapy for CRC. The AVF2107 study found that bevacizumab, a humanized IgG monoclonal antibody, targets VEGF-A and improves both PFS and OS in mCRC (RR: 44.0% *vs* 34.8%; OS: 20.3 mo *vs* 15.6 mo; HR: 0.66, $P = 0.001$; PFS: 10.6 mo *vs* 6.2 mo; HR: 0.54, $P = 0.001$).

In the E3200 trial, patients with CRC who progressed after FOLFOX therapy had a better PFS (7.3 mo *vs* 4.7 mo, HR: 0.61, $P = 0.001$) and OS (12.9 mo *vs* 10.8 mo, HR: 0.75, $P = 0.0011$) as well as a better RR (22.7% *vs* 8.6%, $P = 0.0001$) with a combination of FOLFOX and bevacizumab than FOLFOX alone. Bevacizumab is the only antibody approved by the FDA as a first- and second-line VEGF-targeted therapy for CRC. Another FDA-approved medication for second-line therapy of mCRC is ramucirumab, a completely humanized monoclonal VEGFR-2-targeted IgG antibody. Compared to FOLFIRI-placebo, a

combination of ramucirumab and FOLFIRI significantly improved PFS (5.7 mo *vs* 4.5 mo; HR: 0.79, P = 0.0005) and OS (13.3 mo *vs* 11.7 mo, HR: 0.84, P = 0.022) based on the phase III RAISE trial. Table 2 enlists various anti-VEGF/VEGFR and anti-epidermal growth factor (EGF)/EGFR monoclonal antibodies that have been approved and are undergoing preclinical and clinical trials. All these medications increased OS from a few weeks to months. However, some tumor characteristics, such as genetic changes in endothelial cells, vasculogenic mimicry, and the unique therapeutic response of each tumor, interfere with these antiangiogenic therapeutic approaches. Furthermore, angiogenic treatments promote a hypoxic environment, which promotes tumor invasiveness[48].

ICIs as immune boosters: The most common immunomodulatory antibodies are ICIs. ICIs are immune brakes that prevent checkpoint proteins from interacting with their companion proteins. The important immune checkpoints and their immunological inhibitors are listed in Table 2. One important target protein is cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4). CTLA-4 controls T cell activation and transmits inhibitory signals to T cells[49]. CTLA-4 inhibition by the anti-CTLA-4 antibody was shown to inhibit tumor progression by upregulating effector T cell activity and suppressing regulatory T cells [50]. The FDA has approved low-dose ipilimumab (CTLA-4 inhibitor) in combination with nivolumab for previously treated microsatellite instability-high and deficient mismatch repair (MSI-H/dMMR) mCRC[51].

Programmed cell death receptor programmed cell death protein 1 (PD-1) is another ICI target; it is a type 1 transmembrane protein that interacts with programmed cell death ligand 1 (PD-L1) (highly expressed in inflamed cells) and PD-L2 (expressed only on antigen-presenting cells). The interaction of PD-1 and PD-L1/PD-L2 is immunosuppressive, limiting the function of T effector cells to minimize the over storm of immune responses[52,53]. However, in CRC, overexpression of PD-1 and PD-L1/PD-L2 causes more than required immunosuppression[54]. Monoclonal antibodies were developed to bind and prevent PD-1/PD-L1 interactions and to assist T cells in killing cancerous cells by restoring their activation, proliferation, function, and downstream immune signaling[55]. There are five FDA-approved PD-1 inhibitors; three are approved for CRC (Table 2).

Pembrolizumab and nivolumab (PD-1 inhibitors) are used in CRC. Pembrolizumab improves CRC patients with dMMR/MSI-H based on the KEYNOTE-177 trial. Results showed a RR of up to 78% compared to 11% of patients with proficient mismatch-repair and microsatellite stability CRC[56]. Another successful PD-1 inhibitor is nivolumab, which shows durable responses with a 69% OS rate of 12 mo among patients with the dMMR mCRC[51]. Further, a higher RR of up to 94% in MSI-H/dMMR mCRC has been observed in the phase II CheckMate study (NCT02060188), which used the combination of nivolumab (a PD-1 targeting antibody) and ipilimumab (a CTLA-4-targeting antibody)[57]. This implies that the combination of immune checkpoint therapy can significantly increase the effectiveness of the treatment for MSI-H/dMMR mCRC patients.

Other potential immune checkpoints are lymphocyte-activation gene 3 (LAG-3), T cell immunoglobulin, and mucin domain-3-containing molecule 3 (TIM-3). They play an important role in T cell regulation and preventing autoimmune disorders. However, in CRC, LAG-3[58] and TIM-3[59] are overexpressed in the CRC microenvironment, which diminishes the effectiveness of T effector cells. Relatlimab is a monoclonal antibody that binds to LAG-3 and restores T cell effectiveness. Numerous clinical trials are currently being conducted on it (NCT03642067 and NCT05328908). IBI104 is a brand-new, highly-promising antibody that inhibits TIM-3-mediated suppressive signaling and as a result is crucial for the regulation of T cells. No research on the role of IBI104 in CRC has been conducted, and it can be added to the list of new explorable T cell boosters in CRC.

T-cell boosting therapies

Adoptive cell transfer therapy: Adoptive cell transfer therapy (ACT) is a cell-based therapy that uses cells from the patient (autologous transfer) or from other donors (allogeneic transfer) to improve immune function[60]. The ACT is performed in three ways: using tumor-infiltrating lymphocytes (TILs), inserting CAR, and modifying TCR. TILs are produced from the tumor-reactive T cells from the patients, expanded *ex vivo*, and infused in the patients. TILs are capable of identifying several targets in cancer cells. Numerous active clinical trials are investigating the potential of TILs to treat CRC (NCT01174121, NCT03935893, and NCT03610490). However, a significant shortcoming of ACT-TIL is the inability to produce tumor-specific T cells when employing patients' own TIL.

Another ACT is CAR-T cells, in which T cells are derived from a patient or donor and fused with variable antibody fragments specific to the target antigen[61]. T cells are taken from a patient (autologous) or human leucocyte antigen-matched donor (allogeneic), cultivated *ex vivo*, and genetically transformed as CAR-T cells by inserting the CAR onto the T cells in the CAR approach. The main target of CAR-T cells are carcinoembryonic antigens (CEA), guanylyl cyclase C[62,63], tumor-associated glycoprotein 72[64], epithelial cell adhesion molecule[65], and major histocompatibility complex class I-related chain A and B. A clinical trial is ongoing targeting CEA to treat CRC liver metastases (NCT05240950).

Another newly developed ACT strategy includes altering TCR. Although it appears similar to CAR-T cells, its antigen-recognition processes are different. ACT, like many other approaches, has many drawbacks. Due to the necessity to create tumor-specific lymphocytes for each patient, this strategy is

Table 2 Immunotherapeutic agents and vaccines against colorectal cancer

Antibodies/antigenic composition	Origin	Target/CRC stage	Approval date/trial number/yr	Description/interventions	Inference
Monoclonal antibodies					
Cetuximab	Chimeric	EGFR	February 12, 2004 July 6, 2012	Cetuximab alone for mCRC For mCRC cetuximab + FOLFIRI	Adding cetuximab to first-line chemotherapy in patients with WT *KRAS* mCRC was statistically beneficial for OS and PFS[153]
Panitumumab	Humanized	EGFR	September 27, 2006 May 23, 2014 June 29, 2017	For mCRC panitumumab + FOLFOX for WT *KRAS* mCRC. For WT *RAS* mutation mCRC	In WT *KRAS* mCRC, PFS was improved, objective response was higher, and there was a trend toward improved OS with panitumumab-FOLFOX4[42,43,154]
Nimotuzumab	Humanized	EGFR	NCT05278728. Completed NCT05278728. Completed	Phase II study nimotuzumab along with radiotherapy and concurrent capecitabine Phase IIa study of nimotuzumab to treat CRC	No significant outcomes Ongoing
Necitumumab	Human	Cetuximab-resistant EGFR	NCT00835185. Completed	Phase II study necitumumab plus modified FOLFOX6 for locally advanced and mCRC	First-line necitumumab + mFOLFOX6 was active with manageable toxicity in locally advanced or mCRC
Bevacizumab	Humanized	VEGF	February 26, 2004	For mCRC	The addition of bevacizumab to 5-fluorouracil-based combination significantly increased patient survival[155,156]
Ramucirumab	Human	VEGFR-2	April 24, 2015	Ramucirumab with FOLFIRI as second-line treatment for mCRC	The addition of ramucirumab to FOLFIRI improved patient outcomes in the RAISE trial[157]
Nivolumab	Human	PD-1	August 1, 2017	Nivolumab approved for MSI-H/dMMR mCRC	Nivolumab provided durable responses and disease control in pre-treated patients with dMMR/MSI-H mCRC [51]
Ipilimumab	Human	CTLA-4	July 11, 2018	Nivolumab plus low dose ipilimumab approved for previously treated MSI-H/dMMR mCRC	Clinical effect with nivolumab + low-dose ipilimumab was significant and long-lasting for MSI-H/dMMR mCRC[57]
Cemiplimab	Human	PD-1	NCT04157985. Ongoing	Phase III study: evaluating length of treatment with cemiplimab and other inhibitors in solid tumor patients	Ongoing
Atezolizumab	Humanized	PD-L1	NCT02788279. Completed NCT05118724. Ongoing NCT05456165. Ongoing	Phase III study: atezolizumab with or without cobimetinib *vs* regorafenib in previously treated mCRC Phase II study: atezolizumab with/without IMM-101 in patients with MSI-H/dMMR stage III CRC ineligible for oxaliplatin Phase II study: atzolizumab in combination with neoantigen	Did not meet its primary endpoint of improved OS with atezolizumab plus cobimetinib or atezolizumab *vs* regorafenib Ongoing Ongoing

				targeting vaccine	
Avelumab	Human	PD-L1	NCT03854799. Ongoing	Phase II study: avelumab + capecitabine combined with radiation	Ongoing
			NCT03475953. Ongoing	Phase I/II Study: regorafenib plus avelumab in solid tumors	Ongoing
Dostarlimab	Humanized	PD-1	NCT04165772. Ongoing	PD-1 blockade in dMMR, locally advanced rectal cancer	Ongoing: dMMR, locally advanced rectal cancer was highly sensitive to single-agent PD-1 blockade. Longer follow-up is needed to assess the duration of response
Pembrolizumab	Humanized	PD-1	June 29, 2020	Pembrolizumab for first-Line treatment of patients with unresectable or metastatic MSI-H or dMMR CRC	Approved based on Phase III Keynote-117 Trial in which pembrolizumab significantly reduced the risk of disease progression or death by 40%[158]
Relatimab	Human	LAG-3	NCT05328908. Ongoing	Phase III study of nivolumab-relatlimab fixed-dose combination *vs* regorafenib or TAS-102 in participants with mCRC	Ongoing
			NCT03642067. Ongoing	Study of nivolumab and relatlimab in patients with MSS advanced CRC	Ongoing
Peptide based vaccines[80]					
SART3	-	Metastatic	2001	Used with adjuvant incomplete Freund's adjuvant	Increased cellular immune responses to both CRC cells and the vaccinated peptide
Recombinant Ep-CAM (with liposome carrier)	-	I-III	2001	Used with adjuvant alum	The overall immune response was safe and effective for patients with CRC and advanced cancer against Ep-CAM
		II-IV	2004	Used with adjuvant GM-CSF	
		Metastatic	2004	Used with adjuvant GM-CSF	
CTP37-DT	-	III-IV	2002	Used with adjuvant Nor-MDP (Muramyl dipeptide)	Longer OS with an excellent safety profile in patients with CRC
Recombinant CEA expressed in baculovirus system	Expressed in baculovirus-insect cell system	Stage I-III	2004	Used with adjuvant alum and GM-CSF	Potent and long lasting antigen specific IgG and T cell response
Survivin-2B Human	-	Metastatic	2004	Used with adjuvant UFT (uracil-tegafur)	Excellent safety profile with potent immune response against HLA-A24-expression in patients with CRC
G17DT (N-terminus of gastrin 17)	-	Metastatic	2014	Used with adjuvant diphtheria toxoid	In combination with irinotecan this vaccine has an acceptable immune response with significantly longer survival
OCV-C02	-	Metastatic	2017	Two peptide epitopes derived from RNF43 and TOMM34 and used with adjuvant montanide ISA 51	Safe immune response in recurrent or advanced stage CRC patients resistant to standard chemotherapy
RNF43 and TOMM34-derived peptides	-	III	2018	Used with uracil-tegafur/leucovorin, montanide ISA 51	Strong immune response with increased OS in patients with stage III CRC
PolyPEPI1018	-	Metastatic	2020	Used with adjuvant montanide ISA 51 Human	Safe and well-tolerated and induced robust CRC-specific T cell responses, similar to

					personalized neoantigen vaccines
mRNA-based vaccines[80]					
NCI 4650 (mRNA 4650)	-	Metastatic	2019	-	Partly safe and neoantigen specific CD8 and CD4 T cells responses against CRC neoepitopes
mRNA 4157	-	Metastatic	2019	In combination with pembrolizumab	Partly safe and strong neoantigen specific T cell responses against CRC neoepitopes
V 941 (mRNA 5671)	-	Metastatic	2019, NCT03948763	In combination with pembrolizumab	KRAS vaccine clinical trial is underway, and the results are eagerly awaited
RO 7198457 (RG 6180)	-	Metastatic	2020	In combination with atezolizumab	Partly safe and strong neoantigen specific immune responses
Cell based vaccines[80]					
Tumor cell	Tumor cell	II and III	2000	In combination with BCG	Less potency with 5-yr OS of 84.6%
Cancer Vax	Tumor cell	IV	2001	In combination with BCG	Significant increase in anti-TA90 IgG and IgM titers, and the OS was 21.9 mo
HSPPC-gp96	Tumor cell	IV	2003	-	Two-year overall survival and disease-free survival improved
CEA mRNA	DCs	IV	2003	In combination with IL-2	Well tolerated and safe immunization observed in patients with advanced malignancies
OPA-DC	DCs	Metastatic	2011	CEA peptide-loaded DCs matured with a combination of OK432, prostanoid, and interferon-α	Increased CEA-specific cytotoxic T cell response and NK cell levels in 8 patients with stable disease
Autologous tumor lysate DC (ADC)	DCs	Metastatic	2016	-	Not recommended: the use of ADC alone, in a phase III trial
Autologous tumor antigens-loaded DC	DCs	Metastatic	2018	In combination with 5-fluorouracil	Treatment was safe and had shown particularly prominent IL-12 production for immunization against neoantigens
Vector based vaccines					
ALVAC-CEA/B7	Canary pox virus vector	Metastatic	2008; 2013	In combination with chemotherapy	Acceptable safety profile and induced CEA-specific T cell responses in patients with mCRC
AVX701	Alphavirus vector	III	2010	VRP expressing CEA	Well tolerated and elicit robust CEA-specific T cell and antibody responses in patients with CRC
GI-6207	*Saccharomyces cerevisiae*	Metastatic	2014	-	Strong antigen-specific CD8+ T cells and CD4+ T responses and extended stable disease
GI-6301	*Saccharomyces cerevisiae*	Metastatic	2015	-	Decreased tumor density and serum CEA levels in CRC treated patients

pLADD	*Listeria monocytogenes*	Metastatic	2017, NCT03189030	*Listeria* bacterial vector in combination with neoantigens	Induced neoantigen-specific CD8+ T cells and gamma delta T cells
Cholera	Bacteria	I-IV	2018	-	Cholera vaccination largely decreased the mortality rate of CRC
GI-4000	*Saccharomyces cerevisiae*	Metastatic	2018	-	Excellent safety profile and favorable immunogenicity in the majority of subjects
ADXS-NEO	-	Metastatic	2019	Bacteria expressing personalized tumor antigens	Increased CD4+/CD8+ T cell-mediated immune response

ADC: Antibody drug conjugate; BCG: Bacillus Calmette–Guérin; CEA: Carcinoembryonic antigen; CRC: Colorectal cancer; CTLA-4: Cytotoxic T-Lymphocyte-associated antigen-4; DCs: Dendritic cells; dMMR/MSI-H: Microsatellite instability high and deficient mismatch repair; EGFR: Epidermal growth factor receptor; Ep-CAM: Epithelial cell adhesion molecule; FOLFIRI: 5-flurouracil, leucovorin, and irinotecan; FOLFOX4/6: 5-flurouracil, leucovorin, and oxaliplatin; GM-CSF: Granulocyte macrophage colony-stimulating factor; HLA: Human leukocyte antigen; HSPPC-gp96: Heat shock protein peptide glycoprotein Complex-96; Ig: Immunoglobin; IL: Interleukin; LAG-3: Lymphocyte activation gene 3; mCRC: Metastatic colorectal cancer; MSS: Microsatellite stable; NK: Natural killer cell; Nor-MDP: Nor-muramyl dipeptide; OS Overall survival; PFS: Progression-free survival; PD-1: Programmed cell death receptor 1; PD-L1: Programmed cell death ligand 1; RNF43: Ring finger protein 43; SART3: Squamous cell carcinoma antigen identified by T cells 3; TOMM34: Translocase of outer mitochondrial membrane 34; VEGF: Vascular endothelial growth factor; VEGFR: Vascular endothelial growth factor receptor; WT: Wild-type.

technically and economically demanding for both the business and patients. Second, the allogeneic transplant patient is frequently at risk of graft-versus-host disease. Although ACT offers considerable therapeutic promise, several issues still need to be carefully considered.

Vaccines: Cancer vaccines elicit an immune response by exposing tumor-associated antigens (whether in free form or expressed on the cell surface) to the immune system, leading to immune cell-mediated cancer cell death. Several clinical trials have been conducted over the past two decades introducing novel vaccines against CRC and other carcinomas[66]. Several possible tumor-associated antigens have been targeted over the past decades against CRC, such as squamous cell carcinoma antigen identified by T cells 3[67], survivin[68], CEA[69], melanoma-associated antigen[70], translocase of outer mitochondrial membrane 34[71], insulin-like growth factor–II mRNA binding protein 3[72], EGFR[73], transmembrane 4 superfamily member 5 protein[74], VEGFR1, Wilms tumor 1 protein[75], and ring finger protein 43[76]. These vaccines activate local immune cells by releasing tumor antigens and increase immune cell, like T cells and dendritic cells, infiltration to the site of action[77].

Several vaccination strategies have been developed against cancers based on antigenic composition. Depending upon the molecular composition of the antigen, vaccine methods can be classified as molecular-based, cell-based, and vector-based. Molecular-based vaccines consist of full-length peptides and DNA and mRNA vaccines. The CRC clinical trials showed that the mRNA and DNA vaccines have demonstrated impressive antitumor response with remarkable efficacy and safety profiles compared to the peptide vaccines. Cell-based vaccines consist of native and genetically modified tumor cells and activated dendritic cell vaccines. These vaccine strategies have reported limited efficacy in several trials but have shown potential efficacy in combination with chemotherapy and immunotherapy[78,79].

Live attenuated viruses, yeasts, and bacterial vectors are vector-based vaccines. The oncolytic viral vectors are used for the live attenuation virus vaccine strategy; however, due to increased immunogenicity, the clinical efficacy remains limited. The live attenuated bacterial and yeast vector-based vaccine are the emerging option for therapeutic vaccines against CRC[80]. These different type of vaccines discussed above have been evaluated in several clinical trials in the past decade, listed in Table 2.

Role of cytokines in CRC: Various cells, primarily immune cells (T cells, neutrophils, and macrophages), endothelial cells, fibroblasts, and other stromal cells, secrete cytokines[81]. Due to the complex network of cytokines in immune responses, cytokine-based medications are a complex task requiring a thorough understanding of cytokine biology and modern biotechnology to maximize antitumor activity while minimizing toxicity. Many cytokines therapy trials are currently ongoing for various cancer[82], but for CRC, there is a need for preclinical studies to assess their unexpected toxicity. From a future perspective, cytokines can be essential molecules because of their capacity to increase and reactivate natural killer (NK) cells and T lymphocytes, encourage lymphocyte infiltration of tumors, and persist in the tumor microenvironment (TME).

Despite the fact that immunotherapy is a cutting-edge and intriguing cancer treatment method, it comes with long-term effects and shortcomings. The main limitation of monoclonal antibodies is the decrease in efficacy because of the short half-life[83]. Immune checkpoints defend the body against infections and autoimmune diseases to maintain immune system equilibrium. ICIs induce the activation

of T lymphocytes. However, sustained overactivation of these cells causes immune-related side effects including systemic toxicity[84]. ICIs do not elicit a response in all patients as their T cells are not potent enough to recognize malignant cells. Immunotherapy that boosts T cells does not work against solid tumor cells. Immunosuppressive cells that release chemokines like CXCL1, CXCL5, and others are prevalent in solid tumor cells, and they also have a lot of fibrous matrix[85,86].

CAR-T cells are not very effective in infiltration of solid tumor cells because of their architecture[87]. For each patient using the ACT approach, tumor-specific lymphocytes had to be produced. As a result, it is difficult financially and technically for both the industry and the patients. In the long run, the patients are at a significant risk of developing cytotoxicity, such as B cell hyperplasia, cytokine release syndrome, and graft-versus-host disease[83].

In cases of vaccination, several trials have reported limited efficacy. This is due to the rejection upon identification as a foreign material[88]. In cytokine base therapy, increased levels of cytokines like interleukin-6 and interferon-γ in the bloodstream cause life-threatening poisoning. High toxicity and excessive immune response are caused by immunological signaling and immune cell stimulation brought on by an excess of cytokines[89]. When cytokines are used in excess for an extended period of time, neurological issues like hallucinations, comas, seizures, and verbal difficulties can also arise. Cytotoxicity and a cytokine storm are caused by them[83].

Other approaches

Non-coding RNA-mediated therapy: According to high-throughput genome-scale research, 5%-10% of the transcribed sequences are translated into mRNA or non-coding RNA (ncRNA), out of which only 1% is composed of protein-coding genes and the remaining 4%-9% is transcribed into ncRNAs. As a result, ncRNAs make up a sizable fraction of all RNA molecules[90]. Short regulatory ncRNAs, such as miRNAs and siRNAs, were first identified for their function and clinical significance. The regulatory functions of miRNAs in nearly all physiological and pathological processes in the body, including carcinogenesis, have been widely acknowledged. Several miRNAs are dysregulated in plasma samples of CRC patients; therefore, they have good diagnostic value for CRC screening[90].

Apart from tumor diagnosis and prognosis, ncRNAs can be interesting therapeutic targets for CRC given their tumor suppressive and oncogenic properties. Some ncRNAs play a crucial role in tumorigenesis by losing their tumor suppressive activity, and some are aberrantly overexpressed in CRC, contributing to the oncogenic activity. Therefore, these two mechanisms are used for the development of ncRNA-oriented therapies[91]. Over the past two decades, several synthetic miRNAs and siRNAs have been administered to animal models of various diseases. However, the proper delivery of synthetic miRNAs and siRNAs at the required site of action remains questionable. Several difficulties, including the inability of negatively charged genes to enter negatively charged cellular membranes, gene destruction by plasma nucleases, non-specificity towards targeted cells, and other issues, make *in vivo* direct administration of naked therapeutic genes impractical and challenging. Therefore several drug delivery strategies such as gene transfection with the help of viral or non-viral vectors, nanodelivery system, and others are safe and effective for delivery of siRNAs and miRNAs to the site of action[92].

Ever since the discovery of the potential role of miRNAs as therapeutic targets, several studies have been conducted aimed at various mechanisms such as miRNA-mediated chemosensitization and miRNA mimicking for tumor suppression and oncogenic miRNA targeting[93]. miRNA/siRNA combinatorial therapy with various chemotherapeutic and immunotherapeutic agents has increased the sensitivity of these drugs to cancers[94]. However, most of the studies performed on CRC are limited to animal models and CRC cell lines, and none were extrapolated to CRC patients[95]. Despite the advances in research, no miRNA or siRNA therapy are FDA approved for clinical usage against CRC or any other cancer, but several are in clinical trials (Table 3).

Oncolytic viral therapy: Oncolytic viral therapy or immuno-oncolytic virotherapy employs native or sometimes genetically modified viruses called oncolytic viruses to predominantly infect cancerous cells while avoiding healthy ones[96]. It has emerged as a promising treatment option for CRC. Oncolytic viruses are thought to exert antitumor activity *via* two distinct mechanisms: induction of systemic antitumor immunity and selective replication within neoplastic cells that have a direct lytic effect on the tumor cells. The specificity of oncolytic viruses for tumors can be increased by selective genetic modifications such as the expression of viral surface proteins that bind to cellular receptors found only on cancerous cells, deletion of virus fatal genes, and the addition of different immunostimulatory genes [97].

In past decades, several oncolytic viruses have been evaluated experimentally against CRC, including adenovirus, vaccinia virus, herpes simplex virus, vesicular stomatitis virus, measles virus, tanapox virus, echovirus, reovirus, and Newcastle disease virus. Several oncolytic viruses were also tested clinically in CRC patients as monotherapy, and combinatorial therapy of oncolytic viruses with chemotherapeutics[98], radiotherapy[99], and immunotherapeutics have also been examined against CRC[100]. In the first phase I/II trial, patients with refractory CRC treated with herpes simplex mutant NV120 had good safety profiles and increased chemosensitization[101]. A phase I clinical trial of an oncolytic Western Reserve strain genetically modified with deletion of vaccinia growth factor and thymidine kinase (vaccinia virus mutant) had shown an excellent safety profile in 17 patients with

Table 3 microRNAs and small interfering RNAs as therapeutics for colorectal cancer in clinical trials

Therapeutic name	Target gene/protein	Route of administration	Phase/status	Clinical trial identifier	Outcome
siRNA targeted therapeutics					
ALN-VSP02	*VEGF, KSP*	Systemic	Phase I (2011)/terminated	NCT00882180	It was well-tolerated and had antitumor activity
		IV infusion	Phase I (2012)/completed	NCT01158079	
Atu027	*PKN3*	Systemic	Phase I (2012)	NCT00938574	It was safe in patients with advanced solid tumors
		IV infusion	Phase I/II (2016)/completed	NCT01808638	
CALAA-01	*RRM 2*	Systemic; IV infusion	Phase I (2013)/terminated	NCT00689065	It was well tolerated during the initial dose escalation portion of the phase Ia study
siRNA-EphA2-DOPC	*EphA2*	Systemic; IV infusion	Phase I 2015/active	NCT01591356	It was well tolerated at all doses tested in preclinical studies
TKM-PLK1 (TKM-080301)	*PLK-1*	Systemic; IV infusion	Phase I/II (2016)/completed	NCT02191878	It was tolerated and showed preliminary antitumor efficacy
DCR-MYC (DCRM1711)	*MYC*	Systemic	Phase I (2017)	NCT02110563	It was well tolerated and showed promising initial clinical and metabolic responses across various dose levels
		IV infusion	Phase Ib/2 (2016)/terminated	NCT02314052	
NBF-006	*GSTP*	Systemic; IV infusion	Phase1 (2019)/active	NCT03819387	Significant tumor growth inhibition and overall survival benefit was observed
miRNA targeted therapeutics					
MRX34	miR-34a mimic	IV infusion	Phase I/terminated-2016. Phase I-II/withdrawn-2016	NCT01829971 NCT02862145	Unexpected severe immune-mediated toxicities observed

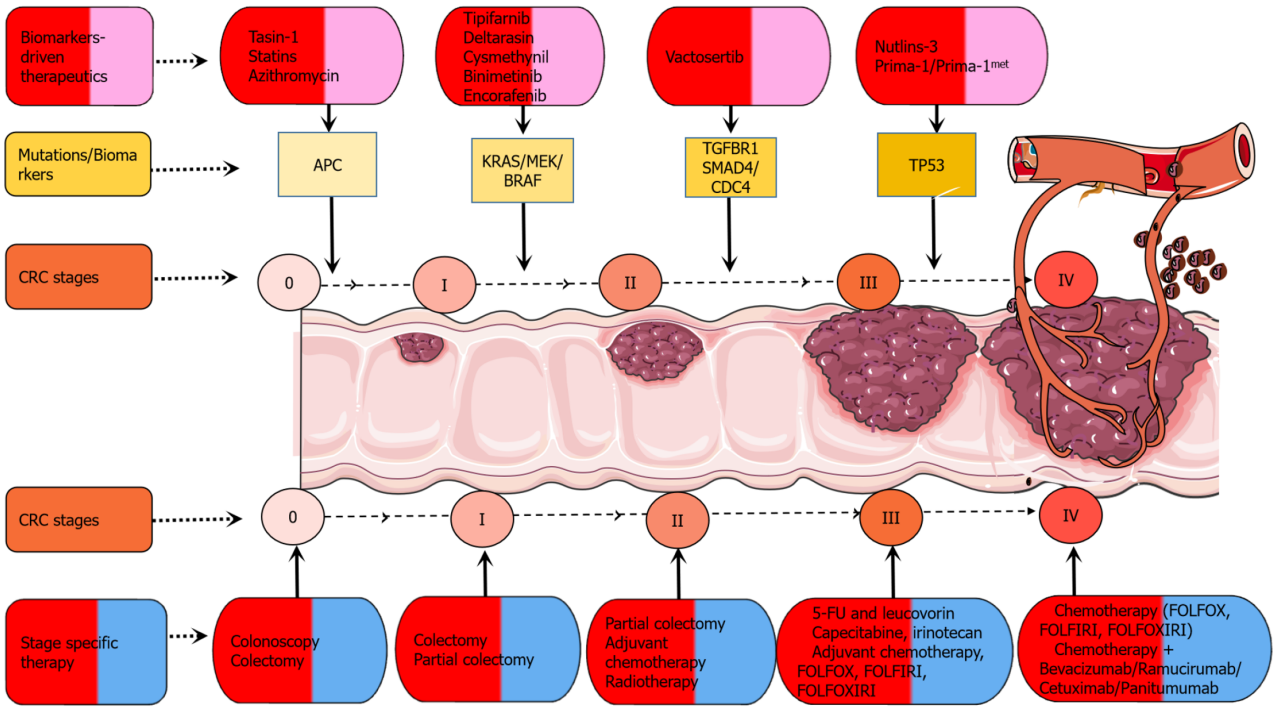
DCR-MYC: Lipid nanoparticle-formulated small inhibitory RNA; EphA2: Ephrin type-A receptor 2; GSTP: Glutathione S-transferase pi gene; IV: Intravenous; KSP: Kinesin spindle protein; miRNA: MicroRNA; PKN3: Protein kinase N3; PLK-1: Polo-like kinase 1; RRM2: Ribonucleotide reductase regulatory subunit M2; siRNA: Small interfering RNA; VEGF: Vascular endothelial growth factor.

advanced and refractory CRC. However, only 1 patient experienced a true benefit from the therapy [102]. This therapy was intratumoral, and another trial with the same agent, when given intravenously in 11 patients, had established safety but limited antitumor activity[103].

A phase II clinical trial of FOLFOX/bevacizumab with or without an oncolytic reovirus pelareorep in 103 patients with mCRC showed a significantly improved response (combined therapy); however, the OS was poor[104]. In another case, patients with stage IV CRC treated with a combined regimen of oncolytic enterovirus, FOLFOX/bevacizumab, and surgical resection (RIGVIR) had impressive efficacy with complete remission for 7.7 years after diagnosis[105]. Despite the intensive research in this field, none of the oncolytic viral therapy is FDA approved for routine clinical use against CRC. Challenges like evading host antiviral immunity and the successful delivery of the virus to the target site cause a hindrance to achieve the optimal antitumor activity of oncolytic viruses. However, several promising strategies like using stem cells or immune cells as carriers are in the pipeline and may increase the antitumor activity of oncolytic viruses.

Cancer stage specific therapy: The cancer stage determines how it will be treated, as given in Figure 2, although other aspects may also be significant. Stage 0 CRC does not spread past the inner lining of the colon; therefore, a colonoscope can be used most of the time to remove the polyp. A partial colectomy can be performed if the cancer is too large to be eliminated by local excision[106]. Many cancers that were a remnant of a polyp are included in stage I and have penetrated further into the layers of the colon wall. They have not migrated to surrounding lymph nodes or outside of the colon wall itself. The complete removal of the cancerous polyp may not require further treatment; however, if the polyp is high-grade, more surgery may be recommended. If the cancer is not generated from the polyp, partial colectomy is the standard treatment[107].

Stage II CRC has penetrated the wall of the colon and adjacent tissue but has not reached the lymph nodes. These require partial colectomy followed by adjuvant chemotherapy and/or radiotherapy to reduce the risk of relapse. However, adjuvant chemotherapy is not always used for stage II cancers due to severe adverse effects. Stage III CRC has penetrated the adjacent lymph nodes but has not migrated to the other body parts. The partial colectomy and adjoining lymph nodes followed by chemotherapy (FOLFOX or CAPOX) is the standard treatment regimen for this stage of CRC.



DOI: 10.4240/wjgs.v15.i4.495

Figure 2 Biomarker-driven therapeutics and cancer stage specific therapeutic strategies. Drugs like tasin-1, statins, and azithromycin specifically target adenomatous polyposis coli (APC). Drugs such as tipifarnib, deltarasin, and cysmethynil target *KRAS* mutations in colorectal cancer (CRC), and binimetinib and encorafenib target *BRAF*-V600 mutations in CRC. Vactosertib is a potent and selective transforming growth factor-beta receptor I kinase inhibitor. Small molecule nutlins-3 is an MDM2 antagonist blocking the interaction between MDM2 and p53. Small molecules prima-1/prima-1met convert mutant p53 to an active conformation. There are stage-specific therapies for different stages. For stage 0, colonoscopy and colectomy are recommended. For stage I, colectomy and partial colectomy are recommended. For stage II, partial colectomy, adjuvant chemotherapy, and radiotherapy are recommended. For stage III, chemotherapy includes 5-fluorouracil (5-FU), 5-FU/leucovorin, capecitabine, irinotecan, adjuvant chemotherapy, and combinational chemotherapy [5-FU + leucovorin + oxaliplatin (FOLFOX), 5-FU + leucovorin + irinotecan (FOLFIRI), 5-FU + leucovorin + oxaliplatin + irinotecan (FOLFOXIRI)]. For stage IV, chemotherapy, combinational chemotherapy, and immunotherapy include bevacizumab, ramucirumab, cetuximab, and panitumumab.

Cancers in stage IV have migrated to distant organs and tissues from the colon. The liver is where colon cancer spreads most frequently, although it can also affect the lungs, brain, peritoneum (the lining of the abdominal cavity), or distant lymph nodes. The treatment depends upon the severity of metastases. If the cancer is spread to a few small areas, it can be removed by surgery along with partial colectomy. If the metastases spread to many of the organs, chemotherapy is the primary treatment, and surgery may be an option if the tumor size shrinks[108,109].

Natural products for CRC treatment: Recent studies have uncovered the importance of numerous natural products as anticancerous agents because it enhances their quality of life due to their low toxicity and long-lasting nature. Numerous chemotherapeutic agents (almost 50%-60%) are well studied that are obtained from animals, plants, microorganisms, and marine microorganisms to exert anti-cancerous effects[110]. Some of the important natural anticancer agents against CRC are given in Table 1. These natural products are categorized as alkaloids, polysaccharides, polyphenols, terpenoids, and polyunsaturated fatty acids based on their chemical makeup.

Berberine is an isoquinoline natural alkaloid derived from the root, rhizomes, stem, and bark of various plants like *Berberis vulgaris*, European barberry, Oregon grape, and tree turmeric. Berberine inhibits nuclear factor-kappa B and Wnt/β-catenin signaling pathways and exerts an antiproliferative and antiapoptotic effect in cancer. It negatively regulates the action of arylamine N-acetyltransferase in a colon cancer cell line[111] and alters drug resistance by modulating pgp-10 expression in cancer cells [112].

Another alkaloid is irinotecan (CPT-11), a hydrophilic compound derived from camptothecin, which blocks RNA synthesis and prevents DNA synthesis by inhibiting DNA topoisomerase I[113]. CPT-11 effects have been enhanced in CRC when combined with 5-FU/formyltetrahydrofolate[114]. Piperine, an alkaloid of black pepper, enhances the bioavailability, increases absorption, and has favorable effects on the brush border epithelium ultrastructure[115]. Piperine arrests the cell cycle in the G1 phase by inhibiting the expression of cyclin D1 and D3 as well as their dependent kinases 4 and 6 in HT-29 colon carcinoma[116].

Some polysaccharides with anticancer properties, like fucoidan, obtained from seaweed, are a sulfated polysaccharides. Fucoidan plays a major role in suppressing the toxicity of anticancerous drugs

in CRC[117]. Many polyphenols also play a significant role in preventing gastrointestinal malignancies. Curcumin is the most common polyphenol downregulating the gene products implicated in antiapoptosis, cell proliferation, invasion, and angiogenesis[118]. Curcumin shows anticancerous activities in *in vitro* (breast, cervical, colon, gastric, hepatic, leukemia, oral epithelial, ovarian, pancreatic, and prostate cancer cell lines) and preclinical animal models. Five studies of the anticancerous activities of curcumin in CRC were in phase I clinical trials. Each clinical trial found that curcumin is risk-free and has few side effects[119].

Gingerol is another potent polyphenol with various properties like antiemetic, antihyperlipidemic, anti-inflammatory, antioxidant, antiulcer, antihypertensive, immuno-stimulant, and cardiotonic. It regulates multiple cell signaling pathways and their constituents like AP-1, growth factors, p53, COX-2, mitogen-activated protein kinase (MAPK), VEGF, nuclear factor-kappaB, and cyclin D1, which further contribute to cancer initiation and progression[120,121]. In the human colon cancer cell line LoVo, 6-gingerol in a dose-dependent manner reduced the cell viability by arresting the cell cycle in the G2/M phase[122]. A phase II study revealed that andrographolide, a terpenoid, activates various proapoptotic signaling cascades and induces apoptosis (NCT01993472). Polyunsaturated fatty acids such as eicosapentaenoic acid and docosahexaenoic acid have shown the ability to treat malignancies including CRC, breast cancer, and pre-existing adenocarcinoma[123].

Role of probiotics in CRC: Probiotics are becoming progressively significant in basic and clinical examination. Studies have established a substantial relationship between probiotics and CRC and how some strains of good bacteria, *i.e.* probiotics, can have a therapeutic and preventive effect against CRC. Studies have shown that probiotics can also lower secondary complications arising from chemotherapies. In a CRC animal model, probiotic supplementation diminished the formation of aberrant crypts, improving the antitumor impact of 5-FU chemotherapy.

Probiotics can influence intestinal physiology either directly or indirectly by modulating endogenous microflora. Previously, researchers cocultured HT29 colorectal carcinoma cells with *Propionibacterium acidipropionici* strain CNRZ80, *Propionibacterium freudenreichii* subsp. *Freudenreichii* strain ITG18, and *Propionibacterium freudenreichii* subsp. *Shermanii* strain SI41. These strains were found to have a potent cytotoxic effect[124]. Another great bacterial variety, *Lactobacillus*, is a gut-resident probiotic that benefits host health. A study on *Lactobacillus casei* BL23 significantly protected mice against CRC development; specifically, *Lactobacillus casei* BL23 treatment reduced histological scores and proliferative index values[125]. Another *in vivo* study with *Lactobacillus plantarum* strains YYC-3 and YYCS prevented the occurrence of colon tumors and mucosal damage in APCMin/+ mice fed a high-fat diet. However, YYC-3 had a more robust anticancer effect[126].

Some anaerobic microscopic organisms process prebiotics like oligosaccharides into short-chain fatty acids. Short-chain fatty acids, such as acetate, propionate, and butyrate, have many beneficial effects like improving tight junctions, antiproliferative function[127], and anti-inflammatory function by stimulating immunosuppressive cytokines such as interleukin-10[128]. According to the findings, administering specific fecal bacteria, also known as fecal microbiota transplantation (FMT), into a patient's colon may improve a the response to immunosuppressive medications that increase the capacity of the immune system to identify and eradicate tumor cells. Numerous clinical trials have shown cure rates of about 90% when repeated FMTs are included for the treatment of recurrent *Clostridioides difficile* infection[129,130]. By replacing CRC-associated dysbiosis and restoring eubiosis in chronic illnesses, the adoption of FMT protocols could lessen the activation of inflammatory, proliferative, and procarcinogenic pathways as well as microbiota-induced genotoxicity. Even though fecal transplantation has not been well investigated in CRC, future studies will significantly advance this field of study[131].

Biomarker-driven therapy: Conventional drugs are less effective, non-specific, and have more secondary consequences than benefits. Therefore, it is necessary to focus research on a different direction. The following signaling pathways in CRC are dysregulated: *APC* (Wnt pathway), *RAS, RAF, KRAS, RET, MAPK, P53*, and *SMAD*. Figure 2 lists therapeutic agents that target these mutations at particular stages of CRC. CRC shows a sequence of mutations. The very first step in the chromosomal instability pathway begins with the *APC* mutations. APC is a tumor suppressor protein that leads to familial and sporadic types of CRC. It coordinates with axin, β-catenin, and glycogen synthase kinase-3 β and regulates β-catenin in the Wnt signaling pathway. Tasin-1 and statins are drugs that target APC. Tasin-1 induces endoplasmic reticulum stress-dependent jun N-terminal kinase activation and apoptosis in mutated APC human colon cancer cells. It also suppresses AKT activity in a cholesterol-dependent manner[132]. *APC* mutations are followed by the mutational activation of oncogene *KRAS* and *SMAD-4* and inactivation of tumor suppressor gene *p53*. About 40%-50% of CRC patients have *KRAS* mutations.

Mutated *RAS* enhances the activation of downstream signaling pathway molecules like *RAF* and MAP kinase. It leads to a malfunctioning GTPase activity and more frequently affects exons 2, 33, and 34. Drugs like tipifarnib, deltarasin, and cysmethynil target *RAS* and *KRAS* mutations in CRC. Cysmethynil inhibits cell growth in the colon cancer cell line in an isoprenylcysteine carboxyl methyltransferase-dependent fashion[133]. SMAD4 is a tumor suppressor protein and an important molecule of transforming growth factor-beta. Truncated and mutated SMAD-4 is involved in tumor progression

and metastasis. It promotes distant metastasis as compared to lymphatic metastasis of CRC[134]. SMAD-4 is targeted *via* the drug vactosertib. In phase I/II (NCT03724851) trials, vactosertib in combination with pembrolizumab significantly decreased the transforming growth factor-beta-related vactosertib responsive gene signature, and the extent of decrease was more significant in responders compared to non-responders[135].

Mutation in *p53* contributes to 35%-40% of sporadic CRC and almost half in all other cancers[136]. p53 is a tumor suppressor protein involved in various processes like cell cycle, apoptosis, and angiogenesis regulation. A preclinical study on nutlins-3, an Mdm2 inhibitor in the mouse azoxymethane colon cancer model, reduced both cell proliferation and apoptosis[137]. A study on a small molecule PRIMA-1MET, a mutant p53 reactivator, has shown promising results in restoring the wild-type structure of p53 and inducing massive p53-dependent apoptosis[138].

The CpG island methylator phenotype route of CRC pathogenesis is linked to *BRAF* hypermethylation, which results in truncated BRAF. BRAF is stimulated by RAS and involved in various processes like apoptosis, cell growth, cell proliferation, cell differentiation, cell survival, and cell migration. This mutation is 8%-10% in CRC patients. This is important for the EGFR-mediated cell signaling pathway, MAP kinase pathway, and Bcl-2 expression. The truncated BRAF is targeted by vemurafenib and encorafenib drugs, which reduce signaling through the aberrant MAPK pathway. A phase II study (NCT02164916) has shown that addition of vemurafenib improved PFS and the primary endpoint (HR: 0.50, P = 0.001)[139]. In the phase III CRC study (NCT02928224), encorafenib plus cetuximab improved OS, objective RR, and PFS in previously treated patients in the metastatic setting compared with standard chemotherapy[140].

Most promising therapy among new therapeutic approaches

The aforementioned strategies are innovative methods for creating contemporary cancer treatments, and they are characterized by benefits, including specificity, effectiveness, minimal to no side effects, a higher survival rate, and a lower risk of CRC recurrence. Based on their similarities and differences, these strategies might be grouped. Natural products, probiotics, and oncolytic viral treatments have various anticancer qualities and can be given at any stage of CRC, which is one similarity. However, biomarker-driven therapy and RNA-based therapy target specific molecular entities depending on their expression at a particular stage, making them extremely stage-specific.

The function of therapy, whether diagnostic, prognostic, preventative, or therapeutic, is another commonality in the similarity index. Probiotics and naturopathic remedies serve largely as preventative [141]. However, RNA-based therapy, oncolytic viral therapy, and biomarker-driven therapy have therapeutic potential[93,98-100,142,143]. In addition, RNA-based methods can be used for prognostic and diagnostic purposes[144]. These methods also differ in how they work; for example, certain natural products and RNA-based therapies work at the mRNA level to halt translation by degrading mRNA. Natural products also have several anticancer properties, such as antiproliferative, antiapoptotic, and RNA/DNA synthesis prevention. On the other hand, oncolytic viral medicines cause cellular lysis by inducing systemic antitumor immunity and selective replication within neoplastic cells, which have a lytic effect on the tumor cells. Additionally, probiotics play a preventative role by enhancing tight junction and antiproliferative activity.

Overall, each strategy has its benefits and drawbacks. But RNA-based treatments have drawn more attention, primarily because of their versatility in modifying a wide range of targets and their capacity to target disease genes that were previously inaccessible for manipulation. The inability of the negatively charged RNA to enter negatively charged cellular membranes; poor cellular uptake, non-specificity, and RNA destruction by nucleases in the plasma are a few difficulties that must be addressed[145]. Advances in medicinal chemistry and nanotechnology will help to solve those issues, and RNA-based therapies will become more widely adopted. RNA-based therapies and oncolytic viral therapies hold the most promising potential. One of the main advantages of oncolytic viruses are they can be engineered to target specific tumor cells without damaging healthy cells. The specificity of oncolytic viruses for tumors can be increased by selective genetic modifications such as the expression of viral surface proteins that bind to cellular receptors found only on cancerous cells, deletion of virus fatal genes, and addition of different immunostimulatory genes[97].

CONCLUSION

Conclusion and future directions

Human genomic, transcriptional, proteomic, and epigenetic information has never been more accessible than now thanks to advances in medical sciences and electronics. Since every patient's TME is unique, a single CRC treatment strategy was never an option. Moreover, individualized therapeutic approaches are required due to tissue heterogeneity. Although conventional cytotoxic drugs are always the first line of treatment for solid tumors, drug resistance causes patients to develop incurable recurring CRC. As a result of these shortcomings, the development of novel approaches with significant benefits and minimal drawbacks as future perspectives is required. Radiotherapy is also a promising option for rectal

cancer patients. But, it has some plausible and long-term toxicity effects on vital organs that must be overcome by modifying radiation intensities[12].

Chemotherapy has become the mainstay of CRC treatment due to studies conducted in recent decades showing that utilizing it has increased the OS time of CRC patients, particularly those with metastases, to approximately 20 mo[20]. Chemotherapy has several drawbacks, including systemic toxicity, an unsatisfactory RR, fever, mucositis, stomatitis, leukopenia and thrombocytopenia[21], and a lack of tumor-specific selectivity. Recently, this has led to the idea of molecular targeted therapy for CRC.

Various monoclonal antibodies against angiogenic factors/receptors have been developed, including anti-EGFR/EGF, anti-VEGFR/VEGF, and ICIs (CTLA-4, PD-1/PD-L1, TIM-3, anti-LAG-3), which act directly on cancer cells by boosting immune cells such as T cells and NK cells. The impediment of antiangiogenic treatments is that they make cancers impervious to them. Tumor-associated fibroblasts continuously secrete proangiogenic growth factors like EGF, insulin-like growth factor, and particularly platelets-derived growth factor-C, which is a key factor for maintaining angiogenesis even in the presence of antiangiogenic therapies[146]. To address these issues and treat this fatal cancer, more target-specific treatment methods, such as immunotherapeutic and target-specific approaches, including ACT therapies[60], vaccines, and cytokine-based therapies[66], are required. ACT, vaccines, and cytokine-based therapies can defeat the inadequacies raised because of chemotherapeutic drugs as they have the ability to increase and reactivate effector NK and T lymphocytes, promote lymphocyte infiltration of tumors, and persist in the TME. Therapeutic cancer vaccines have the potential to be as effective as monotherapies when used in premalignant cancer and carcinoma in situ. Many cytokine therapy trials are currently ongoing for various cancers[82]. But for CRC, there is a need for preclinical studies to assess their unexpected toxicity.

Along with the aforementioned approaches, new emerging approaches for treating CRC, including RNA interference, oncolytic viral therapy, use of natural products, probiotics, and biomarker-driven therapy, have shown promising results. RNA interference has been proposed as another remedial approach that offers significant benefits over customary medicines, with high explicitness and intensity and low toxicity[147]. Utilizing genetically altered oncolytic viruses is another remedial strategy. Currently, only one oncolytic virus therapy has been FDA approved to treat cancer. T-VEC (Imlygic®) is a modified herpes simplex virus that targets tumor cells and aids in their demise. It has been approved for specific melanoma patient subsets. Numerous studies have shown that many natural products have potent anti-CRC effects and could replace chemotherapy agents in treating CRC.

Furthermore, the composition of microbiota appears to influence the development of CRC. As per scientific literature, utilizing probiotics can assist with forestalling CRC growth[148] by utilizing anticarcinogenic activity *via* potential biologically host-dependent and strain-specific physiological mechanisms[141]. The time has come to modify the available therapeutic approaches and foster novel methodologies with negligible drawbacks and higher advantages for CRC treatments.

FOOTNOTES

Author contributions: Kumar A performed the conceptualization, wrote the original draft preparation, and contributed to software, visualization and investigation, and reviewing and editing; Gautam V, Sandhu A, and Sharma A wrote the original draft preparation; Rawat K wrote the original draft preparation and performed the proofreading; Saha L contributed to the conceptualization, supervision, and reviewing and editing.

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

Country/Territory of origin: India

ORCID number: Lekha Saha 0000-0001-5925-7159.

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

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World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2023 April 27; 15(4): 520-533

DOI: 10.4240/wjgs.v15.i4.520

ISSN 1948-9366 (online)

REVIEW

Harnessing interventions during the immediate perioperative period to improve the long-term survival of patients following radical gastrectomy

Lin-Bo Liu, Jian Li, Jian-Xiong Lai, Sen Shi

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

P-Reviewer: Kanaoujiya R, India; Zhi X, China

Received: December 15, 2022
Peer-review started: December 15, 2022
First decision: January 3, 2023
Revised: January 4, 2023
Accepted: March 30, 2023
Article in press: March 30, 2023
Published online: April 27, 2023

Lin-Bo Liu, Sen Shi, Department of General Surgery (Vascular Surgery), The Affiliated Hospital of Southwest Medical University, Luzhou 646000, Sichuan Province, China

Lin-Bo Liu, Department of Vascular Surgery, The Third Hospital of Mianyang, Sichuan Mental Health Center, Mianyang 621000, Sichuan Province, China

Jian Li, Jian-Xiong Lai, Department of General Surgery, The Third Hospital of Mianyang, Sichuan Mental Health Center, Mianyang 621000, Sichuan Province, China

Sen Shi, Cardiovascular and Metabolic Diseases Key Laboratory of Luzhou, Luzhou 646000, Sichuan Province, China

Sen Shi, Key Laboratory of Medical Electrophysiology, Ministry of Education and Medical Electrophysiological Key Laboratory of Sichuan Province, Luzhou 646000, Sichuan Province, China

Corresponding author: Sen Shi, MD, Surgeon, Department of General Surgery (Vascular Surgery), The Affiliated Hospital of Southwest Medical University, No. 25 Taiping Street, Jiangyang District, Luzhou 646000, Sichuan Province, China. shisen80@163.com

Abstract

Although the incidence and mortality of gastric cancer (GC) have been decreasing steadily worldwide, especially in East Asia, the disease burden of this malignancy is still very heavy. Except for tremendous progress in the management of GC by multidisciplinary treatment, surgical excision of the primary tumor is still the cornerstone intervention in the curative-intent treatment of GC. During the relatively short perioperative period, patients undergoing radical gastrectomy will suffer from at least part of the following perioperative events: Surgery, anesthesia, pain, intraoperative blood loss, allogeneic blood transfusion, postoperative complications, and their related anxiety, depression and stress response, which have been shown to affect long-term outcomes. Therefore, in recent years, studies have been carried out to find and test interventions during the perioperative period to improve the long-term survival of patients following radical gastrectomy, which will be the aim of this review.

Key Words: Radical gastrectomy; Perioperative events; Gastric cancer; Survival;

Metastasis

Core Tip: During the relatively short perioperative period, patients undergoing radical gastrectomy will suffer from various perioperative events, which have been shown to affect long-term outcomes. Therefore, in recent years, studies have been carried out to identify and test interventions during the perioperative period to improve the long-term survival of patients following radical gastrectomy. As the majority of these interventions are already safely applied clinically for other indications, are cost-effective and can be administered conveniently, if the desired survival benefits are prospectively confirmed, considerable economic and social improvements can be achieved at little financial cost.

Citation: Liu LB, Li J, Lai JX, Shi S. Harnessing interventions during the immediate perioperative period to improve the long-term survival of patients following radical gastrectomy. *World J Gastrointest Surg* 2023; 15(4): 520-533
URL: https://www.wjgnet.com/1948-9366/full/v15/i4/520.htm
DOI: https://dx.doi.org/10.4240/wjgs.v15.i4.520

INTRODUCTION

Although the incidence and mortality of gastric cancer (GC) have been declining gradually in recent decades, its survival improvement is relatively poorer than that of other common malignancies, such as colorectal and breast cancer[1]. In 2020, there were an estimated 768793 GC-related deaths[2]. Therefore, strategies aiming to decrease the burden of GC are being extensively explored globally. Currently, radical surgical removal of the primary GC is the preferred choice for patients whose disease is still locally resectable[1]. Unfortunately, postoperative development of recurrence and metastasis, the main cause of morbidity and mortality of GC, is inevitable in some patients, especially in those with advanced disease[3]. As no visible evidence of metastasis is the prerequisite for radical gastrectomy, postoperative relapses mainly result from occult cancer cells whose spreading has already occurred or been induced during the perioperative period by the surgery itself or its related events, including anesthesia, pain, intraoperative blood loss, allogeneic blood transfusion, postoperative complications (POCs), and their related anxiety, depression and stress response.

The notion that surgical trauma may enhance the risk of cancer metastasis was already noticed by the ancient Greeks, who cautioned against disturbing cancers[4]. In the 1960s, surgeons found that long-term survival was only moderately improved compared to historical nonoperated controls, and even rapid recurrence and progression were found in patients with cancer following radical resection, indicating the promoting effects of surgery on the spread of cancer cells[4]. However, these negative effects were largely ignored; only when perioperative adjuvant therapies have gained success in survival improvement has interest in this theory reemerged. Typically, perioperative adjuvant therapies for metastasis prevention are administered at least one month before or after surgery for cancer, including GC. The immediate perioperative period is rarely exploited for such interventions, largely owing to concerns over contraindications to surgery[5]. Such a concept has changed in recent years, as the significance of this timeframe in determining long-term oncological outcomes is widely recognized [5]. Therefore, various interventions have been explored during the perioperative timeframe, and some of them show great promise. As the recurrence and metastasis rates are higher and radical gastrectomy is relatively more extensive than surgeries for other malignancies, the immediate perioperative period of radical gastrectomy may be a critical timeframe to improve the prognosis of GC.

In this review, we briefly discuss the mechanisms underpinning the negative effects of radical gastrectomy and its related events and then describe the measures that could be harnessed to mitigate their cancer-promoting effects while improving the long-term survival of patients following radical gastrectomy, with the hope of transforming the perioperative period from a prominent facilitator of cancer recurrence to a window of opportunity for improving oncological outcomes in patients with GC.

PERIOPERATIVE PHYSIOLOGICAL RESPONSE TO GASTRECTOMY AND ITS RELATED EVENTS

In clinical settings, extensive surgery for GC always provides no additional survival benefits and even leads to poor survival in some patients[6,7]. Other necessary events during the perioperative period,

including anesthesia and analgesia, can shorten the long-term survival of patients with GC if the modality or agents are administered inappropriately[8]. Adverse events during gastrectomy or postoperative recovery, such as intraoperative blood loss, allogeneic blood transfusion, and POCs, were all proven to be independent negative prognostic factors for patients following curative gastrectomy[8]. In addition, concomitant anxiety, depression and stress response can aggravate the cancer-promoting effects of gastrectomy and its related events. The perioperative physiological responses that underpin the cancer-promoting effects of radical surgery and its related events have been extensively studied in surgical oncology and have been excellently reviewed in previous publications[5]. Conclusions relevant to GC have also been discussed in our previous review[8]. Briefly, gastrectomy and its related events activate the sympathetic nervous system (SNS) and inflammatory response, also referred to as the surgical stress response, leading to enhanced growth of residual cancer cells, which may be preexisting micrometastases, incompletely resected fractions of tumor cells or disseminated from the primary tumor during the operation. In addition, following the activation of the surgical stress response, antitumor immunity is suppressed and fails to eliminate these residual cancer cells[5]. Therefore, measures that can alleviate the acute stress response to surgery and liberate the suppression of antitumor immunity are the focus of studies aiming to harness the immediate perioperative period for improving the long-term survival of patients with GC.

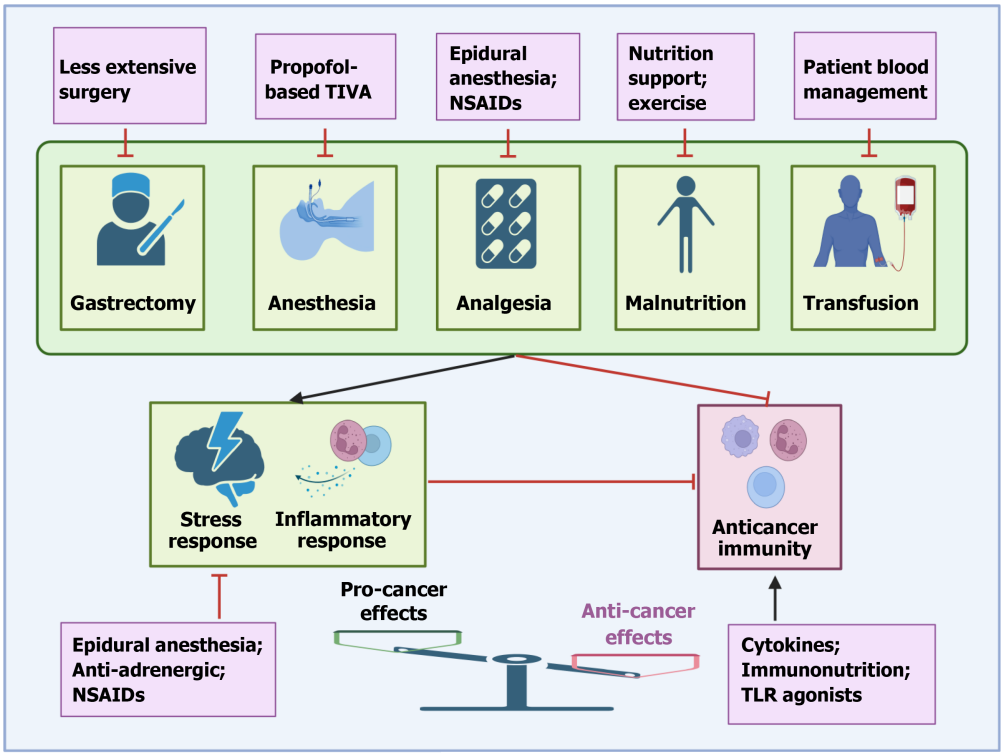
POTENTIAL PERIOPERATIVE INTERVENTIONS

For a long time, surgeons did everything just for operation and believed that the side effects of surgery must be borne. Therefore, it is not necessary to complicate the perioperative timeframe by additional interventions due to the relatively short time span of tumor evolution- or justified and/or speculated concerns over contraindications to surgery[9]. However, this concept has been challenged by three foundations. First, after curative resection, all visible cancer cells are removed, and the probability of future recurrence or metastasis mainly originates from minimal residual cancer cells, whose metastatic progression can be efficiently arrested or prevented by relatively minimal effort and innocuous therapies. In contrast, when these residual cancer cells evolve into larger and more self-sustaining diseases, this goal becomes more difficult or even impossible. Second, some existing interventions have been demonstrated to be tolerable or circumventable contraindications to surgery and can be administered safely during the perioperative period. Third, a robust biological rationale supports the likely antimetastatic efficacy of various interventions during the perioperative period, including appropriate operation, anesthesia and analgesia selection, approaches to limit stress-inflammatory responses and to preserve or activate anticancer immunity (Figure 1).

Gastrectomy administered appropriately

Historically, a series of randomized controlled trials (RCTs) have been conducted to compare the safety and survival benefit between radical gastrectomy with different intensities[10]. The primary principle for surgical management and clinical trial design of curatively resected GC is a balance between resection of tissues with possible cancer cell colonization to achieve long-term survival and acceptable postoperative early death. This high-quality evidence suggests that extensive gastrectomy has few advantages in improving long-term survival compared to less extensive surgery, and some extended resections even lead to increased recurrence or metastasis, indicating that the material benefit conferred by extended surgery may be offset by higher early mortality and increased recurrence resulting from an extensive surgical stress response[6,7]. Therefore, decision-making on surgical approaches for GC should be guided by the latest scientific evidence, and extended gastrectomy without survival benefit should be avoided. Within the modern knowledge of GC management, even in the West, the most appropriate surgery for GC is gastrectomy with D2 lymphadenectomy transabdominally but avoids inevitable paraaortic lymph node dissection, splenectomy, pancreatectomy, and bursectomy[10]. Minimally invasive surgery, such as endoscopic resection and laparoscopic or robotic gastrectomy for early or even advanced GC, is widely adopted as an alternative to traditional open gastrectomy. Although improved long-term survival has not been observed in these studies, less blood loss, fewer POCs, faster recovery, and reduced surgical stress have been found in patients undergoing minimally invasive surgery[11,12]. Therefore, minimally invasive surgery for GC is recommended whenever the conditions of surgeons and patients are feasible. Theoretically, the reduced surgical stress during minimally invasive surgery may translate into a long-term survival benefit when other antimetastatic interventions are coadministered perioperatively.

Nevertheless, both minimally invasive and traditional surgical approaches for GC are highly technically demanding, with a high incidence of intraoperative blood loss and POCs in less experienced hands. Numerous data support the negative effects of intraoperative blood loss, transfusion and POCs on prognosis in patients following radical gastrectomy[8]. In addition, the inferior short-term and long-term outcomes following radical gastrectomy in the East compared with the West were not only determined by more advanced stage and comorbidities but also by the low incidence of GC and uncommon regional specialization. Several other studies have also found that the outcomes of patients



DOI: 10.4240/wjgs.v15.i4.520

Figure 1 Potential perioperative interventions for improving the survival of gastric cancer patients following curative resection. A robust biological rationale supports the likely antimetastatic efficacy of various interventions during the perioperative period, including appropriate operation, anesthesia and analgesia selection, approaches to limit stress-inflammatory responses and preservation or activation of anticancer immunity. The figure in this review was created with BioRender.com. NSAIDs: Nonsteroidal anti-inflammatory drugs; TLR: Toll-like receptor; TIVA: Total intravenous anesthesia.

with GC were better in experienced and high-volume hospitals[13,14]. Therefore, from the viewpoint of survival benefit, gastrectomy should be centralized in high-throughput centers with the ability to provide standardized perioperative management for GC.

Choosing the most appropriate anesthesia and analgesia

Patients diagnosed with locally resectable GC will require anesthesia for endoscopic examination or gastrectomy, and analgesics are commonly prescribed for pain relief following surgery. Currently, several modalities and agents are widely applied for general anesthesia and postoperative analgesia, while total intravenous anesthesia (TIVA), inhalation anesthesia and neuraxial anesthesia are the most studied in cancer surgery. Evidence from studies in GC suggests that these modalities and agents have distinct effects on the stress response, inflammation, anticancer immunity, cancer progression and long-term survival. Inhalational anesthetics, including isoflurane and sevoflurane, have been observed to provide some degree of cytoprotection to organs, which may also support the survival of cancer cells [15]. Although data in GC are lacking, *in vivo* data in other cancer types demonstrate that volatile anesthetics might promote immunosuppression and support tumor cell growth and spreading[16,17]. In contrast, propofol-based TIVA, an alternative to inhalational anesthesia, has appealing anticancer properties and has been extensively studied in GC. Administration of propofol has been shown to inhibit GC cell proliferation, migration and invasion *in vitro* while preserving the cellular immune function of patients undergoing curative gastrectomy[18,19]. Consistent with this evidence, the findings of several retrospective studies or meta-analyses demonstrated that in patients undergoing gastrectomy, long-term survival is better in patients anesthetized with propofol-based TIVA than in those with volatile anesthesia[20]. However, what calls for special attention is that all these studies were retrospectively designed, and selection bias cannot be neglected, providing a limited reference for the choice of anesthesia type during gastrectomy. Currently, a number of prospective trials elucidating the effects of propofol on cancer recurrence and patient survival are ongoing (NCT01975064, NCT03034096, NCT02660411, NCT02840227), and their results may raise the possibility that propofol-based TIVA could become the standard anesthesia approach for cancer surgery, including gastrectomy.

Epidural anesthesia has been widely used jointly with or as an alternative to general anesthesia or for postoperative analgesia in patients undergoing gastrointestinal cancer surgery. Limited clinical evidence suggests the survival benefit of epidural anesthesia for patients with GC[21,22]. The association between epidural anesthesia and decreased cancer recurrence following surgery might reflect the multifaceted effects of this anesthetic and analgesic modality. The addition of epidural

anesthesia to general anesthesia significantly decreased the expression of various inflammatory mediators and increased the proportion and activity of antitumor immune cells in patients undergoing GC surgery[23,24]. SNS blockade and inhibition of perioperative lymph flow both contribute to the anticancer effect of epidural anesthesia, although they have not been validated in GC[25,26]. Furthermore, as a widely adopted postoperative analgesic technique, epidural anesthesia significantly decreases the prescription of opioids for postoperative pain relief[22]. Opioids have been found to promote the growth of cancer and inhibit the antimetastatic activity of immune cells, including natural killer (NK) cells, cytotoxic T lymphocytes, dendritic cells and macrophages[27,28]. Nevertheless, the results from two RCTs including lung or unspecified cancer types did not support the positive effect of epidural anesthesia on overall or cancer-specific survival[29,30]. Therefore, determining whether epidural anesthesia provides a recurrence-preventing effect for patients with GC requires further research.

Inhibiting sympathetic signaling

Activation of the SNS is one of the responses to surgical stress, resulting in increased levels of circulating catecholamines, including adrenaline and noradrenaline. Consistent with this mechanism, the levels of circulating catecholamines were higher in patients undergoing more extended gastrectomy or with an eventful postoperative recovery[5]. Beta 2-adrenergic receptor (β2-AR), the main type of receptor that mediates the biological functions of catecholamines, was found to be overexpressed in cancer tissues from patients with GC and correlated with metastasis and poor prognosis[31]. The activation of β2-AR by catecholamines leads to increased formation of liver and lung metastases by primary GC cells[31]. Mechanisms underlying the cancer-promoting effect of SNS signaling have also been elucidated in various studies. Activation of β2-AR was shown to induce epithelial to mesenchymal transition and cancer stem cell attributes of GC cells[32,33]. Sympathetic nerves can also help establish premetastatic niches in bone by stimulating host bone marrow stromal cells[34]. On the other hand, SNS activation promotes the establishment of an immune-privileged microenvironment, which is beneficial to tumor growth and metastasis formation[35,36]. Therefore, increasing data reported in recent years indicate that perioperative interventions to attenuate SNS activity are promising for reducing the recurrence risk of GC, which can be achieved by pharmaceutical inhibition (β-AR antagonists) or by epidural anesthesia.

Population-based cohort studies have shown that β-AR antagonists (also known as β-blockers), which are widely used in the clinic for hypertension, can significantly decrease the risk for GC[37]. Therefore, as effective strategies to inhibit sympathetic signaling, which is activated by perioperative events, β-blockers may be used as an effective adjunctive strategy to reduce the risk of cancer recurrence. *In vitro* studies, propranolol, the most commonly used nonselective-adrenergic antagonist, showed the ability to induce apoptosis, repress growth, suppress the expression of matrix metalloproteinases and vascular endothelial growth factor, and inhibit the migration of GC cells[38,39]. In a xenograft mouse model, propranolol decreased the levels of phosphorylated AKT, MEK, and ERK proteins and blocked depression-promoted neuroendocrine phenotypic transformation and lung metastasis of GC[31,40,41]. In patients with GC, treatment with propranolol for one week before surgery significantly inhibited the proliferation of cancer, as measured by Ki-67[40]. In other cancer types, the anticancer ability of propranolol has also been found to be associated with enhanced antitumor immunity[42,43]. However, this effect was not observed in GC animal models or patients[40]. Based on the findings of preclinical studies, several clinical trials have been carried out to assess the effects of perioperative β-blockers on oncological outcomes, but none of them have been designed to focus on survival. Only one small RCT in colorectal cancer collected data on the 3-year recurrence rate and revealed a favorable trend toward reduced cancer recurrence in patients receiving β-blockers[44]. Compared with surgery for breast and colorectal cancer, gastrectomy for GC has a relatively higher intensity. It is reasonable to speculate that the intensity of activation of sympathetic responses in radical gastrectomy will be stronger, and β-blockers do have the ability to decrease the surgical responses and have the probability of decreasing the recurrence in GC patients.

Anti-inflammatory therapy

One of the explanations for the lack of effect on long-term outcomes by SNS blockade is that in addition to increased levels of catecholamine, various inflammatory mediators are also abundantly released into circulation during cancer surgery. The levels of inflammatory mediators, including C-reactive protein (CRP), procalcitonin, prostaglandin E2 and plasma cortisol, were elevated significantly after gastrectomy[45,46]. Activation of the inflammatory response plays an important role in residual cancer cell survival and progression through humoral factor release or premetastatic niche establishment[47-49]. A preoperative elevated neutrophil-to-lymphocyte ratio, a systemic inflammation index frequently used in the literature, was shown to have a significant negative effect on survival[50]. Therefore, anti-inflammatory therapy might provide antimetastatic benefits. Selective or nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) for cyclooxygenase (COX) (for example, ibuprofen, celecoxib, and etodolac) are commonly used analgesics following radical gastrectomy, and several studies have shown their anticancer properties. Currently, the most tested anti-inflammatory therapies are selective COX2 inhibitors. In cancer types other than GC, perioperative use of NSAIDs has been shown to attenuate the

inflammatory response, enhance the number and function of antimetastatic immune cells and prevent the formation of metastases in mouse models[51,52]. In the clinical setting, studies have reported that perioperative administration of COX2 antagonists decreases the circulating levels of prostaglandins and catecholamines while preserving anticancer immunity by buffering both the elevation of regulatory T cells and the decline in NK cell counts[5]. The anticancer effect of NSAIDs, especially celecoxib, has also been studied extensively in GC, while data are limited to preclinical or GC prevention settings. For example, a population-based intervention trial revealed that celecoxib treatment alone had beneficial effects on the regression of advanced gastric lesions[53]. Selective COX-2 inhibitors were found to suppress GC cell dissemination through apoptosis induction and migration suppression[54,55]. In a mouse model bearing orthotopic xenografts or with carcinomatous peritonitis induced with a highly metastatic human diffuse-type GC cell line, etodolac, a COX-2 inhibitor, significantly decreased tumor lymphangiogenesis and the total weight of metastatic lymph nodes[56]. In the perioperative setting, only one study reported that preoperative treatment with celecoxib significantly promotes necrosis in GC through the induction of apoptosis and the reduction of microvessel density[57].

Data from these preclinical studies and clinical studies on inflammatory biomarker alterations point to an anticancer effect of NSAIDs. Therefore, several clinical trials have also been performed to investigate the long-term outcome impact of NSAIDs on cancer. A retrospective analysis suggested that intraoperative administration of ketorolac decreases the risk of breast cancer relapse compared with other analgesics[58]. A nationwide cohort study involving 15574 patients revealed that the use of NSAIDs can be associated with a reduced risk of early hepatocellular carcinoma recurrence within 2 years after curative liver resection[59]. However, these studies were retrospectively designed and have inherent limitations. Thus, several RCTs aimed at investigating the effect of perioperative administration of NSAIDs on improving cancer-specific survival are currently ongoing. One of these studies was completed and reported that preoperative administration of ketorolac tromethamine does not increase disease-free survival (DFS) or overall survival (OS) in high-risk breast cancer patients[60]. However, because of the relatively low surgical trauma and low recurrence rate in breast cancer, the results cannot be extrapolated to other cancer types. In addition, as mentioned above, activation of the SNS and inflammatory response have redundant roles in promoting the growth and recurrence of cancer, and anticipated survival improvement cannot be achieved by COX2 inhibitors alone. Therefore, the combination of β-blockers and COX2 inhibitors is being investigated in several RCTs. Primary results revealed that perioperative administration of β-blockers and COX2 inhibitors not only improves immune competence and metastatic biomarkers but also shows a favorable trend toward reduced cancer recurrence in treated patients[44,61]. To date, no such RCTs recruiting patients with GC have been reported or registered. As radical gastrectomy activates a relatively more severe surgical stress response, whether pharmacological blockade of these responses will provide a survival benefit deserves further clinical trials.

Perioperative immune stimulation

Immunosuppression is a widely recognized phenomenon in patients with cancer, especially during the perioperative period[9]. The total lymphocyte count decreased rapidly from preoperative levels, while the expression of lymphocyte activation gene 3 and programmed cell death 1 on lymphocytes was upregulated, indicating impaired cell-mediated immunity after surgery for GC[62]. Potential contributors to perioperative immunosuppression include the stress-inflammatory response, anxiety, hypothermia, blood loss and transfusion, and the direct and indirect effects of anesthetic and analgesic agents[9]. As immunosurveillance critically determines the fate of minimal residual cancer cells, manipulation of anticancer immunity may provide a promising opportunity to improve the long-term survival of patients following curative surgery[63]. To date, various interventions to activate host anticancer immunity have joined the therapeutic armamentarium for the treatment of many advanced-stage cancers; however, few of them have been tested during the perioperative timeframe, owing to several established and theoretical risks pertinent around the time of surgery[9]. Nevertheless, perioperative immune preservation or stimulation could hold various advantages if the interventions meet the following desired attributes: A rapid immunological response, avoidance of tumor-promoting effects, minimal contraindications to surgery, resilience to perioperative stress and a limited capacity to induce stress responses[9]. Potential strategies have been investigated in various cancers, including GC.

Cytokines

Cytokines are essential for an effective anticancer immune response. Treatment with recombinant interleukin-2 (IL-2), a crucial cytokine for various leukocytes, has long been tested in perioperative settings. For example, preoperative treatment with low-dose IL-2 can be safely given in patients with GC and was revealed to prevent postoperative lymphocytopenia and activate peripheral and peritumoral lymphocytes[64]. Furthermore, IL-2 seems to have an impact on the clinical course, reducing the morbidity of surgery and ameliorating OS and DFS[65]. Other cytokines, such as type I interferons and granulocyte colony-stimulating factor, have also been investigated in the perioperative period and were shown to improve anticancer immunity; however, the survival benefits were somewhat heterogeneous[66-68]. Except for these primary promising results, perioperative administration of cytokines has been discontinued in recent years, largely owing to their severe systemic

adverse effects, including the induction of fever, weakness and headaches, which cannot be distinguished from signs of infection and might result in surgery being delayed.

Immunonutrition

In contrast to other strategies to improve anticancer immunity, data on the beneficial effects of immunonutrients administered perioperatively are accumulating in GC[69]. Immunonutrient interventions are nutrition support that is rich in elements beneficial for the homeostasis of immunity, including ω-3-fatty acids, glutamine, arginine, and nucleotides[70]. Although not all studies found similar clinical effects and some conflicting results have been reported, the influence of immunonutrition on immunological levels, nutrition status and postoperative course was convincing. For example, an early 5-d postoperative enteral immunonutrition supplement significantly improved immune function and the inflammatory response in GC patients following gastrectomy[71]. When immunonutrition was supplied before surgery, the abundance of tumor-infiltrating lymphocytes was upregulated in gastrectomy samples[72]. Several meta-analyses also demonstrated the efficacy of perioperative immunonutrition for improving various immunological indices and decreasing the incidence of POCs [69,73,74]. Although the benefit of improving immune function has been consistently reported, few studies have collected survival data. One study concluded that the 60-d mortality was lower in patients receiving immunomodulating enteral nutrition in the perioperative period, but no improvement in 6-mo and 1-year survival was found[75]. The explanations may be that only a small number of patients were included, and in some studies, prolonged use of immunonutrition increased tumor angiogenesis, which may offset the survival benefit of immunonutrition[72,75]. Therefore, whether perioperative immunonutrition support can provide a survival benefit needs further large prospective studies, and the ingredients and duration of immunonutrition should be determined carefully.

Toll-like receptor agonists

Some immunotherapeutic strategies, such as immune checkpoint inhibitors, require repeated administration for weeks or months to induce the desired response, making them inappropriate for perioperative settings. However, other approaches, such as some Toll-like receptor (TLR) agonists, can induce rapid activation of immune responses, which was shown to be effective when administered perioperatively. For example, preoperative treatment with CpG-C oligodeoxynucleotide, a TLR9 agonist, can synergize with propranolol and etodolac to improve cell-mediated immunity and limit metastatic progression in a mouse model[76]. A fully synthetic TLR4 agonist, glucopyranosyl lipid-A, can be safely administered perioperatively and significantly elevates both innate and adaptive immunity, leading to reduced metastatic development[77]. The TLR3 agonist polyinosinic-polycytidylic acid [poly(I:C)] significantly enhanced NK cell activity in preclinical tumor models, healthy human donors and cancer surgery patients[78]. To date, evidence is limited to preclinical models, none of them have been pursued in clinical trials, and the perioperative application potential is not clear in GC. However, as suggested by promising preclinical rationale, research into perioperative immune stimulation is warranted in the future.

Nutrition support and exercise

GC patients always present with malnutrition, largely owing to digestion and absorption dysfunction, obstruction attributed to cancer, and anorexia caused by cancer-released cytokines. Numerous studies have reported that malnutrition is associated with poor prognosis, which may be the result of interference with treatment implementation and impaired anticancer immunity[79-81]. Therefore, perioperative nutrition support was proven to improve immune function, weaken the surgical stress response and decrease POCs, thereby theoretically prolonging the survival of GC[82]. However, no survival data are available to date. On the other hand, preclinical studies have suggested that excessive parenteral nutrition support could potentially promote the proliferation of cancer cells[83]. Accordingly, determining the patients who need nutritional support and how to carry out nutritional support optimally are the focus of future studies.

Physical fitness plays an important role in the successful administration of various cancer therapies, including surgery, and thus may determine the long-term survival of patients postoperatively. Low physical performance, partially determined by the loss of muscle mass plus low muscle strength, is associated with POCs and poor prognosis in GC patients[84-86]. Correspondingly, increasing the physical activity of patients through perioperative exercise, always administered simultaneously with nutrition support, decreased the incidence of POCs and enhanced the recovery course following gastrectomy[87]. However, although prolongation of survival has been achieved by exercise in patients with colorectal cancer, whether perioperative exercise programs have clinical benefits with regard to long-term oncological outcomes in GC patients is unclear[88,89]. Mechanisms underlying the protective effect of exercise on cancer mortality are multifarious. For example, exercise was found to decrease the inflammatory marker CRP, indicating an anti-inflammatory effect[90]. Moderate exercise is known to enhance cellular immunity and to decrease the levels of insulin and insulin-like growth factor[91,92]. In addition, activity-induced changes in the body and mental health also support improved tolerance for and the resultant effectiveness of cancer treatment[93]. Therefore, as a simple and convenient

intervention that can be safely implemented during the perioperative period, exercise may provide the desired survival improvement in patients following gastrectomy.

Patient blood management

Similar to malnutrition, anemia is another most common presentation in GC patients, and the incidence was reported to range from 27% to 44%[94]. Pretreatment anemia predicts increased POCs and decreased long-term survival, including DFS[94]. Therefore, perioperative allogeneic blood transfusion is frequently administered in GC patients. Paradoxically, abundant data suggest that transfusion is intimately associated with cancer recurrence and cancer-related deaths following radical gastrectomy, mainly owing to the inhibition of host immunity and increased risk of POCs[95].

Therefore, in the consideration of long-term survival, the optimization of preoperative anemia treatment is critical for patients with GC. For this purpose, a patient blood management (PBM) strategy was established, which includes different evidence-based interventions, aiming to maintain patients' own blood volume and avoid unnecessary blood transfusion. PBM consists of three parts: Management of anemia through early detection and use of iron preparations to stimulate erythropoiesis; minimization of perioperative blood loss; and optimization of patient-specific physiological tolerance to anemia with a restrictive transfusion strategy[96]. PBM has been successfully applied in orthopedic, cardiac and colorectal surgery, showing the ability to reduce blood transfusion and hospital stay[96]. A Spanish multicenter study applied the PBM strategy to the management of preoperative anemia in GC and reported that PBM can significantly reduce perioperative blood transfusion, especially in patients with preoperative anemia[97]. In addition, reduced postoperative infectious complications, reoperation rate, average hospital stay and mortality were observed in patients under PBM[97]. Although effects on cancer recurrence and long-term survival have not been reported in this study, all short-term benefits mean a possible improved prognosis[97]. PBM requires the completion of laboratory work-up 2-4 wk before surgery, and preoperative iron supplementation at least 7 d before surgery is recommended in patients whose hemoglobin (Hb) is less than 120 g/L and/or ferritin is less than 300 mg/L. For patients with risk factors and/or anemia symptoms, the recommended Hb threshold for blood transfusion is set as 90 g/L; otherwise, transfusion is only recommended for patients with Hb less than 70 g/L[97]. As speculated unfavorable outcomes of delayed surgery for GC, such a long preoperative time spent for PBM may impede its implementation; therefore, only 52% of patients accomplished the preoperative PBM, much higher than that in a previous study on colon cancer, in which only 30% of patients accomplished the preoperative PBM[97,98]. Nevertheless, the implementation of PBM did not significantly prolong the time interval between diagnosis and surgery in the Spanish study[97]. Moreover, there is no evidence that the time required to complete PBM will obviously lead to tumor progression and affect long-term survival. In contrast, the benefits provided by reduced blood transfusion, infectious complications and mortality far exceed the disadvantages of the additional time required for PBM. Therefore, in a German study including some upper gastrointestinal tumors, a preoperative PBM strategy improved the two-year survival rate by 15%, although no subgroup analysis was performed to determine whether the survival benefit remained in GC patients[99]. Therefore, the PBM strategy may balance the contradiction between anemia and transfusion, possibly avoiding the negative effects in both situations while improving the survival of patients following radical gastrectomy, which awaits the results of trials with adequate follow-up.

Enhanced recovery after surgery

In the past decade, the effects of numerous perioperative interventions, including nutrition, minimally invasive surgery, nasogastric/nasojejunal decompression, early postoperative diet and mobilization, on immediate postsurgical outcomes have been studied extensively in radical gastrectomy, and these interventions have been integrated into enhanced recovery after surgery (ERAS), an evidence-based, comprehensive, multimodal approach designed to achieve early recovery for patients undergoing radical gastrectomy[100,101]. Published studies on ERAS mainly reported short-term outcomes, with similar POC incidences but reduced postoperative hospitalization and costs[102]. The ERAS approach was also found to improve the postoperative inflammatory response and surgical stress[103,104]. However, no study has yet reported the long-term survival of patients experiencing an enhanced recovery after radical gastrectomy. As the interventions comprising the ERAS approach often overlap with the principles presented herein to limit the deleterious effects of gastrectomy on surgical stress, which may induce the recurrence of GC, it is our recommendation to incorporate them in conjunction with studying oncological outcomes.

CONCLUSION

Globally, most of the one million newly diagnosed GC patients require gastrectomy each year. Gastrectomy and its related events, including anesthesia, analgesia, transfusion, POCs and malnutrition, will expose these patients to various stress responses during the immediate perioperative period. Pathophysiological alterations, such as activation of the SNS and inflammatory response and

suppression of anticancer immunity, can support the survival and growth of residual cancer cells and promote cancer recurrence. Therefore, exploiting perioperative interventions to reduce the risk of recurrence and metastasis has attracted more attention in recent years. Various approaches, including appropriate operation and anesthesia selection, anti-adrenergic, anti-inflammatory, perioperative immune stimulation, nutrition support, exercise, and PBM, have been widely explored in preclinical or clinical settings, and promising results have been reported. Although data on some approaches are limited or lacking in GC at present, some of them did show the potential to improve the long-term survival of patients with various cancers. However, the majority of evidence was provided by retrospective analysis, and conflicting results have also been observed in clinical trials, perhaps owing to the complex pathophysiological alterations and heterogeneity among patients, leading to the lack of consensus on the optimal approach to perioperative care. In addition, along with the accumulating knowledge of the mechanisms underpinning the invasion-metastasis cascade, the concept of drugging metastasis has attracted more attention[105]. The immediate perioperative period represents a critical timeframe for residual cancer cells to complete the invasion-metastasis cascade, providing an important window for enhancing the efficacy of drugs targeting metastasis. Therefore, a detailed understanding of the changes that occur after surgery in each patient is pivotal for the development of new therapeutic strategies and personalized health care to prevent tumor recurrence. Large-cohort prospective RCTs are required to definitively demonstrate the effects of various perioperative interventions on oncological outcomes after radical gastrectomy. As the majority of these interventions are already safely applied clinically for other indications, are cost-effective and can be administered conveniently, if the desired survival benefits are prospectively confirmed, considerable economic and social improvements can be achieved at little financial cost.

ACKNOWLEDGEMENTS

The author thanks the Health Commission of Mianyang City and the Science and Education Department of the Third Hospital of Mianyang for their support. The space limitations of this review have unfortunately meant that we have not been able to separately cite many of the original publications that have contributed substantially to the literature. We sincerely apologize to the authors of these publications.

FOOTNOTES

Author contributions: Liu LB and Li J are equal coauthors of this article; Li J and Shi S designed the review; Liu LB, Lai JX and Li J reviewed the literature; Liu LB and Lai JX drafted the manuscript; Shi S revised the manuscript; All authors read and approved the final version of the manuscript.

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

Country/Territory of origin: China

ORCID number: Lin-Bo Liu 0000-0003-4952-7084; Jian Li 0000-0002-5807-2360; Jian-Xiong Lai 0000-0001-8483-4587; Sen Shi 0000-0003-1060-621X.

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

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World J Gastrointest Surg 2023 April 27; 15(4): 534-543

DOI: 10.4240/wjgs.v15.i4.534

ISSN 1948-9366 (online)

MINIREVIEWS

Nutrition in acute pancreatitis

Srikanth Gopi, Anoop Saraya, Deepak Gunjan

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: Shalaby MN, Egypt; Susak YM, Ukraine

Received: November 29, 2022
Peer-review started: November 29, 2022
First decision: December 26, 2022
Revised: January 10, 2023
Accepted: March 21, 2023
Article in press: March 21, 2023
Published online: April 27, 2023

Srikanth Gopi, Anoop Saraya, Deepak Gunjan, Gastroenterology and Human Nutrition Unit, All India Institute of Medical Sciences, New Delhi 110029, India

Corresponding author: Deepak Gunjan, MD, Associate Professor, Gastroenterology and Human Nutrition Unit, All India Institute of Medical Sciences, Room 3111, 3rd Floor, Teaching Block, New Delhi 110029, India. drdg_01@rediffmail.com

Abstract

Acute pancreatitis (AP) has varying severity, and moderately severe and severe AP has prolonged hospitalization and requires multiple interventions. These patients are at risk of malnutrition. There is no proven pharmacotherapy for AP, however, apart from fluid resuscitation, analgesics, and organ support, nutrition plays an important role in the management of AP. Oral or enteral nutrition (EN) is the preferred route of nutrition in AP, however, in a subset of patients, parenteral nutrition is required. EN has various physiological benefits and decreases the risk of infection, intervention, and mortality. There is no proven role of probiotics, glutamine supplementation, antioxidants, and pancreatic enzyme replacement therapy in patients with AP.

Key Words: Acute pancreatitis; Enteral; Parenteral; Nutrition; Malnutrition

Core Tip: Nutrition improves the outcomes of acute pancreatitis (AP). In mild AP, solid food can be given when the patient is pain-free and hungry. In moderately severe and severe pancreatitis, feeding can begin as early as possible if there are no contraindications for an oral diet. If the patient does not tolerate an oral diet, tube feeding can be tried; and in case of gastric outlet obstruction or gastroparesis, nasojejunal tube feeding is preferred. Parenteral nutrition should be provided in case of complete intolerance or contraindications to oral/enteric feed or supplemented along with enteral feed if energy targets are not met.

Citation: Gopi S, Saraya A, Gunjan D. Nutrition in acute pancreatitis. *World J Gastrointest Surg* 2023; 15(4): 534-543
URL: https://www.wjgnet.com/1948-9366/full/v15/i4/534.htm
DOI: https://dx.doi.org/10.4240/wjgs.v15.i4.534

INTRODUCTION

Acute pancreatitis (AP) is an acute inflammatory condition of the pancreas, leading to systemic inflammation, organ failure, infection, morbidity, and mortality. It is a frequent cause of emergency visits and its incidence is rising globally[1]. AP is a catabolic state and malnutrition sets in early, progresses rapidly, and is associated with poor prognosis. The management of AP is centered on fluid resuscitation, early nutrition, adequate analgesia, various organ supports, management of local complications, and rehabilitation of the patient. There is no pharmacotherapy available for AP, however, nutritional intervention has shown various benefits in the management of AP. Hence, nutritional management is the cornerstone in the management of AP and is to be emphasized on regular basis to achieve a better outcome in AP. In this review, we shall discuss the practical aspects of nutrition in AP under two categories: (1) Mild AP; and (2) Moderately severe AP (MSAP) and severe AP (SAP).

NUTRITIONAL MANAGEMENT IN MILD AP

Among the patients of AP, nearly 80%-85% will have acute interstitial pancreatitis, usually with mild severity and no risk of mortality. Mild AP is usually self-limiting with an uncomplicated course. Patients do not have local complications or organ failure, and pain subsides early. A low-fat, soft oral diet can be initiated as early as possible when patients feel hungry and are pain-free. Compared with the stepwise introduction of diet from a liquid diet to an oral diet, a full-calorie solid oral food is similarly tolerated and is associated with better calorie intake and a shorter hospital stay[2-4].

NUTRITIONAL MANAGEMENT IN MSAP AND SAP

Acute necrotizing pancreatitis occurs in 15%-20% of patients, which can be MSAP or SAP with a 5%-30% risk of mortality depending on organ failure and infective complications[5]. These MSAP and SAP will be associated with prolonged hospitalizations, infectious complications, requiring invasive interventions, malnutrition, morbidity, and mortality.

