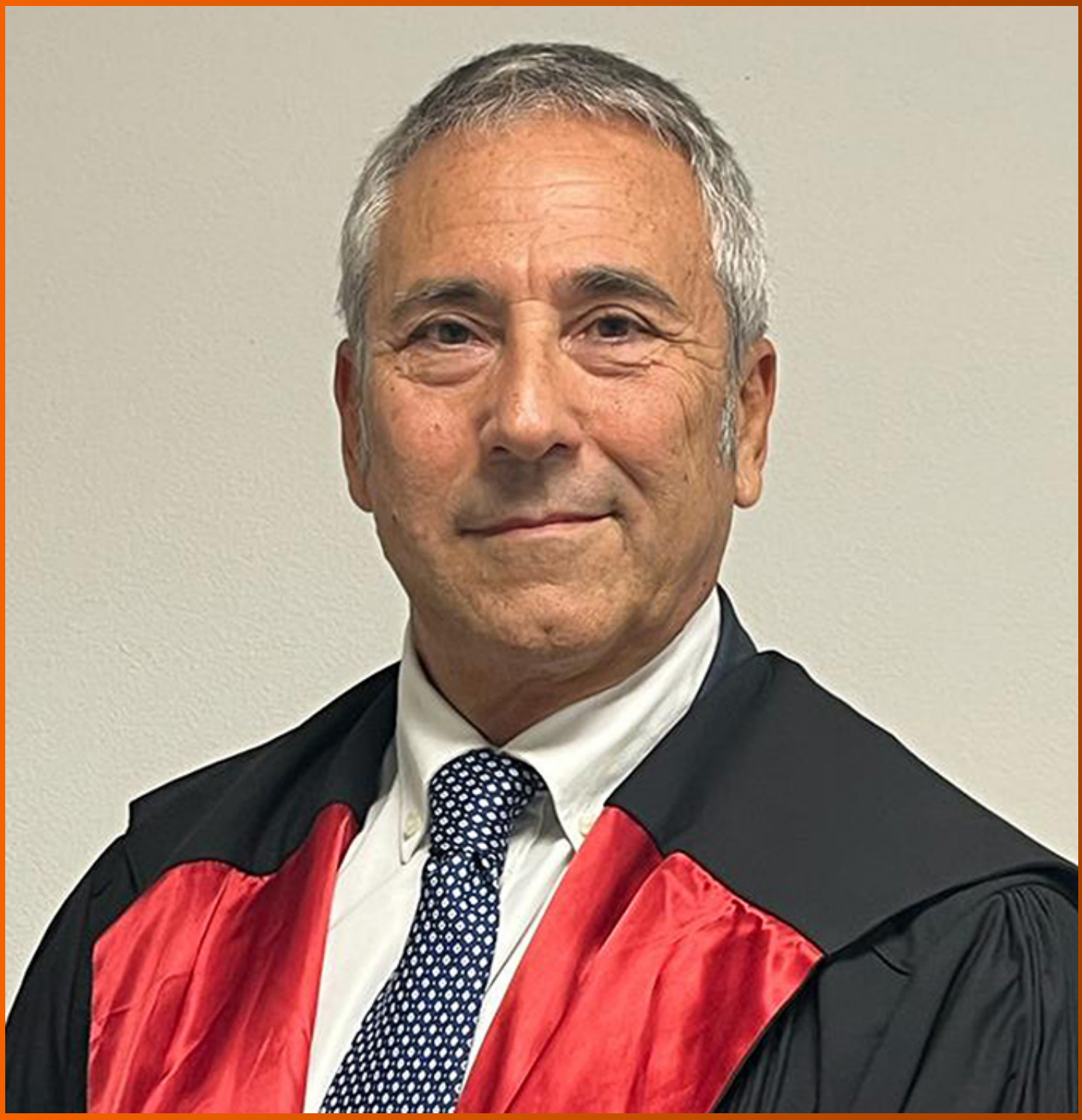
ISSN 1948-9366 (online)

World Journal of

Gastrointestinal Surgery

World J Gastrointest Surg 2024 January 27; 16(1): 1-259



Published by Baishideng Publishing Group Inc

World Journal of Gastrointestinal Surgery

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AIMS AND SCOPE

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

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

INDEXING/ABSTRACTING

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

RESPONSIBLE EDITORS FOR THIS ISSUE

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

POLICY OF CO-AUTHORS

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

PUBLICATION DATE
January 27, 2024

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World J Gastrointest Surg 2024 January 27; 16(1): 1-5

DOI: 10.4240/wjgs.v16.i1.1

ISSN 1948-9366 (online)

EDITORIAL

Novel prognostic factors after radical resection of hepatocellular carcinoma: Updating an old issue

Lapo Bencini

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: Farid K, Egypt; Wang SM, China

Received: October 29, 2023
Peer-review started: October 29, 2023
First decision: December 12, 2023
Revised: December 12, 2023
Accepted: January 8, 2024
Article in press: January 8, 2024
Published online: January 27, 2024

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Abstract

In this editorial, I comment on the article by Li *et al* published in the recent issue of the *World Journal of Gastrointestinal Surgery* in 2023, investigating the role of some novel prognostic factors for early survival after radical resection of liver cancer. Liver cancer is an important burden among Asian and Western populations, despite recent advances in both medicine (from virus eradication to systemic target therapies) and surgery. However, survival after proven radical surgery remains poor, with recurrences being the rule. Many prognostic scores have been developed and validated to select those patients who will best benefit from radical liver surgery, although the final general and oncological outcomes continue to be highly jeopardized. Unfortunately, no single biomarker can resolve all these issues for hepatocellular carcinoma, and it remains to be proven whether some of them main-tain predictive power in the long-term follow-up. In the ongoing era of "preci-sion" medicine, the novel prognostic markers, including immune inflammatory and nutritional indexes could be of great help in better stratify surgical candi-dates.

Key Words: Hepatocellular carcinoma; Liver cancer resection; Liver surgery; Prognostic factors; Immune index; Nutritional index

Core Tip: Survival after radical surgery for liver cancer remain poor, with important perioperative complications and many organ recurrences. Prognostic scores have been developed and validated to select those patients who will best benefit from radical liver surgery, although the final general and oncological outcomes continue to be highly jeopardized. Some novel prognostic markers, including immune inflammatory and nutritional indexes could be of great help in better stratify surgical candidates.

Citation: Bencini L. Novel prognostic factors after radical resection of hepatocellular carcinoma: Updating an old issue. *World J Gastrointest Surg* 2024; 16(1): 1-5
URL: https://www.wjgnet.com/1948-9366/full/v16/i1/1.htm
DOI: https://dx.doi.org/10.4240/wjgs.v16.i1.1

INTRODUCTION

Liver cancer represents a leading cause of cancer death worldwide, with an overall percentage of almost 5%, second only to colonic and lung cancers[1]. Nevertheless, there are some important geographic differences in the epidemiologic features of liver cancer, mainly related to the wide variation in exposure to different risk factors for chronic hepatitis, such as viral infections, alcohol consumption, obesity, diabetes, and toxins[2,3]. However, if there is a trend toward a reduction in some of these factors (*i.e.*, mass vaccination, control of diabetes with metformin, reduction in alcohol intake, aspirin and statin intake)[4], there are others expected to increase, such as obesity in Western and developing countries, leading to a general trend toward a global burden to increase by 55% by 2040[1,5].

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer because it includes up to 85% of cases, with a disappointing prognosis and long-term survivorship, despite a multimodal, aggressive, medical/surgical approach[6].

The state of prognostic factors in surgically resected patients is one of the hot topics when dealing with primary liver cancer (HCC) because most of them have a prolonged natural history due to recent improvements in both medical and surgical therapies. However, for such patients, surgery can be harmful, while in liver, recurrences are frequent, and survival is poor.

Many prognostic scores have been developed and validated to select those patients who will best benefit from radical liver surgery[7], although the final general and oncological outcomes continue to be highly jeopardized. Unfortunately, no single biomarker can resolve all these issues for HCC, and it remains to be proven whether some of them maintain predictive power in the long-term follow-up. In the ongoing era of "precision" medicine, the novel prognostic markers, including immune inflammatory and nutritional indexes could be of great help in better stratify surgical candidates.

For HCC, the most commonly reported scoring and staging systems include the Child-Pugh score, the ALBI (Albumine/Bilirubine) score, the Model for End-Stage Liver Disease (MELD) score, the Barcellona Clinic Liver Cancer (BCLC, updated 2022), and the Japanese HCC Score. Despite peculiar application in specific contexts (*i.e.*, transplant candidates or Japanese), a panel of experts recommends the use of BCLC to drive the management of HCC, with the Child-Pugh score to assess liver function, although the ALBI score should be implemented in future studies[6].

Among the proposed algorithms, surgery (including liver resection and transplantation) remains one of the main options for fit patients, suffering from a mild burden of cancer and good liver function[7]. The 5-year survival after radical resection is approximately 70%, with 80% recurrence[8,9] and a perioperative mortality rate below 5%, even in cirrhotic patients[10]. Moreover, surgery remains superior to other local therapies, such as transarterial chemoembolization (TACE) or radiation or systemic therapy, even in the case of multiple resectable nodules with some vascular involvement[11]. Indications for surgery are reported in the European Association for the Study of the Liver recommendations[12].

Despite the therapeutic option chosen, it would be essential to select those patients who may better benefit from the medical proposal, identifying some clinical or molecular characteristics that are able to influence the treatment response and the natural history of disease. Tumor burden and spread (including the number and dimension of the lesion and the presence of extrahepatic disease), together with the assessment of liver function, are grossly employed but are not able to obtain a deeper stratification of patients in similar BCLC classes[4,7].

The use of the old biomarkers alpha fetoprotein (AFP), ALBI and Child-Pugh score are supported by robust literature evidence, but some recent molecular signatures have been studied to define interpatient heterogeneity. A very promising association of atezolizumab plus bevacizumab is the object of the IMBrave phase 3 trial, identifying gene signatures for T-cell and myeloid inflammation that were correlated with prognosis[4,13,14]. According to these findings, combination therapy with immune checkpoint inhibitors (ICIs) could become the standard of care for advanced HCC.

Several other inflammatory markers, including the neutrophil-to-lymphocyte ratio and the C-reactive/AFP-based CRAFITY score, may play a role in the ongoing course of immune-oncology[15-18]. Interestingly, immunotherapy also seems to be promising in both neoadjuvant and adjuvant settings, where sorafenib failed to show survival advantages[19-21].

In nonalcoholic fatty liver disease, the tumor immune microenvironment is impaired, mainly due to CD4+ T cells, which alter the efficacy of ICI therapies, as proven by the reduced response (27% *vs* 35%) in this subset of patients when considering the results of the IMBrave 150 trial)[10,14]. These considerations could introduce the concept of "personalized" medicine.

From an ideal point of view, we could find some novel biomarkers that are able to achieve early diagnosis and surveillance for recurrence and to drive treatment choice and prognosis, mainly permitting the selection of patients with the best balance between harm and outcome. At the state of the art, no single biomarker can show all these requisites and is merely utopistic that it will happen further. It is more likely to identify several biomarkers or a mixture of them to be targeted in different contexts with different purposes.

Piñero published a very comprehensive review of the well-known and novel biomarkers for HCC, although they concluded that AFP still remains the most performant in predicting surgical outcomes[22].

Without a well-codified biologically based predictive biomarker, the surgical candidates, according to the BCLC algorithm, include a multitude of patients, with a wide range of long-term outcomes, while most of them are expected to develop early recurrences (within one year). A second challenge is that even those patients successfully operated on maintain a poor long-term prognosis, not only related to recurrence (*i.e.*, liver failure or distant spread).

To address some of these challenges, Li *et al*[23] reported some correlations between the systemic immune inflammatory index (SII) and geriatric nutritional risk index (GNRI) and HCC operation prognosis (radical resection). The assessment of the immune/inflammatory response before surgery was recently developed[24,25], together with the nutritional status in older people, and the study raises some interesting issues[26].

The study was retrospective and included data from 100 Chinese HCC patients. The SII was calculated using a previously published formula based on neutrophil, platelet, and lymphocyte counts, while the GNRI originated from albumin and the ratio between actual weight/ideal weight. The Authors investigated the predictive efficacy of the SII and GNRI in radically resected HCC patients using receiver operating characteristic curves, and the relationships between these indexes and survival using Kaplan–Meier or Cox regression.

After 1 year of follow-up, 24 patients died, and 76 survived. According to the proper statistical calculations, the main results were that the SII and GNRI combination was higher in predicting outcome than the SII or GNRI alone, and the SII was higher than the GNRI. Moreover, the proportion of advanced tumors, according to the TNM stage, was higher in patients with SII > 309.14. Interestingly, older patients (> 70 years) had lower GNRI scores.

The main finding of this study was that the 1-year survival rate was lower in those patients who had a preoperative SII > 309.14 and GNRI ≤ 98, both of which were identified as independent for survival by Cox regression analysis. In detail, impaired SSI reduced the chance of being alive ten times and GNRI 4 times after one year of follow-up.

The results of this study support that in a subgroup of older malnourished patients and patients with activated abnormal inflammatory and immune responses, the benefits of radical surgery for HCC should be carefully balanced with risks. In addition, when considering the proportion of "patients at risk" in this cohort, almost half of them (47%) were within the cutoff for the impaired inflammatory/immune response group, and 20% could be considered "malnourished", highlighting the clinical importance of those issues.

However, it remains to be proven whether these novel prognostic tools maintain predictive power in the long-term follow-up, even with patients retreated with alternative locoregional or systemic therapies that can prolong survival. Further similar studies are also needed for prospective validation of the GNRI index in older or frail patients and its relationship with survival. In other words, the present study excluded those patients who died in the perioperative period, while a correlation with nutritional status could be advocated. Finally, the definition of survival reduction could be integrated with the incidence of liver recurrences, which best predict the treatment outcomes in the early period.

The importance of the tumor microenvironment in driving its progression and invasion has been largely studied[27]. From a perspective point of view, the authors of the present study[23] hypothesize that the SII is an efficient inflammatory immune index reflecting immune function and inflammatory responses. In brief, an increase in the SII indicates an increase in platelets and neutrophils and a decrease in lymphocytes, suggesting an enhanced inflammatory response with weak immune functioning. On the other hand, disease-related malnutrition, caused by both reduced nutritional intake and high tumor metabolism, correlates to the incidence of perioperative complications and, definitely, to survival[28,29]. These explanations are very interesting and support the theoretical background of Lin and coworkers' findings[23].

Nevertheless, due to a scarce source of well-conducted, liver resection-addressed papers, a word of caution should be maintained to decide which of the immune/nutritional indexes are to be included in the final decision of resect/not resect patients suffering from HCC.

CLINICAL IMPLICATIONS

Liver surgery for HCC is still gravated by perioperative complications, especially in older patients, and in those with uneventful recovery early (within one year), recurrence and survival are not completely satisfactory. Two issues should be balanced in this context. First, in Asian and Western countries, the population is aging, with older patients being at greater risk for surgical complications and postoperative cirrhotic/healthy liver failure. Second, the oncological/surgical outcome must be matched with alternative, local, less invasive approaches, such as percutaneous ablation or TACE.

CONCLUSION

The decision to candidate older patients affected by HCC to receive resective surgery should be multidisciplinary. Several preoperative factors should be considered, including comorbidities, anesthesiologic risks, liver function and burden of cancer. In the ongoing era of "precision" medicine, the novel prognostic markers, including nutritional assessment and systemic inflammatory responses, seem promising for stratifying patients with a better prognosis.

FOOTNOTES

Author contributions: Bencini L ideated and completed the whole manuscript.

Conflict-of-interest statement: Lapo Bencini has nothing to disclose.

Country/Territory of origin: Italy

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S-Editor: Lin C
L-Editor: A
P-Editor: Xu ZH

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World J Gastrointest Surg 2024 January 27; 16(1): 6-12

DOI: 10.4240/wjgs.v16.i1.6

ISSN 1948-9366 (online)

EDITORIAL

Prospects in the application of ultrasensitive chromosomal aneuploidy detection in precancerous lesions of gastric cancer

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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): 0
Grade E (Poor): 0

P-Reviewer: Kotelevets SM, Russia

Received: November 18, 2023
Peer-review started: November 18, 2023
First decision: December 6, 2023
Revised: December 11, 2023
Accepted: December 26, 2023
Article in press: December 26, 2023
Published online: January 27, 2024

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Abstract

Gastric cancer (GC) is a prevalent malignant tumor within the digestive system, with over 40% of new cases and deaths related to GC globally occurring in China. Despite advancements in treatment modalities, such as surgery supplemented by adjuvant radiotherapy or chemotherapeutic agents, the prognosis for GC remains poor. New targeted therapies and immunotherapies are currently under investigation, but no significant breakthroughs have been achieved. Studies have indicated that GC is a heterogeneous disease, encompassing multiple subtypes with distinct biological characteristics and roles. Consequently, personalized treatment based on clinical features, pathologic typing, and molecular typing is crucial for the diagnosis and management of precancerous lesions of gastric cancer (PLGC). Current research has categorized GC into four subtypes: Epstein-Barr virus-positive, microsatellite instability, genome stability, and chromosome instability (CIN). Technologies such as multi-omics analysis and gene sequencing are being employed to identify more suitable novel testing methods in these areas. Among these, ultrasensitive chromosomal aneuploidy detection (UCAD) can detect CIN at a genome-wide level in subjects using low-depth whole genome sequencing technology, in conjunction with bioinformatics analysis, to achieve qualitative and quantitative detection of chromosomal stability. This editorial reviews recent research advancements in UCAD technology for the diagnosis and management of PLGC.

Key Words: Gastric cancer; Precancerous lesions of gastric cancer; Molecular typing; Ultrasensitive chromosomal aneuploidy detection; Adjuvant therapy; Application prospects

Core Tip: The purpose of this editorial is to provide an overview of the current diagnostic and therapeutic guidelines for gastric precancerous lesions, and to explore the potential clinical application of ultrasensitive chromosomal aneuploidy detection in the field of gastric cancer prevention and control. By doing so, this article aims to advance future research in this area.

Citation: Qian ST, Xie FF, Zhao HY, Liu QS, Cai DL. Prospects in the application of ultrasensitive chromosomal aneuploidy detection in precancerous lesions of gastric cancer. *World J Gastrointest Surg* 2024; 16(1): 6-12
URL: https://www.wjgnet.com/1948-9366/full/v16/i1/6.htm
DOI: https://dx.doi.org/10.4240/wjgs.v16.i1.6

INTRODUCTION

Gastric cancer (GC) is the third leading cause of cancer-related deaths globally, with the highest incidence particularly in East Asia, Central, and Eastern Europe[1]. The number of incidences of GC will likely increase in the future due to higher socioeconomic status and aging populations[2]. In recent times, the prevalence of pan-cancer screening and gastroscopy has led to early identification and treatment of a growing number of patients in the initial (gastric pre-cancer) phase. The use of endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) has significantly enhanced patient survival. However, the majority of cases are still diagnosed at an advanced stage, resulting in the majority of patients succumbing to GC[3]. Despite the advancements in medical technology, a significant number of patients are reluctant to undergo endoscopy. Thus, researchers are still actively investigating the stages of precancerous lesions of gastric cancer (PLGC) and searching for more expedited and streamlined diagnostic approaches. These remain pressing issues in current PLGC research.

Due to the subtle symptoms of GC, the condition is typically discovered at an advanced stage in patients who seek medical attention, leading to higher mortality rates and a poorer prognosis. Advancements in next-generation sequencing and other genomic technologies have spurred new research into the molecular characteristics of GC[4]. Gene mutations, chromosomal aberrations, differential gene expression, and epigenetic alterations are some of the genetic and epigenetic factors that influence the pathogenesis of GC. Thus, The Cancer Genome Atlas (TCGA) network proposes a four-subtype classification scheme for GC based on the molecular biology of potential tumors for each subtype, including Epstein-Barr virus (EBV)-positive, microsatellite instability (MSI), genome stability (GS) type, and chromosome instability (CIN) type [5]. One of the most frequent genetic alterations is CIN, often referred to as chromosomal copy number aberration (CNA). The ultrasensitive chromosomal aneuploidy detection (UCAD) technology relies on low-coverage whole-genome sequencing (LC-WGS) to diagnose or predict a patient's tumor risk by identifying chromosomal CNA in a sample.

The purpose of this editorial is to offer an updated overview of the established diagnostic and treatment criteria for gastric precancerous lesions. It covers emerging diagnostic and treatment techniques, and explores the potential for deploying UCAD technology as an early diagnostic tool.

PLGC: EARLY PREVENTION AND CURRENT STATUS IN CLINICAL DIAGNOSIS

At this stage, the clinical consensus of PLGC can be categorized into atrophy (loss of gastric glands), intestinal metaplasia (replacement of gastric epithelium by intestinal epithelium), and dysplasia (intraepithelial neoplasia, including low-grade intraepithelial neoplasia and high-grade intraepithelial neoplasia)[6].

Helicobacter pylori (*H. pylori*) infection, the most common chronic bacterial infection in humans, is the strongest known risk factor for gastric carcinogenesis. Chronic and persistent inflammation resulting from *H. pylori* in the stomach lining may give rise to progressive atrophic gastritis and intestinal metaplasia[7].

H. pylori strains have a cytotoxin-associated gene A (CagA) that encodes a 120-140 kDa CagA protein, an oncoprotein that affects tumor cells. It also contains additional virulence factors, including vacuolating cytotoxin A, duodenal ulcer-promoting gene A protein, outer inflammatory protein A, and gamma-glutamyl transpeptidase. Most individuals infected with *H. pylori* are asymptomatic, yet have an increased risk of developing peptic ulcers or gastric adenocarcinoma[8,9].

In addition to *H. pylori*, age, tobacco and alcohol consumption, high salt intake and a diet low in fruits and vegetables, familial susceptibility, previous gastric surgery, and pernicious anemia are all relevant risk factors. It is clear that control of the above risk factors is an important basis for the prevention of PLGC[10].

Screening for cancer risk factors is a straightforward process; however, precisely identifying at-risk groups for early screening poses a challenge. To mitigate this, it is essential to implement effective strategies that optimize the selection of individuals who are most likely to benefit from early screening. The primary diagnostic method currently used is endoscopic biopsy, with the challenge being the identification of individuals at risk of developing PLGC in the absence of positive signs[11]. It is apparent that endoscopy, as an invasive medical examination, receives limited acceptance from

certain demographics who may also be restricted by underlying diseases and age. The development and implementation of novel early cancer diagnostic tools must adhere to the reliability, reproducibility, and cost control standards set by the World Health Organization. Furthermore, they must prioritize ease of use and patient comfort[12].

Available studies have shown a significant level of heterogeneity in the histopathology and molecular biology of GC. Screening for hallmark molecules of PLGC involves identifying genetic or protein markers that can be used for early diagnosis and prognostic determination. Most of the screened molecules such as oncogenes, intercellular adhesion molecules, growth factors, and certain hormone receptors exhibit deficiencies in sensitivity, specificity, and reliability, with only a few being recognized.

A paper published in Nature a few years ago by TCGA proposed dividing GC into four subtypes based on molecular characteristics[13].

EBV-positive phenotype is frequently associated with PIK3CA mutations, DNA hypermethylation, and amplification of JAK2, CD274, and PDCD1LG2. MSI is a type characterized by a high mutation rate, including mutations in genes that activate oncogene signaling pathways. The GS type, which occurs most often in the histologically diffuse form, is caused by mutations in RHOA or fusions of GTPase-activating protein genes in the THO family. CIN type, which has the hallmark heterozygous chromosomes and in situ amplification of the receptor lysine kinase.

The conventional method of devising treatment plans based on tumor phenotypic characteristics will be replaced by a mode that considers gene alterations instead[14]. Utilizing single gene expression changes can direct targeted medication therapy, which is a more rational, efficient and personalized mode of treatment compared to chemotherapy for the same morphology type. Additionally, multi-gene detection will become an essential research area[15].

GUIDELINES FOR THE TREATMENT OF PLGC: STANDARDS AND DEVELOPMENTS

Early GC without lymph node metastasis may be treated through endoscopic or surgical means, depending on the extent of tumor invasion. Adjuvant radiotherapy or chemotherapy is not necessary after surgery.

Locally advanced GC or early GC with lymph node metastasis should be managed using comprehensive surgical treatment. The decision of direct radical surgery *vs* preoperative neoadjuvant chemotherapy, before radical surgery, depends on the depth of tumor invasion and whether or not lymph node metastasis is present. For patients with locally advanced GC who have undergone successful radical surgery, adjuvant treatment planning (including adjuvant chemotherapy and, if necessary, adjuvant chemoradiotherapy) should be based on the postoperative pathological staging.

Recurrent or metastatic GC requires comprehensive treatment consisting mainly of medication. Palliative surgery, radiotherapy, interventional therapy, and local therapies should also be administered as needed, along with optimal supportive therapies, including analgesia, stenting, and nutrition support. It is essential to give supportive therapies actively at the appropriate time[16].

Endoscopic techniques

EMR is the endoscopic removal of mucosal lesions, in whole or in part, for the diagnosis and treatment of superficial tumors of the gastrointestinal tract[17].

ESD is a new technology developed on the basis of EMR. According to the lesions with different parts, sizes and infiltration depths, special electrocautery knives such as IT knives, Dual knives, Hook knives, *etc.* are selected for endoscopic gradual separation of tissues between the mucous membrane layer and the intrinsic muscular layer, and finally the lesion mucous membrane and submucosal layer are completely removed[18].

Other endoscopic treatments include laser therapy, argon knife, microwave therapy, *etc.* They can only remove the tumor, but cannot obtain complete pathological specimens or be sure that the tumor is completely removed. Therefore, they are mostly used for the treatment of precancerous gastric lesions and require close follow-up after treatment, and are not recommended as the first choice of treatment for early GC[19,20].