Etiopathogenesis of malnutrition in AP

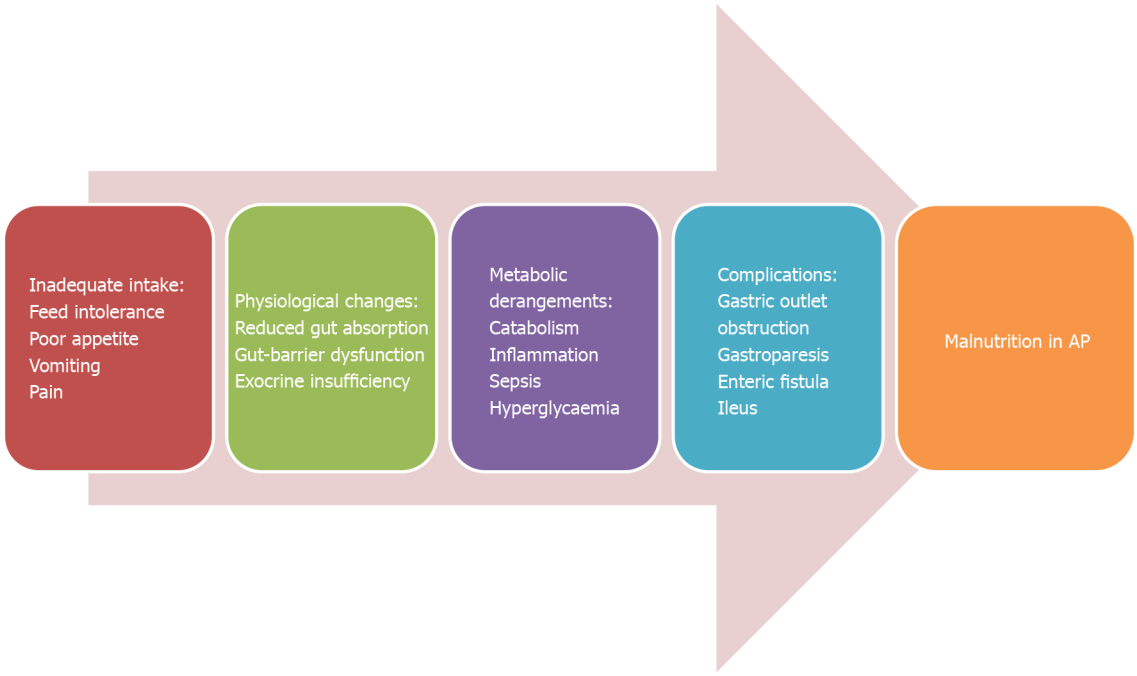
Studies on resting energy expenditure (REE) in AP are limited and have shown that most patients with severe AP and AP with sepsis are hypermetabolic based on gold standard indirect calorimetry (> 110% of predicted energy expenditure by Harris-Benedict equation)[6,7]. Hyperglycemia is often observed during AP and is related to pancreatic necrosis and infections. It is characterized by hyperglucagonemia and relative hypoinsulinemia in the early phase leading to increased gluconeogenesis, while relative hypoinsulinemia extends into the late phase also[8]. Hence, glucose monitoring and control are essential.

In necrotizing AP, severe inflammation in the early phase and sepsis in the later phase leads to increased protein catabolism[9]. In necrotizing AP, skeletal muscle mass and muscle density decrease significantly and rapidly within a month, and it was observed that a decrease in muscle density of ≥ 10% in 1 mo was an independent predictor of mortality[10]. There is increased lipolysis and impaired lipid clearance due to relative hypoinsulinemia and serum triglyceride levels require monitoring in those with severe hypertriglyceridemia as etiology of AP and those in intravenous lipid emulsions.

Malnutrition develops rapidly, is common, especially in necrotizing AP, and is multifactorial (Figure 1). The probable causes are: (1) Decreased oral intake due to pain, nausea and vomiting secondary to gastroparesis or gastric outlet obstruction, intra-abdominal hypertension (IAH) and inappropriate fasting; (2) Increased catabolism in severe AP, and AP with sepsis; (3) Alcoholism; (4) Intestinal failure due to ileus or enteric fistulas; and (5) Exocrine and endocrine dysfunction during AP [11].

Nutritional assessment of patient and energy requirement

The purpose of nutritional assessment is to assess if a patient is at risk of malnutrition, and the current nutritional status of the patient and to plan personalized nutritional support for a patient depending on the severity of AP and the patient's current clinical status. Nutritional risk is defined by the present nutritional status and risk of impairment of present status, due to increased requirements caused by stress metabolism of the clinical condition. All patients with predicted mild to moderate AP need to be screened using validated tools like nutritional risk screening (commonly known as NRS)-2002 or nutrition risk in the critically ill (commonly referred to as NUTRIC) score, and those with predicted severe AP need to be considered at nutritional risk with no screening[12]. This helps to identify patients at high nutrition risk, and these are more likely to benefit from early enteral nutrition (EN) with improved outcomes[13]. There are various definitions of the diagnostic criteria for malnutrition, and Global Leadership Initiative on Malnutrition (commonly known as GLIM) criteria for the diagnosis of



DOI: 10.4240/wjgs.v15.i4.534

Figure 1 Various probable causes of malnutrition during the course of acute pancreatitis. AP: Acute pancreatitis.

malnutrition were proposed by major nutritional societies for a uniform definition globally[14]. Serum markers like albumin, pre-albumin, or transferrin should be avoided in nutritional assessment in AP, as those serum markers are not truly reflective of malnutrition[15].

Indirect calorimetry is the gold standard for the assessment of calorie requirement, especially in critically ill patients but rarely used given its limited availability. The predicted REE can be calculated using predictive equations like the Harris-Benedict equation or by a simpler weight-based equation of 25-30 kcal/kg/day[13]. In healthy adults, the Harris-Benedict equation can provide an approximate estimate of REE in kcal/day, and the same equation can be used for critically ill patients without any modification. Adjusted body weight is preferred for patients with obesity, edema, or ascites[16].

In those who are not critically ill, like mobile patients without organ failure, an additional 10%-20% of the calculated value from the equation is added to account for physical activity and thermogenesis. In patients who are not critically ill and with malnutrition like low BMI (BMI < 18.5 kg/m^2), an additional 300-500 kcal is added to improve their nutritional status[16]. The protein requirements are higher than the healthy controls given higher protein catabolism, especially in severe AP and AP with sepsis. Weight-based protein intake (1.2-2 g/kg/day) can be used to target daily protein requirements[13]. A mixed source of energy from carbohydrates, proteins, and fats is preferable. Micronutrients should be supplemented in patients with suspected or confirmed deficiencies, especially in patients with a history of chronic alcohol consumption or pre-existing malnutrition. In patients on total parenteral nutrition (PN), daily supplementation of multivitamins and trace elements is required as per the recommended daily allowances[11].

A proportion of patients with MSAP or SAP on tube feeding cannot tolerate a complete feed that achieves all calorie requirements owing to various reasons like pain, vomiting, and others[17]. In a randomized controlled trial (RCT) of critically ill patients, permissive underfeeding (40%-60% of estimated caloric requirements) as compared to standard enteral feeding (70%-100% of estimated caloric requirements) was found to have similar clinical outcomes like mortality, infections, and hospital stay with no serious adverse events. An important caveat in that study is that both groups received a similar protein intake of 1.2-1.5 g/kg/day[18]. Hence, in critically ill patients who cannot tolerate entire calorie targets, we can continue with permissive underfeeding. In patients with poor tolerance to tube feeding or those on PN, trophic feeding, *i.e.* small-volume enteral feeding to stimulate the gut, not to meet the calorie requirements, may help to maintain the intestinal physiology, prevent mucosal atrophy, and improve gut barrier dysfunction[19].

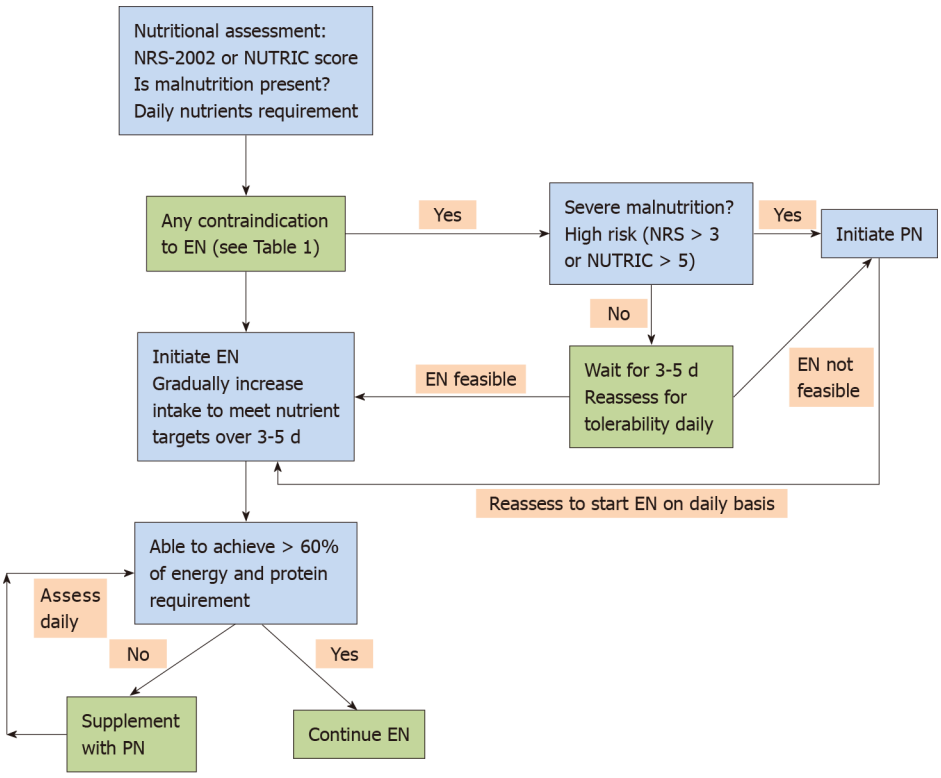
Preferred route of nutrition

An oral diet is preferred in patients who can take it orally. In patients, who are not able to feed orally, EN by tube feeding is preferred over PN[12]. In addition to meeting the nutritional targets, EN has additional advantages like beneficial gastrointestinal, immunological, and metabolic responses[20]. In conditions with contraindications to EN (Table 1), patients should be assessed for initiating PN (Figure 2)[21,22].

Table 1 Contraindications of enteral nutrition[22]

Contraindications of EN
Uncontrolled shock (low dose EN can be initiated once the shock is controlled with fluids and vasopressors with close monitoring for any signs of bowel ischemia).
Uncontrolled hypoxemia, hypercapnia, or acidosis (EN can be initiated in patients with stable hypoxemia, and compensated or permissive hypercapnia and acidosis.)
Active upper gastrointestinal bleeding (EN can be initiated once bleeding is controlled)
Gastric aspirate of > 500 mL/6 h
Abdominal compartment syndrome or intra-abdominal pressure of > 20 mm Hg
Bowel obstruction or ileus
Bowel ischemia
High-output fistula without distal feeding access

EN: Enteral nutrition.



DOI: 10.4240/wjgs.v15.i4.534

Figure 2 Flowchart of the initiation of nutrition in patients with acute pancreatitis. EN: Enteral nutrition; NRS: Nutritional risk screening; NUTRIC: Nutrition risk in the critically ill; PN: Parenteral nutrition.

Physiological benefits of early EN in AP

The earlier concept of "pancreatic rest" in AP by continuing patient fasting has fallen out of favor, as the benefits and safety of early EN in AP are now well established in RCTs[12,23]. The gut barrier dysfunction in AP is implicated in increased bacterial translocation and subsequent infection of pancreatic necrosis or collections. EN can improve gut barrier dysfunction and preserve the gut mucosal integrity, prevent bacterial translocation, stimulate gut motility, and improve splanchnic circulation[12,24,25] (Figure 3). EN is the recommended mode of nutritional support in AP. Compared with PN, EN decreases systemic infections, multiorgan failure, hospital stay, mortality, and the need for surgical interventions and the benefit is more pronounced in severe AP (Figure 4)[23,24,26,27].

Optimal timing for initiating early EN in AP

EN must be started after adequate fluid resuscitation and at least a relatively stable hemodynamic

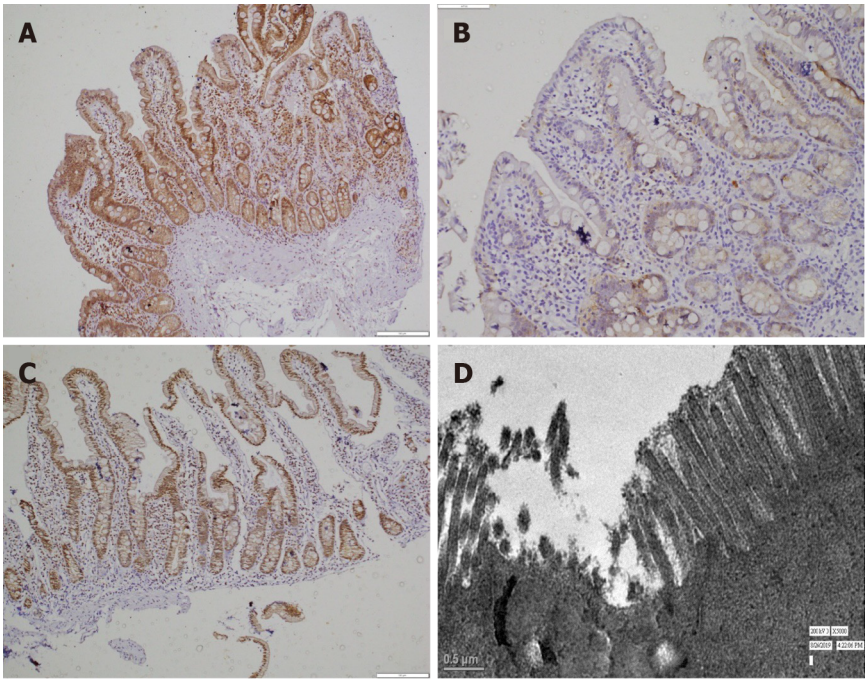


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Figure 3 Gut barrier dysfunction and its restoration after enteral nutrition. A: Duodenal biopsy from control shows intact claudin-3 positivity on immunohistochemistry in both villi and crypts throughout the mucosa (× 200); B: Biopsy taken from acute pancreatitis (AP) shows loss of claudin-3 positivity in the duodenal villi and crypts (× 200); C: Biopsy taken from AP post-enteral nutrition shows positivity (significant improvement) in the duodenal villi and crypts (× 200). Ultrastructural changes in duodenal epithelia of patients with AP on electron microscopy show disordered microvilli.

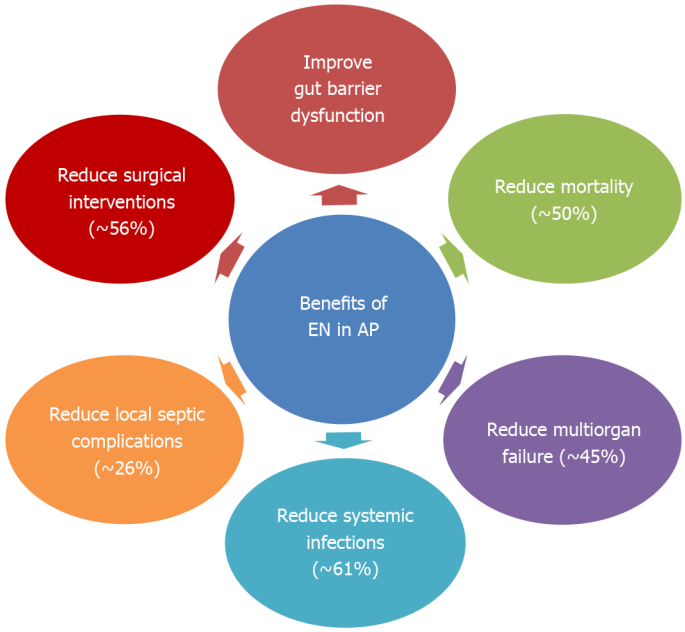

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Figure 4 Evidence-based physiological and clinical benefits of enteral nutrition compared with total parenteral nutrition in acute pancreatitis[24,26]. AP: Acute pancreatitis; EN: Enteral nutrition.

status. Meta-analyses have shown that early EN started within 24-48 h of admission is feasible, tolerated, and associated with lower mortality, organ failure, and infections[28,29]. Two recent RCTs found no difference in mortality, organ failure, or infections between early EN started within 24 h or an oral diet started after 72 h of admission[30,31]. Another prospective cohort study observed that the 3rd d after hospital admission was the best cutoff to reduce infections, with better tolerance and nutritional improvement[32]. A possible explanation is that most of the patients in these two RCTs were not critically ill, and that the benefit of early EN is more pronounced in severe AP compared with other

categories of severity[26]. Hence, patients who are not critically ill can be safely started on an oral diet when symptoms improve or an enteral diet, *i.e.* tube feeding, can be considered after admission if an oral diet is not tolerated. In critically ill patients not tolerating an oral diet, existing data suggest that the EN must be initiated within 48-72 h of admission[5,21]. A RCT is required to justify the benefits of early EN within 24-48 h in this specific group of critically ill patients.

Choice of formulation for EN

EN can be provided by elemental or semi-elemental or polymeric diets. Elemental diets are completely predigested commercial formulations with the simplest form of nutrients. They contain simple carbohydrates and individual amino acids, are low in fat, and contain medium-chain triglycerides. Semi-elemental formulations are commercial feeds with partially predigested enteral formulations (simple carbohydrates, oligopeptides of varying length, and medium-chain triglycerides), whereas polymeric formulations have intact macronutrient components (complex carbohydrates, whole proteins, and long-chain triglycerides). Most earlier studies showing benefits with early EN compared with parental nutrition or no nutrition were done with a semi-elemental diet while some recent studies done with polymeric formulations also showed benefits[33-35]. A pilot RCT compared a semi-elemental diet with a polymeric diet and showed that both were similarly tolerated and absorbed while hospital stay and weight loss were lower with a semi-elemental diet[36]. A meta-analysis compared semi-elemental and polymeric formulations indirectly using PN as a reference and found that feeding tolerance, complications and mortality were similar in both groups[33]. Hence, the guidelines recommend a standard polymeric diet for EN in AP including critically ill patients[12,13].

A polymeric diet can be from two sources: commercial formulations and kitchen-based preparations. Commercial formulas became more desirable, as they are easy to prepare, less prone to microbial contamination, and provide the desired amount of nutrients. However, commercial formulations are more expensive and have less palatability compared with the kitchen-based diet. Kitchen-based diets are easily available, cost-effective in healthcare settings with limited resources, more palatable, and more acceptable to patients. The concerns of a kitchen-based diet are a long time in preparation, increased risk of microbiological contamination, and uncertainty on their nutritional value, especially with nonstandardized recipes[37,38]. In a recently conducted pilot RCT in patients with MSAP and SAP, we observed that both a kitchen-based diet and commercial polymeric formulations were similarly tolerated (personal communication). In summary, EN in any form is beneficial, and the choice should depend on the availability of formulations and cost.

Preferred route of EN

Nasogastric tube feeding is cheaper, easier to insert, and convenient compared to nasojejunal tube feeding. Physiologically, the nasojejunal tube is thought to decrease pancreatic stimulation and secretion, and probably decrease pain and complications, but RCTs have found no differences between nasogastric and nasojejunal feeding in complication rate, refeeding pain, and hospital stay. A recent Cochrane review concluded that there is insufficient evidence to prove superiority or equivalence or inferiority of nasojejunal feeding over nasogastric feeding[39-42]. So, all patients who do not tolerate oral diet should be initiated on EN through the nasogastric or nasojejunal route. Nasojejunal tube feeding should be preferred if a patient has delayed gastric emptying, gastric outlet obstruction due to pancreatitis, or patients with high-risk of aspiration[21].

Continuous vs intermittent bolus feeding

Although intermittent bolus feeding is physiological and has theoretical advantages, existing data showed an increased incidence of diarrhea with intermittent feeds without additional clinical benefit in critically ill patients[43]. Hence, continuous feeding is preferred over intermittent feeding in EN in critically ill patients, although direct evidence is not available in patients with AP.

Role of PN in AP

Although EN is the preferred nutrition over PN in AP, the following are the indications for PN in AP (Figure 2): (1) Complete intolerance to EN; (2) Unable to meet nutritional targets with EN alone; and (3) Contraindication to EN.

Role of other supplements in AP

Immuno-nutrition: (1) Glutamine: Glutamine, a nonessential amino acid, is essential for the survival, proliferation, and function of immune cells. During catabolic/hypercatabolic circumstances, the requirement for glutamine increases rapidly during hypercatabolic states and may lead to impairment of the immune function. A meta-analysis showed the benefit of glutamine supplementation by a reduction in infections, mortality, and hospital stay, and a subgroup analysis showed that those benefits were seen only in patients receiving PN and intravenous glutamine[44]. The risk of bias in the included studies was due to the small sample size and heterogeneity in the severity of the disease. According to European Society for Clinical Nutrition and Metabolism guidelines, intravenous L-glutamine at a dose of 0.2 g/kg/day should be given in patients on total PN owing to contraindications or nonfeasibility of

EN[12]; and (2) Antioxidants: A meta-analysis assessed the effects of antioxidants (including glutamine and other antioxidants) and observed that the antioxidants resulted in a reduction in complications and hospital stay but not mortality[45]. As the results were attributed to glutamine, and a recent Cochrane review did not find any clinical benefit of antioxidants, guidelines do not recommend antioxidant mixtures in AP[12,46].

Probiotics: In experimental models of AP, probiotics were shown to decrease intestinal permeability and hence proposed to reduce infections and mortality[47]. However, in a meta-analysis of clinical trials on patients with AP, there was no benefit of probiotics on infections or mortality, and in one of the RCTs, a multispecies probiotic combination was associated with increased mortality compared to a placebo[48,49]. Currently there is no evidence to support the use of probiotics in AP and the guidelines do not recommend probiotics[12].

Pancreatic enzyme replacement therapy: In a meta-analysis, the prevalence of exocrine insufficiency in AP during admission was 65%, more commonly seen with severe AP and persisted during follow-up in 35% of cases[50]. In an RCT, pancreatic enzyme replacement therapy in AP did not show any statistically significant clinical benefit and only 35% of patients had exocrine insufficiency[51]. Although the data are inadequate, there may be a role of enzyme supplementation in AP with exocrine insufficiency to improve absorption and nutrition[12]. However, recent evidence does not support the generalized use of pancreatic enzyme replacement therapy (PERT) in patients with AP.

SPECIAL SITUATIONS

IAH

Normal intra-abdominal pressure is 5-7 mmHg in critically ill patients and IAH is diagnosed when intra-abdominal pressure (IAP) is increased to ≥ 12 mmHg. As most patients with IAH will have ileus, abdominal distension, or high gastric residue, EN can be initiated *via* the nasojejunal route in patients with IAH[12,52].

If the IAP is < 15 mmHg, early EN can be initiated preferably *via* the nasojejunal route or nasogastric tube. If the IAP > 15 mmHg, it is preferable to initiate the feed *via* the nasojejunal route with caution at a slow rate (20 mL/h) and increase it gradually, as tolerated, monitor IAP, and withhold EN if the pressure increases further. In case of an IAP of > 20 mmHg or presence of abdominal compartment syndrome, EN is to be avoided until the IAP reduces, and PN should be initiated[12]. In postoperative patients with an open abdomen, EN, if possible, is associated with mortality benefit, lesser complications, and higher fascial closure rates. Hence, EN should be initiated and tried at least in small amounts and rest supplemented by PN[12].

Post-endoscopic or minimally invasive necrosectomy

Oral nutrition or if not tolerated, EN is safe and can be initiated within the first 24 h after the procedure provided there are no other contraindications to EN[12].

CONCLUSION

In conclusion, AP is associated with increased morbidity and mortality. Many patients require prolonged hospitalization, multiple interventions, and develop malnutrition. Nutritional supplementation is an important part of the armamentarium to improve the outcomes in patients with AP. Oral or EN is the preferred route and can be started as early as possible. In mild AP, an oral diet can be started whenever a patient is free of pain and feeling hungry. In MSAP and SAP, if oral feeding is not tolerated, then tube feeding can be initiated. However, some patients may require PN. There is no clear benefit of probiotics, immuno-nutrition, and PERT; and they should not be recommended based on current evidence.

FOOTNOTES

Author contributions: Gopi S and Gunjan D contributed to the conceptualization, drafting of the manuscript; Saraya A and Gunjan D critically revised the manuscript.

Conflict-of-interest statement: The authors declare that they have no competing interests.

Country/Territory of origin: India

ORCID number: Srikanth Gopi 0000-0002-3459-8448; Anoop Saraya 0000-0002-3921-6752; Deepak Gunjan 0000-0002-0609-3135.

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

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World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2023 April 27; 15(4): 544-552

DOI: 10.4240/wjgs.v15.i4.544

ISSN 1948-9366 (online)

MINIREVIEWS

Surgical treatment for recurrent hepatocellular carcinoma: Current status and challenges

Di Wang, Min Xiao, Zhen-Miao Wan, Xin Lin, Qi-Yong Li, Shu-Sen Zheng

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

P-Reviewer: Elshimi E, Egypt; Kanno H, Japan

Received: December 6, 2022
Peer-review started: December 6, 2022
First decision: December 19, 2022
Revised: January 5, 2023
Accepted: March 21, 2023
Article in press: March 21, 2023
Published online: April 27, 2023

Di Wang, Zhen-Miao Wan, Division of Hepatobiliary and Pancreatic Surgery, Zhejiang Chinese Medical University, Hangzhou 310000, Zhejiang Province, China

Di Wang, Min Xiao, Zhen-Miao Wan, Xin Lin, Qi-Yong Li, Shu-Sen Zheng, Division of Hepatobiliary and Pancreatic Surgery, Jinan Microecological Biomedicine Shandong Laboratory, Jinan 250000, Shandong Province, China

Min Xiao, Xin Lin, Qi-Yong Li, Shu-Sen Zheng, Division of Hepatobiliary and Pancreatic Surgery, Shulan (Hangzhou) Hospital Affiliated to Zhejiang Shuren University Shulan International Medical College, Hangzhou 310000, Zhejiang Province, China

Corresponding author: Shu-Sen Zheng, MD, PhD, Chief Physician, Doctor, Division of Hepatobiliary and Pancreatic Surgery, Shulan (Hangzhou) Hospital Affiliated to Zhejiang Shuren University Shulan International Medical College, No. 848 Dongxin Road, Hangzhou 310000, Zhejiang Province, China. shusenzheng@zju.edu.cn

Abstract

Primary liver cancer is the sixth most commonly diagnosed cancer and was the third leading cause of cancer deaths worldwide in 2020. It includes hepatocellular carcinoma (HCC) (representing 75%-85% of cases), intrahepatic cholangiocarcinoma (representing 10%-15% of cases), and other rare types. The survival rate of patients with HCC has risen with improved surgical technology and perioperative management in recent years; however, high tumor recurrence rates continue to limit long-term survival, even after radical surgical resection (exceeding 50% recurrence). For resectable recurrent liver cancer, surgical removal [either salvage liver transplantation (SLT) or repeat hepatic resection] remains the most effective therapy that is potentially curative for recurrent HCC. Thus, here, we introduce surgical treatment for recurrent HCC. Areas Covered: A literature search was performed for recurrent HCC using Medline and PubMed up to August 2022. Expert commentary: In general, long-term survival after the re-resection of recurrent liver cancer is usually beneficial. SLT has equivalent outcomes to primary liver transplantation for unresectable recurrent illness in a selected group of patients; however, SLT is constrained by the supply of liver grafts. SLT seems to be inferior to repeat liver resection when considering operative and postoperative results but has the major advantage of disease-free survival. When considering the similar overall survival rate and the current situation of donor shortages, repeat liver resection remains an important option for recurrent HCC.

Key Words: Hepatocellular carcinoma; Repeated liver resection; Salvage liver transplantation; Primary liver cancer

Core Tip: This article reviews the previous literature reports on the statistics of surgical treatment of recurrent liver cancer, mainly including re-hepatectomy and salvage liver transplantation. This article focuses on the analysis and comparison of the respective advantages and disadvantages of these two methods and proposes a future vision.

Citation: Wang D, Xiao M, Wan ZM, Lin X, Li QY, Zheng SS. Surgical treatment for recurrent hepatocellular carcinoma: Current status and challenges. *World J Gastrointest Surg* 2023; 15(4): 544-552
URL: https://www.wjgnet.com/1948-9366/full/v15/i4/544.htm
DOI: https://dx.doi.org/10.4240/wjgs.v15.i4.544

INTRODUCTION

In every nation on earth, cancer is the main cause of mortality and a significant roadblock to raising life expectancy[1]. In 2020, primary liver cancer, which is the sixth most often diagnosed cancer, was the third greatest cause of cancer deaths globally[2]. It includes hepatocellular carcinoma (HCC) (representing 75%-85% of cases), intrahepatic cholangiocarcinoma (representing 10%-15% of cases), and other rare types. At present, the diagnosis of HCC is usually based on the standards established by the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases[3]. Curative treatment for HCC modalities includes resection, ablative therapies (such as radiofrequency ablation, percutaneous ethanol injection, and liver transplantation), and palliative treatment [including trans-arterial chemoembolization (TACE) and targeted systemic chemotherapy with sorafenib][4]. Guidelines from countries worldwide recommend surgical resection as the preferred course of treatment for individuals with resectable tumors[5-7]. With more advanced surgical techniques and postoperative care in recent years, the survival rate of patients with HCC has increased, although long-term survival following surgical resection is still hampered by the high tumor recurrence rate[8-11]. Even after surgical resection, which is thought to be the most radical therapy, the recurrence rate has been reported to exceed 50%[12-14].

Recurrent cancers in liver remains have been treated using the therapeutic techniques frequently utilized for original tumors, such as TACE, radiotherapy, local ablative therapy, surgical resection, and liver transplantation[15]. Nonsurgical options are commonly indicated for the treatment of recurrent HCC since second procedures are frequently unacceptably risky due to the presence of multiple tumors or inadequately preserved liver function. The most effective treatment that may be curative for recurrent HCC remains surgical excision [either salvage liver transplantation (SLT) or repeat hepatic resection] for resectable recurrent liver cancer[16]. Here, we aimed to introduce surgical treatment for recurrent HCC.

RECURRENCE OF HCC

The recurrence of HCC can be either intrahepatic or extrahepatic. The rate of extrahepatic recurrence is far lower compared to that of intrahepatic recurrence. Extrahepatic metastasis is usually considered a late systemic disease[17]. Therefore, patients with extrahepatic recurrence usually receive systemic chemotherapy or supportive treatment only[18-20]. The most frequent kind of recurrent HCC, which is observed in 68%-96% of cases, is intrahepatic recurrence[17,21-23]. Clinically, intrahepatic recurrence is generally attributed to two alternative mechanisms: (1) Intrahepatic metastasis from a primary site; and (2) metachronous multicentric carcinogenesis[24]. Numerous studies have demonstrated that microvascular invasion is a major predictor of tumor recurrence and overall survival (OS) following surgical resection and liver transplantation for HCC[25-29]. According to several studies, there is a larger likelihood of microvascular invasion when there is a higher tumor burden (measured in terms of size and quantity)[30,31]. The alpha-fetoprotein level, transfusion, tumor grade, macroscopic portal vein involvement, the existence of satellite nodules, and positive surgical margin are additional recurrence predictors noted by other research[27,32].

REPEATED LIVER RESECTION

A treatment that may be curative for liver tumors is hepatic resection, which gives patients a possibility of long-term survival. Several treatment centers currently recommend repeating hepatectomy as the first line of therapy for recurrent HCC because it is secure and has comparable survival rates to the first hepatectomy[17]. The majority of patients with intrahepatic recurrence, however, are thought to be unsuitable for repeat hepatectomy[33]. At present, there is no uniform, standard for indicating re-hepatectomy; however, the basic principle is the same. Specifically, currently used standards include a Grade A Child-Pugh score of liver function, sufficient volume of residual liver, recurrent tumors are single or multiple nodules confined to one lobe or liver segment, and there is no invasion of the main blood vessels and bile ducts of the hepatic portal[34]. Repeat hepatectomy is performed 7%-30% of the time to treat HCC recurrence[33,35]. The multifocality, location, and degree of cirrhosis have all been linked to the poor incidence of resectability in individuals with intrahepatic recurrence[36].

The first study of second hepatic resections for recurrent HCC in nine patients without single surgical mortality was reported by Nagasue *et al*[37] in 1986. This study showed that repeated hepatic resection was a feasible and beneficial therapeutic approach for patients with recurrent HCCs in the liver residual [37]. Subsequently, several studies reported the feasibility of repeated hepatectomies for intrahepatic HCC recurrence, with it increasing survival time with no significant increase in morbidity and mortality rates[38-41]. According to Wu *et al*[41], therapy of recurrent HCC with a second hepatectomy was successful, even in cases of the disease's second and third occurrences.

The surgical procedure for liver resection is still challenging and associated with complications[20,42, 43]. The more times a hepatectomy is performed, the more challenging resection is[19,38,39,44-49]. Compared to HCC patients that undergo primary hepatectomy, repeat hepatectomy has a higher risk of complications. Such complications include intra-abdominal adhesions caused by the previous hepatectomy, poorer systemic conditions, progressive deterioration of liver function in patients with cirrhosis, inconsistent liver regeneration, and new growth of intrahepatic vascular structures since the previous hepatectomy[41].

Laparoscopic hepatectomy is now frequently accepted as a minimally invasive method for curing HCC[50-52]. When compared to open liver resection, laparoscopic liver surgery is consistently associated with lower complication rates, less intraoperative bleeding, and a shorter hospital stay[53]. For patients with recurring HCC, Chan *et al*[54] demonstrated that laparoscopic re-resection is possible and secure. The authors identified no discernible differences in patient characteristics, preoperative liver function, and tumor features between laparoscopic and open groups, with the laparoscopic group's perioperative blood loss being considerably reduced (100 *vs* 314 mL; $P = 0.014$). Moreover, both the morbidity rate (18.2 *vs* 4.5%; $P = 0.199$) and the length of hospitalization (6 *vs* 5 d; $P = 0.831$) were comparable. Laparoscopic and open groups had three-year OS rates of 60.0% and 89.3%, respectively ($P = 0.279$)[54].

Nonetheless, existing data cannot confirm whether repeated hepatectomy is superior to other methods used to treat recurrent HCC. Due to selection bias, the prognosis of repeated hepatectomy compared with other treatment methods might not be valid. Patients that do not undergo repeated hepatectomy might have poor liver function reserves, or tumor recurrence might be too serious. Repeated hepatectomy as well as alternative treatment methods for recurrent HCC require prospective randomized studies. For patients with primary and secondary liver recurrences, repeated hepatectomy is still the preferred treatment for recurrent liver cancer.

SLT

Since the first attempted human liver transplantation was reported in 1963 by Starzl *et al*[55], surgical techniques and perioperative patient care for liver transplantation have improved, resulting in it now being a common and routine operation. The use of SLT to treat recurrent HCC following primary liver resection has recently been suggested as a way to increase the duration that HCC patients survive[56]. SLT was initially proposed by Majno *et al*[56] and involves the resection or ablation of the primary tumor, followed by transplantation when recurrence develops.

SLT has gained popularity as surgical technology has advanced because of its effectiveness, which is on par with primary transplantation[57,58]. SLT makes it possible for patients to have prompt, efficient, and secure therapy for HCC. Hepatectomy patients who do not have recurrence are exempt from the need for liver transplantation, which helps to address the scarcity of organ donors. SLT is thought to be comparable to primary liver transplantation and has a respectable long-term survival rate, despite the fact that HCC tends to have more aggressive tumor biology[59-61]. In comparison to repeated liver resection or other salvage therapy for HCC recurrence, SLT may also result in higher long-term survival [62-64]. This suggestion was supported in the published meta-analysis by Zheng *et al*[65].

The indications for SLT differ among studies, especially regarding the acceptable extent of recurrent HCC lesions[48,66-68]. It is still controversial what definition is meant by "transplantability criteria in SLT," which refers to standards identifying the individuals who would benefit most from

transplantation for HCC recurrence following hepatectomy[60,69]. The majority of research concurs that a decent post-SLT survival rate may be attained using the Milan criteria for patients with limited recurrence[70]. Zhang *et al*[71] studied the Milan criteria, the University of California San Francisco (UCSF) criteria, and the model for end-stage liver disease (MELD) score to find predictors for SLT. According to the author, the MELD score, Milan, and UCSF criteria were effective at estimating the outcome of SLT. The author emphasized in particular that SLT could be conducted with a favorable prognosis when the Milan criteria were met by the recurring HCC lesions. De Haas claimed that patients with better MELD scores, no preoperative TACE, no postoperative complications following the first hepatectomy, and low T-stage in the excised specimen are the best candidates for SLT[72]. There was no discernible difference in OS and disease-free survival (DFS) rates between the SLT and primary liver transplantation (PLT) groups when Liu *et al*[73] examined the effectiveness of SLT for patients with recurrent HCC following hepatectomy using UCSF criteria.

Previous studies showed that the average operating time lasts 7-10 h[74-76], with an average blood loss of 1.5-3 L[74-77]. Hu *et al*[76] observed a variety of postoperative complications in their review of 888 SLT cases, including intra-abdominal collection or abscesses and intra-abdominal hemorrhage (31% and 7% of patients, respectively). The authors also recorded postoperative infections in 30% of patients. There were 18%, 3%, and 4%, respectively, of biliary complications, renal failure, and vascular problems [76]. The range of postoperative mortality was 2.1% to 11.8%[74,77]. The rates of five-year DFS (37.8%-86%)[68,76-79] and five-year OS (46.6%-88%)[68,74-77] are very different among studies.

COMPARATIVE STUDY OF REPEATED LIVER RESECTION AND SLT

The statistics on survival after the surgical treatment of recurrent liver cancer in recent years are shown in Table 1. SLT and re-resection for recurrent HCC had comparable survival results, according to a cohort study by Chan *et al*[80]. The authors also demonstrated a relationship between poor DFS and preoperative serum alpha-fetoprotein (AFP) levels and the time to recurrence. SLT may thus be more suitable for patients who have a late recurrence and low serum AFP levels[80]. Furthermore, Lim *et al* [81] showed that five-year OS was similar for SLT and second resection strategies; however, SLT achieved better DFS, which might be attributed to several factors. To be more precise, SLT may: (1) Use complete hepatectomy to achieve the safest resection margin; (2) remove clinically undetectable distant micrometastases from the leftover liver; and (3) treat underlying liver disease, avoiding the emergence of HCC in the liver that remains[81]. Patients in the SLT group also had fewer procedures and treatments, and likely had a better quality of life compared to those in the second resection group[81]. Kostakis *et al*[82] backed up this claim by demonstrating that SLT has a clear benefit over recurrent liver resection (RLR) in terms of DFS. The authors did note, however, that SLT seemed to yield less favorable surgical and postoperative outcomes than RLR.

Re-resection has two clear advantages over SLT. First, the technique is not overly complex, and it is a therapy option that is readily available. Second, there are no opportunistic infection risks or immunosuppression-related risks[15]. A recommendation for the second resection first and SLT for unresectable recurrent illness may lessen the strain on the organ donor pool without reducing the likelihood of long-term survival[15].

CONCLUSION

In general, after the second resection for recurrent HCC, long-term survival rates are favorable. SLT has equivalent outcomes to primary liver transplantation for unresectable recurrent illness in a selected group of patients; however, SLT is constrained by the supply of liver grafts. In terms of surgical and postoperative outcomes, SLT appears to be inferior to repeat liver resection; nevertheless, it offers a sizable benefit in terms of DFS compared to repeat liver resection. Repeat liver resection is still an essential option for treating recurrent HCC when taking into account the similar OS rate and current donor scarcity.

The most crucial method for extending patients' life following hepatectomy at the moment is the aggressive treatment of postoperative intrahepatic recurrence. The outcome for long-term survival following resection of recurring liver cancer is generally favorable for resectable cancer. SLT offers outcomes comparable to primary liver transplantation for unresectable recurring illnesses but is constrained by the lack of liver transplant donor availability. Recent advances in systemic and loco-regional treatments for patients with unresectable and advanced HCC have resulted in improved response rates[83]. Consequently, selected patients with initially unresectable HCC have been given the opportunity to achieve adequate tumor downstaging to undergo surgical resection, a "conversion therapy" strategy[83]. For originally unresectable recurrent liver cancer, the potential of "conversion therapy" in transforming some unresectable patients into resectable patients is worth further clinical research. In addition to surgical treatment, TACE, RF ablation, and other forms of local ablation (such as microwave and high-intensity focused ultrasound) are used to treat recurrent liver cancer. It is still

Table 1 Statistics showing survival after surgical treatment of recurrent liver cancer based on published studies spanning 1989 to 2017

Ref.	Study design	Study period	*n*	Treatment	DFS rate (1-, 3-, 5-yr)	OS rate (1-, 3-, 5-yr)	DSS rate (1-, 3-, 5-yr)
Guerrini *et al*[84], 2014	Retrospectivecohort	2000-2011	28	SLT	95.1%, 80.6%, 80.6%	85.1%, 66,4%, 49.2%	NA
Qu *et al*[75], 2015	Retrospectivecohort	2000-2011	111	SLT	NA	75.5%, 56.3%, 49.1%	NA
Yamashita *et al*[62], 2015	Retrospectivecohort	1989–2012	13	SLT	NA, NA, 81%	NA, NA, 75%	NA
Lim *et al*[81], 2017	Retrospectivecohort	1994-2011	17	SLT	NA, 80%, 72%	NA, 71%, 71%	NA
Chan *et al*[3], 2019	Retrospectivecohort	2005-2017	59	SLT	84.8%, 68.2%, 68.2%	NA	95.7%, 74.4%, 66.7%
Yoon *et al*[85], 2022	Retrospectivecohort	2005-2017	42	SLT	91.6%, 78.6%, 76.8%	NA	98.8%, 90.7%, 87.0%
Minagawa *et al*[47], 2003	Retrospectivecohort	1994-2000	67	RLR	50%, 21%, 17%	93%, 70%, 56%	NA
Itamoto *et al*[38], 2007	Retrospectivecohort	1990-2004	84	RLR	56%, 25%, 10%	88%, 67%, 50%	NA
Wu *et al*[41], 2009	Retrospectivecohort	1990-2007	149	RLR	NA, NA, 31.8%	NA, NA, 56.4%	NA
Faber *et al*[86], 2011	Retrospectivecohort	1990-2009	27	RLR	NA	96%, 70%, 42%	NA
Yamashita *et al*[62], 2015	Retrospectivecohort	1989-2012	146	RLR	NA, NA, 16%	NA, NA, 61%	NA
Lim *et al*[81], 2017	Retrospectivecohort	1994-2011	80	RLR	NA, 22%, 18%	NA, 82%, 71%	NA

DFS: Disease-free survival; OS: Overall survival; DSS: Disease-specific survival; SLT: Salvage liver transplantation; RLR: Repeated liver resection; NA: Not available.

necessary to continue exploring how to formulate a reasonable treatment plan on the premise of fully evaluating the status of patients.

Most existing reports on the surgical treatment of recurrent liver cancer are retrospective, with limitations, such as case selection bias, to varying degrees. Thus, it is necessary to raise the standard of clinical evidence-based medicine in the surgical treatment of recurring liver cancer. More clinical studies, especially randomized prospective studies, are required to confirm the safety and effectiveness of the surgical treatment of recurring liver cancer, and to improve guidance on the surgical treatment of recurring liver cancer.

FOOTNOTES

Author contributions: All authors contributed to data collection, analysis, drafting, or revising the article, have agreed on the journal to which the article will be submitted, gave final approval to the version to be published, and agree to be responsible for all aspects of the work.

Supported by the Jinan Microecological Biomedicine Shandong Laboratory, No. JNL-2022022C; and the Health Commission of Zhejiang Province, No. JBZX-202004.

Conflict-of-interest statement: The authors report no conflicts of interest in this work.

Country/Territory of origin: China

ORCID number: Shu-Sen Zheng 0000-0003-1459-8261.

S-Editor: Yan JP
L-Editor: A
P-Editor: Yan JP

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World Journal of Gastrointestinal Surgery

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World J Gastrointest Surg 2023 April 27; 15(4): 553-565

DOI: 10.4240/wjgs.v15.i4.553

ISSN 1948-9366 (online)

MINIREVIEWS

The spectrum of pneumatosis intestinalis in the adult. A surgical dilemma

Giuseppe Tropeano, Marta Di Grezia, Caterina Puccioni, Valentina Bianchi, Gilda Pepe, Valeria Fico, Gaia Altieri, Giuseppe Brisinda

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

P-Reviewer: Hirosawa T, Japan; Yu F, China

Received: December 7, 2022
Peer-review started: December 7, 2022
First decision: February 8, 2023
Revised: February 10, 2023
Accepted: March 21, 2023
Article in press: March 21, 2023
Published online: April 27, 2023

Giuseppe Tropeano, Marta Di Grezia, Caterina Puccioni, Valentina Bianchi, Gilda Pepe, Valeria Fico, Gaia Altieri, Giuseppe Brisinda, Emergency Surgery and Trauma Center, Fondazione Policlinico Universitario A Gemelli IRCCS, Rome 00168, Italy

Giuseppe Brisinda, Department of Surgery, Università Cattolica del Sacro Cuore, Rome 00168, Italy

Corresponding author: Giuseppe Brisinda, MD, Professor, Surgeon, Emergency Surgery and Trauma Center, Fondazione Policlinico Universitario A Gemelli IRCCS, Largo Agostino Gemelli 8, Rome 00168, Rome, Italy. gbrisin@tin.it

Abstract

Pneumatosis intestinalis (PI) is a striking radiological diagnosis. Formerly a rare diagnostic finding, it is becoming more frequently diagnosed due to the wider availability and improvement of computed tomography scan imaging. Once associated only with poor outcome, its clinical and prognostic significance nowadays has to be cross-referenced to the nature of the underlying condition. Multiple mechanisms of pathogenesis have been debated and multiple causes have been detected during the years. All this contributes to creating a broad range of clinical and radiological presentations. The management of patients presenting PI is related to the determining cause if it is identified. Otherwise, in particular if an association with portal venous gas and/or pneumoperitoneum is present, the eventual decision between surgery and non-operative management is challenging, even for stable patients, since this clinical condition is traditionally associated to intestinal ischemia and consequently to pending clinical collapse if not treated. Considering the wide variety of origin and outcomes, PI still remains for surgeons a demanding clinical entity. The manuscript is an updated narrative review and gives some suggestions that may help make the decisional process easier, identifying patients who can benefit from surgical intervention and those who can benefit from non-operative management avoiding unnecessary procedures.

Key Words: Pneumatosis intestinalis; Risk factors; Treatment; Portal venous gas; Portomesenteric pneumatosis

Core Tip: Pneumatosis intestinalis (PI) represents a radiological diagnosis that must be understood correctly in order to follow the appropriate management. It is essential to identify the conditions that can evolve into transmural intestinal ischemia. It is also important to recognize those cases where PI can be managed conservatively. The integration of the clinical presentation, laboratory tests and abnormal abdominal physical examination can give indications on the path to follow. With this narrative review we have tried to provide a comprehensive analysis of the knowledge of this topic by proposing an algorithm to guide clinical decisions.

Citation: Tropeano G, Di Grezia M, Puccioni C, Bianchi V, Pepe G, Fico V, Altieri G, Brisinda G. The spectrum of pneumatosis intestinalis in the adult. A surgical dilemma. *World J Gastrointest Surg* 2023; 15(4): 553-565
URL: https://www.wjgnet.com/1948-9366/full/v15/i4/553.htm
DOI: https://dx.doi.org/10.4240/wjgs.v15.i4.553

INTRODUCTION

Pneumatosis Intestinalis (PI) refers to a spectrum of diseases characterized by the presence of gas in the intestinal wall[1-4]. It was firstly described the 1700s by Du Vernoy, that detected gas in the bowel wall during a cadaver dissection.

The radiographic finding of PI can indicate a spectrum of underlying processes ranging from a benign finding to a life-threating condition. It is possible to distinguish between "primary" and "secondary" PI[5-8]. Primary PI, also known as idiopathic or pneumocystis cystoides, is a pathologic condition characterized by the presence of gas-filled cysts in the sub-mucosa or sub-serosa especially of the colon[9-11]. Secondary PI is usually related to underlying pathological conditions (Table 1) and it is commonly characterized by the presence of linear or curvilinear gas balls in the intestinal wall[9,10,12-21]. Typically, the primary PI is asymptomatic and is not as frequent as the secondary PI (15% *vs* 85%)[1,22].

Because of its rarity, PI is not yet completely clear from a pathophysiological, diagnostic and therapeutic point of view. Although radiographic PI is relatively common, there is no validated clinical tool to guide surgical management. This narrative review aims to summarize the existing evidence to better understand how to manage patients with this condition.

MATERIAL AND METHOD

The review of the literature was conducted with the following method. A search was conducted on Pubmed for all articles published up to September 2022 with the following terms: "Pneumatosis intestinalis" OR "Portomesenteric pneumatosis" OR "intestinal pneumatosis". A total of 206 articles were detected.

After evaluation of the full text, only 20 manuscripts were included for the draft of this review according to their pertinence in regards of the main topics. Inclusion criteria take in type of publication, study setting, reported outcome and date to publication.

Exclusion criteria were clinical case report, studies focused on specific groups. In particular, excluding case report, some of the 186 articles were excluded for being age specific (*i.e.*, pediatric patients), other for being focused on certain procedures or pathologies (*e.g.*, post-endoscopic procedures, pneumatosis cystoides) or, furthermore, for being of different area of interest (*e.g.*, articles focused just on imaging appearance).

The reference list of the articles evaluated in full text was screened for any other relevant article and those articles were evaluated according to the same criteria.

PATHOGENESIS

The pathogenesis of PI is still unclear and probably is a combination of different theories considering how many diseases can be associated with pneumatosis[7,23,24].

Three are the main theories about the gas origin within the intestinal wall. There is the "mechanical theory" that speculates an intraluminal origin of gas: It seems to be a combination of an increased intraluminal pressure and an increased gut permeability[25]. It is possible that mucosal disruption due to inflammation or ischemia can predispose to an increase of intestinal wall permeability with the formation of small cysts in which the gas is trapped[26,27].

Table 1 Underlying pathological conditions

Pathological conditions	
Trauma[21,64-67]	Blunt/penetrating abdominal trauma
	Surgical anastomosis or bypass
Mechanical[68]	Pyloric obstruction or stenosis
	Duodenal obstruction or stenosis
	Bowel obstruction (volvulus, carcinoma, malrotation, intussusception)
Autoimmune[69-71]	Lupus enteritis
	Celiac sprue
	Polymyositis
	Dermatomyositis
	Polyarteritis nodosa
	Mixed connective tissue diseases
	Graft versus host disease
	Primary immunodeficiency
Malignancies[15]	Gastrointestinal cancer
	Leukemia
	Lymphoma
	Other malignancies
Inflammation[14,72]	Inflammatory bowel disease
	Appendicitis
	Diverticulitis
	Cholelithiasis
	Sarcoidosis
Vascular conditions[73]	Ischemia or infarction
	Diabetes
Pulmonary disease[74,75]	Chronic obstructive pulmonary disease
	Cystic fibrosis
	Asthma
Drugs[13,19,76-79]	Corticosteroids
	Chemotherapy and immunotherapy
	Immunosuppression
	Lactulose
	Trichloroethylene
	Sorbitol
	Alpha-glucosidase inhibitor
	Practolol
Diagnostic/therapeutic procedures[80,81]	Endoscopy
	Enema/colon idrotherapy
	Barium studies
Connective tissue disease/neurological[82,83]	Scleroderma
	Multiple sclerosis
	Hirschsprung disease

Other conditions[17,84]	Quadriplegia
	Amyloidosis
	Hemodialysis
	Pseudo-obstruction
	Whipple disease
	Cytomegalovirus infection
	COVID-19 infection

COVID-19: Corona virus infectious disease-2019.

The second theory hypothesizes that the source of the gas is the chest through the retroperitoneum from the alveolar rupture along vascular channels[25,28]. It is demonstrated for example in patients with asthma or bronchitis, in which alveolar air runs from the mediastinum descending to the mesenteric root and vessels[29].

The last theory is the "bacterial" one. It postulates that the gas produced from gas-producing bacteria can reach the intestinal wall if associated with mucosal injury. This theory was suggested from the evidence of the high hydrogen content of the cyst, that suggests a bacterial origin[30]. It seems that bacteria cause a higher hydrogen tension than the nitrogen tension in blood, causing an exit of hydrogen in the intraluminal compartment[25].

All these theories try to explain different aspects of a complex finding, related to several diseases and several clinical conditions from asymptomatic to fatal. It is probably due to this complexity that it is a challenge for the surgeon to predict the severity of PI and the need for surgery[31-34].

CLINICAL AND LABORATORY ASSAY CORRELATION

Usually, PI was considered as a predictive sign of bowel ischemia, but with the improvement of the imaging techniques and its wider use, it was found also in asymptomatic patients[35,36]. For that reason, different studies tried to find a correlation between clinical findings, laboratory data and imaging, in order to distinguish between PI that needs surgery from PI that doesn't have any clinical significance[37,38].

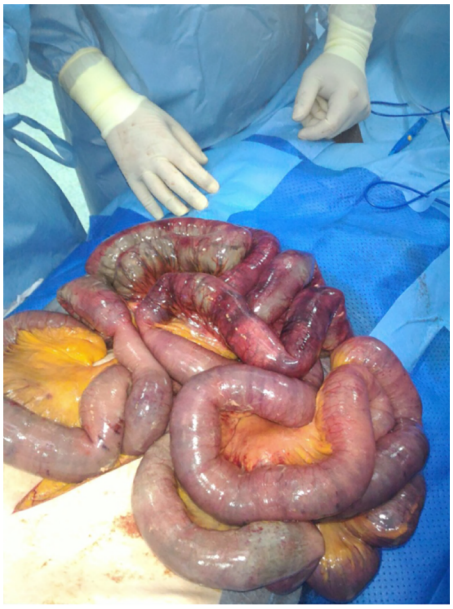
Clinical findings

Hemodynamic instability, hypotension, sepsis, abdominal rigidity or peritonism, adynamic ileus are associated with pathological PI. These signs and symptoms are directly related to transmural intestinal infarction (Figure 1); these patients need to be evaluated from a surgeon and often need a surgical exploration[39]. The surgical challenge is the patient that is hemodynamically stable, with or without abdominal pain but not peritonitis, in which it is more difficult to decide how to proceed[37].

The more common symptoms in patients with PI associated with bowel vascular impairment are abdominal pain, weight loss, constipation or diarrhea, less frequently bleeding or ileus[40]. Despite the clinical presentation, it seems that the severity of symptoms is not correlated with the severity of the amount of intramural gas at the computed tomography (CT) scan[41,42]. It is more reasonable to believe that the clinical manifestation of PI is related to the underlying diseases[25].

Laboratory data

Several studies tried to identify some laboratory values that could help among the management strategies. Morris *et al*[10] found that pH values are higher in patients treated successfully conservatively than in patients that underwent to surgery as well as lactate are lower in the non-operative group than in the operative one. Moreover, Ferrada *et al*[39] found that lactate, creatinine, blood urea nitrogen (BUN), potassium and white blood cells (WBC) are higher in patients with pathologic PI (underlying bowel ischemia/infarction) than in benign PI (self-limiting cause which not requires surgical intervention). On the contrary, hemoglobin, hematocrit and bicarbonate are lower in patients with pathologic PI. Treyaud *et al*[43] analyzed many laboratory tests, finding that only WBC correlate significatively with an underlying bowel ischemia.



DOI: 10.4240/wjgs.v15.i4.553

Figure 1 Intraoperative finding of diffuse ileal ischemia. (Personal observation).

Laboratory tests can also correlate with clinical outcome. Among these studies, Bani Hani *et al*[44] demonstrate that high lactate, low arterial CO_2, low serum albumin and BUN are correlated with a worst outcome in patients with PI and in particular BUN is the most strongly associated. Also, Horowitz *et al*[45] tried to understand which laboratory test can predict the outcome of these patients. They found out that low bicarbonate levels (< 20 mmol/L), low pH (< 7.35) and lymphopenia (< 2.000/L) correlate with poor outcome. Although almost each laboratory test has been investigated in different studies, for some studies peritonitis and clinical exam remain the strongest predictors of outcome[39,44].

RADIOLOGICAL DIAGNOSIS

PI can be considered as a manifestation of a pathologic condition. It is not possible to discriminate the presence of PI on the basis of physical examination nor by the presence of a particular symptom. Diagnosis is typically radiological, and it is based on finding linear or circular collections of gas in the bowel wall. CT scan is the gold standard for establishing the presence of PI along with, in some cases, the associated pathological conditions[46-48]. According to some studies, radiographic location seems also to have a clinical relevance since small bowel PI has a higher incidence of transmural ischemia than PI at colonic locations[39].

Moreover, according to some studies, also the radiological pattern of bubbles seems to be related to different underlying diseases. It is possible to recognize three different patterns: Cystoid or bubble-like pattern (Figure 2), in which gas looks like several cysts along the bowel wall and it is characteristic of the idiopathic PI; a linear pattern (Figure 3), in which gas has a curvilinear shape along the bowel and usually it is more associated with transmural infarction than the previous one; the circumferential pattern (Figure 4), in which gas appears circular along the bowel wall[49,50].

Conversely, Bani Hani *et al*[44] found that all the radiological distinctions between cystic or bubbly *vs* linear or curvilinear types of PI and the presence or absence of mesenteric stranding and thickening of bowel wall are not predictive of bowel ischemia. A recent machine learning model suggests that combined radiographic and clinical features can identify pathologic PI and aid in patient selection for surgery[37].

MANAGEMENT

PI is not pathognomonic of bowel ischemia but should be a sign suspicious for alteration of the bowel vascularization. In this perspective, the treatment of PI should be guided by the underlying disease and the clinical conditions and not by the CT findings[51].

For what concerns the PI management, there should be a huge difference between symptomatic and asymptomatic patients. It is already known that PI is detectable in complete asymptomatic patients and CT scan alone cannot predict which patient will experience true intestinal ischemia[10]. Indeed, it is

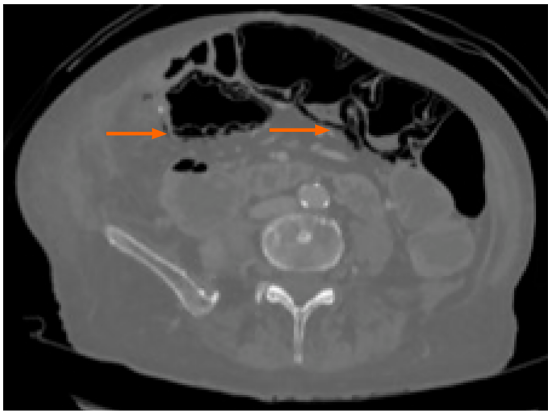


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Figure 2 Computed tomography-scan with evidence of cystoid or bubble-like pattern pneumatosis intestinalis, identified by the orange arrow. (Personal observation).

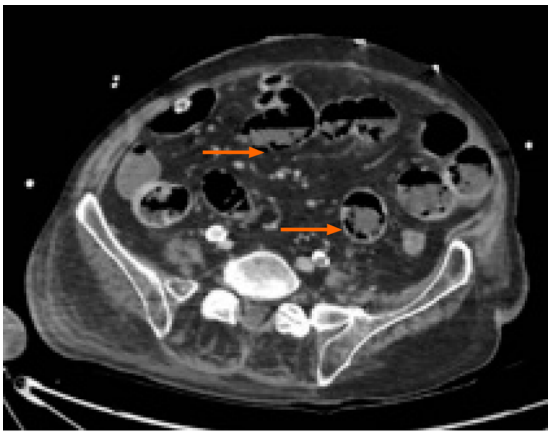

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Figure 3 Computed tomography-scan documenting a linear pattern at the level of the colonic wall, identified by the orange arrow. (Personal observation).

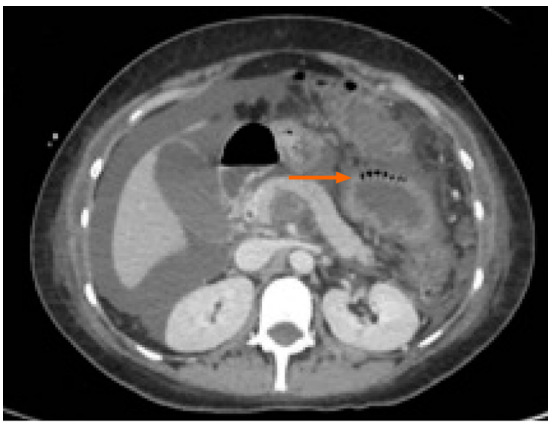

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Figure 4 Computed tomography-scan documenting circumferential pattern pneumatosis intestinalis, identified by the orange arrow. (Personal observation).

rare, but still possible, to find signs of PI in the CT scans of patients with mixed connective tissue diseases or bone marrow transplant, without any kind of clinical significance and in which conservative treatment with intestinal rest and antibiotics was successful[52,53]. Shinagare *et al*[54] reported a correlation between molecular targeted therapy (Bevacizumab, Sunitinib, Erlotinib, Cetuximab,

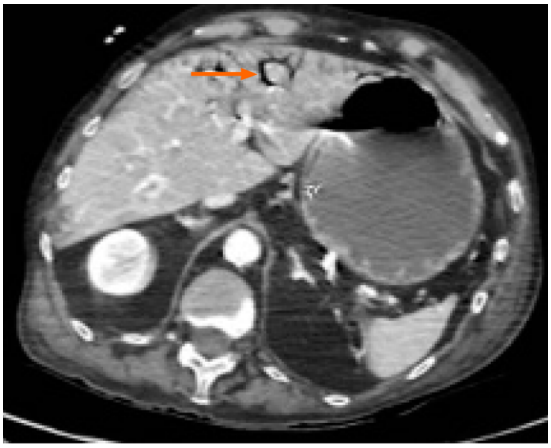

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Figure 5 Computed tomography-scan documenting localized portal venous gas, identified by the orange arrow. (Personal observation).

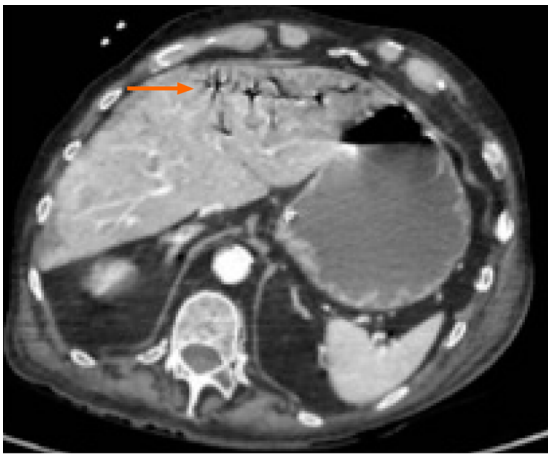

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Figure 6 Computed tomography-scan documenting diffuse portal venous gas, identified by the orange arrow. (Personal observation).

Sorafenib, Ipilimumab) and CT scan findings of PI with no clinical significance. Other clinical conditions associated with "benign" PI are bowel infections or inflammations, neoplastic bowel wall damage, ulceration, overdistension and previous gastrointestinal surgery[24,55-57].

Something that can help the surgeon in the decision-making process is the presence/absence of pneumatosis portalis. Pneumatosis portalis can be localized (Figure 5) or spread to multiple portal vessels (Figure 6). According to Knechtle *et al*[3], the presence of portomesenteric pneumatosis (PMP) is associated with a 37% of mortality. Usually, it is an ominous prognostic sign, due to a large amount of gas that migrate from the bowel wall to the veins, and it correlates with an advanced stage of PI and ischemia[50]. Although over the years the significance of PMP was questioned several times, there are many studies that underling the relation between PMP and outcome[58-60]. Wiesner *at al*[55] noticed that PMP was pathognomonic of transmural infarction in the 81% of patients and if PI and PMP were detected simultaneously in the same CT-scan, patient has the 91% of possibilities to have transmural bowel ischemia. Moreover, also Lassandro group[50] found a correlation between the PMP and the transmural ischemia, observing that the 91.5% of patients with PMP at the CT scan had also a proven bowel ischemia/infarction during surgery (Figure 7).

Summarizing, the management of peritonitic patients, with high lactate or low pH, and with PMP at the CT scan can be clear but it is still very hard to determine how to manage an asymptomatic patient with suspicious linear gas balls in the bowel wall. The results of the main clinical studies are shown in Table 2.

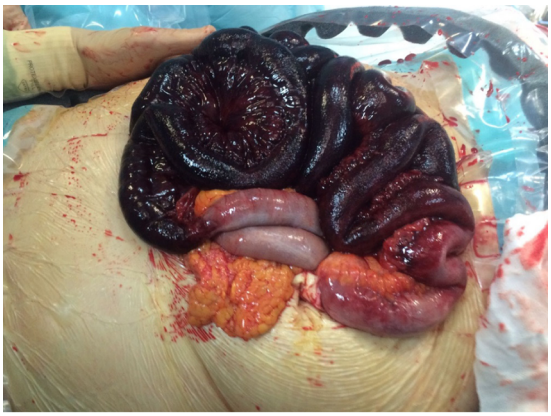
NEW PERSPECTIVES

Considering the high complexity of this topic, we tried to formulate an algorithm in order to guide the

Table 2 Clinical studies in patients with pneumatosis intestinalis

Author	Type of study	Patients, *n*	Results
Ferrada *et al* [39]	Prospective Multicenter	One hundred twenty-seven patients with PI at CT scan	Mortality in the pathologic PI group *vs* benign PI group: 34% *vs* 13.9%. Patients with pathologic PI had hemodynamic instability, sepsis, peritonitis. The radiographic location is significant: Small bowel has a higher incidence of transmural ischemia than colon. Hepatic portal venous gas is suggestive for pathologic PI
Treyaud *et al*[43]	Retrospective Monocenter	One hundred eighty-seven patients with pi at CT scan	Location of PI nor the length of intestinal involvement correlate significantly with ischemia. The radiologic features that correlate with ischemia are PMP (P =0.009) and the decreased mural contrast-enhancement (P < 0.001). Among the laboratory tests, only WBC (> 12.000/mmc) correlates with bowel ischemia (P =0.03)
Morris *et al* [10]	Retrospective Monocenter	One hundred four patients with PI at CT scan	Mortality rate: 22%; 52% of patients were treated conservatively, with a mortality rate of 6%. Mortality rate of patients with PMP was 43%. No difference found in laboratory values between groups
Lassandro *et al*[49]	Retrospective Monocenter	One hundred two patients with PI at CT scan	Fifty-two percent of patients had surgical confirmation of bowel ischemia. 42.2% of patients had a bubblelike whereas in 59% it was linear. 75.5% of patients with linear pattern had bowel infarction. Mortality rate is 30.4%; it raises to 50% when PI is associated to PMP
Pickhardt *et al*[85]	Retrospective Monocenter	Five thousand three hundred sixty-eight Colonography scans, 0.11% with colonic PI	PI with curvilinear configuration. No clear if it was a pre-existing condition. No significant complications
Kernagis *et al*[48]	Retrospective Monocenter	Fifteen patients with PI at CT scan	Nine patients (60%) of symptomatic patients had transmural bowel infarction (4 small bowel, 5 colon)
Wiesner *et al*[55]	Retrospective Monocenter	Twenty-three patients with PI or PMP at CT scan and bowel ischemia	Twenty-two percent of patients showed partial mural bowel infarction, 78% of patients showed transmural bowel infarction. 70% of bubblelike PI was associated with bowel ischemia instead of the 88% of linear pattern. 81% of patients with PMP showed transmural infarction. Overall mortality 53%
Shinagare *et al*[54]	Retrospective Monocenter	Forty-eight patients with cancer and PI at CT scan	Thirty-nine patients were receiving molecular targeted therapy. Bevacizumab and Sunitinib were the most common drugs associated with PI. Median duration of molecular targeted therapy before PI or perforation was 3 mo. Asymptomatic patients 70.8%. Conservative PI treatment 100%
Huzar *et al* [9]	Retrospective Monocenter	One thousand one hundred twenty-nine patients admitted to Burn ICU	PI at CT scan 1.3%. Mortality rate of patients with PI was 73%. Explorative laparotomy in 2-3 h from the CT scan in 94% of the patients. PI involved both small bowel and colon 60%. Nonsurvivors had greater base deficit (P = 0.03), open abdomen after surgery (P = 0.004)
Horowitz *et al*[45]	Retrospective Monocenter	Twenty-eight gynecological cancer patients and PI at CT scan	Patients symptomatic for abdominal pain 80%. Patients that did poorer were patients with preoperative acidosis, lower level of bicarbonate and lymphopenia

PI: Pneumatosis intestinalis; CT: Computed tomography; PMP: Portomesenteric pneumatosis; WBC: White blood cells; ICU: Intensive care unit.



DOI: 10.4240/wjgs.v15.i4.553

Figure 7 Intraoperative finding of transmural infarction with intestinal necrosis. (Personal observation).

surgeon in his decisional process (Figure 8). Analyzing data available in literature and data based on our experience, we selected some risk factors correlated with the presence of bowel ischemia at surgical exploration. We were able to identify some anamnestic, laboratory and radiological risk factors synthesized in Table 3.

Table 3 Risk factors in patients with pneumatosis intestinalis

Risk Factors	
Anamnestic	Vascular disease
	Atrial fibrillation
Major laboratory risk factors (blood sample)	Lac > 4 mmol/L
	LDH > 400 UI/L
	pH < 7.31
	BUN > 50 mg/dL
Minor laboratory risk factor (blood sample)	WBC > 15.000/L
	Creatinine > 2 mg/dL
	HCO^{3-} < 18 mmol/L
	Potassium 5.5 mmol/L
Radiological	Portomesenteric pneumatosis
	Pneumoperitoneum
	Free peritoneal fluid

LDH: Lactate Dehydrogenase; BUN: Blood urea nitrogen; WBC: White blood cells.

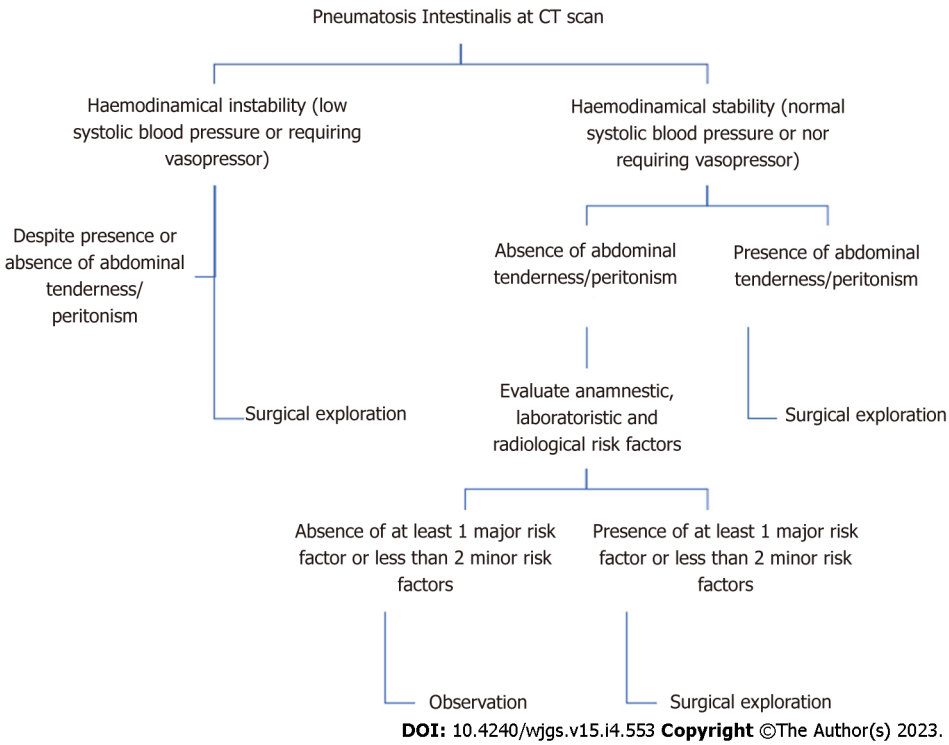


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Figure 8 Algorithm to guide clinical decisions in patients with pneumatosis intestinalis. CT: Computed tomography.

Laboratory parameters were then divided in major and minor risk factors. We wrote down a study protocol formulating an algorithm in order to help the surgeon decide if to undertake an operative or non-operative treatment. Patients are being enrolled treating them according to our algorithm (Figure 8).

In case of PI at the CT scan, distinction between hemodynamically stable or unstable patients is crucial. In case of instability surgical exploration is mandatory. In case of stability, clinical presentation plays a central role, considering as symptomatic the presence of abdominal tenderness or peritonism. If the patient is symptomatic, operative treatment is advocated. Otherwise, we rely on some anamnestic, laboratory and radiological parameters considered as risk factors (Table 3). We decided to surgically

treat asymptomatic patients if the following scenario is present. At least one anamnestic and radiological risk factor plus at least one major risk factor or two minor risk factors.

CONCLUSION

Taking into account all the possible causes and outcomes, PI represents a radiological finding which has to be correctly figured out in order to pursue the right management. It is crucial to identify the underlying condition in order to discriminate between patients who are at risk of transmural infarction from those with whom this condition could be managed without surgery[36,61]. Integration between clinical presentation, laboratory tests and abnormal abdominal physical examination can give hints about the pathway to follow. The aim is to promptly treat PI on vascular basis to avoid necrosis progression and to abstain from unnecessary and potentially harmful laparotomy/laparoscopy[32,62,63]. With this narrative review we tried to give a comprehensive analysis of the knowledge of this topic proposing an algorithm to guide clinical decisions. This manuscript has some limitations. Only one of the studies included was prospective (all the other were retrospective). The algorithm proposed, even if based on guidelines concerning various conditions in the setting of emergency care, should be validated by a prospective study.

FOOTNOTES

Author contributions: Tropeano G and Di Grezia M equally contributed to the drafting of the manuscript and must both be considered first author; Tropeano G, Di Grezia M, Puccioni C, Bianchi V and Brisinda G designed the research; Bianchi V, Pepe G, Fico V and Altieri G performed the research and selected the articles; Tropeano G, Di Grezia M and Puccioni C analyzed the data; Tropeano G, Di Grezia M, Puccioni C and Brisinda G reviewed the selected manuscripts and wrote the paper; All the authors read and approved the final manuscript.

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

Country/Territory of origin: Italy

ORCID number: Giuseppe Tropeano 0000-0001-9006-5040; Marta Di Grezia 0000-0002-0191-7545; Caterina Puccioni 0000-0001-6092-7957; Valentina Bianchi 0000-0002-8817-3760; Gilda Pepe 0000-0001-9852-6243; Valeria Fico 0000-0003-1619-4164; Gaia Altieri 0000-0002-0324-2430; Giuseppe Brisinda 0000-0001-8820-9471.

S-Editor: Li L
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World Journal of Gastrointestinal Surgery

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World J Gastrointest Surg 2023 April 27; 15(4): 566-577

DOI: 10.4240/wjgs.v15.i4.566

ISSN 1948-9366 (online)

MINIREVIEWS

Surgical aspects of small intestinal neuroendocrine tumors

Amram Kupietzky, Roi Dover, Haggi Mazeh

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

P-Reviewer: Chisthi MM, India; Losurdo G, Italy

Received: December 9, 2022
Peer-review started: December 9, 2022
First decision: February 8, 2023
Revised: February 25, 2023
Accepted: March 27, 2023
Article in press: March 27, 2023
Published online: April 27, 2023

Amram Kupietzky, Roi Dover, Haggi Mazeh, Department of Surgery, Hadassah Medical Organization and Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem 91240, Israel

Corresponding author: Haggi Mazeh, FACS, MD, Associate Professor, Department of Surgery, Hadassah Medical Organization and Faculty of Medicine, Hebrew University of Jerusalem, 24035 POD, Jerusalem 91240, Israel. hmazeh@hadassah.org.il

Abstract

Small intestinal neuroendocrine tumors (NETs) are a heterogeneous group of epithelial tumors with a predominant neuroendocrine differentiation. Although NETs are usually considered rare neoplasms, small intestinal NETs are the most common primary malignancy of the small bowel, with an increasing prevalence worldwide during the course of the past few decades. The indolent nature of these tumors often leads to a delayed diagnosis, resulting in over one-third of patients presenting with synchronous metastases. Primary tumor resection remains the only curative option for this type of tumor. In this review article, the various surgical aspects for the excision of small intestinal NETs are discussed.

Key Words: Small bowel; Small intestine; Neuroendocrine tumors; Surgery; Metastases

Core Tip: Small intestinal neuroendocrine tumors (SINETs) are the most common primary malignancy of the small bowel. While many patients present with mesenteric and liver metastases the primary tumor resection poses a surgical challenge. In this review article, the various surgical aspects for the excision of small intestinal NETs are discussed.

Citation: Kupietzky A, Dover R, Mazeh H. Surgical aspects of small intestinal neuroendocrine tumors. *World J Gastrointest Surg* 2023; 15(4): 566-577
URL: https://www.wjgnet.com/1948-9366/full/v15/i4/566.htm
DOI: https://dx.doi.org/10.4240/wjgs.v15.i4.566

INTRODUCTION

Small intestinal neuroendocrine tumors (SINETs) are neoplasms that arise from enterochromaffin cells, the endocrine cells of the small bowel[1]. These cells can be found from the ligament of Treitz to the ileocecal valve, though most are present in the distal 60 cm of the terminal ilium[2]. These tumors account for over 37% of small intestinal tumors, making them the most common small intestinal cancer [3]. SINETs are associated with an annual incidence of 0.67-1.20 per 100000 population in the United States, and their diagnosis has increased worldwide over the past half-century, most likely due to increased health care utilization and advances in imaging and diagnostic methods[4-7]. SINETs can manifest at any age, however, the incidence increases with age, with a mean age at diagnosis of between 60-65 years[3,8,9]. Although NETs are more prevalent in females than in males, in most SINETs series no gender predilection is demonstrated, with some series demonstrating a slight male preponderance[3, 8-11]. SINETs have a variable malignant potential and were traditionally subdivided into three grades based on histopathological differentiation, Ki-67 proliferative index, mitotic rate, and invasiveness behavior[12]. Recently, the World Health Organization (WHO), in its 5th edition of classification of tumors of the digestive system, published a renewed system, divided to two new categories: NETs that are welldifferentiated and a second category for neuroendocrine carcinomas that are poorly differentiated, this differentiation is based on molecular differences (Table 1)[13,14]. SINETs are staged according to the American Joint Committee on Cancer staging system (Table 2).

As with other neuroendocrine tumors, SINETs can potentially produce and secrete several hormones, the most prominent of which are serotonin, bradykinin, histamine, and tachykinin peptide[15-17]. These hormonal agents are responsible of the paraneoplastic syndrome associated with SINETs: The carcinoid syndrome[18]. This syndrome typically consists of episodic attacks of facial and torso flushing, diarrhea, breathlessness, and wheezing and is usually present in patients with liver metastases[19,20]. Advanced manifestation of carcinoid syndrome is typically associated with fibrosis, which may eventually lead to carcinoid heart disease[21,22]. The common manifestation of this desmoplastic reaction is mesenteric fibrosis, which in turn can cause bowel obstruction and bowel ischemia[23]. Though historically referred to as "carcinoid", most SINETs are nonfunctioning tumors, and patients may present with nonspecific symptoms such as abdominal pain, weight loss, partial bowel obstruction, and gastrointestinal (GI) bleeding[24,25].

SINETs are thought to have greater malignant potential than other NETs, irrespective of primary tumor size[26,27]. At the time of diagnosis, patients usually present with tumors larger than 2 cm with muscularis propria invasion[28]. The majority of patients (80%) will present with a metastatic disease to regional lymph nodes, and over 30% of patients will have hepatic metastases[7,27,29,30]. Despite the advanced stage at diagnosis, the prognosis is exceptional, with a median overall survival of 14 years in local disease, and median overall survival of over 5 years when metastatic disease is diagnosed[7].

Surgery remains the only curative modality for SINETs. Resection of the primary tumor, nodal metastases, and mesenteric masses remain the most important initial treatment, advocated even in the presence of a locally advanced or metastatic disease[31]. The objective of this article is to review the available literature on the surgical management of SINETs.

PREOPERATIVE WORKUP

SINETs secrete several biochemical tumor markers, that can be elevated in body fluids. Laboratory testing of these markers may help in establishing the diagnosis of SINETs and enable an accurate biochemical surveillance. These markers include chromogranin A and urine levels of 5-hydroxyindole acetic acid, among other secreted amines[32,33]. Chromogranin A levels may have a prognostic value, as higher levels in the serum have been linked to an increased tumor cell mass[34]. It is therefore recommended that these two biomarkers should be obtained as part of patients preoperative workup, and for follow-up after surgery[35].

Cross sectional abdominal imaging plays a pivotal role in preoperative diagnosis and the initial staging of SINETs, as imaging studies provide information regarding the location of the primary tumor, the extent of local invasion, and the presence of metastatic lesions[36]. Cross sectional imaging can also help plan the surgical resection, as it aids to identify the relation of the mesenteric tumor to the main mesenteric vessels, particularly the superior mesenteric artery (SMA) and superior mesenteric vein (SMV).

The imaging modalities used in the preoperative evaluation include anatomical imaging modalities, such as computed tomography (CT) and magnetic resonance imaging (MRI), and functional imaging modalities, such as positron emission tomography (PET) and single-PECT (SPECT) including octreotide scintigraphy and MIBG scintigraphy[36].

The optimal CT scan protocol should include 3-phases, an arterial phase, a venous phase, and a delayed phase. The primary tumor and metastases typically appear hyperdense on the arterial phase with a washout during the delay portal venous phase[37]. Although the reported sensitivity of this modality varies greatly between studies, it is generally accepted that the sensitivity in the detection of

Table 1 World Health Organization classification 2019 and grading criteria for neuroendocrine neoplasms of the gastrointestinal tract

Terminology	Differentiation	Grade	Ki-67 proliferative index (%)	Mitotic index (per 10 high-power fields)
NET, G1	Well-differentiated	Low	< 3	< 2
NET, G2	Well-differentiated	Intermediate	3-20	2-20
NET, G3	Well-differentiated	High	> 20	> 20
NEC, SCNEC	Poorly differentiated	High	> 20	> 20
NEC, LCNEC	Poorly differentiated	High	> 20	> 20
Mixed neuroendocrine-non-neuroendocrine neoplasm	Well or poorly differentiated	Variable	Variable	Variable

NEC: Neuroendocrine carcinoma; SCNEC: Small cell type neuroendocrine carcinoma; LCNEC: Large cell type neuroendocrine carcinoma.

Table 2 The American Joint Committee on Cancer 8th edition staging of small intestinal neuroendocrine tumors

Tumor	Description
TX	The primary tumor cannot be evaluated
T0	No evidence of primary tumor
T1	Tumor ≤ 1 cm and only involves the lamina propria or submucosa
T2	Tumor > 1 cm or invades muscularis propria
T3	Tumor invades through muscularis propria intoSub-serosal tissues without serosal invasion
T4	Tumor invades serosa or other organs
Lymph nodes	
NX	Lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Lymph node metastasis < 12 nodes
N2	Lymph node metastasis ≥ 12 nodes or mesenteric masses > 2 cm
Metastases	
M0	No distant metastasis
M1	Distant metastasis
M1a	Metastasis limited to the liver
M1b	Metastases in at least one extrahepatic site
M1c	Both hepatic and extrahepatic metastases
Stage	
Stage I	T1, N0, M0
Stage II	T2 or T3, N0, M0
Stage III	T4, N0, M0; any T, N1 or N2, M0
Stage IV	Any T, any N, M1

primary SINETs is lower than 50%[38]. CT enteroclysis has a higher detection rate, with sensitivity of up to 85%[39]. The detection rate can be further improved when considering mesenteric lymphadenopathy as an indicator of a SINET, even when a primary mass or bowel wall thickening are not observed[40]. MRI has the advantage of decreased radiation when compared with CT and is recommended in patients with renal failure or patients with an allergy to iodine contrast material. It has been argued that the MRI may be superior in detecting small liver metastasis when compared to CT, and that the CT may be more sensitive at detecting mesenteric disease. To date, there is a consensus that either one can be used in the preoperative evaluation[35,41,42].

The functional study traditionally utilized was the somatostatin receptor scintigraphy (SRS). In SRS a radiolabeled octreotide, a somatostatin analog (SSA), is administered to patients and allows detection of local and distant disease. Recently, this functional study has been replaced with a superior functional test, the PET-CT with 68 Ga-labeled DOTA-conjugated peptides. This test has higher detection rates of small primary tumors and their metastases, with a sensitivity of up to 95% compared with conventional techniques, such as CT, MRI, and SRS[43,44].

Due to the multifocal nature of SINETs, found in 20%-44% of patients, the gold standard localization remains intraoperative palpation of the small intestine[45-47].

Surgery in asymptomatic patients with a metastatic disease

Due to their indolent nature, metastatic SINETs are often discovered incidentally upon abdominal imaging. Symptomatic patients suffering from abdominal pain, GI bleeding, obstruction, or carcinoid syndrome have an indication for surgery. However, in metastatic asymptomatic patients, surgical resection of the primary tumor is up to debate. In general, patients with metastatic disease in whom surgical resection with curative intent can be achieved, surgery should be performed. The benefits of surgical resection of liver metastases and the primary tumor have been demonstrated in terms of overall survival, with survival rates of 60%-80% at 5 years and with low mortality (0%-6%)[48]. When compared to patients who do not undergo surgery, the survival rate with liver metastases at 5 years is as low as 30%[49]. If a curative surgical resection approach seems no longer achievable, the benefit of resecting the primary tumor is not as clear. Regarding overall survival, two large metanalyses demonstrated that primary tumor resection in the presence of unresectable liver metastasis improved overall survival, with a pooled 5-year overall survival of roughly 73.1% *vs* 36.6% when the primary tumor is not resected[50,51]. Both studies warrant that the results should be interpreted with caution due to a potential selection and publication bias. The selection bias stems from the assumptions that patients that had better prognosis or fewer comorbidities were offered surgery while those with comorbidities or advanced disease were not. In 2018, a retrospective single center study with a cohort of 363 asymptomatic patients with stage IV SINETs found no difference in overall survival in patients who underwent upfront local resection within 6 mo of diagnosis *vs* those who did not[52].

The benefit of upfront surgical resection on patient-oriented outcomes, was recently evaluated in a retrospective propensity-matched comparative cohort study of 522 patients. Bennet *et al*[53] identified that early resection of the primary tumor in metastatic SINETs, was associated with a reduction in unplanned acute care admissions and subsequent small bowel-related surgery, compared to non-operative management. The authors conclude that upfront small bowel resection should be routinely discussed with patients diagnosed with metastatic SINETs. Regardless to whether the overall survival is affected by upfront resection, due to the natural history of this disease and the relatively long survival, patients will eventually become symptomatic and resecting the primary tumor at diagnosis can avoid future symptoms.

An additional benefit of surgery may be in slowing the progression of hepatic metastases in patients with unresectable disease. In a retrospective study by Givi *et al*[54] focusing on the progression of liver disease, 60 patients who underwent primary tumor resection were compared with 24 patients who did not. The authors identified a significant difference in time to progression of liver disease between patients who had their primary tumor resected compared to those who did not (56 mo *vs* 25 mo, $P < 0.005$), and conclude that the primary neoplasm resection could delay progression of liver metastases.

Surgical mortality following SINET resection must be discussed with asymptomatic patients, with a reported range from 0% to 9%, and no prospective data comparing outcomes in patients operated on electively and those undergoing emergency surgery[50].

The current North American Neuroendocrine Tumor Society (NANETS) guidelines recommend upfront resection of primary SINETs in asymptomatic patients with metastatic disease, in selected patients, after factoring in patient specific issues such as performance status and degree of liver replacement[55]. The European Neuroendocrine Tumor Society (ENETS) 2016 guidelines stress that a direct causal relationship between primary tumor resection in asymptomatic patients and an improved overall outcome has not been proven to date, and therefore they recommend a case-to-case interdisciplinary discussion[35].

SYNCHRONOUS SMALL BOWEL TUMORS

On attentive palpation of the small intestine during surgery, 13%-45% of patients are found to have multifocal primary tumors[46,56-58]. These tumors can arise synchronously and independently or as a single clone with subsequent local and discontinuous metastasis *via* submucosal lymphatic dissemination[59,60]. A recent retrospective study by Choi *et al*[46] of 179 patients with surgically managed SINETs, demonstrated multifocal small bowel tumors in 81 patients (45.3%). When comparing clinicopathologic factors between patients with multifocal small bowel tumors and those without, no

difference in tumor characteristics or in their clinical course was identified. However, they did demonstrate that synchronous tumors tend to be small and often submucosal, and easily missed when the bowel is palpated using graspers laparoscopically. They conclude that an open exploration of the small bowel with a direct bimanual palpation should be performed in all SINET surgeries.

Several techniques have been described to enable carful bowel palpation during laparoscopic surgery, including the use of the soft-tissue wound retractor and the hand-assisted laparoscopic device. Wang *et al*[61] described a successful laparoscopic SINET resection using these methods in 6 patients with unknown primary. Figueiredo *et al*[62] compared laparoscopic resection and open resection in a cohort of 73 patients. Laparoscopic technique was performed in 12 patients. They identified similar rates of multiple tumors when comparing both groups. To date, the trials comparing laparoscopic resection and open surgery are small and retrospective, and sufficient evidence is missing. However, the ENETS 2016 consensus states that the potential benefits of minimally invasive surgery should be weighed against the risk of missing multiple synchronous small SINETs, and that a minimally invasive approach can be considered[35].

SURGICAL APPROACH TO THE MESENTERIC ROOT

Recent studies have shown that the majority of patients with SINETs have lymph node metastases at presentation, and that a proper lymphadenectomy can increase the overall survival significantly[63,64]. Watzka *et al*[64] defined a proper lymphadenectomy as one that includes more than 6 lymph nodes that are resected with the primary tumor. They advocate that by doing so, there was an associated improved 5-year survival rate of 82.2% compared to 40.0% in patients with a less radical lymph node dissection. Landry *et al*[29] demonstrated in a retrospective analysis of 1364 patients with SINETs, that the excision of more than 7 nodes is associated with a better cancer-specific survival even after adjusting for age and tumor size. Zaidi *et al*[65] used a cohort of 199 patients and identified that a minimum of 8 lymph nodes were required for an accurate lymph node staging and that 4 or more positive lymph nodes were associated with earlier disease recurrence[65].

Current guidelines urge for a segmental resection with a wide lymphadenectomy. This includes a regional lymph node dissection along the segmental vessels of the small bowel up to their junction with the main trunk of the SMV[55,66]. This practice may be challenging technically. As SINETs invade the serosa they cause an intense desmoplastic reaction that produces mesenteric fibrosis. This fibrosis can lead to vascular encasement, making it extremely difficult to preserve the vascular supply to the rest of the bowel.

It has been proposed, that as with breast cancer and melanoma surgeries, SINET patients can benefit from intraoperative lymphatic mapping using blue dye[60]. It has been hypothesized that due to the extensive mesenteric fibrosis, the lymphatic drainage of the small bowel can be obstructed and SINETs may develop alternative lymphatic drainage paths. Wang *et al*[63] preformed lymphatic mapping procedures in 112 SINET surgeries and found that this practice changed the traditional resection margins in 92% of these cases. They concluded that lymphatic mapping could help preserve intestinal length without hampering the surgical outcomes and may even improve long-term survival. To date, this practice is not standardized and further research is needed to prove its necessity[35].

Ohrvall *et al*[66] described a staging classification used to determine whether the mesenteric involvement is operable. Stage 1 consisted of involved nodes located close to the SINET. Stage 2 of nodes along the distal arterial branches of the mesenteric artery. Stage 3 included nodes extending along the SMA trunk without encasing it. Stage 4 included nodal involvement encasing the SMA or the retroperitoneum. While stages 1 to 3 are considered operable, with a carful dissection around the vessels and over the nodes up to the root of the mesentery, stage 4 are considered inoperable. Partelli *et al*[47] proposed a similar classification scheme consisting of three types, with type A including a resectable mesenteric disease, type B a borderline resectable disease, and type C consisting of a locally advanced or irresectable disease causing encasement of the SMA and SMV[47]. Due to the complex nature of these surgeries, it is recommended that the pre-operative evaluation and the surgical procedures should be performed in specialized NET centers[55].

Patients with vascular encasement can suffer from severe symptoms due to the impeded arterial supply to the small intestine or from inadequate venous drainage of the small bowel. Hellman *et al*[67] described a non-surgical treatment technique by an insertion of a self-expandable stent through the stenotic SMV, in a small cohort of seven patients. They demonstrated that by doing so, an 80% resolution of symptoms in four patients was achieved. Other palliative techniques described include surgical intestinal bypass in patients with bowel obstruction secondary to unresectable disease[35]. Non-operative management in these patients include symptomatic treatment with somatostatin analogues, nutritional support, and palliative care, although a detailed discussion of these treatments is beyond the scope of this review[68].

SURGICAL THERAPY OF LIVER METASTASES

Liver metastases are relatively common among SINET patients, with an incidence of 30%-50% at initial presentation[26,69]. These metastases can cause an excessive hypersecretion of hormones resulting in a carcinoid syndrome and can lead to liver failure due to hepatic replacement by tumor. Therefore, the goals of treatment of hepatic disease include biochemical and tumor control[42]. Surgery is generally proposed when curative intent is possible, though debulking with a threshold of 90% of hepatic metastatic disease has been shown to improve quality of life and overall survival[70]. Several studies have found that an R2 resection, is comparable to an R0 resection in terms of overall survival and disease specific survival[71-73]. Thus, surgical cytoreduction should be attempted in patients with an adequate performance status and a sufficient postoperative future liver remnant. Although a detailed discussion of these treatments is beyond the scope of this review, this generally includes major hepatic resections along with parenchymal-sparing procedures such as nonanatomic parenchymal resections, enucleations, and intraoperative ablation. In selected patients, with diffuse unresectable liver metastatic disease liver transplantation may be possible therapy option[48].

PROPHYLACTIC CHOLECYSTECTOMY IN SINET PATIENTS

Somatostatin analogue treatment is the mainstay antisecretory therapy in functioning SINET and has become the first line therapy for the control of carcinoid symptoms[74,75]. Recent research demonstrates that beyond the symptomatic control, SSAs have an antiproliferative effect and inhibit tumor growth[76, 77]. These have established SSA as the first-line treatment of functional and nonfunctional metastatic SINETs[78].

Long-term therapy with SSAs has its toll. The most serious adverse complication described with long-term SSA is biliary stone formation[79]. Previous small retrospective studies found that the prevalence of gallstones in patients on SSAs is as high as 52%[80,81]. A recent retrospective study by Brighi *et al*[82] demonstrated, in a cohort of 164 patients with a diagnosis of neuroendocrine neoplasms without a history of biliary stone, that 60 (36.6%) developed gallbladder stones after a mean of 36.7 mo from when SSA therapy was started, yet only 17 patients suffered from a symptomatic biliary disease. In a multicenter retrospective from 7 Italian centers, including a cohort of 478 patients started on SSA with a diagnosis of NET, 129 (27%) developed biliary stone disease, and 36 patients (7.5% of the cohort) developed biliary complications[83]. In this cohort the use of prophylactic ursodeoxycholic acid did not have a protective effect, however previous surgery for primary SINET was a significant risk factor for developing gallstones. Based on these data, the authors recommend a prophylactic cholecystectomy in all patients undergoing surgery for primary GI-NETs.

Regarding the surgical risk, preforming a concurrent prophylactic cholecystectomy at time of surgery for SINETs, did not increase postoperative morbidity in cholecystectomy *vs* no cholecystectomy groups (11.8% *vs* 11.1%, respectively; $P = 0.79$) or mortality (1.4% *vs* 0.6%, respectively; $P = 0.29$), in a large cohort of 1300 patients[84].

In the 2016 ENET guidelines for NET of the of the jejunum and ileum, the authors conclude that a cholecystectomy may be performed as a prophylactic measure against the development of gallstones in patients that will require SSA therapy, however, they stress that the benefit of this has never been prospectively proven[35]. In the ENET latest (2022) guidelines for carcinoid syndrome, this practice is further questioned, as the authors warn that a prophylactic cholecystectomy may worsen diarrhea in patients with previous small bowel resection[85].

The NANETS Consensus Guidelines for the surgical management of SINETs, recommend preforming a prophylactic cholecystectomy only in patients who are likely to receive SSA therapy, and only at the time of the initial small bowel operation[55]. Patients who aren't planned for an abdominal operation and are receiving SSA should only undergo a cholecystectomy if biliary symptoms develop.

We believe that as long as prospective, multi-center, and randomized trials are lacking, patients should be informed about the option of preforming a simultaneous cholecystectomy, including the risks and benefits of this practice, and a joint consent should be reached.

PERIOPERATIVE OCTREOTIDE TREATMENT

Manipulation of SINETs during surgery, or even the administration of anesthetic agents, can lead to a sudden spike of circulating levels of serotonin and other vasoactive substances. This can cause sudden hemodynamic instability, known as a carcinoid crisis, a potentially life-threatening event[86]. Early reports have suggested that the administration of octreotide, an SSA, can rapidly reverse the symptoms and potentially resolve this crisis[87,88]. Furthermore, it has been generally accepted that the prophylactic administration of octreotide perioperatively can prevent a carcinoid crisis. In 2011, Kinney *et al*[89] described a cohort of 119 patients with metastatic NET undergoing abdominal surgery, of those patients, 45 received intraoperative octreotide and not one of them experienced intraoperative complic-

ations while of the 73 patients who did not receive octreotide eight (11.0%) suffered from intraoperative complications. They concluded that the use of octreotide intraoperatively was associated with a decreased frequency of intraoperative complications, however, due to the retrospective nature of this study, they cannot infer any causal relationship.

Based on the report by Kinney *et al*[89] a retrospective study was conducted by Massimino *et al*[90] that analyzed 97 patients with GI NETS who have undergone intraabdominal operations performed by a single surgeon, 90% were treated with prophylactic octreotide, and 56% received at least one additional intraoperative dose. Intraoperative complication occurred in 24% of the patients, without correlation to octreotide administration. The authors conclude that preoperative and intraoperative boluses of octreotide are insufficient for preventing intraoperative complications in patients with carcinoid yet suggest that a continuous infusion of octreotide may be more effective. A follow-up prospective study was published by Condron *et al*[91] in 2016. They enrolled 127 patients with carcinoid tumor, who have undergone 150 surgeries under a continuous octreotide infusion of 500 μg/h. They found that 30% experienced intraoperative complications associated with a carcinoid crisis, and concluded that octreotide infusions do not prevent intraoperative crises.

Woltering *et al*[92] published a retrospective study in 2016 on 150 consecutive patients with stage IV SINETs who underwent a total of 179 cytoreductive surgeries, and received a continuous 500 μg/h infusion of octreotide preoperatively, intraoperatively, and postoperatively. They considered episodes of hypotension lasting longer than 10 min as carcinoid crisis. The incidence of intraoperative carcinoid crisis was significantly lower than that of previous studies, 3.4% (6/179).

Finally, Kwon *et al*[93] published a retrospective study in 2019 on 75 patients with metastatic NETs who underwent liver resection, ablation, or embolotherapy. Twenty-nine patients received preoperative octreotide and 48 patients received an intraoperative infusion. As many as 32% of the patients experienced a carcinoid crisis or hemodynamic instability throughout the procedures. None of the prophylactic octreotide regimens were associated with a lower incidence of carcinoid crisis or hemodynamic instability. Despite their results, the authors suggest continuing the use of perioperative octreotide, given its overall safety profile, until larger prospective studies convincingly demonstrate a lack of efficacy.

Despite the lack of sufficient supporting evidence, most guidelines recommend perioperative prophylactic octreotide treatment with a continuous intravenous infusion starting from 12 h before surgery and continuing for at least 48 h postoperatively[94].

CONCLUSION

SINETs are uncommon neoplasms, with an increasing incidence worldwide. As surgery remains the only curative treatment modality, surgeons will be facing increasing numbers of these patients, yet there are still several unanswered questions regarding their optimal surgical management. A significant part of the surgical common practice discussed in this review is based on expert opinions and small retrospective trials, and further prospective, multi-center, and randomized trials are required to shed lighter on important aspects of the surgical management of SINET patients. Nevertheless, it can be concluded, that patients with SINETs should be treated at high-volume experienced endocrine surgery centers where a multidisciplinary team is a routine part of patients' evaluation and participates in decision making.

FOOTNOTES

Author contributions: Kupietzky A, Dover R, and Mazeh H had substantial contributions to conception, writing and critically reviewing the research and manuscript; all authors have read and approve the final manuscript.

Conflict-of-interest statement: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. There was no external funding for this manuscript.

Country/Territory of origin: Israel

ORCID number: Haggi Mazeh 0000-0002-8425-1776.

S-Editor: Chen YL
L-Editor: A
P-Editor: Zhao S

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World Journal of Gastrointestinal Surgery

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World J Gastrointest Surg 2023 April 27; 15(4): 578-591

DOI: 10.4240/wjgs.v15.i4.578

ISSN 1948-9366 (online)

MINIREVIEWS

Tumor budding in gastric cancer

Shuo-Meng Xiao, Jian Li

Specialty type: Oncology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Chen X, China; Lotz G, Hungary; Mokni M, Tunisia

Received: December 21, 2022
Peer-review started: December 21, 2022
First decision: February 1, 2023
Revised: February 4, 2023
Accepted: March 21, 2023
Article in press: March 21, 2023
Published online: April 27, 2023

Shuo-Meng Xiao, Department of Gastric Surgery, Sichuan Cancer Hospital, Chengdu 610041, Sichuan Province, China

Jian Li, Department of General Surgery, The Third Hospital of Mianyang, Sichuan Mental Health Center, Mianyang 621000, Sichuan Province, China

Corresponding author: Jian Li, MM, Surgeon, Department of General Surgery, The Third Hospital of Mianyang, Sichuan Mental Health Center, No. 190 East Section of Jiannan Road, Youxian District, Mianyang 621000, Sichuan Province, China. 654747973@qq.com

Abstract

The tumor, nodes, metastasis (TNM) staging system has long been the gold standard for the classification and prognosis of solid tumors. However, the TNM staging system is not without limitations. Prognostic heterogeneity exists within patients at the same stage. Therefore, the pursuit of other biomarkers with the potential to classify patients with cancer has never stopped. One of them, tumor budding (TB), has gained much success in colorectal cancer. In recent years, TB in gastric cancer has attracted much attention from researchers, beginning to reveal the molecular and biological aspects of this phenomenon in gastric cancer, and has emerged as a promising prognostic biomarker in gastric cancer, predicting disease progression and unfavorable survival. Therefore, it is time and essential to provide a holistic overview of TB in gastric cancer, which has not been achieved and is the aim of this review.

Key Words: Tumor budding; Gastric cancer; Poorly differentiated cluster; Prognosis; Lymph node metastasis

Core Tip: Tumor budding has gained much success in colorectal cancer and has begun to attract much attention from researchers proficient in gastric cancer. Tumor budding showed promising prognostic potential in gastric cancer with the ability to predict disease progression and unfavorable survival. Therefore, it is time and essential to provide a holistic overview of tumor budding in gastric cancer, which has not been achieved and is the aim of this review, in which we summarize the current data on tumor budding in gastric cancer and discuss its clinical application prospects and challenges.

Citation: Xiao SM, Li J. Tumor budding in gastric cancer. *World J Gastrointest Surg* 2023; 15(4): 578-591
URL: https://www.wjgnet.com/1948-9366/full/v15/i4/578.htm
DOI: https://dx.doi.org/10.4240/wjgs.v15.i4.578

INTRODUCTION

Gastric cancer (GC) is one of the most common malignancies worldwide and is most commonly diagnosed in Eastern Asia, Central and Eastern Europe and South America[1]. Along with the eradication of *Helicobacter pylori*, the most associated risk factor for intestinal-type GC, the incidence of GC has dramatically decreased in countries and areas with high prevalence over the past 50 years[2]. However, despite tremendous triumphs, GC remains the fifth most common cancer and ranks fourth in the list of cancer-related deaths. According to GLOBCAN 2020, there have been more than 1 million new cases of GC, which caused 768793 deaths worldwide in 2020[1]. In recent years, the management of GC has advanced greatly, and multimodal treatment, including radical gastrectomy, perioperative chemotherapy, targeted therapy and immunotherapy, has been successfully applied to GC patients; however, the long-term survival is still dismal[3]. This is mainly attributed to delayed diagnosis, advanced disease, poor response to therapy and, an often overlooked reason, the lack of standardized and reproducible biomarkers for personalized health care.

In the clinical management of GC, several clinicopathological characteristics have long been used to classify patients with GC based on their prognostic and/or predictive significance[4]. The gold standard for classification of GC remains to be the tumor, nodes, metastasis (TNM) staging system, complemented by World Health Organization histologic categorization, cancer grade, Lauren subtypes, tumor size, neural and lymphovascular invasion. Some emerging new but less clinically translated prognostic biomarkers have also been explored, including the positive lymph node ratio (LNR), circulating tumor cells (CTCs) and neutrophil-lymphocyte ratio (NLR)[5-7]. However, the survival outcomes of GC patients remain heterogeneous, and some early-stage patients will experience recurrence or metastasis. Therefore, searching for new precise and reproducible biomarkers for personalized health care in GC has never been stopped. One of the promising factors is tumor budding (TB), also referred to as sprouting, which was first described by Imai more than 60 years ago to characterize isolated single or no more than four cancer cells at the invasive front[8]. Although first described in GC, TB is now most successfully applied in colorectal cancer and has become part of routine histopathological diagnostics to direct many clinical decisions[9]. The associations of TB with disease progression and survival have also been investigated in GC by various research groups in recent years. However, due to the lack of methodological standardization, findings reported across studies varied substantially, leaving the exact role of TB in GC unclear. Therefore, in this review, we aimed to summarize the evidence from the literature regarding TB assessment in GC to provide an overview of the clinical and prognostic role of TB in GC. We also discuss the methodological shortcomings, inconsistent scoring systems and future directions.

FINDINGS REGARDING TB IN GC

In GC, isolated single or small clusters of cancer cells have long been identified at the expansive border of the main tumor mass, but their significance has not been recognized[10]. Therefore, twenty years following the first attempt to explore the prognostic value of tumor cell dissociation (TCD), used synonymously to describe TB in GC patients, no studies on the same topic have been published[10]. Such a strange ignorance may be due to a lower prevalence of GC in Western countries compared to colorectal cancer, in which the assessing and reporting standardizations have been established[11]. In addition, the complex histological composition of GC, for example, almost all diffuse-type GC belongs to high-grade TB, may lead to conceptual difficulty. In addition, the lack of a consistent assessment and reporting criteria also limits the application of this biomarker in GC. However, during the International Tumor Budding Consensus Conference (ITBCC), a consensus was achieved for colorectal cancer on the definition of TB (single cancer cells or cell clusters of up to 4 cancer cells), assessment method (buds scored in the hotspot on a hematoxylin and eosin-stained slide using a 20× objective lens, followed by normalization to a field area of 0.785 mm^2) and clinically relevant cutoff values (5 and 10 buds are used to categorize TB as low grade (Bd1), intermediate grade (Bd2) and high grade (Bd3), respectively)[11]. Therefore, the publication of ITBCC guidelines promotes research on TB in GC, and the corresponding publications have increased rapidly in recent years.

Despite the methodical variety, increased TB density has consistently been found to correlate with adverse features in GC, including tumor size, poor differentiation, Lauren class, advanced T stage, lymph node metastasis, distant metastasis, TNM stage, lymphovascular invasion (LVI), perineural invasion (PNI), and nonradical resection (Table 1). One meta-analysis pooled data from 7 of these

Table 1 Previous studies on tumor budding in gastric cancer

Ref.	Country	Period	Cases	Lauren	Specimen	Staging	Assessment (%)	TB higher in	Outcomes (Multivariate analysis)
Gulluoglu *et al*[33], 2015	Turkey	1993-2013	126	I+D	Surgical resected	pT1a-1b	PTB, 400 ×; Positive/HPF (31)	LNM	LNM; pT1a: OR = 38.6 (1.91-781.70); pT1b: OR = 8.87 (2.79-22.16)
Che *et al*[68], 2017	China	2007-2010	296	I+D	Surgical resected	I-IV	PTB, 400 ×; ≥ 5 buds, on average 10 HFP (49)	T stage, N stage, metastasis, TNM stage, differentiation	OS: 1.568 (1.044-2.354)
Olsen *et al* [16], 2017	United States	1999-2013	52	I	Surgical resected	NA	Total-TB, 200 ×; ≥ 1 bud, median of 10 HFP (63)	Poor differentiation, LVI, PNI, T stage, N stage	Recurrence: $P = 0.08$; LNM: $P = 0.51$
Kemi *et al* [61], 2019	Finland	1983-2016	583	I+D	Surgical resected	I-IV	PTB, ITBCC; Bd1/2 (44.9), Bd3 (55.1)	Year of surgery, age, sex, T stage, Lauren class, grade; R	OS; Total: HR = 1.40 (1.12-1.76); I: HR = 1.39 (1.03-0.87); D: HR = 1.54 (1.01-1.2.34)
Du *et al*[34], 2019	China	2010-2016	621	I+D	Surgical resected	pT1b	PTB, 200 ×; ≥ 1 bud/HPF (67)	NA	LNM; Total: OR = 3.3 (1.9-5.9); Well/moderately differentiated: OR = 3.3 (1.9-5.9)
Heckl *et al* [69], 2019	Germany	1997-2009	426	I+D	Surgical resected	I-IV	PTB, ITBCC; Bd0 (24.9), Bd1/2 (22.8), Bd3 (52.3)	NA	NS
Dao *et al*[18], 2020	Vietnam	2012-2015	109	I+D	Surgical resected	I-III	PTB, ITBCC; Bd1/2 (54.1), Bd3 (45.9)	Histopathological type, Differentiated grade, Lauren class, LVI, PNI, N stage	OS, HR = 20.899, $P < 0.001$; DFS, HR = 12.7, $P < 0.001$
Ulase *et al* [13], 2020	Germany	1997-2009	456	I+D	Surgical resected	I-IV	PTB, ITBCC; Bd0 (25.2), Bd1/2 (22.8), Bd3 (52.0)	Sex, Lauren class, differentiated grade, T stage, N stage, metastasis, TNM stage, LNR, LVI, PNI, R, HER-2, MSI, MET	OS, Total, I, D: NS. TSS, Total, I: NS; D: NA
Zhang *et al* [25], 2020	China	2001-2003	147	I+D	Surgical resected	I-III	PTB, 200 ×; ≥ 6 buds, median of 5 HFP (46.3)	Tumor size, N stage, TNM stage, Lauren class, TILs	10-yr OS, HR = 7.16 (3.35-15.29)
Qi *et al*[57], 2020	China	2000-2008	153	I	Surgical resected	I-III	PTB and ITB, 400 ×; PTB: ≥ 8 buds, median of 5 HFP (48.4); ≥ 13 buds, median of 5 HFP (43.8)	PTB: Age, sex, location, N stage; ITB: Tumor size, N stage, TNM stage, grade	OS, PTB: HR = 1.92 (2.24-10.63); ITB: HR = 2.79 (2.24-10.63)
Cao *et al*[17], 2021	China	2009-2015	137	I+D	ESD and Surgical resected	pT1	PTB, NA; Positive (58.4)	Age, HP infection, N stage, recurrence, death	Recurrence, HR = 4.95, $P = 0.01$; Death, HR = 2.33, $P = 0.043$
Sun *et al*[21], 2021	China	2004-2007	122	I+D	Surgical resected	I-IV	PTB, 200 ×; > 5 buds, median of 10 HFP (57)	Lauren class, differentiation, LNM, metastasis, TNM stage	NA
Yim *et al*[32], 2021	Korea	2010-2021	289	I+D	Surgical resected	pT1	TB-YN: Present (57.1); TB-ITBCC: Bd2/3 (40.1); total-TB, ≥ 5 buds (419); SRCC excluded: mTB-YN: Present (48.8); mTB-ITBCC: Bd2/3 (29.1); total-mTB, ≥ 5 buds (29.8)	LNM	LNM, TB-YN: HR = 24.36 (3.15-188.17); TB-ITBCC: HR = 15.91 (5.41-46.80); Total-TB: HR = 25.50 (6.97-93.25); mTB-YN: HR = 21.07 (4.75-93.37); mTB-ITBCC: HR = 35.10 (12.11-101.76); Total-mTB: HR = 52.69 (15.69-179.97)
Kucuk[70], 2021	Turkey	2015-2020	43	I+D	Surgical resected	pT2-4	PTB, ITBCC; Bd1 (30.2), Bd2 (25.6), Bd3 (44.2)	Grade; T stage; N stage, differentiation	NA
Pun *et al*[15],	Canada	2000-	76	I	Surgical	IA-IV	PTB, ITBCC; Bd1 (21), Bd2 (21), Bd3 (58)	T stage, LNM, TNM stage, LVI, PNI,	OS: HR = 3.93 (0.34-45.44)

2022		2018			resected			death, recurrence	
Jesinghaus *et al*[43], 2022	Germany	2001-2013	167	I	Surgical resected	ypI-IV	PTB, ITBCC; Bd1 (29), Bd2 (25), Bd3 (46)	T stage, N stage, metastasis, TNM stage, R	OS: Bd2: HR = 2.60 (1.14-5.95); Bd3: HR = 4.74 (2.25-10.03)
Szalai *et al* [14], 2022	Hungary	2008-2018	290	I+D	Surgical resected	IA-IV	PTB, ITBCC; Bd0 (1), Bd1 (6.6), Bd2 (13.8), Bd3 (78.6)	Lauren class, R; PNI; LVI; T stage, TNM stage, differentiation, LNM	OS, Total: HR = 1.65 (1.11-2.45); I: HR = 1.99 (1.23-3.22). DFS, Total, I: NS

D: Diffuse; DFS: Disease-free survival; ESD: Endoscopic submucosal dissection; HPF: High power field; HR: Hazard ratio; I: Intestinal; ITB: Intratumoral budding; ITBCC: International Tumor Budding Consensus Conference; LNM: Lymph node metastasis; LNR: Lymph node ratio; LVI: Lymphovascular invasion; MSI: Microsatellite instability; NA: Not available; NS: No significance; OR: Odds ratio; OS: Overall survival; PNI: Perineural invasion; PTB: Peritumoral budding; R: Resection status; SRCC: Signet ring cancer cell; TB: Tumor budding; TILs: Tumor infiltrate lymphocytes; TSS: Tumor-specific survival.

studies and showed that TB, regardless of the methods used to determine it, was associated with overall cancer stage, lymph node metastasis, LVI and tumor differentiation in GC[12]. Among these clinicopathological characteristics, Lauren class and lymph node metastasis may have practical significance. In studies that included all Lauren subtypes, more than 90% of diffuse-type GC will be classified as high-grade TB, whose effects will be discussed in the sections below. Regarding lymph node metastasis, an important determinant of survival in GC patients, nearly all studies have explored its association with TB and demonstrated that high TB activity promotes the spreading of cancer cells to regional lymph nodes (Table 1). In reports by Ulase *et al*[13] and Szalai *et al*[14], not only lymph node metastasis itself but also the lymph node ratio (LNR) was significantly increased in patients with high-grade TB. In the context of early GC, this predictive value can be applied to identify patients who need additional curative gastrectomy, which will be discussed in the sections below.

As early as 1992, Gabbert *et al*[10] performed the first attempt to explore the prognostic value of TB in GC patients, although "TCD" was used to describe detached cancer cells in their report. Patients with GC were classified into four grades using a semiquantitative approach, and it was proven that patients with a higher density of detached cancer cells have poor survival independent of other prognostic factors[10]. Since then, the prognostic value of TB in GC has been overlooked. However, in the last decade, more evidence has emerged, except for a few studies, in which the majority of studies proved a poor prognosis in GC patients with high-grade TB (Table 1). One meta-analysis on the association between TB and GC has been published, in which 7 studies were included, and the prognostic value remained significant in the pooled results[12]. Nine of these studies reported the effects of TB on overall survival (OS), and only Pun *et al*[15] and Ulase *et al*[14] found that the prognostic significance of TB was lost in multivariable analyses for total cases or intestinal-type GC. Both studies assessed TB according to ITBCC guidelines; therefore, the conflicting findings may result from other confounding factors[13,15]. Two studies also set recurrence and death as the primary outcomes, and both reported a higher recurrence or death rate in patients with high-grade TB[16,17]. In addition to OS, only three studies reported the effects of TB on disease-free survival (DFS) or tumor-specific survival (TSS), and only one study was able to demonstrate the independent prognostic value for DFS in GC, while the other two studies reported that the association between TB and DFS or TSS was statistically significant only in univariate analysis[13,14,18]. Such findings are very intriguing, as high TB activity is intimately associated with adverse features in GC that may promote recurrence and metastasis, which will theoretically lead to poor cancer-specific survival. The conflicting findings may be due to the limited studies

reporting the results of DFS and the retrospective design in all published studies. In retrospective studies, information on the exact disease recurrence status of some patients is difficult to collect. Regarding the value of TB in predicting DFS, a definite conclusion cannot be drawn at present, and more prospective studies with sufficient samples from various centers are needed.

MECHANISMS LINKING TB AND POOR PROGNOSIS

From the viewpoint of pathology, TB is a phenotype identified in various malignancies, in which the main cancer mass invades the adjacent stroma through finger-like projections, and a number of them eventually detach from the main cancer, leading to the formation of single cell or small cell clusters (Figure 1)[19]. Therefore, TB constitutes a distinctive part of the tumor microenvironment (TME), representing the first step of the cancer invasion-metastasis cascade. Currently, epithelial-mesenchymal transition (EMT), except for some debates, is widely accepted as an important biological program activated in the cancer invasion-metastasis cascade[20]. Therefore, TB has long been hypothesized as a specific histological manifestation of EMT, providing the significant prognostic potential of TB in various cancer types[8].

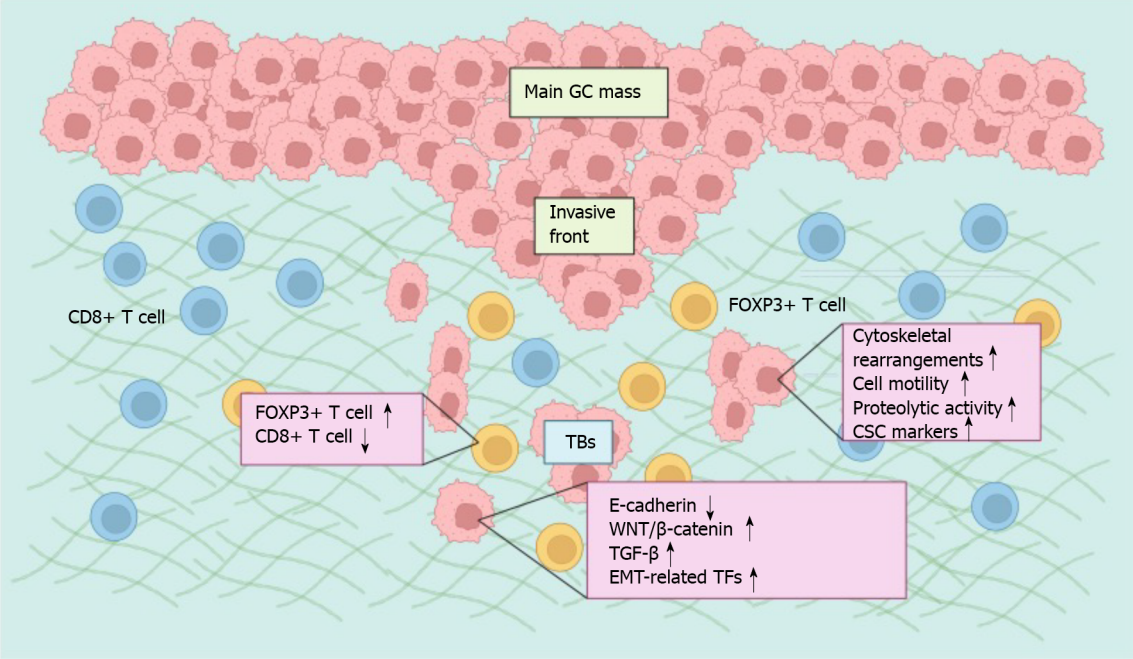
The association between TB and EMT has been extensively investigated in various solid tumors and has been reviewed in detail previously[8]. For example, E-cadherin, a critical protein responsible for cell-cell adhesion, is decreased when cancer cells lose their epithelial phenotype, especially within TBs at the invasive front of cancers[8]. In contrast, master regulators of EMT, including EMT-associated transcription factors (ZEB1, ZEB2, TWIST1, TWIST2, SNAI1 and SNAI2) and signaling pathways (WNT/β-catenin, TGF-β), are significantly overexpressed or activated in cancer cells obtained from TB [8]. TB also shares many invasive abilities endowed by EMT, such as cytoskeletal rearrangements, cell motility and increased proteolytic activity[8]. Furthermore, cancer stem cell markers, including CD44, LGR5 and ALDH1, often test positive on TB cells, indicating the anoikis resistance, self-renewal and metastasis-establishing capacity of these dissociated cells[8]. This evidence suggests that TB cells represent the morphological phenotype of EMT and are often identified adjacent to or within the endothelium of either lymphatic or blood vessels microscopically, indicating their possible intravasation and dissemination process. Studies on the association of TB and EMT or cancer stem cells (CSCs) are very limited in GC. In the invasive front of intestinal-type GC tissues, TB scores were positively correlated with the expression of ZBTB7A, which was shown to increase the expression of EGFR, leading to the activation of the PI3K-AKT-mTOR pathway and MAPK-ERK pathway, therefore greatly altering the expression of EMT markers[21]. In addition, although not examined specifically in TB cells, several studies have found elevated expression of EMT and CSC biomarkers at the invasive front of GC, supporting the activation of EMT and CSC programs in TB cells in GC tissues[22-24].

An attacker-defender model has been proposed to describe the interactions between TB cells and anticancer immunosurveillance. In this model, TB cells represent the attacker owing to their aggressive attributes, while innate and adaptive immune cells mediate the counterattack[8]. Therefore, the predictive and prognostic potential were improved significantly by the integration of TB and the immune microenvironment. In the invasive front of GC, TB counts were inversely associated with a high microsatellite instability (MSI) phenotype, owing to the local immune response capable of eradicating TB cells with increased generation of neoantigens[13]. The immune microenvironment analysis around TB in GC revealed that TB density is negatively correlated with the number of tumor-infiltrating lymphocytes (TILs), and the density of TILs changed from CD8+ > FOXP3+ > OX40+ > GrB+ T cells in the nonbudding area to FOXP3+ > CD8+ > OX40+ > GrB+ T cells in the budding area, indicating a privileged immune environment created by TB cells[25]. The recruitment of immunosuppressive cells enables evasion of the antitumor immune response by cancer cells and is proposed to be a critical step toward progression. Thus, the prognosis was significantly poor in patients who had a lower density of TILs and a higher density of TB[25].

Elucidating the acquisition of the EMT state and the immune escape mechanisms of TB as well as the interactions between TB cells and the surrounding stroma has the potential to reveal novel therapeutic targets. Thus, except for standardizing the assessment of TB as a promising predictive and prognostic biomarker in GC, the mechanisms underlying these clinical associations need to be further explored.

THE APPLICATION PROSPECT OF TB IN GC

Currently, several GC subtyping systems based on molecular markers have been proposed by various research organizations, such as The Cancer Genome Atlas and Asian Cancer Research Group[26,27]. However, these molecular tests are still costly, which hinders their wide application in clinical practice. A major advantage of GC patient stratification based on TB is that it can be counted along with conventional histopathological examination in H&E-stained tissue sections simultaneously without extra costs. Therefore, if more high-quality evidence is accumulated and consensus on definition and assessment methods is achieved in GC, TB could potentially be considered relevant in the following different



DOI: 10.4240/wjgs.v15.i4.578

Figure 1 The mechanism of tumor budding in gastric cancer. Various signaling pathways are activated in budding cells, leading to increased expression of epithelial-mesenchymal transition (EMT)-related transcription factors and the loss of cell-cell adhesion. Tumor budding (TB) also shares many invasive abilities endowed by EMT, such as cytoskeletal rearrangements, cell motility and increased proteolytic activity. Furthermore, TB cells often display attributes of cancer stem cells (CSCs). The density of tumor-infiltrating lymphocytes changed from CD8+ > FOXP3+ T cells in the nonbudding area to FOXP3+ > CD8+ T cells in the budding area. This figure was created with BioRender.com. GC: Gastric cancer; TB: Tumor budding; EMT: Epithelial-mesenchymal transition; CSC: Cancer stem cells.

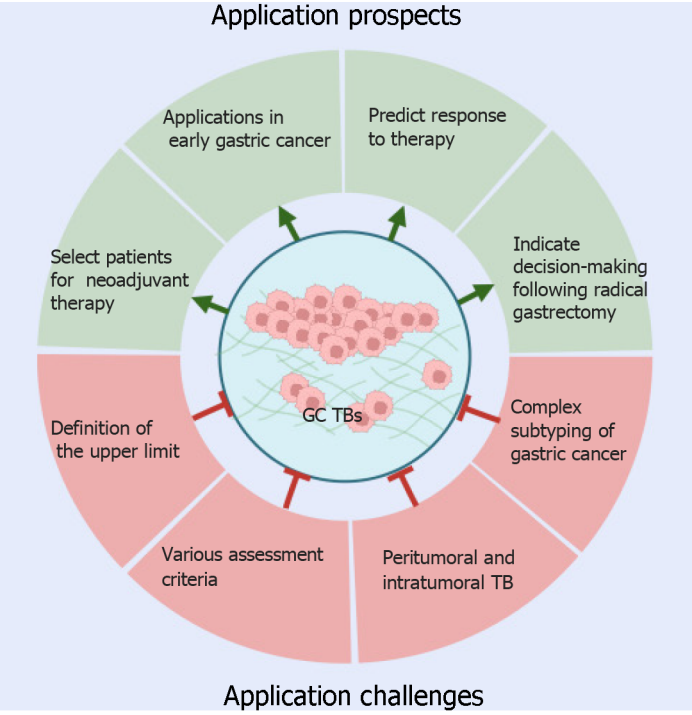
clinical scenarios (Figure 2).

Selecting patients for neoadjuvant therapy

Due to unspecific symptoms and delayed presentation, GC is often diagnosed in an advanced stage, which requires preoperative chemotherapy to improve the curative resection rate and long-term survival. Currently, the preoperative treatment decision is determined mainly by TNM staging and patient performance status, and indications and modalities are recommended variously across different countries due to the lack of reliable prognostic and predictive biomarkers[28]. In addition to radically resected specimens, TB was also assessed in endoscopic biopsies with far less available cancer tissue and has been found to provide prognostic information[29]. In this regard, TB is a promising biomarker candidate that serves to select patients for neoadjuvant therapy. A study including both esophageal and gastroesophageal adenocarcinoma found that TB in preoperative endoscopic biopsies is strongly associated with poor survival[30]. Intriguingly, such prognostic significance was found only in stage II but not stage III cancers[30]. One possible explanation for such divergence may be that other strong negative prognostic factors in stage III cancers dilute the patient stratification capability of TB, which can very well exhibit its influence on long-term outcomes in stage II cancers[30]. However, in most countries, patients with stage II GC are often recommended to receive radical gastrectomy directly[28]. As the recurrence and metastasis of cancer following radical surgery is mainly due to distant disseminated cancer cells before surgery, whether neoadjuvant therapy is feasible and can improve long-term survival in patients with stage II GC warrants further prospective randomized controlled trials.

Applications in early GC

An increasing number of patients with early GC have been treated by endoscopic mucosectomy and endoscopic submucosal dissection because of their similar survival outcomes but lower incidence of complications[31]. Initially, endoscopic resection was only applied to patients with an absolute indication that the risk of lymph node metastasis is less than 1%; then, indications were expanded and relative indications were established to identify additional patients suitable for endoscopic treatment, which raises the requirement for improving the accuracy of histopathological examination on endoscopically resected specimens to predict lymph node metastasis, in which case additional radical gastrectomy is needed[31]. TB is a well-known predictor for lymph node metastasis in early-stage colorectal cancer and has already been considered a standard to determine the curability following endoscopic resection[9]. Recently, it has also emerged as a potential risk factor for lymph node metastasis in GC. However, the majority of these studies included patients with all stages, and only a few studies specifically focused on early GC. In a study reported by Yim *et al*[32], the risk for lymph



DOI: 10.4240/wjgs.v15.i4.578

Figure 2 Application prospects and challenges of tumor budding in gastric cancer. Tumor budding (TB) could potentially be considered relevant in the selection of patients for neoadjuvant therapy, management of early gastric cancer (GC) following endoscopic resection, therapy response prediction, and decision-making after radical gastrectomy. However, before its routine clinical application, several challenges need to be overcome: Standardization of the definition and assessment of peritumoral and intratumoral TB in GC according to subtypes. This figure was created with BioRender.com. GC: Gastric cancer; TB: Tumor budding.

node metastasis in early GC with high-grade TB (Bd2 and Bd3) increased by nearly 16 times, and the predictive efficacy was obviously improved when TB was added to conventional clinicopathological factors[32]. In this study, the risks of TB for lymph node metastasis in patients with pT1a and pT1b were not determined separately[32]. As only 4.3% of patients with pT1a disease developed lymph node metastasis, the predictive value may mainly work in pT1b patients[32]. In another study, although TB was reported to be the only variable that remained significant as an independent predictor of lymph node positivity in both pT1a and pT1b diseases, there were only 5 patients with pT1a found to be lymph node positive, and only 2 of them had high-grade TB[33]. Therefore, as the number of pT1a patients with TB is small, the application potential of TB in this subgroup of patients is still unknown at present. Therefore, a multicenter clinicopathologic study only included patients with pT1b disease and concluded that TB is a significant high-risk factor for lymph node metastasis in submucosal early GC [34]. Supporting these findings indirectly, additional gastrectomy with lymph node dissection needs to be considered when high-grade TB is observed in endoscopically resected specimens, especially in cancers invading the submucosa. Except for these studies assessing TB activity in surgically resected specimens, one study also assessed TB activity in endoscopically resected specimens and found that patients with high-grade TB activity who only underwent endoscopic therapy had a lower DFS and OS rate than patients who received an additional radical gastrectomy[21]. Collectively, TB is a powerful independent predictor of lymph node metastasis and poor survival in early GC; thus, it is recommended that radical gastrectomy should be applied to patients with high-grade TB scores in their endoscopic resected specimens.

On the other hand, currently, the majority of guidelines on GC recommend that D1 lymph node dissection is sufficient in patients with early GC who are treated with curative surgery[35-37]. However, the evidence supporting such a recommendation was based on studies including patients without further stratification. Because high TB scores indicate a higher probability of lymph node involvement, whether more extensive lymph node dissection is required in early GC with high TB activity warrants validation in comparative trials.

Predicting response to therapy

Although GC is one of the most common malignancies worldwide, a relatively small number of options for effective therapy are available to clinicians compared with other solid cancers. Currently, chemotherapy based on fluoropyrimidine, platinums, taxanes, and irinotecan is still the foundation of treatment for advanced GC[3]. However, no robust biomarkers for predicting the response to these

drugs have been developed. Therefore, the administration of these drugs is only based on the clinical stage and the performance of patients. As a cost-effective histopathological biomarker, TB has been explored to predict the response to chemotherapy in some cancers, and a poor response was reported in patients with high TB activity[38]. However, data in GC are limited, possibly owing to the difficulty of obtaining tissues for TB assessment in advanced GC, in which setting it is feasible to assess therapy response.

Nevertheless, TB assessment in surgically resected specimens may provide indirect information for therapy response for other strategies, such as targeted therapy and immunotherapy, which were introduced into the multidisciplinary treatment of GC in recent years. For example, TB activity is inversely correlated with the expression of HER-2 but positively correlated with the expression of MET [13]. Both HER-2 and MET are well-defined therapeutic targets in cancer, and several agents targeting them have already advanced to clinical practice[39]. However, as robust predictive biomarkers for these targeted therapies have been developed, the clinical application significance of TB in these scenarios is limited.

In contrast, there is an unmet need to identify better predictive biomarkers of response to immunotherapy at present. TB is regarded as a special morphology of EMT, which has been shown to correlate with the activation of various immune checkpoint molecules, including programmed cell death protein 1 ligand[40]. Thus, whether high TB activity may be a potential predictor of immune checkpoint inhibitor therapy deserves further research. However, in GC, increasing peritumoral inflammation leads to decreased TB activity due to inflammation-related destruction of cancer cells at the invasive front, although the survival influence was not evaluated[13]. In addition, MSI-high tumors are often characterized by a pushing border type invasion front, no or low TB and a strong peritumoral inflammatory infiltrate[13]. The immune microenvironment analysis around TB in GC has revealed that TB density is negatively correlated with the number of TILs, indicating a privileged immune environment created by TB cells[25]. Therefore, these findings indicate that high-grade TB in GC may represent a promising negative biomarker for immunotherapy.

Collectively, the predictive value of TB in response to therapy is only speculated from indirect evidence, while direct supporting data are lacking in the present literature. In consideration of its assessment convenience and lack of additional cost, the predictive values can be easily verified when the efficacy of various therapy strategies is explored in clinical trials.

Applications in the management following radical gastrectomy

Currently, early-stage GC is believed to have a very high 5-year survival rate after endoscopic resection or curative gastrectomy; therefore, adjuvant therapy is not recommended in such patients. However, recurrence and metastasis are still inevitable in a small number of these patients[41]. Therefore, in addition to helping identify patients with high lymph node metastasis probability following endoscopic resection for whom an additional gastrectomy should be considered, TB also provides critical information regarding the decision of adjuvant chemotherapy after curative surgery. On the other hand, all guidelines on the management of GC recommended that all patients with locally advanced GC should receive adjuvant chemotherapy after curative resection. However, more than half of the patients with stage II who receive only curative gastrectomy will not experience recurrence; therefore, whether assessment of TB will help decision-making in these scenarios needs to be investigated in future studies.

In the postneoadjuvant therapy setting, although ypTNM and tumor regression grade (TRG) have been routinely examined in resected specimens, other prominent prognostic histopathological parameters are usually omitted, and clinical guidelines directing further management of these patients are still lacking[42]. Therefore, additional biomarkers with potential prognostic or predictive value in this specific condition are urgently needed to stratify patients into groups with different prognoses that may require different management. In contrast to TB assessment in primary gastrectomy specimens, there has only been one study investigating the prognostic relevance of TB in resected GC specimens following preoperative therapy[43]. In 167 intestinal-type GC patients in the post neoadjuvant setting, TB was reported according to the ITBCC recommendation and was identified as an independent prognostic factor, even after adjusting for post neoadjuvant stage and TRG[43]. The authors concluded that post neoadjuvant assessment of TB categories according to the ITBCC criteria is feasible and that the prognostic power of TB is not disrupted by chemotherapy effects[43]. Although data are limited and more evidence is needed in GC, parallel with the consistent findings in other cancer types, such as esophageal, colorectal, and breast cancer, the routine implementation of TB assessment in the post neoadjuvant setting may be feasible and essential in patients with GC[44-46].

Therefore, assessment of TB would aid clinicians in decision-making. By this, they would make adjuvant therapy in patients more likely to experience recurrence or, on the other hand, avoid unnecessary side effects in those least likely.

CHALLENGES LIMITING THE APPLICATION OF TB IN GC

Despite the abovementioned promising clinical application potential in GC, TB is still not routinely

assessed in daily practice, largely owing to the lack of GC-specific standardized assessment methods, including definition, cutoff determination, and location to count. In addition, the complex histopathological heterogeneity of GC further impedes the consistent validation of this biomarker in various studies (Figure 2).

Four cancer cells to define the upper limit of TB

Throughout the literature, a single tumor cell or a cluster of no more than four cohesive tumor cells separated from the main cancer mass is consistently used to define TB, and an agreement has been achieved in colorectal cancer at the ITBCC[11]. However, although clinical applications have already gained great success in colorectal cancer, this cutoff is an arbitrary determination, and whether it is the best definition feasible for GC has not been extensively validated. Although the prognostic power of TB is not affected by the number of cells that define a cluster in other cancer types and studies have recurrently demonstrated its prognostic and predictive values in GC, no prospective large cohort studies have compared the differences among TBs defined by various upper limits, except for another tumor cluster presentation with more than four cancer cells, poorly differentiated clusters (PDCs), which have been proposed.

PDCs have been investigated in several cancer types and have shown prognostic potential[47]. Compared with TB, whose accurate determination may be challenged when TBs are mixed with degenerating normal glands or inflammatory stoma without cytokeratin immunohistochemical staining, PDCs are more easily and accurately recognized[48]. Therefore, in colorectal cancer, PDCs were found to have stronger prognostic potential than TBs[49-51]. Theoretically, TB and PDCs indeed represent the same biological phenomenon, EMT, which underlies their prognostic roles. Therefore, some authors have integrated them into a single scoring system and proved the value of the combined effects in prognosis for squamous cell carcinomas[52,53]. Only a limited number of studies have been conducted to explore the prognostic value of PDCs in GC, and findings from these studies are somewhat different from those in other cancer types. In a study with a small sample size (n = 50), a positive association between PDC categories and poor prognosis was observed[54]. In contrast, in another study with a relatively large sample size (n = 290), the presence of PDCs was marginally associated with the features of local tumor spread, such as PNI, LVI and advanced T stage, but not with lymph node metastasis and poorer survival[14]. Therefore, the application of PDCs in GC prognosis is inconclusive at present.

In addition, PDCs represent another group of cancer cell clusters with more than 4 cells but are not a new definition of TB. Therefore, whether the upper limit of four cancer cells is truly the optimal choice in GC warrants further validation. Nevertheless, both TB and PDCs are defined by the number of tumor cells residing in the invasive front or the center of the cancer mass, and they are just quantitative but not qualitative characteristics. In other words, are TB and PDCs observed on tissue slides truly TB and PDCs? In fact, some cancer cells, which were determined to be detached cells/cell clusters from the main cancer mass in the two-dimensional plane of histological sections, are actually found to be part of the main tumor in 3D reconstruction[55]. In addition, is EMT or CSC programs activated in all TBs and PDCs counted by pathologists according to the present recommended criteria? In fact, the invasive and metastatic potential of TB cells varies substantially, suggesting overt differences in the prognosis of patients with colorectal cancer depending on the profile of CSC markers in TB cells[56]. Therefore, more studies are needed to investigate whether assessment of TB with activation of EMT or CSC programs will provide stronger prognostic and predictive values.

Various criteria to assess TB and to define high-grade TB

Before and even after the publication of the ITBCC guidelines, the methods used to assess TB in GC varied across studies. For example, Gabbert *et al*[10] examined the TCD, used synonymously to describe TB, at the invasive front of GC by using semiquantitative scoring (TCD0-3). Then, some studies reported the mean or median TB counts of several hotspots at the cancer invasive front, and cutoffs ranging from 1 (presence or absence) to 10 have been used to categorize GC into low- and high-grade TB (Table 1). After the publication of the ITBCC guidelines, most studies reported and classified TB in GC according to the ITBCC guidelines, and in some studies, small modifications have been made. For example, some authors classified bud 0 as Bd0, and some authors defined high-grade TB activity as Bd3 or the integration of Bd2 and Bd3 (Table 1). However, few cutoffs have been *de novo* established based on a GC cohort and validated in a separate validation cohort. Therefore, similar to the upper limit of TB definition, the optimal cutoffs to define different TB activities are also not clear, especially in diffuse-type GC, the majority of which may fall within high-grade TB according to ITBCC criteria. To date, only one study has determined the cutoff value of the TB score by receiver operating characteristic curves, and the optimal cutoff value of the TB score was set to 5, which had the best predictive significance for lymph node metastasis[21]. However, only 122 total and 71 intestinal-type patients were included, which may prevent generalization. In another study, the authors compared the differences in prognostic values among different categorizations of TB[32]. This study showed that TB activity classified by ITBCC criteria predicts lymph node metastasis better than TB presence, at least in early GC[32]. Therefore, although the ITBCC criteria are now adopted as the standard method to assess TB for reproducibility, the optimal definition of high-grade TB in GC is still unclear.

Peritumoral and intratumoral TB

Traditionally, TB was assessed mainly at the invasive front of cancer, termed peritumoral budding (PTB). However, as the pathologists who prepare and read tissue slides may not be the same, it is difficult to ensure that the invasive front used to determine PTB truly represents the patients' cancer infiltration state, leading to inaccurate predictive and prognostic values[57]. In addition, in some conditions, it is impossible to determine the invasive front of GC. For example, the majority of GC patients were initially diagnosed by biopsies, which were often obtained from the cancer center rather than from its invasive front, and the biopsy specimens are the only tissues available for TB assessment because some patients may not undergo gastrectomy for unresectability or poor performance status. In the conditions of some early GC, it is also difficult to specify an invasive front in the intrusive cancer. Moreover, after neoadjuvant therapy, the architecture of cancer is often disrupted to some extent, especially in cancers with a strong response. The invasive front is hard to determine, and assessing peritumoral TB is very difficult or infeasible. Thus, intratumoral TB from the cancer center was suggested in those cases and was demonstrated to have a very high correlation with peritumoral TB activity[58,59]. A significant positive correlation between ITB and PTB was also found in GC, and on the same slide, the number of ITB was higher than that of PTB[57]. Both ITB and PTB predicted a shorter OS, while the simultaneous presence of ITB and PTB had a stronger prognostic value[57]. Some authors have tried to assess both peritumoral TB and intratumoral TB, also referred to as total TB, which seems to be superior to peritumoral TB in several cancer types. In GC, although statistical significance has not been achieved, total TB showed a tendency to predict lymph node metastasis better[32]. Therefore, assessment of ITB activity may not only provide similar predictive and prognostic value as PTB but can also replace PTB when the assessment of the latter is infeasible.

Complex subtyping of GC

In contrast to other cancer types, such as colorectal cancer and breast cancer, many biomarkers have not yet achieved full application in the routine clinical prognostic and predictive categorization of GC patients due to the complex histopathological characteristics of GC and the lack of consistent explicitness in all subtypes. The widely used simple histopathological classification system, proposed by Lauren in 1965, divides GC into intestinal, diffuse and mixed types[60]. In studies on the association between GC and TB, some studies included all subtypes, while others only included intestinal-type GC (Table 1). As indicated by its definition, diffuse GC grows with a highly dissociative pattern that would assign the majority of them into the high-grade TB category, which may confound the prognostic power of TB in patients with intestinal-type GC. Therefore, whether a GC with a diffuse or mixed component should be included to assess TB is still under debate. Some authors stated that TB and tumor grade are not the same, as high TB was not consistently found in all poorly differentiated cancers; thus, excluding this subgroup of patients is not necessary[13]. In contrast, Kemi *et al*[61] concluded that assessing TB in diffuse-type GC provides no prognostic information based on findings from 583 patients; therefore, routinely examining TB in diffuse-type GC is not recommended.

Signet ring cell (SRC) cancer, a distinctive subtype classified in the WHO classification system, is another poorly cohesive GC, which may also increase the difficulty of TB counting. Theoretically, SRC cancer belongs to diffuse-type GC and is more likely to display TB activity. However, compared with other poorly cohesive cancers, SRC-type GC showed a favorable prognosis in patients with early disease [62,63]. Therefore, Yim *et al*[32] developed a modified TB determining method, which excluded SRCs to overcome this contradiction. In early GC, modified TB was more predictive of lymph node involvement than conventional TB. In contrast, SRC-matched TB had no significant association with lymph node metastasis; rather, it showed a greater tendency toward patients without lymph node metastasis[32]. This finding was also supported by targeted genomic sequencing data, which found that many EMT-related molecules are not involved in the early onset of SRC cancer[63-65]. Therefore, as an EMT marker, SRCs are inappropriate to be identified as TBs for GC. Currently, such a conclusion may only be applied to early GC, as no such findings have been reported in advanced GC, in which a higher percentage of SRC is also inversely related to tumor aggressiveness and predicts better survival[66,67].

CONCLUSION

Although TB is promising in the management of GC in several clinical scenarios, further research is needed before its implementation in routine practice. There are many unknowns about the roles of TB in the management of GC. Considering the assessment method, although consensus has already been achieved in colorectal cancer and the ITBCC criteria are now widely accepted as the standardized method in studies on other cancer types, inconsistent criteria are still used to assess TB in GC. Therefore, multicenter studies are needed to yield a standardized methodology in GC similar to that in colorectal cancer for clinical decision-making. As in many settings in GC, it is difficult to determine the invasive front of cancer in available tissues, and studies on the use of ITB in these settings need further exploration. As discussed above, the complex histopathological subtypes of GC cause inconsistent conclusions, indicating the requirement for exploring the applications in each subgroup separately. In

addition, TB is intimately associated with activation of EMT and CSC programs, leading to an increased capability for cancer cell dissociation, migration and metastasis. The interactions between TB and the immune microenvironment also facilitate the spread of GC. Therefore, as an easily available and cost-effective biomarker, TB assessment holds important prognostic, predictive and potentially therapeutic implications. A deeper understanding of the molecular and pathogenetic mechanisms underpinning TB may lead to an area of 'anti-TB therapies' in GC.

ACKNOWLEDGEMENTS

The author thanks the Health Commission of Mianyang City and the Science and Education Department of the Third Hospital of Mianyang for their support. The space limitations of this review have unfortunately meant that we have not been able to separately cite many of the original publications that have contributed substantially to the literature. We sincerely apologize to the authors of these publications. All figures in this review were created with BioRender.com.

FOOTNOTES

Author contributions: Li J designed the review; Li J and Xiao SM reviewed the literature; Xiao SM drafted the manuscript; Li J revised the manuscript; all authors read and approved the final version of the manuscript.

Conflict-of-interest statement: There are no conflicts of interest to report.

Country/Territory of origin: China

ORCID number: Shuo-Meng Xiao 0000-0002-8695-8142; Jian Li 0000-0002-5807-2360.

S-Editor: Yan JP
L-Editor: A
P-Editor: Yan JP

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World Journal of Gastrointestinal Surgery

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World J Gastrointest Surg 2023 April 27; 15(4): 592-599

DOI: 10.4240/wjgs.v15.i4.592

ISSN 1948-9366 (online)

MINIREVIEWS

Initial management of suspected biliary injury after laparoscopic cholecystectomy

Antti Siiki, Reea Ahola, Yrjö Vaalavuo, Anne Antila, Johanna Laukkarinen

Specialty type: Virology

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: Moshref L, Saudi Arabia; Thapar P, India

Received: December 28, 2022
Peer-review started: December 28, 2022
First decision: January 12, 2023
Revised: January 26, 2023
Accepted: March 15, 2023
Article in press: March 15, 2023
Published online: April 27, 2023

Antti Siiki, Reea Ahola, Yrjö Vaalavuo, Anne Antila, Johanna Laukkarinen, Department of Gastroenterology and Alimentary Tract Surgery, Tampere University Hospital, Tampere 33521, Finland

Johanna Laukkarinen, Faculty of Medicine and Health Technology, University of Tampere, Tampere 33521, Finland

Corresponding author: Antti Siiki, MD, PhD, Surgeon, Department of Gastroenterology and Alimentary Tract Surgery, Tampere University Hospital, Teiskontie 35, Tampere 33521, Finland. antti.siiki@fimnet.fi

Abstract

Although rare, iatrogenic bile duct injury (BDI) after laparoscopic cholecystectomy may be devastating to the patient. The cornerstones for the initial management of BDI are early recognition, followed by modern imaging and evaluation of injury severity. Tertiary hepato-biliary centre care with a multidisciplinary approach is crucial. The diagnostics of BDI commences with a multiphase abdominal computed tomography scan, and when the biloma is drained or a surgical drain is put in place, the diagnosis is set with the help of bile drain output. To visualize the leak site and biliary anatomy, the diagnostics is supplemented with contrast enhanced magnetic resonance imaging. The location and severity of the bile duct lesion and concomitant injuries to the hepatic vascular system are evaluated. Most often, a combination of percutaneous and endoscopic methods is used for control of contamination and bile leak. Generally, the next step is endoscopic retrograde cholangiography (ERC) for downstream control of the bile leak. ERC with insertion of a stent is the treatment of choice in most mild bile leaks. The surgical option of re-operation and its timing should be discussed in cases where an endoscopic and percutaneous approach is not sufficient. The patient's failure to recover properly in the first days after laparoscopic cholecystectomy should immediately raise suspicion of BDI and this merits immediate investigation. Early consultation and referral to a dedicated hepato-biliary unit are essential for the best outcome.

Key Words: Cholecystectomy; Laparoscopy; Bile duct injury; Iatrogenic; Adverse event; Complication

Core Tip: A rare, but potentially disastrous bile duct injury (BDI) after laparoscopic cholecystectomy may easily go unnoticed at first. Thus, any unwell patient or anyone not recovering properly in the first post-operative days after surgery should be considered as having a surgical complication unless proven otherwise. The right initial management in suspected BDI is essential for prognosis. Early referral to a hepato-biliary unit, combination of modern imaging modalities and consequent evaluation of the severity grade of the injury are the foundations of management. The initial treatment options range from percutaneous and endoscopic methods to surgery, the timing and details of which need a multi-disciplinary hepato-biliary approach.

Citation: Siiki A, Ahola R, Vaalavuo Y, Antila A, Laukkarinen J. Initial management of suspected biliary injury after laparoscopic cholecystectomy. *World J Gastrointest Surg* 2023; 15(4): 592-599
URL: https://www.wjgnet.com/1948-9366/full/v15/i4/592.htm
DOI: https://dx.doi.org/10.4240/wjgs.v15.i4.592

INTRODUCTION

Rare bile duct injury (BDI) after cholecystectomy should be recognized early to allow prompt diagnosis and treatment[1-3]. As most cholecystectomies are operated on laparoscopically, BDI occurs in 0.2%-0.9% of patients; the variation depends on whether all bile leaks or only surgically reconstructed injuries are included[4-6]. Commonly graded by Strasberg´s classification[7], bile duct injuries are graded from A to E, where A represents a simple cystic duct leak and C-E complex injuries to the hepatic ducts or common bile duct (CBD)[7-9] (Figure 1). Most post-cholecystectomy bile leaks are mild type A-B lesions, where endoscopic treatment combined with external drainage is usually successful[10-12]. More severe grades often require re-operation or even a combination of endoscopy, interventional radiology and surgery[4,13,14]. Surgical repair of BDI should be avoided between two and six weeks after the cholecystectomy due to the elevated risk of postoperative morbidity and hepaticojejunostomy stricture compared to re-operation at some earlier or later time point[15]. At worst, BDI may lead to morbidity and mortality[11], series of re-interventions, long hospitalization and substantial costs[1,16,17]. BDI has a considerable impact on long-term quality-of-life; *e.g.* surgically repaired BDI may require re-interventions for strictured hepatico-jejunostomy anastomosis in 10%-20%[3,14,18].

REFERRAL AND DIAGNOSIS IN SUSPECTED BDI

Most mild bile duct injuries are recognized a few days after the operation[6,10,19,20]. Prompt referral and evaluation with modern imaging is crucial whenever a patient is not recovering properly after any type of cholecystectomy[2,11,19]. The clinical symptoms of BDI are vague: symptoms such as abdominal pain, fever, sepsis and jaundice are not specific. Liver function tests and inflammatory markers may be normal in the early phase. Noteworthy, elevated liver function test results are associated with biliary obstruction or vascular damage, but in cases with bile leak these are usually normal. The only symptom of the most common iatrogenic injury, a leak from the cystic duct (Strasberg A), is often the patient's unspecific deterioration early in the postoperative course. The key to correct diagnosis is high level of suspicion with consequent swift consultation or referral to a tertiary centre when the patient is unwell in the early days after cholecystectomy[2,10,19,21]. It is known that severe BDIs, especially with concomitant vascular injury, are best treated by early referral to the unit with the most experience and extensive resources for interventional radiology, advanced endoscopy and complex reconstructive surgery[8,22-24].

In the emergency department, abdominal imaging should be performed urgently to rule out any post-operative complications (Figure 2). While transabdominal ultrasound may visualize a fluid collection or dilation of the intrahepatic biliary ducts, a multi-phase abdominal computed tomography (CT) scan is required for BDI diagnosis. The common findings are perihepatic fluid accumulation around the right perihepatic space, gallbladder fossa and inferiorly into the right paracolic gutter[25]. Contrast enhanced CT with arterial phase is necessary to exclude the possibility of arterial injury with associated hypoperfusion of the liver due to damage typically to the right branch of the hepatic artery, occurring in up to 20% of BDIs[23]. CT scan may be followed by hepato-biliary specific contrast media enhanced magnetic resonance imaging (MRI) to identify the leak site and accurately identify the biliary anatomy. When contrast enhanced MRI is not available, standard magnetic resonance cholangio-pancreatography (MRCP) without contrast allows evaluation of the fluid-filled bile ducts and provides indirect evidence of a leak[25]. MRI may also reveal CBD stones predisposing to leak from the stump of the cystic duct.

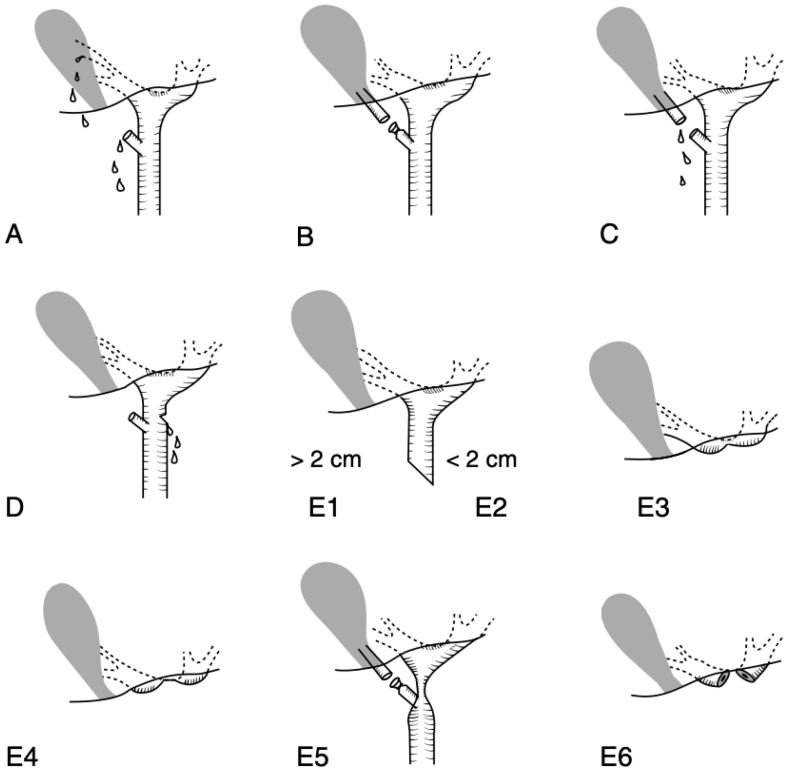


Figure 1 Classification of the bile duct injuries after cholecystectomy. A: Schematic classification of bile duct injuries in laparoscopic cholecystectomy. Originally developed by Strasberg *et al* in 1995[7]. A bile leak from the cystic duct stump or minor biliary radical in the gallbladder fossa; B: Occluded right posterior sectoral duct; C: Bile leak from the divided right posterior sectoral duct; D: Bile leak from the main bile duct without major tissue loss; E1: Transected main bile duct with a stricture more than 2 cm from the hilus; E2: Transected main bile duct with a stricture less than 2 cm from the hilus; E3: Stricture of the hilus with right and left ducts in communication; E4: Stricture of the hilus with separation of right and left ducts; E5: Stricture of the main bile duct and the right posterior sectoral duct; E6: complete excision of the extrahepatic ducts involving the confluence (this injury is not described in Strasberg's original classification). Citation: Connor S, Garden OJ. Bile duct injury in the era of laparoscopic cholecystectomy. *Br J Surg* 2006; 93(2): 158-168. Copyright ©John Wiley & Son´s Ltd 2006. Published by John Wiley & Son´s Ltd[8].

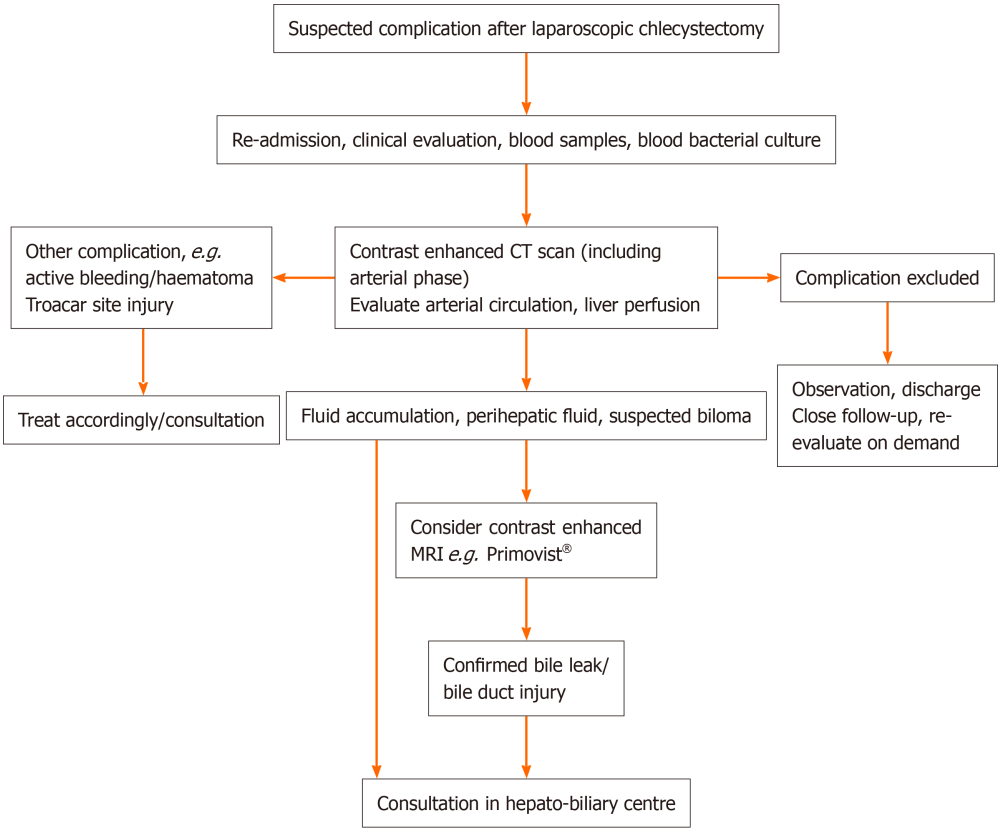
In evaluating the extent of the BDI, it is often useful to consult the original notes from the time of the primary operation. Sometimes crucial information can be obtained on how the anatomy appeared during the cholecystectomy and ascertaining if the critical view of safety was obtained[26,27], how the intra-operative cholangiography (*e.g.*, anatomy, stones, sludge) appeared[28] and what the pre-operative MRI or CT looked like[29,30], or whether the gallbladder was acutely or chronically inflamed, thereby increasing the risks for BDI[4,20,31].

CONTAINING THE CONTAMINATION

The first step in the initial management of BDI is to contain the contamination (Figures 2 and 3). The placement of a percutaneous drain in the biloma is often enough to control the infection combined with wide-spectrum antibiotic treatment. When a drain is placed in the accumulation or a surgical bile-producing drain is left in place in cholecystectomy, samples for bacterial culture and drain bilirubin should be obtained. In cases where interventional radiology is unavailable, especially in a septic patient, emergency laparoscopic lavation may be considered to contain the contamination followed by surgical drains[13]. In these cases, drainage or laparoscopic lavation may be performed in the referring hospital to avoid delays. However, reconstructive surgery for BDI should not be attempted before the severity grade of BDI and possible associated vascular injury are properly evaluated. At the latest, the referral to or consultation with a tertiary hepato-biliary unit should be made at this point, even before any interventions[1,2,19,21,24].

TREATMENT: CONTROLLING THE LEAK

After proper imaging and external drainage, endoscopic retrograde cholangiography (ERC) is the preferred next step in most cases (Figures 2 and 3). When bile drain output continues for more than ca



DOI: 10.4240/wjgs.v15.i4.592

Figure 2 Initial diagnostic flowchart in suspected complication after laparoscopic cholecystectomy. Any patient not recovering correctly in the immediate post-operative phase should be referred and evaluated for the possibility of a complication. Early consultation with the hepato-biliary unit is recommended when bile duct injury or other severe complication of laparoscopic cholecystectomy is suspected. CT: Computed tomography; MRI: Magnetic resonance imaging; MRCP: Magnetic resonance cholangio-pancreatography. (Primovist: Bayer AG, Leverkusen, Germany).

24 h, ERC is often indicated. Endoscopy is used to locate the leak and determine its severity grade and also to treat the bile leak with sphincterotomy and stents. In ERC a leak is carefully visualized with fluoroscopy by injecting pressurized contrast medium over an occlusion balloon[32]. Generally, the most common forms of mild BDI, type A leak from the cystic duct or aberrant duct from the gallbladder fossa, can be easily diagnosed and treated with standard ERC[12,33]. It is often wise to have a hepato-biliary surgeon present in the endoscopy room to see live fluoroscopy findings when a complex BDI is suspected.

When a complete transection of CBD is not present, trans-papillary downstream control of the leak by ERC allows healing in more than 90% of biliary leaks[9,10,34]. In ERC occult CBD stones obstructing the bile flow and predisposing to leak can also be easily removed. In the European guideline, it is recommended to insert a temporary plastic biliary stent rather than to decompress the CBD with sphincterotomy only: stenting provides faster leak resolution than sphincterotomy alone[34]. Stents seem to be equally effective whether biliary sphincterotomy is performed or not. However, while biliary sphincterotomy may be associated with some complications, it is usually necessary for the removal of retained stones. In simple grade A leaks, without bile duct stones, a single plastic stent inserted for four to eight weeks is often enough without sphincterotomy[34]. However, when a stent has been inserted, biliary sludge, stones, or occasionally even a persistent leak may be found at the time of stent removal. Thus, a stent may be preferable to sphincterotomy alone, which can be considered a mere secondary alternative when stone clearance is confirmed and second endoscopy for stent removal would be too risky[9,34]. However, a recent randomised controlled trial proved that after appropriate patient selection in a simple Strasberg type A leak, endoscopic sphincterotomy may be a safe and cost-effective single procedure without stent insertion[12].

When biodegradable biliary stents are available, stent removal in second endoscopy may be avoided [35]. However, in that case, an adequate sphincterotomy followed by careful cleansing of the CBD of stones and sludge should be performed at the index ERC.

In case of more complex BDI, ERC also gives more detailed information for locating the bile leak. It helps to assess the relation of the lesion to the hilum and the main biliary ducts even if the lesion itself may not eventually be treatable by endoscopy only[33]. When only the right hepatic duct is injured or anomalous right segmental biliary branches draining to the cystic duct have been damaged, ERC may be misinterpreted as having no leak despite drain bile output[8]. In this scenario, comparing ERC

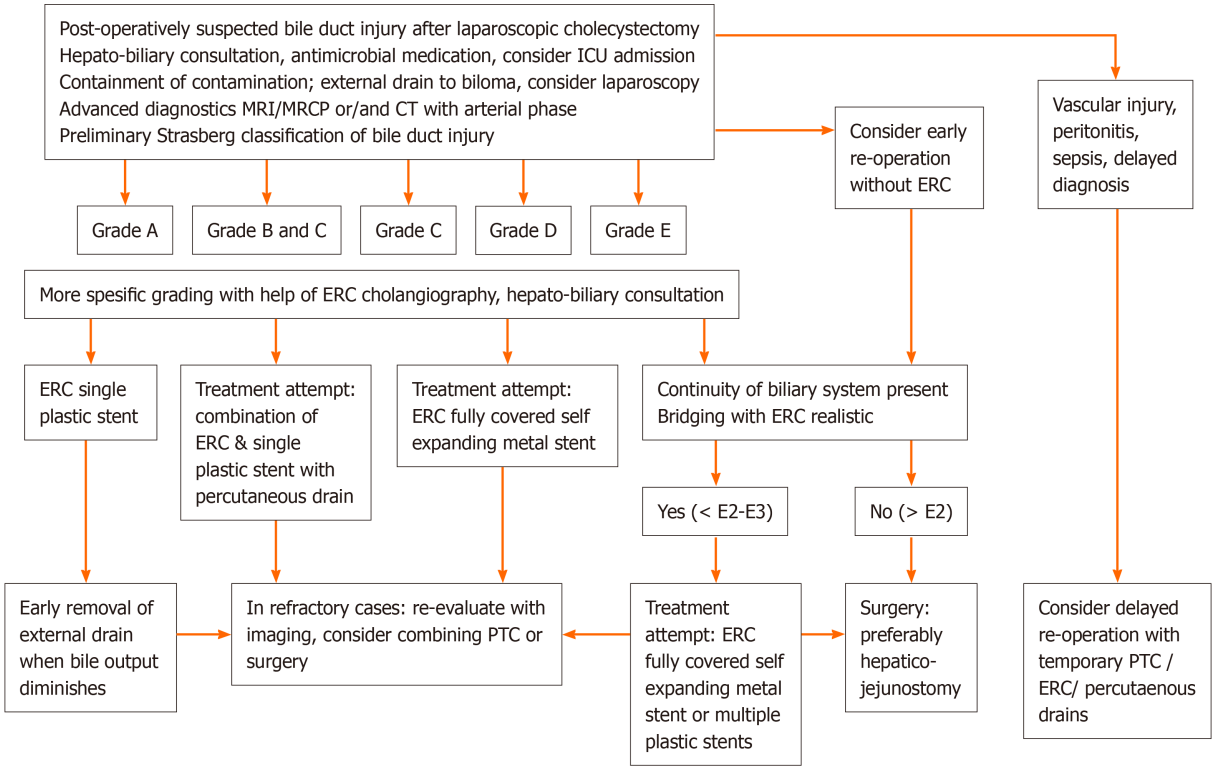


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Figure 3 Flow chart of containment and initial treatment in bile leak or bile duct injury. Reconstructive surgery should be planned and performed by hepato-biliary specialists only. ICU: Intensive care unit; CT: Computed tomography; MRI: Magnetic resonance imaging; MRCP: Magnetic resonance cholangio-pancreatography; ERC: Endoscopic retrograde cholangiography; PTC: Percutaneous transhepatic cholangiography catheter drainage; FCSEMS: Fully covered self-expandable metal stent.

cholangiography to pre-operative MRI may be the way to diagnose this type of lesion correctly[29]. A fistulography performed *via* the catheter drain may also help in determining the extent of the lesion[9]. When the bile duct is disconnected or the main branches entirely transected, early surgery or a combination of external drainage of biloma and percutaneous transhepatic cholangiogram catheter (PTC) for proximal control may be necessary in the early phase in order to gain time for definitive treatment[8].

Instead of plastic stents, self-expanding large bore covered metal stents may be used in ERC in iatrogenic BDI[32,36,37]. Correctly positioned, they may successfully bridge and seal even grade D injuries to the CBD and common hepatic duct[38]. The benefits of self-expanding metal stents are their greater diameter and the sealing effect of the plastic or silicone covering of the stents[36]. Large diameter stents with 8-10 mm bore may be associated with faster leak resolution than plastic stents with 3 mm (10F) calibre[35]. However, care should be taken not to insert a stent with too large a diameter into a narrow normal CBD to prevent circumferential ischaemia and consequent biliary stricture due to stent expansion. Most importantly, before embarking on percutaneous or endoscopic treatment of complex lesions, all diagnostic methods should be undertaken with multi-disciplinary evaluation of the surgical or endoscopic options in a hepato-biliary centre[19,21,24].

SURGICAL OPTIONS

Surgery is the mainstay treatment in cases not manageable by ERC[8]. When BDI is identified during the cholecystectomy, immediate surgical repair should be attempted[16,31]. In these cases, it is important to call a senior surgeon into the operation, carefully evaluate the anatomy and the extent of the lesion with cholangiography[21,28] if this has not been done at an earlier phase of the operation. In the prevention of BDI, a bail-out strategy by stopping further dissection and performing *e.g.*, partial cholecystectomy may be indicated[18,27,39]. Open conversion with Kocher mobilisation or laparoscopic suture, placement of a T-tube with external drainage or even reconstruction with roux-Y hepaticojejunostomy may be considered, depending on the lesion (Figures 1-3), the condition of the patient and the expertise of the surgical team. In complex cases, the best solution may be to do nothing further but call a hepato-biliary specialist during the surgery or place drains and consequently transfer the patient to a centre providing definitive care[8]. When CBD stones are present, it is important to remove them in the

same procedure with repair by choledochoscopy *via e.g.*, choledochotomy. Early or immediate repair may give a good prognosis when performed by experienced specialists only[8,19,40]. In practice, the prerequisites for immediate or early reconstruction with roux-Y hepatico-jejunostomy are: an experienced hepato-biliary team present, the entire biliary tree well visualised in cholangiography, no sepsis or severe biliary peritonitis, no significant co-morbidities and no vascular injury.

According to the literature, the optimal timing of definite reconstructive re-operation varies[9,15]. However, when a complex BDI unamenable to treatment by ERC is diagnosed after the operation, early surgical repair is generally not recommended, especially when diagnosis is delayed or sepsis, biliary peritonitis or arterial injury are concomitant[8,9]. In these cases, the definitive reconstruction should preferably be delayed for up to a few months and preceded by *e.g.*, PTC, multiple drains and also adequate nutritional support[8]. Due to the high risk of morbidity and late stricture formation, surgical reconstruction should be avoided for at least from weeks two to six post-operatively[15]. While the options for re-operation range from reconstruction with roux-Y hepaticojejunostomy[11] to liver resections and even up to liver transplantation[22], any reconstructive late-phase surgery should be performed in an expert hepato-biliary centre[8,19,24].

CONCLUSION

Laparoscopic cholecystectomy is a safe procedure with low morbidity and mortality[4,5]. Any unwell patient with abdominal problems in the immediate post-operative period after cholecystectomy should be managed and referred to specialist care by reason of suspected complication until this possibility can be excluded[1,2,6,19]. Early recognition of BDI improves survival[28]. In addition to BDI related morbidity and mortality[11,14], substantial cost stresses the importance of proper initial management [16,17].

In the surgical emergency department, evaluation starts with blood samples and multi-phase abdominal CT scan[25]. The first step in the treatment of BDI is to contain contamination by percutaneous radiologic catheter drainage, which usually allows time for further decision-making as well as bacterial culture and bile analysis of the drain output[13]. The second step is the evaluation of leak severity, which in practice means contrast-enhanced MRI or MRCP[25] followed by ERC, cholangiography and placement of a temporary stent for down-stream control[33]. The diagnostics of the severity of BDI thus requires a combination of modern imaging modalities. When endoscopic treatment is not sufficient, urgent multi-disciplinary evaluation for further interventional radiologic procedures or re-operation and their optimal timing are called for[8]. While in complex lesions, surgery is the preferred treatment, immediate or early repair by non-specialists is not recommended[8,40]. The long-term consequences of rare severe BDI may be devastating to the patient and the health care system[14,16,17]. Any reconstructive surgery should be performed in an expert hepato-biliary centre[22,24,40].

Although BDI or bile leak may be inevitable when large numbers of patients are operated on[26], for the most common simple leaks prognosis after ERC is excellent[20,32,36]. Additionally, the vast majority of complex BDIs can be successfully managed surgically in experienced hepato-biliary centres[4,19,24,40]. However, for the prevention of BDIs, all guidelines stress the importance of proper surgical training, paying due attention to the critical view of safety, use of intraoperative cholangiography to ascertain the anatomy and understanding the role of bail-out strategy[18,21,27,30,39]. In BDI, early recognition, diagnosis and referral are essential[2,19,24], thus a structured algorithm-based approach for the evaluation and referral pattern of complications of laparoscopic cholecystectomy could be useful, possibly similar to that developed for pancreatic surgery[41].

FOOTNOTES

Author contributions: Siiki A, Ahola R, Vaalavuo Y, Antila A and Laukkarinen J contributed to the manuscript drafting and revision.

Conflict-of-interest statement: The authors declare no relevant conflict of interest. Authors Siiki and Laukkarinen have received lecture fees from Boston Scientific, Cook Medical and Olympus Europe.

Country/Territory of origin: Finland

ORCID number: Antti Siiki 0000-0002-1098-0108; Reea Ahola 0000-0002-9702-2729; Yrjö Vaalavuo 0000-0002-1494-2184;

Anne Antila 000-0001-9623-8264; Johanna Laukkarinen 0000-0002-8239-4861.

Corresponding Author's Membership in Professional Societies: Finnish Society of Gastrointestinal Surgery.

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

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World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2023 April 27; 15(4): 600-620

DOI: 10.4240/wjgs.v15.i4.600

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Basic Study

Acinous cell AR42J-derived exosome miR125b-5p promotes acute pancreatitis exacerbation by inhibiting M2 macrophage polarization *via* PI3K/AKT signaling pathway

Zhi Zheng, Feng Cao, Yi-Xuan Ding, Jiong-Di Lu, Yuan-Qiao Fu, Lin Liu, Yu-Lin Guo, Shuang Liu, Hai-Chen Sun, Ye-Qing Cui, Fei Li

Specialty type: Medicine, research and experimental

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Tian L, China; Uhlmann D, Germany

Received: October 30, 2022
Peer-review started: October 30, 2022
First decision: January 3, 2023
Revised: January 5, 2023
Accepted: March 8, 2023
Article in press: March 8, 2023
Published online: April 27, 2023

Zhi Zheng, Yuan-Qiao Fu, Department of General Surgery, Beijing Friendship Hospital, Capital Medical University, Beijing 100050, China

Feng Cao, Yi-Xuan Ding, Jiong-Di Lu, Yu-Lin Guo, Shuang Liu, Hai-Chen Sun, Ye-Qing Cui, Fei Li, Department of General Surgery, Xuanwu Hospital, Capital Medical University, Beijing 100053, China

Lin Liu, Department of Gastroenterology, The Second Affiliated Hospital of Baotou Medical College, Baotou 014040, Inner Mongolia Autonomous Region, China

Corresponding author: Fei Li, MD, PhD, Deputy Director, Professor, Surgeon, Department of General Surgery, Xuanwu Hospital, Capital Medical University, No. 45 Chang-chun Street, Xi-Cheng District, Beijing 100053, China. feili36@ccmu.edu.cn

Abstract

BACKGROUND

The incidence rate of acute pancreatitis (AP), which is a pathophysiological process with complex etiology, is increasing globally. miR-125b-5p, a bidirectional regulatory miRNA, is speculated to exhibit anti-tumor activity. However, exosome-derived miR-125b-5p in AP has not been reported.

AIM

To elucidate the molecular mechanism of exosome-derived miR-125b-5p promoting AP exacerbation from the perspective of the interaction between immune cells and acinar cells.

METHODS

Exosomes derived from AR42J cells were isolated and extracted in active and inactive states by an exosome extraction kit, and were verified *via* transmission electron microscopy, nanoparticle tracking analysis, and western blotting. RNA sequencing assay technology was used to screen differentially expressed miRNAs in active and inactive AR42J cell lines, and bioinformatics analysis was used to predict downstream target genes of miR-125b-5p. The expression level of miR-125b-5p and insulin-like growth factor 2 (IGF2) in the activated AR42J cell line and AP pancreatic tissue were detected by quantitative real-time polymerase

chain reaction and western blots. The changes in the pancreatic inflammatory response in a rat AP model were detected by histopathological methods. Western Blot was used to detect the expression of IGF2, PI3K/AKT signaling pathway proteins, and apoptosis and necrosis related proteins.

RESULTS

miR-125b-5p expression was upregulated in the activated AR42J cell line and AP pancreatic tissue, while that of IGF2 was downregulated. *In vitro* experiments confirmed that miR-125b-5p could promote the death of activated AR42J cells by inducing cell cycle arrest and apoptosis. In addition, miR-125b-5p was found to act on macrophages to promote M1 type polarization and inhibit M2 type polarization, resulting in a massive release of inflammatory factors and reactive oxygen species accumulation. Further research found that miR-125b-5p could inhibit the expression of IGF2 in the PI3K/AKT signaling pathway. Additionally, *in vivo* experiments revealed that miR-125b-5p can promote the progression of AP in a rat model.

CONCLUSION

miR-125b-5p acts on IGF2 in the PI3K/AKT signaling pathway and promotes M1 type polarization and inhibits M2 type polarization of macrophage by inhibiting IGF2 expression, resulting in a large release of pro-inflammatory factors and an inflammatory cascade amplification effect, thus aggravating AP.

Key Words: Acute pancreatitis; Exosome; miR-125b-5p; Macrophage; Mechanism

Core Tip: Our study confirmed that miR-125b-5p can promote the inflammatory response of acute pancreatitis (AP), and its potential targets were found *via* RNA sequencing assay. However, the likely mechanism remains unclear. Consequently, our study intends to elucidate the molecular mechanism of exosome-derived miR-125b-5p in promoting AP exacerbation from the perspective of the interaction between immune cells and acinar cells.

Citation: Zheng Z, Cao F, Ding YX, Lu JD, Fu YQ, Liu L, Guo YL, Liu S, Sun HC, Cui YQ, Li F. Acinous cell AR42J-derived exosome miR125b-5p promotes acute pancreatitis exacerbation by inhibiting M2 macrophage polarization *via* PI3K/AKT signaling pathway. *World J Gastrointest Surg* 2023; 15(4): 600-620
URL: https://www.wjgnet.com/1948-9366/full/v15/i4/600.htm
DOI: https://dx.doi.org/10.4240/wjgs.v15.i4.600

INTRODUCTION

Acute pancreatitis (AP) is a common clinical inflammatory disease of the digestive system, with an increasing trend worldwide[1,2], which is a pathophysiological process with complex etiology. At present, there are no consistent and effective therapies for treatment of AP, resulting in a high mortality rate. The fundamental reason is that the underlying mechanism of AP pathogenesis is not been fully understood[3]. During severe AP, inflammatory mediators released from the pancreas enter the liver. Then, inflammatory mediators produced by the liver spread to the lungs, activate alveolar macrophages, release monocyte chemoattractant protein-1, platelet-activating factor, and reactive oxygen species (ROS), causing lung parenchyma injury[4]. However, previous research has mainly focused on the influence of macrophages on remote organ injury of AP. Few studies have been conducted on the intrinsic macrophages of the pancreas, and a majority of them have focused on the changes of the AP phenotype. Furthermore, there is lack of research on the potential molecular biological mechanisms causing the phenotypic changes.

Previous studies have established that exosomes, as a form of extracellular vesicles, are involved in the pathophysiological process of various diseases and playing a biological regulatory role[5]. Bonjoch *et al*[6] demonstrated that in the rat model of AP, plasma exosomes can effectively activate alveolar macrophages, promote M1 polarization, and secrete a large number of proinflammatory factors such as interleukin (IL)-1β and IL-6 that participate in AP-related acute lung injury (ALI)[6]. In addition, studies by Jiménez-Alesanco *et al*[7] also found that upregulation of miR-155 and decreased expression of miR-21 and miR-122 in plasma-derived exosomes can activate M1-type polarization and promote the release of inflammatory factors, thereby aggravating the progression of AP[7]. This suggests that in the course

of the pathogenesis of AP, exosomes derived from acinar cells may participate in the regulation of local pancreatic inflammatory injury, macrophage activation, and extra-pancreatic organ injury *via* their intrinsic proinflammatory miRNAs.

Additionally, miR-125b-5p is a bidirectional regulatory miRNA, which has been found to have low expression in bladder cancer and high expression in stage I lung cancer[8-10]. Therefore, researchers speculate that it can be used as a potential means of diagnosis and treatment in the future. At present, miR-125b-5p inhibits the proliferation and migration of bladder tumor cells by inhibiting the *HK2* gene, suggesting that it can exhibit anti-tumor activity[10]. Additionally, miR-125b-5p can promote cardiomyocyte self-remodeling after ischemia by improving cardiomyocyte apoptosis[11]. Previous studies have shown that miR-125b-5p is highly expressed in exosomes secreted by acinar cells, proposing that it might play a role in the pathogenesis of AP[12]. Therefore, miRNAs may play a biological regulatory role in local pancreatic inflammatory injury, macrophage activation, and extra-pancreatic organ injury in the course of AP through a certain mechanism. However, exosome-derived miR-125b-5p in AP has not been reported.

Therefore, we aimed to elucidate the molecular mechanism of exosome-derived miR-125b-5p promoting AP exacerbation from the perspective of the interaction between immune cells and acinar cells.

MATERIALS AND METHODS

Cell cultures

AR42J and RAW264.7 cell lines were purchased from the Shanghai Institutes for Biological Science (Shanghai, China). The AR42J and RAW264.7 cell lines were cultured in RPIM-1640 and DMEM high glucose media, respectively. Ten percent fetal bovine serum and 1% penicillin/streptomycin double antibody solution were added to the medium. The cells were cultured in a 37 ℃, 5% CO_2 incubator to promote stable cell growth.

Isolation and purification of acinous cell AR42J exosomes

Culture medium was collected when AR42J cells reached 70%–80% confluency in the culture dish. The collected culture medium was centrifuged at 2000 × *g* with a centrifugation radius of 11 cm for 30 min, thereby removing cell debris and apoptotic bodies. The supernatant was retained and 0.5 volume of exosome isolation reagent (Invitrogen, CA) was added, and the samples were incubated at 4 ℃ overnight. The samples were centrifuged at 10000 × *g* and 4 ℃ at with a radius of 11 cm for 60 min, and the supernatant was discarded. The samples were resuspended in PBS and stored in separate package at –80 ℃. According to the operation instructions, the particle size distribution and concentration of AR42J exosomes were measured using a Zeta View instrument.

Transmission electron microscope experiment

Transmission electron microscope was used to observe the morphology of exosomes and determine damage of the exosome membrane during the extraction process. Exosomes were fixed and purified with 2% paraformaldehyde (Electron Microscopy Science, United States). Then, the fixed exosomes were dropped onto a carbon-coated copper grid and fixed with 2% paraformaldehyde for 30 s. Finally, the carbon-coated copper grid was examined using transmission electron microscope (JEM-1400 plus, Japan).

Transient transfection

AR42J cells were cultured to approximately 50% in 6-well plates, and the medium was changed into serum-free medium. Exosomes were isolated from the culture medium supernatant and resuspended in 500 mL of sterile 1 × PBS for precipitation. miR-125b-5p mimic and negative control mimic were transferred into exosomes by Exo-Fect™ Exosome Transfection Reagent (System Biosciences, United States). First, a 150-mL transfection reaction system was configured, which included 10 mL Exo-Fect solution, 20 pmol miRNA, 70 mL sterile 1 × PBS, and 50 mL purified exosomes. Second, the reaction system was placed on a shaker at 37 ℃ for 10 min, then 30 mL ExoQuick-TC was added and placed on ice for 30 min to terminate the reaction. Third, the samples were centrifuged at 13000–14000 rpm for 30 min. The supernatant was discarded, and the transfected exosome precipitates were resuspended in 300 mL of 1 × PBS. The transfected exosomes were added to the AR42J cell line, at least 150 mL of transfected exosomes should be added to each well, and cultured in 6-well plates to approximately 1 × 10^5 cells.

Quantitative real-time polymerase chain reaction

The RNAprep Prue Cell/Bacteria Kit and miRelute miRNA isolation kit (TIANGEN, China) were used for the extraction of total RNA and miRNA from AR42J cells and pancreatic tissue according to the protocol. The FastKing RT Kit and miRcute Plus miRNA First-strand cDNA Synthesis Kit (TIANGEN,

China) were used to reverse transcribe RNA to cDNA. The LightCycler 480 system (Roche Molecular Diagnostics, Pleasanton, United States) was used to perform quantitative real-time polymerase chain reaction (RT-qPCR). The expression of miRNA and mRNA was evaluated by the $2^{-\Delta\Delta Ct}$ method and normalized to GAPDH or U6, respectively.