Surgery and chemotherapy

PLGC surgery is divided into radical surgery and non-radical surgery. Radical surgery should completely remove the primary lesion and thoroughly clear the regional lymph nodes, mainly including standard surgery, modified surgery and extended surgery; non-radical surgery mainly includes palliative surgery and tumor reduction surgery[21,22].

Chemotherapy is divided into palliative chemotherapy, adjuvant chemotherapy, neoadjuvant chemotherapy, and conversion therapy.

Neoadjuvant chemotherapy is recommended for locally advanced GC without distant metastases (T3/4, N+). The regimen should consist of a two-drug combination of platinum and fluorouracil or a three-drug combination based on the two-drug regimen combined with paclitaxel. It should not be used as a single agent[11].

The GC management process is shown in Figure 1.

UCAD APPLICATION PROSPECTS

In the article "*Hallmarks of cancer: The next generation*" in *Cell*, the authors systematically summarized various hallmarks of cancer development. They highlighted genomic instability (or chromosomal instability) as the fundamental cause of cancer development, present in almost all malignant tumors. Thus, genomic instability is considered the root cause of

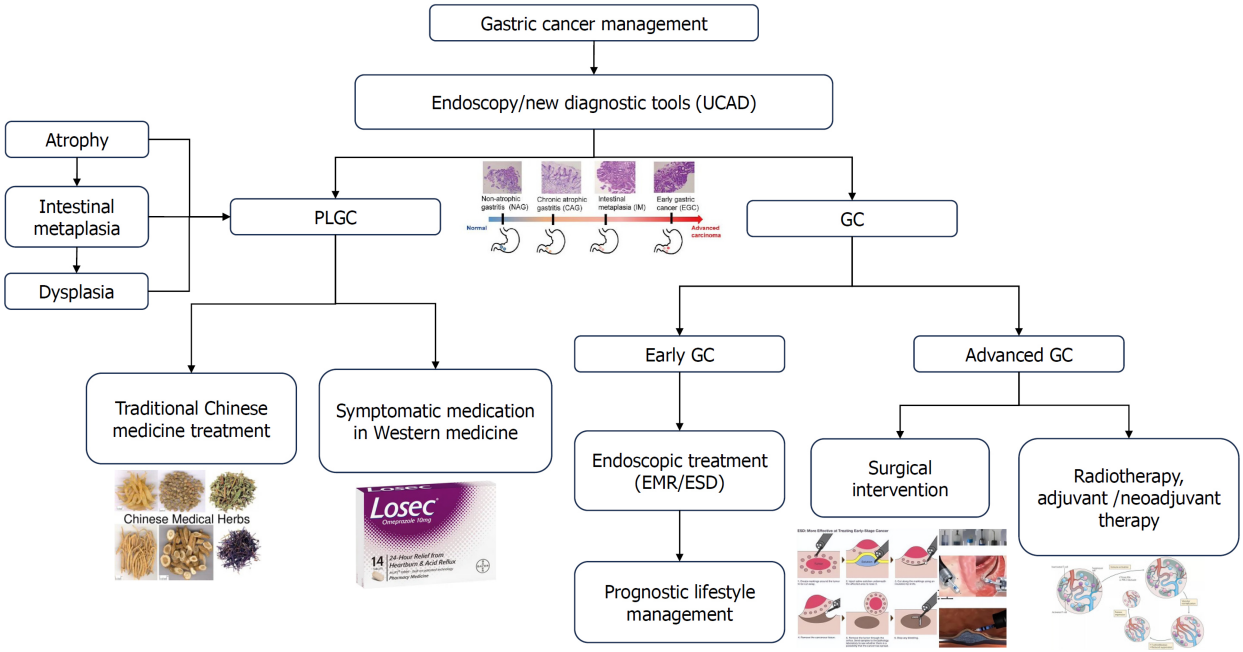

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Figure 1 The gastric cancer management process. EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection; GC: Gastric cancer; PLGC: Precancerous lesions of gastric cancer; UCAD: Ultrasensitive chromosomal aneuploidy detection.

cancer[23].

CIN is a feature of certain cells that results in the production of daughter cells that have an altered chromosome number or structure. This is a common feature in cancer cells. The fundamental aspects of chromosomal instability include changes in chromosome copy number, which leads to the emergence of cells with aneuploidy, as well as alterations in chromosome structure. These changes can include polyploidy, chromosomal translocations, genomic chaos, and non-clonal chromosomal aberrations[24].

The mechanism behind cancer cells is the irregular distribution of chromosomes during mitosis in zygote cells and the persistence of errors in chromosome segregation. This leads to modifications in chromosome copy number, as well as intrachromosomal segment amplification or deletion[25].

The substantial loss, gain, and rearrangement of DNA accumulate, resulting in chromosomal instability. This instability leads to extensive genomic complexity, which is a hallmark of cancer that is either present or expected. Chromosomal instability is strongly associated with tumor staging, metastasis, poor prognosis, and treatment resistance. This includes the loss or amplification of driver genes, focal rearrangements, extrachromosomal DNA, micronucleus formation, and the activation of innate immune signaling. These mechanisms lead to the diversification of tumor subclones in terms of space and time. This facilitates metastasis, accelerates the phenotypic adaptation of tumors, promotes cellular immortality, the escape from immune surveillance, and the development of resistance to drug treatments, among other processes[26].

CIN has been extensively studied as an innovative test. Using patient-derived tumor organoids to imitate colorectal cancer, researchers confirmed the existence of anaphase chromatin bridges in colorectal cancer cell lines. Causes consisted of insufficient disassembly of sister chromatids, telomere fusion producing bicentric chromosomes, and incomplete replication. These manifestations of CIN are prevalent in organs resembling colorectal cancer and have a significant impact on tumor evolution and therapeutic response. The levels of CIN and tolerance to mitotic errors play a crucial role in shaping the aneuploid landscapes and karyotypic heterogeneity[27].

Copy number and structural changes due to CIN are common features of multiple myeloma (MM). Primary and secondary genetic events caused by CIN lead to an increase in malignant plasma cell genomic instability by interfering with cell cycle checkpoints, thus accelerating proliferation. Thus, an assessment of CIN in MM and its precursor states may help to mitigate the progression of symptomatic disease and the risk of relapse[28].

CIN plays a role in the development of some subtypes of diffuse infiltrating gliomas. In isocitrate dehydrogenase-mutant astrocytomas, copy number variation (CNV) levels rise overall with tumor grade, duration, and proximity of infiltrating cells within the same tumor. The detection of CIN through CNV, DNA methylation, and/or gene expression profiling can effectively identify gliomas influenced by this molecular mechanism[29].

UCAD is a cutting-edge approach for identifying cellular chromosomal instability. This technique leverages body fluid free DNA or tissue genomic DNA as a template and utilizes LC-WGS, together with bioinformatics analysis, to identify chromosomal instability at the genome-wide scale. This technique has the potential to aid in the detection of tumors, monitor the effectiveness of treatment, and assess the likelihood of recurrence and metastasis. Samples including peripheral blood, exfoliated cells, menstrual blood, fresh and frozen tissues, formalin-fixed paraffin-embedded, urine, and others, can be analyzed for diagnostic purposes.

UCAD has been applied in clinical studies at this stage. Ye *et al*[30] collected samples of pancreatic cystic fluid from 102 patients with pancreatic cystic neoplasms (PCN) and employed UCAD to examine distinct CIN characteristics among different types of PCN. The deletion of chr3p and chr6p was used to define subtypes of serous cystadenoma. Meanwhile, the gain of chr1q and chr8q was associated with latent malignant PCN and facilitated the detection of high-risk intraductal papillary mucinous neoplasm.

Wang *et al*[31] collected plasma samples from 47 patients suspected of having lesions in the biliary tract. They utilized UCAD to analyze free DNA for CNV analysis through low-coverage whole genome sequencing. The results demonstrated the most frequent copy number gains in chr3q (7/29) and chr8q (6/29), with the most prevalent copy number losses noted in chr7p (6/29), chr17p (6/29), and chr19p (6/29). The sensitivity and specificity of the plasma CNV assay for the diagnosis of biliary tract cancer were 89.7% and 88.9%, respectively.

Feng *et al*[32] obtained 196 plasma samples from two groups of patients: a discovery cohort of individuals with PLC who were not eligible for surgery, and a validation cohort of patients who underwent pathologically confirmed hepatectomies. Of the 172 individuals, 22 (95.7%) surgically ineligible hepatocellular carcinomas were identified as having CNV in at least 1 of the 29 segments. 54 (69.4%) of the hepatocellular carcinomas eligible for surgery received positive screenings, and subsequently, confirmed to be cancerous by pathologic examination. Additionally, 26/27 non-cancers were identified with negative screenings.

Ye *et al*[33] gathered mucosal samples from 40 patients with GC from the hospital. 20 were microbiome-enriched, 5 tested positive for EBV DNA, and 15 had *H. pylori* DNA. Meanwhile, 20 of the samples were found to have CIN. UCAD can be used to identify 3 distinct subtypes of GC in the Chinese population, providing valuable guidance for future research on GC treatment and prevention. UCAD can identify three distinct subtypes of GC in the Chinese population. This finding could provide valuable guidance for further research on the prevention and treatment of GC.

CONCLUSION

In recent years, there has been an acceleration in precision treatment for PLGC, however, obstacles remain. The evolving endoscopic technology and surgical treatment have not sufficiently addressed the high recurrence rate after surgery. While there is a clinical benefit trend in anti-HER2 therapy and anti-CLDN18.2 monoclonal antibody therapy, additional research is necessary to optimize treatment and maximize patient benefit[34,35]. Early diagnostic treatment remains a pressing and essential need for improvement with a significant demand for less invasive or non-invasive testing and highly specific biomarkers[36]. Research efforts must focus on developing more convenient, comfortable, and highly accurate diagnostic tests, like tests on body fluids such as peripheral blood, urine or saliva, and gastric fluids, for early assessment of the likelihood of patient progression. Early treatment is critical for reducing the risk of developing GC.

In this context, UCAD has been researched and applied as a new test for early prevention in patients with positive early sequencing results or for gastroscopy and treatment to timely remove lesions at a stage when PLGC has not progressed. With the gradual decrease in the cost of second-generation sequencing, UCAD assays are expected to become more cost-effective in the near future. Meanwhile, the UCAD assay can capture both human and microbiome DNA while detecting specimens from mucosal, blood, and urine sources. This convenience, comfort, and information make it a superior technology for GC subtyping compared to other methods. Overall, this new approach may improve diagnostic and therapeutic strategies for PLGC in a cost-effective manner, achieving true precision.

ACKNOWLEDGEMENTS

We gratefully acknowledge the kind cooperation of all authors in the preparation of this paper.

FOOTNOTES

Author contributions: Cai DL designed the overall concept and outline of the manuscript; Qian ST contributed to the design and writing of the manuscript; Xie FF, Zhao HY, and Liu QS contributed to the editing the manuscript, illustrations, and review of literature.

Conflict-of-interest statement: All authors have no conflict-of-interest to disclose.

Country/Territory of origin: China

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S-Editor: Zhang H

L-Editor: A
P-Editor: Zhang YL

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World Journal of Gastrointestinal Surgery

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World J Gastrointest Surg 2024 January 27; 16(1): 13-20

DOI: 10.4240/wjgs.v16.i1.13

ISSN 1948-9366 (online)

MINIREVIEWS

Prognostic value of ultrasound in early arterial complications post liver transplant

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Specialty type: Gastroenterology and hepatology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Tovikkai C, Thailand

Received: November 21, 2023
Peer-review started: November 21, 2023
First decision: December 11, 2023
Revised: December 21, 2023
Accepted: January 8, 2024
Article in press: January 8, 2024
Published online: January 27, 2024

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Abstract

Liver transplantation is the primary therapeutic intervention for end-stage liver disease. However, vascular complications, particularly those involving the hepatic artery, pose significant risks to patients. The clinical manifestations associated with early arterial complications following liver transplantation are often non-specific. Without timely intervention, these complications can result in graft failure or patient mortality. Therefore, early diagnosis and the formulation of an optimal treatment plan are imperative. Ultrasound examination remains the predominant imaging modality for detecting complications post liver transplantation. This article comprehensively reviews common causes and clinical presentations of early hepatic artery complications in the post-transplantation period and delineates abnormal sonographic findings for accurate diagnosis of these conditions. Overall, ultrasound offers the advantages of convenience, safety, effectiveness, and non-invasiveness. It enables real-time, dynamic, and precise evaluation, making it the preferred diagnostic method for post-liver transplantation assessments.

Key Words: Liver transplantation; Vascular complication; Arterial complication; Ultrasound

Core Tip: The clinical manifestations associated with early arterial complications following liver transplantation are often nonspecific. Without timely intervention, these complications can result in graft failure or patient mortality. Early diagnosis and the formulation of an optimal treatment plan are imperative. Ultrasound examination remains the predominant imaging modality for detecting complications post liver transplantation. And ultrasound has the advantages of convenience, safety, effectiveness, and non-invasiveness, and enables real-time, dynamic, and accurate evaluation, making it the preferred diagnostic method for post-liver transplantation evaluation.