Cell counting Kit-8 for detecting cell viability

The density of AR42J cells was adjusted to 3×10^3 cells/mL, and the cell suspension was seeded in 96-well plates with 100 mL per well in six replicates. The cells were cultured in a 37 ℃, 5% CO_2 incubator to promote stable cell growth. The experiment was divided into four groups: Control group, exosome-only group, negative control (NC)-exo group, and 125-exo group. At 0, 4, 6, 8, 10, 12, and 24 h after cell adhesion, liquid was removed per well. Ten microliters of RPPI-1640 medium with 10% CCK-8 reagent was added to 100 mL per well, and the 96-well plates were incubated for 1–2 h. Then, the absorbance at 450 nm was measured by using a microplate reader to calculate the cell survival rate.

Flow cytometry and cell apoptosis

Cells were seeded on 6-well plates at a concentration of 1×10^6 cells/per well and treated with NC-exo or 125-exo for 8 h. Subsequently, cells were digested and collected, and the supernatant was discarded. Cells were washed once with pre-cooled PBS, digested with 0.25% trypsin, centrifuged at 500 × *g* for 5 min, then resuspended in 400 mL of 1 × binding buffer. A cell cycle staining kit (Yeasen, China, Cat No. 4040301) was used to detect the cell cycle. Cycle apoptosis was detected by Annexin V-APC/7-AAD apoptosis detection kit (Nanjing KeyGen Biotech, China). The percentage of cell cycles and cell apoptosis was evaluated by Guava easyCyte HT system (Millipore). The experiment was repeated in triplicate.

Enzyme linked immunosorbent assay

The contents of tumor necrosis factor-alpha (TNF-α), IL-6, and C-reactive protein (CRP) in the supernatant of the different groups were detected by enzyme linked immunosorbent assay (ELISA) kits (R&D Systems, MN, United States). The standard and sample were diluted in proportion, and an appropriate amount of each was added to the corresponding reaction well and incubated for 2 h at 25 ℃. The liquid in the reaction well was discarded, and washing solution was added and rinsed repeatedly, and then blot dried. Enzyme-labeled antibodies corresponding to TNF-α, IL-6, and CRP were added respectively, and the plates were incubated again for 2 h at 25 ℃. The liquid was removed, and wells rinsed with the washing solution three times. The reaction substrate was added to each well, and the reaction was kept out of light for 30 min and then stopped by addition of the termination solution. The optical density value was measured by a microplate reader, and the standard curve was drawn to calculate the effective concentration of each inflammatory factor.

Western blotting

To lyse the cells and pancreatic tissue, RIPA lysis buffer (Beyotime Biotechnology, Jiangsu, China) was used. This solution contains a protease inhibitor cocktail (Roche, United States). To detect the protein amount present in the lysates, Bradford reagent (Sigma, United States) was used, then 30 μg of protein per row was run on 10% SDS-PAGE gels and immunoblotted onto a 0.22 m polyvinylidene fluoride membrane (Merck Millipore, Darmstadt, Germany). The membranes were incubated for 1 h with 5% non-fat milk solution (BD Biosciences, United States) dissolved in TBST. After adding primary antibodies against CD9 (Abcam, Cambridge, United Kingdom), CD81 (Abcam, Cambridge, United Kingdom), CD63 (Abcam, Cambridge, United Kingdom), TSG101 (Protein Tech Group, IL, United States), CD206 (Protein Tech Group, IL, United States), inducible nitric oxide synthase (iNOS) (Abcam, Cambridge, United Kingdom), insulin-like growth factor 2 (IGF2) (Protein Tech Group, IL, United States), Bax (Protein Tech Group, IL, United States), Bcl-2 (Protein Tech Group, IL, United States), HMGB1 (Protein Tech Group, IL, United States), PI3K (Protein Tech Group, IL, United States), p-PI3K (Protein Tech Group, IL, United States), AKT (Protein Tech Group, IL, United States), p-AKT (Protein Tech Group, IL, United States), β-tubulin (Protein Tech Group, IL, United States), β-actin (Protein Tech Group, IL, United States), and GAPDH (Abcam, ab8245, 1:1000), the membrane was incubated at 4 ℃ overnight. The secondary antibody specific to primary antibody was then added. An Odessey CLx system showed the presence of protein bands (LI-GOR, United States).

RNA sequencing assay

RNA sequencing assay (RNA-seq) was performed by a service provider (HWayen Biotechnologies Company, Shanghai, China). Total RNA from AP model cells and normal cells was extracted using TRIzol reagent (Sigma-Aldrich, MO, United States) and quantified with a NanoDrop ND-2000 (Thermo Fisher Scientific, Inc., MA, United States). RNA integrity was evaluated by an Agilent Bioanalyzer 2100 (Agilent Technologies, CA, United States). A TruSeq RNA Sample Prep Kit v2 (Illumina Inc, CA, United States) was used to generate RNA-seq cDNA libraries. The workflow of sample preparation included isolation of polyadenylated RNA, RNA fragmentation, synthesis of cDNA, ligation of barcoded adapters, and PCR amplification. After the DNA size and purity of the cDNA library were checked and

qualified, clusters of cDNA libraries were generated and sequenced on the Illumina platform at Shanghai HWayen Biotechnologies Company (Shanghai, China). The raw sequencing reads were processed by removing failed reads, low-quality reads, and those with joint contamination, finally retaining only the high-quality read results. The raw reads of each sample were mapped to the rat reference genome to generate the RNA-seq data.

Differentially expressed genes analysis

Differentially expressed genes screened by RNA-seq were identified, for which, $P < 0.05$ was considered statistically significant. In order to further clarify the function of differentially expressed RNAs, Kyoto Encyclopedia of Genes and Genomes databases (KEGG, http://www.genome.jp/kegg) was used for enrichment and screening of related signaling pathways.

Luciferase activity assays

The 3¢-untranslated regions (UTR) of IGF2 constructs containing the predicted miR-125b-5p seed-matching sites from the cDNA library was amplified by PCR, then cloned into pmiR-RB-ReportTM-3'-UTR [wild type and mutant (MUT) type] and 50 nM miR-125b-5p mimics, 100 nM miR-125b-5p inhibitor, and negative control miRNA (Ribobio, Guangzhou, China) using Lipofectamine 3000 (Invitrogen, United States) according to the manufacturer's protocol. After 48 h, cells were lysed with a dual luciferase assay kit (Ribobio, Guangzhou, China), and luciferase activities were calculated and normalized to the control.

AP animal model analysis

All experimental procedures and feeding management methods involving animals were reviewed and approved by the ethics committee of XuanWu Hospital, Capital Medical University (No. 2020-158). The international guidelines for the use and management of experimental animals were strictly followed. Wistar rats were purchased at least 1 wk prior to the experiment to fully adapt to the environment (23 ℃, 50% humidity, 12 h/12 h light/dark, ad libitum food and water), and they were starved, with access to only water, 12 h prior to AP modeling. Anesthesia was induced by intraperitoneal injection of pentobarbital sodium solution (40 mg/kg). The AP model was induced by retrograde injection of 3.5% sodium taurocholate solution (0.15 mL/100 g) into the biliopancreatic duct. The rats were sacrificed 24 h after the establishment of the AP model. The blood samples were centrifuged at 876 × *g* for 15 min at 4 ℃, and the upper serum was stored at –80 ℃. Some pancreatic tissues were washed with saline and frozen in liquid nitrogen for tissue protein extraction. The remaining pancreatic tissues were fixed in 4% paraformaldehyde and embedded in paraffin after 48 h for hematoxylin and eosin staining and immunohistochemical staining.

Immunohistochemistry

The pancreatic tissue samples of rats were processed for immunohistochemical analysis. Pancreatic tissue was fixed in 10% formalin solution. Then, tissue paraffin was embedded. The embedded tissue wax blocks were cut into 5–8 μm slices and attached to glass slides and baked in an oven at 67 ℃ for 48 h. The tissue sections were dewaxed and rehydrated. The endogenous peroxidase activity was blocked by adding methanol containing 3% H_2O_2 and soaked for 15 min, and antigen repair. The primary antibody was diluted with antibody diluent at a ratio of 1:100 and dropped on the slide at 4 ℃ overnight. Then, approximately 100 μL of the working solution of the secondary antibody was added and incubated for 15 min at 25 ℃. Finally, DAB color development, hematoxylin counterstained and dehydrated and transparent were performed.

Immunohistochemical analysis and imaging software were used to determine and analyze the range and intensity of immunohistochemical staining. When the number of positive cells was 0%, it was marked as 0; marked as 1 at less than 25%; marked as 2 at 25%–50%; marked as 3 at 50%–75%; and marked as 4 at 75%–100%. When the intensity of staining was weakly positive, it was marked as 1; marked as 2 at moderately positive; and marked as 3 at intensity positive. The final immune score was the product of the staining intensity value and the positive cell range value (range 0–12 points).

Statistical analysis

GraphPad Prism 8.0 software (Graph Pad Software, La Jolla, CA, United States) was used for statistical analysis, each experiment was repeated at least three times, and data were calculated as mean ± SD. Measurement data were analyzed by the student's *t* test or one-way analysis of variance. Linear correlation was used to analyze the expression correlation between miR-125b-5p and IGF2. $P < 0.05$ was considered statistically significant.

RESULTS

Extraction and identification of exosomes from AR42J cells in activated and inactive states

Exosomes were isolated and extracted from the supernatant of the AR42J cell line in non-activated and activated states, respectively (Figure 1A and B). Transmission electron microscopy was used to observe the exosomes in two different states, which both had a typical "dish" shape. Particle size analysis showed that the diameter of AR42J exosomes in the inactive state ranged from 68.3 to 181.9 nm, with an average of 121.4 nm, and the concentration of exosomes was 3.3×2^{10} particles/mL. In the activated state, the diameter of AR42J exosomes ranged from 82.1 to 197.5 nm, with an average of 132.8 nm, and the concentration of exosomes was 6.23×2^{10} particles/mL (Figure 1C and D). Western blotting confirmed the expression of exosome markers, including CD9, CD81, and TSG101 (Figure 1E).

Differentially expressed miRNAs in AR42J cell lines between non-activated and activated states were screened

To further identify miRNAs differentially expressed in AR42J cell lines between activated and inactive states, RNA-seq was used for screening. Among them, miR-125b-5p, miR-27b-3p, miR-195-5p, miR-27a-3p, miR-106b-5p and miR-183-5p were all the differentially expressed miRNAs screened using RNA-seq. miRDB, miRWalk, and Targetscan data were used to predict their downstream binding target genes (Figure 2A). Further research revealed that miR-125b-5p was upregulated in the activated state and downregulated in the non-activated state (Figure 2B). KEGG pathway analysis showed that the differentially regulated RNAs mainly functioned in signal transduction. Furthermore, these results showed that the IGF2-PI3K/AKT signaling pathway may be the signaling pathway of miR-125b-5p which promotes the exacerbation of AP (Figure 2C).

Expression of miR-125b-5p and IGF2 in vitro and vivo AP models

In order to determine whether miR-125b-5p is involved in the regulation of inflammatory progression of AP, the expression of miR-125b-5p and IGF2 in activated and inactivated AR42J cell lines was analyzed using RT-qPCR. Compared with the inactive AR42J cell line, miR-125b-5p expression was significantly increased in the activated AR42J cells, but IGF2 expression was significantly decreased (Figure 3A–C). Meanwhile, RT-qPCR was used to analyze the expression of miR-125b-5p and IGF2 of pancreatic tissue of normal and AP rat models. The experimental results showed that the expression of miR-125b-5p was increased in pancreatitis tissues, while that of IGF2 was decreased (Figure 3D and E). Statistical analysis showed that miR-125b-5p was negatively correlated with IGF2 protein expression ($r = -0.913$; $P = 0.008$) (Figure 3F and G). Consequently, above results revealed that miR-125b-5p was upregulated and IGF2 was downregulated in AP *in vitro* and *in vivo* experiments.

Establishment of exosomes overexpression miR-125b-5p transfection system

Exosomes transfected with miR-125-5p mimic and negative control miRNA (mimic NC) were added to AR42J cells in order to evaluate the endocytosis efficiency of exosomes transporting miR-125b-5p into AR42J cells. AR42J cells containing miR-125b-5p mimic were detected by RT-qPCR (Figure 4A). Compared with mimic NC, the expression of miR-125b-5p was significantly increased in AR42J cells treated with the miR-125b-5p mimic, indicating that the expression of miR-125b-5p was increased in AR42J cells and achieved through the exosomal transport of AR42J.

To further clarify whether the above changes in miR-125b-5p were achieved through exosomal transport, Texas red-labeled siRNA was transfected into exosomes as the positive control group of the experiment. After 24 h of cell culture, Texas-red labeled siRNA can be seen in the cytoplasm of AR42J cells under an immunofluorescence microscope (Figure 4B). Therefore, the above experiments confirmed that exosomes derived from the AR42J cell line could effectively deliver miR-125b-5p to AR42J cells *in vitro*.

Exosomes transport miR-125b-5p to promote the necrosis and apoptosis of AR42J cells in the activated state

To further explore the function and effect of miR-125b-5p on the AP cell model, the CCK-8 assay was used to evaluate the effect of miR-125b-5p on the viability of AR42J cells in the activated state. The results showed that compared with the PBS group, the exosome group overexpressing miR-125b-5p promoted the necrosis of AR42J cells in the activated state. After 8 h, the cell absorbance value of exosome group overexpressing miR-125b-5p was significantly lower than that of PBS group (PBS group: 1.705 ± 0.120 *vs* miR-125b-5p mimic group: 0.975 ± 0.064, $t = 7.59$, $P = 0.016$) (Figure 5A).

The cell cycle and apoptosis were analyzed by flow cytometry, and the results showed that the proportion of G0/G1 in the overexpression miR-125b-5p group was higher than that in the NC group. In addition, the percentage of cells in G0/G1 phase of the cell cycle decreased from 60.37 ± 1.7% (miR-125b-5p overexpression group) to 51.25 ± 1.4% (NC group) (Figure 5B). Compared with the NC group, the apoptosis of AR42J cell line treated with miR-125b-5p overexpression group was significantly increased in the activated state (Figure 5C).

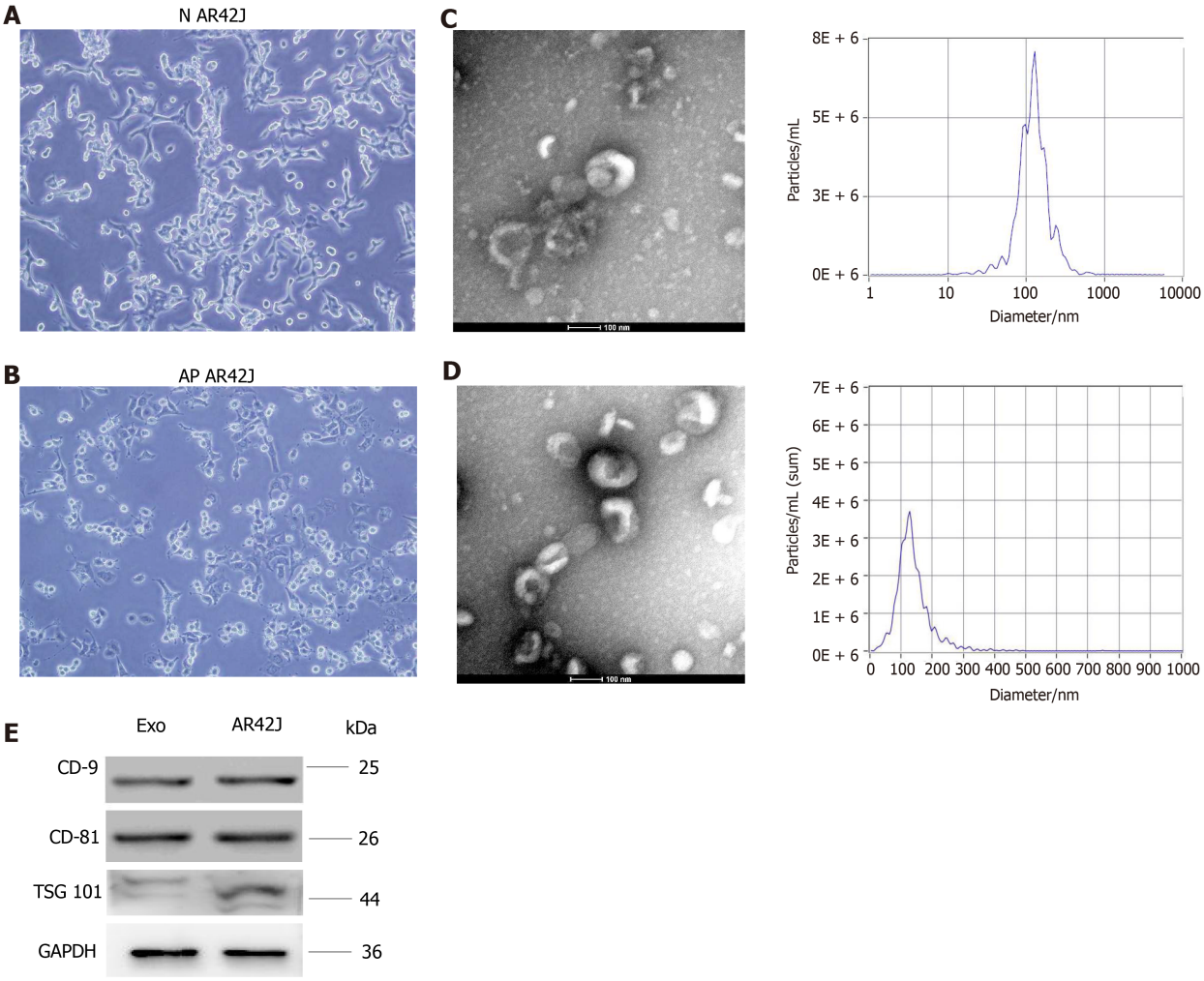

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Figure 1 Isolation and characteristics of exosomes derived from normal acinous cell AR42J and active AR42J. A: Morphology of AR42J cell line in the inactive state; B: Morphology of AR42J cell line in the activated state; C: Non-activated AR42J exosome morphology shown by transmission electron microscope (TEM) at 100nm scale. The diameter of exosomes derived from AR42J in the inactive state ranged from 68.3–181.9 nm, with an average of 121.4 nm, and the concentration of exosomes was 3.3 × 2^{10} particles /mL; D: Morphology of AR42J exosomes in activated state as shown by TEM at 100 nm scale. The diameter of exosomes derived from AR42J in the activated state ranged from 82.1–197.5 nm, with an average of 132.8 nm, and the concentration of exosomes was 6.23 × 2^{10} particles /mL; E: The positive expression of exosome marker, which include CD9, CD81 and TSG101, was confirmed by Western blot. AP: Acute pancreatitis; N: Normal.

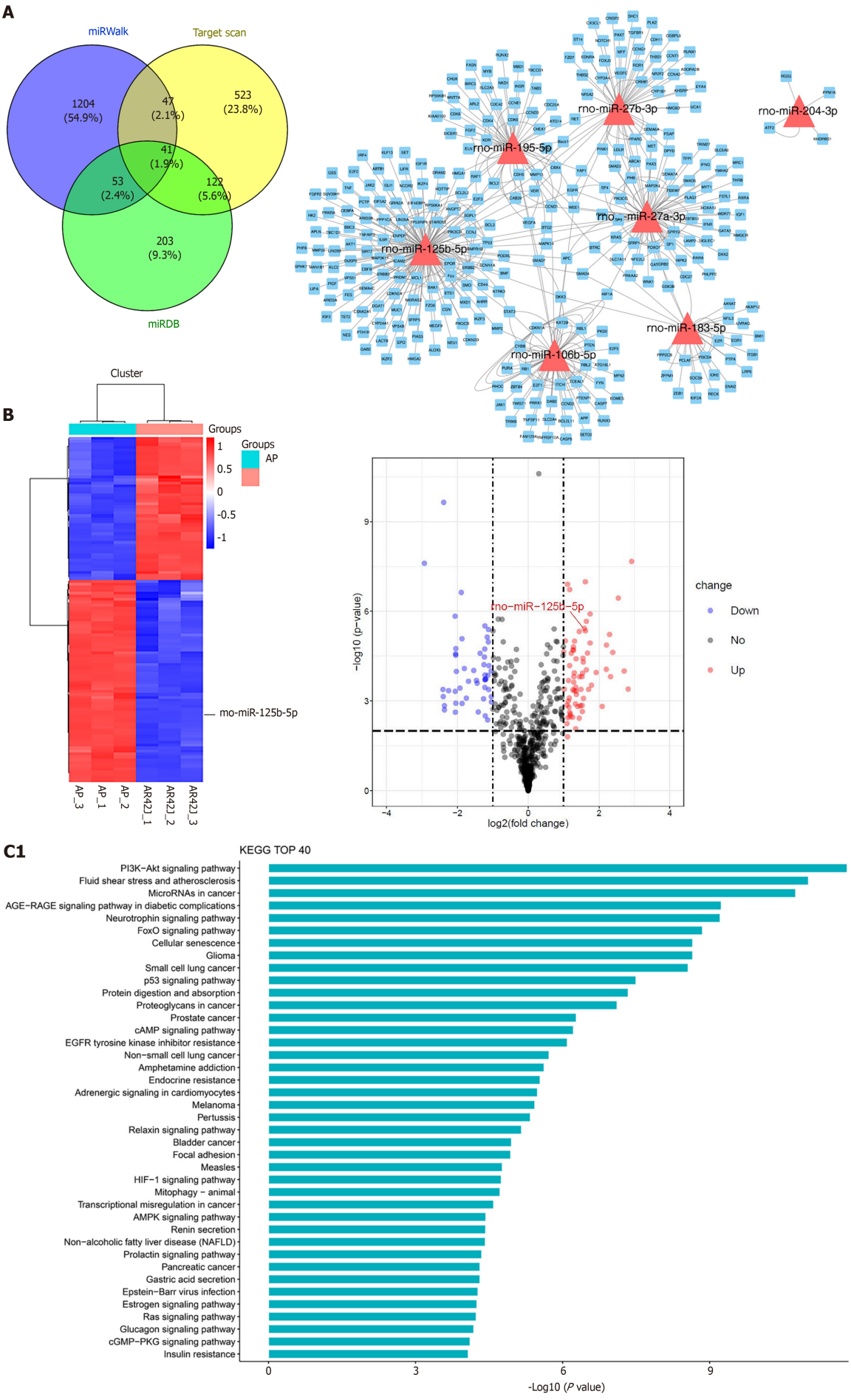
Meanwhile, western blot showed that overexpression of miR-125b-5p reduced the expression of IGF2 protein in activated AR42J cells (Figure 5D). The expression of apoptosis-related gene, BAX, increased, while the expression of apoptosis-related gene Bcl-2 decreased. In addition, the expression of the necrosis-related gene, HMGB-1, showed an upward trend (Figure 5E). Therefore, based on the above experiments, miR-125b-5p can promote the death of activated AR42J cells by inducing cell cycle arrest and apoptosis.

Exosomes that transport miR-125b-5p promote the inflammatory injury of AR42J cells in activated state

The corresponding ELISA kits were used to detect the inflammatory factors IL-6, TNF-α, and CRP in AR42J cells treated with overexpressing miR-125b-5p exosomes in the activated state. Compared with the AP group, the levels of IL-6 (158.86 ± 1.49 pg/mL *vs* 171.286 ± 2.36 pg/mL, P = 0.0076), TNF-α (105.86 ± 9.33 pg/mL *vs* 134.38 ± 8.98 pg/mL, P = 0.0106), and CRP (83.1 ± 8.32 pg/mL *vs* 129.04 ± 15.16 pg/mL, P = 0.024) in the miR-125b-5p overexpression group were increased, which confirmed that miR-125b-5p can promote cellular inflammatory injury (Figure 6).

miR-125b-5p promotes AP exacerbation by inhibiting IGF2 protein expression in the PI3K/AKT signaling pathway

According to the analysis of miRDB, miRWalk, and Targetscan databases, IGF2 may be a potential


A
miRWalk
Target scan
miRDB
1204 (54.9%)
47 (2.1%)
523 (23.8%)
41 (1.9%)
53 (2.4%)
122 (5.6%)
203 (9.3%)
rno-miR-27b-3p
rno-miR-204-3p
rno-miR-195-5p
rno-miR-27a-3p
rno-miR-125b-5p
rno-miR-183-5p
rno-miR-106b-5p
B
Cluster
Groups
Groups
AP
1
0.5
0
-0.5
-1
mo-miR-125b-5p
AP_3
AP_1
AP_2
AR42J_1
AR42J_2
AR42J_3
rno-miR-125b-5p
change
Down
No
Up
−log10 (p-value)
log2(fold change)
C1
KEGG TOP 40
PI3K−Akt signaling pathway
Fluid shear stress and atherosclerosis
MicroRNAs in cancer
AGE−RAGE signaling pathway in diabetic complications
Neurotrophin signaling pathway
FoxO signaling pathway
Cellular senescence
Glioma
Small cell lung cancer
p53 signaling pathway
Protein digestion and absorption
Proteoglycans in cancer
Prostate cancer
cAMP signaling pathway
EGFR tyrosine kinase inhibitor resistance
Non−small cell lung cancer
Amphetamine addiction
Endocrine resistance
Adrenergic signaling in cardiomyocytes
Melanoma
Pertussis
Relaxin signaling pathway
Bladder cancer
Focal adhesion
Measles
HIF−1 signaling pathway
Mitophagy − animal
Transcriptional misregulation in cancer
AMPK signaling pathway
Renin secretion
Non−alcoholic fatty liver disease (NAFLD)
Prolactin signaling pathway
Pancreatic cancer
Gastric acid secretion
Epstein−Barr virus infection
Estrogen signaling pathway
Ras signaling pathway
Glucagon signaling pathway
cGMP−PKG signaling pathway
Insulin resistance
-Log10 (P value)

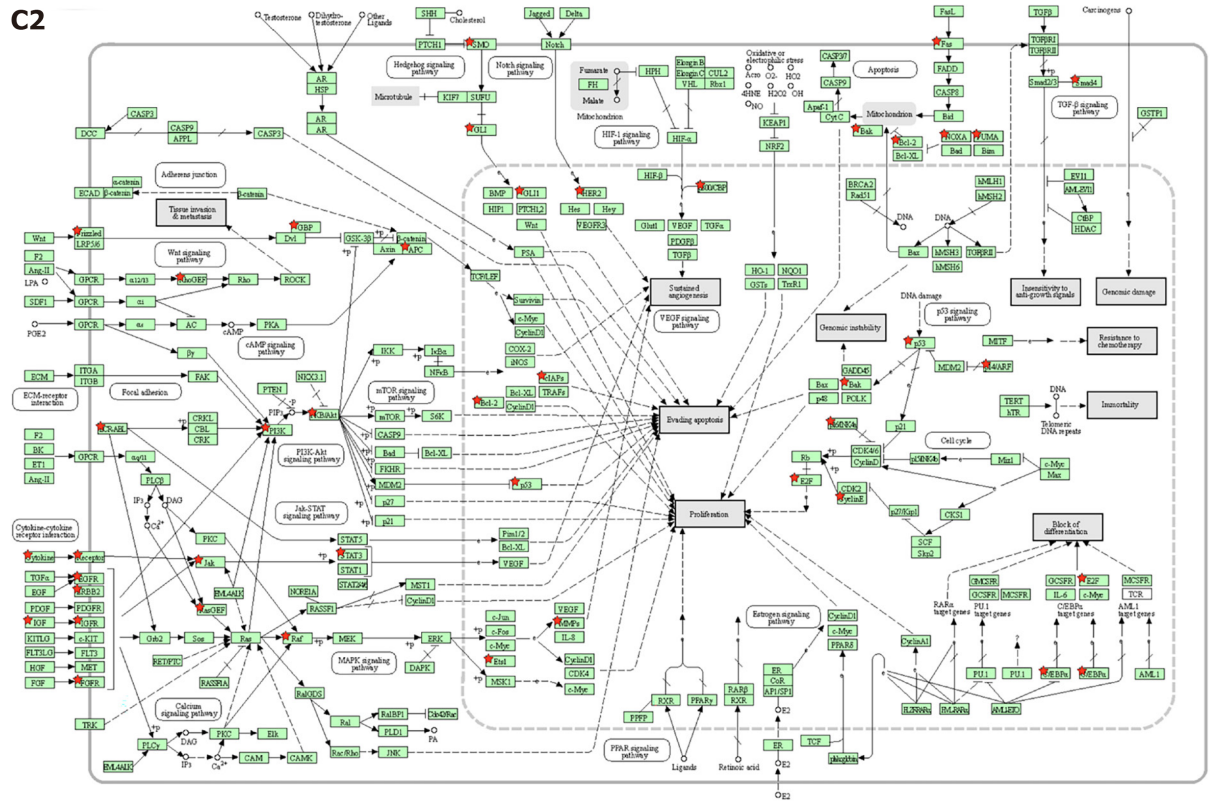


Figure 2 Differentially expressed miRNAs in AR42J cell lines between non-activated and activated states were screened. A: RNA-seq was used to screen differentially expressed miRNAs. miRDB, miRWalk and Targetscan data were used to predict downstream binding target genes; B: The heat map and Volcano plot revealed that miR-125b-5p was up-regulated in activated state and down-regulated in non-activated state; C: The Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis was performed on target genes of differentially expressed miR-125b-5p, and KEGG top 40 signaling pathways were enriched. Among them, PI3K/AKT signaling pathway may be the signaling pathway of miR-125b-5p. AP: Acute pancreatitis.

target of miR-125b-5p. Among them, the 3¢-UTR of IGF2 had highly conserved binding sites at positions 1627–635 and 1844–1852 (Figure 7A). In addition, miRNAs were co-transfected by vectors containing wild-type (WT) or MUT IGF2 3¢-UTR fusion luciferase as well as miR-125b-5p mimics or negative controls. Dual luciferase assay showed that overexpression of miR-125b-5p could reduce WT luciferase activity in AR42J cells. However, the MUT IGF2 3¢-UTR completely restored luciferase activity (Figure 7B). Western blot analysis confirmed that compared with the AP group, the overexpression of miR125b-5p promoted the phosphorylation and activation of PI3K/AKT signaling pathway, thus promoting the aggravation of inflammatory responses (Figure 7C).

Overexpression of miR-125b-5p promoted M1-type polarization of macrophages and the release of inflammatory factors

RAW264.7 cells containing miR-125b-5p mimic were detected by RT-qPCR. Compared with mimic NC, the expression of miR-125b-5p was significantly increased in RAW264.7 cells treated with miR-125b-5p mimic, which confirmed the increased expression of miR-125b-5p in RAW264.7 cells (Figure 8A).

In order to further explore the effect of miR-125b-5p on macrophage polarization, we added exosomes containing overexpressed miR-125b-5p to the RAW264.7 cell line stimulated by IL-4, and then determined the polarization of macrophages through *in vitro* experiments. Among them, the surface marker of M1 macrophages was iNOS, and the surface marker of M2 macrophage was CD206. It was found that overexpression of miR-125b-5p could inhibit M2 type polarization and promote M1 type polarization of macrophages compared with the control group [(11.67 ± 4.49) *vs* (54.33 ± 5.73), t = 8.280, P = 0.0012)] (Figure 8B–D).

Western blots showed that compared with the NC group, the expression of iNOS was upregulated and the expression of CD206 was downregulated in the overexpression group, which further confirmed that miR-125b-5p could promote M1 polarization and inhibit M2 polarization of macrophages (Figure 8E).

ELISA kits were used to detect IL-6 and CRP inflammatory factors in the RAW264.7 cell line which was treated with overexpressed miR-125b-5p exosomes. Compared with the mimic-NC group, the level of IL-6 (99.106 ± 13.29 pg/mL *vs* 142.778 ± 13.58 pg/mL, P = 0.0314) and CRP (120.181 ± 20.41 pg/mL *vs* 180.557 ± 15.98 pg/mL, P = 0.0301) were increased in the miR-125b-5p overexpression group, which

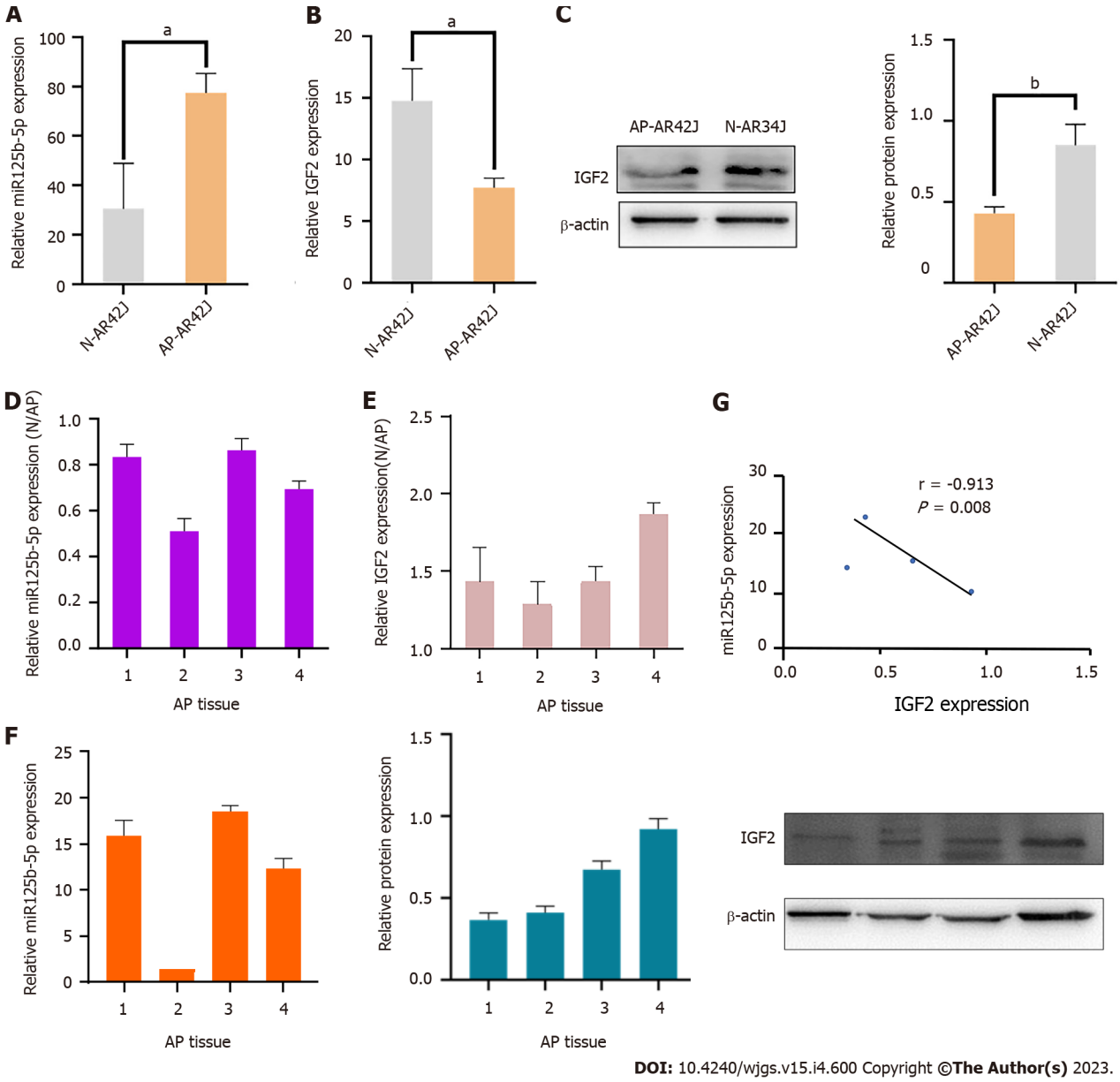


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Figure 3 Expression of miR-125b-5p and insulin-like growth factor 2 *in vitro* and *in vivo*. A: Quantitative real-time polymerase chain reaction (RT-qPCR) was used to detect the expression of miR-125b-5p in AR42J cell lines in activated and inactive state; B: RT-qPCR was used to detect the expression of insulin-like growth factor 2 (IGF2) in AR42J cell lines under activated and inactive state; C: Western blot was used to detect the expression level of IGF2, and β-actin was used as the internal reference; D: RT-qPCR was used to detect the expression of miR-125b-5p in normal pancreatic tissues and pancreatitis tissues; E: RT-qPCR was used to detect the expression of IGF2 in normal pancreatic tissues and pancreatitis tissues; F: The mRNA and protein expression of miR-125b-5p and IGF2 in 4 cases of pancreatitis tissues were detected by RT-qPCR and Western blot. Among them, sample 2 was used as the standard to calculate the fold change of miR-125b-5p expression in other samples by comparing the miR-125b-5p/U6 ratio in sample 2. Western blot was used to detect the expression level of IGF2, and β-actin was used as the internal reference. The experiment was repeated three times and is expressed as mean ± SD; G: miR-125b-5p was negatively correlated with IGF2 protein expression level, $^{a}P < 0.05$, $^{b}P < 0.005$. AP: Acute pancreatitis; IGF2: Insulin-like growth factor 2; N: Normal.

confirmed that miR-125b-5p could promote the release of inflammatory factors from macrophages (Figure 8F). Meanwhile, compared with the mimic-NC group, overexpression of miR-125b-5p exosomes can promote the ROS production in the RAW264.7 cell line (55.964 ± 5.03 *vs* 86.375 ± 10.76, $P = 0.0224$), thereby improving the level of cellular oxidative stress (Figure 8G).

Overexpression of miR-125b-5p promotes PI3K/AKT signaling pathway phosphorylation and inflammatory response

The experiments were divided into three group, which included NC group (RAW264.7 cell line treated with IL-4 for 24 h), mimic group (exosomes overexpressing miR-125b-5p were added to RAW264.7 cell line treated with IL-4) and mimic-NC group (mimic-NC exosomes were added to RAW264.7 cell line treated with IL-4). It was found that compared with the NC group, overexpression of miR-125b-5p could activate the PI3K/AKT signaling pathway, which further aggravated the inflammatory response

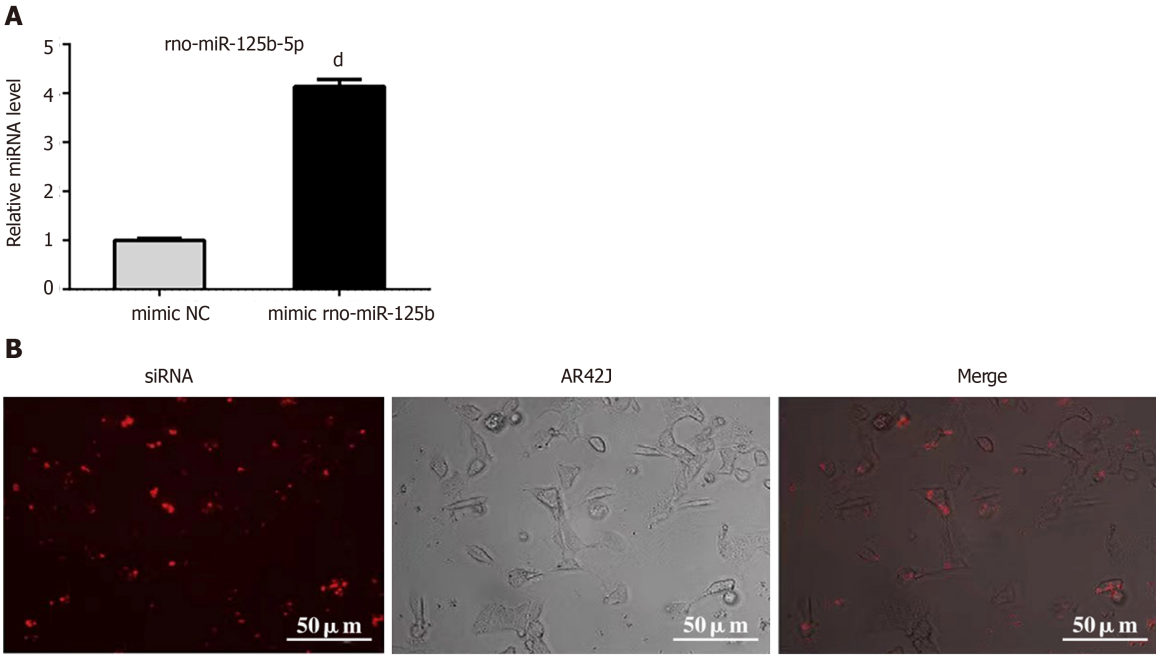

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Figure 4 Establishment of exosome overexpression miR-125b-5p transfection system. A: The expression of miR-125b-5p was significantly increased in AR42J cells treated with miR-125b-5p mimic; B: Fluorescently-labeled siRNA was observed in the cytoplasm of the AR42J cell line. Data are representative of three independent experiments and presented as the mean ± SD of the mean, $^{d}P < 0.0001$. NC: Negative control.

(Figure 9).

Exosomes transport miR125b-5p to promote the aggravation of inflammation in vivo

To further investigate whether miR-125b-5p could promote the aggravation of AP *in vivo*, the AP model was induced by retrograde and slow injection of 3.5% sodium taucholate solution (0.15 mL/100 g) into the biliopanatic duct. The experiment was divided into sham group, AP group, and miR-125b-5p overexpression group (EXO group), with 5 rats in each group. In the sham group, the rats were operated on the abdomen without other drugs. In the AP group, normal saline was injected into Wistar rats *via* the tail vein. In the overexpression group, exosomes overexpressing miR-125b-5p were injected into Wistar rat *via* the tail vein. After 24 h, the rats were sacrificed, and the changes of inflammatory indices in the three groups were observed. The results showed that compared with the AP group, calcium foci were observed in the abdominal cavity of rats in the overexpression group, and the amount of ascites was significantly increased (1.63 ± 0.261 mL *vs* 2.56 ± 0.249 mL, $P = 0.0131$). Meanwhile, the expression of miR-125b-5p increased in AP and EXO group (Figure 10A and B). The levels of IL-6, TNF-α, CRP, and ROS in the serum of the three group were detected by ELISA. Compared with the AP group, the levels of IL-6 (195.86 ± 6.28 pg/mL *vs* 227.14 ± 2.54 pg/mL, $P = 0.0033$), TNF-α (159.19 ± 15.09 pg/mL *vs* 198.81 ± 9.35 pg/mL, $P = 0.0301$), CRP (164.52 ± 21.51 pg/mL *vs* 245.14 ± 15.83 pg/mL, $P = 0.0095$) inflammatory factors, and ROS (119.69 ± 15.59 *vs* 184 ± 18.83, $P = 0.0181$) were increased in the miR-125b-5p overexpression group (Figure 10C). Histopathology confirmed that compared with the AP group, the degree of pancreatic tissue edema and necrosis was severe in the miR-125b-5p overexpression group. The pathological score and dry/wet ratio of pancreatic tissue were 12.6 ± 1.2 ($P = 0.0021$) and 2.46 ± 0.07 ($P = 0.0019$), respectively (Figure 10D and E).

Western blot analysis showed that, compared with the AP group, the expression of BAX and HMGB-1 was increased, while the expression of Bcl-2 was decreased in the miR-125b-5p overexpression group (Figure 10F). In addition, the expression of IGF2 protein in the miR-125b-5p overexpression group was decreased, and the activation of PI3K/AKT signaling pathway was promoted (Figure 10G). Therefore, the above evidence indicates that miR-125b-5p can promote the aggravation of AP *in vivo*.

DISCUSSION

AP is a common digestive system disease, which seriously affects the short and long-term life quality and prognosis of patients[13]. Therefore, it is necessary to understand the pathogenesis of AP in order to finding the best treatment strategy. In the pathogenesis of AP, the inflammatory cascade caused by acinar cell injury and immune system activation is an important factor for the occurrence and

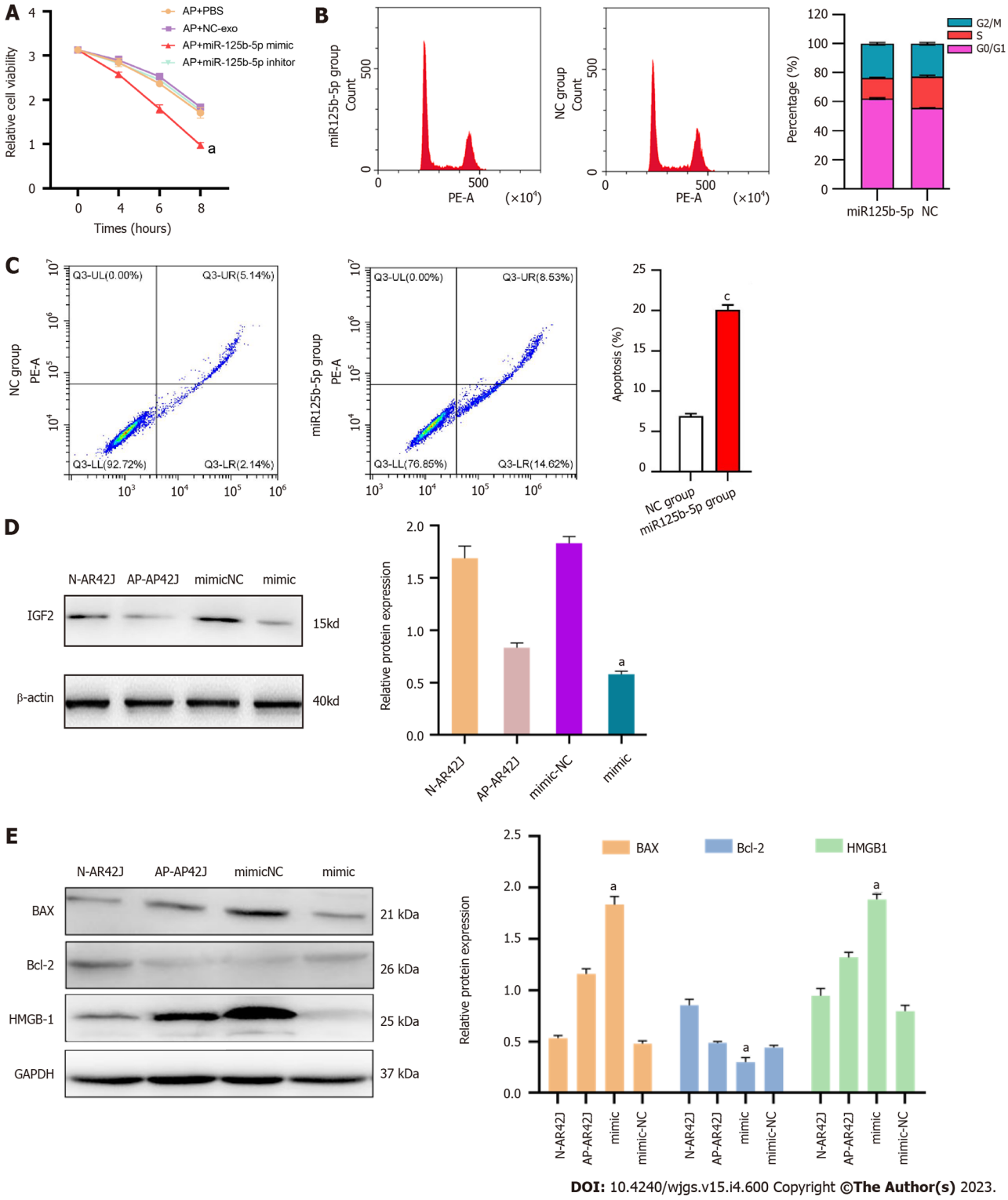

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Figure 5 miR-125b-5p overexpression could promote necrosis and apoptosis of AR42J cells in the activated state. A: miR-125b-5p overexpression promoted the necrosis of AR42J cells in the activated state; B: Flow cytometry analysis confirmed that the percentage of cells in G0/G1 phase increased in AR42J cells in the activated state treated with the miR-125b-5p overexpression group; C: The percentage of apoptotic cells increased as confirmed by flow cytometry; D and E: The expression of insulin-like growth factor 2, BAX, Bcl-2 and HMGB-1 was confirmed by Western blot, $^{a}P < 0.05$, $^{c}P < 0.0005$. AP: Acute pancreatitis; IGF2: Insulin-like growth factor 2; N: Normal; NC: Negative control.

progression of the disease. In recent years, exosomes, immune cells, and immune microenvironment changes are hot spots in the research direction of inflammatory immunity. In addition to participating in the regulation of AP acinar cell injury, exosomes may play a regulatory role in macrophage polarization [14]. However, this mechanism in AP is still unclear; furthermore, there is lack of research on pancreatic resident macrophages[15]. Therefore, the inflammation caused by AP acinar cell injury is combined with the imbalance of the immune microenvironment to explain the potential pathogenic mechanism of AP

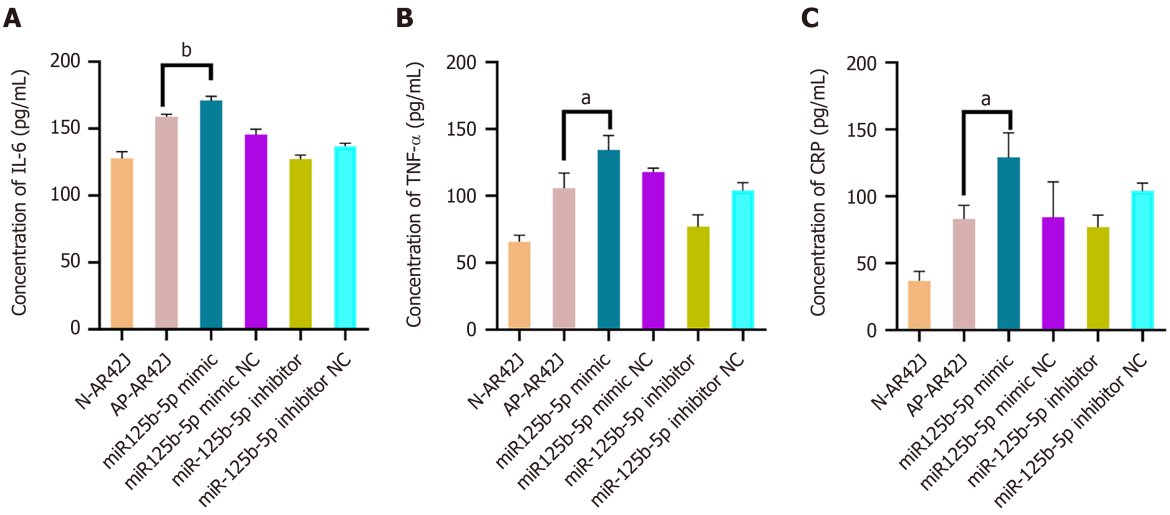

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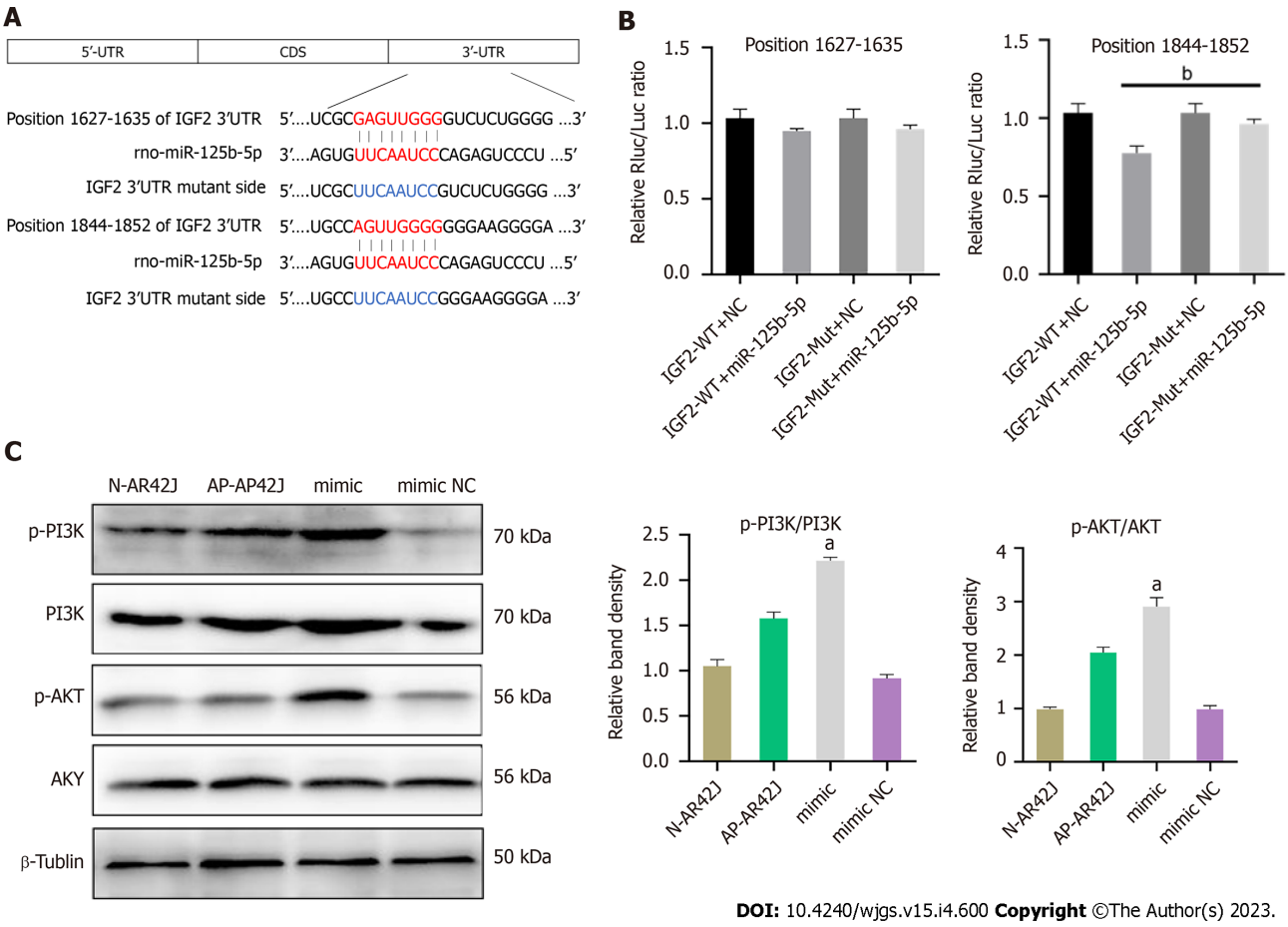
Figure 6 miR-125b-5p overexpression promotes inflammatory injury of AR42J cells in activated state. A: Interleukin-6 level was determined by enzyme linked immunosorbent assay (ELISA); B: Tumor necrosis factor-alpha level was determined by ELISA; C: C-reactive protein level was determined by ELISA, $^{a}P < 0.05$, $^{b}P < 0.005$. IL: Interleukin; TNF-α: Tumor necrosis factor-alpha; CRP: C-reactive protein.

evolution from the perspective of inflammatory immunity, which makes up for the limitation of existing research that only explores from a single perspective. This study establishes the connection between immune cells and pancreatic acinar cells, and reveals the characteristics of the pathogenesis from the perspective of immune cell and acinar cell interaction, which can better elucidate the molecular mechanism of miR-125b-5p promoting AP progression.

In recent years, exosomes have been proven to be an important biological information transmitter, participating in intercellular communication by transporting their internal active substances. Studies have shown that exosomes are closely related to the development of various inflammatory disease and are widely involved in the pathophysiological process of disease[16]. Some studies have also found that exosomes play a significant role in the process of macrophage activation, and the genetic material carried in them can play a biological regulatory role in macrophage activation[14]. In addition, macrophage activation also affects the development of AP to a certain extent, and its activation degree is also considered to be closely related to the severity of AP and the occurrence of local complications[15]. Some studies have found that plasma derived exosomes can effectively reach alveolar macrophages and promote the M1 type polarization of macrophages during AP, secrete a large amount of IL-1β, IL-6, CCL-2 and can also trigger NOD-like receptor protein 3-dependent pyrophosphorylation, release inflammatory factors, and jointly induce the occurrence of ALI[6,17]. However, exosomes derived from different cells may play different regulatory roles on inflammatory response. Studies have shown that exosomes derived from bone marrow mesenchymal stem cells promote the anti-inflammatory phenotype M1 polarization of macrophages by negatively regulating CysLT2R, thus achieving the effect of reducing brain injury[18]. Therefore, in order to exclude the influence of exosomes from different sources in the inflammatory response, this study selected exosomes from rat pancreatic exocrine cell line (AR42J cell line) and used their homology to better explain the influence of exosomes derived from pancreatic cells on the course of AP. In order to further explore how exosomes cause inflammatory injury, some scholars have found that in the rat model of AP, the expression of miR-155 in plasma-derived exosomes is up-regulated, while the expression of miR-21 and miR-122 is down regulated, which can activate pancreatic and alveolar macrophages M1-type polarization to release inflammatory factors that promote the progression of AP[7]. Therefore, we believe that miRNAs in exosomes may act as intercellular communication mediators and play a regulatory role in local pancreatic inflammatory injury, macrophage activation and extra-pancreatic organ injury by acting on their downstream signaling pathways. In the future, differentially expressed miRNAs will be further applied to the exploration of AP treatment. Our previous studies have confirmed that exosomes derived from AR42J cells in the non-activated state can reduce the level of apoptosis and oxidative stress of acinar cells, reduce the level of inflammation, and reduce pancreatic tissue damage during the AP[12]. The mechanism may be related to the inhibition of downstream MAPK and nuclear factor-kappaB signaling pathways, so as to achieve an anti-inflammatory purpose. In this study, we found that exosomes derived from AR42J in the activated state can promote inflammatory injury of acinar cells and aggravate AP progression[12]. RNA-seq results showed that miR-125b-5p was a differentially expressed miRNA in AR42J cell lines between the two different states. RT-qPCR analysis confirmed that the expression of miR-125b-5p was significantly increased in the activated AR42J cell line and AP tissues. In addition, studies have shown that overexpression of miR-125b-5p can cause cell cycle arrest and apoptosis, thus

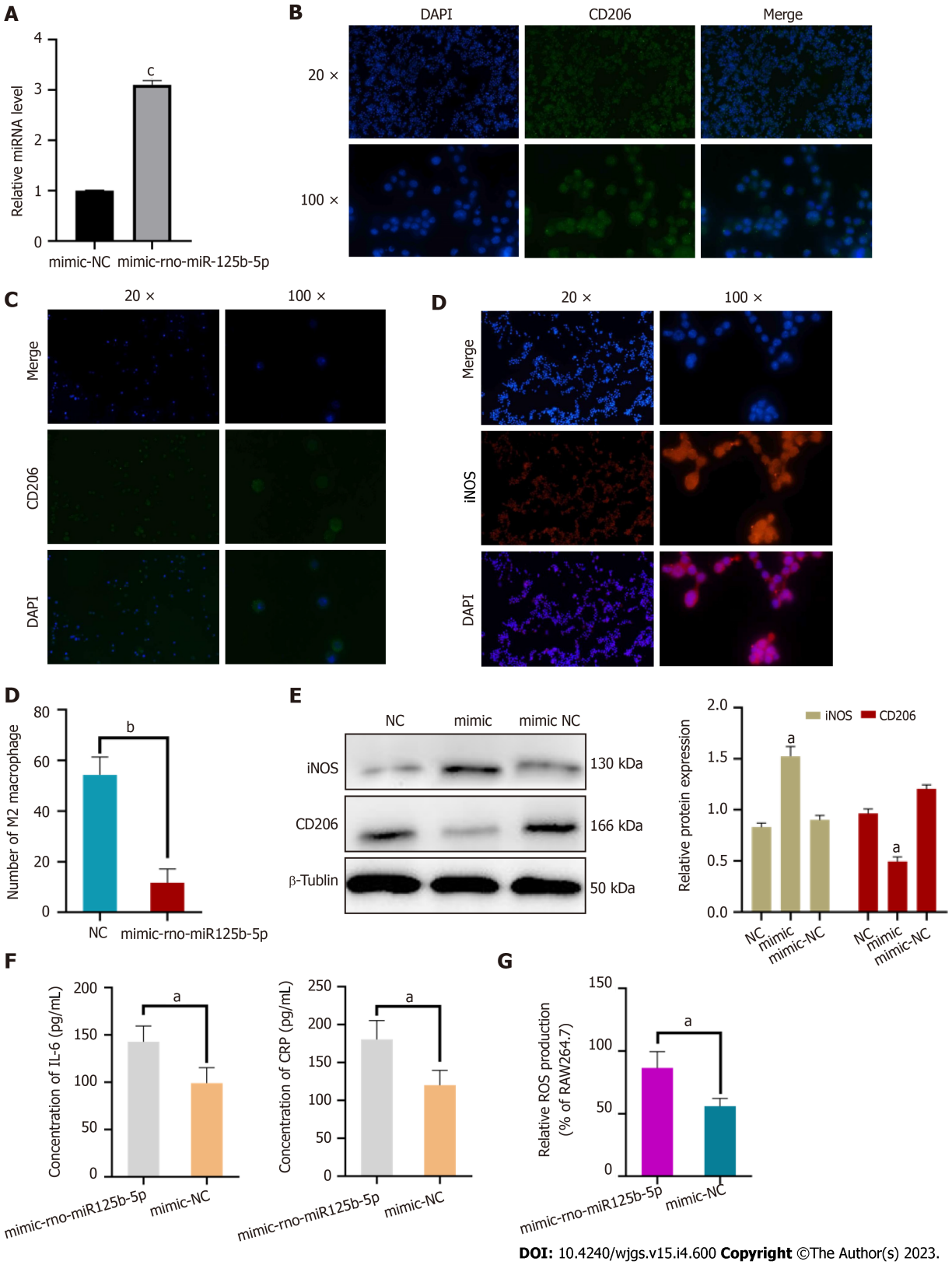


DOI: 10.4240/wjgs.v15.i4.600

Figure 7 miR-125b-5p promotes acute pancreatitis exacerbation by inhibiting insulin-like growth factor 2 protein expression in PI3K/AKT signaling pathway. A: The potential binding sites of miR-125b-5p in the 3¢-untranslated regions (UTR) of wild-type insulin-like growth factor 2 (IGF2) (red part). The blue section is the mutation site in mutant IGF2 3¢-UTR sequence; B: Luciferase activity in IGF2 3¢-UTR of wild-type and mutant was detected after transfection of miR-125b-5p mimics and negative control miRNAs. The normalized luciferase activity of the transfected control miRNA was set to a relative luciferase activity of 1; C: The protein expression of PI3K/AKT signaling pathway was confirmed by western blot. $^{a}P < 0.05$, $^{b}P < 0.005$. AP: Acute pancreatitis; IGF2: Insulin-like growth factor 2; N: Normal; NC: Negative control; WT: Wild-type; MUT: Mutant; UTR: Untranslated regions; CDS: Coding sequence.

promoting the death of AR42J cells in the activated state. CCK-8 results showed that overexpression of miR-125b-5p could inhibit the proliferation of AR42J cells. The experimental results showed that the cell absorbance value of the exosome group which overexpressed miR-125b-5p was significantly lower than that of the PBS group after 8 h of treatment (1.705 ± 0.120 *vs* 0.975 ± 0.064, $t = 7.590$, $P = 0.016$). Cell cycle results showed that G0/G1 ratio in miR-125b-5p overexpression group was higher than that of NC group. The percentage of cells in G0/G1 phase decreased from 60.37 ± 1.7% (miR-125b-5p overexpression group) to 51.25 ± 1.4% (NC group). These results showed that the apoptosis of AR42J cells in the activated state was significantly increased in the miR-125b-5p overexpression group. ELISA tests confirmed that overexpression of miR-125b-5p could aggravate cellular inflammatory injury, and the results showed that the level of IL-6, TNF-α and CRP in the overexpression group were higher than those in the control group (IL-6: 158.86 ± 1.49 pg/mL *vs* 171.286 ± 2.36 pg/mL, $P = 0.0076$; TNF-α: 105.86 ± 9.33 pg/mL *vs* 134.38 ± 8.98 pg/mL, $P = 0.0106$; CRP: 83.1 ± 8.32 pg/mL *vs* 129.04 ± 15.16 pg/mL, $P = 0.024$).

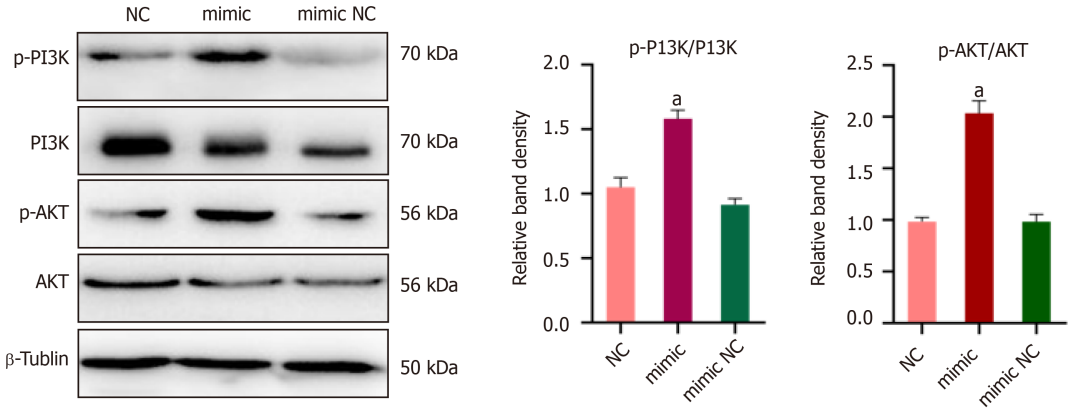
The pathogenesis of AP initiates the innate immune system of the body and plays an important role in promoting the evolution of its disease course, of which the monocyte/macrophage system is the most important effector cell[19-21]. Monocytes originate from bone marrow stem cells, reach various tissues of the body with blood, and differentiate into macrophages of different tissues. Macrophages are important components of the innate immune system of the body. They have the function of antigen presentation and secretion of various cytokines, play an important role in the pathophysiological process such as inflammation and metabolism, and are also the key factors for the body to maintain its own stability. Macrophages are highly heterogeneous, plastic and diverse, and polarize into two activation states with different phenotypes and biological function depending on their microenvironments and exogenous stimuli. When stimulated by interferon-αand lipopolysaccharide, macrophages often undergo M1 type polarization and play a proinflammatory function. When stimulated by IL-4, macrophages often undergo M2 polarization, thus exerting anti-inflammatory and injury repair



DOI: 10.4240/wjgs.v15.i4.600

Figure 8 miR-125b-5p promoted M1-type polarization of macrophages and the release of inflammatory factors. A: Construction of overexpression miR-125b-5p in RAW264.7 cell line; B: Negative control group: RAW264.7 cells stimulated with interleukin (IL)-4 for 24 h showed M2 polarization of macrophages; C: miR-125b-5p overexpression group: exosomes overexpressing miR-125b-5p were added to RAW264.7 cell line stimulated with IL-4 to inhibit M2 polarization of macrophages; D: miR-125b-5p overexpression group: Exosomes overexpressing miR-125b-5p were added to RAW264.7 cell line stimulated with IL-4 to promote M1 polarization of macrophages. Immunofluorescence counting showed that the number of M2 macrophages in the overexpression group was decreased compared with the control group; E: Western blot showed that the protein expression level of inducible nitric oxide synthase and CD206 in the RAW264.7 cell line; F: IL-6 and C-reactive protein level were determined by enzyme linked immunosorbent assay; G: miR-125b-5p overexpression promoted reactive oxygen species accumulation in the RAW264.7 cell line ($P = 0.0224$), $^{a}P < 0.05$, $^{b}P < 0.005$, $^{c}P < 0.0005$. NC: Negative control; DAPI: 4',6-diamidino-2-phenylindole; iNOS: Inducible

nitric oxide synthase; IL: Interleukin; CRP: C-reactive protein; ROS: Reactive oxygen species.



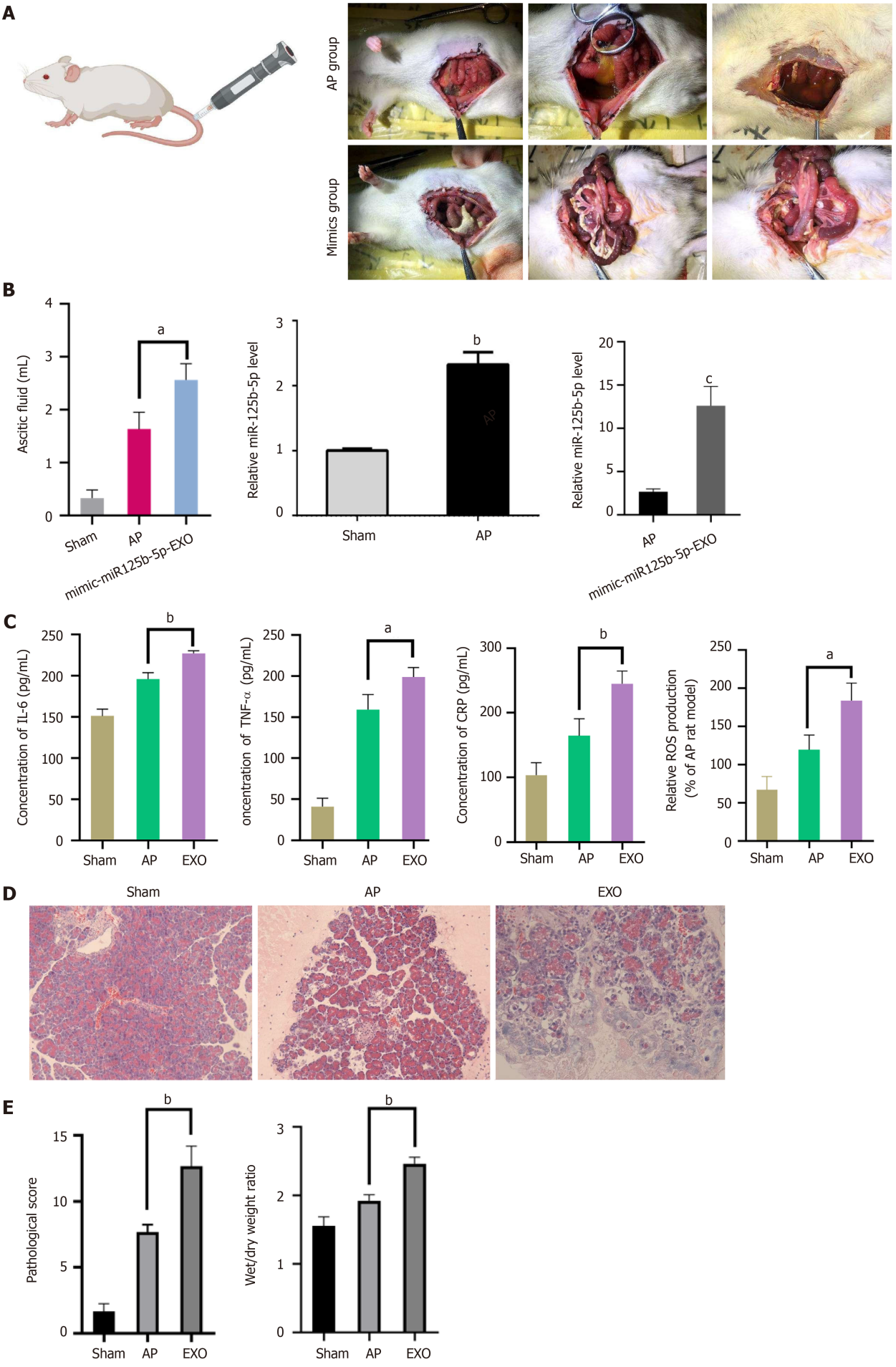
DOI: 10.4240/wjgs.v15.i4.600

Figure 9 miR-125b-5p promotes PI3K/AKT signaling pathway phosphorylation and inflammatory response in RAW264.7 cell line. A western blot was used to confirm the protein expression of the PI3K/AKT signaling pathway in RAW264.7 cell line, $^{a}P < 0.05$. NC: Negative control.

functions[22]. It has been found that macrophages are mainly M1 polarized in the course of AP, and play an important role in the continuous development and amplification of the inflammatory response. It is an important determinant of the severity of AP and an effective therapeutic target to control inflammatory damage[19,23]. At the early stage of AP, necrotic acinar cells release a large number of damage-associated molecular patterns to induce monocytes in the blood to migrate widely, recruit them into pancreatic tissues and become macrophages. Under the stimulation of various factors, M1 polarization occurs, releasing a large number of proinflammatory factors and inflammatory mediators, thus forming the interaction between acinar cells and macrophages in the pancreas. In this study, we found that overexpression of miR-125b-5p can inhibit M2 type polarization of macrophages and promote M1 type polarization, and trigger inflammatory cascade amplification effect by releasing inflammatory factors, thus leading to the progression of AP. The results of cell fluorescence test showed that the number of M2 macrophages in miR-125b-5p overexpression group was less than that in the control group [(54.33 ± 5.73) *vs* (11.67 ± 4.49), $t = 8.280$, $P = 0.0012$)]. Among them, the expression of iNOS protein, the surface marker of M1 macrophages, was increased. While the expression of CD206 protein, the surface marker of M2 macrophages, was decreased. In addition, the experimental results also found that miR-125b-5p can promote macrophages to secrete inflammatory factors such as IL-6 and CRP, and aggravate inflammatory responses (IL-6: 99.106 ± 13.29 pg/mL *vs* 142.778 ± 13.58 pg/mL, $P = 0.0314$; CRP: 120.181 ± 20.41 pg/mL *vs* 180.557 ± 15.98 pg/mL, $P = 0.0301$).

Bioinformatics analysis and dual luciferase assays confirmed that IGF2 is a target gene of miR-125b-5p, which inhibits M2 polarization of macrophages through PI3K/AKT signaling pathway, thus promoting the exacerbation of AP. *In vitro* experiments confirmed that overexpression of miR-125b-5p could reduce the expression of IGF2 in activated AR42J cell line, and could also cause the upregulation of apoptosis-related genes, *BAX*, and necrosis-related genes, *HMGB-1*, and the downregulation of *Bcl-2*. In addition, we also found that miR-125b-5p can promote the phosphorylation of PI3K/AKT signal pathway in the activated AR42J cell line and RAW264.7 cell line, thus activating this pathway to promote the exacerbation of inflammatory response. *In vivo* experiments found that the degree of abdominal inflammation was more obvious in rats of the overexpression group, with a large number of calcium foci and ascites, accompanied by pancreatic tissue edema and necrosis, which further confirmed that miR-125b-5p could promote the aggravation of AP *in vivo*.

Although this study revealed, to a certain extent, that the inflammatory cascade response caused by acinar cells injury and immune system activation is an important factor in the occurrence and progression of the disease, there are still some limitations that need to be further explored in the future. First, although this study confirmed that miR-125b-5p can inhibit M2 polarization of macrophages and promote M1 polarization, and thus trigger the massive release of inflammatory factors, thereby aggravating the inflammatory response, the results of this study were only obtained through *in vitro* experiments, and were not verified *in vivo* experiments. The results of macrophage polarization of pancreatic tissue in animal models were lacking. Therefore, subsequent experiments need to carry out fluorescent staining and western blotting on pancreatic tissue of rat AP models in the miR-125b-5p overexpression group to determine the recruitment and polarization of macrophages in the pancreatic tissue. In addition, it is also necessary to flow separate macrophages in serum to determine the change of M1/M2 ratio, to further clarify the effect of miR-125b-5p on macrophage polarization. Second, this


A
AP group
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B
Ascitic fluid (mL)
Sham
AP
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AP
mimic-miR125b-5p-EXO
C
Concentration of IL-6 (pg/mL)
Sham
AP
EXO
oncentration of TNF-α (pg/mL)
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Relative ROS production (% of AP rat model)
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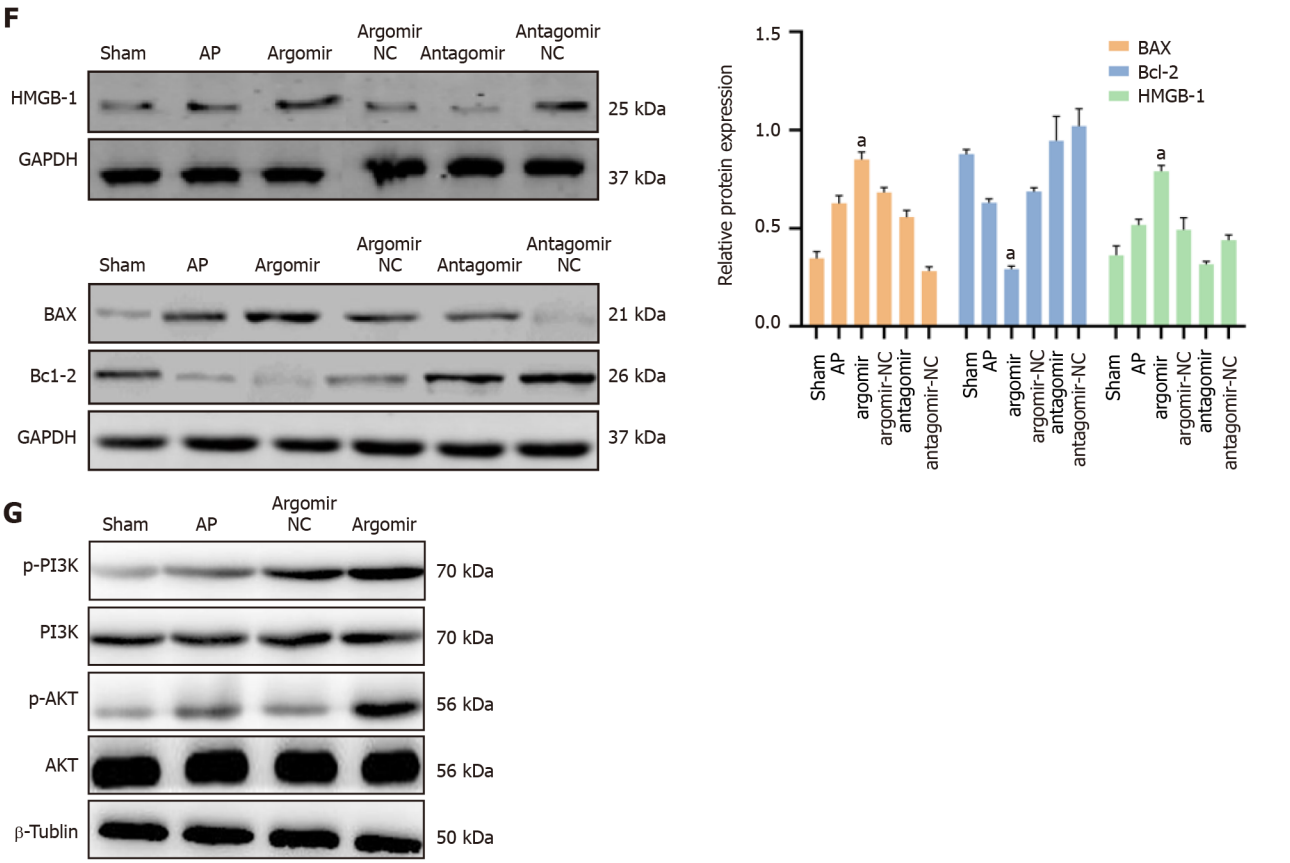

DOI: 10.4240/wjgs.v15.i4.600

Figure 10 miR125b-5p promotes the aggravation of inflammation *in vivo*. A: Intraperitoneal condition of rats in acute pancreatitis (AP) group and overexpression group; B: Ascites volume of rats in the three groups. The expression of miR-125b-5p in pancreatic tissues of sham group, AP group and overexpression group was detected by quantitative real-time polymerase chain reaction; C: The level of interleukin-6, tumor necrosis factor-alpha, C-reactive protein and reactive oxygen species was determined by enzyme linked immunosorbent assay; D: Histopathological image of rat pancreas in three groups; E: Pancreatic histopathology score and dry/wet ratio; F: Western blot showing the expression of BAX, Bcl-2, HMGB-1 and insulin-like growth factor 2 in the pancreatic tissues; G: Western blot showing the expression of p-PI3K, PI3K, p-AKT and AKT in the pancreatic tissues, $^{a}P < 0.05$, $^{b}P < 0.005$, $^{c}P < 0.0005$. IGF2: Insulin-like growth factor 2; TNF-α: Tumor necrosis factor-alpha; AP: Acute pancreatitis; IL: Interleukin; TNF-α: Tumor necrosis factor-alpha; CRP: C-reactive protein; ROS: Reactive oxygen species; NC: Negative control.

study only explored the molecular mechanism of AP aggravation from the perspective of miR-125b-5p overexpression, and did not further verify whether silencing miR-125b-5p could reduce the severity of AP. Therefore, it is necessary to further confirm the role of miR-125b-5p in the course of AP through *in vivo* and *in vitro* experiments.

CONCLUSION

Based on the above experimental results, it was confirmed that miR-125b-5p can inhibit M2 polarization of macrophages and promote M1 polarization by regulating the IGF2 expression, thus aggravating the inflammatory response of AP. Among them, PI3K/AKT signaling pathway may be one of the important mechanisms leading to the progression of AP. Therefore, it has potential clinical value to control the pathogenesis of excessive inflammatory responses in AP by inhibiting the inflammatory cascade between acinar cells and macrophages mediated by miR-125b-5p in the future, which can effectively reduce inflammatory damage and improve the prognosis of AP.

ARTICLE HIGHLIGHTS

Research background

Acute pancreatitis (AP) is a common clinical inflammatory disease of the digestive system, with an increasing trend worldwide, which is a pathophysiological process with complex etiology. At present,

there are no consistent and effective therapies for treatment of AP, resulting in a high mortality rate.

Research motivation

miR-125b-5p, a bidirectional regulatory miRNA, is speculated to exhibit anti-tumor activity. However, exosome-derived miR-125b-5p in AP has not been reported.

Research objectives

We aimed to elucidate the molecular mechanism of exosome-derived miR-125b-5p promoting AP exacerbation from the perspective of the interaction between immune cells and acinar cells.

Research methods

RNA-seq technology was used to screen differentially expressed miRNAs in AR42J cell lines, and bioinformatics analysis was used to predict downstream target genes of miR-125b-5p. The expression level of miR-125b-5p and insulin-like growth factor 2 (IGF2) in the activated AR42J cell line and AP pancreatic tissue were detected by quantitative real-time polymerase chain reaction and western blots. The changes in the pancreatic inflammatory response in a rat AP model were detected by histopathological methods. Western Blot was used to detect the expression of IGF2, PI3K/AKT signaling pathway proteins, and apoptosis and necrosis related proteins.

Research results

miR-125b-5p expression was upregulated in the activated AR42J cell line and AP pancreatic tissue, while that of IGF2 was downregulated. In addition, miR-125b-5p was found to act on macrophages to promote M1 type polarization and inhibit M2 type polarization, resulting in a massive release of inflammatory factors and reactive oxygen species accumulation. Further research found that miR-125b-5p could inhibit the expression of IGF2 in the PI3K/AKT signaling pathway. *In vivo* experiments revealed that miR-125b-5p can promote the progression of AP in a rat model.

Research conclusions

miR-125b-5p acts on IGF2 in the PI3K/AKT signaling pathway and promotes M1 type polarization and inhibits M2 type polarization of macrophage by inhibiting IGF2 expression, resulting in a large release of pro-inflammatory factors and an inflammatory cascade amplification effect, thus aggravating AP.

Research perspectives

It has potential clinical value to control the pathogenesis of excessive inflammatory responses in AP by inhibiting the inflammatory cascade between acinar cells and macrophages mediated by miR-125b-5p in the future, which can effectively reduce inflammatory damage and improve the prognosis of AP.

FOOTNOTES

Author contributions: Zheng Z, Cao F, Ding YX, Lu JD, Fu YQ and Liu L are equally contributed to this work; Zheng Z, Ding YX and Lu JD designed the study; Liu L, Guo YL, Liu S, Sun HC and Cui YQ performed the experiments; Zheng Z and Lu JD wrote the manuscript; Sun HC, Fu YQ and Cui YQ performed statistical analysis; Li F and Cao F revised the manuscript; All authors read and approved the final manuscript.

Supported by The Beijing Municipal Science and Technology Commission, Capital Research and Demonstration Application of Clinical Diagnosis and Treatment Technology, No. Z191100006619038 and No. Z171100001017077; and The Capital Health Research and Development of Special, No. 2020-1-2012.

Institutional review board statement: The research was given the go-ahead by the hospital's Ethics Committee and Animal Ethics Committee, which is in Xuanwu Hospital, Capital Medical University, No. 2020-158.

Institutional animal care and use committee statement: All experimental procedures and feeding management methods involving animals have been reviewed and approved by the Animal Experiment Ethics Committee of Xuanwu Hospital of Capital Medical University, No. 2020-158.

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: Data are available from the corresponding authors upon request.

ARRIVE guidelines statement: The authors have read the ARRIVE guidelines, and the manuscript was prepared and revised according to the ARRIVE guidelines.

Country/Territory of origin: China

ORCID number: Fei Li 0000-0003-2297-7704.

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

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World J Gastrointest Surg 2023 April 27; 15(4): 621-633

DOI: 10.4240/wjgs.v15.i4.621

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Case Control Study

Skeletal muscle mass and quality before preoperative chemotherapy influence postoperative long-term outcomes in esophageal squamous cell carcinoma patients

Daichi Ichinohe, Takahiro Muroya, Harue Akasaka, Kenichi Hakamada

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

P-Reviewer: Lin Q, China; Liu D, China; Liu Y, China

Received: November 11, 2022
Peer-review started: November 11, 2022
First decision: January 23, 2023
Revised: February 8, 2023
Accepted: March 23, 2023
Article in press: March 23, 2023
Published online: April 27, 2023

Daichi Ichinohe, Takahiro Muroya, Harue Akasaka, Kenichi Hakamada, Department of Gastroenterological Surgery, Hirosaki University Graduate School of Medicine, Hirosaki 0368562, Aomori, Japan

Corresponding author: Kenichi Hakamada, MD, PhD, Professor, Department of Gastroenterological Surgery, Hirosaki University Graduate School of Medicine, 5 Zaifucho, Hirosaki 0368562, Aomori, Japan. hakamada@hirosaki-u.ac.jp

Abstract

BACKGROUND

Previous reports have focused on muscle mass as a prognostic factor in esophageal cancer.

AIM

To investigate how preoperative body type influences the prognosis of patients with esophageal squamous cell carcinoma who underwent neoadjuvant chemotherapy (NAC) and surgery.

METHODS

The subjects were 131 patients with clinical stage II/III esophageal squamous cell carcinoma who underwent subtotal esophagectomy after NAC. Skeletal muscle mass and quality were calculated based on computed tomography images prior to NAC, and their statistical association with long-term outcomes was examined retrospectively in this case-control study.

RESULTS

The disease-free survival rates in the low psoas muscle mass index (PMI) group *vs* the high PMI group were 41.3% *vs* 58.8% (P = 0.036), respectively. In the high intramuscular adipose tissue content (IMAC) group *vs* the low IMAC group, the disease-free survival rates were 28.5% *vs* 57.6% (P = 0.021), respectively. The overall survival (OS) rates for the low PMI group *vs* the high PMI group were 41.3% *vs* 64.5% (P = 0.008), respectively, and for the high IMAC group *vs* the low IMAC group, they were 29.9% *vs* 61.9% (P = 0.024), respectively. Analysis of the OS rate revealed significant differences in patients aged 60 years or older (P = 0.018), those with pT3 or above disease (P = 0.021), or those with lymph node metastasis (P = 0.006), aside from PMI and IMAC. Multivariate analysis

demonstrated that pT3 or above [hazard ratio (HR): 1.966, 95% confidence interval (CI): 1.089-3.550, P = 0.025), lymph node metastasis (HR: 2.154, 95%CI: 1.118-4.148, P = 0.022), low PMI (HR: 2.266, 95%CI: 1.282-4.006, P = 0.005), and high IMAC (HR: 2.089, 95%CI: 1.036-4.214, P = 0.022) were significant prognostic factors for esophageal squamous cell carcinoma.

CONCLUSION

Skeletal muscle mass and quality before NAC in patients with esophageal squamous cell carcinoma are significant prognostic factors for postoperative OS.

Key Words: Esophageal squamous cell carcinoma; Muscle mass; Muscle quality; Neoadjuvant chemotherapy; Body composition

Core Tip: Esophageal cancer patients are often nutritionally malnourished, and their muscle mass is often decreased. In addition to loss of muscle mass, it is often associated with loss of muscle quality. In this study, the prognosis of esophageal squamous cell carcinoma patients was found to be influenced by muscle composition before preoperative chemotherapy. The prognosis is not only affected by muscle mass but also by muscle quality.

Citation: Ichinohe D, Muroya T, Akasaka H, Hakamada K. Skeletal muscle mass and quality before preoperative chemotherapy influence postoperative long-term outcomes in esophageal squamous cell carcinoma patients. *World J Gastrointest Surg* 2023; 15(4): 621-633

URL: https://www.wjgnet.com/1948-9366/full/v15/i4/621.htm

DOI: https://dx.doi.org/10.4240/wjgs.v15.i4.621

INTRODUCTION

Esophageal cancer continues to have a poor prognosis, with a low 5-year survival rate of 20%[1]. Poor prognostic factors are due to the tendency of the cancer to metastasize at an early stage[2,3] and to easily invade nearby vital organs such as the lungs, large blood vessels, heart, and trachea, indicating that the cancer is already advanced at the time of diagnosis[4]. Therefore, the standard treatment is a combination of chemotherapy and radiotherapy in addition to surgery[5]. However, the prognosis remains poor.

In recent years, preoperative sarcopenia has been identified as a factor that reduces short-term postoperative prognosis and outcomes after gastrointestinal cancer surgery[6]. Sarcopenia is defined as the loss of function associated with muscle mass loss and quality[7]. Factors such as cancer status, underlying disease, advanced age, and sex are involved. Preoperative muscle mass loss has been reported as a postoperative complication or prognostic factor in gastric[8], hepatocellular[9], biliary[10], pancreatic[11], and colorectal cancers[12]. Recently, it has been suggested that, in addition to muscle mass, fatty degeneration of muscle and muscle quality changes also affect prognosis[13]. Low skeletal muscle mass has been reported to influence the occurrence of postoperative respiratory complications in esophageal cancer[14-16] and is a factor for poor short-term outcomes[17,18].

Esophageal cancer is often complicated by preoperative nutritional deficits due to reduced oral intake caused by stenosis. Therefore, sarcopenia is often complicated preoperatively[19]. In addition, esophageal cancer surgery is highly invasive, which promotes catabolism creating a nutritional disadvantage[20]. Moreover, the multidisciplinary treatment combinations of chemotherapy and radiotherapy used in esophageal cancer can also contribute to nutritional impairment[21].

Multidisciplinary treatment for esophageal cancer is available in a variety of forms, including pre- and postoperative chemotherapy[22] and preoperative chemoradiotherapy[23,24]. The multidisciplinary approach is used in Europe and the United States for adenocarcinoma; in Japan and East Asian countries, however, this is more common for squamous cell carcinoma[4]. In Japan, preoperative chemotherapy and subtotal esophagectomy with three-field lymph node dissection is the standard treatment[5]. Therefore, assessing the impact of sarcopenia on short-term and long-term outcomes after esophageal cancer surgery requires a consistent examination of the disease and treatment context.

The present study included Japanese patients with squamous cell carcinoma of the esophagus who underwent preoperative chemotherapy and subtotal esophagectomy with three-field lymph node dissection as the standard therapy. We examined the effect of muscle mass and quality before preoperative chemotherapy on long-term prognosis in these patients.

MATERIALS AND METHODS

Patients

Of the 182 consecutive esophageal cancer patients who underwent esophagectomy between January 2009 and December 2013 at our hospital in Aomori, Japan, 131 were recruited for the study. In our hospital, one surgeon specializes in upper gastrointestinal surgery and performs 30 or more esophageal cancer surgeries per year. The selected subjects underwent subtotal esophagectomy with three-field lymph node dissection after completion of two courses of 5-fluorouracil plus cisplatin as neoadjuvant chemotherapy (NAC) for clinical stage II/III esophageal squamous cell carcinoma. They had no residual tumors. Six patients with positive resection margins were excluded (Figure 1).

Treatment protocol

All patients were examined by esophagogastroduodenoscopy and diagnosed histologically with esophageal squamous cell carcinoma (adenocarcinoma was excluded because the inclusion criterion for NAC is squamous cell carcinoma) confirmed by biopsy. They were then examined by routine 1-mm slice contrast-enhanced computed tomography (CT) and positron emission tomography-CT, and staged according to the TNM classifications (7th edition)[25] of the Union for International Cancer Control.

Two courses of 5-fluorouracil plus cisplatin therapy were administered. NAC for clinical stage II or III esophageal squamous cell carcinoma was administered according to the Japan Clinical Oncology Group 9907 trial[5]. The regimen was: (1) Day 1: Cisplatin 80 mg/m^2 intravenous infusion; (2) days 1-5: 5-fluorouracil 800 mg/m^2 intravenous infusion; and (3) cycle frequency every 21 d for 2 cycles.

The effect of chemotherapy was evaluated according to the Response Evaluation Criteria in Solid Tumors guidelines (version 1.1[26]). Right thoraco-laparotomic subtotal esophagectomy and three-field lymph node dissection were performed after two courses of NAC. For reconstruction, retrosternal route gastric tube reconstruction was performed unless the patient was post-gastrectomy. Postoperatively, the patient was treated in the intensive care unit for systemic management. After discharge, blood examinations were performed every 3 mo and radiological examinations every 6 mo.

Patient demographics and nutritional status

Age, body mass index (BMI), performance status, and American Society of Anesthesiologists physical status were determined from the medical records of the patients. The white blood cell count, neutrophil count, lymphocyte count, high sensitivity C-reactive protein level, and serum albumin level were investigated according to preoperative blood chemistry data. Neutrophil-to-lymphocyte ratio (used as a nutrition index), Prognostic Nutritional Index, Geriatric Nutritional Risk Index, and modified Glasgow prognostic score were calculated as evaluation criteria.

Image analysis

For skeletal muscle mass measurement, computed tomography (CT) images before NAC were used. The bilateral psoas muscle areas were measured at the third lumbar vertebral level through tracing using Digital Imaging and Communications in Medicine viewer software, EV Invite® (PSP Corporation, Tokyo, Japan) (Figure 2). The value calculated by dividing the psoas muscle area by the square of the height was determined as the psoas muscle mass index (PMI) [= (cross-sectional area of bilateral psoas muscle)/(height)^2 (cm^2/m^2)].

For skeletal muscle quality measurement using CT values, the bilateral multifidus muscles were traced at the third lumbar vertebral level (the same as the level of the psoas muscle cross-sectional area measurement), and the mean CT value of this region was calculated. In addition, subcutaneous fat was traced at four sites at the same level, and the mean CT value was determined. The mean CT value of the multifidus muscle was divided by the mean CT value of the subcutaneous fat at the four sites, and the calculated value was regarded as the intramuscular adipose tissue content (IMAC) [= mean CT value of bilateral multifidus muscle (HU)/mean CT value of four points of subcutaneous fat (HU)][27,28].

Definition of muscle mass loss and muscle quality changes

In this study, a receiver operating characteristic curve against overall survival (OS) was prepared using precalculated PMI with the optimum cutoff value of PMI set at 4 (area under the curve: 0.538, sensitivity: 61.0%, specificity: 78.3%). Patients with PMI < 4 and PMI ≥ 4 were designated as belonging to the low and high PMI groups, respectively, and compared.

Similarly, a receiver operating characteristic curve for IMAC was prepared, and the optimum cutoff value was set at 0.36 (area under the curve: 0.538, sensitivity: 61.0%, specificity: 78.3%). Patients with IMAC ≥ -0.36 and IMAC < -0.36 were designated as belonging to the high and low IMAC groups, respectively.

Evaluation of outcomes

Postoperative complications were defined according to the Clavien-Dindo classification[29], with Clavien-Dindo grade ≥ 3 defined as the presence of complications. For analysis of outcomes, OS and disease-free survival (DFS) rates were used.

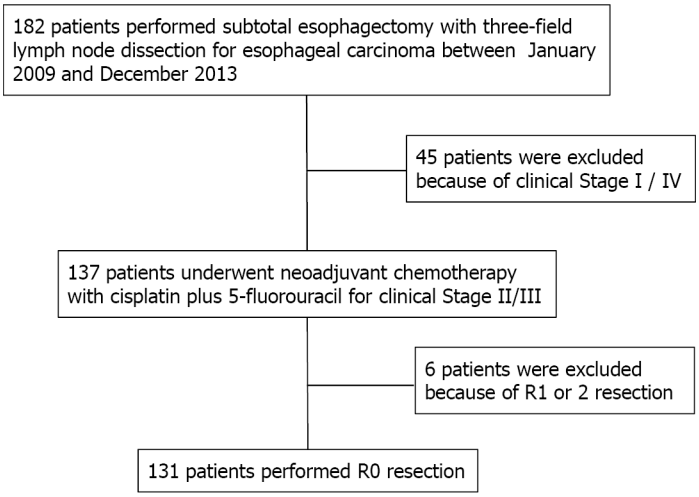


Figure 1 Patient selection process.

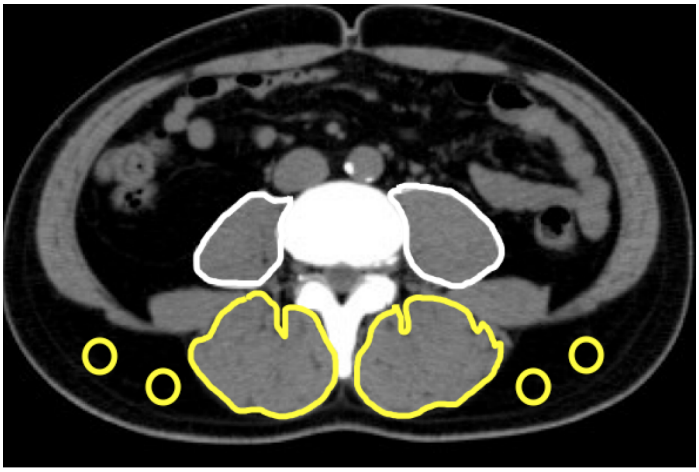


Figure 2 Measured area of muscle.

Statistical analysis

For statistical analysis, SPSS® Statistics (Version 22.0; IBM Corp., Armonk, NY, United States) was used. All variables are presented as median values. In univariate analysis, continuous and non-continuous variables were analyzed using the Mann-Whitney *U* test and χ^2 test, respectively. Survival curves were prepared using the Kaplan-Meier method. For multivariate analysis, the log rank test was used, and analysis was performed using the Cox proportional hazards model. *P* values < 0.05 were regarded as significant.

Registration and ethical approval

Although this study was a retrospective study, ethical considerations required approval because of the use of biometric data. This study is registered with the Research Registry (Unique Identifying Number 7880) and was approved by the Ethics Committee (Approval number: 2020-38). This article is reported in line with the STROBE criteria[30].

RESULTS

Patients' characteristics

The median age of the 131 patients was 64 years (range: 44-78 years), and the median BMI was 21.4 kg/m^2 (range: 14.7-27.7 kg/m^2). The clinical stages were stage II in 68 patients and stage III in 63 patients. The determination of the effect of NAC following the Response Evaluation Criteria in Solid

Tumors guidelines was complete response in 2 patients, partial response in 79, stable disease in 42, and progressive disease in 8. The rate of response to NAC was 61.8% compared with the disease control rate of 93.9%. The median number of postoperative hospitalization days was 18 (range: 11-225); reoperation was performed on 4 patients (3.1%). There was no postoperative mortality at the hospital nor was there any mortality within 90 d following surgery. The median duration of postoperative follow-up was 60.9 mo (range: 3.9-100.3 mo).

The median PMI value was 4.94 (2.12-8.98). When the cases were classified setting the cutoff value of PMI at 4, the low and high PMI groups included 36 (27.5%) and 95 (72.5%) patients, respectively. In the between-group comparison, BMI and Geriatric Nutritional Risk Index were significantly lower in the low PMI group compared to the high PMI group, but no significant difference was noted for age, nutrition index, or chemotherapy response rates.

Similarly, in the comparison of IMAC, representing muscle quality, age was significantly higher in the high IMAC group. Details are presented in Table 1.

Influence of muscle mass loss and muscle quality changes on surgical outcomes

A Clavien-Dindo classification of three or more severe complications was noted in 53 patients (40.5%). Failure of sutures was seen in 3 patients (2.3%), and respiratory complications were noted in 28 (21.4%). When comparing PMI, no significant difference was noted in operative time, blood loss, or postoperative complication. There were no significant differences in tumor-associated factors. The results of IMAC were similar (Table 1).

Impact of muscle mass loss and muscle quality changes on DFS

The 5-year DFS rates in the low and high PMI groups were 41.3% and 58.8%, respectively (P = 0.036). For IMAC, the 5-year DFS rates were 28.5% and 57.6% in the high and low IMAC groups, respectively (P = 0.021) (Figure 3A and B).

Impact of muscle mass loss and muscle quality changes on OS

The 5-year OS rates in the low and high PMI groups were 41.3% and 64.5%, respectively (P = 0.008), showing a significant difference between the two groups. Regarding IMAC, the 5-year OS rates of the high group *vs* the low group were 29.9% and 61.9%, respectively (P = 0.024), which were significantly different (Figure 3C and D).

Univariate analysis of the OS rate revealed significant differences in patients aged 60 years or older (P = 0.018), those with pT3 or above disease (P = 0.021), and those with lymph node metastasis (P = 0.006). When these factors were subjected to multivariate analysis using the Cox proportional hazards model, pT3 or above [hazard ratio (HR): 1.966, 95% confidence interval (CI): 1.089-3.550, P = 0.025], low PMI (HR: 2.266, 95%CI: 1.282-4.006, P = 0.005), and high IMAC (HR: 2.089, 95%CI: 1.036-4.214, P = 0.022) were significantly different and regarded as independent poor prognostic factors (Table 2).

DISCUSSION

The first finding of the present study was that lower skeletal muscle mass (low PMI) and changes in skeletal muscle quality (high IMAC) before preoperative chemotherapy had an impact on OS. To assess skeletal muscle mass, a cross-sectional area of the psoas muscle at the level of the lumbar spine L3 in the abdominal CT images before preoperative chemotherapy was used. Dual-energy X-ray absorptiometry and bioelectrical impedance analysis are methods to measure skeletal muscle mass. However, unlike CT imaging before preoperative chemotherapy, these methods require additional examination and raise the issue of invasive radiation exposure[31]. These measurement methods are not standardized for measuring muscle mass[32]. In addition, it has been reported that it is difficult to standardize and assess muscle quality[33-35].

In this study, the cross-sectional area of the psoas muscle at the lumbar L3 level was used to assess muscle mass. Essentially, it was necessary to assess muscle mass by volume rather than area. The cross-sectional area of the psoas muscle is maximal at the level of the lumbar spine L3 and thus can be assessed as representative of the volume[36,37]. There are systematic reviews/meta-analyses of sarcopenia using a technique that measures skeletal muscle mass at L3 in patients undergoing abdominal surgery. The method used to measure muscle mass in this study was reasonable because it is cited as a factor affecting perioperative complications and prognosis in previous reports[38,39].

The same lumbar spine L3 level in CT images used to assess skeletal muscle mass was also used to assess skeletal muscle. We calculated the degree of fat content within the multifidus muscle in those CT images based on the CT values. For this method, muscle quantity and quality were assessed at the same L3 level as abdominal CT imaging studies. The advantage was that no additional metrics were needed to assess changes in quality as a new parameter.

One modality of assessing muscle quality from CT images is the IMAC method[27,28], which evaluates the degree of fat content in muscle and quantifies the degree of fat degeneration. Fat degeneration of muscle has been reported to correlate with muscle weakness and loss of function[40,

Table 1 Clinicopathological characteristics of patients

	All	Preoperative	Preoperative	*P* value	Preoperative	Preoperative	*P* value
	n = 131	Low PMI, *n* = 36	High PMI, *n* = 95		High IMAC, *n* = 17	Low IMAC, *n* = 114	
Age, yr	64 (44-78)	63 (50-75)	65 (44-78)	0.749	68 (44-74)	64 (45-78)	0.034
Gender (male/female)	120/11	28/8	92/3	0.001	15/2	105/9	0.635
Preoperative body mass index	21.4 (14.7-27.7)	19.9 (14.7-24.2)	21.6 (15.9-27.7)	0.001	21.6 (18.4-25.6)	21.2 (14.7-27.7)	0.194
PS ≥ 1	12 (9.2%)	4 (11.1%)	8 (8.4%)	0.736	1 (5.9%)	16 (9.6%)	0.708
ASA-PS (2/3)	112/19	30/6	82/13	0.782	14/3	98/16	0.713
Albumin (g/dL)	4.1 (2.9-4.9)	3.9 (3.1-4.8)	4.1 (2.9-4.9)	0.127	4.0 (3.5-4.5)	4.1 (2.9-4.9)	0.471
CRP (mg/dL)	0.11 (0.01-7.37)	0.11 (0.02-7.37)	0.11 (0.01-6.48)	0.905	0.16 (0.20-4.53)	0.10 (0.01-7.37)	0.160
Neutrophil-lymphocyte ratio	1.66 (0.24-22.33)	2.10 (0.29-14.06)	1.54 (0.24-22.33)	0.293	1.95 (0.59-7.73)	1.54 (0.24-22.33)	0.171
Prognostic nutritional index	49.05 (35.70-106.15)	46.65 (35.70-68.00)	49.30 (37.30-106.15)	0.098	48.40 (40.75-53.35)	49.33 (35.70-106.15)	0.135
mGPS (0/1/2)	105/21/5	27/8/1	78/13/4	0.515	12/5/0	93/16/5	0.232
GNRI	105.9 (81.7-121.4)	99.0 (86.8-108.8)	107.2 (81.7-121.4)	0.001	106.1 (86.1-121.4)	105.4 (97.3-111.6)	0.356
Clinical T-stage (1/2/3/4)	3/68/57/3	1/14/20/1	2/54/37/2	0.390	1/6/10/0	2/62/47/3	0.090
Clinical N-stage (0/1/2/3)	51/35/36/9	13/11/9/3	38/24/27/6	0.889	7/5/3/2	44/30/33/7	0.735
Clinical stage (II/III)	68/63	18/18	50/45	0.846	10/7	58/56	0.609
Tumor response to chemotherapy							
CR/PR/SD/PD	2/79/42/8	0/21/13/2	2/58/29/6	0.852	0/6/9/2	2/73/33/6	0.090
Pre NAC PMI	4.94 (2.40-8.86)	3.66 (2.40-4.43)	5.39 (3.34-8.86)	0.001	4.76 (3.28-6.64)	5.01 (2.40-8.86)	0.558
Pre NAC IMAC	-0.46 (-1.07--0.19)	-0.47 (-1.07--0.28)	-0.46 (-1.06--0.19)	0.248	-0.32 (-0.75--0.19)	-0.48 (-1.07--0.33)	0.001
Operative time (min)	443 (328-882)	444 (328-882)	443 (339-786)	0.495	452 (328-882)	440 (350-786)	0.472
Intraoperative bleeding (mL)	730 (150-3015)	652 (330-2550)	732 (150-3015)	0.258	750 (450-2550)	718 (150-3015)	0.247
Postoperative complications (C-D ≥ 3)							
Any complication	53 (40.5%)	16 (44.4%)	37 (38.9%)	0.690	5 (29.4%)	48 (42.1%)	0.430
Respiratory complication	28 (21.4%)	8 (22.2%)	20 (21.1%)	1.000	4 (23.5%)	24 (21.1%)	1.000
Anastomotic leakage	3 (2.3%)	2 (5.6%)	1 (1.1%)	0.183	0 (0%)	3 (2.6%)	1.000
Pathological tumor grading							
G1/G2/G3/Gx	14/77/38/2	3/24/8/1	11/53/30/1	0.534	1/9/7/0	13/68/31/2	0.600
pT-Stage (0/1/2/3/4)	7/27/21/73/3	1/7/5/21/1	6/19/16/52/2	0.985	0/2/4/11/0	7/25/17/62/3	0.796
pN-Stage (0/1/2/3)	46/17/30/38	11/8/11/6	35/9/19/32	0.059	3/2/5/7	43/15/25/31	0.399
pStage (0/1/2/3)	4/18/36/73	0/6/10/20	4/12/26/53	0.640	0/2/2/13	4/16/34/60	0.279
Reoperation	4 (3.1%)	1 (2.8%)	3 (3.2%)	1.000	0 (0%)	4 (3.5%)	0.651
Length of hospital stay (d)	18 (11-225)	18 (11-225)	18 (11-112)	0.630	20 (11-225)	18 (11-112)	0.432
30 d mortality	0	0	0		0	0	
90 d mortality	0	0	0		0	0	
Harvested number of LNs	91 (42-194)	102 (44-194)	90 (42-184)	0.360	82 (49-130)	91 (42-194)	0.092

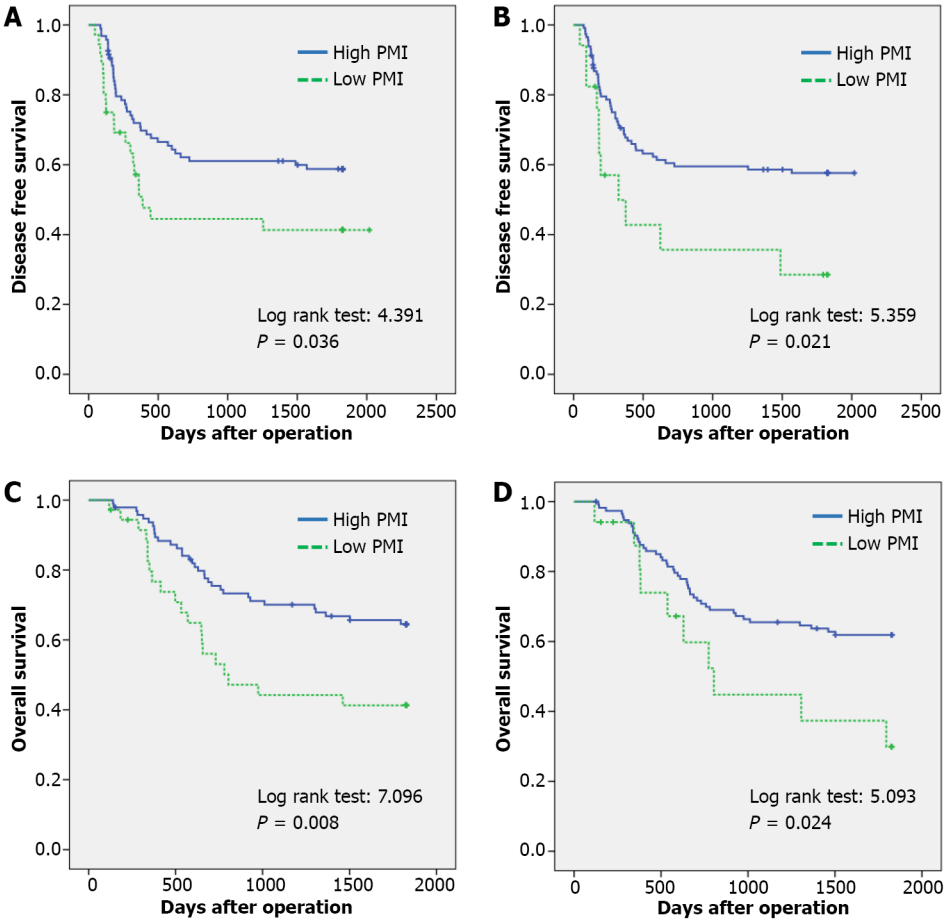
PMI: Psoas muscle mass index; IMAC: Intramuscular adipose tissue content.

Table 2 Univariate and multivariate analyses of factors associated with overall survival

		1-year survival	3-year survival	5-year survival	Univariate analysis	*P*	Multivariate analysis	*P*
					Log rank		HR, 95%CI	
Age, yr	≥ 60	88.0	58.0	51.1	5.604	0.018	2.031	0.054
	< 60	91.9	75.7	75.7			0.986-4.183	
BMI	< 22	92.0	64.0	59.8	0.108	0.743		
	≥ 22	87.3	62.6	57.4				
PS	0	89.8	65.7	59.6	1.640	0.200		
	1	81.8	45.5	45.5				
ASA	2	87.2	60.4	55.7	1.812	0.178		
	3	100.0	78.9	73.3				
Stage	II	86.4	65.2	59.0	0.051	0.821		
	III	91.9	61.0	57.6				
PNI	≥ 50	87.5	58.9	58.9	0.006	0.937		
	< 50	90.3	66.5	57.9				
NLR	≥ 2.5	93.5	54.2	54.2	0.600	0.439		
	< 2.5	87.7	66.0	59.8				
mGPS	0	88.4	64.9	59.9	0.493	0.483		
	1-2	92.0	56.0	52.0				
GNRI	≥ 98	87.8	62.1	56.8	0.498	0.480		
	< 98	93.3	66.7	63.3				
Operative time (min)	≥ 450	89.1	63.2	55.4	0.039	0.843		
	< 450	89.1	63.1	60.3				
Blood loss (mL)	≥ 730	93.7	64.8	61.4	0.570	0.450		
	< 730	84.6	61.5	55.4				
Postoperative complication	Present	88.1	63.7	57.5	0.026	0.873		
	Absent	89.7	62.8	58.9				
pT	0-2	90.9	80.0	69.1	5.350	0.021	1.966	0.025
	3-	87.7	50.3	50.3			1.089-3.550	
pN	0	93.5	82.6	73.7	7.465	0.006	2.154	0.022
	1-	86.7	52.1	49.6			1.118-4.148	
IMAC	< -0.40	89.4	65.5	61.9	5.093	0.024	2.089	0.022
	≥ -0.40	87.4	44.8	29.9			1.036-4.214	
PMI	≥ 4.0	93.6	70.1	64.5	7.096	0.008	2.266	0.005
	< 4.0	76.7	44.2	41.3			1.282-4.006	

BMI: Body mass index; PMI: Psoas muscle mass index; IMAC: Intramuscular adipose tissue content.

41]; for this reason, it can be used to assess muscle quality. In fact, muscle quality changes, determined by the IMAC method, have been reported as poor prognostic factors in nonalcoholic fatty liver disease [27], liver transplantation[42,43], hepatocellular carcinoma[44,45], pancreatic cancer[46], and cholangiocarcinoma diseases[13,47]. As mentioned above, it is reasonable to employ this same technique to assess the status of fatty degenerative changes in muscle and the relationship to the prognosis of patients undergoing preoperative chemotherapy for esophageal cancer.



DOI: 10.4240/wjgs.v15.i4.621

Figure 3 Loss of muscle mass and quality affects disease-free survival and overall survival. A and B: Disease-free survival; C and D: Overall survival.

In the present study, the results showed that a decrease in skeletal muscle mass and muscle quality changes affected OS. However, from previous reports on sarcopenia, the mechanism by which it affects the prognosis remains unclear. A cancer-bearing state is considered a systemic, chronic inflammatory condition. This may lead to the secretion of inflammatory cytokines interleukin (IL)-6, IL-8, tumor necrosis factor-alpha (TNF-α), and myostatin, and this may affect the entire body[48]. Increased secretion of the proinflammatory cytokine IL-6 itself and IL-6 mediated by TNF-α has been reported to reduce skeletal muscle mass[49]. It has also been reported that myostatin is a cytokine that potently reduces skeletal muscle, and its secretion increases in chronic inflammatory conditions, resulting in a decrease in skeletal muscle mass[50]. We consider that the combination of the effects of these cytokines leads to a malignant cycle of decreased skeletal muscle mass in a cancer-bearing state.

From an immunological point of view, IL-6, IL-8, and TNF-α cytokines are involved. IL-6 decreases the function of dendritic cells and T lymphocytes[51]. IL-8 and TNF-α also induce immunosuppressive myeloid-derived suppressor cells[52,53]. The actions of these cytokines are thought to suppress host immunity. Conversely, the secretion of IL-15, which is important for the maintenance of natural killer cell function, is reduced as a result of a decrease in the skeletal muscle, which is a secretory organ[54]. This inhibits the function of natural killer cells[55]. A decrease in IL-15 has been reported to increase adipose tissue[56], which may be linked to fat degeneration in muscle. We hypothesize that the chronic inflammatory state, which is a cancer-bearing state as described above, reduces skeletal muscle from inflammatory cytokines and, at the same time, suppresses immunity, which may worsen the prognosis.

Fat degeneration of muscle (a change in muscle quality) causes an increase in adipose tissue and the secretion of transforming growth factor-beta (TGF-β)[57]. It has been shown that TGF-β has an inhibitory effect on immune system cells such as T cells, B cells, natural killer cells, and dendritic cells, resulting in a suppression of immunity against cancer[58,59]. We presume that the long-term immunosuppressed state caused by the muscle mass loss and muscle quality changes may have resulted in a poor prognosis. These results suggest that muscle-strengthening interventions for patients with poor muscle composition may improve their prognosis in the future.

Limitation

This study was limited to surgical cases of esophageal squamous cell carcinoma in Japanese patients who received NAC. Therefore, other races and adenocarcinomas were not included. The number of subjects analyzed was 131, which is not a large survey, and there is a male/female ratio imbalance.

CONCLUSION

Changes in skeletal muscle mass and muscle quality before NAC in esophageal squamous cell carcinoma in Japanese is a prognostic factor of OS.

ARTICLE HIGHLIGHTS

Research background

Recently, muscle has been reported as an important prognostic factor. Not only muscle mass but also muscle quality has been reported to affect prognosis. Therefore, it is important to reveal how muscle composition is affected in patients undergoing preoperative chemotherapy for esophageal squamous cell carcinoma.

Research motivation

Esophageal cancer has a poor prognosis, and perioperative complications can be serious. It is important to consider prognostic factors in patients with esophageal cancer.

Research objectives

If body composition is a factor affecting prognosis, then preoperative chemotherapy and preoperative interventions can improve prognosis. In other words, a program to improve body composition before chemotherapy or before surgery can improve the prognosis of esophageal cancer patients. The objective was to determine the effect of muscle mass and quality on overall survival (OS) in esophageal squamous cell carcinoma.

Research methods

In this study, we measured a cross-sectional area of the psoas muscle from computed tomography images. We evaluated muscle quality based on computed tomography values of the psoas muscle and subcutaneous fat. This was novel because both muscle mass and muscle quality were measured from the same image.

Research results

In this study, prognostic factors were found in patients who received preoperative chemotherapy for esophageal squamous cell carcinoma. Muscle mass as well as muscle quality and body composition before chemotherapy impacted disease-free survival and OS.

Research conclusions

In this study, body composition was a prognostic factor for esophageal squamous cell carinoma patients. This suggests that muscle itself may be an immune system. Furthermore, the prognosis may be improved noninvasively if body composition is improved before chemotherapy or surgery.

Research perspectives

Further studies are required to support our data. Randomized controlled trials to examine the prognostic change with and without the intervention of body composition improvement programs before chemotherapy and before surgery should be conducted.

ACKNOWLEDGEMENTS

Many thanks to Shari Joy Berman for her help in proofreading the English.

FOOTNOTES

Author contributions: Ichinohe D contributed to conception, methodology, investigation, data curation, original drafting, reviewing, and editing of the manuscript, and generation of figures; Muroya T contributed to conception,

methodology, data curation, and generation of figures; Akasaka H contributed to data curation; Hakamada K contributed to reviewing and editing of the manuscript, and supervised the study.

Institutional review board statement: The Institutional Review Board of Hirosaki University Hospital provided approval for this study (Approval No. 2020-038).

Informed consent statement: With regard to informed consent, Hirosaki University Hospital uses an opt-out format on its website and does not obtain individual consent.

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

Data sharing statement: Data available upon reasonable request. Please contact daichii@hirosaki-u.ac.jp.

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: Japan

ORCID number: Daichi Ichinohe 0000-0003-0577-1958; Kenichi Hakamada 0000-0001-6513-1202.

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

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World Journal of Gastrointestinal Surgery

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World J Gastrointest Surg 2023 April 27; 15(4): 634-642

DOI: 10.4240/wjgs.v15.i4.634

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

In situ subtotal spleen resection combined with selective pericardial devascularization for the treatment of portal hypertension

Hai-Lin Li, Shang-Lei Ning, Yan-Jing Gao, Tao Zhou, Yu-Xin Chen

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: Allon R, Israel; Honda M, Japan

Received: December 19, 2022
Peer-review started: December 19, 2022
First decision: January 9, 2023
Revised: January 24, 2023
Accepted: March 23, 2023
Article in press: March 23, 2023
Published online: April 27, 2023

Hai-Lin Li, Shang-Lei Ning, Yu-Xin Chen, Department of Hepatobiliary Surgery, General Surgery, Qilu Hospital of Shandong University, Jinan 250012, Shandong Province, China

Yan-Jing Gao, Tao Zhou, Department of Gastroenterology, Qilu Hospital of Shandong University, Jinan 250012, Shandong Province, China

Corresponding author: Yu-Xin Chen, MD, Professor, Surgeon, Department of Hepatobiliary Surgery, General Surgery, Qilu Hospital of Shandong University, No. 107 Wenhua west Road, Jinan 250012, Shandong Province, China. yxchen@sdu.edu.cn

Abstract

BACKGROUND

Hypersplenism and esophageal varices bleeding are the major complications of portal hypertension (PHT). In recent years, increasing attention has been given to spleen preservation operations. The mode and long-term effects of subtotal splenectomy and selective pericardial devascularization for PHT remain controversial.

AIM

To investigate the clinical efficacy and safety of subtotal splenectomy combined with selective pericardial devascularization for the treatment of PHT.

METHODS

This was a retrospective study of 15 patients with PHT who underwent subtotal splenectomy not preserving the splenic artery or vein combined with selective pericardial devascularization in the Department of Hepatobiliary Surgery, Qilu Hospital of Shandong University from February 2011 to April 2022. Fifteen propensity score-matched patients with PHT who underwent total splenectomy at the same time served as the control group. The patients were followed for up to 11 years after surgery. We compared the postoperative platelet levels, perioperative splenic vein thrombosis, and serum immunoglobulin levels between the two groups. Abdominal enhanced computed tomography was used to evaluate the blood supply and function of the residual spleen. The operation time, intraoperative blood loss, evacuation time, and hospital stay were compared between the two groups.

RESULTS

The postoperative platelet level of patients in the subtotal splenectomy group was

significantly lower than that in the total splenectomy group ($P < 0.05$), and the postoperative portal system thrombosis rate in the subtotal splenectomy group was also much lower than that in the total splenectomy group. The levels of serum immunoglobulins (IgG, IgA, and IgM) showed no significant differences after surgery compared with before surgery in the subtotal splenectomy group ($P > 0.05$), but serum immunoglobulin IgG and IgM levels decreased dramatically after total splenectomy ($P < 0.05$). The operation time in the subtotal splenectomy group was longer than that in the total splenectomy group ($P < 0.05$), but there were no significant differences in the amount of intraoperative blood loss, evacuation time, or hospital stay between the two groups.

CONCLUSION

Subtotal splenectomy not preserving the splenic artery or vein combined with selective pericardial devascularization is a safe and effective surgical treatment for patients with PHT, not only correcting hypersplenism but also preserving splenic function, especially immunological function.

Key Words: Subtotal splenectomy; Portal hypertension; Surgical treatment; Splenic function; Selective pericardial devascularization

Core Tip: Partial spleen resection is beneficial for benign lesions in normal spleens. However, many issues regarding subtotal spleen resection for portal hypertension remain elusive. We performed subtotal spleen resection *in situ* without preserving the splenic artery and vein for portal hypertension and evaluated perioperative complications and clinical effects retrospectively. Follow-up results showed that subtotal splenectomy is a safe and effective surgical treatment for patients with portal hypertension, not only correcting hypersplenism but also preserving splenic function.

Citation: Li HL, Ning SL, Gao YJ, Zhou T, Chen YX. *In situ* subtotal spleen resection combined with selective pericardial devascularization for the treatment of portal hypertension. *World J Gastrointest Surg* 2023; 15(4): 634-642

URL: https://www.wjgnet.com/1948-9366/full/v15/i4/634.htm

DOI: https://dx.doi.org/10.4240/wjgs.v15.i4.634

INTRODUCTION

Portal hypertension (PHT) is common in China, and liver cirrhosis caused by chronic hepatitis B virus infection is the main pathogenic factor. Esophagogastric variceal hemorrhage and hypersplenism are the main causes of death and affect the quality of life of patients. For patients with esophagogastric variceal hemorrhage that cannot be controlled by endoscopic treatment, total splenectomy and selective pericardial devascularization are the main surgical methods for the treatment of PHT in China. However, a sharp increase of platelet level and portal system thrombosis after surgery is a major complication affecting the surgical outcome and can even lead to death. We summarized subtotal splenectomy not preserving the splenic artery or vein and selective pericardial devascularization for the treatment of PHT. The follow-up results showed that the clinical efficacy was rather good, and the surgical approach was safe and effective.

MATERIALS AND METHODS

Case data

We retrospectively collected the clinical data of 15 patients with PHT who underwent subtotal splenectomy and selective pericardial devascularization in the Department of Hepatobiliary Surgery, Qilu Hospital of Shandong University, from February 2011 to April 2022. Among them, 6 patients were male and 9 were female, with a median age of 48 years. The causes of PHT included chronic hepatitis B in 10 patients, autoimmune hepatitis in 3 patients, and idiopathic PHT in 2 patients. Eleven patients underwent open surgery, 1 patient underwent assisted laparoscopic surgery, and 3 patients underwent complete laparoscopic surgery. Fifteen patients with PHT who underwent total splenectomy were selected as the control group after propensity score matching. The surgical protocol and postoperative follow-up were approved by the patients and their families. All procedures were conducted in

accordance with the Declaration of Helsinki. This study was reviewed and approved by the Ethics Committee of Qilu Hospital of Shandong University.

Indications and contraindications

The indications for study inclusion were as follows: (1) A history of upper gastrointestinal bleeding; (2) patients who were suitable for emergency surgery for severe esophageal and gastric varices bleeding; (3) Child-Pugh classification of liver function A or B; (4) number of platelets below 30×10^9/L caused by hypersplenism; and (5) patients who were not suitable for EIS or EVL or who had failed treatment.

The contraindications for study inclusion were as follows: (1) Child-Pugh classification of liver function C; (2) relative contraindications for surgery with ICG R15 > 40%; (3) main portal vein, splenic vein, or mesentery superior venous thrombosis; and (4) patients with severe dysfunction of the heart, lung, kidney, or other vital organs who could not tolerate surgery or anesthesia.

Surgical procedure

Open surgery: The left subcostal incision was favored for good surgical exposure. The gastrocolic ligament was cut, and a 0.2 cm diameter silicone tube was inserted into the right gastroepiploic vein. Then, the free portal vein pressure was dynamically measured at the level of the right atrium. The main trunk of the splenic artery was dissected along the upper edge of the pancreas and double ligated 3-5 cm away from the splenic hilum. The gastrosplenic ligament and the short gastric blood vessels were cut, and then we dissected the tail of the pancreas and the splenic hilum (Figure 1A and B). After the splenic vein was ligated and cut, we tried to preserve the integrity of the splenophrenic ligament, splenorenal ligament, and splenocolic ligament around the lower pole of the spleen as much as possible. For the total splenectomy group, the splenocolic ligament was generally disconnected first after ligation of the splenic artery, which facilitated the dissection of the large spleen from the lower pole to the upper pole. Finally, the spleen was lifted out of the abdominal cavity. The spleen was cut approximately 1 cm away from the ischemic line using an ultrasonic scalpel, and larger blood vessels were ligated or sutured on the cut surface. A splenic artery aneurysm with a size of approximately 2.5 cm was resected in one patient, followed by selective pericardial devascularization. The lower end of the esophagus was dissociated by approximately 7 cm, and the main coronary vein and vagus nerve were preserved. After checking that there was no obvious bleeding, the residual spleen was wrapped with omentum majus and placed in the retroperitoneal wound *in situ*. One young patient underwent distal splenorenal shunt and selective pericardial devascularization. The splenophrenic ligament at the upper pole of the spleen was thicker, and we preserved the upper pole of the spleen. In another patient, both the lower and upper poles of the spleen had blood supply after the splenic blood vessels were cut off, so both the upper and lower poles were preserved (Figure 1C). The tissue between the splenic hilum and the retroperitoneum was able to meet the blood supply in some areas of the splenic hilum after the splenic arteries and veins were separated from the tail of the pancreas, and the tissue around the splenic hilum was preserved (Figure 1D).

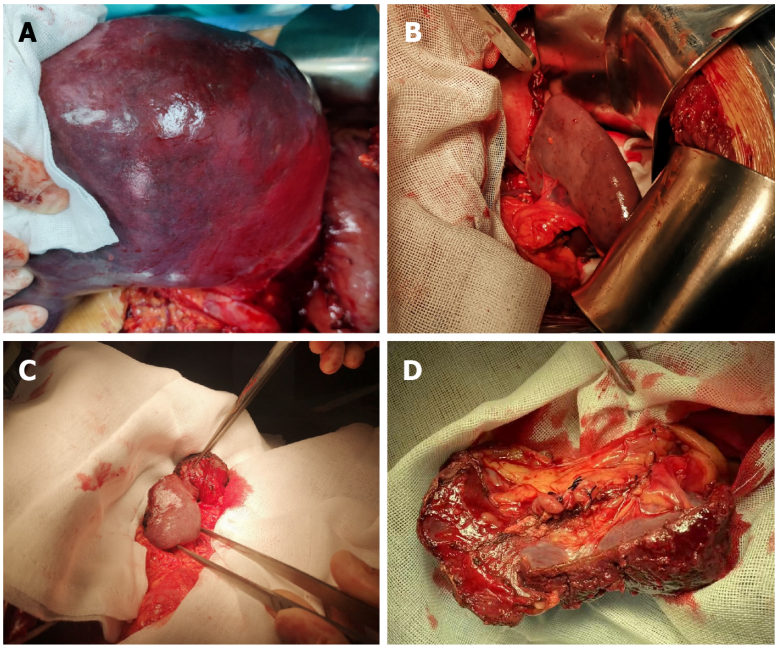
Laparoscopic surgery: The observation hole was selected below the umbilicus, and the position of the surgical hole was selected according to the projection of the skin surface of the spleen. After the gastrocolic ligament was severed with an ultrasonic scalpel, the main trunk of the splenic artery was dissected along the upper edge of the pancreas and double clipped 3–5 cm away from the splenic hilum. Then, the upper pole of the spleen was completely exposed after the gastrosplenic ligament and short gastric vessels were severed, and the splenic pedicle was gradually ligated from the upper pole to the lower pole. For the total splenectomy group, perisplenic ligaments were dissected from the lower pole to the upper pole. The surgeon should pay special attention to the tail of the pancreas; the splenic vein was cut off with a laparoscopic stapler. The treatment of the residual spleen was the same as that of open surgery. One patient had severe tortuous veins around the esophagus and the fundus of the stomach, and we converted to open surgery for subsequent pericardial devascularization.

Detection indicators and methods

Peripheral blood hemoglobin and platelet levels were measured before surgery and 1, 3, 5, and 7 d after surgery. Perioperative enhanced computed tomography (CT) and vascular ultrasound were used to evaluate whether thrombosis had formed in the portal vein system. Abdominal enhanced CT was used to assess the residual splenic blood supply and hyperplasia status. The operative time, intraoperative blood loss, postoperative gastrointestinal function recovery time, hospital stay, and other indicators were also summarized in this study.

Statistical analysis

SPSS 25.0 was used for statistical analysis. The data of the paired and unpaired groups were analyzed by *t* test, repetitive measurement deviation analysis was used for PLT level comparisons, and $P < 0.05$ was considered statistically significant.



DOI: 10.4240/wjgs.v15.i4.634

Figure 1 Open surgery of patient. A: Ischemia line is clear on the splenic surface; B: The appearance of the preserved lower pole of the spleen is good, and blood supply is from the splenocolic ligament; C: The upper pole and the lower pole of the spleen are preserved at the same time during the operation; D: The spleen tissue at the splenic hilum was preserved during the operation.

RESULTS

Peripheral blood platelet level and perioperative portal system thrombosis

The longest postoperative follow-up time was 11 years, and the free portal vein pressure decreased significantly after surgery in both the total and subtotal splenectomy groups (Figure 2A). The platelet level increased significantly 3 mo after surgery ($P < 0.05$), indicating that the symptoms of hypersplenism were significantly relieved (Figure 2B). Furthermore, the postoperative platelet level of patients in the subtotal splenectomy group was significantly lower than that in the total splenectomy group (Figure 2C), indicating that subtotal splenectomy could effectively delay the sharp increase in platelets after surgery. In the subtotal splenectomy group, only one case of portal system thrombosis was found 1 mo after surgery, but 4 cases were found in the total splenectomy group. The results demonstrated that subtotal splenectomy could reduce the incidence of perioperative portal system thrombosis compared with total splenectomy.

Serum immunoglobulin level changes and residual splenic function monitoring

The levels of serum immunoglobulins (IgG, IgA, and IgM) 6 mo after surgery were not significantly different from those before surgery ($P > 0.05$) in the subtotal splenectomy group, but the levels of serum immunoglobulins IgG and IgM decreased dramatically after total splenectomy ($P < 0.05$) (Table 1). Although the residual spleen of one patient showed small-scale necrosis (Figure 3A), the patient had no discomfort, and collateral circulation could be seen between the residual spleen and the retroperitoneal tissue (Figure 3B), indicating that this procedure not only preserved splenic function but also acted as a shunt between the portal and systemic circulation. The remaining splenic hyperplasia of the patient, who was followed up for 11 years, was relatively significant within 3 years after surgery (Figure 3C), but the hyperplasia slowed down over time. According to our limited case study, splenic hyperplasia after subtotal resection is faster in young patients and relatively slow in elderly patients. During the follow-up period, the overall quality of life of this patient was good, and there was no hypersplenism.

Operation time, intraoperative blood loss, evacuation time, and hospital stay evaluation

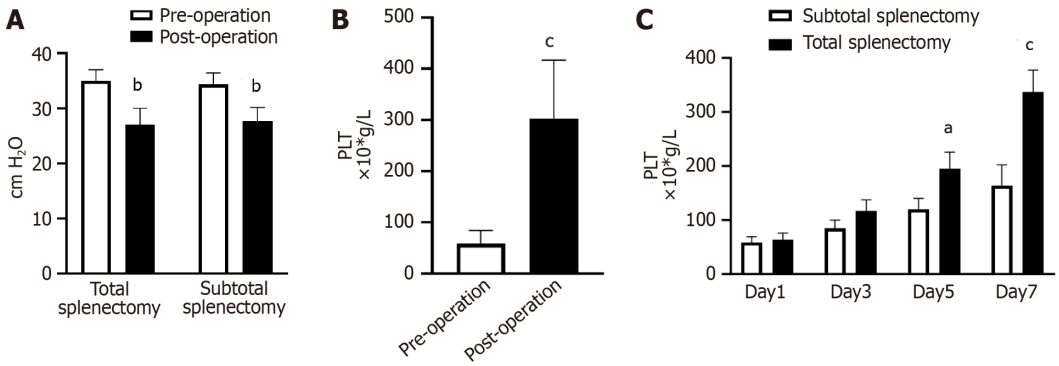
There were no deaths during the perioperative period. The operation time of the subtotal splenectomy group was longer than that of the total splenectomy group ($P < 0.05$), but there were no significant differences in the amount of intraoperative blood loss, evacuation time, or hospital stay between the two groups (Table 2).

Table 1 Comparison of serum immunoglobin levels in patients with portal hypertension before and after subtotal and total splenectomy (*n* = 15, mean ± SD)

	Subtotal splenectomy			Total splenectomy		
	Pre-operation	Post-operation	*P* value	Pre-operation	Post-operation	*P* value
IgG (g/L)	14.5 ± 2.4	13.4 ± 2.9	> 0.05	13.7 ± 1.6	8.3 ± 2.0	< 0.05
IgA (g/L)	2.3 ± 0.4	2.1 ± 0.5	> 0.05	2.4 ± 0.4	2.2 ± 0.5	> 0.05
IgM (g/L)	0.80 ± 0.12	0.84 ± 0.18	> 0.05	0.85 ± 0.05	0.60 ± 0.07	< 0.05

Table 2 Comparison of operational indices between the total and subtotal splenectomy groups (*n* = 15, mean ± SD)

	Total splenectomy	Subtotal splenectomy	*P* value
Operation time (min)	168.67 ± 28.50	198.33 ± 29.92	0.010
Blood loss (mL)	117.33 ± 42.33	119.33 ± 38.63	0.893
Evacuation time (d)	2.19 ± 0.62	2.28 ± 0.77	0.736
Hospital stay (d)	8.60 ± 1.40	8.86 ± 1.29	0.613



DOI: 10.4240/wjgs.v15.i4.634

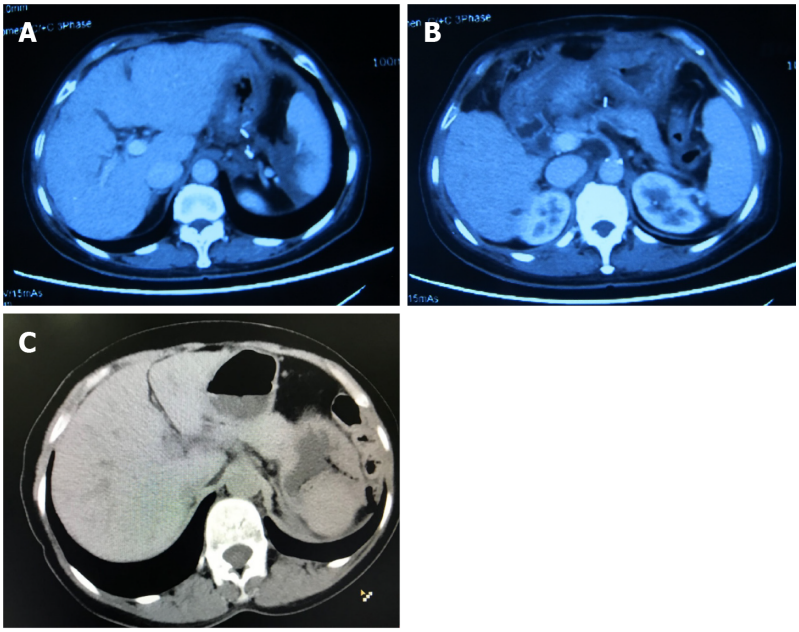
Figure 2 Peripheral blood platelet level and perioperative portal system thrombosis. A: The free portal vein pressure after subtotal splenectomy decreased significantly after surgery ($^bP < 0.01$ *vs* pre-operation); B: The platelet level increased significantly 1 mo after subtotal splenectomy. ($^cP < 0.001$ *vs* pre-operation); C: The platelet level after subtotal splenectomy increased more slowly than that after total splenectomy ($^aP < 0.05$, $^cP < 0.001$ *vs* subtotal splenectomy).

DISCUSSION

PHT is a group of clinical syndromes caused by the persistent elevation of hepatic portal vein pressure, which usually presents with esophagogastric varices, hypersplenism and severe ascites. Approximately 20%–30% of patients will have upper gastrointestinal bleeding. Because of the donor liver lack and complicated postoperative management for liver transplantation, total splenectomy combined with selective pericardial devascularization is the main surgical approach for the treatment of PHT in China. This procedure not only reduces the free portal vein pressure but also decreases the chance of esophagogastric venous bleeding[1].

With further understanding of spleen anatomy and its immune function, increasing attention has recently been given to spleen preservation operations. Recent studies have shown that the spleen plays an important role in hepatic function protection, infection control, and tumor immunity in patients with PHT[2]. Total splenectomy in patients with liver cirrhosis reduces the ability of the body to remove particulate matter from the blood and aggravate immune dysfunction. These patients are more prone to postoperative infection than patients without cirrhosis[3,4]. In addition, total splenectomy can also cause a relative increase in inhibitory T lymphocytes (Ts) and a significant decrease in helper T lymphocytes (Th) and serum IgM levels, inhibiting antitumor immunity[5].

The clinical application of spleen-preserving surgery has been increasing, especially for patients with splenic trauma and benign splenic tumors. Omentum autologous spleen graft implantation is currently the most widely used spleen-preserving surgical procedure. The omentum majus can provide sufficient blood supply for splenic implants, which could meet the physiological needs of the body[6]. Because patients with PHT usually have severe cirrhosis and the coagulation function and nutritional conditions



DOI: 10.4240/wjgs.v15.i4.634

Figure 3 Computed tomography images. A: Abdominal computed tomography showed small-scale necrosis of the residual spleen; B: New collateral circulation formed between the residual spleen and retroperitoneal tissue; C: Residual spleen showed obvious hyperplasia 11 years after the operation.

of patients are generally poor, the application of spleen-preserving surgery for cirrhosis patients remains relatively rare. We retrospectively analyzed the clinical data of 15 cases of subtotal splenectomy not preserving splenic vessels combined with selective pericardial devascularization for the treatment of PHT. The platelet levels on days 5 and 7 were significantly lower than those in the total splenectomy group, indicating that subtotal splenectomy correlated with a delayed increase in platelets and a reduced incidence of portal system thrombosis in patients with cirrhosis. There were no significant differences in serum IgG, IgA, or IgM in the subtotal splenectomy group 6 mo after surgery, indicating that the immune function of the residual spleen in patients with PHT after subtotal splenectomy was rather good. However, serum IgG and IgM decreased significantly after total splenectomy, which was consistent with previous reports[7]. Although the operation time of spleen-preserving surgery was prolonged, there were no significant differences in intraoperative blood loss, postoperative recovery time of gastrointestinal function, or hospital stay.

In addition, some scholars have conducted in-depth studies on the clinical effects of subtotal splenectomy with preservation of the upper pole of the spleen. Chu *et al*[7,8] found that the levels of collagen, elasticity, and reticular fibers in the residual spleen after subtotal splenectomy and retrosternal omentum fixation in patients with liver cirrhosis and hypersplenism were not significantly different from those in the preoperative spleen. Radioisotope scanning also showed normal phagocytosis of the residual spleen[7,8]. Petroianu A *et al*[9] performed subtotal splenectomy with preservation of the upper pole of the spleen in patients with schistosomiasis-related PHT, and the residual spleen was supplied by some short gastric vessels and was in good condition.

Since most patients with PHT have severe esophageal and gastric fundus varices, we think that preservation of the upper pole of the spleen and some short gastric vessels may increase the chance of upper gastrointestinal bleeding. However, preservation of the lower pole of the spleen will be beneficial for the long survival of patients. We recommend that the splenic artery should be ligated approximately 3 cm from the splenic hilum to avoid uncontrollable massive hemorrhage during the operation and to preserve the residual splenic blood supply from the pancreatic tail as much as possible. Traditionally, splenic vein congestion and splenic sinus dilation caused by PHT are the main causes of hypersplenism. Recent studies have shown that splenic vascular hyperplasia and fibrosis are also important reasons for hypersplenism[10]. We should be careful to keep the splenocolic ligament intact from the beginning because the splenocolic and splenorenal ligaments are the main blood supply to the residual spleen after the splenic vessels are cut off, which increases the difficulty of the operation to a certain extent. Although the splenocolic ligament thickens to varying degrees in patients with PHT, it is necessary to avoid pulling and moving the spleen during surgery. The lower part of the splenophrenic and splenorenal ligaments create conditions for the establishment of collateral circulation between the residual spleen and the retroperitoneal tissue in the later stage and ultimately play a role in shunting[11,12]. Finally, the tangent line of the spleen and the size of the residual spleen are determined by the ischemic line on the spleen surface. Generally, spleen transection approximately 1.0 cm away from the ischemic line can reduce intraoperative bleeding and maintain the tissue activity of the residual spleen.

In addition, the current surgical methods for spleen preservation in patients with PHT include peritoneal dissection at the left upper pole of the kidney and insertion and proper fixation of the residual spleen[13].

For patients with PHT, there is currently no unified standard for the size of the residual spleen. Generally, preserved splenic tissue, which is slightly smaller than the normal spleen, is sufficient to maintain splenic function in patients with PHT. Some studies have demonstrated that the residual spleen should be smaller than 5 cm × 3 cm[14], but it was also reported that spleen size should be comprehensively considered based on liver cirrhosis, platelets, spleen size, and other factors[15]. In summary, *in situ* subtotal splenectomy and selective pericardial devascularization is safe and feasible for patients with PHT.

CONCLUSION

The study analyzed the clinical data of subtotal splenectomy not preserving splenic vessels combined with selective pericardial devascularization for patients with PHT. The platelet levels after subtotal splenectomy were significantly lower than those in the total splenectomy group and portal system thrombosis rate decreased in the subtotal splenectomy group. Consistent with previous reports, serum IgG and IgM decreased significantly after total splenectomy, however, the immune function of the residual spleen lower pole after subtotal splenectomy was rather good.

During the operation, we think that preservation of the lower pole of the spleen *in situ* is more suitable and beneficial for the long survival of patients. Follow-up data also demonstrated that the blood supply from splenocolic and splenorenal ligaments was enough for residual spleen and collateral circulation could be established between the residual spleen and retroperitoneal tissue spontaneously. *In situ* subtotal splenectomy not preserving the splenic artery or vein combined with selective pericardial devascularization is an effective and safe surgical treatment for patients with PHT.

ARTICLE HIGHLIGHTS

Research background

Liver cirrhosis caused by chronic hepatitis B virus infection is the main pathogenic factor of portal hypertension (PHT) in China. For patients with serious esophagogastric variceal hemorrhage that cannot be controlled by endoscopic treatment, total splenectomy and selective pericardial devascularization are the main surgical methods for the treatment of PHT in China.

Research motivation

As we know, the sharp increase of platelet level and portal system thrombosis after total splenectomy is a serious complication affecting the surgical outcome and can even lead to death. More and more attention has been paid to spleen preservation operations recently. However, the long-term effects of subtotal splenectomy for PHT remain controversial.

Research objectives

The objective of the study was to explore the clinical efficacy and safety of subtotal splenectomy *in situ* combined with selective pericardial devascularization for the treatment of PHT.

Research methods

The study summarized the clinical data of PHT patients who received subtotal spleen resection and selective pericardial devascularization. We compared the postoperative platelet level, perioperative spleen vein thrombosis, and serum immunoglobulin level with the control group. Abdominal enhanced computed tomography was used to evaluate the blood supply of the residual spleen. The operation time, intraoperative blood loss and other parameters were also evaluated statistically.

Research results

The follow-up results showed that the surgical approach was safe and effective. The postoperative platelet level of patients in the subtotal splenectomy group was significantly lower and the postoperative portal system thrombosis rate was also much lower than that in the total splenectomy group. The levels of serum immunoglobulins (IgG, IgA, and IgM) showed no significant difference after operation in the subtotal splenectomy group.

Research conclusions

In situ subtotal splenectomy not preserving the splenic artery and vein combined with selective pericardial devascularization is a safe and effective surgical treatment for patients with PHT, not only

correcting hypersplenism but also preserving the immunological function of spleen.

Research perspectives

Subtotal splenectomy is suitable for specific PHT patients but the mode and long-term effects requires further study.

FOOTNOTES

Author contributions: Chen YX designed and performed the operation; Li HL and Ning SL contributed to acquisition, interpretation and analysis of clinical data and wrote the manuscript; Gao YJ and Zhou T designed the research and contributed to critical revision of the manuscript for important intellectual content; and all authors approved the final version of the manuscript.

Supported by Chinese Postdoctoral Science Foundation, No. 2022M711911.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of Qilu Hospital of Shandong University.

Informed consent statement: The surgical protocol and postoperative follow-up were approved by the patients and their families. All procedures were conducted in accordance with the Declaration of Helsinki.

Conflict-of-interest statement: There is no conflict of interest associated with the author or coauthors contributing to this manuscript.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at email address: yxchen@sdu.edu.cn. Participants gave informed consent for data sharing.

Country/Territory of origin: China

ORCID number: Hai-Lin Li 0000-0001-5150-3693; Shang-Lei Ning 0000-0002-8394-5047; Yan-Jing Gao 0000-0001-8153-3754; Tao Zhou 0000-0002-4083-6940; Yu-Xin Chen 0000-0002-4653-5276.

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

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World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2023 April 27; 15(4): 643-654

DOI: 10.4240/wjgs.v15.i4.643

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

Risk factors for blood transfusion and its prognostic implications in curative gastrectomy for gastric cancer

Lucas Eiki Kawakami, Pedro Barzan Bonomi, Marina Alessandra Pereira, Fabrício Oliveira Carvalho, Ulysses Ribeiro Jr, Bruno Zilberstein, Luciana Ribeiro Sampaio, Luiz Augusto Carneiro-D'Albuquerque, Marcus Fernando Kodama Pertille Ramos

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: Kinami S, Japan; Manojlovic N, Serbia

Received: December 23, 2022
Peer-review started: December 23, 2022
First decision: February 3, 2023
Revised: February 12, 2023
Accepted: March 30, 2023
Article in press: March 30, 2023
Published online: April 27, 2023

Lucas Eiki Kawakami, Pedro Barzan Bonomi, Marina Alessandra Pereira, Ulysses Ribeiro Jr, Bruno Zilberstein, Luiz Augusto Carneiro-D'Albuquerque, Marcus Fernando Kodama Pertille Ramos, Department of Gastroenterology, Instituto do Cancer, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo 01249000, Brazil

Fabrício Oliveira Carvalho, Luciana Ribeiro Sampaio, Blood Transfusion Unit, Instituto do Cancer, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo 01249000, Brazil

Corresponding author: Marcus Fernando Kodama Pertille Ramos, PhD, Doctor, Surgical Oncologist, Department of Gastroenterology, Instituto do Cancer, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Av Dr Arnaldo, 251, Sao Paulo 01249000, Brazil. marcus.kodama@hc.fm.usp.br

Abstract

BACKGROUND

Gastric cancer (GC) is still a prevalent neoplasm around the world and its main treatment modality is surgical resection. The need for perioperative blood transfusions is frequent, and there is a long-lasting debate regarding its impact on survival.

AIM

To evaluate the factors related to the risk of receiving red blood cell (RBC) transfusion and its influence on surgical and survival outcomes of patients with GC.

METHODS

Patients who underwent curative resection for primary gastric adenocarcinoma at our Institute between 2009 and 2021 were retrospectively evaluated. Clinicopathological and surgical characteristics data were collected. The patients were divided into transfusion and non-transfusion groups for analysis.

RESULTS

A total of 718 patients were included, and 189 (26.3%) patients received perioperative RBC transfusion (23 intraoperatively, 133 postoperatively, and 33 in both

periods). Patients in the RBC transfusions group were older (P < 0.001), and had more comorbidities (P = 0.014), American Society of Anesthesiologists classification III/IV (P < 0.001), and lower preoperative hemoglobin (P < 0.001) and albumin levels (P < 0.001). Larger tumors (P < 0.001) and advanced tumor node metastasis stage (P < 0.001) were also associated with the RBC transfusion group. The rates of postoperative complications (POC) and 30-d and 90-d mortality were significantly higher in the RBC transfusion group than in the non-transfusion group. Lower hemoglobin and albumin levels, total gastrectomy, open surgery, and the occurrence of POC were factors associated with the RBC transfusion. Survival analysis demonstrated that the RBC transfusions group had worse disease-free survival (DFS) and overall survival (OS) compared with patients who did not receive transfusion (P < 0.001 for both). In multivariate analysis, RBC transfusion, major POC, pT3/T4 category, pN+, D1 lymphadenectomy, and total gastrectomy were independent risk factors related to worse DFS and OS.

CONCLUSION

Perioperative RBC transfusion is associated with worse clinical conditions and more advanced tumors. Further, it is an independent factor related to worse survival in the curative intent gastrectomy setting.

Key Words: Stomach neoplasms; Blood transfusion; Red blood cells; Postoperative complications; Survival; Prognosis

Core Tip: This is a retrospective study to investigate the association of perioperative red blood cell (RBC) transfusion with surgical and survival outcomes in patients with gastric cancer. Our findings demonstrated that patients who received RBC transfusion had poorer preoperative clinical conditions and more aggressive tumors, and were submitted to more invasive procedures. The rates of postoperative complications and 30-d and 90-d mortality were also significantly higher in patients who received RBC transfusions compared to those who did. Further, receiving an RBC transfusion was an independent factor associated with worse survival.

Citation: Kawakami LE, Bonomi PB, Pereira MA, Carvalho FO, Ribeiro Jr U, Zilberstein B, Sampaio LR, Carneiro-D'Albuquerque LA, Ramos MFKP. Risk factors for blood transfusion and its prognostic implications in curative gastrectomy for gastric cancer. *World J Gastrointest Surg* 2023; 15(4): 643-654
URL: https://www.wjgnet.com/1948-9366/full/v15/i4/643.htm
DOI: https://dx.doi.org/10.4240/wjgs.v15.i4.643

INTRODUCTION

In 2020, gastric cancer (GC) was the fifth most diagnosed neoplasm and the fourth cause of death by neoplasms[1]. Although its incidence and mortality rates have decreased in the last two decades, in 2025, GC will be accountable for more than one million cases and eight hundred thousand deaths[2]. GC is frequently associated with perioperative blood loss, whether by its biological behavior or its most important treatment, radical gastrectomy. Therefore, anemia and blood transfusion in the perioperative setting are a common concern[3,4].

The Transfusion Requirements in Critical Care trial (1999) was the first study to show worse outcomes related to excessive use of blood components in critical care patients, and since then, more restrictive use of transfusions has been recommended[5]. In the last ten years, surgeons and oncologists have studied the continuous pro-inflammatory status triggered by surgical tissue damage, postoperative complications (POC), and blood transfusions[6]. This effort confirmed the association between transfusion and higher recurrence rates in colorectal, pancreatic, and biliary tract cancers[6-8]. However, the current literature seems to struggle to find an answer for the impact of blood components on the outcomes of curative intent treatment in GC. The debate on how blood transfusion impacts survival and POC in GC is a complex topic, given the heterogeneity of results found in recent years. One side supported blood transfusion as an independently associated risk factor for inferior results; the other concluded that using blood components is a confounding factor for the worse prognosis since patients needing transfusions presented unfavorable clinical conditions previous to the surgical procedure and more advanced tumors at pathological staging compared to patients who did not receive transfusions[9-11].

Thus, this study aimed to evaluate the influence of perioperative red blood cell (RBC) transfusion on surgical and survival outcomes of patients with GC. We also examined the factors related to the risk of receiving a blood transfusion.

MATERIALS AND METHODS

Patient selection and study design

This is a retrospective cohort of patients with GC who underwent gastrectomy with curative intent in an oncological reference center from February 2009 to December 2021. Non-adenocarcinoma tumors (lymphoma, gastrointestinal stromal tumor, and neuroendocrine tumors) were excluded, as well as palliative surgery, diagnostic laparoscopy, previous hematological disorders, and patients with synchronic neoplasms.

Data collection and definitions

The following clinical variables were evaluated: Age, sex, preoperative body mass index (BMI), neutrophil-lymphocyte ratio (NLR), hemoglobin, albumin level, and performance status based on the American Society of Anesthesiologists (ASA) classification. Charlson-Deyo comorbidity index (CCI) was used to measure comorbidities without including age and GC as comorbidity[12]. Tumor node metastasis (TNM) staging was determined according to the 8th edition of the American Joint Committee on Cancer[13].

Experienced surgeons performed surgical procedures. The surgical approach (open or laparoscopic) was carried out based on the surgeon's decision after a multidisciplinary meeting composed of the oncology, surgery, radiology, and pathology departments. The extension of gastric and lymph node (LN) dissection followed the recommendations of the Japanese Gastric Cancer Association (JGCA)[14]. The classification proposed by Baiocchi *et al*[15] was employed to define intraoperative complications. Intraoperative blood loss was measured in milliliters, and the length of the surgical procedure was assessed in minutes.

For analysis, the patients were divided into two groups: Patients who received an RBC transfusion and those who did not. In addition to the RBC transfusion, we also describe the transfusion of platelet concentrate (PC) and fresh frozen plasma (FFP). Regarding the moment in which the administration occurred, the following periods were considered: Intraoperative and postoperative (until the 30th day).

POC were graded according to Clavien-Dindo's classification. Clavien III to V was considered major complications[16]. Mortality at 30 and 90 d after the surgical procedure was also assessed. Adjuvant or perioperative platin-based chemotherapy was administered according to clinical indications (T3, T4, and regional LN metastasis)[17].

Surgical and oncological teams performed postoperative follow-up medical appointments every 3 mo in the first year and every 6 mo in the following years. The attending clinician assigned to each case determined recurrence based on laboratory tests, CT, or endoscopy reports. Lost to follow-up was defined as an absence for more than 12 mo in follow-up visits.

We obtained all data by reviewing the patient's medical chart and blood center system. The hospital ethics committee approved the study (CAAE: 59337222.7.0000.0068) and it was registered online in the national research projects database (www.plataformabrasil.org.br).

Statistical analysis

The Chi-square test was used to compare categorical variables between the two groups, and the *t*-test or Mann-Whitney test for continuous variables. Univariate and multivariate binary regression analyses were used to identify risk factors for receiving perioperative RBC transfusion. Odds ratios (ORs) with 95%CI were calculated.

Survival was estimated using the Kaplan-Meier method, and the log-rank test was used to identify differences between the survival curves. The Cox proportional hazards model was used to identify risk factors independently associated with survival outcomes. The results are reported as hazard ratios (HRs) with 95%CIs. Disease-free survival (DFS) was calculated from the date of surgery to recurrence or death from any cause. Overall survival (OS) was the duration between the date of surgery to death. All patients alive were censored at the date of the last follow-up. All tests were two-sided, and $P < 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS software, version 20.0 (SPSS Inc, Chicago, IL).

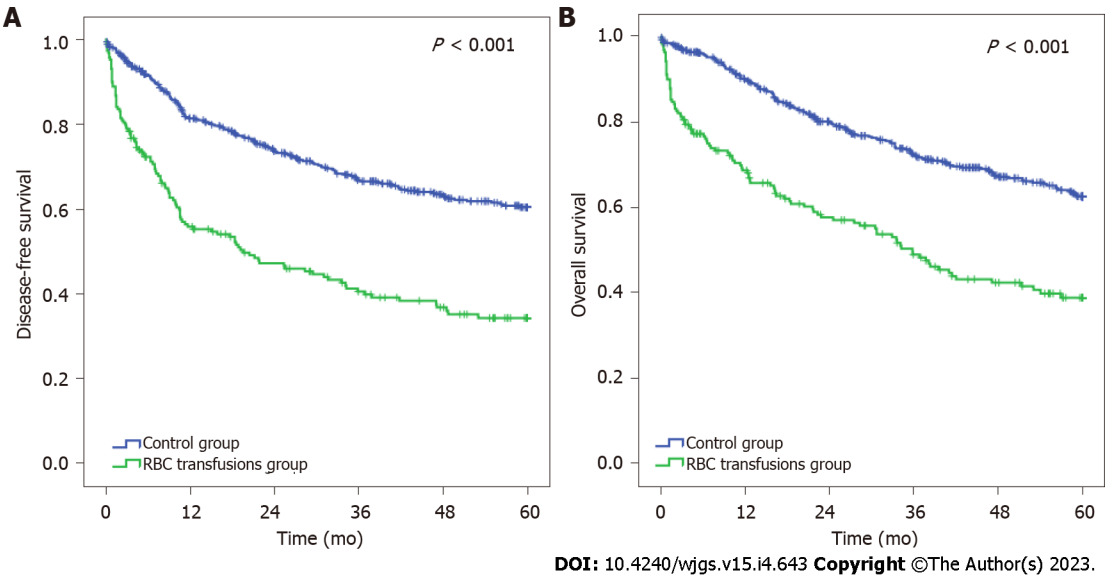
RESULTS

Population description

During the selected period, 718 patients underwent radical gastrectomy with curative intent. Among them, 189 (26.3%) patients received perioperative RBC transfusion (RBC transfusion group). The

Table 1 Clinical characteristics of patients according to perioperative red blood cell transfusion

Variable	Non-transfusion	Red blood cell transfusion	*P* value
	n = 529 (%)	*n* = 189 (%)	
Sex			0.318
Female	215 (40.6)	69 (36.5)	
Male	314 (59.4)	120 (63.5)	
Age (yr), mean ± SD	61.3 ± 12.4	65.6 ± 11.6	< 0.001
Body mass index (kg/m²), mean ± SD	24.6 ± 4.6	23.7 ± 11.6	0.019
Hemoglobin (g/dL), mean ± SD	12.5 ± 2.1	10.8 ± 2.2	< 0.001
Albumin (g/dL), mean ± SD	4.0 ± 0.6	3.7 ± 0.7	< 0.001
Neutrophil-lymphocyte ratio, mean ± SD	2.65 ± 2.77	3.26 ± 2.75	0.010
American Society of Anesthesiologists			< 0.001
I/II	404 (76.4)	11 (58.7)	
III/IV	125 (23.6)	78 (41.3)	
Charlson-Deyo comorbidity index			0.014
0	360 (68.1)	110 (58.2)	
≥ 1	169 (31.9)	79 (41.8)	
Preoperative chemotherapy			0.095
No	237 (44.8)	98 (51.9)	
Yes	292 (55.2)	91 (48.1)	



DOI: 10.4240/wjgs.v15.i4.643

Figure 1 Disease-free survival and overall survival of patients according to perioperative red blood cell transfusion. RBC: Red blood cell.

remaining 529 (73.6%) patients who did not receive any perioperative RBC formed the non-transfusion group.

Among 189 patients who received RBC transfusion, 23 underwent transfusion in the intraoperative period, 133 in the postoperative period, and 33 in both periods (intra and postoperative). Besides RBC transfusion, FFP transfusions occurred in 12 patients (6.4%) and 2 patients (1.1%) also received PC transfusion.

Patients in the RBC transfusion group had older age ($P < 0.001$), higher CCI ($P = 0.014$), ASA III/IV score ($P < 0.001$), and lower BMI ($P = 0.016$) compared with patients who did not receive a transfusion. Higher NLR ($P = 0.010$) and lower preoperative hemoglobin ($P < 0.001$) and albumin levels ($P < 0.001$) were also associated with the RBC transfusions group. There was no difference regarding preoperative

Table 2 Surgical and postoperative characteristics of patients according to perioperative red blood cell transfusion

Variable	Non-transfusion	Red blood cell transfusion	*P* value
	n = 529 (%)	*n* >= 189 (%)	
Type of resection			< 0.001
Subtotal	337 (63.7)	91 (48.1)	
Total	192 (36.3)	98 (51.9)	
Surgical access			< 0.001
Open	396 (74.9)	168 (88.9)	
Minimally invasive	133 (25.1)	21 (11.1)	
Type of lymphadenectomy			< 0.001
D1	104 (19.7)	72 (38.1)	
D2	425 (80.3)	117 (61.9)	
Operation time (min), mean ± SD	243.5 ± 74.3	246.6 ± 77.3	0.636
Intraoperative blood loss (mL), mean ± SD	299.7 ± 336.7	342.0 ± 362.6	0.186
Intraoperative complications			0.209
No	508 (96.0)	178 (94.2)	
Yes	21 (4.0)	11 (5.8)	
Length of postoperative stay (d), mean ± SD	10.4 ± 7.2	21.6 ± 17.4	< 0.001
Postoperative complications (Clavien-Dindo)			< 0.001
0/I/II (minor)	488 (92.2)	112 (59.3)	
III/IV/V (major)	41 (7.8)	77 (40.7)	
Adjuvant chemotherapy			0.001
No	287 (54.3)	129 (68.3)	
Yes	242 (45.7)	60 (31.7)	
Mortality			
30-d	8 (1.5)	19 (10.1)	< 0.001
90-d	16 (3.1)	36 (19.0)	< 0.001

chemotherapy between the groups (P = 0.095). Complete clinical characteristics are demonstrated in Table 1.

Regarding surgical procedures and postoperative features demonstrated in Table 2, total gastrectomy (P < 0.001) and open surgery (P < 0.001) were more frequent in the RBC transfusion group. There was no difference regarding the duration of surgery (P = 0.636), intraoperative complications (P = 0.209), and intraoperative blood loss (P = 0.186) between the two groups. Length of hospital stay was higher in the transfusion group (10.4 d *vs* 21.6 d, P < 0.001). Considering the postoperative outcomes, the rates of POC (P < 0.001) and mortality at 30 and 90 d were significantly higher in the transfusion group (P < 0.001).

The pathological characteristics of the two groups are shown in Table 3. Larger tumor size (P < 0.001), intestinal Lauren type (P = 0.002), pT3/T4 (P < 0.001), and advanced pathological TNM (pTNM) stages (P < 0.001) were more frequent in the RBC transfusion group. The presence of lymphatic (P = 0.027), vascular (P = 0.017), and perineural (P = 0.001) invasions was also associated with the transfusion group.

In multivariate analysis, low preoperative hemoglobin (P < 0.001), low albumin (P = 0.017), total gastrectomy (P = 0.011), open surgical access (P = 0.034), and occurrence of major POC (P < 0.001) were independent factors associated to a higher risk of receiving perioperative RBC transfusions (Table 4).

Survival analysis

The median follow-up time for the entire cohort of cases was 35.6 mo. During the follow-up period, 174 patients had disease recurrence and 261 died.

Patients who received perioperative RBC transfusions had worse DFS and OS than the non-transfusion group (P < 0.001) (Figure 1). The median DFS and OS for the RBC transfusion group were 19.5 and 35.8 mo, respectively.

Table 3 Pathological characteristics of patients according to perioperative red blood cell transfusion

Variable	Non-transfusion	Red blood cell transfusion	*P* value
	n >= 529 (%)	*n* = 189 (%)	
Tumor size (cm), mean ± SD	4.3 ± 2.6	6.0 ± 3.6	< 0.001
Tumor location			0.039
Lower	327 (61.8)	95 (50.3)	
Middle	130 (24.6)	60 (31.7)	
Upper	64 (12.2)	29 (15.3)	
Diffuse	8 (1.5)	5 (2.6)	
Lauren histologic type[1]			0.002
Intestinal	276 (52.6)	124 (66.0)	
Diffuse/mixed	249 (47.4)	64 (34.0)	
Histological differentiation[1]			0.056
Well/moderate	245 (46.7)	103 (54.8)	
Poor	280 (53.3)	85 (45.2)	
Lymphatic invasion			0.027
No	293 (55.4)	87 (46.0)	
Yes	236 (44.6)	102 (54.0)	
Vascular invasion			0.017
No	364 (68.8)	112 (59.3)	
Yes	165 (31.2)	77 (40.7)	
Perineural invasion			0.001
No	304 (57.5)	83 (43.9)	
Yes	225 (42.5)	106 (56.1)	
pT status			< 0.001
pT1/T2	248 (46.9)	54 (28.6)	
pT3/T4	281 (53.1)	135 (71.4)	
Lymph nodes harvested, mean ± SD	41.5 ± 19.4	39.2 ± 19.5	0.175
pN status			0.126
pN0	244 (46.1)	75 (39.7)	
pN+	285 (53.9)	114 (60.3)	
pTNM stage			< 0.001
I/II	329 (62.2)	86 (45.5)	
III/IV	200 (37.8)	103 (54.5)	

[1]This information was not available in 5 medical records.
pTNM: Pathological tumor node metastasis.

In multivariate analysis, total gastrectomy, more advanced pT stage, LN metastasis, D1 Lymphadenectomy, the occurrence of POC, and perioperative RBC transfusion were independent factors associated with worse DFS (Table 5).

ASA, type of gastrectomy, lymphadenectomy, pT, pN, POC, and perioperative RBC transfusion were factors significantly associated with OS in the multivariate model (Table 5).

Perioperative RBC transfusion remained an independently associated risk factor for both DFS [hazard ratio (HR) = 1.49, 95%CI: 1.14-1.94, P = 0.003] and OS (HR = 1.34, 95%CI: 1.02-1.77, P = 0.038).

Table 4 Univariate and multivariate analyses of factors associated with risk of receiving perioperative red blood cell transfusion

Variable	Univariate			Multivariate		
	OR	95%CI	*P* value	OR	95%CI	*P* value
Male *vs* female	1.19	0.85-1.68	0.319			
Age ≥ 65 yr *vs* < 65 yr	1.48	1.06-2.07	0.02	1.2	0.79-1.81	0.394
Charlson ≥ 1 *vs* 0	1.53	1.09-2.15	0.015	1.22	0.76-1.97	0.402
ASA III/IV *vs* I/II	2.27	1.60-3.23	< 0.001	1.18	0,72-1.94	0.507
HB < 11 g/dL *vs* ≥ 11 g/dL	4.7	3.30-6.70	< 0.001	4.32	2.76-6.78	< 0.001
ALB < 3.5 g/dL *vs* ≥ 3.5 g/dL	3.49	2.29-5.31	< 0.001	1.86	1.12-3.09	0.017
Total gastrectomy *vs* distal	1.89	1.35-2.65	< 0.001	1.71	1.13-2.60	0.011
Open surgery *vs* MIS	2.69	1.64-4.41	< 0.001	1.91	1.05-3.47	0.034
Major POC *vs* non/minor POC	8.18	5.32-12.59	< 0.001	8.83	5.28-14.79	< 0.001
Intraoperative intercurrence *vs* none	1.49	0.71-3.16	0.293			

ASA: American Society of Anesthesiologists; OR: Odds ratio; HB: Serum hemoglobin; ALB: Serum albumin; MIS: Minimally invasive surgery; POC: Postoperative complications.

DISCUSSION

During the progression of GC, cachexia and uncontrolled tumor bleeding may induce severe anemia leading to life-threatening conditions and worse clinical outcomes. In this scenario, perioperative RBC transfusion is indicated to improve performance and decrease morbidity in the postoperative period[4,18,19]. On the other hand, recent advances in immunology have questioned the role of immunosuppression triggered by transfusion and its impact on tumor recurrence in gastrointestinal tract neoplasms [20-22].

In our retrospective cohort composed of 718 patients, perioperative RBC transfusions were related to worse DFS and OS. It is crucial to recognize expressive baseline differences between patients who received RBC transfusions and those who did not. Patients in the transfusion group were older and presented more unfavorable clinical conditions. Further, a higher frequency of total gastrectomy, open surgery, and advanced tumors was observed in the transfusion group. Other studies also reported the same heterogeneity noted in the analyzed population[9-11,23]. Even though, after multivariate analysis, we found that perioperative RBC transfusion was an independent factor related to recurrence and survival.

Although there is a vast amount of literature investigating the impact of blood components on the oncologic prognosis of GC patients, the current data still present discordant results[11,24,25]. This situation will probably be extended since it is difficult to perform a randomized controlled trial (RCT) in this scenario since in many situations the need for transfusion is a life-threatening condition. Further, most meta-analyses stress that current studies lack high-quality data[26]. In the recent retrospective studies that found no impact of RBC transfusions on long-term survival, some of them applied propensity-score matched analysis; however, preoperative hemoglobin and intraoperative blood loss remain as factors that could not be matched between groups[11,27]. Despite the knowledge of the relevance of anemia in the perioperative setting, conflicting data persist around the impact of intraoperative blood loss on OS and DFS of GC patients[28-30]. Grasso *et al*[31] carried out prospective studies comparing different hemoglobin threshold values for the indication of transfusion may be an alternative to define this issue.

The current hypothesis that explains the biological association between blood components and poorer oncological outcomes is that transfusion-related immunomodulation (TRIM) acts as a propagating factor for the TH2 immune response, favoring a pro-tumoral environment through inhibition of interleukin (IL)-2 and stimulation of suppressor T cells, allowing tumor spread and recurrence[20-22]. The recent application of immunotherapy in gastrointestinal tract cancers provided additional data by demonstrating that TRIM could be acting as an opponent and negatively impacting its effectiveness and survival[32]. Another important topic related to the immune response is the data provided by Lange *et al*[33] that showed no difference in using leukocyte depletion in long-term survival, underlining that specific constituents of allogeneic blood may mediate the TRIM effect. This same result was detected when RBC transfusions were applied to other neoplasms[34].

Preoperative hemoglobin and albumin were independent factors associated with RBC transfusions. Since GC causes feeding and bleeding disturbances, aggressive protocols for improving hematologic and nutritional preoperative status must be paramount in clinical compensation ahead of surgical

Table 5 Univariate and multivariate analyses of factors associated with disease-free and overall survival

	Univariate			Multivariate		
	HR	95%CI	*P* value	HR	95%CI	*P* value
Disease-free survival						
Male *vs* female	1.27	0.99-1.62	0.051			
Age ≥ 65 yr *vs* < 65 yr	1.25	0.99-1.57	0.059			
Charlson ≥ 1 *vs* 0	1.33	1.05-1.68	0.018	1.22	0.93-1.60	0.159
ASA III/IV *vs* I/II	1.83	1.44-2.33	< 0.001	1.24	0.93-1.66	0.149
Total gastrectomy *vs* distal	1.77	1.41-2.33	< 0.001	1.45	1.14-1.84	0.002
D1 *vs* D2	1.61	1.25-2.07	< 0.001	1.4	1.06-1.85	0.017
pT3/T4 *vs* pT1/T2	2.87	2.19-3.76	< 0.001	2.05	1.50-2.79	< 0.001
pN+ *vs* pN0	2.81	2.17-3.65	< 0.001	1.97	1.47-2.65	< 0.001
Major POC *vs* non/minor POC	2.86	2.19-3.73	< 0.001	2.15	1.62-2.86	< 0.001
Non-CMT *vs* received CMT	1	0.79-1.26	0.995			
Perioperative RBC transfusion *vs* non	2.39	1.88-3.02	< 0.001	1.49	1.14-1.94	0.003
Overall survival						
Male *vs* female	1.25	0.97-1.61	0.084			
Age ≥ 65 yr *vs* < 65 yr	1.41	1.11-1.80	0.006	1.24	0.95-1.61	0.113
Charlson ≥ 1 *vs* 0	1.35	1.06-1.73	0.017	1.11	0.83-1.49	0.473
ASA III/IV *vs* I/II	2.02	1.57-2.61	< 0.001	1.36	1.01-1.85	0.048
Total gastrectomy *vs* distal	1.65	1.29-2.10	< 0.001	1.33	1.03-1.71	0.027
Lymphadenectomy D1 *vs* D2	1.81	1.39-2.35	< 0.001	1.51	1.11-2.05	0.008
pT3/T4 *vs* pT1/T2	2.92	2.19-3.90	< 0.001	2.19	1.57-3.06	< 0.001
pN+ *vs* pN0	2.7	2.06-3.56	< 0.001	1.87	1.37-2.56	< 0.001
Major POC *vs* non/minor POC	3.33	2.53-4.38	< 0.001	2.65	1.97-3.56	< 0.001
Non-CMT *vs* received CMT	1.05	0.83-1.34	0.678			
Perioperative RBC transfusion *vs* non	2.33	1.81-2.99	< 0.001	1.34	1.02-1.77	0.038

ASA: American Society of Anesthesiologists; HR: Hazard ratio; POC: Postoperative complications; CMT: Chemotherapy; RBC: Red blood cell.

treatment. Current data support those policies in clinical and financial terms since Jericó *et al*[35] demonstrated reduced direct and indirect spent resources, lower hospital length of stay, and readmissions succeeding radical gastrectomy[36].

Interestingly, D1 lymphadenectomy was associated with worse DFS and OS. D2 lymphadenectomy is considered a more aggressive procedure and the standard in GC treatment. However, even though 42% of our population were composed of patients with more advanced stages III/IV, some of them did not have the clinical conditions to perform D2 lymphadenectomy. So, the employment of D1 lymphadenectomy rarely was an oncological indication as proposed in the 2018 JGCA guideline for GC treatment [14]. It was mainly indicated for patients with unfavorable medical conditions to reduce POC and mortality, as previously reported by our service[37].

Open surgical access was associated with the transfusion group. Minimally invasive surgery causes less tissue damage to the abdominal wall with reports of less intraoperative blood loss on several RCTs [38-40]. However, intraoperative blood loss, although higher in the transfusion group, did not show a significant difference between our groups. Intraoperative blood loss is a variable that is difficult to measure in clinical practice. The retrospective nature of the study also makes accurate measurement difficult. Despite this possible bias, we also found that there was no difference between the groups in the occurrence of intraoperative complications, a variable that is very well documented. Baiocchi *et al* [15] reported a low 2% incidence of intraoperative complications in GC surgery. In our study, a 4.45% incidence of intraoperative complications was reported, represented mainly by intraoperative bleeding. Those numbers indicate adequate documentation of the intraoperative complications in our medical reports and eventually, intraoperative blood loss did not differ between the groups. Therefore, our best

efforts should focus on better patient perioperative management to avoid RBC transfusion[41].

Regarding POC, the multivariate analysis indicated that major POC presented the highest OR related to RBC transfusion among the eight selected variables. It must also be emphasized that the transfusion in the postoperative period was more frequent than in the pre and intraoperative periods. The importance of POC was already stressed in 2020 through a meta-analysis evaluating their repercussions on GC survival[42]. A plausible reason for cancer recurrence is the pro-inflammatory state caused by surgical trauma, where IL-6 suppresses the specific and non-specific immune responses. This mechanism could be synergically associated with IL-2 suppression caused by TRIM since a retrospective analysis found a signature of cytokines (including IL-2 and IL-6) and angiogenic factors associated with poor DFS and OS[43]. Further, POCs may prevent patients to return to the intended oncological treatment, a known prognostic factor[44].

The performance of retrospective studies has some limitations inherent to its design. Despite the relevant number of patients included for a Western center, the numerous variables evaluated are confounding factors for the adequate definition of the association between RBC transfusion and prognosis. We chose multivariate logistic regression to adjust the potential bias of covariates. Ultimately, perioperative transfusion of RBC was an independent prognostic factor together with known prognostic factors such as pTNM stage, demonstrating a good accuracy of the performed analyses. As another limitation, we must point out that our data were collected over 13 years, so variations and advances in oncological treatments and surgical techniques may cause additional heterogeneity.

CONCLUSION

In GC patients undergoing curative surgeries, poor clinical status, more extensive surgical procedures, and advanced tumor stages are common features in patients receiving RBC transfusions. In addition to being associated with higher rates of POC and mortality, receiving an RBC transfusion proves to be an independent factor associated with worse survival.

ARTICLE HIGHLIGHTS

Research background

Anemia and intraoperative blood loss are frequent issues in gastric cancer (GC) surgical treatment. The current literature still debates the impact of perioperative blood transfusion on GC survival.

Research motivation

Red blood cell (RBC) transfusions are sometimes required for patients undergoing surgery for GC. However, the prognostic impact of perioperative RBC transfusion in GC is controversial.

Research objectives

We analyzed the influence of RBC transfusions on the prognosis of patients with gastric adenocarcinoma undergoing gastrectomy with curative intention.

Research methods

We retrospectively evaluated all GC patients who underwent gastrectomy between 2009 and 2021. Patients were divided into transfusion group and non-transfusion group for analysis. RBC transfusions that occurred intraoperatively and postoperatively within 30 d were considered.

Research results

A total of 718 patients were included, and 189 (26.3%) patients received RBC transfusions. Patients who received transfusions had unfavorable clinical and pathological characteristics, and underwent more extensive surgical procedures. Patients who received RBC transfusions had worse survival compared to those who did not. In multivariate analysis, receiving an RCB transfusion was an independent factor associated with poor disease-free survival (DFS) and overall survival (OS).

Research conclusions

Even though the patients who receive RCB transfusion have worse clinical conditions, we found that perioperative transfusion represents an independent factor associated with poor prognosis, with worse DFS and OS.

Research perspectives

The application of blood component transfusion in randomized clinical trials presents ethical

limitations; however, the current design of retrospective studies still interferes with controlling confounding factors. With this study, we endorse a favorable position for increasing preoperative and postoperative care to avoid RBC transfusion. Further, our findings provide additional data for future meta-analysis.

FOOTNOTES

Author contributions: Kawakami LE and Bonomi PB contributed to data retrieval, critical analysis, and manuscript drafting; Pereira MA contributed to data retrieval, critical analysis, statistical analysis, and manuscript review; Carvalho FO and Sampaio LR contributed to data retrieval and manuscript review; Ribeiro Jr. U, Zilberstein B, and Carneiro-D'Albuquerque LA contributed to critical analysis and manuscript review; Ramos MFKP contributed to study design, data retrieval, critical analysis, and manuscript drafting.

Institutional review board statement: The study was approved by the Hospital Ethics Committee and registered online (https://plataformabrasil.saude.gov.br; CAAE: 59337222.7.0000.0068).

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: Brazil

ORCID number: Lucas Eiki Kawakami 0000-0003-3666-0062; Pedro Barzan Bonomi 0000-0001-9540-3512; Marina Alessandra Pereira 0000-0002-6865-0988; Fabrício Oliveira Carvalho 0000-0002-6262-9424; Ulysses Ribeiro Jr 0000-0003-1711-7347; Bruno Zilberstein 0000-0002-1809-8558; Luciana Ribeiro Sampaio 0000-0003-4888-3546; Luiz Augusto Carneiro-D'Albuquerque 0000-0001-7607-7168; Marcus Fernando Kodama Pertille Ramos 0000-0003-0200-7858.

S-Editor: Zhang H
L-Editor: Wang TQ
P-Editor: Zhang H

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World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2023 April 27; 15(4): 655-663

DOI: 10.4240/wjgs.v15.i4.655

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Clinical Trials Study

Endoscopic ultrasound-guided intraportal injection of autologous bone marrow in patients with decompensated liver cirrhosis: A case series

Shao-Peng Zheng, Ao-Jian Deng, Jing-Jing Zhou, Ling-Zhi Yuan, Xiao Shi, Fen 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): 0
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Fusaroli P, Italy; Tomizawa M, Japan

Received: October 17, 2022
Peer-review started: October 17, 2022
First decision: January 3, 2023
Revised: January 31, 2023
Accepted: March 21, 2023
Article in press: March 21, 2023
Published online: April 27, 2023

Shao-Peng Zheng, Ao-Jian Deng, Jing-Jing Zhou, Ling-Zhi Yuan, Xiao Shi, Fen Wang, Department of Gastroenterology, Third Xiangya Hospital of Central South University, Changsha 410013, Hunan Province, China

Shao-Peng Zheng, Ao-Jian Deng, Ling-Zhi Yuan, Fen Wang, Hunan Key Laboratory of Non-resolving Inflammation and Cancer, Central South University, Changsha 410000, Hunan Province, China

Corresponding author: Fen Wang, MD, PhD, Doctor, Professor, Department of Gastroenterology, Third Xiangya Hospital of Central South University, No. 138 Tongzi Road, Changsha 410013, Hunan Province, China. wfen-judy@csu.edu.cn

Abstract

BACKGROUND

Recently, stem cell therapy has been extensively studied as a promising treatment for decompensated liver cirrhosis (DLC). Technological advances in endoscopic ultrasonography (EUS) have facilitated EUS-guided portal vein (PV) access, through which stem cells can be precisely infused.

AIM

To investigate the feasibility and safety of fresh autologous bone marrow injection into the PV under EUS guidance in patients with DLC.

METHODS

Five patients with DLC were enrolled in this study after they provided written informed consent. EUS-guided intraportal bone marrow injection with a 22G FNA needle was performed using a transgastric, transhepatic approach. Several parameters were assessed before and after the procedure for a follow-up period of 12 mo.