Citation: Zhao NB, Chen Y, Xia R, Tang JB, Zhao D. Prognostic value of ultrasound in early arterial complications post liver transplant. *World J Gastrointest Surg* 2024; 16(1): 13-20
URL: https://www.wjgnet.com/1948-9366/full/v16/i1/13.htm
DOI: https://dx.doi.org/10.4240/wjgs.v16.i1.13

INTRODUCTION

Liver transplantation stands as the primary therapeutic approach for end-stage liver disease. Continuous advancements in surgical techniques and the application of novel immunosuppressive agents contribute to ongoing improvements in the success rate and overall survival in patients undergoing liver transplantation procedures. Despite these advancements, vascular complications, particularly those involving the hepatic artery, pose significant risks to patients. During the early stages following liver transplantation (within the first 30 d), proper hepatic artery function is crucial for hepatic arterial blood flow. During later stages, collateral circulation, including arteries such as the phrenic artery, right gastric artery, and gastroduodenal artery, becomes important for maintaining hepatic blood supply. It is now understood that the establishment of effective collateral circulation is pivotal for determining the prognosis of hepatic artery complications. The clinical manifestations of these complications are closely linked to factors such as timing, severity, and the specific type of onset. Insufficient hepatic arterial blood flow can lead to abnormal liver function, hepatic infarction, and the formation of hepatic abscesses. Additionally, since the hepatic artery is the sole blood supply to the biliary tract, hepatic artery-related ischemia may result in biliary stricture, obstruction, and the formation of bile ducts. Ultrasound examination remains the primary imaging modality for diagnosing complications post liver transplantation. This article comprehensively reviews common causes and clinical presentations of early hepatic artery complications in the post-transplantation period and outlines abnormal sonographic findings for accurately diagnosing these conditions.

NORMAL HEPATIC ARTERY

During the intraoperative phase, an ultrasound examination is typically conducted to evaluate the hepatic artery anastomosis. The normal internal diameter of the hepatic artery typically ranges from 2 to 5 mm. Two strong echo points are typically identified near the anastomosis. To assess blood flow dynamics, peak systolic velocity, end-diastolic velocity, and resistance index are measured at the donor and recipient sides of the anastomosis following angle correction. Anastomotic stenosis presence and severity can be evaluated by comparing the velocity at the anastomotic site with that at the recipient side. Postoperatively, direct visualization of the anastomosis site through gray ultrasound scans is often challenging. The surgical approach has a significant impact on the proper hepatic artery's position, resulting in a lower overall success rate of continuous visualization. Color Doppler ultrasound is primarily employed to trace the artery's path, and spectral measurements are taken at the brightest position of the Color Doppler blood flow signal, primarily used to identify the presence of high-speed turbulence. Hepatic artery spectrum examination plays a crucial role, as a favorable arterial spectral waveform and appropriate hepatic artery flow velocity typically indicate a successful anastomosis, even in cases where the hepatic artery anastomosis cannot be directly visualized by ultrasound. The hepatic artery runs alongside the portal vein, often selected as a reference due to its larger inner diameter. A normal hepatic artery spectrum displays a regular pulsation pattern with a rapid rise in systole and a slow decline in diastole. Parameters for assessing hepatic artery resistance include a resistance index between 0.5 to 0.8 and an artery systolic acceleration of less than 80 ms. Instantaneous increases in the resistance index (RI > 0.8) often occur within 2 d after surgery, followed by a subsequent return to normal hepatic arterial parameters. It has been established that the maximum blood flow velocity during systole in the hepatic artery should not exceed 200 cm/s[1].

HEPATIC ARTERY THROMBOSIS

Hepatic artery thrombosis (HAT) represents a serious complication following liver transplantation, with an incidence rate ranging from 3% to 5%[2,3]. Early risk factors for HAT encompass ABO-blood type incompatibility, prolonged cold ischemia time for the donor's liver, acute rejection reaction, hepatic artery spasm, intimal dissection, perianastomotic hematoma compression, arterial torsion, undersized donor hepatic artery diameter, and mismatched anastomotic size[4,5]. HAT leads to a reduction in blood supply to the liver, particularly in the early postoperative period, and can result in severe complications, with mortality rates reaching 20%-60%. Clinical presentations of HAT include severe hepatic pain, fever, ascites, abrupt elevation of serum aminotransferases, decreased bile flow, altered bile properties, prolonged prothrombin time, and sepsis. Rapid progression of HAT can lead to biliary complications, graft necrosis, and mortality. Therefore, early diagnosis and timely treatment of HAT are crucial[6].

HAT is characterized by the absence of color Doppler and spectral Doppler signals in the region of the hepatic artery's course. However, blood flow signals may still be detected in some HAT cases due to the development of hepatic arterial collateral circulation, which can occur as early as 2 wk postoperatively. Color Doppler ultrasound can detect blood flow signals in the hepatic artery after the formation of collateral circulation, showing tardus-parvus waveforms with specific features (RI < 0.5 and SAT > 80 ms). It is important to note that the inability to detect hepatic artery blood flow signals using Doppler ultrasound is not a definitive diagnostic criterion for hepatic artery occlusion. Studies indicate that the accuracy of using color Doppler in diagnosing HAT is only 64%, influenced by factors such as operator experience, equipment sensitivity, and the fine caliber of the hepatic artery, leading to a significant number of false-positive cases[7]. Contrast-enhanced ultrasound (CEUS) has significantly improved the visualization of hepatic vessels. In specific imaging modes, CEUS can present hepatic artery images similar to digital subtraction angiography (DSA) in the arterial phase after intravenous ultrasound contrast combined with low mechanical index, thereby enhancing the sensitivity and specificity of HAT diagnosis[8]. With a 100% diagnostic sensitivity for HAT, CEUS emerges as a highly reliable method for detecting this complication[9,10]. Therefore, when color Doppler does not clearly show the hepatic artery after liver transplantation, an immediate CEUS examination is warranted, allowing for accurate diagnosis while avoiding unnecessary invasive angiography[12] (Figure 1).

HEPATIC ARTERY STENOSIS

Hepatic artery stenosis (HAS) is a relatively common vascular complication after liver transplantation, with a high incidence ranging from 5% to 11%[13]. While not as severe as HAT, significant HAS or progressive stenosis can lead to complications such as bile duct and liver ischemic necrosis and even liver failure. The gold standard for diagnosing HAS is hepatic artery angiography, and the degree of narrowing is classified as mild (< 50%), moderate (50% to 75%), or severe (> 75%). HAS often occurs at the anastomosis site, anastomotic acceptor segment, or donor segment. Various risk factors contribute to the development of HAS, including surgical technique, vascular endothelial damage, rejection, prolonged donor cold ischemia time, small donor artery size, and hypercoagulability. Clinical manifestations of HAS include elevated serum aminotransferase levels, increased bilirubin, liver abscess, ischemic cholangitis, bile duct stenosis, or necrosis. Severe HAS may even present with graft non-function[14].

Direct visualization of the HAS site by ultrasound is typically challenging, relying on the indirect diagnosis of intrahepatic artery changes. A tardus-parvus waveform in the hepatic artery spectrum is indicative of HAS[15], with the mechanism being the significant narrowing of the proximal artery leading to a drop in perfusion pressure in the distal segment. The specificity of the tardus-parvus waveform for diagnosing HAS is approximately 81.9%[16]. However, it should be borne in mind that a tardus-parvus waveform does not necessarily confirm the presence of HAS, as it can be observed in various conditions such as severe aortic atherosclerosis, arteriovenous fistulas, artery-bile duct fistulas, extensive collateral circulation, large-area hepatic necrosis, or systemic hypotension[17]. A more reliable diagnostic criterion for HAS is the measurement of high-velocity blood flow above 200 cm/s near the hepatic artery anastomosis (Figure 2). CEUS can provide direct visualization of the site of HAS, showing focal stenosis at the anastomosis site, bead-like or segmental intrahepatic or extrahepatic arterial stenosis, and diffuse stenosis. However, the limitations of CEUS, such as difficulty visualizing hepatic artery anastomosis due to gas interference and abdominal wall fat, should be considered[18,19], and it may have limited diagnostic value for HAS.

HEPATIC ARTERY ANEURYSM

Hepatic artery aneurysm (HAA) is relatively rare following liver transplantation[20,21]. There are three main types of HAA: Congenital or acquired true HAA caused by factors such as atherosclerosis, fungal infections, necrotizing vasculitis, and polyarteritis; traumatic or iatrogenic hepatic pseudoaneurysm (hepatic artery pseudoaneurysm, HAP)[22]; and hepatic dissection aneurysm (hepatic dissecting aneurysm, HDA)[23] resulting from causes like surgical suture injury or percutaneous hepatic artery angiography. HAA typically remains clinically silent until rupture. When an aneurysm becomes too large and compresses the portal system, symptoms such as jaundice and portal hypertension may occur. Ruptured HAA can lead to life-threatening gastrointestinal bleeding and intra-abdominal bleeding. DSA is the gold standard for diagnosing HAA[24], revealing tumor-feeding arteries. Most HAAs present as sac-like or nodular structures with contrast stasis inside, while arterial damage and extravasation of contrast medium are direct signs for diagnosis. The purpose of ultrasound examination is to diagnose HAA earlier before rupture and provide a more accurate treatment

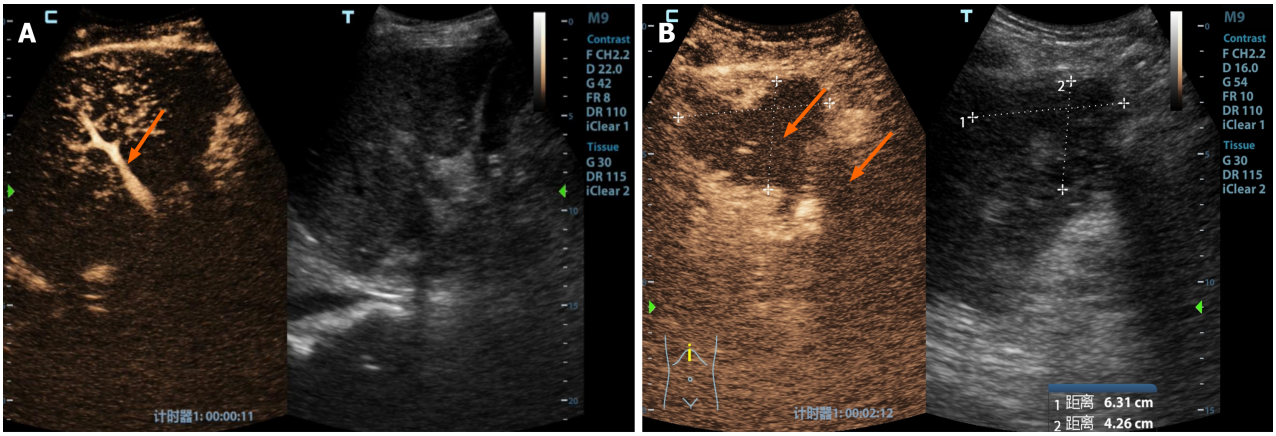

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Figure 1 A 32-year-old male patient underwent a piggyback liver transplant for decompensated cirrhosis and acute liver failure. A: This assessment occurred 15 d postoperatively. Routine ultrasound imaging had failed to reveal hepatic arteries within both the liver and extrahepatic regions. Contrast-enhanced ultrasound showed that the portal vein was prematurely visible (indicated by the orange arrow), while neither intrahepatic nor extrahepatic arteries displayed any enhancement; B: Furthermore, multiple ischemic lesions within the liver were observed in the arterial (phase I), portal (phase II), and late phases (phase III), indicating a lack of enhancement (as indicated by the orange arrow). Surgical confirmation subsequently identified a diffuse formation of arterial thrombosis within the hepatic artery.