RESULTS

Four males and one female with a mean age of 51 years old participated in this study. All patients had hepatitis B virus-related DLC. EUS-guided intraportal bone marrow injection was performed in all patients successfully without any complications such as hemorrhage. The clinical outcomes of the patients revealed improvements in clinical symptoms, serum albumin, ascites, and Child-Pugh

scores throughout the 12-mo follow-up.

CONCLUSION
The use of EUS-guided fine needle injection for intraportal delivery of bone marrow was feasible and safe and appeared effective in patients with DLC. This treatment may thus be a safe, effective, non-radioactive, and minimally invasive treatment for DLC.

Key Words: Endoscopic ultrasonography; Fine needle injection; Portal vein; Decompensated liver cirrhosis; Bone marrow

Core Tip: In this study, we showed that the use of endoscopic ultrasonography (EUS)-guided fine needle injection for intraportal delivery of stem cells was feasible and safe and appeared effective in patients with decompensated liver cirrhosis (DLC). And it is the first attempt to investigate the feasibility and safety of fresh autologous bone marrow injection into the portal vein under EUS guidance in patients with DLC.

Citation: Zheng SP, Deng AJ, Zhou JJ, Yuan LZ, Shi X, Wang F. Endoscopic ultrasound-guided intraportal injection of autologous bone marrow in patients with decompensated liver cirrhosis: A case series. *World J Gastrointest Surg* 2023; 15(4): 655-663
URL: https://www.wjgnet.com/1948-9366/full/v15/i4/655.htm
DOI: https://dx.doi.org/10.4240/wjgs.v15.i4.655

INTRODUCTION

Cirrhosis refers to a late stage of liver fibrosis caused by chronic liver damage due to various etiologies such as alcohol and viral hepatitis. Liver cirrhosis (LC) is the 11th most common cause of death worldwide[1]. The most frequent clinical manifestations of hepatic decompensation include ascites, variceal bleeding, hepatic encephalopathy, and jaundice. The prognosis of these patients is worse and significantly shorter than that of patients with compensated cirrhosis[2]. Despite various medical therapies, the morbidities and mortality associated with decompensated LC (DLC) is high. To date, liver transplantation is the only curative treatment for DLC. However, the shortage of donor livers, immunological rejection, surgical complications, and high cost greatly limit the clinical application of liver transplantation.

In recent years, stem cell therapy has been extensively studied as a promising treatment for DLC. Stem cells can not only differentiate into hepatocytes, but also play an important role in anti-fibrosis, anti-inflammation, and the immune regulation of liver diseases[3-7]. Thus, stem cell therapy has the potential to restore normal liver function by increasing the number of normal hepatocytes and improving the pathological structure of liver tissue. However, the application of this therapy has been hindered due to the genomic instability and the tumorigenicity of stem cells[8,9].

Strategies such as liver-targeted stem cell therapy can not only increase the number of therapeutic stem cells in the liver but also reduce the distribution of stem cells in non-targeted organs and the total amount of infused stem cells, and therefore reduce the risk of malignant transformation of stem cells. With the recent technological advancements in endoscopic ultrasonography (EUS) and its instrumentation, EUS offers a potential access to the portal vein[10-12], through which the stem cells can be precisely delivered to the liver. Due to the proximity of the portal vein to the gastrointestinal tract, EUS-guided access to the portal venous system has been studied as an alternate approach to standard routes for portal vein angiography and portal pressure gradient measurement. To date, data on EUS-guided intraportal fine needle injection (FNI) of stem cells or bone marrow in patients with DLC remain scarce. In this prospective study, we performed fresh autologous bone marrow injection into the portal venous system of patients with DLC under the guidance of EUS and evaluated its safety and efficacy during a 12-mo period of follow-up.

MATERIALS AND METHODS

In this study, patients with DLC were enrolled for EUS-guided intraportal autologous bone marrow infusion between January 2020 and February 2020. This study was reviewed and approved by the institutional ethics committee of the local hospital (No: 2018-S403; date: December 26, 2018). Registration

number of this study was ChiCTR2000035269 in Chinese Clinical Trial Registry. Written informed consent was obtained from all enrolled patients. All methods related to this study were carried out in accordance with the ethical standards of the declaration of Helsinki concerning research involving human subjects. Patients satisfying the following criteria were enrolled in this study.

Inclusion criteria

The inclusion criteria were: (1) Age > 18 years; (2) DLC with ascites; (3) alcoholic or posthepatitic cirrhosis; and (4) endoscopy was tolerable after anesthesia evaluation.

Exclusion criteria

The exclusion criteria were: (1) Pregnant or lactating women; (2) patients with severe anemia and coagulation dysfunction (international normalized ratio > 1.5); (3) failure of hemostasis treatment for gastrointestinal bleeding in the past month; (4) presence of spontaneous peritonitis, hepatic encephalopathy, hepatorenal syndrome, and acute infection; (5) presence of coexisting severe heart, lung, kidney, blood system, or other diseases, or history of mental illness; and (6) malignant tumor of the liver or other organs.

Therapeutic methods

Bone marrow sampling: All patients were given the standard medical treatment for LC and under antiviral therapy against hepatitis B after hospitalization. After preoperative evaluation and enrollment in this study, autologous bone marrow sampling was performed. The aspiration of bone marrow were performed in the sterile operating room. The right posterior superior iliac spine was selected as the puncture site, and the skin was cleaned with 70% alcohol. The skin, subcutaneous tissues, and periosteum overlying the selected site for puncture were infiltrated with local anesthesia, and serial punctures from multiple sites were performed. With needles passing perpendicularly into the cavity of the ileum at a point just near the right posterior superior iliac spine, about 30 mL of the patients' bone marrow was collected in a syringe containing 10 mL of heparin saline (62.5 U/mL). And the bone marrow samples were subjected to transplantation immediately after aspiration in the same sterile operating room. In addition, 1 mL of bone marrow was collected for flow cytometry to count the total number of nucleated cells and the proportion of $CD34^+$ cells, which have the character of plasticity and can change into hepatocytes.

Endoscopic procedure: The EUS-guided portal vein puncture was performed by experienced endosonographers using an endoscopic ultrasound system (EU-ME2, Olympus, Tokyo, Japan), a linear echoendoscope (UCT-260, Olympus, Tokyo, Japan), and a 22G FNA needle (Cook Medical, Winston-Salem, NC, United States). First, under intravenous anesthesia with propofol, the echoendoscope was introduced into the stomach transorally. Then, after identification of the portal vein (PV), the endoscopic FNA needle was advanced through the liver parenchyma into the lumen of the PV under Doppler imaging. After puncturing the intrahepatic PV, the stylet was withdrawn from the needle and blood was aspirated before injection to confirm the position of the needle. Then, through the FNA needle, a total of 40 mL of fresh autologous bone marrow fluid (30 mL of fresh autologous bone marrow and 10 mL of heparin saline) was injected into the PV at an approximate rate of 1 mL/min under continuous ultrasonic monitoring. Needle placement was meticulously monitored during injection to ensure consistency. It usually takes about 30-40 min for the whole injection, and the injection is administered under the guidance of endoscopic ultrasound, which helps us to maintain the infusion rate and needle stability. Following completion of the infusion, the FNA needle was gradually removed. Upon withdrawal of the needle, just prior to leaving the liver capsule, color Doppler imaging was used to ensure that there was no flow in the needle track. Finally, the needle was removed, followed by compression at the puncture site for about 5 min using the ultrasonic stylet. Before withdrawing the echoendoscope, intrahepatic or perihepatic hemorrhage or hematoma was ruled out by color Doppler. Subsequently, the patient was placed under close observation and the ongoing medical treatment was continued.

Follow-up

The endpoint of the follow-up period was 12 mo after the procedure. During the follow-up visits, clinical history was collected and a physical examination, laboratory tests, and abdominal ultrasonography were performed. The main clinical symptoms noted were the presence/absence of ascites, variceal bleeding, hepatic encephalopathy, and jaundice. Laboratory tests included a complete hemogram, liver function tests, coagulation profile, serum hyaluronic acid, serum laminin, serum collagen IV, and serum procollagen III. Abdominal ultrasound emphasized the grade of ascites, the PV diameter, portal vein thrombosis, and neoplastic lesions in the liver. At the same time, elastography was performed by ultrasound to estimate the liver stiffness (LS) and the fat attenuation parameters.

Statistical analysis

The quantitative variables are described as the mean ± SD. The changes in the parameters relative to

baseline at 1 mo, 3 mo, 6 mo, and 12 mo after treatment were determined using analysis of variance (ANOVA) with Fisher's protected least-significant difference test. The IBM® SPSS® for Windows version 25.0 software was used for statistical data analyses.

RESULTS

Baseline characteristics

In this study, five patients (4 males and 1 female) were included. The etiology of cirrhosis in all patients was hepatitis B virus infection. The mean age of the patients was 51 (range 30-71) years. The main clinical symptoms were abdominal distention (3/5), gastrointestinal bleeding (1/5), edema (1/5), and abdominal pain (1/5). The total number of nucleated cells in 30 mL bone marrow was 300-500 × 10^6 and the percentage of $CD34^+$ cells was 0.52%-1.73%. Detailed characteristics are shown in Table 1. The follow-up period was 12 mo.

Feasibility

The intrahepatic part of the PV could be clearly demonstrated by EUS in all patients. Access to the targeted vessel was accomplished without any failures. All patients successfully underwent EUS-guided FNI into the PV with a 22G FNA needle. The precise delivery of a total of 40 mL of bone marrow fluid to the liver was achieved in all patients. The procedure was performed only one time in all patients (Figure 1).

Complications

No complications such as hemorrhage, hematoma, perforation, fever, pain, infection, acute liver failure, or hepatic encephalopathy were observed during or after the procedure. Neither PV thrombosis nor liver neoplastic lesions was detected by abdominal ultrasonography in any patient during the 12-mo follow-up period. No patient died during the follow-up period.

Clinical outcomes

All patients survived during the 12-mo follow-up and exhibited an improvement in their clinical symptoms. Moreover, no patient experienced gastrointestinal bleeding during the follow-up period.

The serum albumin (ALB) level increased in the early postoperative period compared with that before the procedure, and reached the maximum at 6 mo (Figure 2A). In the 12th mo, the serum ALB level decreased slightly but was still within the normal range. The serum ALB levels in the first month and third month after the procedure were higher than the baseline level (35.76 g/L ± 5.87 g/L *vs* 27.58 g/L ± 4.91 g/L, $P < 0.01$; 34.64 g/L ± 4.10 g/L *vs* 27.58 g/L ± 4.91 g/L, $P < 0.05$).

Generally, the grade of ascites detected by abdominal ultrasonography was reduced in the early postoperative period and continued to decrease during the first 6 mo after the procedure. However, there was a slight increase in size in the 12th mo, but it was still smaller than that at baseline (Figure 2B). However, the changes were not statistically significant at each follow-up time point compared with that before treatment.

The trend of Child-Pugh scores was similar to that of ascites (Figure 3A). Specifically, there were four patients with Child-Pugh class A and one patient with class B, and no patient had class C at the sixth month after treatment; however, there were one, three, and one patient with classes A, B, and C at baseline, respectively (Figure 3B).

DISCUSSION

The technology of EUS-FNI uncovers a novel pathway for stem cell infusion for the treatment of DLC. This study demonstrated that the use of EUS-FNI for intraportal delivery of stem cells was feasible and safe and could alleviate severity in patients with DLC.

In this study, we used EUS-FNI to directly transfuse the autologous bone marrow into the PV. Traditionally, stem cell therapy is administered through the peripheral vein[13], the hepatic artery under fluoroscopic guidance[14], and the PV under the guidance of abdominal ultrasound[15]. These approaches are effective, but not without limitations. The peripheral vein method has the limitations of poor targetability as well as high risk of side effects, including the tumorigenesis of normal organs. Compared to the hepatic artery, blood flow through the PV has a larger volume and slower velocity, which is more conducive for the implantation of stem cells. In addition, EUS prevents radiation exposure associated with fluoroscopy. Compared with abdominal ultrasound, EUS has the advantage of improved visualization of blood vessels within and around the liver with less interference by ascites, bowel gas, or abdominal wall fat. Other potential benefits include increased efficiency and convenience to patients who require concurrent esophagogastroduodenoscopy and EUS.

Table 1 Baseline characteristics of patients

Item	P1	P2	P3	P4	P5
Age (yr)	30	71	136	57	54
HGB (g/L)	63.00	107.00	3.91	81.00	115.00
RBC ($\times 10^{12}$/L)	2.15	3.05	28.00	2.74	4.22
PLT ($\times 10^{9}$/L)	61	92	2.18	78	115
WBC ($\times 10^{9}$/L)	2.80	3.34	41.00	2.81	2.07
ALT (U/L)	26	46	52	29	27
AST (U/L)	43	82	38	52	36
TBIL (μmol/L)	28.3	18.3	27.2	10.9	14.9
ALB (g/L)	26.2	23.5	16.0	25.0	36.0
PT (s)	18.0	13.3	40.3	16.0	16.8
APTT (s)	48.6	37.7	23.4	40.5	31.7
TT (s)	20.00	19.50	0.99	20.60	17.90
FIB (g/L)	1.48	1.60	405.76	1.64	1.95
HA (ng/mL)	124.35	674.70	204.40	297.91	123.04
LN (ng/mL)	41.15	33.83	67.56	73.10	25.86
IV-C (ng/mL)	77.16	122.50	81.95	57.27	25.47
PCIII (ng/mL)	74.20	125.50	14.00	58.48	28.56
Ascites (mm)	101	80	11	86	18
PV (mm)	11.0	10.0	24.8	10.0	16.0
LS (KPA)	37.9	29.8	283.0	18.0	20.2
FAP (db/m)	235	220	None	246	243
PVT	None	None	None	None	None
Neoplastic lesions	None	None	9	None	None
Child-Pugh score	10	9	136	9	6

IV-C: Collagen IV; ALB: Albumin; ALT: Alanine aminotransferase; APTT: Activated partial thromboplastin time; AST: Aspartate aminotransferase; FAP: Fat attenuation parameters; FIB: Fibrinogen; HA: Hyaluronic acid; HGB: Hemoglobin; LN: Laminin; LS: Liver stiffness; PC III: Procollagen III; PLT: Platelets; PT: Prothrombin time; PV: Portal vein; PVT: Portal vein thrombosis; RBC: Red blood cells; TBIL: Total bilirubin; TT: Thrombin time; WBC: White blood cells.

Although injury to adjacent vascular structures can be avoided using real-time Doppler, the risk of bleeding during EUS-FNI significantly determines the safety of operation, especially when performing FNI within the PV. The use of an optimally sized puncture needle in FNI can significantly reduce tissue injury and bleeding. Magno *et al*[16] investigated the differences in 19G, 22G, and 25G FNA needles for EUS-guided angiography in a live porcine model. The results revealed that the 25G FNA needle did not bring about any visible vascular injury or bleeding. The 22G needle left a visible puncture mark on the vessels without any active bleeding, while the 19G needle caused a localized vascular hematoma around the large-caliber vessels. However, smaller-caliber needles generated higher resistance to injection of the iodinated contrast. For this reason, the 22G FNA needle was selected to puncture the portal vein under the guidance of EUS. Moreover, a larger gauge needle size allows adequate flow of fresh bone marrow to minimize the time within the needle, and appears to reduce clotting of bone marrow compared with smaller gauge needles[17]. In our study, all patients were successfully treated with fresh autologous bone marrow injected into the PV with a 22G FNA needle under the guidance of EUS. No bleeding-related complications, such as hemorrhage or hematoma, were detected by Doppler. Moreover, no patient developed portal vein thrombosis during the 12-mo follow-up period. These results indicated that EUS-guided intraportal FNI using a 22G FNA needle can be a safe approach for bone marrow infusion.

In addition, the transgastric and transhepatic approach was chosen for the advancement of the needle as it was assumed to be safer than the transduodenal approach. This approach provided a natural

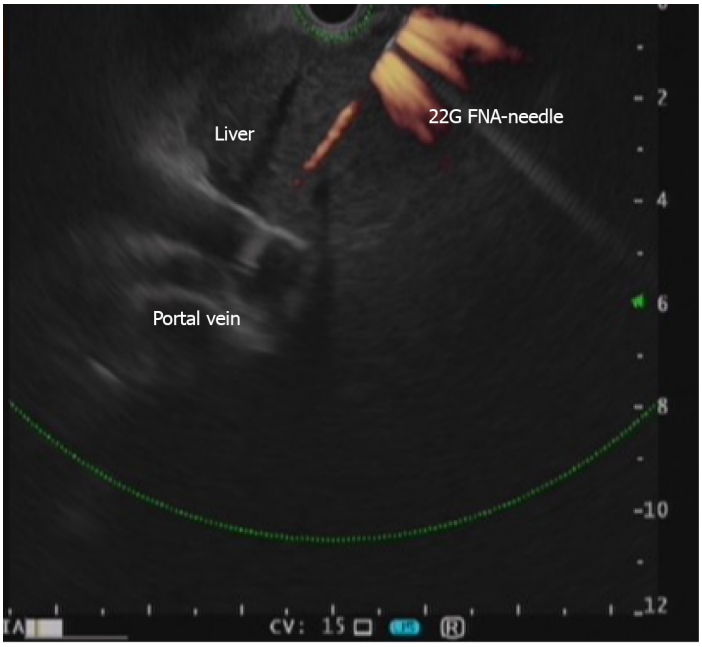

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Figure 1 Endoscopic ultrasonography-guided intraportal fine needle injection of autologous bone marrow.

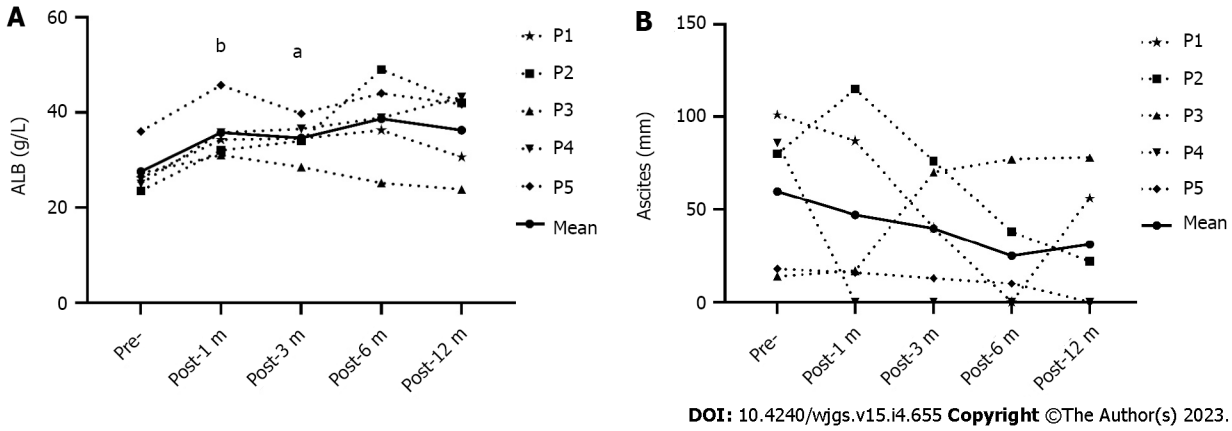

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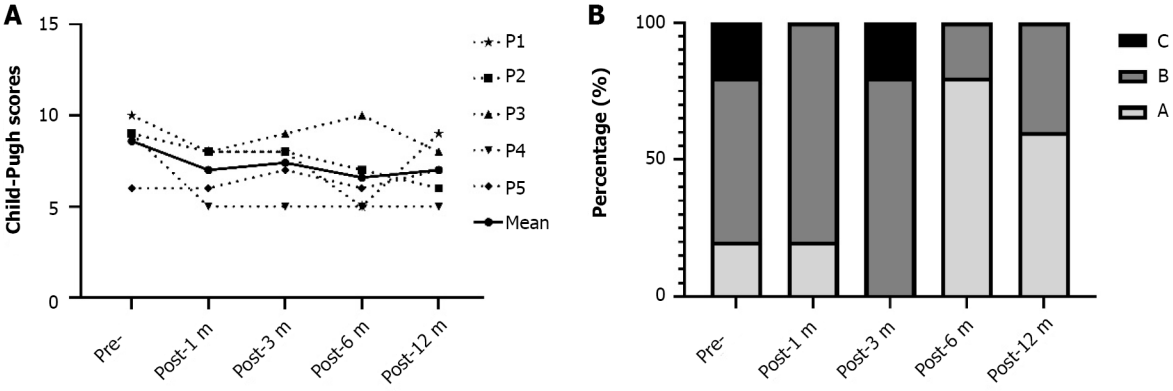
Figure 2 Changes in serum albumin and ascites in patients who underwent endoscopic ultrasonography-guided autologous bone marrow infusion. A: Serum albumin; B: Depth of ascites evaluated by abdominal ultrasound. ALB: Albumin. $^{a}P < 0.05$, $^{b}P < 0.01$.

tamponade of the needle track by the surrounding liver parenchyma during withdrawal, thereby preventing post-procedural bleeding[18]. Accordingly, color Doppler detected no bleeding within the needle track after the removal of needle in the current study. Furthermore, no complications such as perforation, infection, impaired liver function, or PV thrombosis were detected during the follow-up, suggesting that this operation was safe.

Drug delivery by EUS-guided intraportal FNI offers an accurate targetability. The concentration of drug within the liver is augmented while drug concentration in the peripheral circulation is reduced, which can increase the efficacy and reduce the side effects of stem cell therapy. Faigel *et al*[19] performed EUS-guided portal injection chemotherapy (EPIC) for treatment of hepatic metastases in a porcine model. In their study, pigs were treated with irinotecan, doxorubicin, or ALB-bound paclitaxel nanoparticles by either EPIC or systemic injection, and drug delivery by EPIC showed a higher hepatic concentration and a reduction in both systemic and cardiac levels compared to that by injection in systemic circulation. Owing to superior targetability, the volume of bone marrow used in our study was less and the clinical outcomes, especially serum ALB, ascites, and Child-Pugh score, were almost equally beneficial compared to systemic injection in a prior study[13].

There are several limitations of this study. This study was a single center, single arm clinical study. The sample size was small and there was no control group. Moreover, the follow-up period was short. Future multicenter and larger controlled studies with longer follow-up periods are required to



DOI: 10.4240/wjgs.v15.i4.655

Figure 3 Changes in Child-Pugh score and class in patients who underwent endoscopic ultrasonography-guided autologous bone marrow infusion. A: Child-Pugh scores; B: Classes.

determine the real potential of our novel technique for the treatment of DLC. Besides, we did not obtain the evidence of homing of the transplanted bone marrow in the liver, and we will design animal experiments to further prove this hypothesis.

Despite these limitations, the application of EUS-FNI for intraportal stem cell therapy can be combined with the EUS-guided intervention with coils and cyanoacrylate glue in the treatment of both DLC and gastric varices, which is one of its most common complications[20]. Most of all, a comprehensive endoscopic evaluation and therapy of patients with DLC by a gastroenterologist will be practical. In these cases, variceal screening, EUS elastography, EUS-guided portal pressure gradient measurement[21], EUS-guided liver biopsy[22], and EUS-FNI for treatment of varices and DLC may all be conducted in the same endoscopic session.

CONCLUSION

In conclusion, this study demonstrated that the use of EUS-guided FNI for intraportal delivery of bone marrow was feasible and safe and appeared effective in patients with DLC. This treatment may be a safe, effective, non-radioactive, and minimally invasive treatment for DLC.

ARTICLE HIGHLIGHTS

Research background

Bone marrow injection by endoscopic ultrasound (EUS)-guided intraportal fine needle injection (FNI) offers an accurate targetability, and this study proved that the use of EUS-guided FNI for intraportal delivery of bone marrow stem cells was feasible and safe and appeared effective in patients with decompensated liver cirrhosis (DLC).

Research motivation

We conducted this study to investigate the feasibility and safety of fresh autologous bone marrow injection into the portal vein under EUS guidance in patients with DLC.

Research objectives

To investigate the feasibility and safety of fresh autologous bone marrow injection into the portal vein under EUS guidance in patients with DLC.

Research methods

Five patients with DLC were enrolled in this study after they provided written informed consent. EUS-guided intraportal bone marrow injection with a 22G FNA needle was performed using a transgastric, transhepatic approach. Several parameters were assessed before and after the procedure for a follow-up period of 12 mo.

Research results

Four males and one female with a mean age of 51 years old participated in this study. All patients had

hepatitis B virus-related DLC. EUS-guided intraportal bone marrow injection was performed in all patients successfully without any complications such as hemorrhage. The clinical outcomes of the patients revealed improvements in clinical symptoms, serum albumin, ascites, and Child-Pugh scores throughout the 12-mo follow-up.

Research conclusions

The use of EUS-guided FNI for intraportal delivery of bone marrow was feasible and safe and appeared effective in patients with DLC. This treatment may thus be a safe, effective, non-radioactive, and minimally invasive treatment for DLC.

Research perspectives

Future multicenter and larger controlled studies with longer follow-up periods are required to determine the real potential of our novel technique for the treatment of DLC.

FOOTNOTES

Author contributions: Wan F designed the research; Zheng SP, Zhou JJ, Yuan LZ, Shi X, and Wan F performed the research; Zheng SP analyzed the data; Zheng SP and Deng AJ wrote the paper.

Supported by the National Natural Science Foundation of China, No. 82270594; National Natural Science Foundation for Youths of China, No. 882002614 and No. 82103151; Hunan Provincial Natural Science Foundation of China, No. 2020JJ4853; Scientific Research Project of Hunan Provincial Health Commission, No. 202103032097; Outstanding Youth Foundation of Hunan Province, No. 2022JJ20092; Hunan Provincial Natural Science Foundation of China for Youths, No. 2021JJ40935 and No. 2020JJ5609; and Wisdom Accumulation and Talent Cultivation Project of Third Xiangya Hospital of Central South University, No. YX202103.

Institutional review board statement: This study was reviewed and approved by the institutional ethics committee of the local hospital (Approval No. 2018-S403).

Clinical trial registration statement: This study is registered at Chinese Clinical Trial Registry https://www.chictr.org.cn. The registration identification number is ChiCTR2000035269.

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

Conflict-of-interest statement: There are no conflicts of interest to report.

Data sharing statement: The data presented in this study are available on request from the corresponding author.

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: Ao-Jian Deng 0000-0003-4124-0724; Xiao Shi 0000-0001-6762-0202; Fen Wang 0000-0002-1954-4273.

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

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World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2023 April 27; 15(4): 664-673

DOI: 10.4240/wjgs.v15.i4.664

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Clinical Trials Study

Computed tomography perfusion in differentiating portal hypertension: A correlation study with hepatic venous pressure gradient

Jian Dong, Yu Zhang, Yi-Fan Wu, Zhen-Dong Yue, Zhen-Hua Fan, Chun-Yan Zhang, Fu-Quan Liu, Lei 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: Ott G, Germany; van Kester MS, Netherlands

Received: December 20, 2022
Peer-review started: December 20, 2022
First decision: January 9, 2023
Revised: January 11, 2023
Accepted: March 23, 2023
Article in press: March 23, 2023
Published online: April 27, 2023

Jian Dong, Chun-Yan Zhang, Department of Radiology, Beijing Shijitan Hospital, Capital Medical University, Beijing 100038, China

Yu Zhang, Yi-Fan Wu, Zhen-Dong Yue, Zhen-Hua Fan, Fu-Quan Liu, Lei Wang, Department of Interventional Radiology, Beijing Shijitan Hospital, Capital Medical University, Beijing 100038, China

Corresponding author: Lei Wang, MD, Doctor, Department of Interventional Radiology, Beijing Shijitan Hospital, Capital Medical University, No. 10 Tieyi Street, Haidian District, Beijing 100038, China. wanglei800212@126.com

Abstract

BACKGROUND

Hepatic venous pressure gradient (HVPG) is the gold standard for diagnosis of portal hypertension (PH), invasiveness and potential risks in the process of measurement limited its widespread use.

AIM

To investigate the correlation of computed tomography (CT) perfusion parameters with HVPG in PH, and quantitatively assess the blood supply changes in liver and spleen parenchyma before and after transjugular intrahepatic portosystemic shunt (TIPS).

METHODS

Twenty-four PH related gastrointestinal bleeding patients were recruited in this study, and all patients were performed perfusion CT before and after TIPS surgery within 2 wk. Quantitative parameters of CT perfusion, including liver blood volume (LBV), liver blood flow (LBF), hepatic arterial fraction (HAF), spleen blood volume (SBV) and spleen blood flow (SBF), were measured and compared before and after TIPS, and the quantitative parameters between clinically significant PH (CSPH) and non-CSPH (NCSPH) group were also compared. Then the correlation of CT perfusion parameters with HVPG were analyzed, with statistical significance as $P < 0.05$.

RESULTS

For all 24 PH patients after TIPS, CT perfusion parameters demonstrated

decreased LBV, increased HAF, SBV and SBF, with no statistical difference in LBF. Compared with NCSPH, CSPH showed higher HAF, with no difference in other CT perfusion parameters. HAF before TIPS showed positive correlation with HVPG (r = 0.530, P = 0.008), while no correlation was found in other CT perfusion parameters with HVPG and Child-Pugh scores.

CONCLUSION

HAF, an index of CT perfusion, was positive correlation with HVPG, and higher in CSPH than NCSPH before TIPS. While increased HAF, SBF and SBV, and decreased LBV, were found after TIPS, which accommodates a potential non-invasive imaging tool for evaluation of PH.

Key Words: Portal hypertension; Transjugular intrahepatic portosystemic shunt; Hepatic vein pressure gradient; Perfusion; Computed tomography

Core Tip: Transjugular intrahepatic portosystemic shunt (TIPS) is an effective therapy for portal hypertension (PH) related gastro-esophageal variceal bleeding (GEVB). However, the decrease of liver blood supply after TIPS led to a decline in the liver detoxification, which increased potential risk for the occurrence of various complications such as hepatic encephalopathy, liver dysfunction and even liver failure. This study explored the feasibility of computed tomography perfusion imaging in quantitatively evaluating the changes in liver and spleen blood supply in PH related GEVB before and after TIPS, and making correlation analysis between perfusion parameters, hepatic venous pressure gradient and Child-Pugh scores were evaluated.

Citation: Dong J, Zhang Y, Wu YF, Yue ZD, Fan ZH, Zhang CY, Liu FQ, Wang L. Computed tomography perfusion in differentiating portal hypertension: A correlation study with hepatic venous pressure gradient. *World J Gastrointest Surg* 2023; 15(4): 664-673

URL: https://www.wjgnet.com/1948-9366/full/v15/i4/664.htm

DOI: https://dx.doi.org/10.4240/wjgs.v15.i4.664

INTRODUCTION

Portal hypertension (PH) is a main manifestation of increased portal pressure caused by various factors [1-3]. It is commonly caused by liver fibrosis, which leads to a series of complications, such as bleeding from gastroesophageal varices, ascites, infection, *etc.* Some patients progress to liver cancer, with poor prognosis[4]. The diagnostic gold standard for PH is hepatic venous pressure gradient (HVPG) higher than 5 mmHg, and it has been reported that when HVPG was higher than 10 mmHg, patients were classified into clinically significant PH (CSPH)[1,4,5], with the increased rate of complications and poor 1-year survival rate[5,6]. Transjugular intrahepatic portosystemic shunt (TIPS) is an effective technique for the treatment of PH related complications compared to drug therapy and surgical treatment, especially for patients with gastroesophageal variceal bleeding[5,7]. However, the complications after TIPS, such as hepatic encephalopathy, liver dysfunction and even liver failure[8-11], were also concerned for most patients. Therefore, it is necessary to make non-invasively quantitative evaluation of HVPG and liver blood supply changes after TIPS, which is useful for precise treatment for PH patients, especially for TIPS surgery[12].

Multi-modal imaging, including computed tomography (CT) perfusion, functional magnetic resonance imaging and contrast enhanced ultrasonography, have been applied in the assessment of liver cirrhosis, which demonstrated the capability in non-invasive assessment of HVPG and liver blood supply changes[13-15]. It is reported that CT perfusion can acquire quantitative indices such as blood flow and blood volume through continuous dynamic scanning, which can be used to quantify the blood perfusion of target organs, such as stroke, liver, lung tumors, *etc.*[16,17] and it has also been applied in assessment of PH related liver cirrhosis. Therefore, our study is to explore the feasibility of CT perfusion imaging in quantitatively evaluating HVPG, and the blood supply changes in liver and spleen for PH patients, and make correlation analysis between perfusion CT parameters and HVPG.

MATERIALS AND METHODS

Patient data

This prospective study was approved by the Institutional Ethics Committee in our hospital, and all written informed consents were obtained from each participate. All patients with recurrent gastroesophageal variceal bleeding caused by PH were recruited for TIPS surgery therapy from January to June of 2018. The inclusion criteria were: (1) Patients with PH related recurrent gastroesophageal bleeding, and prepared to be performed with TIPS surgery; (2) Child-Pugh score and perfusion CT were evaluated within 2 wk before and after TIPS. The exclusive criteria were: (a) Any other etiology causing gastrointestinal bleeding; (b) Primary and/or secondary liver tumors; and (c) Iatrogenic factors causing liver blood supply changes, such as partial hepatectomy, splenectomy, and TIPS before *etc*; (3) Portal vein and/or hepatic vein lesions affecting liver blood supply, such as portal vein thrombosis leading stenosis higher than 75%, portal vein cavernous transformation, Budd-Chiari syndrome, *etc*; (4) Dysfunction in vital organs, such as cardiac, renal, respiratory failure; and (5) Any factors made the perfusion CT unavailable, such as motion and metal artifacts, allergic to contrast media.

CT perfusion in liver and spleen

Liver and spleen perfusion CT were performed on Revolution CT (GE Healthcare, WI), with the scanning parameters as follows[17-20]: 100 kVp tube voltage, 50 to 200 mA tube current with automated tube current modulations, 14 of noise index, 5 mm slice thickness, 1.0 s rotation speed, 0.992:1 helical pitch, and ASIR was set at proportion of 80%. Contrast media (Omnipaque, 350) volume was fixed as 50 mL, with 50 mL saline chaser, and were injected in 5 mL/s rate through antecubital with a power injector (Stellant, Medtron, Saarbrucken, Germany). The CT perfusion scanning time was set as 80 s, which included three parts of acquisition as follows: 10 scans with 1 s interscan gap firstly, 12 scans with 2 s interscan gap secondly, and 4 scans with 4 s interscan gap finally for each patient. All patients were compressed with a restriction band to reduce respiratory motion, and were instructed to avoid deep and irregular breathing during the procedure, which reduced respiratory motion artifacts.

All perfusion CT raw data were reconstructed with a 2.5 mm slice thickness, and then the images were sent to a commercial software (CT Perfusion 4D AW 4.7, GE healthcare) for post-processions. First, the images mis-registration between different scanning phase were corrected by iterative registration reconstruction technique. Then, the constructed images were sent to commercial software for post-procession, and regions of interest were selected in different area of liver and spleen separately, and then quantitative parameters of perfusion were calculated, including liver blood volume (LBV), liver blood flow (LBF), hepatic arterial fraction (HAF), splenic blood volume (SBV), and splenic blood flow (SBF). The post-processions have been performed for three times, and the results were averaged as the final parameters.

HVPG measurement, TIPS therapeutic effect assessment and follow-up

All patients were performed with TIPS surgery within 2 wk after CT perfusion, and HVPG was measured in the process of TIPS surgery in accordance with guideline[21]. The process was as follows: Firstly, patients were in fast state for more than 8 h before TIPS surgery, and then local anesthesia was performed to cannulate the right internal jugular vein using Seldinger technique, and all the patients were placed a 5-French balloon catheter (Edwards Lifesciences LLC, United States) into the right hepatic vein for measurement of free and wedged hepatic venous pressures, the process were performed for three times at the same point, and the average of the difference between wedged and free hepatic venous pressure were recorded as the final results of HVPG. Then, TIPS surgery would be performed, and all patients underwent perfusion CT within 2 wk after TIPS. The therapeutic effect would be assessed after 3-mo follow-up, with complications recorded, including hemorrhage, hepatic encephalopathy (HE), liver dysfunction, bile leakage.

Statistical analysis

All statistical analysis was performed with Statistical Package for Social Sciences (SPSS) version 24.0 program. Quantitative results were described as mean ± SD. Normal distribution tests were analyzed with Kolmogorov-Smirnov test. Quantitative indices before and after TIPS, including LBV, HAF, LBF, SBV, were compared with pair-sample *t*-test, and the pearson correlation analyses were performed with CT perfusion parameters with HVPG and Child-Pugh scores, and a value of $P < 0.05$ was considered as statistical significance.

RESULTS

Patients characteristics

Thirty-seven patients were recruited in this study at first, and all written informed consents were signed, and 13 patients were excluded finally for the following reasons, including 3 patients with portal

vein stenosis higher than 75% caused by portal vein thrombosis, 3 patients with splenectomy, 2 patients with portal vein cavernous transformation, 2 patients diagnosed as hepatic cell carcinoma and 2 patients with severe artifacts caused by respiratory motion in CT perfusion acquisitions, and 1 patients with serious complications of hepatic coma after TIPS. Finally, 24 patients (3/21, female/male) were enrolled in this study, including 11 hepatitis B, 7 alcoholic liver diseases, 3 drug induced hepatitis, 1 autoimmune hepatitis, 1 primary sclerosing cholangitis and 1 idiopathic PH. Patient general data were listed in Table 1.

CT perfusion parameters changes before and after TIPS

The quantitative parameters of CT perfusion before and after TIPS were compared in Table 2. After TIPS, decreased LBV and increased HAF were found, while no difference was shown in LBF. Whereas for SBF and SBV, both spleen blood flow and blood volume increased significantly after TIPS. The baseline of CT maps and time density curves were shown in Figure 1, and the comparison of colored perfusion maps were shown in Figure 2.

CT perfusion comparisons between CSPH and non-CSPH groups

The comparison of the results of CSPH group (n = 13) with non-CSPH (NCSPH) group (n = 11) was shown in Table 3. Before TIPS, there were no significant differences in the blood flow and blood volume of liver and spleen between the CSPH group and the NCSPH group, while the HAF in NCSPH group was much lower than that in CSPH group. After TIPS, no difference was found between the CSPH and NCSPH groups for all CT perfusion parameters.

Correlation analysis of CT perfusion parameters, HVPG and Child-Pugh score

Among CT perfusion parameters, preoperative HAF was correlated with HVPG (r = 0.530, P = 0.008), suggesting that hepatic arterial perfusion parameters were positively correlated with HVPG. Whereas other perfusion parameters before TIPS, including LBF, LBV, SBF and SBV were not correlated with HVPG. All CT perfusion parameters, including liver perfusion parameters LBF, LBV and HAF, and spleen perfusion parameters SBF and SBV, were not correlated with the Child-Pugh score before TIPS. Besides, no correction was found between HVPG and Child-Pugh score.

Therapeutic effect follow-up and postoperative complications

After TIPS placement, all patients received 2-wk and 3-mo reexamination to evaluate the curative effect. All patients had patency of TIPS stents, and no obvious thrombosis was found, no bleeding occurred again, and the ascites were relieved apparently. In terms of complications, there were 4 patients with HE and 1 patient with hepatic insufficiency within 3 mo, all of which occurred within 2 wk after operation. Among them, there was 1 patient with mild HE, 2 patients with moderate HE and 1 patient with severe HE, and they recovered well after liver protection therapy. One patient with hepatic insufficiency occurred within 3 d after the operation, and recovered within 2 wk after rapid correction.

DISCUSSION

CT perfusion demonstrated capacity in quantitatively evaluating the liver blood supply changes after TIPS surgery. Our results suggested that LBV decreased significantly after TIPS procedure (19.2 ± 5.3 *vs* 12.1 ± 2.4, P < 0.01), while HAF increased (12.3 ± 6.1 *vs* 56.0 ± 8.8, P < 0.01) significantly. These results showed that the total liver blood supply decreased, but the proportion of hepatic artery blood supply increased after TIPS. It is well-known that TIPS is one of the effective methods for the treatment of PH[4,5,7,22], such as PH related gastro-esophageal variceal bleeding, refractory ascites, *etc*[1,4,23]. The reason of this results can be explained as follows: The liver is a dual blood supply organ, and, the proportion of hepatic artery is only about 20%-30%, while the portal vein is more than 70% under normal circumstances. For PH patients after TIPS surgery, part of the portal vein blood supply would be drained directly into inferior vena cava through TIPS stent, so the total blood from portal vein system decreased significantly, and the PH would be alleviated[14,20,22,24]. Then, the compensatory hepatic artery blood supply would be increased, which resulted in the obvious increase in hepatic artery supply proportion [25,26]. However, since the compensated blood supply from hepatic artery is not enough to compensate for the decrease in portal venous blood supply, so the effective blood supply of the liver parenchyma still decreased[13,14,20,24,27]. The decrease of total effective blood supply in liver parenchyma increased the potential risk of the occurrence of hepatic dysfunction, hepatic encephalopathy, and even liver failure after TIPS[8-10].

Spleen parenchyma blood supply changes could also be assessed with CT perfusion. Our results suggested that SBF (107.6 ± 32.1 *vs* 160.6 ± 33.1, P < 0.01) and SBV (12.1 ± 3.0 *vs* 18.7 ± 3.4, P < 0.01) increased significantly after TIPS. For patients with PH, due to the presence of varicose veins, the formation of collateral circulation and a large amount of ascites caused by the high pressure of the portal venous system, the amount of blood returning to the liver is blocked, thereby reducing the effective circulating blood volume of the body[1,4,13,26]. After TIPS, portal venous blood flow can be

Table 1 Patients general data

Characteristic	Value
Sex (female/male), *n*	3/21
Age (yr), mean ± SD	51.3 ± 9.7
Height (cm), mean ± SD	168.7 ± 6.1
Weight (kg), mean ± SD	63.4 ± 12.5
Previous episodes of variceal bleeding, mean ± SD	3 ± 2
Treatment history, *n* (%)	
β blockade only	2 (8.3)
Sclera therapy only	4 (16.7)
β blockade and sclerotherapy	18 (75.0)
Child-Pugh stage, *n* (%)	
A	5 (20.8)
B	18 (75.0)
C	1 (4.2)
Ascites, *n* (%)	
None	16 (66.7)
Mild	2 (8.3)
Severe	6 (25.0)
HVPG in mmHg, *n* (%)	
< 10	11 (45.8)
≥ 10	13 (54.2)

HVPG: Hepatic venous pressure gradient; SD: Standard deviation.

Table 2 Perfusion computed tomography parameters changes before and after transjugular intrahepatic portosystemic shunt

Parameters	Before TIPS	After TIPS	*P* value
Liver parenchyma			
LBF	97.2 ± 32.2	85.8 ± 37.9	0.232
LBV	19.2 ± 5.3	12.1 ± 2.4	< 0.001
HAF ($\times 10^{-2}$)	12.3 ± 6.1	55.3 ± 9.9	< 0.001
Spleen parenchyma			
SBF	107.6 ± 32.1	160.6 ± 33.1	< 0.001
SBV	12.1 ± 3.0	18.7 ± 3.4	< 0.001

TIPS: Transjugular intrahepatic portosystemic shunt; LBF: Liver blood flow; LBV: Liver blood volume; HAF: Hepatic arterial fraction; SBF: Spleen blood flow; SBV: Spleen blood volume.

directly returned to the systemic circulation through the TIPS shunt, which increases the effective circulating blood volume. Therefore, the arterial blood supply is significantly increased after TIPS[24]. As we all know, the blood supply of the spleen only comes from the arterial system, which explains the increase of SBV and SBF, and may also be an important factor for the increase of HAF in liver.

CT perfusion showed capacity in discriminating CSPH and NCSPH group. It is reported that the rate of various complications in CSPH group is significantly higher than NCSPH group[28]. So, it is necessary to discriminate CSPH and NCSPH non-invasively. Our results suggested that before TIPS, HAF in CSPH group was significantly higher than NCSPH group (18.2 ± 10.9 *vs* 5.4 ± 2.8, $P < 0.01$), which means the arterial proportion of liver blood supply in CSPH is much higher than NCSPH group.

Table 3 Computed tomography perfusion comparisons between clinically significant portal hypertension and non-clinically significant portal hypertension before and after transjugular intrahepatic portosystemic shunt

Parameters	NCSPH (*n* = 11)	CSPH (*n* = 13)	*P* value
Before TIPS			
Liver parenchyma			
LBF	103.6 ± 23.3	91.7 ± 38.3	0.377
LBV	19.5 ± 2.9	18.9 ± 6.9	0.796
HAF ($\times 10^{-2}$)	5.4 ± 2.8	18.2 ± 10.9	0.001
Spleen parenchyma			
SBF	95.9 ± 25.1	117.4 ± 34.9	0.102
SBV	12.4 ± 3.5	12.0 ± 2.7	0.747
After TIPS			
Liver parenchyma			
LBF	77.5 ± 33.9	92.8 ± 41.0	0.336
LBV	11.3 ± 2.4	12.7 ± 2.2	0.165
HAF ($\times 10^{-2}$)	54.4 ± 11.4	56.0 ± 8.8	0.711
Spleen parenchyma			
SBF	150.0 ± 35.7	169.9 ± 29.1	0.153
SBV	19.2 ± 3.8	18.3 ± 3.0	0.522

CSPH: Clinically significant portal hypertension; NCSPH: Non-clinically significant portal hypertension; TIPS: Transjugular intrahepatic portosystemic shunt; LBF: Liver blood flow; LBV: Liver blood volume; HAF: Hepatic arterial fraction; SBF: Spleen blood flow; SBV: Spleen blood volume.

but no statistical difference was found in LBF and LBV, which means HAF is the only index of CT perfusion in discriminating CSPH with NCSPH before TIPS surgery. However, after TIPS surgery, all CT perfusion parameters, including LBF, LBV and HAF showed no statistical difference between CSPH and NCSPH group. This is because part of the portal vein blood supply into liver had been conducted into inferior vena cava directly through TIPS shunt, so the hemodynamics of liver blood supply had been changed after TIPS. Therefore, HAF of CT perfusion can be used to discriminate CSPH and NCSPH before TIPS.

HAF in CT perfusion could be used as a non-invasive index to assess HVPG. Our results showed that HAF had a positive correlation (r = 0.553, P = 0.008) with HVPG, indicating that with the increase of HVPG, the proportion of hepatic artery blood supply increased gradually in the liver parenchyma. It is reported that HVPG is a surrogate for portal vein pressure[28], so with the increase of HVPG, the portal venous pressure would also increase, and then the resistance of liver blood supply would increase significantly. However, since the hepatic artery blood pressure is much higher than portal vein pressure, so the liver arterial blood supply would continuously drain into liver parenchyma, and the compensated arterial supply even increased with the increase of portal vein pressure and HVPG[20,26]. This is why HAF demonstrated positive correlation with HVPG. However, HVPG showed no correlation with LBV, LBF, SBV and SBF, and this is because many factors can influence the effective blood supply in liver parenchyma, which is partially consistent with the previous studies[14,19]. In addition, all CT perfusion parameters of the liver showed no correlation with the Child-Pugh score, suggesting that the Child-Pugh score can only be used to evaluate the liver function, and can't reflect the blood supply in the liver parenchyma.

In addition, all TIPS stents were re-examined 2 wk and 3 mo after TIPS surgery in this study, and no shunt restenosis occurred. In terms of complications, there were 4 patients with HE, and 1 patient with hepatic insufficiency, and hepatic insufficiency occurred before operation and 1 d after operation. It was speculated that many factors, such as a long course of disease, recurrent preoperative gastrointestinal bleeding, severe refractory ascites with large amount of hydrothorax, could be correlated with the occurrence of these complications. After reviewing the patient's data in our study, 4 HE patients showed more than 20% decrease in LBV and LBF, and 40% increase in HAF after TIPS, which is much higher than other patients without complication. Therefore, CT perfusion accommodates a potential predictor for complications after TIPS in PH patients. However, due to the limitation of the sample size, it needs to expand the sample size of the study on whether LBV and LBF can be used as preoperative predictors for postoperative complications after TIPS.

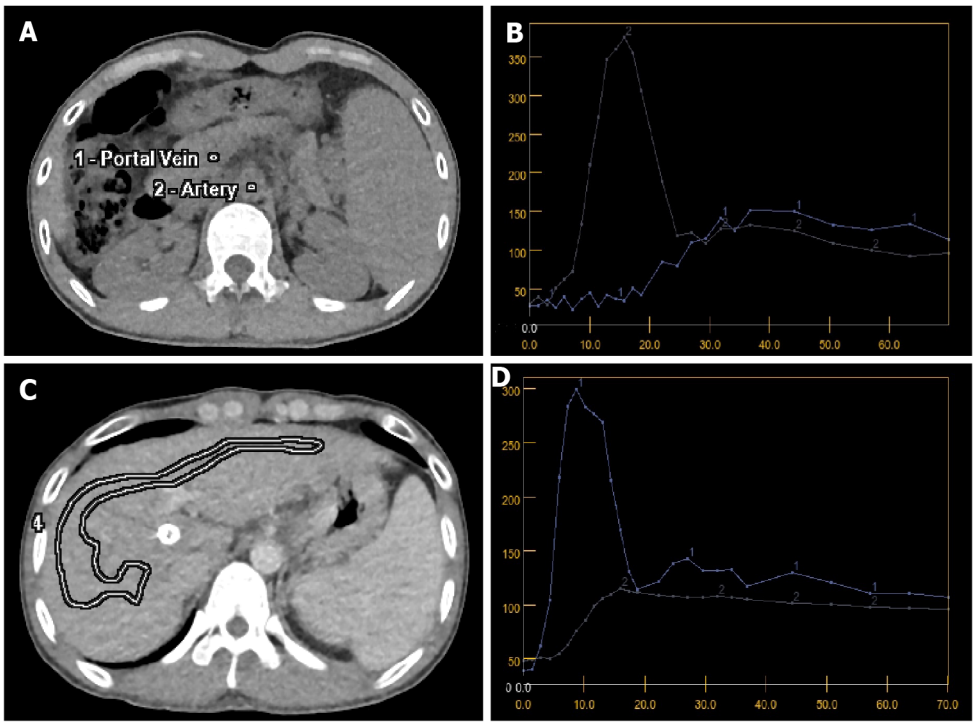

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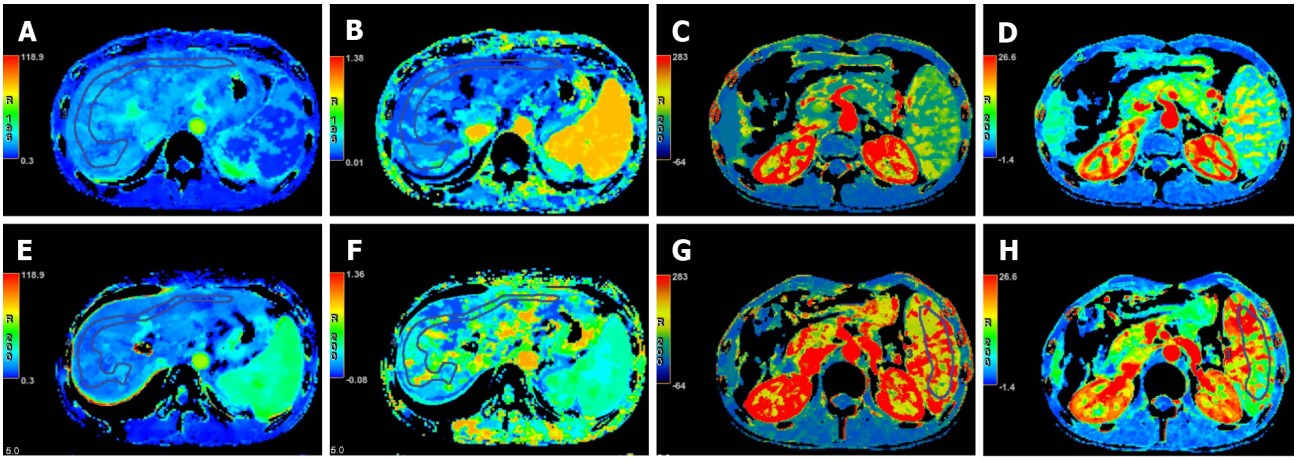
Figure 1 Baseline of computed tomography maps and time density curves before and after transjugular intrahepatic portosystemic shunt. A: Baseline of computed tomography (CT) map with regions of interests for input arterial abdominal artery and portal vein before transjugular intrahepatic portosystemic shunt (TIPS); B: Time-density curve of CT perfusion before TIPS, and axis X is time axis with unit of second, while axis Y is density axis with unit of Hounsfield; C: Region of interest in liver parenchyma for perfusion parameters after TIPS; D: Time-density curve of CT perfusion after TIPS, and axis X is time axis with unit of second, while axis Y is density axis with unit of Hounsfield.



DOI: 10.4240/wjgs.v15.i4.664 **Copyright** ©The Author(s) 2023.

Figure 2 A 37-year-old patient with 2 times gastroesophageal bleeding for more than 10-year history of hepatitis B. A-D: Colored map of computed tomography (CT) perfusion parameters were shown as liver blood volume (LBV), hepatic arterial fraction (HAF), spleen blood flow (SBF), and spleen blood volume (SBV) before transjugular intrahepatic portosystemic shunt (TIPS); E-H: Colored map of CT perfusion parameters were shown as LBV, HAF, SBF, and SBV after TIPS. All CT perfusion parameters were calculated with average of multiple irregular regions of interest in the color maps, which showed decreased LBV and increased HAF, SBF and SBV.

There are some limitations in our studies. Firstly, the sample size is small; secondly, the portal vein thrombosis is a factor leading to the decreased hepatic blood flow, and whether their blood perfusion of the liver will change needs to be further studied; thirdly, many other factors affecting the effective blood volume of liver parenchyma have not been discussed, such as the presence of venous collaterals in the liver, umbilical vein patency, gastric-renal shunt, spleen-kidney shunt; fourthly, Laennec type of pathological grading in liver fibrosis should be included to conduct multivariate analysis for further exploration.

CONCLUSION

In conclusion, HAF, an index of CT perfusion, showed potential capability in noninvasive assessment of HVPG, and demonstrated capability in discriminating CSPH with NCSPH before TIPS surgery, which is important for patients with higher risk. For PH patients after TIPS surgery, the blood volume in liver parenchyma would be decreased significantly, which can be quantitatively assessed with CT perfusion, and it accommodates a potential predictor for complications after TIPS in PH patients, and it is useful for making full evaluations and even take precautions before surgery.

ARTICLE HIGHLIGHTS

Research background

The gold standard for diagnosis of portal hypertension (PH) is the value of hepatic venous pressure gradient (HVPG), which is also widely used in risk stratification for these patients. However, HVPG were limited for the potential risks and invasiveness during the acquisitions, so it is necessary to develop a non-invasive method to assess HVPG. In our study, computed tomography (CT) perfusion was applied to evaluate the blood supply changes before and after transjugular intrahepatic portosystemic shunt (TIPS) surgery, and to investigate the feasibility in non-invasive evaluation of HVPG.

Research motivation

We explore this research to evaluate the feasibility of CT perfusion as the non-invasive surrogate for HVPG, and assess the liver blood supply changes after TIPS, which had the potential application in predicting the occurrence of complications.

Research objectives

The aiming of this study is to investigate the correlation of CT perfusion parameters with HVPG in PH, and quantitatively assess the blood supply changes in liver and spleen parenchyma before and after TIPS.

Research methods

We prospectively recruited 24 PH patients who were performed TIPS surgery for treatment of gastroesophageal bleeding in our hospital. All the patients underwent CT perfusion before and after TIPS surgery. Quantitative parameters, including liver blood volume (LBV), liver blood flow (LBF), hepatic arterial fraction (HAF), spleen blood volume (SBV) and spleen blood flow (SBF), were compared before and after TIPS, and the correlation with HVPG was also analyzed.

Research results

After TIPS, decreased LBV, increased HAF, SBV and SBF were found. HAF before TIPS showed positive correlation with HVPG ($r = 0.530$, $P = 0.008$).

Research conclusions

HAF demonstrated potential use in discriminating clinically significant PH (CSPH) than non-CSPH before TIPS. While increased HAF, SBF and SBV, and decreased LBV were found after TIPS, which accommodates a potential non-invasive imaging tool for evaluation of PH.

Research perspectives

Multi-modality research of baseline assessment for PH, including anatomical information, lab results, ultrasonography and functional magnetic resonance imaging should be explored in the future.

FOOTNOTES

Author contributions: Dong J, Liu FQ and Wang L designed the report; Zhang Y, Wu YF, Yue ZD, and Fan ZH collected the clinical data; Wang L and Zhang CY analyzed the data and wrote the paper; Dong J and Liu FQ performed quality control; Liu FQ contributed to administrative and financial support.

Supported by the National Natural Science Foundation of China General Program, No. 81871461.

Institutional review board statement: This study was approved by the Ethics Committee of the Beijing Shijitan Hospital, Capital Medical University (No. 201801).

Clinical trial registration statement: This study is registered at ClinicalTrials.gov, registration number

ChiCTR1800015268 (https://www.chictr.org.cn/showproj.aspx?proj=26048).

Informed consent statement: Written informed consent was obtained from each patient.

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: Jian Dong 0000-0002-2643-0370; Lei Wang 0000-0002-4374-059X.

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

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World J Gastrointest Surg 2023 April 27; 15(4): 674-686

DOI: 10.4240/wjgs.v15.i4.674

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Observational Study

Ligamentum teres hepatis as a graft for portal and/or superior mesenteric vein reconstruction: From bench to bedside

Wen-Tao Zhu, Hai-Tao Wang, Qing-Hai Guan, Fan Zhang, Chang-Xi Zhang, Feng-Ai Hu, Bao-Lei Zhao, Lei Zhou, Qiang Wei, Hai-Bin Ji, Ting-Liang Fu, Xing-Yuan Zhang, Rui-Tao Wang, Qiang-Pu Chen

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

P-Reviewer: Fernández-Placencia RM, Peru; Shah OJ, India

Received: December 12, 2022
Peer-review started: December 12, 2022
First decision: January 11, 2023
Revised: February 6, 2023
Accepted: March 15, 2023
Article in press: March 15, 2023
Published online: April 27, 2023

Wen-Tao Zhu, Fan Zhang, Chang-Xi Zhang, Bao-Lei Zhao, Lei Zhou, Qiang Wei, Hai-Bin Ji, Xing-Yuan Zhang, Qiang-Pu Chen, Department of Hepatobiliary Surgery, Binzhou Medical University Hospital, Binzhou 256600, Shandong Province, China

Hai-Tao Wang, Department of Hepatobiliary Surgery, Binzhou Medical University Affiliated Yantai Hospital, Yantai 264110, Shandong Province, China

Qing-Hai Guan, Department of Hepatobiliary Surgery and Clinical Nutrition Center, Binzhou Medical University Hospital, Binzhou 256600, Shandong Province, China

Feng-Ai Hu, Department of Clinical Medicine Laboratory, Binzhou Medical University Hospital, Binzhou 256600, Shandong Province, China

Ting-Liang Fu, Department of Pediatric Surgery, Binzhou Medical University Hospital, Binzhou 256600, Shandong Province, China

Rui-Tao Wang, Department of Hepatobiliary Surgery, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710061, Shannxi Province, China

Corresponding author: Qiang-Pu Chen, MD, Professor, Department of Hepatobiliary Surgery, Binzhou Medical University Hospital, No. 661 Huang He Er Road, Binzhou 256600, Shandong Province, China. drchenqiangpu@163.com

Abstract

BACKGROUND

Pancreaticoduodenectomy combined with portal vein (PV) and/or superior mesenteric vein (SMV) resection in patients with pancreaticobiliary malignancy has become a common surgical procedure. There are various grafts currently used for PV and/or SMV reconstruction, but each of these grafts have certain limitations. Therefore, it is necessary to explore novel grafts that have an extensive resource pool, are low cost with good clinical application, and are without immune response rejection or additional damage to patients.

AIM

To observe the anatomical and histological characteristics of the ligamentum teres hepatis (LTH) and evaluate PV/SMV reconstruction using an autologous LTH graft in pancreaticobiliary malignancy patients.

METHODS

In 107 patients, the post-dilated length and diameter in resected LTH specimens were measured. The general structure of the LTH specimens was observed by hematoxylin and eosin (HE) staining. Collagen fibers (CFs), elastic fibers (EFs), and smooth muscle (SM) were visualized by Verhoeff-Van Gieson staining, and the expression of CD34, factor VIII-related antigen (FVIIIAg), endothelial nitric oxide synthase (eNOS), and tissue type plasminogen activator (t-PA) were detected using immunohistochemistry in LTH and PV (control) endothelial cells. PV and/or SMV reconstruction using the autologous LTH was conducted in 26 patients with pancreaticobiliary malignancies, and the outcomes were retrospectively analyzed.

RESULTS

The post-dilated length of LTH was 9.67 ± 1.43 cm, and the diameter at a pressure of 30 cm H_2O was 12.82 ± 1.32 mm at the cranial end and 7.06 ± 1.88 mm at the caudal end. Residual cavities with smooth tunica intima covered by endothelial cells were found in HE-stained LTH specimens. The relative amounts of EFs, CFs and SM in the LTH were similar to those in the PV [EF (%): 11.23 ± 3.40 *vs* 11.57 ± 2.80, $P = 0.62$; CF (%): 33.51 ± 7.71 *vs* 32.11 ± 4.82, $P = 0.33$; SM (%): 15.61 ± 5.26 *vs* 16.74 ± 4.83, $P = 0.32$]. CD34, FVIIIAg, eNOS, and t-PA were expressed in both LTH and PV endothelial cells. The PV and/or SMV reconstructions were successfully completed in all patients. The overall morbidity and mortality rates were 38.46% and 7.69%, respectively. There were no graft-related complications. The postoperative vein stenosis rates at 2 wk, 1 mo, 3 mo and 1 year were 7.69%, 11.54%, 15.38% and 19.23%, respectively. In all 5 patients affected, the degree of vascular stenosis was less than half of the reconstructed vein lumen diameter (mild stenosis), and the vessels remained patent.

CONCLUSION

The anatomical and histological characteristics of LTH were similar to the PV and SMV. As such, the LTH can be used as an autologous graft for PV and/or SMV reconstruction in pancreaticobiliary malignancy patients who require PV and/or SMV resection.

Key Words: Ligamentum teres hepatis; Pancreaticoduodenectomy; Portal vein; Superior mesenteric vein; Vascular grafting; Pancreaticobiliary malignancy

Core Tip: The anatomical, histological and clinical studies using the recanalized ligamentum teres hepatis (LTH) to reconstruct the portal vein (PV) and/or superior mesenteric vein (SMV) were studied. It was found that the post-dilated length and diameter of the LTH were suitable for PV and/or SMV reconstruction. The histological structure of the LTH wall was similar to the PV. High vascular patency rate and good clinical effects were acquired in clinical application. It was demonstrated that there is both basic and clinical rationale for the use of LTH in PV and/or SMV reconstruction since it does not cause additional injury or increase medical costs and has good clinical effects.

Citation: Zhu WT, Wang HT, Guan QH, Zhang F, Zhang CX, Hu FA, Zhao BL, Zhou L, Wei Q, Ji HB, Fu TL, Zhang XY, Wang RT, Chen QP. Ligamentum teres hepatis as a graft for portal and/or superior mesenteric vein reconstruction: From bench to bedside. *World J Gastrointest Surg* 2023; 15(4): 674-686
URL: https://www.wjgnet.com/1948-9366/full/v15/i4/674.htm
DOI: https://dx.doi.org/10.4240/wjgs.v15.i4.674

INTRODUCTION

Locally advanced carcinoma of the pancreatic head or ampulla of Vater often involves the portal vein (PV) and/or the superior mesenteric vein (SMV). Partial removal of the PV or SMV for complete surgical resection of the tumor is indicated[1-4]. A graft as a conduit or patch for PV and/or SMV reconstruction is needed. The most commonly used grafts include autogenous, homologous or artificial blood vessels[5-9]. However, these grafts have their own limitations. Therefore, it is necessary to explore more suitable grafts for PV and/or SMV reconstruction.

The ligamentum teres hepatis (LTH) is a fibrous remnant of the obliterated umbilical vein, which has the potential to be used as a graft[10,11]. Since the 1990s, the LTH has been described as a graft for reconstruction of the biliary tract, stomach or duodenum[12-14]. However, there are few studies on the

use of LTH as a vascular graft during a pancreatoduodenectomy (PD) procedure, and systematic studies have not been performed. The aim of the present study was to understand the vascular characteristics of the LTH in the laboratory and assess clinical outcomes of the LTH as a vascular graft for PV and/or SMV reconstruction in patients with pancreaticobiliary malignancy.

MATERIALS AND METHODS

Morphometric study

Collection of LTH specimens: LTHs were obtained from 107 patients undergoing upper abdominal surgery in Binzhou Medical University Hospital. The surgical procedures included radical resections for gastric cancer (n = 54), hilar cholangiocarcinoma (n = 27) and pancreatic cancer (n = 26).

Specimen harvest and preparation: During the procedure, the entire LTH was excised. After removing the superficial fat layer, the LTH was placed in normal saline.

Recanalization of LTH: The remnant lumen of the LTH was identified and recanalized using a mosquito clamp (Figure 1A) and a 3 mm probe (Figure 1B), then gradually dilated using probes of 5-10 mm in diameter until the endothelial creases completely disappeared. The distal end of the LTH was tightly clamped, and a bolus of normal saline was injected into the lumen from the proximal end to further enlarge the lumen (Figure 1C).

Measurement of the recanalized LTH: The length and the outer diameter of the recanalized LTH were measured using a ruler and Vernier calipers, respectively, at a hydrostatic pressure of 30 cm H_2O. The diameters of the LTH vessels were measured at 1 cm intervals over the entire length of the vessel.

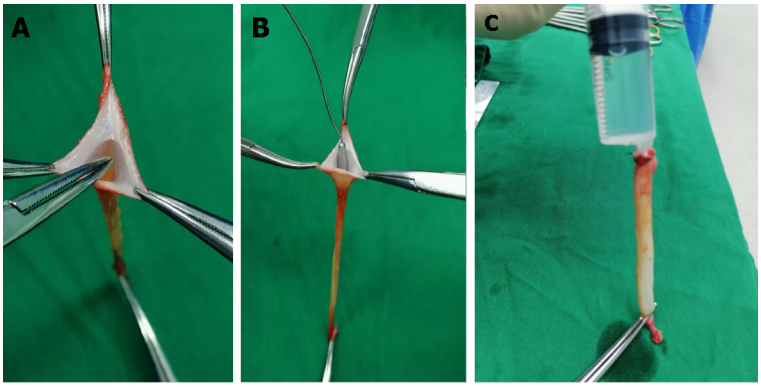
Histological and immunohistochemical studies

Specimen harvest and preparation of LTH and PV: Forty LTH specimens were obtained from patients undergoing upper abdominal surgery at Binzhou Medical University Hospital, and PV specimens were obtained from 40 donor livers at The First Affiliated Hospital of Xi'an Jiaotong University. LTH and PV specimens were fixed with 10% neutral formaldehyde solution and embedded in paraffin. Cross sections (5 μm) were prepared for hematoxylin and eosin (HE), Verhoeff-Van Gieson (VVG), and immunohistochemistry staining.

The solutions purchased from Shanghai Sheng Gong Biological Engineering Technology Service (Shanghai, China) included hematoxylin, eosin, 10% and 2% $FeCl_3$, Weigert's iodine, 5% sodium thiosulfate, VVG stain and phosphate-buffered saline (PBS). Mouse monoclonal anti-human CD34, rabbit monoclonal anti-human factor VIII-related antigen (FVIIIAg), rabbit polyclonal anti-human endothelial nitric oxide synthase (eNOS), and rabbit polyclonal anti-human tissue type plasminogen activator (t-PA) antibodies were purchased from Santa Cruz Biotechnology (CA, United States). SP-9000 Histostain TM-plus kits and concentrated ZLI-9031 diaminobenzidine (DAB) kits were purchased from Beijing Zhongshan Jinqiao Biotechnology (Beijing, China).

Determination of the relative contents of collagen fibers (CFs), elastic fibers (EFs) and smooth muscle (SM) was performed in 40 sections of both LTHs and PVs. Sections were deparaffinized with xylene and immersed in VVG working solution to stain for 1 h. The sections were rinsed three times with distilled water and then immersed in 2% $FeCl_3$ for 2 min for color separation. After immersion in 5% sodium thiosulfate solution for 1 min, the sections were washed with running water for 5 min, then restained with VVG staining solution for 5 min. The sections were rapidly dehydrated with a gradient alcohol series and cleared with xylene before sealing with Rhamsan gum. Under a light microscope, the left intersection point of the horizontal axis and LTH rings were used as the sampling window. Forty fields from 40 sections (one field/section) of both LTH and PV tissues were selected at a high magnification (× 400). Using the Motic medical image analysis system (MMD6.0 A), the relative content of EFs, CFs and SM in the wall of LTH and PV specimens were analyzed.

Detection of the distribution and function of LTH endothelial cells was also performed in 40 sections of both LTHs and PVs. Sections were deparaffinized with xylene and immersed in 3% H_2O_2 solution to inactivate endogenous enzymes. The sections were then washed with PBS prior to heat-induced antigen retrieval and incubated with normal goat serum at room temperature for 15 min. Then, the sections were incubated with primary antibodies, including anti-CD34 (1:100 dilution), anti-FVIIIAg (1:50 dilution), anti-eNOS (1:200 dilution) and anti-t-PA (1:200 dilution). After overnight incubation at 4 °C, sections were incubated with secondary antibodies (biotinylated universal secondary antibody, ready-to-use secondary antibody) for 15 min at 37 °C. Next, sections were incubated with horseradish peroxidase streptavidin for 15 min at 37 °C followed by the DAB reagent for 3-10 min to visualize color. The reaction time was controlled by observation under a light microscope. The sections were counter-stained with hematoxylin for 5 min. After dehydration and clearing, the sections were sealed with Rhamsan gum and observed.



DOI: 10.4240/wjgs.v15.i4.674

Figure 1 Ligamentum teres hepatis recanalization. A and B: The remnant lumen of the ligamentum teres hepatis was identified and recanalized using a mosquito clamp (A) and a 3 mm probe (B); C: A bolus of normal saline was injected into the lumen from the proximal end to further enlarge the lumen.

Clinical study

Subjects: Two hundred and sixty-four patients underwent a PD procedure at Binzhou Medical University Hospital from September 2003 to July 2019. Among the 264 patients, 39 patients underwent PD combined with PV and/or SMV resection. The vascular resection rate was 14.77%. Among these 39 patients, 26 patients underwent PD combined with PV and/or SMV resection and reconstruction using a recanalized LTH and were included in this study. Among the 26 patients, 25 patients underwent an open PD, and 1 patient underwent a laparoscopic PD. All 26 patients were evaluated preoperatively by physical examination and blood tests. Contrast-enhanced computed tomography (CT) was performed to assess the status of vascular infiltration.

Inclusion criteria included: (1) Patients who underwent PD combined with PV and/or SMV resection and reconstruction with LTH for malignant tumors of the bile duct, pancreas, Vater's ampulla and duodenum; and (2) Clinical data were available.

Exclusion criteria included: (1) Patients who underwent PD combined with PV and/or SMV resection and reconstruction without grafts or using other grafts; and (2) Patients whose clinical data were not available.

Surgical procedure

Preparation of LTH grafts: Based on the intraoperative findings, if there was PV and/or SMV involvement of more than one-third of the circumference and 3 cm in length, then resection and reconstruction of the involved vein was performed. The LTH was then excised and recanalized as described above. After recanalization, LTH was trimmed into a tubular graft or patch according to the defect extent of the PV and/or SMV. The trimmed LTH was preserved in heparinized saline for grafting.

Vascular reconstruction: The proximal and distal portion of the involved vein was clamped with nontraumatic clips, and the venous occlusion time was documented. The splenic vein (SV) was also controlled if needed. The tumor along with the involved PV and/or SMV segment was resected en bloc. If the extent of the PV and/or SMV resection was more than one-third but less than one-half of the circumference of the vein, then a patch of LTH was used for reconstruction (Figure 2A and B, Video 1). If the resected segment of the involved PV and/or SMV was more than 3 cm in length, LTH was used as an interposition graft (Figure 2C and D, Video 2).

All anastomoses were performed using continuous 5-0 prolene sutures. Before completion of the anastomosis, both the stump of the recipient's vein and the graft were rinsed with heparinized saline and flushed by release of the PV clamp to remove any clots. Upon completion, the anastomosis was checked for leaks and refilling. The types of surgical procedure, total operative time, estimated blood loss and vascular occlusion time were recorded. The operations were performed by the same surgeon with more than 15 years of experience in hepatobiliary surgery.

Postoperative management, complications and assessment of vascular patency: All patients received anticoagulant therapy with low molecular weight heparin (4100 IU; every 12 h) in the 1st postoperative week. Aspirin or low-dose warfarin was initiated from the 8th postoperative day in all patients and continued for 3 mo. The postoperative complications were recorded and classified using the International Study Group of Pancreatic Surgery and Clavien-Dindo classification[15,16]. PV/SMV blood flow was monitored using Doppler ultrasound. The patency of the reconstructed PV/SMV was evaluated by contrast-enhanced abdominal CT (Figure 3). The degree classification of reconstructed vein stenosis was based on the classification method of Kleive *et al*[17]. The date of last follow-up was June 2022.

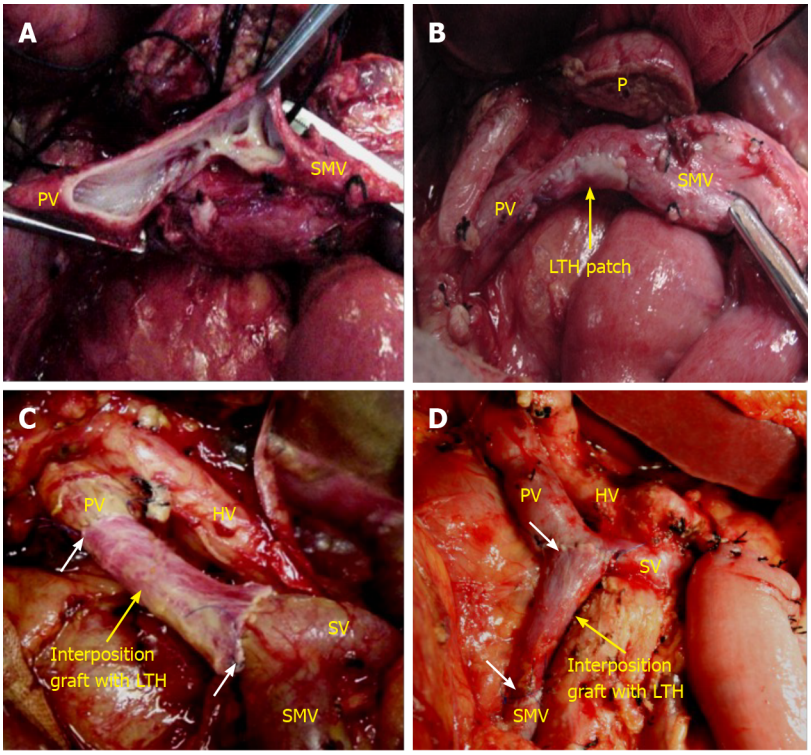


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Figure 2 Vascular reconstruction. A: Tangential resection of the involved vein with the preservation of portal vein (PV)-splenic vein (SV)-superior mesenteric vein (SMV) confluence; B: Vein reconstruction with ligamentum teres hepatis (LTH) patch; C: PV reconstruction with an interposition LTH graft with the preservation of SV-SMV confluence; D: Repair of the SMV with an interposition LTH graft with the preservation of PV-SV confluence. The white arrows indicate the anastomosis line. LTH: Ligamentum teres hepatis; PV: Portal vein; SMV: Superior mesenteric vein; SV: Splenic vein; P: Pancreas; HA: Hepatic artery.

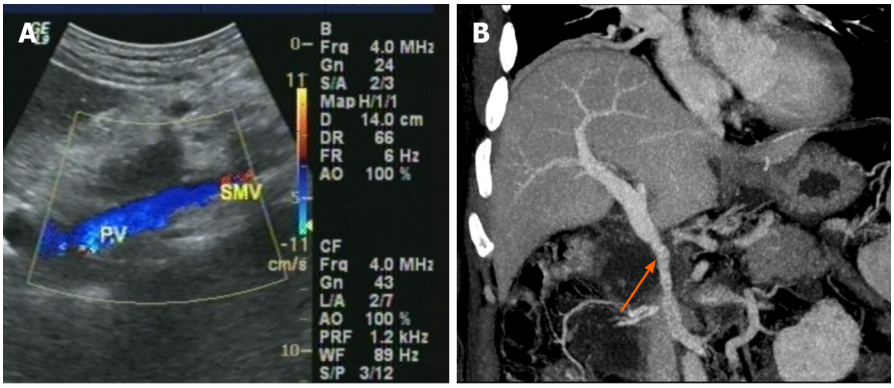

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Figure 3 Images of the reconstructed portal vein and/or superior mesenteric vein. A: Doppler ultrasound showed a patent vascular lumen; B: Enhanced computed tomography scan revealed a patent vascular lumen (orange arrow). PV: Portal vein; SMV: Superior mesenteric vein.

This study was approved by the Ethics Committee of Binzhou Medical University Hospital (2019-LW-023). This study has been registered with the Chinese Clinical Trial Registry (Registration No. ChiCTR1900027098 https://www.chictr.org.cn). Written informed consent to participate was obtained from all patients.

Statistical analysis

The SPSS 18.0 software (SPSS, Chicago, IL, United States) was used for all statistical analyses. The variables were expressed as mean ± SD or medians with interquartile ranges. Intergroup comparisons of the data were made using independent sample *t*-tests. A *P* value of less than 0.05 was considered statistically significant. Reconstructed vascular lumen patency and overall survival were estimated using the Kaplan-Meier method.

RESULTS

Morphologic characteristics of LTH

The LTH was successfully dilated in 104 specimens yielding a success rate of 97.20%. The length of the dilated segments was 9.67 ± 1.43 cm (range: 6.9-13.0 cm). The diameters of the dilated LTH were 12.82 ± 1.32 mm (range: 10.9-17.2 mm) at the cranial end and 7.06 ± 1.88 mm (range: 3.0-12.1 mm) at the caudal end (Table 1).

Microscopic appearance of LTH

Residual cavities with smooth tunica intima covered with endothelial cells were found in all 40 LTH specimens (Figure 4A and B).

Relative content of EFs, CFs and SM

VVG staining revealed that LTH specimens were composed of EFs, CFs and SM components similar to the PV specimens (Figure 4C and D). Analysis using the Motic medical image analysis system (MMD 6.0A) showed that there were no significant differences in the relative content of EFs, CFs and SM between LTHs and PVs, as shown in Table 2.

Distribution and function of endothelial cells in LTH

Immunohistochemical staining revealed the expression of CD34, FVIIIAg, eNOS and t-PA in the cytoplasm of endothelial cells in both LTH and PV specimens (Figure 4E-L), suggestive of the synthesis of CD34, FVIIIAg, eNOS and t-PA in endothelial cells of the LTH.

Clinical data

Demographic characteristics: In a total of 26 cases, the proportion of males and females was equal. The median age was 62 years (interquartile range 53.25-69.25). This case series included patients with pancreatic cancer (n = 19), cholangiocarcinoma (n = 4) and ampullary carcinoma (n = 3).

Intraoperative parameters and complications: PV, SMV and PV plus SMV reconstructions were conducted in 16, 9 and 1 case(s), respectively. The intraoperative data are shown in Table 3.

Postoperative outcomes: The overall morbidity rate was 38.46% (n = 10) (Table 4), and there were no graft-related complications. Two patients (7.69%) died within 30 d after surgery. One patient died of gastrointestinal hemorrhage caused by bleeding from the pancreatoenteric anastomosis, and the other died of pancreatic fistula-associated severe abdominal bleeding caused by gastroduodenal artery stump bleeding. The median postoperative hospital stay was 20 d (interquartile range: 16.75-25.00 d), and the median survival was 7 mo (interquartile range: 5.00-11.25 mo). No patients were lost to follow-up (Figure 5A). The vascular cumulative stenosis curve was shown in Figure 5B. Vascular stenosis was found within the 2nd postoperative week in 2 cases. One case of vascular stenosis was identified at 1 mo, one at 3 mo and one at 1 year. No vascular stenosis was identified later than 1 year postoperative, and the longest follow-up was 122 mo. The postoperative vein stenosis rates at 2 wk, 1 mo, 3 mo and 1 year were 7.69%, 11.54%, 15.38% and 19.23%, respectively. In all 5 patients, the degree of the vascular stenosis was less than half of the reconstructed vein lumen diameter (mild stenosis), and the vessels remained patent.

DISCUSSION

PD combined with PV and/or SMV resection and reconstruction may be required for locally advanced periampullary and pancreatic head carcinoma with PV and/or SMV involvement. This procedure has been confirmed to improve the R0 resection rate and patient survival[4,18,19]. Grafts used for vein reconstruction can be obtained from various veins, such as the internal jugular vein, femoral vein, external iliac vein, gonadal vein, great saphenous vein, splenic vein, left renal vein and the falciform ligament of the liver[20-28]. However, harvesting autologous grafts requires an additional surgery and increases risk of damage to the major vessels[22,27]. LTH, as a remnant derived from the obliterated umbilical vein, can be dilated to form a conduit with potential venous characteristics[13,14]. The LTH has been used as a vascular graft to reconstruct the PV and/or SMV since 2003 in our medical center and has achieved good clinical results[29]. Few successful cases have been subsequently reported[30, 31], but no larger sample sizes are available.

In the present study, the morphometric findings of the LTH revealed that it is suitable for PV and/or SMV reconstruction in terms of its length and diameter, which were demonstrated in our previous study[32]. The LTH diameters were measured at a pressure of 30 cm H_2O, which simulates the physiological status of the mean PV pressure of 18 cm H_2O (13-24 cm H_2O)[33].

Table 1 Diameter of the dilated ligamentum teres hepatis

Measure point[1]	Cases	Diameter in mm
1	104	12.82 ± 1.32
2	104	12.10 ± 1.29
3	104	11.19 ± 1.15
4	104	10.30 ± 1.09
5	104	9.55 ± 1.09
6	103	8.87 ± 1.12
7	84	8.19 ± 1.30
8	67	7.60 ± 1.32
9	44	7.37 ± 1.16
10	20	7.06 ± 1.88

[1]At 1 cm intervals from the cranial end to the caudal end.

Table 2 Relative content and stiffness index of fibers in the ligamentum teres hepatis and portal vein

	EF (%)	CF (%)	SM (%)	C/E
LTH	11.23 ± 3.40	33.51 ± 7.71	15.61 ± 5.26	3.27 ± 1.22
PV	11.57 ± 2.80	32.11 ± 4.82	16.74 ± 4.83	3.94 ± 0.85
P value	0.62	0.33	0.32	0.16

$P < 0.05$ was considered statistically significant. C/E: Collagen/elastic (stiffness index); CF: Collagen fiber; EF: Elastic fiber; LTH: Ligamentum teres hepatis; PV: Portal vein; SM: Smooth muscle.

Table 3 Intraoperative data from 26 total patients

Variable	Value
Type of venous resection + reconstruction	
Tangential + patch, *n* (%)	5 (19.23)
Segmental + interposition, *n* (%)	21 (80.77)
Length of the segmental resected vein in mm	40 (35-50)
Length of the interposition graft in mm	40 (30-40)
Operative time in min	485 (397.50-572.75)
Blood loss at surgery in mL	200 (150-300)
Vein clamping time in min	50 (40-60)

Data are expressed as medians and interquartile ranges unless otherwise indicated.

Studying the structure of the LTH wall is essential to evaluate its potential as a graft for PV/SMV reconstruction. VVG staining revealed that EF, CF and SM content in the LTH wall were similar to PVs, which suggested that the LTH had characteristics similar to major abdominal vessels, such as vascular stiffness as well as contraction, and relaxation properties[34-38]. Therefore, the relative abundance of EFs, CFs and SM suggests that histologically LTH can be used as a graft to reconstruct the PV and/or SMV.

After PV and/or SMV reconstruction, vascular patency is key for a technically successful procedure [26,27]. Vascular endothelial cells act as a vascular barrier and mediate hemostatic and antithrombotic functions, which can affect the patency of blood vessels and reduce the risk of thrombosis[39,40]. HE staining showed that the inner surface of LTH was smooth and covered with endothelial cells. Immuno-

Table 4 Postoperative outcomes

Postoperative complications	Patients
Grade I	3
Bile leakage	2
Pulmonary infection	1
Grade II	5
Pancreatic leakage	1
Delayed gastric emptying, grade B	1
Pulmonary infection	2
Gastrointestinal hemorrhage	1
Grade III	2
Gastrointestinal bleeding	1
Lymphorrhea requiring abdominocentesis	1
Grade IV	0
Grade V, death	2
Overall morbidity, *n*/total (%)	10/26 (38.46)
Overall mortality, *n*/total (%)	2/26 (7.69)

Data are expressed as *n*, unless otherwise indicated.

histochemical staining revealed the expression of FVIIIAg and CD34 at the inner surface of LTH, confirming the presence of vascular endothelial cells.

Nitric oxide and t-PA, which are synthesized by endothelial cells, play important roles in thrombosis prevention. Abnormal eNOS function is associated with an increased risk of endothelial dysfunction [40], which in turn can be mitigated by upregulating eNOS expression[41]. Previous studies demonstrated that increasing t-PA production reduced thrombus formation[42-44]. The current study found that eNOS and t-PA can be expressed in LTH endothelial cells, suggestive of its anti-thrombosis function.

The surgical procedure, operating time, blood loss, PV clamping time, overall perioperative morbidity rate and mortality rate in this case series was similar to previous studies[23,45,46]. Postoperative partial thrombosis led to vascular stenosis in 5/26 patients, which was less than that reported in previous studies[6,45]. No patients developed uncontrollable portal hypertension or liver dysfunction. It is suggested that LTH as a graft for PV and/or SMV reconstruction is safe and reliable.

We acknowledge that the clinical study is limited by its retrospective nature and the small number of patients. Larger prospective studies should be conducted in the future to validate the findings of this study. However, this study is one of the largest studies that exclusively focused on patients with venous reconstruction using a recanalized LTH graft during PD.

CONCLUSION

In conclusion, the recanalized length of the LTH was suitable for reconstruction of the PV and SMV, and the dilated diameter and histological characteristics of the LTH were similar to the PV and SMV. Using the LTH as an autologous graft to reconstruct these vessels has achieved good clinical results and fits ideal characteristics including a wide range of sources, low cost, good histocompatibility and does not cause additional damage to patients. Based on the present study, we recommend the LTH as an autologous graft for PV and or SMV reconstruction in patients suffering from pancreaticobiliary cancer with PV/SMV involvement.

ACKNOWLEDGEMENT

The funding bodies had no role in the design of the study, the collection, analysis, or interpretation of the data or writing the manuscript.

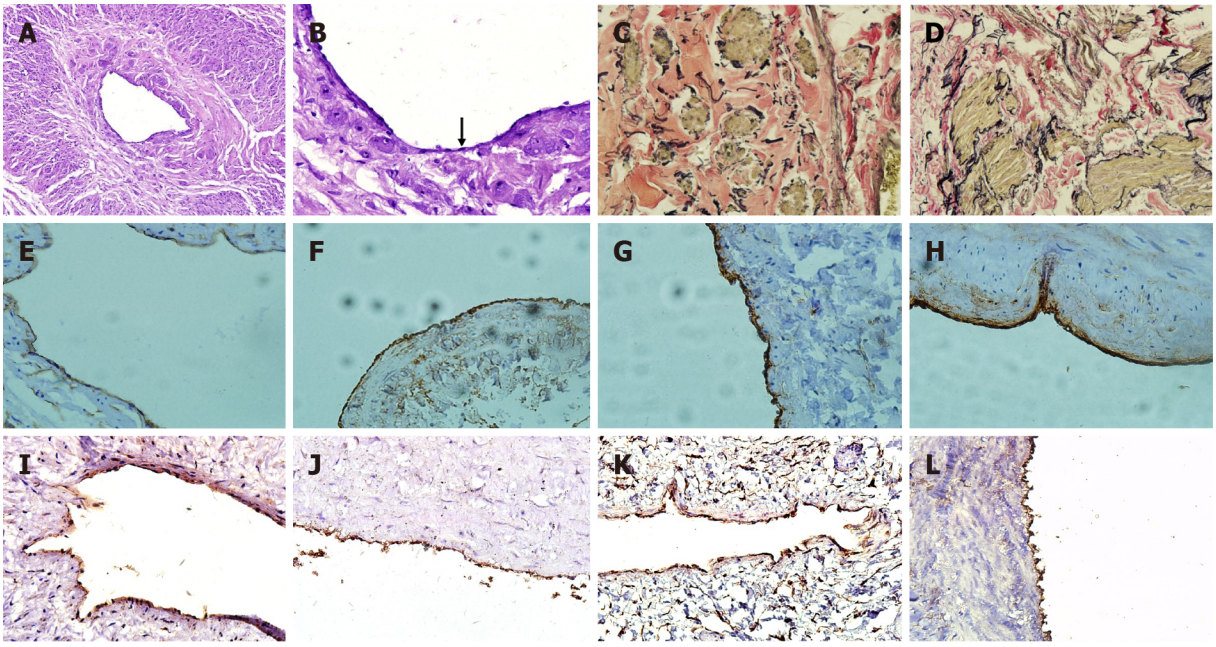

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Figure 4 Distribution and function of endothelial cells and relative content of collagen fibers, elastic fibers and smooth muscle in ligamentum teres hepatis. A: The ligamentum teres hepatis (LTH) lumen (× 100 magnification); B: Endothelial cells (black arrow, × 400 magnification); C: LTH after Verhoeff-Van Gieson (VVG) staining (× 400 magnification); D: The portal vein (PV) after VVG staining. Elastic fibers (red), collagen fibers (black) and smooth muscle (yellow) (× 400 magnification); E: CD34 expression in LTH endothelial cells (× 400 magnification); F: CD34 expression in PV endothelial cells (× 400 magnification); G: Factor VIII-related antigen (FVIIIAg) expression in LTH endothelial cells (× 400 magnification); H: FVIIIAg expression in PV endothelial cells (× 400 magnification); I: Endothelial nitric oxide synthase (eNOS) expression in LTH endothelial cells (× 400 magnification); J: eNOS expression in PV endothelial cells (× 400 magnification); K: Tissue type plasminogen activator (t-PA) expression in LTH endothelial cells (× 400 magnification); L: Tissue type plasminogen activator expression in PV endothelial cells (× 400 magnification).

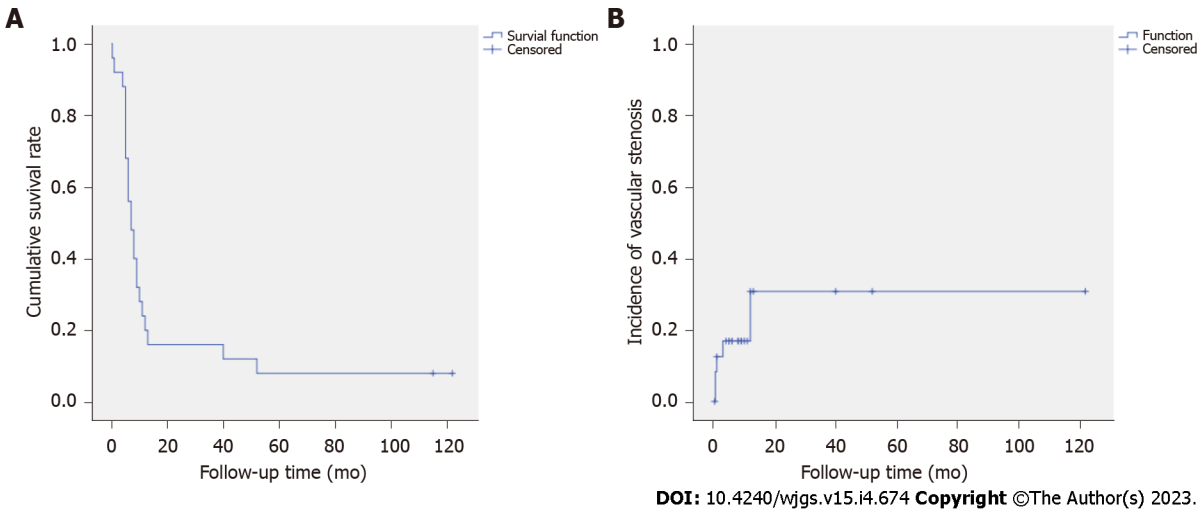

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Figure 5 Postoperative cumulative survival and vascular stenosis rate curve. A: The cumulative survival curve of the 26 patients undergoing pancreatoduodenectomy with venous resection and reconstruction; B: The vascular stenosis rate curve of the 26 patients undergoing portal vein and/or superior mesenteric vein reconstruction with ligamentum teres hepatis.

ARTICLE HIGHLIGHTS

Research background

Grafts may be required for portal vein (PV) and/or superior mesenteric vein (SMV) reconstruction during a pancreaticoduodenectomy (PD) procedure combined with PV and/or SMV resection. These grafts, including autogenous, homologous and artificial blood vessels, each have their own limitations. Therefore, it is necessary to explore more suitable grafts for PV and/or SMV reconstruction.

Research motivation

The ligamentum teres hepatis (LTH) is a fibrous remnant of the obliterated umbilical vein and can be recanalized. If the diameter and the histological characteristics of the dilated LTH tube wall are similar to the PV and SMV, and if the dilated LTH can be successfully used for PV and SMV reconstruction clinically, a novel PV and SMV graft will be acquired that has many sources, no additional medical costs and no immune rejection response.

Research objectives

To evaluate the feasibility of using the LTH as an autologous substitute for the reconstruction of the PV and/or SMV during PD and to provide basic and clinical evidence for using the LTH as an autologous graft for the PV and/or SMV reconstruction.

Research methods

The dilated length, diameter, tube wall histological characteristics and endothelial cell function of the LTH were measured and observed, and the results were compared to the PV and SMV for the first time. The outcomes of 26 patients who underwent PD where the LTH was used for PV and/or SMV reconstruction were studied, which is the largest sample size to date that exclusively focused on patients with venous reconstruction using a recanalized LTH graft during PD. The patency of the reconstructed PV and/or SMV using LTH as the autologous graft was reported for the first time.

Research results

The length, diameter and histological characteristics of the LTH tube wall were similar to the PV and/or SMV. The tunica intima of the LTH was covered with endothelial cells, and these cells functioned normally. The LTH as an autologous graft for PV and/or SMV reconstruction was successfully used in the clinic. However, larger prospective studies should be conducted in the future to validate the findings of this study.

Research conclusions

The LTH can be used as an autologous graft for PV and/or SMV reconstruction.

Research perspectives

The establishment of a homologous blood vessel bank using the LTH as grafts is expected.

FOOTNOTES

Author contributions: Zhu WT, Wang HT and Chen QP contributed to the conception and design; Zhu WT, Wang HT, Zhao BL, Wei Q and Ji HB contributed to the analysis and interpretation; Zhu WT, Wang HT, Zhang CX, Hu FA, Guan QH, Zhang XY and Wang RT collected the data; Zhu WT, Zhou L and Fu TL wrote the article; Chen QP and Zhang F critically revised the article; Zhu WT, Wang HT, Guan QH, Zhang F, Zhang CX, Hu FA, Zhao BL, Zhou L, Wei Q, Ji HB, Zhang XY and Chen QP approved the final article; Wei Q and Ji HB completed the statistical analysis; Chen QP and Zhao BL obtained fundings; Chen QP takes overall responsibility.

Supported by the Science and Technology Research and Development Program of Shandong Province, No. 2009GG10002047; the National Natural Science Fund, No. 81502069.

Institutional review board statement: This study was approved by the Ethics Committee of Binzhou Medical University Hospital, No. 2019-LW-023.

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

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

Data sharing statement: The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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: China

ORCID number: Wen-Tao Zhu 0000-0002-3432-0606; Hai-Tao Wang 0000-0001-9564-149X; Qing-Hai Guan 0000-0002-9408-8538; Fan Zhang 0000-0001-8028-8398; Chang-Xi Zhang 0000-0003-2427-6477; Feng-Ai Hu 0000-0002-4491-4862; Bao-Lei Zhao 0000-0002-1987-6067; Lei Zhou 0000-0003-4615-645X; Qiang Wei 0000-0003-0668-6579; Hai-Bin Ji 0000-0001-6606-4929; Ting-Liang Fu 0000-0002-3048-1357; Xing-Yuan Zhang 0000-0002-1817-8048; Rui-Tao Wang 0000-0003-0487-0575; Qiang-Pu Chen 0000-0002-8427-8266.

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

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World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2023 April 27; 15(4): 687-697

DOI: 10.4240/wjgs.v15.i4.687

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Observational Study

Efficacy and safety analysis of transarterial chemoembolization and transarterial radioembolization in advanced hepatocellular carcinoma descending hepatectomy

Rui Feng, De-Xin Cheng, Tao Song, Long Chen, Kai-Ping Lu

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: Abe K, Japan; Mahmud N, United States

Received: January 17, 2023
Peer-review started: January 17, 2023
First decision: March 1, 2023
Revised: March 9, 2023
Accepted: March 23, 2023
Article in press: March 23, 2023
Published online: April 27, 2023

Rui Feng, De-Xin Cheng, Department of Interventional Medicine, Zhejiang Provincial People's Hospital, People's Hospital of Hangzhou Medical College, Hangzhou 310000, Zhejiang Province, China

Tao Song, Cancer Center, Department of Radiation Oncology, Zhejiang Provincial People's Hospital, People's Hospital of Hangzhou Medical College, Hangzhou 310000, Zhejiang Province, China

Long Chen, Department of Radiotherapy, Zhejiang Provincial People's Hospital, People's Hospital of Hangzhou Medical College, Hangzhou 310000, Zhejiang Province, China

Kai-Ping Lu, Department of Vascular Surgery, Zhejiang Provincial People's Hospital, People's Hospital of Hangzhou Medical College, Hangzhou 310000, Zhejiang Province, China

Corresponding author: Kai-Ping Lu, MM, Associate Chief Physician, Department of Vascular Surgery, Zhejiang Provincial People's Hospital, People's Hospital of Hangzhou Medical College, No. 158 Shangtang Road, Gongshu District, Hangzhou 310000, Zhejiang Province, China. lukaiping158@126.com

Abstract

BACKGROUND

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors in the world, which is seriously threatening the lives of patients. Due to the rapid development of the disease, patients were in the middle and advanced stages at the time of diagnosis and missed the best time for treatment. With the development of minimally invasive medicine, interventional therapy for advanced HCC has achieved promising results. Transarterial chemoembolization (TACE) and transarterial radioembolization (TARE) are currently recognized as effective treatments. This study aimed to investigate the clinical value and safety of TACE alone and combined with TACE in the treatment of progression in patients with advanced HCC and to find a breakthrough for the early diagnosis and treatment of patients with advanced HCC.

AIM

To investigate the efficacy and safety of hepatic TACE and TARE in advanced descending hepatectomy.

METHODS

In this study, 218 patients with advanced HCC who were treated in the Zhejiang Provincial People's Hospital from May 2016 to May 2021 were collected. Of the patients, 119 served as the control group and received hepatic TACE, 99 served as the observation group and were treated with hepatic TACE combined with TARE. The patients in two groups were compared in terms of lesion inactivation, tumor nodule size, lipiodol deposition, serum alpha-fetoprotein (AFP) level in different periods, postoperative complications, 1-year survival rate, and clinical symptoms such as liver pain, fatigue, and abdominal distension, and adverse reactions such as nausea and vomiting.

RESULTS

The observation group and the control group had good efficacy in treatment efficiency, reduction of tumor nodules, reduction of postoperative AFP value, reduction of postoperative complications, and relief of clinical symptoms. In addition, compared with the control group, the treatment efficiency, reduction of tumor nodules, reduction of AFP value, reduction of postoperative complications, and relief of clinical symptoms in the observation group were better than those in the TACE group alone. Patients in the TACE + TARE group had a higher 1-year survival rate after surgery, lipiodol deposition was significantly increased and the extent of tumor necrosis was expanded. The overall incidence of adverse reactions in the TACE + TARE group was lower than that in the TACE group, and the difference had statistical significance ($P < 0.05$).

CONCLUSION

Compared with TACE alone, TACE combined with TARE is more effective in the treatment of patients with advanced HCC. It also improves postoperative survival rate, reduces adverse effects, and has a better safety profile.

Key Words: Hepatic arterial chemoembolization; Transarterial radiation embolization; Liver cancer; Downward treatment; Efficacy; Security

Core Tip: The transarterial radioembolization (TARE) technique treats hepatocellular carcinoma (HCC) by perfusing radionuclide microspheres into the HCC lesion through the hepatic arterial route and releasing ionizing radiation through the radionuclide carried by the microspheres. With the development of materials science, stable radionuclide microspheres have been widely applied in clinical practice. On this basis, we found that the combined effect of transarterial chemoembolization and TARE techniques could increase the inactivation of HCC lesions, expand the scope of tumor necrosis, increase postoperative survival rate, and improve the life quality of patients. It has high clinical value in the descending treatment of patients with HCC.

Citation: Feng R, Cheng DX, Song T, Chen L, Lu KP. Efficacy and safety analysis of transarterial chemoembolization and transarterial radioembolization in advanced hepatocellular carcinoma descending hepatectomy. *World J Gastrointest Surg* 2023; 15(4): 687-697
URL: https://www.wjgnet.com/1948-9366/full/v15/i4/687.htm
DOI: https://dx.doi.org/10.4240/wjgs.v15.i4.687

INTRODUCTION

Hepatocellular carcinoma (HCC), as a common malignant tumor, has been one of the leading causes of cancer-related death worldwide[1]. As for the prevalence of the hepatitis B virus, patients with HCC are more common in China[2]. Currently, clinical surgical treatment including hepatectomy and liver transplantation is the most effective treatment for patients with HCC to achieve long-term survival or even a radical cure[3]. However, many patients with liver cancer are diagnosed in the middle and advanced stages. Due to factors such as large tumors and large vascular accumulation, surgical resection is not possible, resulting in missed optimal timing of treatment and increased mortality from liver cancer[4]. Therefore, how to transform inoperable intermediate and advanced HCC into surgically resectable is one of the research hotspots in recent years.

The post-descending resection of HCC refers to the conversion of initially advanced liver cancer into relatively early liver cancer through local, systemic, or comprehensive therapy, so that some HCCs are converted from unresectable to resectable. The aims of descending HCC treatment are the

disappearance of intrahepatic and extrahepatic parts of the tumor, the reduction of the giant tumor, the disappearance of the venous cancer thrombus, or the compensatory enlargement of the uninvaded liver [5,6]. It has been reported that the current treatment methods for HCC mainly include TACE, comprehensive hepatic artery ligation, transarterial radioembolization (TARE), and comprehensive therapy[7, 8]. TACE, as the most widely used non-surgical treatment, could embolize the arterial blood supply of tumors, reduce tumor load and delay tumor progression[9]. The TARE technique, which combines embolic substances with radioactive substances to embolize the corresponding lesion through a catheter, has great potential in reducing total body irradiation and reducing effects on healthy livers [10]. Previous studies have shown that TACE, as a more effective and less invasive non-surgical treatment option, has become an important tool for adjuvant therapy. However, it has also been reported that the long-term effect of TACE alone is not significant[11,12]. Based on this, the study retrospectively analyzed the clinical data of patients with intermediate and advanced HCC and investigated the efficacy and safety of TACE alone and TACE combined with TARE in the treatment of patients with intermediate and advanced HCC, hoping to provide a more effective basis for the second surgical resection of patients with mid and advanced liver cancer.

MATERIALS AND METHODS

General information

A total of 218 patients with moderately advanced HCC admitted to Zhejiang Provincial People's Hospital from May 2016 to May 2021 were selected for the study, including 111 males and 107 females, aged 28-77 years. According to Child-Pagh liver function rating criteria[13,14], 68 cases were grade A, 102 cases were grade B, and 48 cases were grade C. The tumor diameter ranged from 2.5 to 17.6 cm, with 90 cases with tumor diameters less than 5 cm, and 128 cases with diameters greater than 5 cm. All subjects had voluntarily signed informed consent. The 119 patients treated with TACE alone were classified as the control group. 99 patients treated with TACE combined with TARE were classified as the observation group. The control group was treated with the modified Seldinger puncture and catheterization, while the observation group was treated with hepatic arterial chemoembolization followed by high-energy X-ray arterial radioembolization combination therapy.

There was no significant difference in general data among the groups ($P > 0.05$). The data were comparable, as shown in Table 1.

Inclusion and exclusion criteria

Inclusion criteria: (1) Patients with HCC who met the diagnostic criteria of HCC in the diagnosis and treatment criteria of liver cancer[15]; (2) Patients without any other relevant treatment before TACE or TACE + TARE treatment; (3) Patients treated with TACE alone or TACE combined with TARE after TACE; (4) All patients were diagnosed by imaging examination [such as computed tomography (CT), ultrasound, magnetic resonance, *etc.*] combined with tumor markers and other tests to confirm the diagnosis; and (5) All patients were with advanced HCC or unable or unwilling to undergo surgery due to other reasons (tumor location, severe liver cirrhosis, old age, cardiopulmonary insufficiency, *etc.*).

Exclusion criteria: (1) Patients with severe heart, brain, or kidney diseases; (2) Patients with incomplete clinical data, imaging data, relevant laboratory test results or those who cannot be followed up; and (3) Patients with severe mental illness and mental retardation that could not cooperate with the treatment.

Methods

The control group was treated with TACE using a modified Seldinger puncture placement method[16, 17].

All procedures were performed by the right femoral artery, and the superior mesenteric and celiac arteriography were examined by DSA. The size, structure, and course of the hepatic artery tumor were observed. Perfusion chemotherapy was administered first with 5-FU (1-1.5 g), Cisplatin (40-50 mg), and Adriamycin (40-50 mg) every 4 wk for 3 times, followed by iodinated oil (15-20 mL) pills.

The observation group was treated with TACE combined with TARE. First, interventional therapy was performed by the above method, with an interval of 4-6 wk between interventions. The radiation therapy was performed after or between interventions, with a general interval of 3-5 wk between interventions and radiation therapy. The methods and doses of radiotherapy were as follows: high-energy X-ray (18 mV) was used[18]. Local field radiation was used for liver lesions within 10 cm in diameter, with a field of 12 cm × 12 cm or less, and 160 CGy-200 CGy/d for both fields. The whole liver or sub-total liver moving strip irradiation was performed for liver lesions beyond 10 cm. Among the 99 cases in the observation group, 58 cases had focal field radiation of liver tumor, completing 3800 CGy of tumor irradiation. 41 cases had 4 rounds of whole liver mobile strip radiation, completing 2200-3000 CGy of liver central plane dose. Patients were given oxygen during the operation, their vital signs were monitored, and food rich in vitamins and high protein was given after the operation.

Table 1 Comparison of general data in each group

	TACE group (*n* = 119)	TACE + TARE group (*n* = 99)	χ^2	*P* value
Gender			0.512	0.604
Male	63	48		
Female	56	51		
Age (yr), mean ± SD	56.78 ± 5.68	55.89 ± 5.45	1.173	0.242
Child-Pagh liver function rating			0.463	0.765
Grade A	36	32		
Grade B	60	42		
Grade C	23	25		
Tumor diameter			0.862	0.755
< 5 cm	48	42		
< 5 cm	71	57		

TACE: Transarterial chemoembolization; TARE: Transarterial radioembolization.

Observation indicators

Lesion inactivation: According to World Health Organization objective efficacy criteria[19,20]: complete remission (CR): the lesions disappeared completely and are maintained for more than one month; partial remission (PR): the two diameters of the lesion were reduced by more than 50% and the maintenance lasted for more than one month; nature change: the lesions were reduced less than 50% or enlarged less than 25% and maintained for more than one month; progress development: the lesions were enlarged by more than 25% or new lesions appeared. Blood routine examination was performed once a week during the treatment period, and liver CT was repeated every 3 mo to evaluate the efficacy and calculate the effective rate (Figure 1A and B). The effective treatment rate = (CR + PR) × 100%.

Tumor nodules: During the treatment period, the patients were treated with immune enhancement and liver protection. After the treatment, the liver and kidney functions were reexamined. After 2 mo, the CT imaging changes were observed to detect the tumor nodule size.

Deposition of lipiodol: Patients with HCC could be treated with lipiodol interventional embolization, which is based on the principle that lipiodol binds more strongly to hepatocellular tumor cells than hepatocytes. The higher the lipiodol filling density, the greater the degree of the deposition, the greater and more complete the degree of tumor necrosis, and its contraction is more obvious, thus prolonging the survival of patients. According to the amount of lipiodol in tumor tissue, there are 5 grades[21]: Grade 0 (without lipiodol deposition), Grade I (lipiodol retention in lesions < 10%), Grade II (< 50%), Grade III (> 50%), and Grade IV (the whole lesion is full of iodine oil). The deposition of lipiodol in patients was observed according to the above standards.

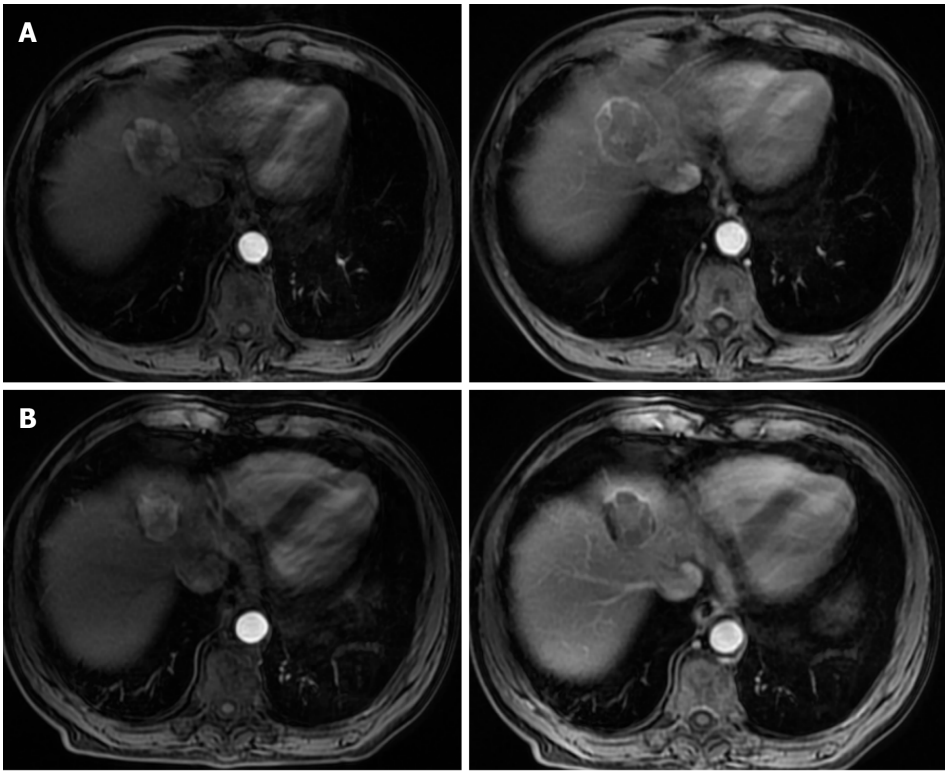
Serum alpha-fetoprotein level in different periods: After treatment, the levels of liver function, kidney function, and blood routine were reexamined. Serum alpha-fetoprotein (AFP) levels in the control group and observation group were observed in different periods, such as 1 mo, 3 mo, 6 mo, and 1 year after the operation.

Postoperative complications and 1-year survival rate: After the treatment, the incidence of complications such as postoperative fever, pleural effusion, cholecystitis, and hepatic encephalopathy was observed in the control group and the observation group, and the 1-year survival rate was statistically analyzed and compared between the two groups.

Clinical symptoms and adverse reactions of patients: Clinical symptoms include liver pain, fatigue, abdominal distension, and so on. Scoring standard[22]: no symptoms-0 points; occasional symptoms-1 point; frequent symptoms-2 points; symptoms persist for a long time and affect daily activities-3 points. Adverse reactions mainly include nausea, vomiting, hair loss, and so on.

Statistical analysis

All data were processed and analyzed using SPSS 21.0 software. The measurement data was expressed as mean ± SD, the comparison between groups was analyzed by *t*-test, the counting data were expressed as *n* (%), and the comparison was analyzed by χ^2 test. All the differences were statistically significant at $P < 0.05$.



DOI: 10.4240/wjgs.v15.i4.687

Figure 1 Contrast-enhanced computed tomography scans of patients with hepatocellular carcinoma. A: Contrast-enhanced computed tomography (CT) scan image of the pre-operative hepatocellular carcinoma (HCC) patient; B: Contrast-enhanced CT scan image of the post-operative HCC patient.

RESULTS

Objective efficacy-lesion inactivation

By observing the inactivation of lesions treated with different interventions in the two groups, we found that both the TACE group and TACE + TARE group had better treatment effective rate (CR + PR), and the effective rate of the TACE + TARE group (68.69%) was higher than that of the TACE group (42.86%). The levels of CR and PR in the TACE + TARE group were significantly different from those in the TARE group ($P < 0.05$). The results showed that TACE + TARE combined intervention therapy has significantly higher therapeutic efficiency and better efficacy than TACE alone (Table 2).

Tumor nodules

Further observation of the size of tumor nodules in the two groups of patients with different intervention treatments showed that the size of tumor nodules in the TACE group and TACE + TARE group were reduced to some extent. In TACE + TARE group, the tumor nodules were less than 50% or stable at 73.74%, which was better than that of the TACE group (47.89%). In the TACE + TARE group, the tumor nodules decreased significantly compared with the TACE group, and the difference was statistically significant ($P < 0.05$). The results indicated that TACE + TARE combination treatment could reduce tumor nodule size and inhibit cancer progression compared with TACE alone (Table 3).

Lipiodol deposition

One month later, CT was reexamined to observe the deposition of lipiodol in all cases. The deposition of lipiodol to grade III-IV in the TACE + TARE group (63.64%) was significantly better than that in TACE alone (48.74%) ($P < 0.05$), which indicated that the combination treatment of TACE + TARE could significantly increase lipiodol deposition and enlarge tumor necrosis compared with TACE alone (Table 4).

Serum AFP level in different periods

AFP is an acidic glycoprotein, which exists in the liver and yolk sac at the early stage of fetal development, and gradually disappears shortly after birth. The content of normal people is extremely low, and when the content is significantly increased, it helps in the diagnosis of primary liver cancer[23, 24]. The results of this study showed that the AFP levels in both groups decreased after the operation, but the AFP levels of the TACE + TARE group were significantly lower than those of the control group in each period after the operation ($P < 0.05$), which indicated that the combined therapy had a better

Table 2 Comparison of inactivation of lesions in Table 2 groups, *n* (%)

Group	CR	PR	NC	PD	The effective rate of treatment
TACE group (n = 119)	25 (21.01)	26 (21.84)	38 (26.89)	30 (18.49)	51 (42.86)
TACE + TARE group (n = 99)	34 (34.34)	34 (34.34)	16 (21.21)	15 (23.23)	68 (68.69)
χ^2	0.040	0.057	0.011	0.097	< 0.001
P value	0.027	0.040	0.007	0.068	< 0.001

CR: Complete remission; PR: Partial remission; NC: Nature change; PD: Progress development.

Table 3 Comparison of tumor nodules in groups, *n* (%)

Group	Tumor nodules			
	> 50%	< 50%	Stable	Increase
TACE group (n = 119)	39 (32.78)	28 (23.53)	29 (24.37)	23 (19.33)
TACE + TARE group (n = 99)	20 (20.20)	36 (36.36)	37 (37.37)	6 (6.06)
χ^2	0.054	0.041	0.053	0.008
P value	0.038	0.028	0.037	0.004

TACE: Transarterial chemoembolization; TARE: Transarterial radioembolization.

Table 4 Comparison of lipiodol deposition in groups, *n* (%)

Group	Lipiodol deposition					
	Grade 0	Grade I	Grade II	Grade III	Grade IV	Grade III + IV
TACE group (n = 119)	18 (29.41)	23 (29.41)	20 (21.85)	30 (25.21)	28 (23.53)	58 (48.74)
TACE + TARE group (n = 99)	8 (29.41)	8 (11.11)	10 (15.15)	38 (38.38)	35 (35.35)	63 (63.64)
χ^2	0.165	0.030	0.152	0.037	0.045	< 0.001
P value	0.110	0.018	0.217	0.052	0.077	< 0.001

TACE: Transarterial chemoembolization; TARE: Transarterial radioembolization.

effect (Table 5).

Postoperative complications and 1-year survival rate

Postoperative complications and 1-year survival were compared between the TACE + TARE group and the control group. The total incidence of fever, cholecystitis, ascites and hepatic encephalopathy in the TACE + TARE group (36.37%) was higher than that in the TACE group (34.45%), but the difference was not statistically significant (P > 0.05). In addition, the 1-year survival rate of the TACE + TARE group was significantly higher than that of the TACE group (P < 0.05). The above results indicated that TACE + TARE combined therapy had better safety, and TACE + TARE combined therapy could better improve the 1-year survival rate of patients (Table 6).

Clinical symptoms and adverse reactions of patients

Clinical symptoms such as pain in the liver area, weakness, and abdominal distension were observed in each group. It was found that there was no significant difference in clinical symptom scores between the TACE group and TACE + TARE group before treatment (P > 0.05). After treatment, the scores of clinical symptoms in the TACE + TARE group were significantly lower than those in the control group (P < 0.05). In addition, the overall incidence of adverse reactions such as nausea, vomiting, and alopecia in the TACE group was 25.21%, and that in the TACE + TARE group was 14.14%. The data showed that the overall incidence of adverse reactions in the TACE + TARE group was lower than that in the TACE group, and the difference was statistically significant (P < 0.05), which indicated TACE alone or combined with TARE had a higher therapeutic effect and better safety on clinical symptoms such as

Table 5 Comparison of serum alpha-fetoprotein levels in different stages (mean ± SD)

Group	AFP (μg/L)			
	1 mo after the operation	3 mo after the operation	6 mo after the operation	1 year after the operation
TACE group (n = 119)	38.33 ± 4.78	38.67 ± 5.32	36.45 ± 3.24	31.53 ± 3.54
TACE + TARE group (n = 99)	36.45 ± 5.68	35.53 ± 4.45	32.37 ± 3.47	28.78 ± 3.25
χ^2	2.654	4.669	8.963	5.926
P value	0.009	< 0.001	< 0.001	< 0.001

AFP: Alpha-fetoprotein; TACE: Transarterial chemoembolization; TARE: Transarterial radioembolization.

Table 6 Comparison of postoperative complications and 1-year survival rate in groups, *n* (%)

Complications	TACE group (n = 119)	TACE + TARE group (n = 99)	χ^2	P value
Fever	6 (5.04)	6 (6.06)	0.976	0.743
Hydrothorax	16 (13.45)	15 (5.05)	0.869	0.720
Cholecystitis	4 (3.36)	6 (6.06)	0.533	0.343
Hepatic encephalopathy	15 (12.61)	9 (9.09)	0.543	0.409
Total complication rate	41 (34.45)	36 (36.37)	0.880	0.769
1-yr survival rate	25 (21.00)	33 (33.33)	0.058	0.040

TACE: Transarterial chemoembolization; TARE: Transarterial radioembolization.

liver pain, fatigue, and abdominal distension in patients with advanced HCC (Tables 7 and 8).

DISCUSSION

Clinically, HCC is considered to be a malignant tumor of the digestive system with a high incidence. However, most patients have an insidious condition and are diagnosed in the middle and advanced stages, therefore, interventional surgery has become an important option[25-27]. With the continuous application of combined technology in clinical application, TACE combined with TARE technology has better efficacy in patients with mid or advanced HCC[8,10]. Since Goldstein first reported the treatment of HCC with TACE in 1976, TACE has been rapidly developed and further developed worldwide[11,28]. TACE is mainly suitable for patients with unresectable HCC and well liver function, and its efficacy is positive, which can improve the survival rate of HCC patients in this stage[2,29-31]. However, TACE is difficult to achieve a radical cure of cancer due to factors such as ectopic blood supply, angiogenesis, and portal vein blood supply around the tumor, and the tumor control rate of TACE alone is only about 20%[32,33]. Therefore, comprehensive treatment based on TACE has become a research hotspot in recent years. By analyzing the clinical efficacy of TACE alone and TACE + TARE combined therapy, the study aims to provide some data support for the treatment of advanced HCC patients.

The TARE technique involves the infusion of radionuclide microspheres into HCC lesions through hepatic artery access, and the ionizing radiation is released through the nuclide carried by the microspheres to treat HCC[34-38]. Meanwhile, radiotherapy has a wide range of applications, which are not limited by anatomical location and tumor localization. However, it is found that radiotherapy alone is difficult to achieve effective radiation doses for some tumors, and some HCC patients are insensitive to radiotherapy. In addition, the production of radioactive microspheres is expensive, which undoubtedly increases the economic burden of patients to a certain extent[39,40]. Therefore, the combination of TARE with other methods is one of the mainstream trends. On this basis, this study aimed to investigate the clinical efficacy and related adverse reactions of TACE + TARE in the treatment of advanced HCC patients, hoping to provide some help for the prevention and treatment of advanced HCC.

In this study, 99 patients with intermediate or advanced HCC were treated with TACE + TARE, and 119 patients with intermediate or advanced HCC were treated with TACE as the control. The lesion inactivation, tumor nodule size, and serum AFP level in different periods were compared between the observation group and the control group to observe the efficacy of TACE and TARE combined

Table 7 Clinical symptom score (mean ± SD)

Group	Hepatic pain		Fatigue		Abdominal distension	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
TACE group (n = 119)	2.31 ± 0.56	2.07 ± 0.63	2.67 ± 0.87	2.35 ± 0.54	2.93 ± 0.62	2.37 ± 0.55
TACE + TARE group (n = 99)	2.29 ± 0.58	1.56 ± 0.72	2.54 ± 0.58	1.45 ± 0.63	2.79 ± 0.58	1.26 ± 0.66
χ^2	0.258	5.576	0.720	11.357	1.709	13.545
P value	0.796	< 0.05	0.205	< 0.001	0.089	< 0.001

TACE: Transarterial chemoembolization; TARE: Transarterial radioembolization.

Table 8 Comparison of adverse reactions in groups, *n* (%)

Group	Nausea	Vomiting	Hair loss	Total incidence
TACE group (n = 119)	11 (9.24)	9 (7.56)	10 (8.40)	30 (25.21)
TACE + TARE group (n = 99)	5 (5.05)	5 (5.05)	4 (4.04)	14 (14.14)
χ^2	0.357	0.634	0.303	0.063
P value	0.237	0.451	0.191	0.043

TACE: Transarterial chemoembolization; TARE: Transarterial radioembolization.

treatment. The results showed that the effective rate of TACE + TARE combined therapy was significantly increased and the tumor nodule size was significantly reduced compared with TACE alone group. This suggests that combination therapy could significantly improve the therapeutic effect and inhibit the malignant progression of the tumor.

It has been reported that the higher the density and range of lipiodol filling, the more deposition, the larger and more complete the range of tumor necrosis, and the more obvious the reduction, thus prolonging the survival time of HCC patients[21]. The results of this study showed that the degree of lipiodol deposition to grade III to IV in the TACE + TARE group was significantly better than that in the TACE group, which indicated that the synergistic effect of the TACE + TARE group could expand the range of tumor necrosis, reduce the tumor area and enhance the therapeutic effect. In addition, the study also found that there was no significant difference in postoperative complications such as fever, and cholecystitis ascites in the TACE group, and the one-year survival rate of the TACE + TARE group was higher than that of the TACE group. Meanwhile, after treatment, the scores of clinical symptoms such as liver pain, fatigue, and abdominal distension in the TACE + TARE group were significantly lower than those in the TACE group. In addition, the overall incidence of adverse reactions in the TACE + TARE group was lower than that in the TACE group. All the above results indicated that TACE + TARE therapy had higher clinical efficacy and better safety in patients with advanced HCC than TACE alone.

In recent years, more and more studies tend to combine TACE with TARE. Kim *et al*[32] found through Meta-analysis results that TACE combined with radiotherapy was superior to TACE alone in terms of short-term efficacy (CR + PR) remission rate and long-term 1-, 2- and 3-year survival time. In addition, Currie *et al*[41] also reported that TACE alone combined with interventional chemoembolization and radiotherapy could reduce normal liver tissue damage, improve tumor control rate and prolong patient survival time. Also, TACE combined with radiotherapy was significantly better than TACE alone in reducing recurrence rate and metastasis rate[42]. The above study further confirmed the conclusion of this study that compared with TACE alone, TACE combined with TARE could have a better therapeutic effect and clinical value with better safety for patients with advanced HCC. This will provide evidence for the treatment of patients with advanced HCC and provide the possibility for their secondary operation.

However, due to the limitation of sample quantity, the actual efficacy in the clinical application needs to be further verified, and we will discuss it in depth in the future.

CONCLUSION

In conclusion, TACE combined with TARE could increase the inactivation of HCC lesions, reduce tumor

nodules, expand tumor necrosis range, increase postoperative survival rate, reduce postoperative adverse reactions and improve the survival quality of patients, which have high clinical value and better safety in the descending treatment of patients with advanced HCC.

ARTICLE HIGHLIGHTS

Research background

Hepatocellular carcinoma (HCC) is the most common primary malignant tumor of the liver. Transarterial chemoembolization (TACE) and transarterial radioembolization (TARE) is the recommended treatment for intermediate HCC according to the Barcelona Clinic Liver Cancer guidelines.

Research motivation

TARE, as a new interventional therapy, has been gradually applied to the treatment of advanced HCC, and has a good effect on the treatment of advanced HCC.

Research objectives

To explore the efficacy and safety of TACE+TARE in the advanced HCC descending hepatectomy.

Research methods

The patients in the control group and the observation group were compared in terms of focal inactivation, tumor nodule size, lipiodol deposition, serum alpha-fetoprotein (AFP) level in different periods, postoperative complications, 1-year survival rate, and adverse reactions.

Research results

Compared with the control group, the observation group can be effective, reduce tumor nodules, reducing postoperative AFP value, reducing postoperative complications, and relieving clinical symptoms. Compared with the control group, the observation group significantly increased the deposition of lipiodol, expanded the scope of tumor necrosis, increased the 1-year survival rate of patients after surgery, and reduced adverse reactions, the difference was statistically significant ($P < 0.05$).

Research conclusions

Compared with TACE, TACE + TARE is more effective in the treatment of patients with advanced HCC.

Research perspectives

This study may provide a clinical basis for the treatment of patients with advanced HCC.

FOOTNOTES

Author contributions: Feng R and Lu KP designed the study and wrote the manuscript; Feng R and Cheng DX analyzed the data; Song T and Chen L were responsible for revising the paper; all authors have read and agreed to the published version of the manuscript.

Institutional review board statement: The study was approved by Ethics Committee of the Third Hospital of Zhejiang Provincial People's Hospital.

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

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

Data sharing statement: No additional data are available.

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

Country/Territory of origin: China

ORCID number: Kai-Ping Lu 0000-0002-0578-4567.

S-Editor: Gong ZM
L-Editor: A
P-Editor: Gong ZM

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World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2023 April 27; 15(4): 698-711

DOI: 10.4240/wjgs.v15.i4.698

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Prospective Study

Effectiveness of a new approach to minimally invasive surgery in palliative treatment of patients with distal malignant biliary obstruction

Yaroslav M Susak, Leonid L Markulan, Serhii M Lobanov, Roman Y Palitsya, Mariia P Rudyk, Larysa M Skivka

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

P-Reviewer: dos Santos JS, Brazil; Lin L, China

Received: November 17, 2022
Peer-review started: November 17, 2022
First decision: January 23, 2023
Revised: February 5, 2023
Accepted: March 3, 2023
Article in press: March 3, 2023
Published online: April 27, 2023

Yaroslav M Susak, Leonid L Markulan, Serhii M Lobanov, Department of Surgery with the Course of Emergency and Vascular Surgery, O.O. Bogomolets National Medical University, Kyiv 01601, Ukraine

Roman Y Palitsya, Department of Abdominal Surgery, National Military Medical Clinical Centre "Main Military Clinical Hospital", Kyiv 01133, Ukraine

Mariia P Rudyk, Larysa M Skivka, Department of Microbiology and Immunology, Taras Shevchenko National University of Kyiv, Kyiv 01033, Ukraine

Corresponding author: Mariia P Rudyk, PhD, Associate Professor, Department of Microbiology and Immunology, Taras Shevchenko National University of Kyiv, 60 Volodymyrska St, Kyiv 01033, Ukraine. rosiente@gmail.com

Abstract

BACKGROUND

Palliative endoscopic biliary drainage is the primary treatment option for the management of patients with jaundice which results from distal malignant biliary obstruction (DMBO). In this group of patients, decompression of the bile duct (BD) allows for pain reduction, symptom relief, chemotherapy administration, improved quality of life, and increased survival rate. To reduce the unfavorable effects of BD decompression, minimally invasive surgical techniques require continuous improvement.

AIM

To develop a technique for internal-external biliary-jejunal drainage (IEBJD) and assess its effectiveness in comparison to other minimally invasive procedures in the palliative treatment of patients with DMBO.

METHODS

A retrospective analysis of prospectively collected data was performed, which included 134 patients with DMBO who underwent palliative BD decompression. Biliary-jejunal drainage was developed to divert bile from the BD directly into the initial loops of the small intestine to prevent duodeno-biliary reflux. IEBJD was carried out using percutaneous transhepatic access. Percutaneous transhepatic biliary drainage (PTBD), endoscopic retrograde biliary stenting (ERBS), and

internal-external transpapillary biliary drainage (IETBD) were used for the treatment of study patients. Endpoints of the study were the clinical success of the procedure, the frequency and nature of complications, and the cumulative survival rate.

RESULTS

There were no significant differences in the frequency of minor complications between the study groups. Significant complications occurred in 5 (17.2%) patients in the IEBJD group, in 16 (64.0%) in the ERBS group, in 9 (47.4%) in the IETBD group, and in 12 (17.4%) in the PTBD group. Cholangitis was the most common severe complication. In the IEBJD group, the course of cholangitis was characterized by a delayed onset and shorter duration as compared to other study groups. The cumulative survival rate of patients who underwent IEBJD was 2.6 times higher in comparison to those of the PTBD and IETBD groups and 20% higher in comparison to that of the ERBS group.

CONCLUSION

IEBJD has advantages over other minimally invasive BD decompression techniques and can be recommended for the palliative treatment of patients with DMBO.

Key Words: Distal malignant biliary obstruction; Obstructive jaundice; Bile duct decompression; Palliative endoscopic biliary drainage; Internal-external biliary-jejunal drainage

Core Tip: This study compared the new technique of internal-external biliary-jejunal drainage (IEBJD) for bile duct (BD) decompression in patients with obstructive jaundice with commonly used procedures through a retrospective analysis of prospectively collected data. IEBJD was used to divert bile from the BD directly into the initial loops of the small intestine to prevent duodeno-biliary reflux. The application of IEBJD was associated with a decreased incidence of significant complications, a delayed onset of cholangitis and its shorter duration, as well as an increased cumulative survival rate in patients with distal malignant biliary obstruction as compared to commonly used endoscopic ultrasound-guided retrograde and antegrade techniques and internal-external transpapillary biliary drainage.

Citation: Susak YM, Markulan LL, Lobanov SM, Palitsya RY, Rudyk MP, Skivka LM. Effectiveness of a new approach to minimally invasive surgery in palliative treatment of patients with distal malignant biliary obstruction. *World J Gastrointest Surg* 2023; 15(4): 698-711
URL: https://www.wjgnet.com/1948-9366/full/v15/i4/698.htm
DOI: https://dx.doi.org/10.4240/wjgs.v15.i4.698

INTRODUCTION

Patients with jaundice would be ineligible for radical treatment in 70%-85% of cases upon initial examination due to distal malignant biliary obstruction (DMBO)[1,2]. Palliative decompression of the bile ducts (BD) is currently the primary treatment option for the management of patients with obstructive jaundice. This approach allows for pain reduction, symptom relief, and, in some cases, chemotherapy administration[3]. BD decompression not only improves patients' quality of life but also increases their survival rate[4].

In general, there are two main techniques for performing endoscopic ultrasound-guided minimally invasive BD (EUS-BD) decompression: The EUS-rendezvous approach (retrograde) and the EUS-antegrade technique[5,6], and their combination is also possible[7]. Each method has both advantages and disadvantages.

Percutaneous transhepatic biliary drainage (PTBD) is likely to result in: (1) A significant loss of bile, necessitating the oral administration of bile salts and leaving an implantable port under the skin[6]; and (2) the implantation of metastases along the trajectory of stent placement[8], as well as cholangitis development caused by stent malfunction. Nevertheless, compared to other methods, this one is relatively simple and most affordable. Endoscopic retrograde biliary stenting (ERBS) is considered a method of choice for palliative treatment of patients with DMBO[8,9]. However, it is associated with trauma to the major duodenal papilla (papilla of Vater) and pancreas, which increases the risk of bleeding and pancreatitis development[10] and causes the reflux of duodenal content to the BD[11,12]. It leads to cholangitis development and stent obstruction[13]. The proposed antireflux stents[12,14-16]

have not yet found widespread use[17]. In addition, tumor ingrowth and overgrowth, as well as stent occlusion, are potential outcomes[18]. Stents are relatively expensive and difficult to repair and replace [19]. Nevertheless, they provide internal drainage of bile.

Combining the advantages of percutaneous drainage and stenting, internal-external transpapillary biliary drainage (IETBD) involves draining the duodenum while maintaining normal bile outflow. However, there is a high probability of reflux cholangitis. Researchers have polarized opinions about the effectiveness of this approach[9,20-22].

Thus, one of the main reasons for cholangitis being one of the most serious complications of minimally invasive BD decompression techniques, is stent occlusion, which is strongly associated with duodenobiliary reflux. Therefore, avoidance of duodenobiliary reflux is important in preventing stent dysfunction and cholangitis onset[23].

In order to reduce the unfavorable effects of BD decompression in patients with DMBO including cholangitis, the approaches and tools used in minimally invasive procedures, as well as the choice of method, require continuous improvement.

We aimed to develop a technique for internal-external biliary-jejunal drainage (IEBJD) and assess its effectiveness in comparison to other minimally invasive procedures in the palliative treatment of patients with DMBO.

MATERIALS AND METHODS

Study participants

A prospective, randomized, multicenter study was conducted in three hospitals affiliated with the Department of Surgery with a course of emergency and vascular surgery at O.O. Bogomolets National Medical University (Kyiv): Kyiv City Oleksandrivska Clinical Hospital, Kyiv City Clinical Emergency Hospital, and National Military Medical Clinical Center "Main Military Clinical Hospital", Kyiv. A total of 134 patients who underwent palliative decompression of the BD due to DMBO between 2017 and 2021 were included in the study. Approval was obtained from the Ethics Committee of O.O. Bogomolets National Medical University (Protocol No. 25-15-65, as of November 28, 2017), and informed consent was given by all participants before the study. The inclusion criteria were: The presence of mechanical jaundice; age over 18 years; the impossibility of radical surgery; and the technical success of the minimally invasive procedure. The exclusion criteria were: Mechanical BD obstruction without jaundice; age less than 18 years; high operative risk [American Society of Anesthetists (ASA) score of 4]; multiple metastatic liver disease; ascites; hemorrhagic diathesis; coagulopathy (international normalized ratio ≥ 1.5); past history of gastrectomy and reconstruction using the Billroth II or Roux-en-Y technique.

Using MS Excel, patients were randomly assigned to four treatment groups in accordance with the BD decompression procedure (Figure 1). The PTBD group included 33 patients; the IETBD group included 30 patients; the ERBS group included 34 patients; and the IEBJD group included 37 patients. However, due to technical difficulties in implementing the planned method, which was subsequently replaced with another one, the number of patients in the groups changed throughout the course of the study. In particular, two patients were not eligible for ERBS (they underwent PTBD); IETBD turned out to be impossible for two patients (they underwent PTBD); during IEBJD, we did not manage to provide drainage distally to the ligament of Treitz in two cases (they underwent IETBD); and it was impossible to insert the drain tube distally to the tumor of the pancreatic head in one patient (he underwent PTBD). All patients who were randomized to the PTBD group were treated using this BD decompression technique.

Thus, the PTBD group included 38 patients, the IETBD group included 30 patients, the ERBS group included 32 patients, and the IEBJD group included 34 patients.

The PTBD and IETBD procedures were carried out using plastic drain tubes of the Pigtail type 9Fr. For ERBS, Partially Covered Nitinol Self-Expandable Metal Stents with a diameter of 8-10 mm were used.

Methodology of external-internal biliary-jejunal drainage

IEBJD was used to divert bile from the BD directly into the initial loops of the small intestine to prevent duodeno-biliary reflux and reflux cholangitis. In our study, the IEBJD technique was applied using a newly developed biliary-jejunal drainage system. The drain tube has two groups of lateral openings (proximal and distal), between which it is devoid of openings from the distal border of the tumor to the initial loops of the small intestine[24].

IEBJD was carried out using percutaneous transhepatic access. The end of the drain tube with the distal group of lateral openings is located behind the duodeno-jejunal bend in the initial loops of the jejunum, while the proximal group of lateral openings is located in the dilated BD above the stenosis (Figure 2).

Endpoints and variables

Endpoints of the study were the clinical success of the procedure, the frequency and nature of complic-

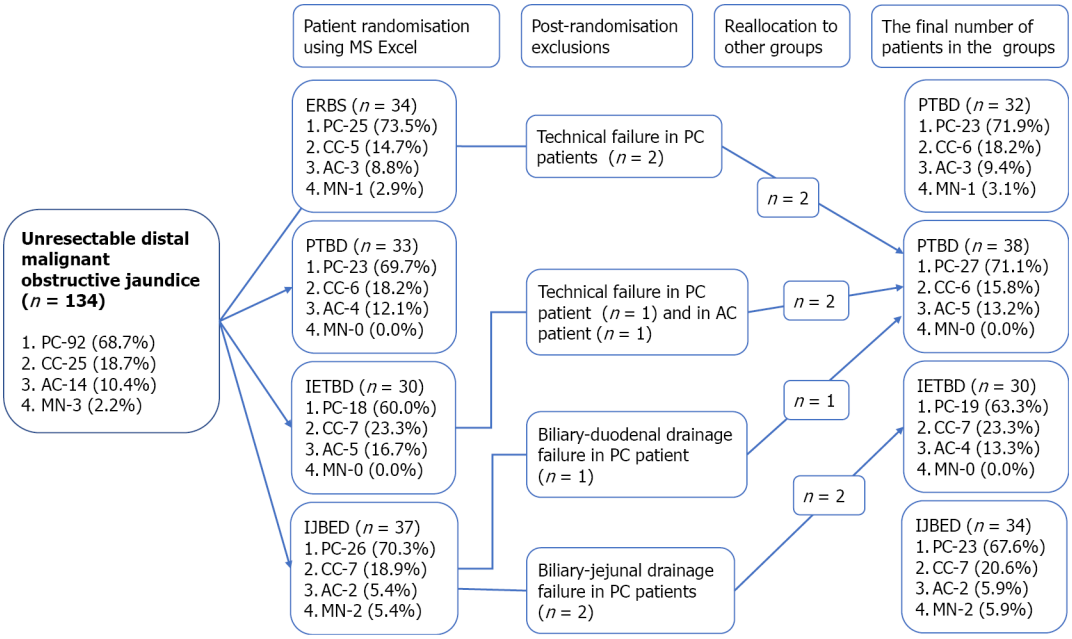

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Figure 1 Patient randomization based on the bile duct decompression techniques used in the study. AC: Ampullary cancer; CC: Cholangiocarcinoma; ERBS: Endoscopic retrograde biliary stenting; IETBD: Internal-external transpapillary biliary drainage; IJBED: Internal-external biliary-jejunal drainage; MN: Metastatic nodes; PC: Pancreatic cancer; PTBD: Percutaneous transhepatic biliary drainage.

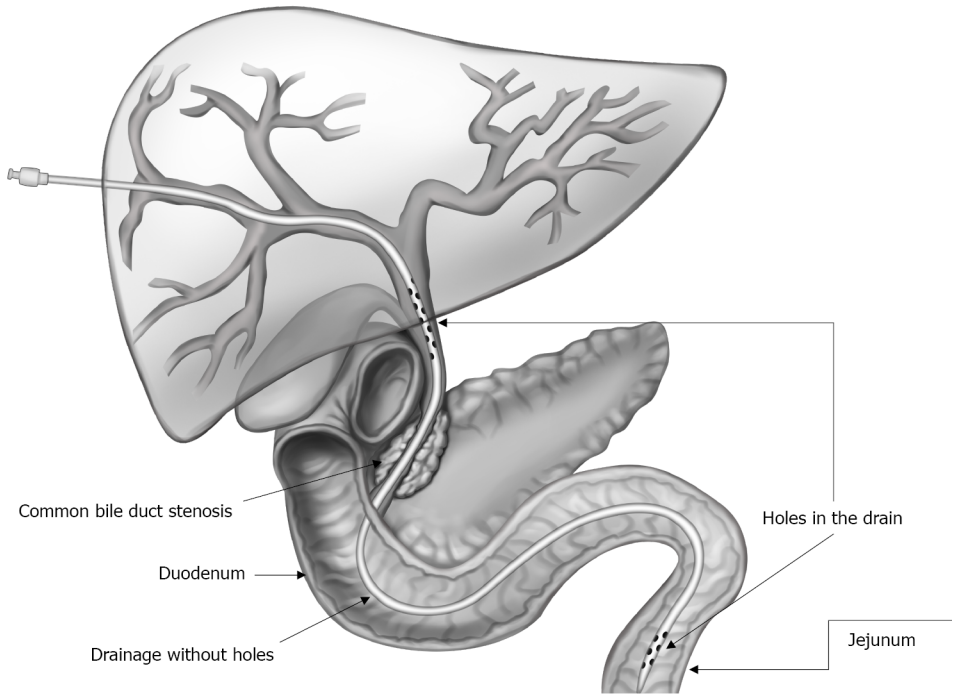

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Figure 2 Layout of external-internal biliary-jejunal drainage placement.

ations from the manipulation, and the cumulative survival rate.

The procedure was considered clinically successful if the serum level of total bilirubin decreased by at least 50% as compared to the baseline value during the first 7 d after manipulation[12].

The Society of Interventional Radiology Clinical Practice Guidelines[25] classified postoperative complications as insignificant or significant.

Significant complications included acute hemobilia, pancreatitis, pneumothorax, sepsis, liver abscess, cholecystitis, biliary peritonitis, bleeding requiring blood transfusion, bile duct rupture, and cholangitis.

The clinical diagnosis of cholangitis was established on the basis of the following criteria: Body temperature above 38.5 °C, leukocyte count > 10 × 10^9/L, and proportion of neutrophils > 70%[26].

Postoperative pancreatitis was graded as "mild" in cases of the onset or progression of abdominal pain and an elevated serum amylase level three or more times above the reference range within 24 h after the procedure, requiring a minimum of 2-3 d of hospitalization. Pancreatitis was graded as "moderately severe" if the patient required hospitalization for 4-10 d, and as "severe" when the patient required hospitalization for more than 10 d, as well as in cases of necrosis and pseudocysts, indicating the need for percutaneous drainage or open pancreatic debridement[27].

Total bilirubin and α-amylase levels in serum were determined using an automatic biochemical analyzer, Olympus AU-800 (Olympus, Japan). Blood tests were performed using the hematological analyzer Mindray BC-2800 (China).

Statistical analysis

Statistical data processing was performed using the statistical package IBMSPPS Statistics 22. To determine whether the observations deviated from the normal curve, the Shapiro-Wilk test was used. Statistical differences were calculated using ANOVA with Tukey's post-hoc test for multiple comparisons and a two-tailed *t*-test (for normally distributed variables) and non-parametric Mann-Whitney *U* test (for non-normally distributed variables) for single comparisons. A Pearson χ^2 test was used for qualitative data. A cumulative survival rate was estimated by the Kaplan-Meier method using the log-rank test. All differences with a *P* value of < 0.05 were considered statistically significant.

Ethics statement

The study protocol was approved by the Ethics Committee of O. O. Bogomolets National Medical University, and informed consent was obtained from all participants before the study.

RESULTS

General characteristics of patients

The general characteristics of study participants are summarized in Table 1. The anamnesis revealed that mechanical jaundice occurred in patients on an average of 15.2 d ± 0.2 d before the manipulation (from 10 d to 22 d). Patients did not have a statistically significant difference in terms of the average duration of jaundice before surgery.

There were no significant differences in the serum level of total bilirubin between the groups. The mean serum level of total bilirubin was 11.36 mg/dL ± 0.04 mg/dL (3.93-22.78 mg/dL).

There was no statistically significant difference between the study groups in terms of average age, sex ratio, cancer stage, TNM criteria, or etiological factors of stricture.

Comparative analysis of clinical outcomes of DMBO patients who underwent various minimally invasive procedures

In the case of PTBD, the technical success was 100%, and it was 94.1% for ERBS, 93.8% for IETBD, and 91.9% for IEBJD (*P* = 0.365).

The clinical success was 94.1% in the IEBJD group, 93.8% in the ERBS group, 86.7% in the IETBD group, and 94.7% in the PTBD group (*P* > 0.582 for all).

Cholangitis, which was diagnosed at admission, subsided within 3-4 d after the procedure.

There were no technical complications (related to the specifics of the manipulation) in any study group. Minor complications occurred both singly and in combination. The groups did not differ statistically in terms of the number of patients with minor complications and their variants (Table 2).

Significant complications occurred in 5 (14.7%) patients in the IEBJD group, in 10 (31.3%) in the ERBS group, in 13 (43.3%) in the IETBD group, and in 8 (21.1%) in the PTBD group (Table 3). In the PTBD and external-internal biliary-jejunal drainage (EIBJD) groups, a significant complication of one type was observed, while in the ERBS and IETBD groups, significant complications of two types were observed in one patient.

The complication rate (*P* = 0.053) did not differ significantly between the groups, but it did differ significantly between the groups where the biliary decompression system connected the lumen of the duodenum to the bile ducts (IETBD and ERBS) and those where it did not (PTBD and IEBJD): 23 (37.1%) *vs* 13 (18.1%), respectively, *P* = 0.013.

The most frequent complication was cholangitis (26 cases, 19.4%). In general, there were no statistically significant differences in the cholangitis rate between the groups (*P* = 0.052). However, when a drain tube or stent was used to connect the lumen of the duodenum to the bile ducts, the frequency of cholangitis was significantly higher than when it was not used: 18 (29.0%) *vs* 8 (11.1%) (*P* = 0.009).

The course of cholangitis in the IEBJD group differed from that in the ERBS and IETBD groups by a longer period before its occurrence after the procedure (*P* < 0.05) and a shorter duration (*P* < 0.05) (Table 4).

Table 1 General characteristics of study participants, *n* (%)

Indicator	Total, *n* = 134	Study group				*P* value
		EIBJD, *n* = 29	ERBS, *n* = 25	IETBD, *n* = 19	PTBD, *n* = 65	
Age in yr, mean ± SD	64.1 ± 11.6	65.8 ± 10.1	61.9 ± 12.9	62.2 ± 13.0	66.0 ± 10.4	0.296
Male/female	69/65	19/15	17/15	14/16	19/19	0.894
Duration of jaundice in d, mean ± SD	15.0 ± 2.0	14.7 ± 1.5	15.5 ± 2.0	14.9 ± 2.6	14.3 ± 1.1	0.250
Total serum bilirubin in mg/dL, mean ± SD	11.3 ± 4.6	12.4 ± 4.5	12.3 ± 4.2	10.1 ± 5.3	10.5 ± 4.2	0.092
Cholangitis before the procedure	19 (14.2)	6 (17.6)	4 (12.5)	4 (13.3)	5 (13.2)	0.928
T stage						
T2	6 (4.6)	1 (2.9)	1 (3.1)	2 (6.7)	2 (5.3)	0.985
T3	78 (58.2)	19 (55.9)	19 (59.4)	18 (60.0)	22 (57.9)	
T4	50 (37.3)	14 (41.2)	12 (37.5)	10 (33.3)	14 (36.8)	
N stage						
N0	8 (6.7)	3 (8.8)	2 (6.3)	3 (10.0)	1 (2.6)	0.922
N1	97 (72.4)	24 (70.6)	24 (75.0)	19 (63.3)	30 (78.9)	
N2	11 (8.2)	3 (8.8)	2 (6.3)	4 (13.3)	2 (5.3)	
Nx	17 (12.7)	4 (11.8)	4 (12.5)	4 (13.3)	5 (13.2)	
M stage						
M0	64 (47.8)	14(41.2)	18 (56.3)	16 (53.3)	16 (42.1)	0.858
M1	53 (39.6)	15 (44.1)	11 (34.4)	10 (33.3)	17 (44.7)	
Mx	17 (12.7)	5 (14.7)	3 (9.4)	4 (13.3)	5 (13.2)	
Grade						
IIB	4 (3.0)	1 (2.9)	1 (3.1)	2 (6.7)	0 (0.0)	0.760
III	47 (35.1)	12 (35.3)	13 (40.6)	10 (33.3)	12 (31.6)	
IV	83 (61.9)	21 (61.8)	18 (56.3)	18 (60.0)	26 (68.4)	
Tumour etiology						
Pancreatic cancer	92 (68.7)	23 (67.6)	23 (71.9)	19 (63.3)	27 (71.1)	0.757
Cholangiocarcinoma	25 (18.7)	7 (20.6)	5 (15.6)	7 (23.3)	6 (15.8)	
Ampullary cancer	14 (10.4)	2 (5.9)	3 (9.4)	4 (13.3)	5 (13.2)	
Metastatic nodes	3 (2.2)	2 (5.9)	1 (3.1)	0 (0.0)	0 (0.0)	

ERBS: Endoscopic retrograde biliary stenting; IEBJD: Internal-external biliary-jejunal drainage; IETBD: Internal-external transpapillary biliary drainage; PTBD: Percutaneous transhepatic biliary drainage.

The patients who underwent IEBJD had the highest cumulative survival rate [239.3 d, 95% confidence interval (CI): 198.9-279.6 d] when compared to other groups (Figure 3). However, patients in the PTBD (102.0 d, 95%CI: 77.6-128.1 d) and IETBD (94.8 d, 95%CI: 54.1-135.5 d) groups had significantly lower cumulative survival rates ($P < 0.01$) than those in the ERBS group (187.8 d, 95%CI: 153.8-221.9 d).

In comparison to other groups, the mortality risk in the IEBJD group was lower 3, 6, 9, 12, and 15 mo after the start of the procedure (Table 5).

The technique aimed to increase the survival rate of patients with distal block by reducing the risk of duodeno-biliary reflux as well as the frequency and duration of reflux cholangitis. In the IEPTB and ERBS groups, there was a high probability of reflux of duodenal contents into the biliary tract through the drain tube and stent, respectively. Analysis of the impact of cholangitis episodes on the survival rate in these groups confirmed the success of the newly developed technique (Figure 4). The average survival time in patients with cholangitis episodes was 93.9 d (95%CI: 70.4-117.4 d), whereas in patients without cholangitis it was 156.1 d (95%CI: 124.9-191.3 d) ($P = 0.009$); the hazard ratio (HR) was 1.96 (95%CI: 1.02-3.79). However, the cholangitis factor had no effect on the survival rate in patients from the EIBJD group (HR = 1.07, 95%CI: 0.32-3.64).

Table 2 Frequency of minor postoperative complications in study groups, *n* (%)

Complication	Study group				*P* value
	EIBJD, *n* = 34	ERBS, *n* = 32	IETBD, *n* = 30	PTBD, *n* = 38	
Pain in the drainage area	6 (17.6)	5 (15.6)	7 (23.3)	7 (18.4)	0.885
Hyperthermia	3 (8.8)	-	2 (6.7)	3 (7,9)	0.423
Bile leakage	1 (2.9)	2 (6.3)	1 (3.3)	2 (5.3)	0.903
Bleeding	3 (8.8)	-	3 (10,0)	4 (10.5)	0.325
Subcapsular biloma	1 (2.9)	3 (9.4)	1 (3.3)	1 (2.6)	0.498
Shingle pain	1 (2.9)	-	1 (3.3)	2 (5.3)	0.642
Total	1 (2.9)	3 (9.4)	1 (3.3)	-	0.223

ERBS: Endoscopic retrograde biliary stenting; IEBJD: Internal-external biliary-jejunal drainage; IETBD: Internal-external transpapillary biliary drainage; PTBD: Percutaneous transhepatic biliary drainage.

Table 3 Frequency and types of significant postoperative complications in study groups, *n* (%)

Indicator	Study group				*P* value
	EIBJD, *n* = 34	ERBS, *n* = 32	IETBD, *n* = 30	PTBD, *n* = 38	
Patients with complications	5 (14.7)	10 (31.3)	13 (43.3)	8 (21.1)	0.053
Number of complications in one patient					
No	29 (85.3)	22 (68.8)	17 (56.7)	30 (78.9)	0.072
One	5 (14.7)	7 (21.9)	10 (33.3)	8 (21.1)	
Two	0 (0.0)	3 (9.4)	3 (10.0)	0 (0.0)	
Type of complication					
Cholangitis	3 (8.8)	8 (25.0)	10 (33.3)	9 (13.2)	0.052
Pancreatitis					
No	32 (94.1)	28 (87.5)	27 (90.0)	38 (100)	0.121
Mild	2 (5.9)	2 (6.3)	3 (10.0)	0 (0.0)	
Moderately severe	0 (0.0)	2 (6.3)	0 (0.0)	0 (0.0)	
Cholecystitis	0 (0.0)	0 (0.0)	1 (3.3)	3 (7.9)	0.157
Liver abscess	0 (0.0)	1 (3.1)	2 (6.7)	0 (0.0)	0.217

ERBS: Endoscopic retrograde biliary stenting; IEBJD: Internal-external biliary-jejunal drainage; IETBD: Internal-external transpapillary biliary drainage; PTBD: Percutaneous transhepatic biliary drainage.

DISCUSSION

Cholangitis is one of the major complications of palliative BD decompression in patients with DMBO. It is recognized as an independent risk factor for liver dysfunction, reduced quality of life, and decreased life expectancy[28].

Cholangitis can develop in cases of gastrointestinal tract infection in patients with an unresectable bilioduodenopancreatic neoplasm due to: (1) Retrograde reflux of intestinal flora during and after the procedure; (2) microbiota dissemination through the external drainage; (3) hematogenous spread of microorganisms; and (4) the contrast reaching the bile ducts. Furthermore, the infection may already be present before the procedure, despite the absence of typical cholangitis manifestations[29,30]. However, duodeno-biliary reflux is the most significant systemic cause of cholangitis. It occurs when the lumen of the duodenum is connected to the lumen of the bile duct, resulting in the disruption or even loss of the barrier function of the sphincter of Oddi[16]. The basal pressure, which is normally created by the sphincter of Oddi (135-202 mm H_2O), is higher than that in the duodenum (80-120 mm H_2O)[31,32]. Phase contractions of the duodenum are accompanied by an increase in pressure and simultaneous

Table 4 Features of cholangitis in study groups

Indicator	Study group			
	EIBJD, *n* = 34	ERBS, *n* = 32	IETBD, *n* = 30	PTBD, *n* = 38
The time period from the procedure until the cholangitis onset, d	106.7 ± 38.4[a]	75.1 ± 14.9[b]	35.3 ± 9.9[b]	44.5 ± 9.9[b]
Cholangitis duration, d	4.7 ± 0.3[a]	9.9 ± 0.5[b]	7.7 ± 0.6[b]	5.3 ± 0.2[a]

[a]Different letters indicate significant differences between study groups (Tukey post-hoc test with Bonferroni correction, $P < 0.05$.
[b]Different letters indicate significant differences between study groups (Tukey post-hoc test with Bonferroni correction, $P < 0.05$). ERBS: Endoscopic retrograde biliary stenting; IEBJD: Internal-external biliary-jejunal drainage; IETBD: Internal-external transpapillary biliary drainage; PTBD: Percutaneous transhepatic biliary drainage.

Table 5 Hazard ratios and 95% confidence intervals for the mortality in patients who underwent internal-external biliary-jejunal drainage as compared to other techniques

Observation period in mo	PTBD	IETBD	ERBS
3	0.39; 0.19-0.82, $P = 0.018$	0.31; 0.14-0.69, $P = 0.005$	0.75; 0.31-1.76, $P = 0.438$
6	0.49; 0.28-0.87, $P = 0.011$	0.34; 0.18-0.66, $P < 0.001$	0.96; 0.56-1.69, $P = 0.982$
9	0.36; 0.22-0.60, $P < 0.001$	0.26; 0.14-0.49, $P < 0.001$	0.78; 0.49-1.22, $P = 0.232$
12	0.39; 0.24-0.64, $P < 0.001$	0.26; 0.14-0.48, $P < 0.001$	0.86; 0.56- 1.32, $P = 0.507$
15	0.38; 0.23-0.62, $P < 0.001$	0.30; 0.17-0.54, $P < 0.001$	0.77; 0.51-1.16, $P = 0.078$

ERBS: Endoscopic retrograde biliary stenting; IETBD: Internal-external transpapillary biliary drainage; PTBD: Percutaneous transhepatic biliary drainage.

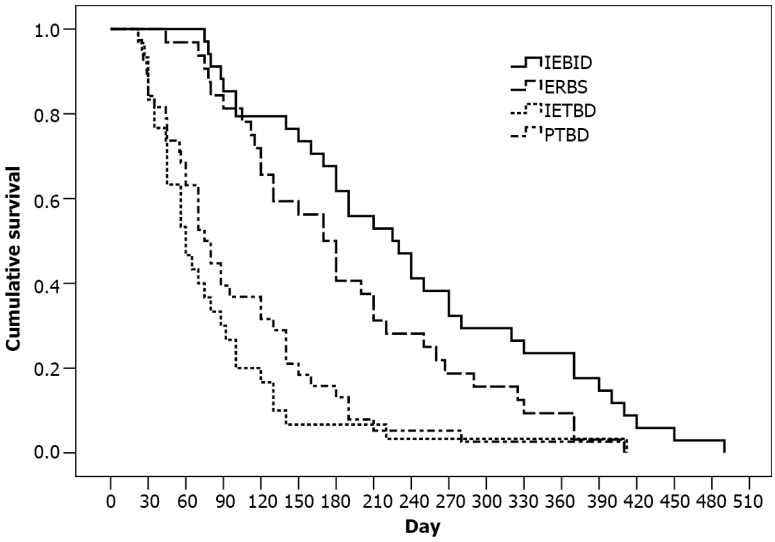

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Figure 3 Kaplan-Meier cumulative survival curves for patients with distal malignant biliary obstruction who underwent various minimally invasive palliative procedures. Patients with internal-external biliary-jejunal drainage had a higher survival rate than the other groups ($P < 0.05$). DMBO: Distal malignant biliary obstruction; ERBS: Endoscopic retrograde biliary stenting; IEBJD: Internal-external biliary-jejunal drainage; IETBD: Internal-external transpapillary biliary drainage; PTBD: Percutaneous transhepatic biliary drainage.

initiation of the sphincter of Oddi contractions, which, in turn, prevent reflux[31]. In contrast, the basal pressure in the common BD is usually in the range of 50-100 mm H_2O and does not prevent reflux, especially in the case of connecting the lumen of the bile duct to the lumen of the duodenum[33]. Duodeno-biliary reflux occurs in 100% of patients after ERBS, as demonstrated by duodenography with barium, but it is not always associated with cholangitis[11,12]. After stenting of the BD, 98% of patients show positive bile cultures[34]. Bacteriobilia after ERBS is associated with *Escherichia coli*, *Klebsiella pneumonia*, *Pseudomonas*, *Enterococcus cloacae*, and other microorganisms that are usually resistant to

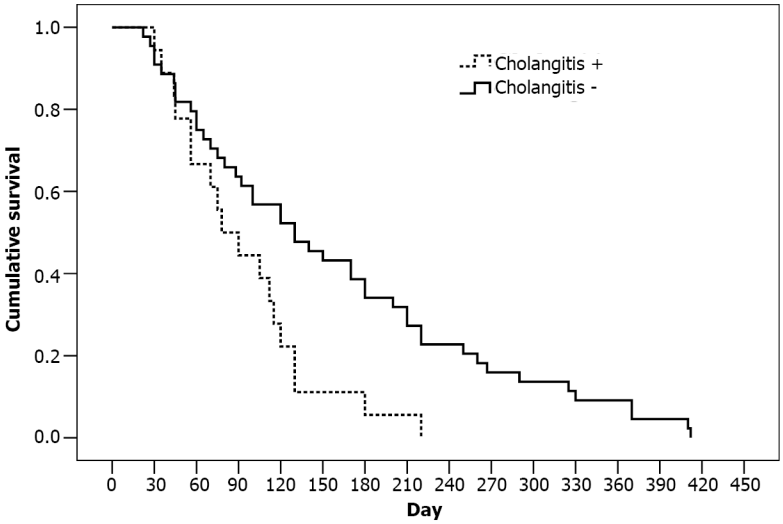

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Figure 4 Kaplan-Meier cumulative survival curves for patients with internal-external transpapillary biliary drainage and endoscopic retrograde biliary stenting depending on the presence of cholangitis episodes. Patients with cholangitis had a lower survival rate compared to those without ($P < 0.05$). ERBS: Endoscopic retrograde biliary stenting; IETBD: Internal-external transpapillary biliary drainage.

commonly used antibiotics[13]. The high incidence of cholangitis after ERBS has prompted an analysis of a two-step approach to radical treatment of pancreatic head cancer. It has been demonstrated that the number of infectious complications and mortality rate are significantly higher in patients who receive two-stage treatment (BD stenting followed by radical surgery) in comparison to patients who receive one-stage treatment[13]. A meta-analysis including 1435 patients with malignant bile duct obstruction revealed a significantly lower frequency of cholangitis in the case of nasobiliary BD drainage (without duodenobiliary reflux) as compared to ERBS (HR = 0.46, $P < 0.00001$)[35]. In our study, cholangitis occurred in 36.0% of patients in the ERBS group during the follow-up period.

Apparently, favorable conditions for duodeno-biliary reflux and cholangitis also develop after IETBD, as evidenced by the results of the study by Xu *et al*[22], who diagnosed cholangitis in 52.4% of patients with IETBD, which coincides with our observations (31.6%).

Duodeno-biliary reflux after ERBS and IETBD is responsible for the reduced duration of stent patency [21,12,36]. This creates a risk of cholangitis. The presence of the food fibers, bile, bacteria, fibrin, debris, granulation tissue, and inflammatory cells in the occlusive material from removed stents confirms the effect of duodeno-biliary reflux on stent/drainage patency[37]. These sediments are usually infected with Gram-negative bacteria[38]. The biliary stent becomes occluded as a result of biofilm formation caused by bacterial colonization. Biofilm formation begins with the priming of the stent surface by various microbial proteins, followed by microbial adhesion to the stent and the formation of an exopolysaccharide matrix, embedding microbial colonies and other particles into the mature biofilm[39,40]. Over time, this leads to increased bile viscosity, slowed bile flow[41], bile stasis, increased deposition of bile salts[42], and the formation of a brown pigment stone (calcium bilirubinate)[43]. Despite the fact that the stent patency rate is frequently used as an indicator of adverse events following successful placement, we did not compare it between the groups because patients died before stent dysfunction occurred. Namely, in the IETBD and PTBD groups, the stent patency was maintained until the death in 16 (84.2%) and 59 (90.8%) patients, respectively, and the average stent patency duration was mainly determined by the life span and was 69.6 d ± 7.2 d and 84.6 d ± 6.6 d, respectively. At the same time, the average stent patency duration among patients who had drainage obstruction prior to death was 94.3 d ± 3.5 d and 155.2 d ± 20.1 d, respectively ($P = 0.078$). In the IEBJD and ERBS groups, the stent patency was maintained until death in 14 (48.3%) and 12 (48.0%) patients, respectively. The average stent patency duration in these groups was longer than that in the IETBD and PTBD groups: 178.9 d ± 11.5 d and 155.3 d ± 14.3 d, respectively. Among other things, this could be attributed to the longer life expectancy of patients. Nevertheless, in patients who had stent dysfunction before death, the stent patency duration was 204.1 d ± 13.1 d (between 131 d and 275 d) and 168.2 d ± 20.1 d (between 98 d and 292 d), respectively ($P = 0.047$). Although the stent patency duration was longer in the IEBJD group, probably due to the absence of reflux of duodenal content, we decided not to emphasize this fact for the aforementioned reasons. Nevertheless, it should be noted that the cumulative survival rate in the ERBS group with preserved stent patency and cholangitis was 157.1 d (95%CI: 132.1-182.1), while without cholangitis it was 269.6 d (95%CI: 230.3-309.0) ($P = 0.005$). Notably, biliary decompression was not interrupted because of drainage dysfunction in any of the patients and was usually continued for the rest of their lives.

To reduce the incidence of stent-associated cholangitis, stents with anti-reflux valves of various shapes (wine glass-shaped, funnel-shaped, or windsock-shaped) and lengths have been developed[12,16,14,15]. Preliminary data suggest that such stents may be potentially beneficial, although more research is required[17]. Despite the fact that they have patency indices comparable to valveless metal stents[15], they have not been widely used and are prone to dislocation[17]. Kuwatani *et al*[43] noted that, currently, there is no ideal stent with constant patency.

Our study aimed to reduce the incidence of reflux cholangitis. Therefore, we used external-internal drainage to provide bile evacuation into the initial loops of the small intestine, bypassing the duodenum. As a result, the major duodenal papilla is not damaged during the procedure, so the probability of duodeno-biliary reflux is minimal and, in our study, it was not observed. Instead, duodenal contents may enter the bile duct from the outside of the drain.

The possibility of emptying the contents of the small intestine into the choledoch cannot be ruled out, despite the fact that the basal pressure in the intestine is lower[44] or similar to that in the choledoch [45]. In our study, duodeno-biliary reflux was not observed. Furthermore, the pressure in the jejunum does not change (82 mm H_2O ± 11 mm H_2O) when the balloon located in the duodenum and simulating the passage of the food is inflated (up to 6 mL), in contrast to a significant increase in the pressure in the duodenum (up to 242 mm H_2O ± 52 mm H_2O) and in the area of duodenojejunal flexure (up to 334 mm H_2O ± 48 mm H_2O)[45].

We carried out IEBJD on 34 patients with DMBO. A control barium X-ray of the stomach and duodenum did not reveal a reflux of contrast into the BD (Figure 5).

Subcapsular biloma and bleeding, two minor complications that were noted during the manipulation procedure, both subsided on their own without the need for a blood transfusion.

A decrease in the serum level of total bilirubin by more than 50% compared to baseline values was detected in 94.1% of cases. Bile leakage was not observed, unlike in the PTBD group.

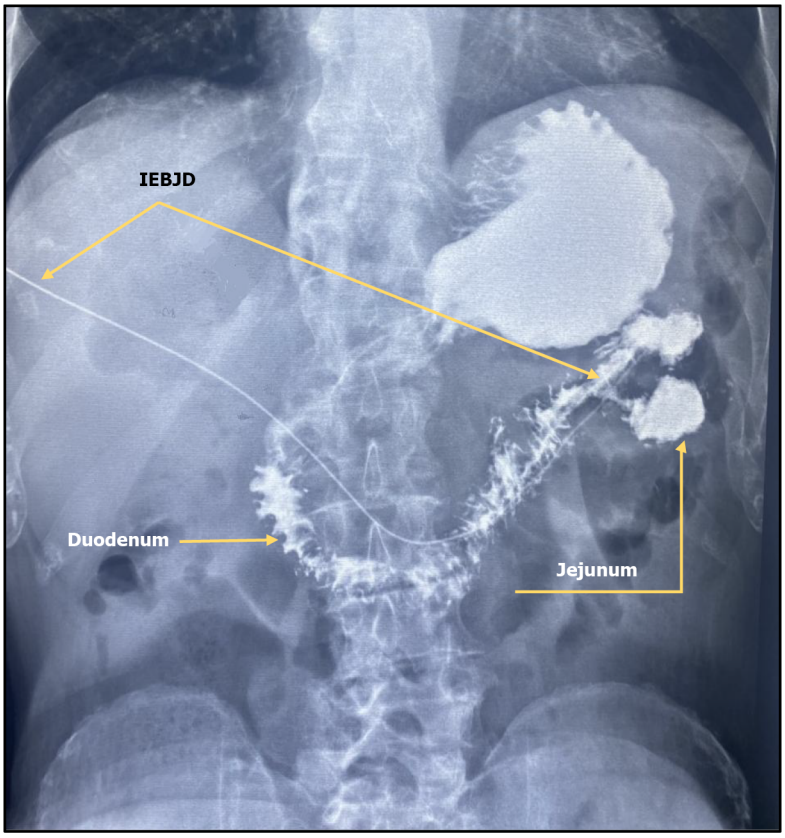
In the postoperative period, significant complications occurred in 5 (14.7%) patients in the IEBJD group, in 10 (31.3%) in the ERBS group, in 13 (43.3%) in the IETBD group, and in 8 (21.1%) in the PTBD group. Although there were no significant differences between the groups (P = 0.053), the frequency of serious complications was significantly higher in the groups with the connection between the duodenal lumen and the bile ducts than in the groups without it: 23 (37.1 %) *vs* 13 (18.1%) patients, respectively (P = 0.013). This can also be referred to cholangitis, which is the most frequent complication: 18 (29.0%) *vs* 8 (11.1%) patients (P = 0.009).

The cumulative survival rate was the highest in the IEBJD group, at an average of 239.3 d (95%CI: 198.9-279.6) (P < 0.05). Three, six, nine, twelve, and fifteen months after the procedure, patients who underwent IEBJD had a lower mortality risk than those who were treated using other techniques. A lower cholangitis onset rate may account for a higher survival rate in the IEBJD group. It has been shown that cholangitis can be associated with a decrease in life expectancy: 93.9 d (95%CI: 70.4-117.4 d) in the groups with a high risk of duodenal-biliary reflux and reflux cholangitis *vs* 156.1 d (95%CI: 124.9-191.3 d) in the groups without cholangitis (P = 0.009) (HR = 1.96, 95%CI: 1.02-3.79). However, cholangitis had no impact on the survival rate in the IEBJD group (HR = 1.07, 95%CI: 0.32-3.64).

In patients with IEJBD, the drain tube is easier to manage in cases of cholangitis symptoms. Antibiotic therapy and drain rehabilitation helped remove cholangitis symptoms within 3-4 d, whereas other methods took 7-14 d.

CONCLUSION

Our findings suggest that IEBJD has advantages over other BD decompression techniques in the palliative treatment of patients with DMBO. However, this technique, like other external-internal drainage systems, causes difficulties for the patient since the drain exits the body and requires a drainage bag. Compared to IEBJD, ERBS has advantages in this regard. Moreover, further development of reliable anti-reflux stents would definitely prioritize ERBS use for palliative BD decompression. Nonetheless, IEBJD is currently a cost-effective treatment option, particularly for patients with a short life expectancy. The study has certain limitations, including a relatively small number of patients in the comparison groups. In addition, the study did not include patients with total bilirubin > 20.47 mg/dL and high operative risk (ASA score of 4).



DOI: 10.4240/wjgs.v15.i4.698

Figure 5 Barium X-ray examination of the stomach and duodenum in a patient 3 mo after external-internal biliary-jejunal drainage for pancreatic head cancer. Contrast reflux in the bile duct is absent. IEBJD: Internal-external biliary-jejunal drainage.

ARTICLE HIGHLIGHTS

Research background

Patients with distal malignant biliary obstruction (DMBO) may benefit from bile duct (BD) decompression using endoscopic biliary drainage since the procedure reduces pain, relieves symptoms, allows for the administration of chemotherapy, improves quality of life, and increases the survival rate. Cholangitis is one of the main complications of palliative BD decompression in patients with DMBO. Therefore, BD decompression techniques require further improvement to reduce the frequency of cholangitis episodes.

Research motivation

Duodeno-biliary reflux (DBR), among others, is regarded as one of the major systemic causes of cholangitis. The aim of the study was to develop a BD drainage technique for bile diversion from the BD directly into the initial loops of the small intestine, preventing DBR and reflux cholangitis.

Research objectives

To develop a technique for internal-external biliary-jejunal drainage (IEBJD) and assess its effectiveness in comparison to other minimally invasive procedures.

Research methods

In our study, the IEBJD technique was applied using a newly developed biliary-jejunal drainage system. It has two groups of lateral openings (proximal and distal), between which the drainage tube is devoid of openings from the distal border of the tumor to the initial loops of the small intestine. IEBJD was carried out using percutaneous transhepatic access.

Research results

The application of the IEBJD technique contributed to a reduction in the incidence of significant postoperative complications, a delayed onset and shorter duration of postoperative cholangitis, and a considerable improvement in the cumulative survival rate of patients with DMBO.

Research conclusions

The IEBJD technique prevents DBR and reflux cholangitis and can be recommended for the palliative treatment of patients with DMBO.

Research perspectives

The clinical success of the newly developed IEBJD technique in a limited patient group necessitates further evaluation of its efficacy in a larger patient cohort, including those with total bilirubin > 20.47 mg/dL and high operative risk (ASA score of 4).

ACKNOWLEDGEMENTS

The authors are very grateful to everyone who took part in this study.

FOOTNOTES

Author contributions: Susak YM participated in the design of the study and supervised its implementation; Markulan LL participated in the study as a chief surgeon and performed surgical procedures; Palitsya RY assisted in surgical procedures; Rudyk MP contributed to data collection and participated in statistical analysis; Skivka LM participated in the design of the study, carried out statistical analysis, and wrote the draft.

Institutional review board statement: The study was reviewed and approved by the Committee on Human Rights Related to Research Involving Human Subjects of Kyiv City Clinical Emergency Hospital (Kyiv, Ukraine) (Approval No. 25-15-65).

Clinical trial registration statement: This study is registered at https://nddkr.ukrintei.ua/view/rk/67a7ff7c333c5bb067a8c3902353ec74, and the registration identification number is 0121U108878.

Informed consent statement: All subjects gave their written informed consent prior to study inclusion.

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

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: Ukraine

ORCID number: Yaroslav M Susak 0000-0002-5102-485X; Leonid L Markulan 0000-0003-2879-5012; Serhii M Lobanov 0000-0002-7519-0772; Mariia P Rudyk 0000-0003-1252-885X; Larysa M Skivka 0000-0002-2171-1085.

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

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World J Gastrointest Surg 2023 April 27; 15(4): 712-722

DOI: 10.4240/wjgs.v15.i4.712

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Randomized Controlled Trial

External use of mirabilite to prevent post-endoscopic retrograde cholangiopancreatography pancreatitis in children: A multicenter randomized controlled trial

Jing-Qing Zeng, Tian-Ao Zhang, Kai-Hua Yang, Wen-Yu Wang, Jia-Yu Zhang, Ya-Bin Hu, Jian Xiao, Zhi-Jian Gu, Biao Gong, Zhao-Hui Deng

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: Parvin S, Bangladesh; Saito H, Japan

Received: November 8, 2022
Peer-review started: November 8, 2022
First decision: November 23, 2022
Revised: December 1, 2022
Accepted: March 20, 2023
Article in press: March 20, 2023
Published online: April 27, 2023

Jing-Qing Zeng, Tian-Ao Zhang, Kai-Hua Yang, Wen-Yu Wang, Jia-Yu Zhang, Jian Xiao, Zhao-Hui Deng, Department of Gastroenterology, Shanghai Children's Medical Center, School of Medicine, Shanghai Jiao Tong University, Shanghai 200127, China

Ya-Bin Hu, Department of Clinical Epidemiology and Biostatistics, Shanghai Children's Medical Center, School of Medicine, Shanghai Jiao Tong University, Shanghai 200127, China

Zhi-Jian Gu, Biao Gong, Department of Gastroenterology, Shanghai Shuguang Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai 200021, China

Corresponding author: Zhao-Hui Deng, PhD, Chief Physician, Department of Gastroenterology, Shanghai Children's Medical Center, School of Medicine, Shanghai Jiao Tong University, No. 1678 Dongfang Road, Shanghai 200127, China. dzhrj@163.com

Abstract

BACKGROUND

Acute pancreatitis is the most common complication of endoscopic retrograde cholangiopancreatography (ERCP). Currently, there is no suitable treatment for post-ERCP pancreatitis (PEP) prophylaxis. Few studies have prospectively evaluated interventions to prevent PEP in children.

AIM

To assess the efficacy and safety of the external use of mirabilite to prevent PEP in children.

METHODS

This multicenter, randomized controlled clinical trial enrolled patients with chronic pancreatitis scheduled for ERCP according to eligibility criteria. Patients were randomly divided into the external use of mirabilite group (external use of mirabilite in a bag on the projected abdominal area within 30 min before ERCP) and blank group. The primary outcome was the incidence of PEP. The secondary outcomes included the severity of PEP, abdominal pain scores, levels of serum inflammatory markers [tumor necrosis factor-alpha (TNF-α) and serum interleukin-10 (IL-10)], and intestinal barrier function markers [diamine oxidase (DAO), D-lactic acid, and endotoxin]. Additionally, the side effects of topical

mirabilite were investigated.

RESULTS

A total of 234 patients were enrolled, including 117 in the external use of mirabilite group and the other 117 in the blank group. The pre-procedure and procedure-related factors were not significantly different between the two groups. The incidence of PEP in the external use of mirabilite group was significantly lower than that in the blank group (7.7% *vs* 26.5%, $P < 0.001$). The severity of PEP decreased in the mirabilite group ($P = 0.023$). At 24 h after the procedure, the visual analog scale score in the external use of mirabilite group was lower than that in the blank group ($P = 0.001$). Compared with those in the blank group, the TNF-α expressions were significantly lower and the IL-10 expressions were significantly higher at 24 h after the procedure in the external use of mirabilite group ($P = 0.032$ and $P = 0.011$, respectively). There were no significant differences in serum DAO, D-lactic acid, and endotoxin levels before and after ERCP between the two groups. No adverse effects of mirabilite were observed.

CONCLUSION

External use of mirabilite reduced the PEP occurrence. It significantly alleviated post-procedural pain and reduced inflammatory response. Our results favor the external use of mirabilite to prevent PEP in children.

Key Words: Children; Endoscopic retrograde cholangiopancreatography; Mirabilite; Chronic pancreatitis; Post-endoscopic retrograde cholangiopancreatography pancreatitis; Randomized controlled trial

Core Tip: This was a multicenter, prospective, randomized controlled study, which aimed to assess the efficacy and safety of the external use of mirabilite to prevent post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP) in children. Our study showed that the external use of mirabilite can reduce the incidence of PEP, relieve post-procedural pain, and regulate inflammatory mediator expression to reduce the inflammatory response. This study suggests that the external use of mirabilite is a safe, effective, and more acceptable option for the prevention of PEP prophylaxis in pediatric patients.

Citation: Zeng JQ, Zhang TA, Yang KH, Wang WY, Zhang JY, Hu YB, Xiao J, Gu ZJ, Gong B, Deng ZH. External use of mirabilite to prevent post-endoscopic retrograde cholangiopancreatography pancreatitis in children: A multicenter randomized controlled trial. *World J Gastrointest Surg* 2023; 15(4): 712-722
URL: https://www.wjgnet.com/1948-9366/full/v15/i4/712.htm
DOI: https://dx.doi.org/10.4240/wjgs.v15.i4.712

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is one of the crucial procedures for the diagnosis and treatment of biliary and pancreatic diseases in children[1,2]. Post-ERCP pancreatitis (PEP) is the most common adverse event; it can be a serious complication following ERCP, occurring in approximately 6.0%-20.7% of children. The rate of PEP varies between case series as it depends on potential patient- and procedure-related risk factors, such as a history of PEP, visualization of the pancreatic duct, guide-wire insertion into the pancreatic duct, diagnostic ERCP, suspected sphincter of Oddi dysfunction, difficult cannulation, pancreatic sphincterotomy, and others[3-7]. Most episodes of PEP are mild and moderate; however, severe pancreatitis still occurs, accounting for a prolonged hospital stay and can be potentially fatal[6,8]. To a certain extent, the occurrence of PEP limits the application of ERCP in children.

To date, only non-steroidal anti-inflammatory drugs (NSAIDs) have been shown to be effective in preventing PEP in adults[9-11]. The role of rectal indomethacin, which is widely used in adults and is often not utilized in children as the method of rectal administration is not acceptable for children, remains questionable. Meanwhile, few reports have investigated prophylactic medicine for PEP in children. Finding an ideal, effective, less invasive, and safe prevention strategy for children is desirable.

Mirabilite, a white granular mineral medicine, primarily composed of hydrous sodium sulfate ($Na_2SO_4 \cdot 10H_2O$), is a well-known traditional Chinese medicine for treating acute pancreatitis[12]. Considering that mirabilite can treat acute pancreatitis, we hypothesized that mirabilite is effective in preventing PEP. Previous clinical evidence has shown that mirabilite is a safe and beneficial treatment

option for children with inflammatory diseases[13,14]. Therefore, this study aimed to investigate the efficacy and safety of the external use of mirabilite as a PEP preventive in the pediatric population in a multicenter, randomized controlled trial.

MATERIALS AND METHODS

This was a multicenter, prospective, randomized controlled study. Patients were recruited from Shanghai Children's Medical Center and Shanghai Shuguang Hospital in China between October 1, 2019 and December 30, 2021 after approval from the human studies review committee at each institution (see Figure 1 for flow diagram).

An investigator, who was blinded to the treatment allocation, recorded the patient demographics, post-ERCP adverse events, follow-up data, and procedure-related parameters, including sphincterotomy, stricture dilation, pancreatic stone extraction, number of cannulation attempts, and contrast agent dose. A screening session and physical examination prior to inclusion were conducted by a medical doctor according to the following inclusion criteria: (1) Age, 0-14 years; (2) Received therapeutic ERCP for chronic pancreatitis; (3) Blood amylase and lipase levels before ERCP were within the normal limits (amylase, 30-110 U/L; blood lipase, 23-300 U/L); and (4) Informed consent was obtained from the patient's guardians, and assent was obtained from patients aged > 8 years. The exclusion criteria were as follows: (1) Organic gastrointestinal disease, such as upper digestive tract stenosis or obstruction; (2) Pancreatitis or use of pancreatic enzyme medication within 7 d; (3) Cardiovascular, hepatic, renal, cerebrovascular, or hematopoietic system disease; (4) Dermatological disorders, such as fresh abdominal wounds, skin lesions, or angioma; and (5) Allergy to contrast agents or mirabilite.

The diagnostic criteria for chronic pancreatitis were the same as those of the International Study Group of Pediatric Pancreatitis: In Search for a Cure[15], which included children with irreversible structural changes in the pancreas, with or without abdominal pain, exocrine pancreatic insufficiency, or diabetes.

We calculated the sample size according to our primary study. The PEP incidence rate in the control group was estimated to be 21% based on historical data from the study institution[6]. Assume that preoperative prevention can reduce the risk of PEP by 50%, the target incidence of PEP in mirabilite external application group was estimated to not exceed 7%. Set $\alpha = 0.05$, two-sided test, $\beta = 0.20$. Calculated by PASS15.0 software, each group needed 99 participants, the estimated dropout rate was 15%, and 117 patients would be included in each group. Institutional review board approval was obtained (the Ethics Committee of Shanghai Children's Medical Center). This study registered with Clinical Trials ChiCTR1900022642. Registered on April 19, 2019, http://www.chictr.org.cn.