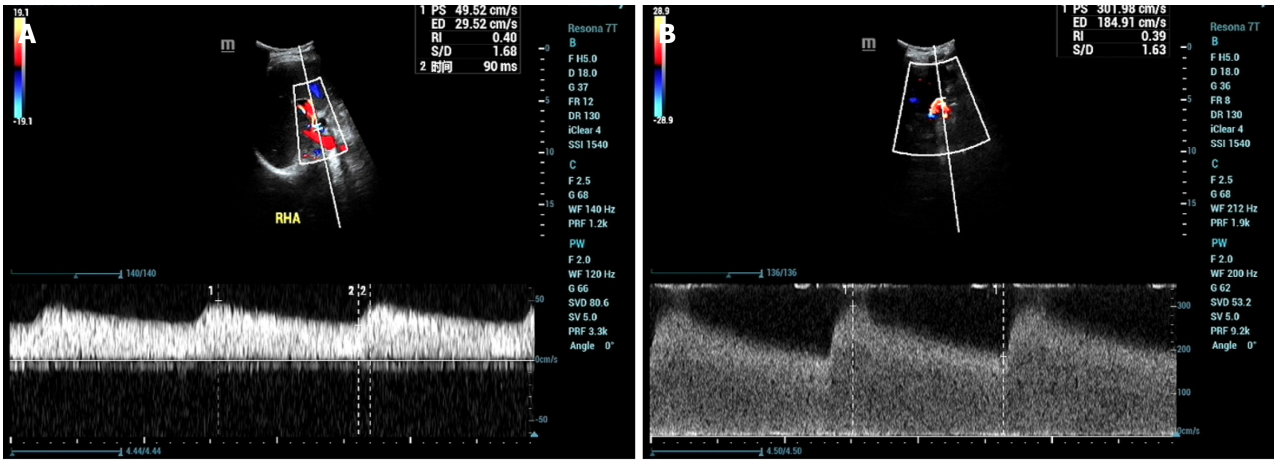

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Figure 2 A 46-year-old male patient who underwent liver transplantation for liver cancer received an ultrasound examination at 1 year and 4 mo postoperatively, revealing hepatic artery stenosis. A: Ultrasound indicated an intrahepatic artery (right hepatic artery) resistive index of 0.40, with a systolic acceleration time of 90 ms; B: Blood flow near the hepatic artery anastomosis reached 302 cm/s.

plan.

Hepatic artery pseudoaneurysm

HAP often occurs at the arterial anastomosis site or at the site of intervention or puncture[25]. The peripheral soft tissue wrapping hematoma forms due to the ruptured hemorrhage of the arterial wall[26,27]. Gray-scale ultrasound shows the cystic anechoic area of the hepatic artery with a clear boundary. Color Doppler presents characteristic red and blue alternating blood flow signals, while spectral Doppler displays arterial blood flow signals. CEUS reveals the synchronous development of the tumor body with the hepatic artery during the arterial stage.

Hepatic dissecting aneurysm

HDA often results from the rupture of the intima and media layers due to various factors, leading to the entry of blood into the medial layer, causing the neoplastic structure to tear, resulting in the stratification of the vessel wall, and dividing the artery into true and false lumens. These lumens may or may not communicate through the rupture site. Ultrasound reveals the following characteristics: (1) Intimal stratification signs, where the separated intima may be fixed or float with the bloodstream. True and false cavities may have inlet and outlet connections or exist as separate structures (Figure 3A); (2) an increase in arterial diameter; (3) blood flow stratification phenomenon, where the separated intima divides arterial blood flow into two layers, representing the blood flow in the true lumen and the false lumen, each with distinct blood flow spectra (Figure 3B); (4) thrombosis in the false lumen; and (5) vascular narrowing in the true lumen.

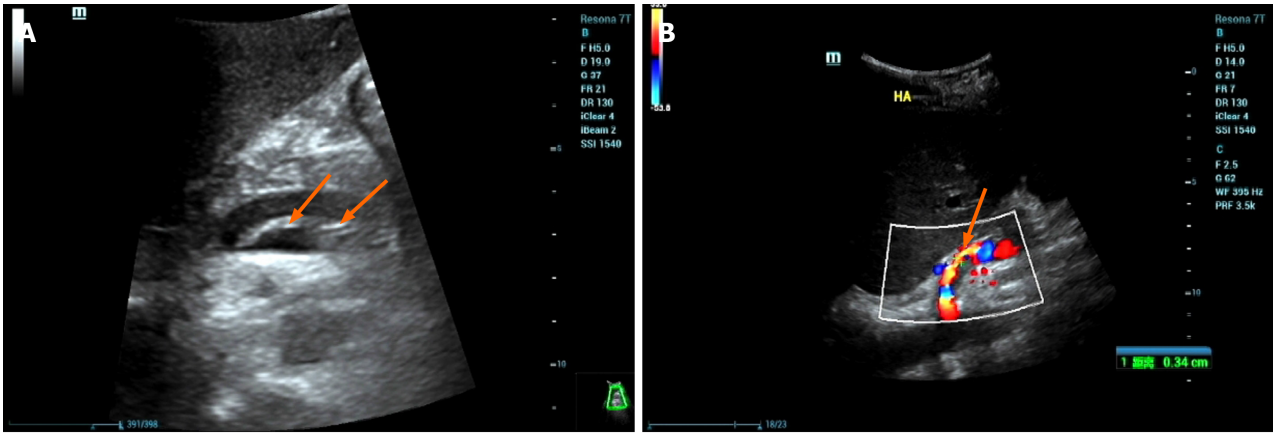

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Figure 3 A 46-year-old male patient with decompensated cirrhosis due to hepatitis B underwent liver transplantation. On postoperative day 1, ultrasound showed no blood flow signals in the hepatic artery, followed by hepatic artery angiography and thrombosis. A: Ultrasound showed intramural-like echoes floating in the proper hepatic artery (arrow); B: Ultrasound showed blood flow in the true lumen of the proper hepatic artery (arrow), with no obvious blood flow signals in the false lumen. Then, the patient underwent hepatic artery stent graft implantation with satisfactory clinical results.

The following features indicate that urgent intervention is necessary for a dissecting aneurysm: (1) Tardus-parvus waveform observed in the hepatic artery of the liver; (2) an increase in peak contraction velocity at the tumor body (> 200 cm/s); and (3) absence of blood flow signal in the liver[28].

HEPATIC ARTERY VASOSPASM

Hepatic artery vasospasm (HAV) is characterized by intense constriction of the arterial vessel wall, resulting in rigidity, narrowing, or occlusion of the affected portion or the entire vessel[29]. This common complication during the recipient's surgical process is often secondary to excessive manipulation and suturing. Despite a lack of sufficient data and widely recognized diagnostic criteria, animal and clinical studies suggest that elevated serum norepinephrine levels may influence HAV[30]. High-risk factors include surgical compression, increased hepatic perfusion resistance, exposure of the hepatic artery to bile, and liver resection[31,32]. The impact of HAV on the transplanted liver remains uncertain, as vascular spasms may reduce hepatic artery flow and potentially induce thrombus formation. Richards *et al*[33] emphasize that vascular spasms in vascular reconstruction tissue can compromise tissue perfusion even with a patent hepatic artery anastomosis.

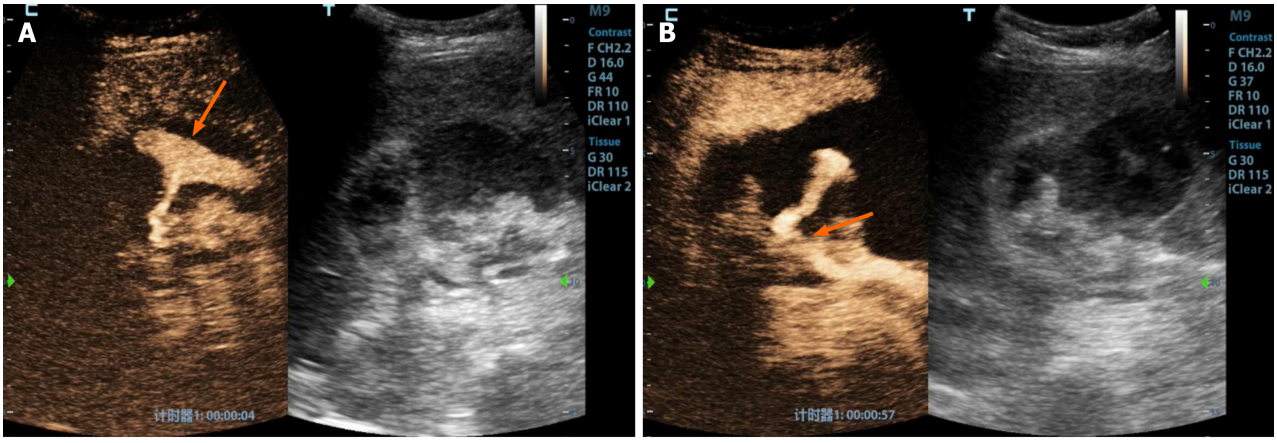
Doppler ultrasound lacks uniform diagnostic criteria for HAV, with manifestations such as arterial shortening, narrowing, absence of focal anastomotic stenosis (resulting in an increased resistance index), and, at times, diastolic flow loss or reversal. Ruling out other causes of increased resistance index is essential. The use of vasodilators can lead to a reduction in the resistance index, and postoperative ultrasound follow-up can support the diagnosis of HAV[31].

HEPATIC ARTERY DISTORTION

Hepatic artery distortion (HAD) is a common condition in liver transplant surgery, where the recipient's hepatic artery is lengthened to reduce tension at the anastomosis site, resulting in a twisted appearance near the liver hilum. This twisting generally does not affect hepatic blood supply, and color Doppler shows a bright blood flow signal in the distorted segment. Spectral Doppler detects high-velocity blood flow in the region, and there is usually no abnormality in the blood flow velocity in the hepatic artery affected by HAD, with liver function remaining generally normal. In traditional two-dimensional imaging modes, the twisted hepatic arteries can overlap and form angular shapes in images, resembling HAS, making it challenging to distinguish between HAS and HAD. Three-dimensional (3D) CEUS overcomes this limitation by displaying vascular structures in three spatial dimensions. It provides a clear representation of the 3D architecture of the hepatic artery without being restricted by changes in vascular curvature. Dynamic 3D reconstruction of Doppler blood flow combines 3D flow data with anatomical structures, offering a more complete understanding of the hemodynamic characteristics of the examined organs and their relationship to anatomy.

HEPATIC ARTERY RUPTURE

Hepatic artery rupture (HAR) carries severe consequences, potentially leading to hemorrhagic shock or even death[34]. Immediate intervention through surgical or vascular procedures is essential once the diagnosis is confirmed. Ruptures



DOI: 10.4240/wjgs.v16.i1.13

Figure 4 A 48-year-old female patient underwent a piggyback liver transplantation procedure due to decompensated cirrhosis resulting from hepatitis B. A: Evaluated 13 d postoperatively, the patient's clinical history revealed a progressive decline in blood pressure and red blood cell count, accompanied by the accumulation of a significant volume of intraperitoneal fluid. Conventional ultrasound examination demonstrated a substantial accumulation of fluid in the porta hepatis region, characterized by hypoechoic features and the presence of numerous fine, low-level echogenic particles suspended within. Contrast-enhanced ultrasound revealed enhanced contrast agent pooling within the intraperitoneal fluid of the porta hepatis, exhibiting a morphology resembling a mushroom cloud (highlighted by the orange arrow); B: Notably, further tracking of the contrast agent leakage within the porta hepatis area (indicated by the orange arrow) indicated that it originated from the hepatic artery anastomosis site.

typically occur near the anastomosis site and can result from various factors, including suture line failure, avascular necrosis of the arterial wall at the anastomosis, arterial wall infection, or aneurysms[35]. Ultrasound findings in cases of HAR include reduced or normal blood flow velocity within the hepatic artery in the liver and a significant accumulation of fluid near the hepatic artery anastomosis site. CEUS is valuable in the diagnosis of HAR, revealing a concentrated area of contrast agent accumulation next to the hepatic artery with consistently higher enhancement levels compared to the surrounding normal liver tissue. This demonstrates continuous extravasation of contrast agents with strong enhancement characteristics (Figure 4).

CONCLUSION

In conclusion, the clinical presentations associated with early arterial complications after liver transplantation are often nonspecific. Without timely intervention, these complications can lead to graft failure or patient mortality. Early diagnosis and the establishment of the best treatment plan are crucial. Ultrasound, with its advantages of convenience, safety, effectiveness, and non-invasiveness, can be evaluated in real time, providing dynamic and accurate information. As a result, it has become the preferred diagnostic method for post-liver transplantation evaluation.

FOOTNOTES

Author contributions: Zhao D and Zhao NB contributed to study conception and design; Zhao D contributed to administrative support; Zhao D and Zhao NB contributed to provision of the study materials, and collection and assembly of the data; Chen Y, Xia R, and Tang JB contributed to data analysis and interpretation; all authors contributed to the writing and final approval of the manuscript.

Supported by the Shenzhen Science and Technology R&D Fund, No. JCYJ20220530163011026; and Shenzhen Third People's Hospital, No. G2022008 and No. G2021008.

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

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L-Editor: Wang TQ
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World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2024 January 27; 16(1): 21-28

DOI: 10.4240/wjgs.v16.i1.21

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Case Control Study

Added value of ratio of cross diameters of the appendix in ultrasound diagnosis of acute appendicitis

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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): 0
Grade E (Poor): 0

P-Reviewer: Montero JA

Received: October 2, 2023
Peer-review started: October 2, 2023
First decision: December 6, 2023
Revised: December 13, 2023
Accepted: December 28, 2023
Article in press: December 28, 2023
Published online: January 27, 2024

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Abstract

BACKGROUND

The maximum outer diameter (MOD) of the appendix is an essential parameter for diagnosing acute appendicitis, but there is space for improvement in ultrasound (US) diagnostic performance.