Intervention

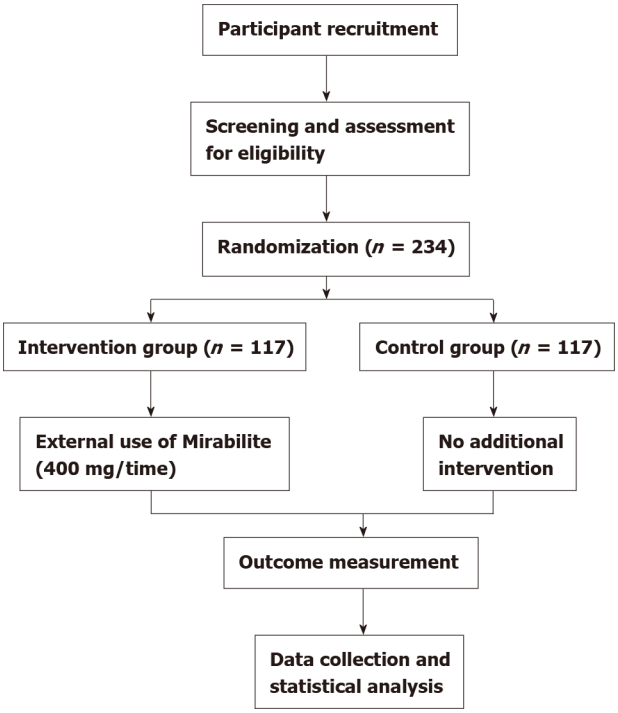
Procedure details: All patients underwent a comprehensive review and specialist consultation before ERCP. This process aimed to ensure an objective and comprehensive analysis, to determine if ERCP was appropriate, and rule out contraindications to endoscopy. Patients were asked to undergo routine preoperative laboratory testing (complete blood count, coagulation, blood amylase and lipase concentrations, and hepatic function markers), upper abdominal ultrasonography, magnetic resonance cholangiopancreatography or computed tomography (CT), and iodine allergy testing.

Each patient was required to fast for 12 h before surgery. Duodenoscopy was performed using a JF240V device (Olympus Corp., Tokyo, Japan). ERCP was conducted by an experienced digestive endoscopy specialist who performed > 30000 ERCPs. The following procedures were performed under radiographic guidance.

Standard post-ERCP treatment: Standard treatment was administered for PEP in both groups, including fasting, pancreatic enzyme control, and maintenance of fluid and electrolyte balance. Complications, such as infection, bleeding, or perforation within 1 mo of discharge were treated accordingly.

Patients in the external use of mirabilite group were administered a topical application of mirabilite (Chinese Medicine Institute, Shanghai, China), in a bag, on the middle and upper abdomen within 30 min before ERCP and until 24 h after ERCP, during which time the mirabilite was replaced every 4 h, whereas those in the blank group did not receive any additional intervention.

The external application of mirabilite (400 g each time) was packaged in custom-made topical bags. Mirabilite bags were designed with a rectangular shape and in two different sizes based on the projected area of the pancreas in pediatric patients. Children aged ≤ 6 years received bags with dimensions of 17 mm × 14 mm, whereas those aged > 6 years received bags with dimensions of 24 mm × 14 mm. Two layers of medical gauze were sewn into rectangular bags, and four 8-cm attachment bands were sewn to the two longer sides. The bags were used for topical application of mirabilite to the abdomen and were attached to the patient's backs using attachment bands.



DOI: 10.4240/wjgs.v15.i4.712

Figure 1 Flow diagram.

Randomization and masking

In this study, patients were randomly assigned to two groups in a 1:1 ratio using block randomization stratified by centers. Randomization was performed before ERCP (about 7 h before ERCP). Mirabilite was administered in the procedure room before or after ERCP by one investigator at each site who did not participate in data collection and analysis. The mirabilite external application package was removed before entering the operation room, the operator and assistant who participated in the ERCP procedures were blinded to the group allocation. Furthermore, the investigator who collected demographic or procedure-related data or who participated in the assessment of post-ERCP complications was blinded to the group allocation.

Assessments and measurements

At 24 h after the procedure, abdominal pain scores [visual analog scale (VAS) scores][16] were recorded. Communicative patients were asked to indicate their level of pain unaided. Pain assessment was completed by legal guardians in non-communicative patients. Serum levels of tumor necrosis factor-alpha (TNF-α), interleukin-10 (IL-10), diamine oxidase (DAO), blood D-lac, and endotoxin were measured in all patients 3 h before ERCP and 24 h after ERCP. Serum TNF-α and IL-10 levels were determined using enzyme linked immune assay (ELISA; Shanghai Hengyuan Bioengineering Institute, Shanghai, China). Moreover, serum DAO, D-lactic, and endotoxins were determined using ELISA (Shanghai Hengyuan Bioengineering Institute, Shanghai, China). According to the criteria[17] for the diagnosis of PEP, abdominal pain, serum amylase levels, and upper abdominal ultrasonography were measured 24 h after ERCP.

According to Cotton's criteria[17], PEP is classified into mild, moderate, and severe pancreatitis (mild, additional hospitalization for 1-3 d; moderate, additional hospitalization for 4-10 d; and severe, hospitalization for > 10 d and in cases of hemorrhagic pancreatitis, phlegmon, or pseudocysts).

Outcomes

Primary outcome: The primary outcome was the incidence of PEP after the procedure. According to consensus criteria[17], PEP was diagnosed if a child met two of the three following criteria after ERCP: A new onset of classical abdominal pain, a plasma amylase or lipase concentration exceeding three times the normal upper limit at 24 h postoperatively, and radiographic (B-type ultrasonography or CT) findings suggestive of pancreatitis.

Secondary outcomes: Additionally, several secondary outcome measures were recorded, including the severity of PEP. Abdominal pain was measured 24 h after ERCP using a VAS as follows: 0 points, no tenderness, no pain; 1-3 points, mild but tolerable discomfort and pain; 4-6 points, sleep quality affected by tolerable discomfort and pain; and 7-10 points, severe discomfort and intolerable pain that severely

affect sleep quality. Inflammatory cytokines were assessed by serum TNF-α and IL-10; and intestinal barrier function was recorded by DAO, D-lactic, and endotoxin levels.

Safety endpoints: The patients were monitored for adverse reactions to mirabilite, including skin damage and diarrhea. The following adverse reactions to ERCP were further monitored: Intestinal perforation, bleeding, bile duct infection, and other procedure-related complications requiring extended hospital stay. Patients were followed up for 1 mo postoperatively.

Statistical analysis

The data of all patients who underwent randomization were analyzed. Counting data were presented as absolute numbers and proportions. Corresponding analysis was performed using the chi-square test or Fisher's exact test when the actual frequency was < 5. Continuous variables without normal distribution in this study were presented with median and interquartile range, and comparisons were made using the Mann-Whitney *U* test between two groups. A two-sided $P < 0.05$ indicated statistical significance. All statistical analyses were performed using R version 3.5.1 (The R Foundation, Vienna, Austria).

RESULTS

A total of 234 patients were included in this study, with 117 in the external use of mirabilite group and 117 in the blank group. The baseline characteristics and ERCP procedure-related parameters were similar between the two groups (Table 1). Cannulation was successful in 234 patients (100%). The overall incidence of PEP in 234 patients was 17.1%; the incidence of PEP in children aged < 6 years was 15.1%, and in those aged ≥ 6 years was 18.8%. No statistical difference was found between the two age groups ($P = 0.460$).

The incidence of PEP in the external use of mirabilite group was significantly lower than that in the blank group (7.7% *vs* 26.5%, $P < 0.001$); the incidence of PEP in the mirabilite and blank groups was statistically significant in different age groups (Table 2). There were nine patients with mild pancreatitis but no moderate and severe pancreatitis in the mirabilite group, whereas in the blank control group, there were 16 patients with mild pancreatitis, 13 with moderate pancreatitis, and 2 with severe pancreatitis. The difference was statistically significant ($P = 0.023$) (Table 3). The VAS scores were significantly lower in the external use of mirabilite group than those in the blank group at 24 h after ERCP ($P = 0.001$) (Table 4). No statistically significant difference was noted in the expression levels of serum TNF-α and IL-10 between the two groups 3 h before the procedure. Compared with the values measured 3 h before the procedure, the expression levels of serum TNF-α and the expression levels of serum IL-10 increased in both groups at 24 h after procedure ($P = 0.016$ and $P < 0.001$, respectively). Compared with those in the blank group, the expression levels of serum TNF-α in the external use of mirabilite group were significantly lower, and the expression levels of serum IL-10 in the external use of mirabilite group were significantly higher at 24 h after the procedure. The differences were statistically significant ($P = 0.032$ and $P = 0.011$, respectively) (Table 5). No significant differences were found in the levels of serum D-lactate, DAO, and endotoxins before and after the procedure between the two groups (Table 6). No side effects due to the external use of mirabilite, such as skin allergy or diarrhea, were observed. Intestinal perforation, bleeding, bile duct infection, and other procedure-related complications, except PEP, did not occur during the 1-mo follow-up.

DISCUSSION

ERCP has been a primary treatment method for biliary and pancreatic diseases and has gradually replaced traditional surgery[18,19]. Although ERCP has many advantages, the high incidence of complications still restricts its widespread use to a certain extent. Among the complications of ERCP, PEP was the most common adverse event. Prophylactic drugs are necessary to reduce PEP, and a safe, effective, and convenient way to administer them is readily acceptable in children. Currently, there is no standard of care for the prevention of PEP in the pediatric population, and adopting adult-based standards is controversial. In our study, the external use of mirabilite significantly lowered the incidence of PEP and improved post-procedural pain, suggesting that external mirabilite use was helpful in preventing PEP in children and was highly acceptable. Our study is the first to evaluate prophylactic medications for pediatric PEP in a multi-center, randomized controlled trial in China.

At our center, the prevalence of PEP was 26.5% in the blank group. This was higher than the incidence of PEP in adults and other countries[1,4,20]. The main reason for the high incidence of PEP in our study population maybe because of patient and disease spectrum selection. The incidence of PEP is not low in Asia, about 10%-20%[6,21]; in a study of Chinese children, the incidence of PEP was 20.7% [6]. Some previous studies have reported a low PEP rate in adults; the spectrum of diseases were mainly biliary diseases, including choledocholithiasis, cholangitis, or biliary stricture[20,22]. In contrast,

Table 1 Baseline and procedure characteristics of patients in each group

	External use of mirabilite group (*n* = 117)	Blank group (*n* = 117)	*P* value
Female, *n* (%)	71 (60.7)	60 (51.3)	0.147
BMI, kg/m^2 (IQR)	15.59 (14.12, 17.27)	15.55 (14.37, 17.64)	0.359
Age, yr (IQR)	6.8 (4.1, 11.8)	7 (4.0, 7.0)	0.971
Medical history, *n* (%)			0.609
Idiopathic pancreatitis	58 (49.6)	62 (53.0)	
Pancreas divisum	20 (17.1)	24 (20.5)	
Pancreaticobiliary maljunction	36 (30.8)	27 (23.1)	
Pancreas divisum accompanied annular pancreas	3 (2.6)	4 (3.4)	
Procedure, *n* (%)			
EPS (major papilla)	25 (21.4)	20 (17.1)	0.407
EPS (minor papilla)	6 (5.1)	5 (4.3)	0.757
EST	9 (7.7)	16 (13.7)	0.139
ERPD	57 (48.7)	57 (48.7)	1.000
ERBD	30 (25.6)	34 (29.1)	0.557
ENPD	15 (12.8)	15 (12.8)	1.000
ENBD	10 (8.5)	8 (6.8)	0.624
Contrast medium			0.866
Contrast agent dose < 5 mL	96 (82.1)	95 (81.2)	
Contrast agent dose ≥ 5 mL	21 (17.9)	22 (18.8)	
Attempts for successful Cannulation (≥ 5 times)	20 (17.1)	20 (17.1)	1.000
Pancreatogram	103 (88.0)	104 (88.9)	0.838

EPS: Endoscopic pancreatic sphincterotomy; EST: Endoscopic sphincterotomy; ERPD: Endoscopic retrograde pancreatic drainage; ERBD: Endoscopic retrograde biliary drainage; ENPD: Endoscopic naso-pancreatic drainage; ENBD: Endoscopic naso-biliary drainage.

previous studies have confirmed that bile duct disease is not a high-risk factor for PEP, but young age, sphincterotomy are high-risk factors for PEP[6,21]. However, this study included children with chronic pancreatic diseases, and most surgeries conducted in the pancreatic duct may account for the high PEP occurrence.

Mirabilite is a well-known traditional Chinese medicine for the treatment of acute pancreatitis[12]. The medicine is applied externally, absorbed through the skin, and does not go through the digestive system; thus, the procedure is simple and safe to conduct, with no risk of an adverse reaction. Research indicates that mirabilite plays a role in moisture absorption, reduction of swelling, heat clearance, toxicity removal, and anti-inflammatory action. In addition, mirabilite has been shown to improve the levels of amylase in the blood, improve pancreatic blood circulation, promote the absorption of necrotic tissue, promote gastrointestinal peristalsis, and decrease a variety of complications, improving the overall prognosis. Wang *et al*[12] have applied mirabilite to reduce pancreatic leakage in severe acute pancreatitis, which lowered intra-abdominal pressure, reduced the secretion of pancreatic amylase, eliminated inflammatory edema, and reduced IL-6 levels in the blood. Animal experiments have shown that Dachengqi decoction, a famous formula in China that comprises mirabilite as the principal component, increased cell viability, reduced acinar necrosis, and provided protection from injury to the pancreas *in vivo* and *in vitro*[23]. However, few reports have researched the efficacy of mirabilite for preventing PEP.

This study found that the incidence and PEP severity in the externally applied mirabilite group was significantly lower than that in the control group. This illustrated that mirabilite can treat acute pancreatitis and may prevent PEP and reduce the severity of PEP. Currently, NSAIDs have been shown to be the only effective drug in preventing PEP in adults, and few reports have investigated prophylactic medicine for PEP in children. In a meta-analysis of randomized controlled trials, the overall incidence of PEP was 7.64% (47/615 patients) in the rectal indomethacin group and 15.15% (95/627 patients) in the placebo group[24]. Similar results have been obtained with external application of mirabilite, which is

Table 2 Incidence of post-endoscopic retrograde cholangiopancreatography pancreatitis in each group

	External use of mirabilite group (*n* = 117)	Blank group (*n* = 117)	*P* value
Overall			< 0.001[1]
PEP	9 (7.7%)	31 (26.5%)	
No PEP	108 (92.3%)	86 (73.5%)	
< 6 years old			0.001[1]
PEP	1 (2.1%)	14 (27.5%)	
No PEP	46 (97.9%)	37 (72.5%)	
≥ 6 years old			0.031[1]
PEP	8 (11.4%)	17 (25.8%)	
No PEP	62 (84.7%)	49 (74.2%)	

[1]Statistically significant.
PEP: Post-endoscopic retrograde cholangiopancreatography pancreatitis.

Table 3 Prevalence and severity of ost-endoscopic retrograde cholangiopancreatography pancreatitis in each group

	External use of mirabilite group (*n* = 9)	Blank group (*n* = 31)	*P* value
Severity of PEP			0.023[1]
Mild	9 (100.0%)	16 (51.6%)	
Moderate	0 (0.0%)	13 (41.9%)	
Severe	0 (0.0%)	2 (6.5%)	

[1]Statistically significant.
PEP: Post-endoscopic retrograde cholangiopancreatography pancreatitis.

Table 4 Visual analog scale score of abdominal pain at 24 h after endoscopic retrograde cholangiopancreatography pancreatitis in each group

Group	VAS score	*Z* value	*P* value
External use of mirabilite group	0 (0, 2)	-3.27	0.001[1]
Blank group	2 (0, 5)		

[1]Statistically significant.
VAS: Visual analog scale.

more acceptable than rectal or oral administration in children. Therefore, this study would be informative to expand the field of prospective research on the prevention of pediatric PEP. Cytokines play a major role in the pathogenesis of acute pancreatitis as part of the underlying systemic inflammatory response, tissue damage, and organ dysfunction. The severity of acute pancreatitis depends on an intricate balance between localized tissue damage with proinflammatory cytokine production and the systemic anti-inflammatory response[13]. TNF-α is a pro-inflammatory cytokine that promotes the inflammatory response, whereas IL-10 is an immunosuppressive cytokine that inhibits inflammation [25]. Anti-inflammatory cytokines and pro-inflammatory factors maintain a balance when no inflammatory responses are occurring. Disruption in this balance leads to an inflammatory response when the anti-inflammatory cytokines are insufficient against the pro-inflammatory factors. For restoration of immunological balance, a proinflammatory response is usually followed by secretion of anti-inflammatory mediators, such as IL-10, which suppress the synthesis and effects of proinflammatory cytokines. In this study, the expression levels of TNF-α and the expression levels of IL-10 increased after ERCP in both groups. However, the TNF-α expression in the external use of mirabilite group at 24 h after the ERCP procedure was significantly lower and the IL-10 expression was higher than that in the blank group, indicating that external use of mirabilite can improve anti-inflammatory function and

Table 5 The levels of serum necrosis factor-alpha and interleukin-10 in each group (MP 25, P75 pg/mL)

		External use of mirabilite group (*n* = 117)	Blank group (*n* = 117)	*P* value
TNF-α	Pre-ERCP 3 h	1.78 (0.00, 3.39)	1.30 (0.00, 4.25)	0.622
	Post-ERCP 24 h	2.42 (1.14, 6.53)	3.41 (1.63, 8.26)	0.032[1]
	P value	0.016[1]	< 0.001[1]	
IL-10	Pre-ERCP 3 h	3.56 (1.49, 6.01)	3.49 (1.24, 6.62)	0.992
	Post-ERCP 24 h	4.60 (2.99, 9.40)	3.76 (1.74, 7.86)	0.011[1]
	P value	< 0.001[1]	0.282	

[1]Statistically significant.
TNF-α: Necrosis factor-alpha; IL-10: Interleukin-10; ERCP: Endoscopic retrograde cholangiopancreatography pancreatitis.

Table 6 The levels of serum D-lactate, endotoxin and diamine oxidase in each group (MP 25, P75 ug/L)

		External use of mirabilite group (*n* = 117)	Blank group (*n* = 117)	*P* value
D-lactate	Pre-ERCP 3 h	190.65 (164.37, 273.58)	224.38 (187.29, 313.58)	0.120
	Post-ERCP 24 h	199.73 (180.57, 233.96)	213.88 (192.04, 314.86)	0.078
	P value	0.849	0.914	
Endotoxin	Pre-ERCP 3 h	5.95 (4.06, 7.83)	5.21 (3.94, 6.91)	0.375
	Post-ERCP 24 h	5.36 (4.09, 8.01)	5.35 (4.50, 7.89)	0.874
	P value	0.762	0.559	
DAO	Pre-ERCP 3 h	0.65 (0.44, 2.47)	0.63 (0.51, 0.97)	0.635
	Post-ERCP 24 h	1.04 (0.52, 2.47)	0.79 (0.585, 0.79)	0.536
	P value	0.410	0.129	

DAO: Diamine oxidase; ERCP: Endoscopic retrograde cholangiopancreatography pancreatitis.

reduce the inflammatory response by down-regulating the secretion of proinflammatory factors and up-regulating the anti-inflammatory factors to alleviate pancreatic injury.

Studies have shown that the release of inflammatory factors may lead to intestinal ischemic hypoxia, resulting in the destruction of the intestinal barrier function that shifts intestinal bacteria and toxins, further causing pancreatic damage[26]. When the intestinal barrier is damaged, DAO, D-lactate, and endotoxins are transferred into the blood circulation through the damaged mucosa in the early stage. In addition, the serum concentrations of D-lactate, DAO could reflect the intestinal permeability in patients with acute pancreatitis[27]. Thus, the detection of plasma levels of DAO and D-lactate can promptly reflect the extent of damage and permeability changes in the small intestine, which are the specificity and sensitivity indicators of intestinal barrier function to evaluate pancreatitis. The present study showed no statistically significant differences in the levels of D-lactate, DAO, and endotoxins in both groups before and after the procedure, suggesting that gastrointestinal mucosal barrier dysfunction was not obvious. This may be because the inflammatory response induced by the procedure is not strong enough to injure the gastrointestinal mucosal barrier function. In this study, no side effects of the external use of mirabilite, such as skin allergy and diarrhea, were observed.

The limitation of this study was that it was an unblinded study, with researcher subjective biases, and it was restricted to the Chinese population. In addition, a suitable control medicine should be used for further studies. Furthermore, the exact mechanisms of action remain relatively unknown and should be investigated further in future studies.

CONCLUSION

Our study showed that the external use of mirabilite can reduce the incidence of PEP, relieve post-procedural pain, and regulate inflammatory mediator expression to reduce the inflammatory response. Further, this study suggests that the external use of mirabilite is a safe, effective, and more acceptable

option for the prevention of PEP prophylaxis in pediatric patients.

ARTICLE HIGHLIGHTS

Research background

Post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) is the most common adverse event following ERCP. Currently, only non-steroidal anti-inflammatory drugs have been shown to be effective in preventing PEP in adults. Few studies have prospectively evaluated interventions to prevent PEP in children.

Research motivation

The occurrence of PEP could limit the application of ERCP in children, for which finding an ideal, effective, less invasive, and safe prevention strategy is desirable.

Research objectives

The objective of this study was to assess the efficacy and safety of external use of mirabilite to prevent PEP in children.

Research methods

We conducted a multicenter, randomized controlled clinical trial. Patients with chronic pancreatitis scheduled for ERCP were enrolled and randomly divided into the external use of mirabilite group and the blank group. The primary outcome was the incidence of PEP. The secondary outcomes included the severity of PEP, abdominal pain scores, levels of serum inflammatory markers, tumor necrosis factor (TNF)-α and interleukin (IL)-10, and intestinal barrier function markers, diamine oxidase (DAO), D-lactic acid, and endotoxin. Additionally, the side effects of topical mirabilite were investigated.

Research results

A total of 234 patients were enrolled, including 117 in the external use of mirabilite group and the other 117 in the blank group. The pre-procedure and procedure-related factors were not significantly different between the two groups. The incidence of PEP in the external use of mirabilite group was significantly lower than that in the blank group (7.7% *vs* 26.5%, $P < 0.001$). The severity of PEP decreased in mirabilite group ($P = 0.023$). At 24 h after the procedure, the visual analog score in the external use of mirabilite group was lower than that in the blank group ($P = 0.001$). Compared with those in the blank group, the TNF-α expressions were significantly lower and the IL-10 expressions were significantly higher at 24 h after the procedure in the external use of mirabilite group ($P = 0.032$ and $P = 0.011$, respectively). There were no significant differences in serum DAO, D-lactic acid, and endotoxin levels before and after ERCP between the two groups. No adverse effects of mirabilite were observed.

Research conclusions

External use of mirabilite reduced the occurrence of PEP. Moreover, it significantly alleviated post-procedural pain and reduced inflammatory response. Our results favor the external use of mirabilite to prevent PEP in children.

Research perspectives

This study illustrated that external use of mirabilite is a safe, effective, and more acceptable option for PEP prophylaxis in pediatric patients. Our findings would be informative to expand the field of prospective research on the prevention of pediatric PEP.

ACKNOWLEDGEMENTS

We thank Dr. Fu Li, the distinguished professor of Shanghai Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, for his review of the manuscript for optimal English language presentation. Moreover, we would like to thank all the staff for their valuable support in participant recruitment.

FOOTNOTES

Author contributions: Zeng JQ and Zhang TA have contributed equally to this work; Deng ZH and Gong B conceived and designed the study and participated in logistical planning of the study; Yang KH, Wang WY, Zhang JY, Xiao J, and Gu ZJ acquired, analyzed, and interpreted the data; Hu YB performed the statistical analysis; Zhang TA and

Zeng JQ contributed significantly to analysis and manuscript preparation; and all authors agreed to be accountable for all aspects of the work.

Supported by Shanghai Municipal Health Commission of China, No. 2018LP018.

Institutional review board statement: This study has been approved by the Institutional Ethnic Committee.

Clinical trial registration statement: The trial was registered in the Chinese Clinical Trial Registry (ChiCTR1900022642).

Informed consent statement: Written informed consent was willingly provided by each patient or their legal guardian.

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

Data sharing statement: All the individual data, except participant data collected during the trial, will share. Study protocol, statistical analysis plans, analytic code, informed consent form, and clinical study report will be available. The data will be made available from the corresponding author (E-mail: dzhrj@163.com), upon reasonable request.

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: Jing-Qing Zeng 0000-0002-7064-6662; Tian-Ao Zhang 0000-0002-8939-2244; Kai-Hua Yang 0000-0002-1389-9137; Wen-Yu Wang 0000-0003-4118-1218; Jia-Yu Zhang 0000-0002-4553-2583; Ya-Bin Hu 0000-0002-8108-0596; Jian Xiao 0000-0002-3942-1924; Zhi-Jian Gu 0000-0002-7965-8280; Biao Gong 0000-0002-3645-2493; Zhao-Hui Deng 0000-0003-0780-9657.

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

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World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2023 April 27; 15(4): 723-739

DOI: 10.4240/wjgs.v15.i4.723

ISSN 1948-9366 (online)

SYSTEMATIC REVIEWS

The global epidemiology of upper and lower gastrointestinal bleeding in general population: A systematic review

Şiir Su Saydam, Megan Molnar, Pareen Vora

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: Samadder S, India; Shen F, China

Received: October 19, 2022
Peer-review started: October 19, 2022
First decision: January 3, 2023
Revised: January 20, 2023
Accepted: March 8, 2023
Article in press: March 8, 2023
Published online: April 27, 2023

Şiir Su Saydam, Megan Molnar, Pareen Vora, Integrated Evidence Generation, Bayer AG, Berlin 13353, Germany

Corresponding author: Pareen Vora, PhD, Director, Integrated Evidence Generation, Bayer AG, Muellerstr. 178, Berlin 13353, Germany. pareen.vora@bayer.com

Abstract

BACKGROUND

Gastrointestinal bleeding (GIB) is a common and potentially life-threatening clinical event. To date, the literature on the long-term global epidemiology of GIB has not been systematically reviewed.

AIM

To systematically review the published literature on the worldwide epidemiology of upper and lower GIB.

METHODS

EMBASE® and MEDLINE were queried from 01 January 1965 to September 17, 2019 to identify population-based studies reporting incidence, mortality, or case-fatality rates of upper GIB (UGIB) or lower GIB (LGIB) in the general adult population, worldwide. Relevant outcome data were extracted and summarized (including data on rebleeding following initial occurrence of GIB when available). All included studies were assessed for risk of bias based upon reporting guidelines.

RESULTS

Of 4203 retrieved database hits, 41 studies were included, comprising a total of around 4.1 million patients with GIB worldwide from 1980–2012. Thirty-three studies reported rates for UGIB, four for LGIB, and four presented data on both. Incidence rates ranged from 15.0 to 172.0/100000 person-years for UGIB, and from 20.5 to 87.0/100000 person-years for LGIB. Thirteen studies reported on temporal trends, generally showing an overall decline in UGIB incidence over time, although a slight increase between 2003 and 2005 followed by a decline was shown in 5/13 studies. GIB-related mortality data were available from six studies for UGIB, with rates ranging from 0.9 to 9.8/100000 person-years, and from three studies for LGIB, with rates ranging from 0.8 to 3.5/100000 person-years. Case-fatality rate ranged from 0.7% to 4.8% for UGIB and 0.5% to 8.0% for LGIB. Rates of rebleeding ranged from 7.3% to 32.5% for UGIB and from 6.7% to 13.5% for LGIB. Two main areas of potential bias were the differences in the operational GIB

definition used and inadequate information on how missing data were handled.

CONCLUSION
Wide variation was seen in estimates of GIB epidemiology, likely due to high heterogeneity between studies however, UGIB showed a decreasing trend over the years. Epidemiological data were more widely available for UGIB than for LGIB.

Key Words: Gastrointestinal bleeding; Gastrointestinal haemorrhage; Epidemiology; Incidence; Mortality; Case-fatality

Core Tip: This review addresses an important literature gap in summarizing the long-term global epidemiology of GIB. Epidemiological data were more widely available for UGIB than for LGIB, which were limited. Estimates of GIB were highly heterogeneous, often due to differences in case definitions, but showed a decreasing trend for UGIB incidence.

Citation: Saydam ŞS, Molnar M, Vora P. The global epidemiology of upper and lower gastrointestinal bleeding in general population: A systematic review. *World J Gastrointest Surg* 2023; 15(4): 723-739
URL: https://www.wjgnet.com/1948-9366/full/v15/i4/723.htm
DOI: https://dx.doi.org/10.4240/wjgs.v15.i4.723

INTRODUCTION

Gastrointestinal bleeding (GIB) is a potentially life-threatening clinical event resulting in more than 400000 hospital admissions in the United States (US) each year, and associated with substantial economic burden for healthcare systems[1,2]. Upper GIB (UGIB) is observed between the mouth and the duodenum, while lower GIB (LGIB) occurs distal to the ligament of Treitz[3,4]. Risk factors for GIB are well-established and include older age, being male, smoking, alcohol use, and medication use[5-13]. Previous reviews on the epidemiology of UGIB have focused on specific etiologies such as peptic ulcer bleeding (PUB)[11,14,15], outcomes associated with risk factors[16-18], or prediction scores[19-21], while reviews on LGIB are lacking. An overarching review of the long-term worldwide epidemiology of GIB would enable the totality of evidence on this topic to be obtained, covering decades that have seen advances in preventative measures and management. This would also help identify areas where data gaps remain, guiding future investigations. We therefore performed a systematic review of the literature with the aim of describing the long-term worldwide epidemiology of UGIB and LGIB in the general population.

MATERIALS AND METHODS

Data sources and search

EMBASE® and MEDLINE databases were queried from 01 January 1965 to September 17, 2019, using searches for the keywords 'epidemiology', 'incidence', 'prevalence', 'mortality', 'case fatality' combined with 'gastrointestinal', 'hemorrhage', 'haemorrhage', 'bleeding' in title or abstract. The search was restricted to studies in humans and those written in English. Deduplication across databases was performed by the embedded function within EMBASE® platform. The complete electronic search strategy is shown in Supplementary Table 1.

Inclusion and exclusion criteria

Following Cochrane Collaboration guidelines[3,4], we included population-based studies reporting either incidence, mortality or case-fatality rates for UGIB and/or LGIB in the general adult population. We included studies on either acute or chronic GIB, and those on variceal or non-variceal UGIB (NVUGIB). We excluded randomized controlled trials and interventional studies because they are not designed to assess epidemiology of a disease and are based on selected groups of individuals. Conference abstracts, editorials, letters, notes, and short surveys were excluded. Studies among patient subgroups (*e.g.*, cirrhotic patients, drug users), and those that investigated only specific GIB etiologies (*e.g.*, PUB, Mallory-Weiss) or degrees of bleeding (*e.g.*, massive LGIB) were also excluded, as were those where GIB was undefined, unspecified as UGIB/LGIB, or where mortality rates were not specified as

being GIB-related. When two or more publications presented data from the same or overlapping population, we included only the study conducted over the most recent period, unless the older data provided more extensive information on study endpoints.

Article screening and data extraction

Titles and abstracts were screened independently by two authors (ŞSS and MM), with disagreements resolved by cross-checks and discussions with the third author (PV). For remaining articles, full-text was reviewed. Details about the study design, population and results were extracted from each article. When rates were not reported explicitly, they were calculated from the available data (including from graphical displays) wherever possible.

Data analysis

Data were presented for UGIB and LGIB separately. Outcome measures were incidence rate, mortality rate and case-fatality rate. Incidence rates were extracted or calculated and presented as the number of patients with GIB divided by person-time, and mortality rates were extracted or calculated as the number of GIB-related deaths divided by person-time; both were expressed *per* 100000 person-years. For estimate calculations, person-time was defined as the population size of the catchment area multiplied by follow-up time (usually approximated as the study duration). Case-fatality rates were extracted or calculated as the percentage of GIB-related deaths among the total number of patients with GIB in the study population. Where available, data on rebleeding were extracted or determined as the percentage of GIB recurrences among patients with GIB. Rates were displayed using forest plots with 95% confidence intervals. Studies that reported incidence rates at different timepoints were displayed graphically to visualize temporal trends. Analyses were conducted using R on RStudio (Version 1.1.423) with ggplot2 and forest plot packages.

Assessment of bias

Risk of bias was assessed at the study level based on published guidance with amendments[22] (Supplementary Table 2). Each study was also evaluated against reporting guidelines for observational studies[23] (Supplementary Table 3). Risk of bias across all studies was not assessed as rates were presented individually for each study, and pooled cumulative estimates were not calculated.

RESULTS

A total of 4793 database hits were retrieved from the search (4203 from EMBASE®, 509 from MEDLINE). Following the screening of titles and abstracts (4415 were excluded), 353 articles remained. After full-text screening, 36 articles were retained for the final review[24-59]. A further five studies were included after screening bibliographies of full-text articles and relevant reviews[60-64](see PRISMA flowchart in Supplementary Figure 1 and hierarchical reason for exclusion in Supplementary Table 4). Of the 41 included studies (covering approximately 4.2 million individuals), 33 studies provided estimates on UGIB (eight specifically on NVUGIB), four on LGIB, and the remaining four reported data on both. Characteristics of the included studies are shown in Tables 1 and 2. Twenty-six studies were from Europe, eight from North America, six from Asia-Pacific and one from the Middle East. Of 33 studies on UGIB, eight reported estimates only for NVUGIB. No population-based study was identified that reported epidemiological variables of interest for variceal UGIB. The diagnostic procedure for GIB was endoscopy in 27 studies, and unclear for the remaining studies. Data sources used were hospital records (19 studies), administrative databases (12 studies), hospital surveys (7 studies), electronic health records, a survey cohort study (one study) and claims data combined with clinical data (one study).

Incidence of UGIB

Twenty-nine studies reported incidence rates for UGIB which ranged from 15.0 *per* 100000 person-years to 172.0 *per* 100000 person-years over 1980 to 2012 (Figure 1), with high heterogeneity across and within countries. Approximately two-thirds of incidence rates (65.5%) were within the range of 50 to 120 *per* 100000 person-years. Four studies reported estimates for NVUGIB incidence ranging from 15.0 *per* 100000 person-years to 108.0 *per* 100000 person-years, also with high heterogeneity between studies[34,38,40,54]. Incidence rates among studies that included GIB only as primary diagnosis were lower than studies that did not restrict inclusion to primary diagnosis only[35,44,52,59,64], except for when the numerator was the number of hospitalizations[42,48]. A hospital-based survey from France that included out-patient diagnosed GIB reported the highest incidence estimate of 143 *per* 100000 person-years for the year 1996[32].

There were thirteen studies that described temporal trends of UGIB incidence within the defined study years. Among these, overall declines in UGIB incidence were seen over time (Figure 2), most notably in Japan, which saw a particularly rapid decline, albeit with a spike in 2003[45]. Other studies described a slight increase in UGIB incidence between 2003–2005 followed by a decline[41,42,44,52,64]. Differences between studies that reported rates from the same country were likely due to different

Table 1 Basic information for studies

Ref.	Study period	Country (region)	Data source[1]	Design	Clinical event
Schlup *et al*[24], 1984	1 September 1980 - 28 February 1982	New Zealand (Dunedin)	Clinical data (Dunedin public hospitals)	P	UGIB
Katschinski *et al*[25], 1989	1 April 1984 - 31 March 1986	UK (Nottingham)	Clinical data (The Nottingham City and University Hospitals)	P	UGIB
Longstreth[26], 1995	1991	USA (San Diego)	Administrative claims database (KPMCP)	R	AUGIB
Bramley *et al*[27], 1996	October 1991 - September 1993	Scotland (Grampian and the Northern Isles)	Clinical data (Aberdeen Royal Infirmary)	P	LGIB
Masson *et al*[28], 1996	October 1991 - September 1993	Scotland (Orkney and Shetland)	Clinical data (Aberdeen Royal Infirmary)	P	UGIB
Blatchford *et al*[60], 1997	September 1992 - Feb 1993	West Scotland	Clinical data (Multicenter)	P	AUGIB
El Bagir *et al*[29], 1997	May 1991 - May 1993	Saudi Arabia (Abha City)	Clinical data (Asir Central Hospital)	P	AUGIB
Longstreth[30], 1997	January 1990 - December 1993	USA (San Diego)	Claims (KPMCP)	R	ALGIB
Soplepmann *et al*[61], 1997	1 August 1992 - 31 July 1994	Finland (Central Finland)	Clinical data (Central Hospital of Central Finland)	P	AUGIB
		Estonia (Tartu)	Clinical data (Tartu University Hospital)		
Vreeburg *et al*[31], 1997	July 1993 - July 1994	Netherlands (Amsterdam area)	Hospital survey (Two university and ten regional hospitals)	P	AUGIB
Czernichow *et al*[32], 2000	1 January - 30 June 1996	France (Finistere, Gironde, Seine Maritime and Somme)	Hospital survey (29 public hospitals and 96 private practices)	P	AUGIB
Paspatis *et al*[33], 2000	February 1998 - February 1999	Greece (Heraklion, Crete)	Hospital survey	P	AUGIB
Tenias Burillo *et al*[34], 2001	April 1995 - March 1999	Spain (Valencia)	Clinical data (Lluis Alcanyis Hospital)	P	NVUGIB
Lewis *et al*[62], 2002	1992 - 1999	USA	Hospital survey (NHDS)	R	UGIB
van Leerdam *et al*[63], 2003	January 2000 - January 2001	Netherlands (Amsterdam area)	Hospital survey (Two university and ten regional hospitals)	P	AUGIB
Targownik *et al*[35], 2006	1993 - 2003	Canada	Administrative database (HPOID)	R	AUGIB
Theocharis *et al*[36], 2008	January 1995- December 1995	Greece (Achaia)	Clinical data (Three regional hospitals)	R	AUGIB
	January - December 2005			P	
Kapsoritakis *et al*[37], 2009	1 December 2005 - 30 November 2006	Greece (Thessaly, Larissa)	Clinical data (University Hospital of Larissa)	P	AUGIB
Lanas *et al*[38], 2009	1 January 1996 - 30 December 2005	Spain	Administrative database (10 hospitals of Spanish NHS)	R	NVUGIB LGIB
Loperfido *et al*[39], 2009	1 October 1983 - 31 December 1985	Italy (Treviso)	Clinical data (Treviso Hospital)	P	AUGIB
	1 January 2002 - 31 March 2004				
Åhsberg *et al*[40], 2010	1 January - 31 December 1984	Sweden (Skåne)	Clinical data (Lund University Hospital)	R	NVUGIB LGIB
	1 January - 31 December 1994				NVUGIB LGIB

	1 January - 31 December 2004				NVUGIB LGIB
Button *et al*[41], 2011	1 April 1999 - 31 March 2007	Wales	Linked administrative database (PEDW)	R	UGIB
Langner *et al*[42], 2011	2000 – 2005	Germany	Administrative database (GHS)	R	UGIB
Crooks *et al*[43], 2012	1 April 1997 - 30 August 2010	England	Linked EHR data (GPRD and HES)	R	UGIB
Laine *et al*[44], 2012	2001 - 2009	USA	Administrative claims database (Premier Perspective)	R	UGIB LGIB
Miyamoto *et al*[45], 2012	1997 - 2008	Japan (Aki-Ota, Hiroshima)	Clinical data	R	UGIB
Mungan *et al*[46], 2012	6 January - 10 March 2009	Turkey	Cohort study (ENERGIB survey)	R	NVUGIB
Nahon *et al*[47], 2012	March 2005 - February 2006	France	Hospital survey (53 hospitals)	P	UGIB
Sangchan *et al*[48], 2012	1 October 2009 - 30 September 2010	Thailand	Claims and clinical data	R	UGIB
Del Piano *et al*[49], 2013	June 2006 - June 2007 and December 2008 - December 2009	Italy	Clinical data (13 hospitals)	P	ANVUGIB
Hreinsson *et al*[50], 2013a	1 January 2010 - 31 December 2010	Iceland (Reykjavik)	Clinical data (National University Hospital of Iceland)	P	ALGIB
Hreinsson *et al*[51], 2013b	1 January 2009 - 31 December 2010	Iceland (Reykjavik)	Clinical data (National University Hospital of Iceland)	P	AUGIB
Cavallaro *et al*[45], 2014	January 2001 - December 2010	Italy (Veneto)	Administrative database (HDRs)	R	UGIB LGIB
Marmo *et al*[53], 2014	March 2003 - March 2004 and April 2007 - May 2008	Italy	Administrative database (PNED1 and PNED2)	P	NVUGIB
O'Byrne *et al*[54], 2014	1 January 2008 - 31 December 2009	Canada (Saskat-chewan)	Clinical data (SHR and RQHR)	R	NVUGIB
Abougergi *et al*[64], 2015	1989 - 2009	USA	Administrative database (NIS)	R	UGIB
Niikura *et al*[55], 2015	1 July 2010 - 31 March 2012	Japan	Administrative claims database (DPC)	R	LGIB
Taha *et al*[56], 2015	2007 - 2012	Scotland (Ayrshire)	Clinical data (University Hospital Crosshouse)	R	UGIB
Lu *et al*[57], 2018	1 January 2008 - 31 December 2012	China	Hospital survey (Eight hospitals)	R	NVUGIB
Park *et al*[58], 2018	February 2011 - December 2013	South Korea (Daegu, Gyeong-sang)	Clinical data (Eight hospitals)	P	UGIB
Wuerth *et al*[59], 2018	2002 - 2012	USA	Administrative database (NIS)	R	UGIB

[1]Clinical data: Hospital records; Hospital survey: Survey or standardized questionnaire being administered to multiple hospitals or healthcare practices to gather clinical records; Administrative database: Inpatient data collected by government or research organizations. Linkage refers to combining information from multiple data sources of the same population, removing duplicates.

EHR: Electronic health records; EMR: Electronic medical records; KPMCP: Kaiser Permanente Medical Care Program; HDRs: Health Discharge Records; HPOID: Health Person-Oriented Information Database; NHS: National Health Services; PEDW: Patient Episode Database for Wales; ENERGIB: European Survey of Non-Variceal Upper Gastro Intestinal Bleeding; GHS: German Hospital Statistics; GPRD: General Practice Research Database; HES: Hospital Episodes Statistics; PNED: Progetto Nazionale Emorragie Digestive; SHR: Saskatoon Health Region; RQHR: Regina Qu'Appelle Health Region; NIS: Healthcare Cost and Utilization Project Nationwide Inpatient Sample; DPC: Diagnosis Procedure Combination; P: Prospective; R: Retrospective; ALGIB: Acute lower gastrointestinal bleeding; AUGIB: Acute gastrointestinal bleeding; ANVUGIB: Acute nonvariceal upper gastrointestinal bleeding; LGIB: Lower gastrointestinal bleeding; NVUGIB: Nonvariceal upper gastrointestinal bleeding; UGIB: Upper gastrointestinal bleeding.

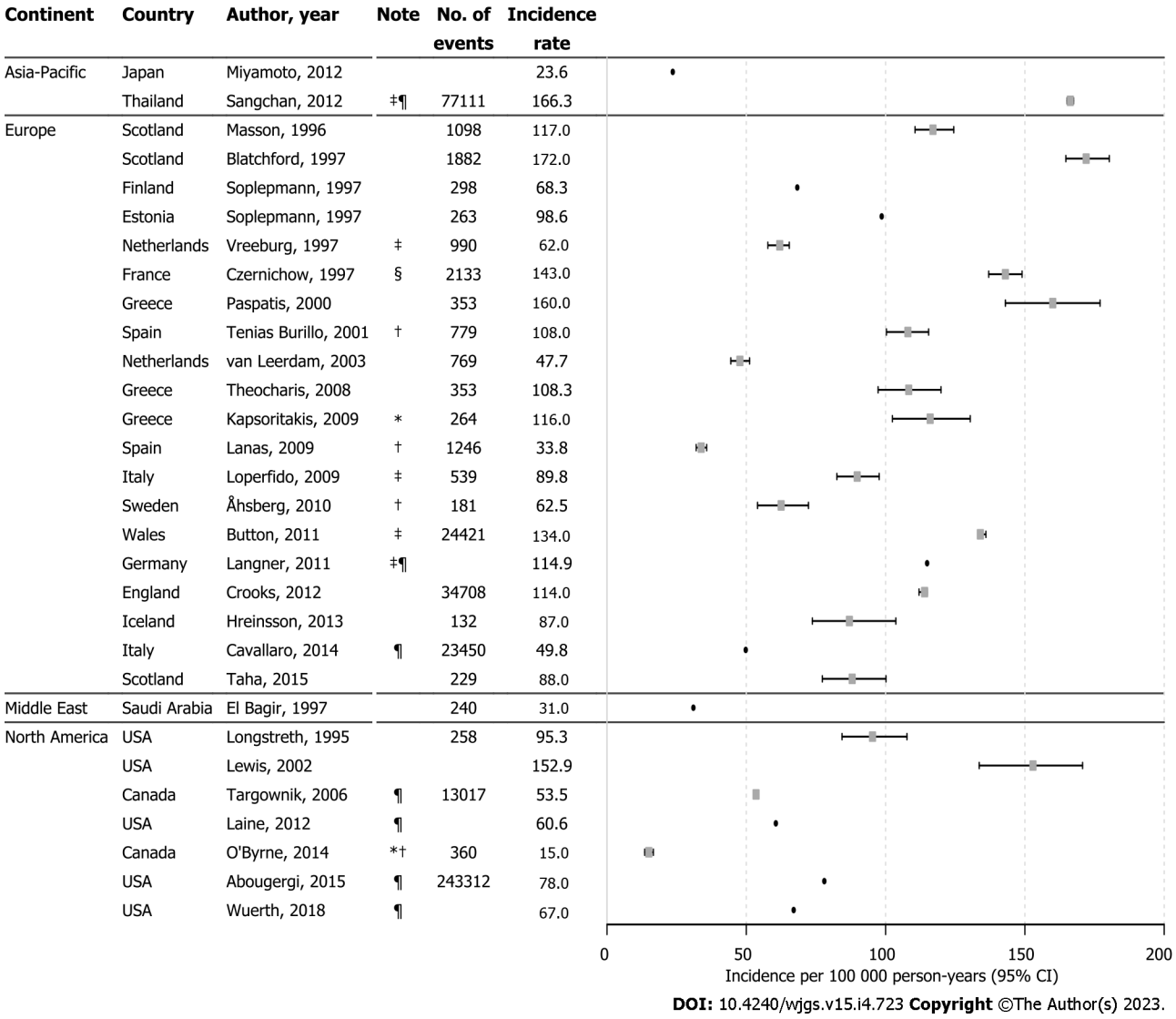
Table 2 Study characteristics, *n* (%)

Ref.	Diagnostic criteria	Total patients, (male)	Age[1], (mean)	Population at risk	Re-bleeding	Diagnostic endoscopy[2]	In-hospital bleeds[3]
Schlup *et al*[24], 1984	Hematemesis and/or melena	112 (58.0)	≥ 15 (61.5)	120000 - 150000	18 (16.1)	Yes	Unclear
Katschinski *et al* [25], 1989	Hematemesis and/or melena	1017 (N/A)	All (N/A[6])	789000	N/A	Yes	Unclear
Longstreth[26], 1995	ICD-9-CM	258 (63.6)	≥ 20 (60.6)	270699	N/A	Yes	Yes
Bramley *et al* [27], 1996	Suspected UGIB or LGIB	252 (46.8)	All (N/A[6])	467760	34 (13.5)	Some	Yes
Masson *et al* [28], 1996	Suspected UGIB or LGIB	1098 (62.2)	All (N/A[6])	468000	N/A	Yes	Yes
Blatchford *et al* [60], 1997	Hematemesis and/or melena; using standard definitions	1882 (64.2)	≥ 15 (N/A[6])	2184285	N/A	Some	Yes
El Bagir *et al* [29], 1997	Hematemesis and/or melena	240 (62.5)	≥ 20 (44.3)	450000	N/A	Yes	Unclear
Longstreth[30], 1997	ICD-9-CM	219 (55.7)	≥ 20 (67.2)	N/A	14 (6.7)	Yes	Yes
Soplepmann *et al*[61], 1997	Hematemesis and/or melena	270 (66.7)	≥ 15 (64.2)	257000	N/A	Yes	Yes
		243 (60.0)	≥ 15 (58.8)	159000	N/A		
Vreeburg *et al* [31], 1997	Hematemesis, melena, hematochezia, or blood admixture upon nasogastric aspiration	951 (60.0)	All (Mdn: 71)	1610900	156 (16.4)	Yes	Yes
Czernichow *et al* [32], 2000	Hematemesis and/or melena	2133 (63)	≥ 18 (Mdn: 68)	2926241	N/A	Yes	Yes
Paspatis *et al* [33], 2000	Hematemesis, melena or other clinical or laboratory evidence of blood loss from the upper GI tract	353 (63.5)	≥ 16 (66.2)	220000	41 (12)	Yes	Yes
Tenias Burillo *et al*[34], 2001	All admitted patients with UGIB	779 (62.1)	Adults (63.4)	180996	N/A	Yes	Unclear
Lewis *et al*[62], 2002	ICD-9-CM	N/A	All (N/A)	N/A	N/A	Unclear	Yes
van Leerdam *et al*[63], 2003	Hematemesis, melena, hematochezia, or blood admixture upon nasogastric aspiration	769 (56.0)	All (N/A[6])	1612439	119 (16.0)	Yes	Yes
Targownik *et al* [35], 2006	ICD-9 and ICD-10-CA	142363[4] (N/A)	≥18 (62.0-66.0)	21944828-24324251	N/A	Unclear	No
Theocharis *et al* [36], 2008	Hematemesis, bloody nasogastric aspiration, or melena and clinical/laboratory evidence of acute blood loss from the upper GI tract	489 (74.4)	> 16 (59.4)	300078	48 (9.9)	Yes	Yes
		353 (72.5)	> 16 (66.1)	326794	26 (7.3)		
Kapsoritakis *et al*[37], 2009	All patients hospitalized for acute UGIB	264 (75.4)	≥ 16 (65.5)	228428	21 (7.9)	Yes	Yes
Lanas *et al*[38], 2009	ICD-9-CM	17663[4] (N/A)	All (N/A[6])	3281973 - 3681822	N/A	Unclear	No
		5769[4] (N/A)					
Loperfido *et al* [39], 2009	ICD-9	532 (72.3)	> 15 (61.0)	231914	191 (32.5)	Yes	Yes
		513 (64.3)	> 15 (68.7)	266791	40 (7.4)		
Åhsberg *et al* [40], 2010	ICD-8	138 (75.0)	Adults (Mdn: 69)	151711	N/A	Yes	Unclear
		69 (46.0)	Adults				

			(Mdn: 69)				
	ICD-9	123 (60.0)	Adults (Mdn: 73)	170727			
		95 (45.0)	Adults (Mdn: 76)				
	ICD-10	181 (59.0)	Adults (Mdn: 77)	289560			
		125 (54.0)	Adults (Mdn: 75)				
Button *et al*[41], 2011	ICD-10	22299[5] (54.4)	≥ 18 (64.1)	N/A	N/A	Some	Yes
Langner *et al* [42], 2011	ICD-9-GM	94232[5] (51.4)	All (N/A[6])	N/A	N/A	Unclear	No
Crooks *et al*[43], 2012	ICD-10 (HES) and Read code system (GPRD)	347085	≥ 18 (N/A[6])	N/A	N/A	Unclear	Unclear
Laine *et al*[44], 2012	ICD-9	N/A	All (N/A)	N/A	N/A	Unclear	No
Miyamoto *et al* [45], 2012	Hematemesis and/or melena	2367 (53.7)	All (67.9)	Approximately 16065	N/A	Yes	Unclear
Mungan *et al* [46], 2012	ICD-9/ICD-10	423 (67.4)	Adults (57.8)	N/A	28 (6.6)	Yes	Yes
Nahon *et al*[47], 2012	Hematemesis and/or melena and/or acute anemia with blood in the stomach	3203 (66.5)	≥ 18 (Mdn: 64.1)	N/A	317 (9.9)	Yes	No
Sangchan *et al* [48], 2012	ICD-10	77111[5] (69.2)	Adults (58.5)	N/A	N/A	Some	No
Del Piano *et al* [49], 2013	Presenting to the emergency room for NVUGIB	1413 (66.0)	All (53.2)	N/A	77 (5.4)	Yes	No
Hreinsson *et al* [50], 2013a	(1) Passage of bright red blood per rectum or maroon colored without hematemesis and (2) Melena with no bleeding in upper GI endoscopy	131 (49.7)	≥ 18 (Mdn: 68)	151008	N/A	Yes	Yes
Hreinsson *et al* [51], 2013b	(1) Hematemesis or coffee ground vomit; (2) Melena; and (3) Rectal bleeding with confirmed bleeding on upper gastroendoscopy and negative colonoscopy	132 (58.0)	18-105 (Mdn: 71)	N/A	N/A	Yes	Yes
Cavallaro *et al* [45], 2014	ICD-9-CM	23450 (59.5)	All (64.2)	4912438	N/A	Unclear	No
		13800 (47.8)					
Marmo *et al* [53], 2014	Hematemesis, melena or dark, tarry materials on rectal examination	2317 (65.9)	≥ 18 (67.9)	N/A	86 (3.7)	Yes	Yes
O'Byrne *et al* [54], 2014	ICD-10	360 (61.7)	17-100 (66.5)	1200000	73 (20.3)	Yes	Yes
Abougergi *et al* [64], 2015	ICD-9-CM	1266426[4] (54.5)	All (Mdn: 67.0-70.0)	N/A	N/A	Yes	No
Niikura *et al* [55], 2015	ICD-10	30846 (52.0)	≥ 20 (Mdn: 74)	N/A	N/A	Unclear	No
Taha *et al*[56], 2015	ICD-10	869[4] (62.5)	All (Mdn: 63)	258370 -260280	N/A	Unclear	Unclear
Lu *et al*[57], 2018	(1) Hematemesis and/or melena; (2) Drainage of coffee grounds or fresh blood in the gastric tube; (3) Positive FOBT; and (4) Varices, but endoscopy confirmed that bleeding was unrelated	2977 (76.5)	≥ 18 (54.7)	N/A	87 (2.9)	Yes	Yes
Park *et al*[58], 2018	Hematemesis, melena, and hematochezia or a suspicious clinical presentation of UGIB such as syncope, epigastric pain, dyspnea, dizziness, altered mental status, or anemia	1424 (74.1)	≥ 16 (62.7)	N/A	110 (7.7)	Yes	No

Wuerth *et al* [59], 2018	ICD-9-CM	2432088 (55.0)	≥ 18 (N/A[6])	N/A	N/A	Some	No

[1]Age category of patients included in the study, given in years. If not defined in the methods, the age range of included participants is stated. Median age is noted, when mean age is not available. Mdn: median.
[2]Endoscopy, colonoscopy, sigmoidoscopy or any other diagnostic screening methods being used to identify or validate the diagnosis of patients as a standard procedure.
[3]Including bleeding events that occurred while the patient is being hospitalized for another disease. In administrative databases, if patients only have a primary diagnosis of GIB, in-hospital bleeds are assumed to not be included.
[4]Total number of patients across the entire study period is provided. Stratified data for each year is available in full text.
[5]The value reflects the number of hospitalizations, not the number of patients.
[6]Distribution of the number of patients is available for each age group.
ICD: International Classification of Diseases (ICD-8: ICD, Eight Revision; ICD-9: ICD, Ninth Revision; ICD-10: ICD, Tenth Revision; ICD-9-CM: ICD-9, Clinical Modification; ICD-9-CA: ICD-9, Canadian Adaptation; ICD-9-GM: ICD-9, German Modification); FOBT: Fecal occult blood test; GI: Gastrointestinal; ANVUGIB: Acute nonvariceal upper gastrointestinal bleeding; LGIB: Lower gastrointestinal bleeding; NVUGIB: Nonvariceal upper gastrointestinal bleeding; UGIB: Upper gastrointestinal bleeding.



DOI: 10.4240/wjgs.v15.i4.723

Figure 1 Forest plot of upper gastrointestinal bleeding incidence rates. This figure displays incidence rates of upper gastrointestinal bleeding *per* 100000 person-years with 95% confidence intervals (when reported) from studies included in the review that reported this information. *Calculated from the available data (not originally presented in the paper). †NVUGIB. ‡Calculated from hospitalizations (not the number of patients). §Included out-patient bleeds. ¶Included UGIB cases only if primary diagnosis. Estimates were marked as a point without 95%CI, when denominator was missing. CI: Confidence interval; NVUGIB: Non-variceal upper gastrointestinal bleeding; UGIB: Upper gastrointestinal bleeding; USA: United States of America.

inclusion criteria and GIB definition. Among two studies from Italy in 2004, one reported a rate of 84.8 *per* 100000 person-years for UGIB incidence with the inclusion of hospital bleeds based on clinical data [39], while the other reported a rate of 52.4 *per* 100000 person-years for emergency GIB-related admissions from administrative data with a larger sample size[52]. In the US, estimates for UGIB incidence from three administrative database studies, which identified GIB using primary diagnosis codes, ranged from 60 to 110 *per* 100000 person-years across several timeframes between 1989 and 2012 [44,59,64]. Also from the US, a hospital-based study reported higher UGIB incidence at 152.9 *per* 100000 person-years over their 1992–1999 study period, where GIB cases were not limited to primary diagnosis only[62].

UGIB-related mortality

Mortality was reported in six studies; UGIB-related mortality was not reported directly in four and so estimates were calculated from available data[28,37,54,61]. Estimates ranged from 0.88 to 9.75 *per* 100000 person-years (Figure 3). Two studies with large sample sizes reported mortality rates for NVUGIB as 1.1 *per* 100000 person-years using clinical data from Spain[38] and 1.83 *per* 100000 person-years in Canada based on administrative claims[54]; these were lower than most mortality estimates of overall UGIB.

UGIB case-fatality

Case-fatality rates for UGIB were reported in 15 studies with estimates ranging from 0.7% to 4.7% (Figure 4**)**. Case-fatality for NVUGIB ranged between 1.6% and 4.0%, with higher rates from studies that restricted to UGIB as the primary diagnosis[25,35,49]. In four studies, the number of UGIB-related deaths was very low, leading to imprecise estimates[24,26,37,46]. UGIB case-fatality rates varied across regions during 1980–2013, although higher rates were reported in earlier years, particularly in Europe.

Incidence of LGIB

Six studies reported incidence rates for LGIB; estimates ranged between 20.5 and 87.0 *per* 100000 person-years[27,30,40,44,50,52], with the lowest estimate from a US claims database in study years from 1990-1993[30] and the highest from a single hospital-based study from Iceland in 2010[50]. In Scotland, the incidence of LGIB was found to be 27 *per* 100000 person-years based on a study using hospital records for the period 1990–1993[27], while for the same period, a claims-based study from the US reported a rate of 20.5 *per* 100000 person-years[30]. Another US claims database study reported a LGIB incidence rate of 41.8 *per* 100000 person-years for the year 2001[44]. Analysis of administrative data from the Veneto region in Italy (with a population around 5 million), reported an incidence of LGIB in 2001 of 27.3 *per* 100000 person-years[52]. Studies reporting time trends in LGIB incidence found that rates fluctuated across time, with higher rates observed during 2001–2005[44,52]. In a hospital study from Sweden, rates decreased from 55.6 to 43.2 *per* 100000 person-years over a 10-year period starting from 1994[40].

LGIB-related mortality

Three studies reported estimates for LGIB-related mortality[27,38,40]. Using data from 10 hospitals within the Spanish National Health System and covering a population of around 4 million, Lanas *et al* [38] demonstrated that LGIB-related mortality increased from 0.2 to 1.0 *per* 100000 person-years between 1996 and 2005. A single-center hospital based study from Grampian and the Northern Isles in Scotland found LGIB-related mortality to be 1.4 *per* 100000 person-years over a 10-year study period (1994–2004) [27], while over the same time period, an increase in LGIB-related mortality was observed in Sweden from 0.59 to 3.45 *per* 100000 person-years[40].

LGIB case-fatality

Six studies reported LGIB case-fatality rates with estimates ranging from 0.5% to 8.0%[27,30,38,40,50,55]. LGIB case-fatality among patients in Spain fluctuated over 1996–2005, increasing from 2.9% in 1996, peaking at 5.0% in 1999, and declining to 2.6% in 2005[38]. Based on 170727 hospital records in Sweden between January-December 1994, LGIB case-fatality increased from 1.0% to 8.0% over a 10-year study period (1994–2004) albeit based on only 69 LGIB cases[40]. Other reported LGIB case-fatality rates range from 0.5% in a US claims database study on 219 cases between 1990 and 1993[30] to 5.1% from a hospital-based study in Scotland with 252 cases over an overlapping period (1991–1993)[27]. More contemporary LGIB case-fatality rates from Japan and Iceland were reported as 2.5%[54] and 1.2%[50], respectively.

Rebleeding (UGIB/LGIB)

Seven studies reported UGIB rebleeding rates. These ranged from 7.3% to 32.5% with rebleeding rates being generally lower in the more contemporary studies. Five studies reported NVUGIB rebleeding rates ranging from 2.9% to 20.3%. Rebleeding rates for LGIB were reported in two studies covering the 1990s; the rates were 13.5%[27] and 6.7%[30].

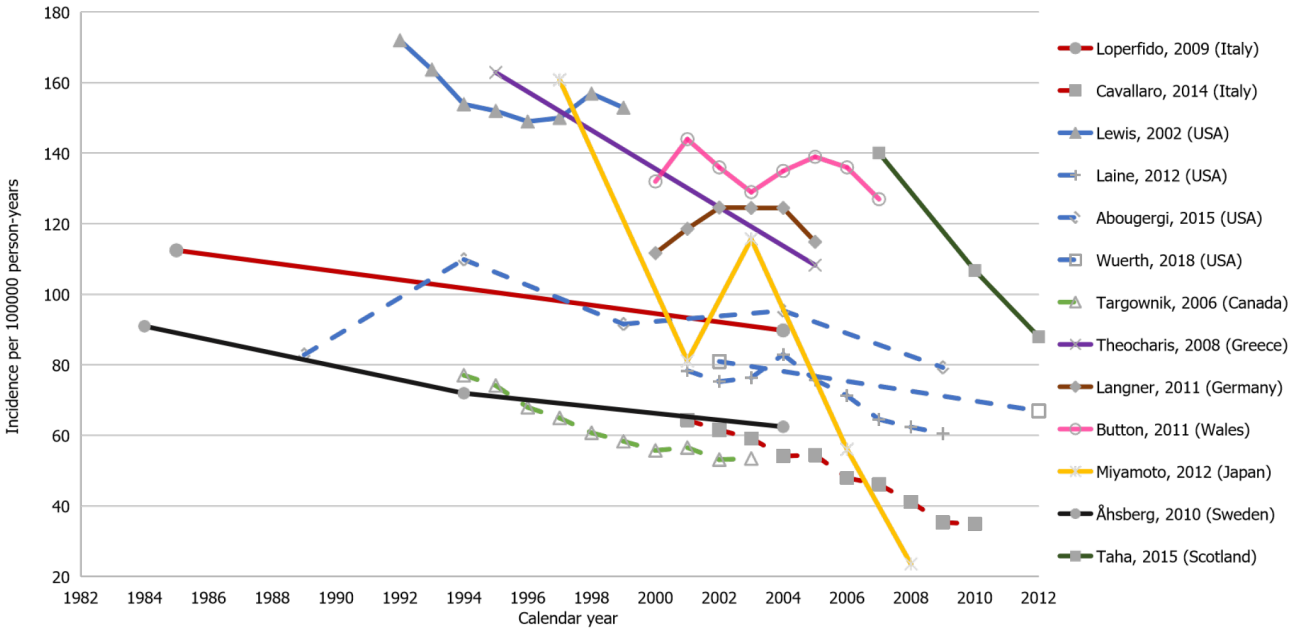


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Figure 2 Temporal trends of upper gastrointestinal bleeding incidence. This figure displays data from studies that reported on incidence rates of upper gastrointestinal bleeding *per* 100000 person-years over time from studies included in the review that reported this information. Note: Studies that include UGIB data only as primary diagnosis are indicated with dashed lines. UGIB: Upper gastrointestinal bleeding. USA: United States of America.

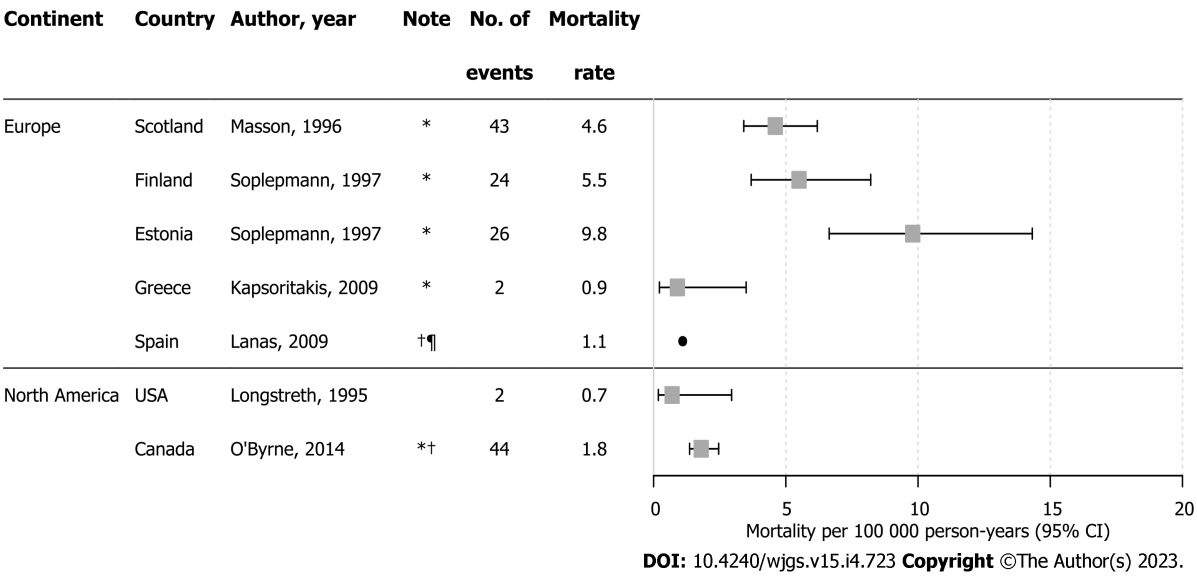

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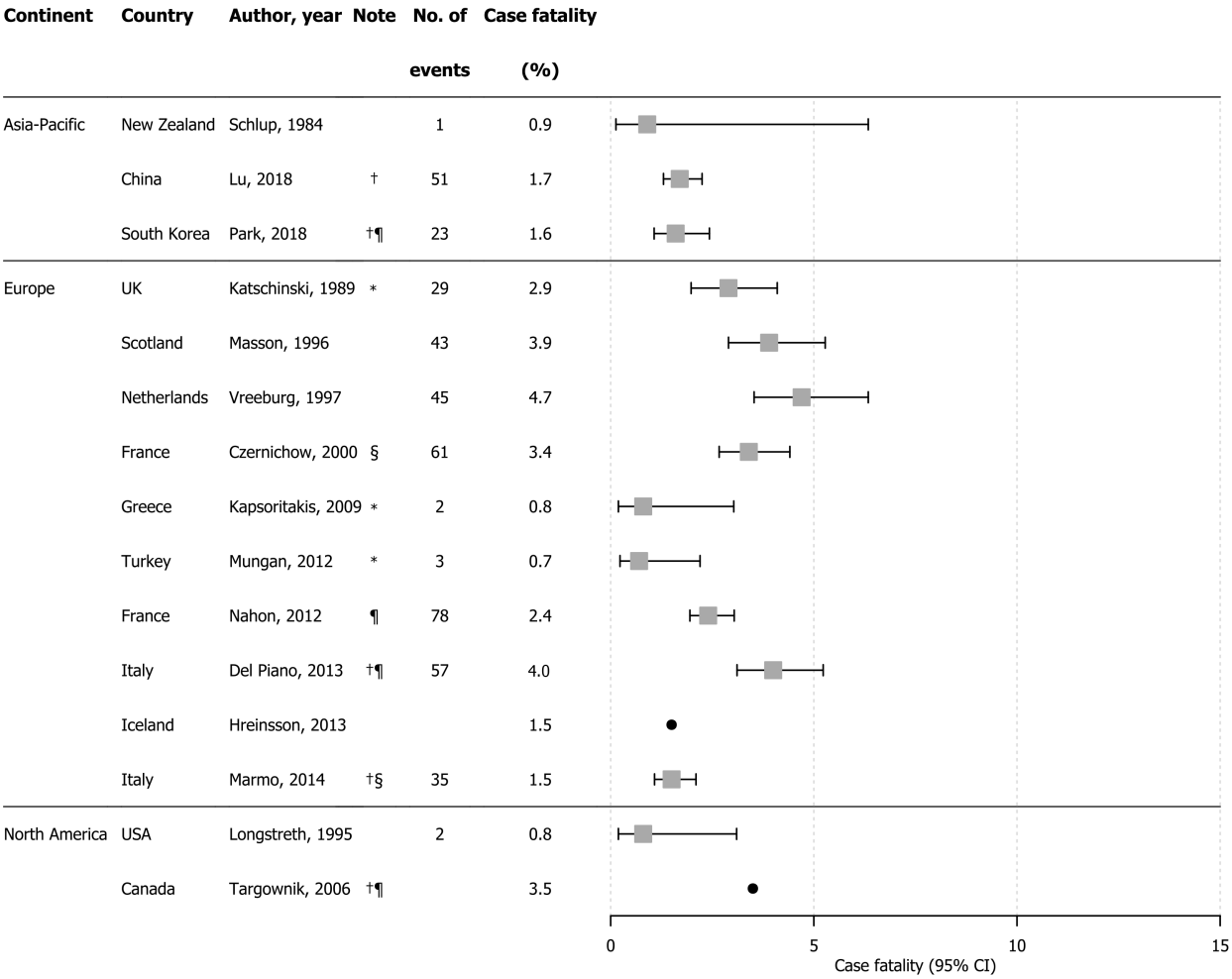
Figure 3 Forest plot of upper gastrointestinal bleeding mortality rates. This figure displays upper gastrointestinal bleeding mortality rates *per* 100000 person-years with 95% confidence intervals (when reported) from studies included in the review that reported this information. Estimates were marked as a point without 95%CI, when denominator was missing. *Calculated from the available data (not originally presented in the paper). †NVUGIB. ‡Calculated from hospitalizations (not the number of patients). §Included out-patient bleeds. ¶Included UGIB cases only if primary diagnosis. CI: Confidence interval; NVUGIB: Non-variceal upper gastrointestinal bleeding; UGIB: Upper gastrointestinal bleeding; USA: United States of America.

Risk of bias and methodological reporting guideline assessment

Two main potential areas of bias were identified: UGIB/LGIB definition and inadequate information on how missing data were handled (Supplementary Figure 2, Supplementary Table 5). Based on the assessment of individual studies, 2 out of 19 studies that used standardized classification methods failed to provide UGIB/LGIB codes, despite adopting ICD criteria for classification[55,56]. Only 12 out of 41 studies described how they handled missing data – by excluding individuals with missing data in their records. The low risk of bias domains were the identification of target population and the appropriate sampling of patients. Thirty-nine percent of studies reported adequate information on the inclusion of patients in the study, and 42% presented thorough descriptive data on patient characteristics



DOI: 10.4240/wjgs.v15.i4.723

Figure 4 Forest plot of upper gastrointestinal bleeding case-fatality rates. This figure displays case-fatality rates of upper gastrointestinal bleeding, with 95% confidence intervals (when reported) from studies included in the review that reported this information. Estimates were marked as a point without 95%CI, when denominator was missing. *Calculated from the available data (not originally presented in the paper). †NVUGIB. ‡Calculated from hospitalizations (not the number of patients). §Included out-patient bleeds. ¶Included UGIB cases only if primary diagnosis. CI: Confidence interval; NVUGIB: Non-variceal upper gastrointestinal bleeding; UGIB: Upper gastrointestinal bleeding; USA: United States of America.

(Supplementary Table 6). Only 29% of studies described the generalizability of their results.

DISCUSSION

Gastrointestinal bleeding is an important clinical event associated with high patient burden and major resource implications for healthcare systems. Our review provides broad insights into the long-term worldwide epidemiology of GIB in the general adult population. Incidence, mortality, and case-fatality rates for GIB were found to vary substantially across and within countries. For UGIB, estimates ranged from 15.0 *per* 100000 to 172.0 *per* 100000 person-years for incidence (with a decline seen over time), 0.9 per 100000 to 9.8 *per* 100000 person-years for UGIB-related mortality, 0.7% to 4.8% for case-fatality, and 7.3%–32.5% for rebleeding. For LGIB, estimates ranged from 20.5 *per* 100000 person-years to 87.0 *per* 100000 person-years for incidence, 0.2 *per* 100000 person-years to 1.0 *per* 100000 person-years for LGIB-related mortality, 0.5% to 8.0% for case-fatality, and 6.7%–13.5% for rebleeding.

Our results are in line with findings from earlier reports of a decreasing trend of UGIB incidence[15], albeit the data were heterogeneous likely due to methodological differences such as inclusion criteria and the operational definition of GIB. These differences resulted mainly from either restriction to hospital cases or the inclusion of patients where GIB was the sole primary diagnosis. For example, a high UGIB incidence of 143 *per* 100000 person-years was observed in France, where 16% of the 2133 included UGIB cases were managed out of the hospital setting[32], compared with a much lower rate of 49.0 *per* 100000 person-years reported in Italy where patients with GIB as the sole primary diagnosis were included[63]. Incidence rates from studies that restricted UGIB cases to those resulting in a hospital admission may have been underestimated. This is noteworthy because over time, UGIB cases

deemed at low risk have tended to be treated on an outpatient basis[35]. Similarly, in terms of deaths, exclusion of deaths before hospital arrival would likely result in mortality underestimation, although the assumption that severe GIB cases would be admitted to inpatient settings could lead to overestimations of case-fatality. The clinical definition of GIB differed across studies, and those that used clinical markers for UGIB (such as anemia) reported higher incidence rates[32,58]. In other studies where cases with another primary diagnosis were excluded, incidence rates were generally lower, and possibly underestimated. In addition, among administrative database studies, differences in inclusion criteria were observed in the standardized codes *(e.g.*, ICD-10) used to ascertain GIB. Diagnostic differences in GIB have been reported by others[3], and in our risk of bias assessment, a high proportion of studies demonstrated a high risk of classification bias for GIB cases. Aside from differences in methodologies, heterogeneity in GIB epidemiology over our decades long inclusion period could be attributed to changes in both the prevalence of risk factors and clinical practice over time. Changes in social deprivation[27,30,60,65], administration of acid suppressive therapy with proton-pump inhibitors[31,49,63,65], as well as risk inducing medication use such as selective serotonin reuptake inhibitors and non-steroidal anti-inflammatory drugs have all been associated with GIB prevalence in the literature[11,39,40,66,67]; a detailed review of these was beyond the scope of this review. Incomplete information on patient characteristics was a domain of high risk, which makes it difficult to assess differences in clinical markers across studies.

The limited data on LGIB were unsurprising because, relative to UGIB, it is less commonly encountered in clinical practice, and research would understandably be more focused on the latter. Diagnosis is also more challenging for LGIB as illustrated in one study where 25% of undefined cases of hematochezia, originally suspected to be sourced from the lower GI tract, were later confirmed as UGIB [40]. Additionally, most therapeutic advancements did not benefit bleeding sites beyond the duodenum [68,69] and surgical interventions were less effective for LGIB compared to UGIB due to difficulties in bleeding localization[52]. This could limit the exploration on the epidemiology LGIB, as less impact would be expected on the management of the event upon lacking advancements and studies presenting data on LGIB would remain limited. Our review also revealed limited published data on UGIB-related mortality and case-fatality. Where reported, UGIB-related mortality was low, possibly indicative that of UGIB death is more commonly a result of advanced comorbidities rather than an excessive bleed *per se*. Previous studies have shown that while peptic ulcer is the most frequent cause of UGIB in hospital settings, death in UGIB cases more commonly occur due to gastric cancer or esophageal varices[25,26,31,61]. With further research on UGIB-related death, clinical management strategies could be devised more effectively to target the predictors of UGIB incidence, independently from those for mortality.

This review has several strengths. We systematically reviewed the literature on the long-term worldwide epidemiology of GIB across geographies, and we are unaware of any previous study to have done this. Systematic reporting of disease epidemiology across geographical regions – where patients may differ in their characteristics and where differences in clinical management through diagnosis and treatment may occur – is important for identifying factors that could influence estimates of occurrence. We identified areas of differences in study methodology and reporting, applying risk of bias assessment, to explicate variability across studies. In terms of limitations, we only included studies written in English, although this has not been associated with systematic bias in other reviews[70,71]. Some articles published before 1991 may not have been captured as database indexing was suboptimal at this time with low sensitivity of keyword search[72]; however, bibliography of relevant articles and reviews were scanned to minimize information bias. Additionally, all studies on variceal bleeding identified during the search were either small and not population-based, and/or had no epidemiological variables of interest reported, therefore we were unable to describe the epidemiology of variceal bleeding. Lastly, estimates were not pooled due to the limited number of included studies and their study heterogeneity, which could limit the applicability of findings to inform about the real-world epidemiology of GIB.

CONCLUSION

Our systematic literature review describes wide ranging estimates of the long-term epidemiology of GIB, which is likely due to high heterogeneity between studies. Overall, the incidence of UGIB showed a decreasing trend over the years. Epidemiological data were more widely available for UGIB than for LGIB.

ARTICLE HIGHLIGHTS

Research background

Gastrointestinal bleeding (GIB) can be a life-threatening medical event; however, reviews on the overall global epidemiology of the condition are lacking. Previous reviews have instead covered risk factors or

prediction scores for GIB or have described the epidemiology of GIB arising from specific etiologies.

Research motivation

No overarching review on the broad and long-term worldwide epidemiology of GIB currently exists. A systematic review would be highly informative for future research in the field to provide a robust overview of GIB incidence, mortality and case-fatality.

Research objectives

The objective was to perform a systematic review of the long-term global epidemiology of both upper GIB (UGIB) and lower GIB (LGIB), covering incidence, mortality and case-fatality of the condition. Such population-based estimates would enable trends over time, and by geography, to be observed, which could have been influenced by changing medical practices, and it would also help identify areas where data are plentiful or lacking.

Research methods

A search strategy using relevant keywords was conducted using EMBASE® and MEDLINE from 1 January 1965 to 17 September 2019. Conference abstracts, editorials, letters, notes, and short surveys were excluded, as well as randomized controlled trials and interventional studies (as these are performed among selected individuals, and do not enable population-based epidemiological estimates to be calculated). Two authors undertook the screening of titles, abstracts and full-texts of papers. Data on the epidemiological variables of interest were extracted.

Research results

Thirty-six studies were included. The main findings were that the incidence of UGIB ranged from 15.0 to 172.0/100000 person-years and the incidence of LGIB ranged from 20.5 to 87.0/100000 person-years, although data for LGIB were more limited than for UGIB. Temporal trends were described in 13 studies and showed an overall decline in upper GIB incidence over time. UGIB mortality rates ranged from 0.9 to 9.8/100000 person-years, and from 0.8 to 3.5/100000 person-years for LGIB; case-fatality rate ranged from 0.7 to 4.8% for UGIB and 0.5 to 8.0% for LGIB.

Research conclusions

Substantial variation exists in estimates of GIB epidemiology worldwide, likely due to high heterogeneity between studies, highlighting a lack of consistency in GIB definitions. As data on LGIB epidemiology were sparse, this area should be further explored in future research.

Research perspectives

The proposed direction of future research would be to obtain contemporary estimates of UGIB and, especially LGIB epidemiology from large, high quality, population-based studies with good case ascertainment and case validation.

ACKNOWLEDGEMENTS

We thank Susan Bromley from EpiMed Communications (Abingdon, UK) for English language editing assistance, funded by Bayer AG.

FOOTNOTES

Author contributions: Saydam SS and Vora P designed the research study; Saydam SS, Molnar M and Vora P performed the research; Saydam SS analyzed the data and wrote the manuscript; All authors have read and approved the final manuscript.

Conflict-of-interest statement: Saydam SS and Vora P are employees of Bayer AG. Molnar M was an employee of Bayer AG at the time the study was carried out.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Country/Territory of origin: Germany

ORCID number: Şiir Su Saydam 0000-0002-0554-8361; Megan Molnar 0000-0003-4937-2887; Pareen Vora 0000-0002-5822-2453.

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

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World J Gastrointest Surg 2023 April 27; 15(4): 740-744

DOI: 10.4240/wjgs.v15.i4.740

ISSN 1948-9366 (online)

CASE REPORT

Idiopathic colopleural fistula presenting with lung abscess and refractory empyema: A case report

Chun-Li Wang, Kung-Chuan Cheng

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: Chen Y, China; Meena DS, India

Received: January 7, 2023
Peer-review started: January 7, 2023
First decision: January 21, 2023
Revised: January 27, 2023
Accepted: March 21, 2023
Article in press: March 21, 2023
Published online: April 27, 2023

Chun-Li Wang, Kung-Chuan Cheng, Division of Colorectal Surgery, Department of Surgery, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung 833, Taiwan

Corresponding author: Kung-Chuan Cheng, MD, Attending Doctor, Division of Colorectal Surgery, Department of Surgery, Kaohsiung Chang Gung Memorial Hospital, No. 123 Dapi Road, Niaosong District, Kaohsiung 833, Taiwan. topguncheng@gmail.com

Abstract

BACKGROUND

Colopleural fistula is a rare condition, and only a limited number of cases have been reported. Here, we report a case of idiopathic colopleural fistula in an adult without any known predisposing factors. The patient presented with a lung abscess and refractory empyema and was successfully treated with surgical resection.

CASE SUMMARY

A 47-year-old man with a history of lung tuberculosis, which had been completely cured 4 years ago, presented to our emergency department with a productive cough and fever for 3 d. Tracing his history, he had undergone left lower lobe segmentectomy of the left lung due to lung abscess one year ago at another hospital. However, he developed refractory empyema postoperatively despite surgical intervention including decortication and flap reconstruction. After admission, we reviewed his previous medical images and noted a fistula tract between the left pleural cavity and splenic flexure. In addition, according to his medical records, bacterial culture of the thoracic drainage showed growth of *Escherichia coli* and *Bacteroides fragilis*. Our lower gastrointestinal series and colonoscopy confirmed the diagnosis of colopleural fistula. The patient underwent a left hemicolectomy, splenectomy, and distal pancreatectomy, and the diaphragm was repaired under our care. No further empyema recurrence was noted during follow-up.

CONCLUSION

Indicative signs of colopleural fistula include refractory empyema accompanied by the growth of colonic flora in the pleural fluid.

Key Words: Colopleural fistula; Lung abscess; Empyema; Colonic flora; Case report

Core Tip: Colopleural fistula is very rare and challenging in diagnosis. We reported a case of idiopathic colopleural fistula in an adult who presented with refractory empyema, and discussed several clinical findings which may help caregivers to diagnose.

Citation: Wang CL, Cheng KC. Idiopathic colopleural fistula presenting with lung abscess and refractory empyema: A case report. *World J Gastrointest Surg* 2023; 15(4): 740-744
URL: https://www.wjgnet.com/1948-9366/full/v15/i4/740.htm
DOI: https://dx.doi.org/10.4240/wjgs.v15.i4.740

INTRODUCTION

Colopleural fistula is a rare condition and its diagnosis is often challenging. Only a limited number of cases of colopleural fistula have been reported, and these were related to Crohn's disease, malignancy, colon diverticulum, or abdominal or thoracic surgery[1-4]. Herein, we report a rare case of idiopathic colopleural fistula in a patient without any known predisposing factors. The patient presented with a lung abscess and refractory empyema and was successfully treated with surgical resection.

CASE PRESENTATION

Chief complaints

A 47-year-old man presented to our emergency department with a productive cough and fever for 3 d.

History of present illness

Tracing his medical history, the productive cough and fever had developed one year ago. The patient initially visited another hospital where chest radiography and computed tomography (CT) revealed a cavitating mass in the left lower lobe of the left lung. The tentative diagnosis was lung abscess; however, the possibility of malignancy could not be excluded, and segmentectomy was performed. However, he developed empyema postoperatively, and several surgical interventions, including decortication, latissimus dorsi flap reconstruction, and intercostal muscle flap reconstruction, were performed, but were unsuccessful at treating the empyema. Bacterial culture of the thoracic drainage showed the growth of *Escherichia coli* and *Bacteroides fragilis*.

History of past illness

The patient has the history of lung tuberculosis, which had been completely cured 4 years ago.

Personal and family history

No relevant personal or family history was recorded.

Physical examination

His vital signs were stable on arrival, and physical examinations showed negative findings except mild crackles on left lung field.

Laboratory examinations

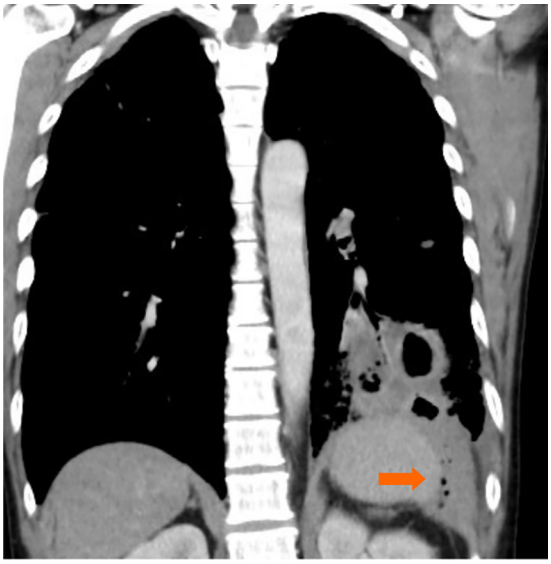
Laboratory data revealed slightly leukocytosis and elevated C-reactive protein, and otherwise were within normal range.

Imaging examinations

After admission to our hospital, we re-evaluated the patient's initial chest CT, and a fistula tract was noted between the left pleural cavity and the abdomen (Figure 1). A lower gastrointestinal series with water-soluble contrast agents confirmed the diagnosis of a colopleural fistula (Figure 2). Colonoscopy revealed negative findings, except for the orifice of the fistula at the splenic flexure (Figure 3).

FINAL DIAGNOSIS

Idiopathic colopleural fistula was diagnosed on this patient.



DOI: 10.4240/wjgs.v15.i4.740

Figure 1 Initial chest computed tomography of the patient showing a fistula tract between the lung abscess and the abdominal cavity (arrow).

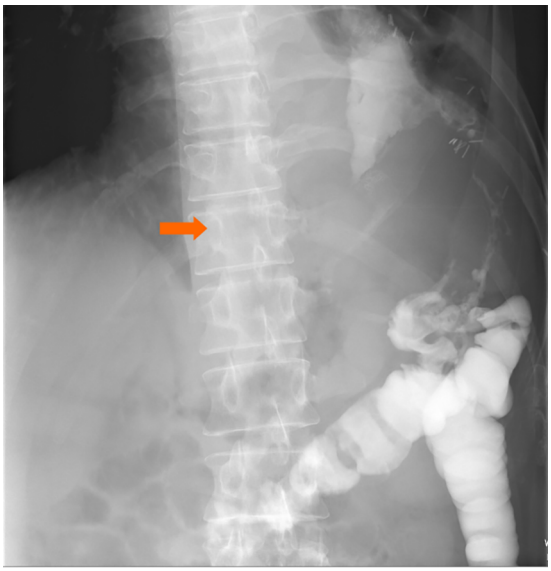


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Figure 2 Lower gastrointestinal series with water-soluble contrast confirming the existence of colopleural fistula (arrow).

TREATMENT

We performed surgery and found dense adhesions between the splenic flexure, spleen, distal pancreas, and stomach. A diaphragm fistula, including a piece of Gerota's fascia with an internal opening was found at the splenic flexure. The patient underwent a left hemicolectomy, splenectomy, and distal pancreatectomy, and the diaphragm was repaired.

OUTCOME AND FOLLOW-UP

No further empyema recurrence was noted during follow-up.

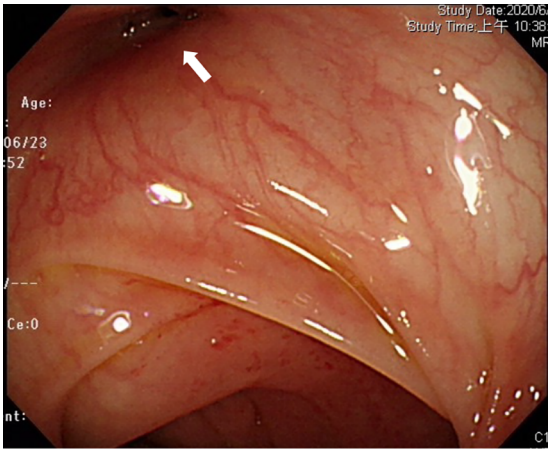

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Figure 3 Fistula opening on colonoscopy (arrow).

DISCUSSION

Colopleural fistula with secondary empyema is an exceptionally rare condition; the rarity delays the diagnosis. Less than 20 cases of colopleural fistula have been reported in the literature. Most cases reported in the past were related to malignancies, Crohn's disease, or iatrogenic causes[1,2,4]. Here, we report a case of colopleural fistula with an initial presentation of a cystic lesion of the lung that caused refractory empyema after surgery. The patient had no history of abdominal/thoracic surgery, and other risk factors, including malignancy, colonic diverticula, or Crohn's disease, were excluded after clinical investigations. To our knowledge, this is the first reported case of idiopathic colopleural fistula.

According to the previously reported cases, diagnosing a colopleural fistula is challenging. The diagnosis was usually established by feculent output from chest drains[1,2,4,5], or by medical images directly revealing the fistula tract[3]. Treatment outcomes were satisfactory. Most studies reported surgical resection for the infected site of the colon, and Hayashi *et al*[5] reported cases treated successfully by conservative treatment after diverting colostomy was performed.

In addition to direct medical imaging findings, some clinical signs or findings may raise suspicion for a colopleural fistula diagnosis. Ibrahim *et al*[6] reported the Sister Leena sign, a direct relationship between the amount of pleural fluid drained and the amount of oral intake. We could not confirm this sign in this case, as we have no records regarding oral intake in this patient. Another finding that may raise suspicion of a colopleural fistula is the growth of unusual flora in the pleural fluid. In this case, the pleural fluid culture grew *Escherichia coli* and *Bacteroides fragilis*, rare organisms in the thoracic cavity but very common in the gastrointestinal tract. Imaging studies, including a lower gastrointestinal series with contrast, colonoscopy, or CT, may help confirm the diagnosis.

There is no established standard management for colopleural fistulas; however, most studies have reported surgical treatment. We performed resections, including left hemicolectomy, splenectomy, and distal pancreatectomy, and repaired the diaphragm in this patient. The patient recovered well without postoperative complications, and no recurrence of empyema was observed during the follow-up.

CONCLUSION

Coloplerual fistula is a rare condition, and its diagnosis is often challenging. Signs that may indicate a colopleural fistula include refractory empyema accompanied by colonic flora growth in the pleural fluid.

FOOTNOTES

Author contributions: Wang CL wrote the original draft; Cheng KC prepared the figures, edited the main text, and supervised the study. Both authors reviewed the manuscript.

Informed consent statement: We obtained the patient's written informed consent to disclose his case. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understand that his identity will be concealed.

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

CARE Checklist (2016) statement: This case report complies with the CARE Checklist (2016).

Country/Territory of origin: Taiwan

ORCID number: Kung-Chuan Cheng 0000-0002-8608-7156.

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

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