AIM

To investigate whether combining the ratio of the cross diameters (RATIO) of the appendix with MOD of the appendix can enhance the diagnostic performance of acute appendicitis.

METHODS

A retrospective study was conducted, and medical records of 233 patients with acute appendicitis and 112 patients with a normal appendix were reviewed. The MOD and RATIO of the appendix were calculated and tested for their diagnostic performance of acute appendicitis, both individually and in combination.

RESULTS

The RATIO for a normal appendix was 1.32 ± 0.16, while for acute appendicitis it was 1.09 ± 0.07. The cut-off value for RATIO was determined to be ≤ 1.18. The area under the receiver operating characteristic curve (AUC) for diagnosing acute appendicitis using RATIO ≤ 1.18 and MOD > 6 mm was 0.870 and 0.652, respectively. There was a significant difference in AUC between RATIO ≤ 1.18 and MOD > 6 mm ($P < 0.0001$). When comparing the combination of RATIO ≤ 1.18 and MOD > 6 mm with MOD > 6 mm alone, the combination showed increased specificity, positive predictive value (PPV), and AUC. However, the sensitivity and negative predictive value decreased.

CONCLUSION

Combining RATIO of the appendix ≤ 1.18 and MOD > 6 mm can significantly improve the specificity, PPV, and AUC in the US diagnosis of acute appendicitis.

Key Words: Acute appendicitis; Diameter; Ratio; Diagnosis; Ultrasound

Core Tip: The maximum outer diameter (MOD) of the appendix has been an essential criterion for diagnosing acute appendicitis, but there is room for improvement in terms of sensitivity, specificity, and accuracy. In this study, we established a new parameter, the ratio of cross diameters on the transverse section of the appendix, for diagnosing acute appendicitis using ultrasound imaging. Combining this parameter with the MOD of the appendix can enhance diagnostic performance, making it more valuable in clinical practice.

Citation: Gu FW, Wu SZ. Added value of ratio of cross diameters of the appendix in ultrasound diagnosis of acute appendicitis. *World J Gastrointest Surg* 2024; 16(1): 21-28
URL: https://www.wjgnet.com/1948-9366/full/v16/i1/21.htm
DOI: https://dx.doi.org/10.4240/wjgs.v16.i1.21

INTRODUCTION

Acute appendicitis is the most common abdominal emergency in the world. The clinical diagnosis of acute appendicitis is based on history, physical examination, laboratory tests, and medical imaging. Although biomarkers and imaging are valuable adjuncts to history and physical examination, accurate preoperative diagnosis is still challenging[1]. Ultrasound (US) has been recommended for the evaluation of suspected appendicitis in recent dacades[2]. Previous studies[2-7] have showed that an appendix with a maximum outer diameter (MOD) of more than 6 mm, scanned at the point of maximum tenderness using US, is the main feature of acute appendicitis. Other findings include incompressibility of the enlarged appendix, presence of appendicoliths, equivocality or loss of mural stratification, increased echogenicity of periappendiceal epiploic appendages, abnormal anechoic focal fluid on graded compression US; and hypervascularity of the appendix wall. The diagnostic performance of US for acute appendicitis varies considerably. Previous studies show that the sensitivity and specificity of US for the acute appendicitis are 0.821 and 0.81, and 0.859 and 0.87, respectively, and the area under the receiver operating characteristic (ROC) curve is 0.9249[3,4]. Chicaiza *et al*[7] found that the MOD of the appendix for the diagnosis of acute appendicitis should be 7 mm instead of 6 mm. The MOD and other features of acute appendicitis are diverse, and they are affected by many factors, which may cause a diagnostic dilemma. The normal appendix appears as an ovoid or round shape on transverse section; when the appendix undergoes acute inflammation, the appendiceal size and tension increase[8-10]. With the progression of the appendix inflammation, the appendix becomes tumefaction, stiff, and incompressible, the shape on transverse section becomes round or closer to round (without perforation), and the ratio of cross diameters on transverse section becomes one or approximate to one[10,11]. Herein, we hypothesize that taking a ratio of the cross diameters (RATIO) on the transverse section of the appendix as an additional diagnostic US parameter is helpful for the evaluation of the appendix. The objective of this study was to investigate whether a combination of the RATIO of the appendix and the MOD of the appendix is valuable for the diagnosis of acute appendicitis.

MATERIALS AND METHODS

Study population

In this cross-sectional retrospective study, medical documents of 21624 consecutive patients who had undergone US of the appendix for suspected acute appendicitis between January 2017 and August 2023 in a tertiary hospital were retrieved, and some selected materials were reviewed. The inclusion criteria were that the patients who underwent US evaluation, the quality of US images was eligible, the patients underwent appendectomy, and the patients without acute appendicitis according to US, other examinations and clinical management. The exclusion criteria were that the patients with acute appendicitis did not have US images (undetected), acute appendicitis occurred perforation, pregnant women in the second and third trimesters, patients with a huge abdominal or pelvic tumor, and appendicitis with appendiceal tumor coexist. If a patient underwent two or more appendiceal US, only the latest US images and results were included. Based on these inclusion and exclusion criteria, 1033 patients were recruited, and 20591 patients were excluded. Finally, 233 patients [37.0 years (interquartile range: 28.0, 49.5)] with US-detected acute appendicitis and undergoing surgical excision were included, and 112 patients [median 31.0 years (interquartile range: 24.0, 39.8)] were selected in a randomized way from 9967 of 20591 patients with the final diagnoses of a normal appendix other than chronic bowel inflammation after US and other examination as a control. The diseases of the patients with a normal appendix included 39 cases of stone in the right ureter and/or kidney, 16 cases of gastritis, 17 cases of ovarian benign diseases, 13 cases of nonspecific fallopian tube inflammation, 5 cases of psoas injury, 9 cases of mesenteric lymphadenitis, and 3 cases of gastric ulcer. Baseline characteristics of the patients with a normal appendix and acute appendicitis are summarized and

compared in Tables 1 and 2.

Acquisition of US images of the appendixes

Patients who were referred to a tertiary hospital with suspected acute appendicitis received an appendix examination by physicians skilled in US. These physicians had between 1 to 30 years of experience in performing appendix USs. Multiparameter US systems (Mindray DC 8, Aloka Prosound α-7, Aloka Prosound α-10, Mindray Resona 7, Phillips EPIQ5, and GE Logiq E9) with a linear array transducer were used for the examination. The working frequencies ranged from 10 MHz to 15 MHz, but lower frequencies were used if the appendix could not be visualized.

During the examination, the US systems were adjusted to the small parts mode for bowel imaging. The patients were positioned supine on the table with their abdominal region fully exposed. The bowel and abdominal cavity were carefully scanned to detect any abnormalities. A graded compression US protocol was performed, allowing visualization of the right psoas muscle and right external iliac artery and vein during compression. Once the appendix was visualized, various characteristics were examined, including its location, shape, size, boundary, luminal and mural echogenicity, thickness and stratification of the appendiceal wall, vascularity, mesoappendix, periappendiceal epiploic appendages, omentum, periappendiceal fluid, and any associating findings (such as lymphadenitis). The size of the appendix was determined at its greatest dimension in both longitudinal and transverse views. The measurement of size in the transverse view was taken at the middle part of the appendix, neither the proximal nor the distal part. Color Doppler flow imaging was used to detect appendiceal vascularity or mural hyperemia. Representative images were saved in the informatics database of the picture archiving and communications system. Figures 1 and 2 show representative sonographies of a normal appendix and acute appendicitis, respectively.

Interpretation of the US images of the appendixes

Two physicians-in-US (radiologists) (a junior with 2 years and a senior physician with 20 years of abdominal US experience) evaluated the images of all the patients. They assessed the shape, size, echogenicity of the appendiceal lumen and wall, thickness and lamina of the appendiceal wall, the ratio on transverse section (dividing the larger diameter by the smaller diameter), appendicolithiasis, and vascularity. Appendicolithiasis was defined as an intraluminal echogenic focus or foci with distal acoustic shadowing. Luminal obstruction was defined as appendicolithiasis in the proximal lumen and was accompanied by fluid or other substances filling the lumen. Fluid in the appendiceal lumen and vascularity in the appendiceal wall were also specific findings for appendicitis. However, the vascularity of the appendiceal wall was difficult to detect by color Doppler flow imaging in the majority of the patients, so the analysis of fluid in the appendiceal lumen and the mural vascularity was waived. The appendix was considered enlarged when its MOD was 6 mm or larger under compression, measured from outer wall to outer wall in the transverse section[2]. Appendiceal wall edema was defined as an obliteration of the layers. Uncomplicated appendicitis was defined as the presence of an enlarged appendix with or without luminal liquid and appendicolithiasis, where the appendiceal wall was continuous, and no periappendiceal fluid was identified.

Histopathological classification

The histopathology of acute appendicitis and its grade was recorded based on the post-surgical evaluation, which was assessed by two certified pathologists. Acute appendicitis was classified as phlegmonous, gangrenous, and perforated appendicitis.

Statistical analysis

Continuous variables with a normal distribution were represented as mean ± SD, while those that did not meet the normal distribution were represented as median (interquartile range). The Kolmogorov-Smirnov test was used for the distribution analysis. Categorical variables were represented as numbers (percentage). Primary descriptive statistics of the study were reported. Independent sample *t*-test and Mann-Whitney *U* test were used for the analysis of continuous variables with and without a normal distribution, respectively. The diagnostic performance of acute appendicitis was studied based on MOD > 6 mm on the transverse section of the appendix and a combination of RATIO ≤ 1.18 and MOD > 6 mm, as determined by literature and this study[2]. The χ^2 test was used for the analysis of categorical variables. McNemar test was used to test the sensitivity, specificity positive predictive value (PPV), and negative predictive value (NPV). The ROC curve was drawn, the area under the ROC curve (AUC) was calculated, and the Youden index was determined to establish the cut-off value for sensitivity and specificity. PPV and NPV were also calculated. All analyses were conducted using SPSS software for Windows, version 26 (IBM Corp, Armonk, NY, United States) and/or Medcalc statistical software version 15.2.2 (Medcalc software BVBA, Ostend, Belgium). A two-tailed $P < 0.05$ was considered statistically significant.

RESULTS

The MODs and RATIOs of the normal appendix and acute appendicitis were 6.5 ± 1.0 mm and 10.7 ± 2.2 mm, and 1.32 ± 0.16 and 1.09 ± 0.07, respectively, with significant differences between them (all $P < 0.001$). The MODs on the transverse section and RATIOs of the normal appendix and acute appendicitis were all normally distributed. The baseline demographic characteristics of the patients and color Doppler US characteristics of the appendix with and without acute inflammation are summarized in Table 1. The ROC curve based on the RATIO of the 233 appendixes showed an AUC of 0.870 (95% confidence interval of 0.830-0.904), the best cutoff value for the RATIO of the appendix in diagnosing acute

Table 1 The baseline characteristics of the patients with a normal appendix and acute appendicitis and sonographic characteristics

Item	Normal appendix (*n* = 112)	Acute appendicitis (*n* = 233)	Statistics ($t/\chi^2/Z$)	*P* value
Sex, *n* (%)			14.288[2]	< 0.001
Male	29 (25.9)	110 (47.2)		
Female	83 (74.1)	123 (52.8)		
Age (yr) M (IQR)	31.0 (24.0, 39.8)	37.0 (28.0, 49.5)	-3.409[3]	0.001
Detectable length (mm) M (IQR)	34.8 (29.8, 43.9)	53.2 (45.0, 64.7)	-10.164[3]	< 0.001
SD (mm, mean ± SD)	4.9 ± 0.9	9.9 ± 2.0	-31.722[1]	< 0.001
LD (mm, mean ± SD)	6.5 ± 1.0	10.7 ± 2.2	-24.340[1]	< 0.001
RATIO (mean ± SD)	1.32 ± 0.16	1.09 ± 0.07	15.071[1]	< 0.001
Mural lamina *n* (%)			49.949[2]	< 0.001
Clear	110 (98.2)	146 (62.7)		
Ambiguous	2 (1.8)	87 (37.3)		
Mural vascularity, *n* (%)			32.694[2]	< 0.001
Present	12 (10.7)	96 (41.2)		
Absent	100 (89.3)	137 (58.8)		
Luminal echogenicity, *n* (%)				
Thread-like high echoic	62 (55.4)	0 (0)		
Anechoic	2 (1.8)	63 (27.0)		
Hypoechoic	36 (32.1)	58 (24.9)	197.308[2]	< 0.001
Isoechoic	9 (8.0)	13 (5.6)		
Hyperechoic, shadowing	1 (0.9)	33 (14.2)		
Complex echoic	2 (1.8)	66 (28.3)		
MOD (mm), *n* (%)				
> 6	77 (68.8)	231 (99.1)	72.971[2]	< 0.001
≤ 6	35 (31.2)	2 (0.9)		
> 7	30 (26.8)	229 (98.3)	206.622[2]	< 0.001
≤ 7	82 (73.2)	4 (1.7)		
> 8	10 (8.9)	212 (91.0)	222.015[2]	< 0.001
≤ 8	102 (91.1)	21 (9.0)		

[1]*t* value.
[2]χ^2 value.
[3]Z value.
M: Median; IQR: Interquartile range; SD: Short diameter on the cross-section; LD: Long diameter on a cross-section; RATIO: LD/SD; MOD: Maximum outer diameter.

appendicitis was ≤ 1.18, with a sensitivity of 91.0% and specificity of 83.0%. The AUC for the RATIO and MOD > 6 mm on the transverse section of the appendix for predicting acute appendicitis were 0.870 and 0.652, respectively; with a significant difference in AUC between RATIO ≤ 1.18 and MOD > 6 mm ($P < 0.0001$). The MOD > 6 mm on the transverse section of the appendix for diagnosing acute appendicitis had a sensitivity of 99.1%, specificity of 31.3%, and AUC of 0.652. The combination of RATIO ≤ 1.18 and MOD > 6 mm on the transverse section of the appendix for diagnosing acute appendicitis had a sensitivity of 90.1%, specificity of 92.0%, PPV of 95.9%, NPV of 81.7%, and AUC of 0.910. When comparing the combination of RATIO ≤ 1.18 and MOD > 6 mm to MOD > 6 mm alone for diagnostic performance, there was a significant increase in specificity, PPV, and AUC, but a decrease in sensitivity and NPV. The diagnostic performances of different reference criteria for the evaluating acute appendicitis are shown in Table 2. Figure 3 illustrates the comparisons among the AUCs of RATIO, MOD > 6mm, and the combination of RATIO ≤ 1.18 and MOD > 6 mm.

Table 2 Diagnostic performances of different criteria for evaluating acute appendicitis

Item	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC (95%CI)
RATIO (1.18)	91.0	83.0	91.8	81.6	0.870 (0.830-0.904)
MOD (> 6 mm)	99.1	31.3	75.0	94.6	0.652 (0.599-0.702)
RATIO + MOD > 6 mm	90.1	92.0	95.9	81.7	0.910 (0.875-0.938)

RATIO: Ratio of the cross diameters of the appendix; MOD: Maximum outer diameter on the transverse section of the appendix; PPV: Positive predictive value; NPV: Negative predictive value; AUC: Area under the receiver operating characteristic curve.

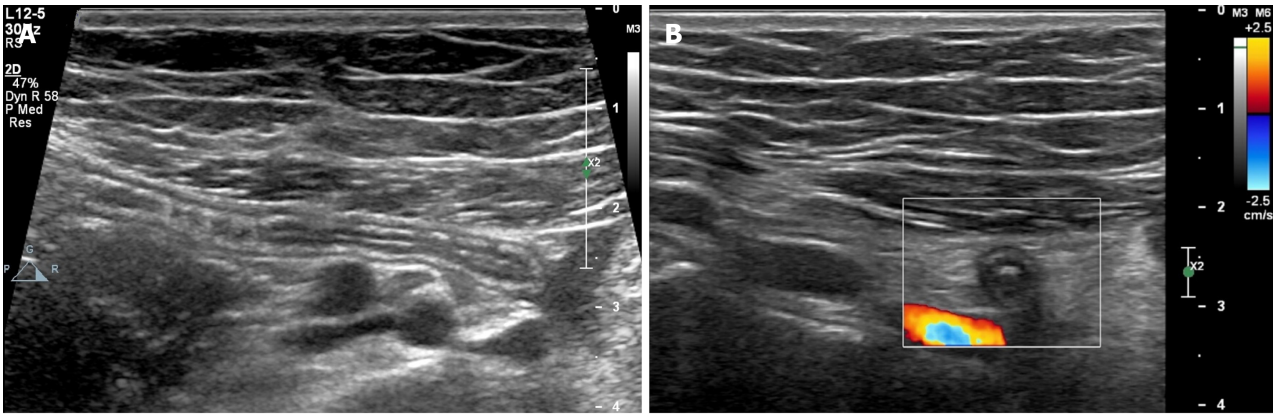

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Figure 1 A normal appendix. A: On the longitudinal view, the appendix appears as a blind-ending structure extending from the cecum in the abdominal cavity, the mural structures are clearly visible, there is no filling in the lumen, and the mucosa appears slightly hyperechoic with a thread-like appearance; B: On the transverse view, the appendix appears as an ovoid shape, the mural structures are visible, there is no filling in the lumen, and the ratio of the cross diameters on the transverse section is 5.9/5.3 = 1.11. Subsequent ultrasound examination revealed that the patient had a right ureter stone (not shown).

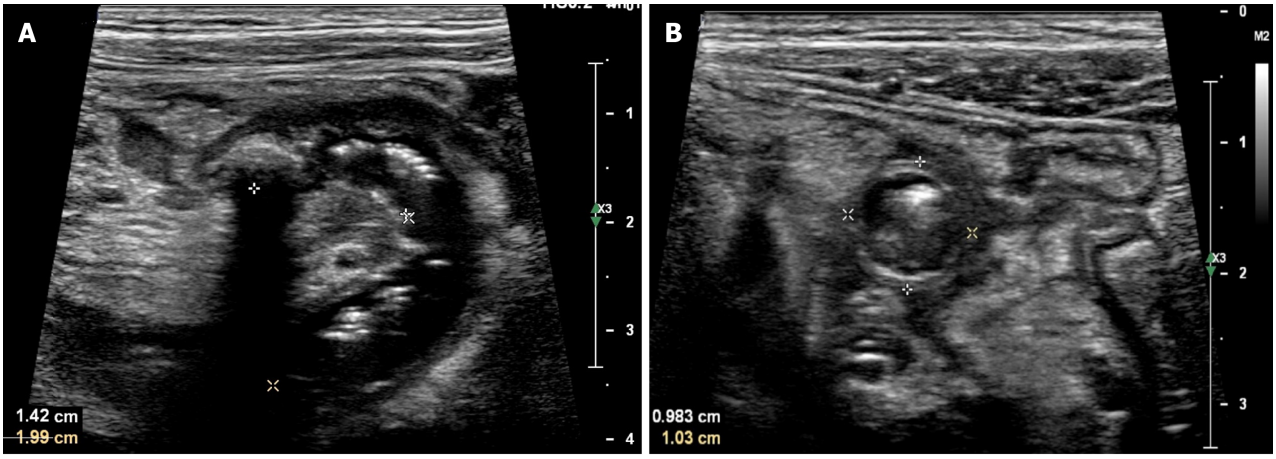

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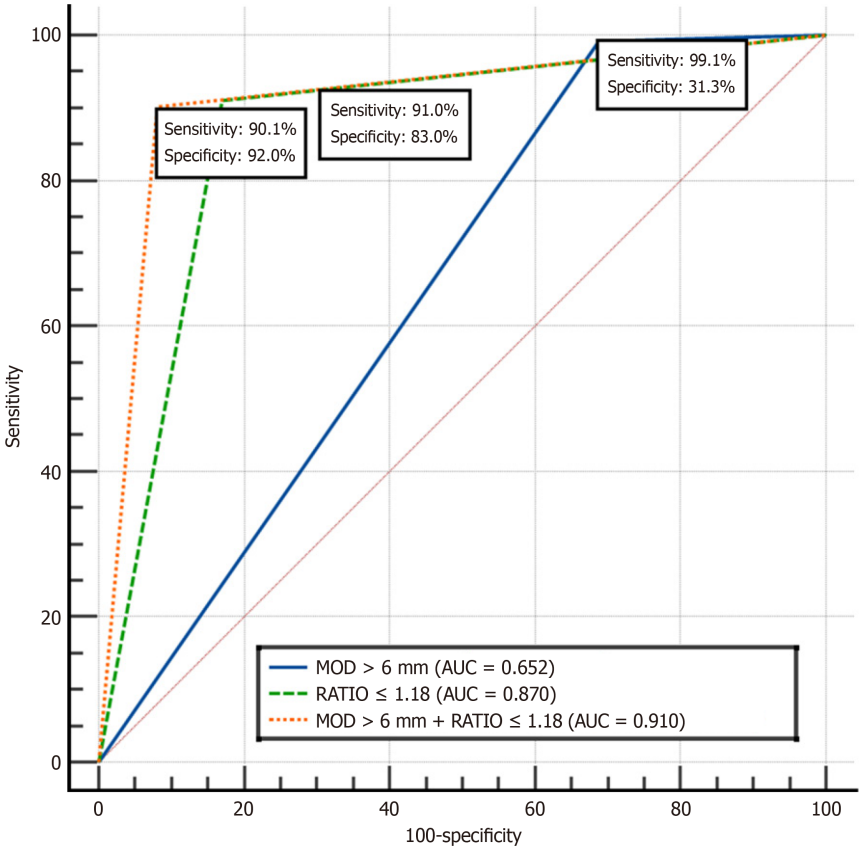
Figure 2 Acute appendicitis. The images obtained using ultrasound from a 12-year-old female patient who presented with right inferior quadrant abdominal pain, tenderness of the abdominal wall, and abdominal guarding. A: On the longitudinal view, the appendix appears as a bent, blind-ending tubular structure extending from the cecum, the mural structures of the appendix are unclear, and there are heterogeneous complex echogenic fillings in the lumen; B: On the transverse view, the appendix appears as a round shape, with dilating lumen, there are heterogeneous complex echogenic fillings in the lumen, and the ratio of the cross diameters on the transverse section is 10/9.8 = 1.02. Postoperative histopathology confirmed that the patient had acute phlegmonous appendicitis.

DISCUSSION

The clinical manifestations of acute appendicitis vary greatly, and the diagnosis is usually comprehensive, often requiring medical imaging for many patients with suspected acute appendicitis[1]. US is an important technique in the study of appendicitis. A meta-analysis has shown that US, computed tomography, and magnetic resonance imaging have comparable and high accuracy in helping diagnose appendicitis[12]. In experienced sonographers or physicians-in-US, US can



DOI: 10.4240/wjgs.v16.i1.21

Figure 3 The receiver operating characteristic curves of ratio of the cross diameters on transverse section of the appendix, maximum outer diameter> 6 mm, and maximum outer diameter > 6 mm + ratio of the cross diameters on transverse section of the appendix. MOD: Maximum outer diameter; AUC: Area under the receiver operating characteristic curve; RATIO: Ratio of the cross diameters of the appendix.

visualize the appendix in the majority of the examined population, except for obese individuals[11,13]. However, some patients may have equivocal sonographic features of the appendix, resembling both a normal appendix and acute appendicitis, such as a slightly thickened appendix or an ovoid shape on transverse section[14]. A study by Sezer *et al*[14] reported that US for the evaluation of acute appendicitis had an overall sensitivity of 71.4%, specificity of 78.5%, PPV of 94.8%, NPV of 33.3%, and accuracy of 72.5%. This suggests that US alone may not be satisfactory for the diagnosis of acute appendicitis. Rettenbacher *et al*[15] found that the presence of an ovoid shape on the transverse section of the appendix, covering the entire appendiceal length on US, can reliably rule out acute appendicitis. However, distinguishing between an ovoid shape and a round shape on sonography can sometimes be challenging when the two cross diameters have a marginal difference. In such cases, introducing the RATIO as a quantifying variable to characterize and analyze the features of the appendix may provide a more objective and reliable approach.

When using MOD > 6 mm as a reference for evaluating the appendix, the outcomes were a sensitivity of 99.1%, specificity of 31.3%, PPV of 75.0%, NPV of 94.6%, and AUC of 0.652. These results were lower than those reported by Rettenbacher *et al*[5],which showed a sensitivity of 100%, specificity of 68%, NPV of 100%, accuracy of 79%, and a lower PPV of 63%. The difference in sample size may contribute to the variation in outcomes. This finding is consistent with the study by Chicaiza *et al*[7], where using a cutoff of MOD 6 mm resulted in sensitivity and specificity of 100% and 43%, respectively, while using a cutoff of MOD 7 mm decreased the sensitivity to 94% and increased the specificity to 71%. Previous studies[16,17] have shown that lymphoid hyperplasia of the appendix, due to hypertrophy of lymphoid follicles in response to gastrointestinal inflammatory diseases, chronic constipation, and cystic fibrosis, can increase the MOD of the appendix. This can result in a noncompressible appendix with a borderline size of 6-8 mm in outer diameter, potentially leading to false-positive diagnoses of acute appendicitis based on MOD[16,17].

In this study, when using MOD > 6 mm and a combination of RATIO ≤ 1.18 and MOD > 6 mm as references for evaluating the appendix, the AUC of the combination of RATIO ≤ 1.18 and MOD > 6 mm increased significantly, along with an increase in specificity and PPV, and a decrease in sensitivity and NPV compared to using MOD > 6mm alone. These findings indicate that the combination of RATIO ≤ 1.18 and MOD > 6mm can address the bias of using MOD > 6 mm alone and significantly improve specificity, PPV, and AUC.

The strengths of this study include a large sample of patients with histopathologically confirmed acute appendicitis, ensuring the reliability of the results. Additionally, the establishment of the RATIO of cross diameters on the transverse section of the appendix introduces a new concept, adding valuable information to the existing literature.

There were some potential limitations in this study. Firstly, the retrospective study design may have resulted in the loss of certain information regarding the appendiceal structure. Secondly, patients with appendiceal perforation and appendiceal tumors were excluded, which means that not all US features of acute appendicitis were collected and analyzed. The appendiceal MOD in patients with appendiceal perforation may be smaller than 6 mm, and the shape and RATIO of the cross diameters on the transverse section of the appendix may differ from those without appendiceal perforation. Additionally, the inter- and intra-observer agreements of appendiceal measurements by different US performers were not determined due to the retrospective design, which may have affected the overall analysis of acute appendicitis. Furthermore, the patients without appendiceal identification and the US visualization rate of the appendix were not analyzed. This may have resulted in missed diagnoses of acute appendicitis with false-negative results, and non-appendiceal findings may have been present alongside appendiceal findings, which were not analyzed. These limitations may compromise the complete understanding of the vermiform appendix and acute appendicitis in this study.

CONCLUSION

A combination of a ratio ≤ 1.18 on the cross diameters on the transverse section of the appendix and MOD > 6 mm can significantly increase the specificity, PPV, and AUC compared to using MOD > 6 mm alone.

ARTICLE HIGHLIGHTS

Research background

Ultrasound (US) is commonly used for diagnosing acute appendicitis, but the diagnostic performance remains for further improvement. The size of the appendix is crucial for distinguishing between a normal appendix and acute appendicitis.

Research motivation

The maximal outside diameter on the cross section of the appendix > 6 mm has been recommended as a cut-off value for diagnosing acute appendicitis, but the minimal outside diameter and the ratio of the two outside diameters have not been adequately studied.

Research objectives

To investigate if the ratio of the two outside diameters on the cross section of the appendix is a useful parameter for diagnosing acute appendicitis.

Research methods

The investigators measured the two outside diameters on the cross section of a normal appendix and acute appendicitis without perforation using ultrasonography and calculated their ratio. The diagnostic performance of the maximal outside diameter, the ratio of two diameters on the cross section of the appendix, and their combination were compared.

Research results

A ratio of the diameter on the cross section of the appendix ≤ 1.18 was identified as a cut-off value for predicting acute appendicitis. The diagnostic performance based on the ratio of two diameters on the cross section of the appendix ≤ 1.18 was significantly higher than that of the maximal outside diameter.

Research conclusions

Combining the maximal outside diameter and the ratio of two diameters on the cross section of the appendix improved diagnostic performance compared to using the maximal outside diameter alone.

Research perspectives

Further prospective studies are needed to validate the findings and the use of a combination of the maximal outside diameter and the ratio of two diameters for US diagnosis of acute appendicitis.

FOOTNOTES

Author contributions: Gu FW participated in the study design, obtained the materials, analyzed the data, and wrote the first manuscript; Wu SZ participated in the study design, data obtaining and analysis, and wrote and revised the manuscript; all authors read and approved the final manuscript.

Institutional review board statement: The study was approved by the ethics committee of First Affiliated Hospital of Hainan Medical University.

Informed consent statement: No informed consent was required, because the data are anonymized.

Conflict-of-interest statement: No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at wsz074@aliyun.com.

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

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S-Editor: Qu XL
L-Editor: A
P-Editor: Xu ZH

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World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2024 January 27; 16(1): 29-39

DOI: 10.4240/wjgs.v16.i1.29

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

Oncological features and prognosis of colorectal cancer in human immunodeficiency virus-positive patients: A retrospective study

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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: Ekine-Afolabi B, United Kingdom; Vance D, United States

Received: September 29, 2023
Peer-review started: September 29, 2023
First decision: November 21, 2023
Revised: November 28, 2023
Accepted: December 19, 2023
Article in press: December 19, 2023
Published online: January 27, 2024

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Abstract

BACKGROUND

Due to the prolonged life expectancy and increased risk of colorectal cancer (CRC) among patients with human immunodeficiency virus (HIV) infection, the prognosis and pathological features of CRC in HIV-positive patients require examination.

AIM

To compare the differences in oncological features, surgical safety, and prognosis between patients with and without HIV infection who have CRC at the same tumor stage and site.

METHODS

In this retrospective study, we collected data from HIV-positive and -negative patients who underwent radical resection for CRC. Using random stratified sampling, 24 HIV-positive and 363 HIV-negative patients with colorectal adenocarcinoma after radical resection were selected. Using propensity score matching, we selected 72 patients, matched 1:2 (HIV-positive:negative = 24:48). Differences in basic characteristics, HIV acquisition, perioperative serological indicators, surgical safety, oncological features, and long-term prognosis were compared between the two groups.

RESULTS

Fewer patients with HIV infection underwent chemotherapy compared to patients without. HIV-positive patients had fewer preoperative and postoperative leukocytes, fewer preoperative lymphocytes, lower carcinoembryonic antigen levels, more intraoperative blood loss, more metastatic lymph nodes, higher node

stage, higher tumor node metastasis stage, shorter overall survival, and shorter progression-free survival compared to patients who were HIV-negative.

CONCLUSION
Compared with CRC patients who are HIV-negative, patients with HIV infection have more metastatic lymph nodes and worse long-term survival after surgery. Standard treatment options for HIV-positive patients with CRC should be explored.

Key Words: Colorectal cancer; Human immunodeficiency virus; Propensity score matching; Oncological features; Surgical safety; Prognosis

Core Tip: This study aimed to compare the differences in oncological features, surgical safety, and prognosis between colorectal cancer (CRC) patients with and without human immunodeficiency virus (HIV) infection. HIV-positive patients with CRC had more metastatic lymph nodes and worse long-term survival compared to patients without HIV infection; however, the risk of surgery was not increased. To our knowledge, our series of 24 postoperative patients represents the largest reported study of HIV-positive patients with CRC.

Citation: Yang FY, He F, Chen DF, Tang CL, Woraikat S, Li Y, Qian K. Oncological features and prognosis of colorectal cancer in human immunodeficiency virus-positive patients: A retrospective study. *World J Gastrointest Surg* 2024; 16(1): 29-39
URL: https://www.wjgnet.com/1948-9366/full/v16/i1/29.htm
DOI: https://dx.doi.org/10.4240/wjgs.v16.i1.29

INTRODUCTION

Since the widespread application of highly active antiretroviral therapy (HAART) starting in 1996, the survival period for patients with Acquired Immune Deficiency Syndrome (AIDS) has significantly increased, and the incidence rates of AIDS-defining cancers, Kaposi's sarcoma, non-Hodgkin lymphoma, and cervical cancer have significantly decreased[1-5]. However, the incidence rates of non-AIDS-defining cancers, such as colorectal cancer (CRC), liver cancer, lung cancer, anal cancer, and Hodgkin's disease, have increased[6,7], in a manner related to the prolonged life expectancy of patients with AIDS. These non-AIDS-defining cancers account for an increasing number of deaths among carriers of human immunodeficiency virus (HIV). According to GLOBOCAN 2020[8] data, approximately 1.93 million new cases of CRC were recorded worldwide in 2020, ranking third in malignant tumors (10.0%), after only breast (11.7%) and lung cancer (11.4%). In addition, approximately 930,000 (9.4%) people died from CRC, ranking it as the second most fatal malignant tumor, after only lung cancer (18.0%). The global number of new cases and deaths from CRC is increasing yearly. Compared to the general population, patients with AIDS have an increased incidence rate of CRC and earlier age of invasion, and are diagnosed at more advanced stages of disease[9].

During routine performance of CRC resection in our institute, our team discovered more suspicious positive lymph nodes in CRC patients with HIV infection. However, reports considering differences in oncological features and prognoses between CRC patients with the same tumor stage and tumor site with and without HIV infection are rare. However, given the prolonged life expectancy and increased risk of CRC among HIV-positive patients, it is important to understand the prognosis and pathological features of CRC in HIV-positive patients. Therefore, in the present study, we aimed to compare the differences in oncological features, surgical safety, and prognoses between patients with and without HIV infection who had CRC at the same tumor stage and tumor site.

MATERIALS AND METHODS

Patients and methods

We extracted the clinical data of patients who were diagnosed with CRC complicated with HIV infection and underwent radical CRC resection between January 1, 2012, and March 31, 2022 at our institute. Twenty-four cases were retrieved. After analysis, we observed that the pathological classification of all HIV-positive patients with CRC was adenocarcinoma, and no preoperative neoadjuvant chemotherapy or radiotherapy was administered. However, because our hospital conducts more than 1000 radical CRC operations every year, to control the sample size, we used random stratified sampling to collect the data of 363 HIV-negative colorectal adenocarcinoma patients who had not received preoperative neoadjuvant chemotherapy or radiotherapy, and had undergone radical CRC resection. We collected data on demographic characteristics, basic preoperative profile, preoperative HIV treatment, perioperative serological indicators, surgical outcomes, oncological characteristics, and patient survival. The authors did not utilize any artificial

intelligence tools.

Statistical analysis

Propensity score matching (PSM) analysis is widely used to minimize intervention or patient selection bias in non-randomized controlled studies and observational studies[10]. Herein, we used PSM to pair HIV-positive and -negative patients to reduce the impact of differences in baseline data between patients with and without HIV infection on the results, especially the effect on the number of metastatic lymph nodes. Before matching, we identified a cohort of patients with nearly 15 times as many patients without HIV infection as patients with HIV infection. However, matching at 1:1 would have resulted in substantial data loss and reduced the statistical power. Therefore, we applied 1:2 matching. Baseline data and variables that may affect the number of peri-intestinal lymph node metastases were applied to construct propensity scores, including age, sex, tumor site, degree of tumor differentiation, and tumor stage. The matching package was used to match the data for propensity scores, and 1:2 matching was adopted, with a caliper width limit of 0.1 SD of the logarithmic score. The matched groups were considered balanced if the standardized mean difference between them after matching was less than 0.1[11]. Categorical variables are expressed as frequencies (%), and continuous variables are expressed as medians (P25, P75). Categorical variables were analyzed using Fisher's exact or Chi-square tests, and continuous variables were analyzed using the Mann-Whitney *U* test. Statistical significance was set at $P < 0.05$. The Kaplan-Meier method was used to compare the overall survival and progression-free survival between the two groups, and the log-rank test was used to determine whether the differences were significant. Calculation of propensity scores and selection of the matched cohort were performed using R version 4.0.2 (R Foundation for Statistical Computing, 2020) with the MatchIt package. Other statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, United States). A biomedical statistician performed a statistical review of the study.

RESULTS

Baseline data

Twenty-four patients with HIV and 363 patients without HIV infection were initially enrolled, of whom a total of 72 were matched by PSM (HIV-positive:negative = 24:48, Table 1). Although the differences in all variables were non-significant both before and after matching, the differences in baseline data, such as tumor site, degree of differentiation, tumor stage, and age, decreased after matching.

Basic features

After PSM, fewer patients with HIV received chemotherapy than those without [29.2% *vs* 62.5%, $P = 0.008$]; however, there were no significant differences in CRC family history, main complications, smoking, drinking, abdominal surgery history, body mass index, or adverse reactions to chemotherapy (Table 2). All patients with HIV infection had latent disease, and no opportunistic infections were recorded. Fifteen patients were diagnosed with HIV infection prior to admission, and others were found to have HIV infection during preoperative screening. Fourteen patients underwent HAART before admission. Most patients were infected with HIV through sexual transmission. The median time difference between HIV and CRC diagnosis was 32 mo (range: 1–192 mo), the median CD4+ cell count before surgery was 459 cells/mm^3 (range: 158–1090 cells/mm^3), and the CD4+/CD8+ median was 0.71 (range: 0.22–2.10). Follow-up of patients with AIDS showed that only one patient was not medication adherent.

Postoperative outcomes

Table 3 presents the major peripheral venous blood indicators of the 72 patients. Compared to patients without HIV infection, patients with HIV infection had fewer preoperative leukocytes [5.36 (3.85, 6.70) *vs* 5.92 (4.95, 7.50), $P = 0.49$], postoperative leukocytes [6.91 (5.36, 8.84) *vs* 8.98 (6.97, 10.89), $P = 0.013$], and preoperative lymphocytes [1.19 (0.77, 1.48) *vs* 1.48 (1.18, 1.90), $P = 0.028$] and lower carcinoembryonic antigen (CEA) levels [2.27 (1.38, 3.10) *vs* 5.44 (2.90, 20.00), $P = 0.012$]. No significant differences were observed in preoperative or postoperative hemoglobin, postoperative lymphocytes, preoperative albumin, postoperative albumin and carbohydrate antigen 19-9 levels, or American Society of Anesthesiologists score. Surgical safety between the HIV-positive and -negative groups is shown in Table 4. Patients with HIV infection experienced greater intraoperative blood loss than those without [100 (50, 100) *vs* 50 (35, 100), $P = 0.46$]; however, no significant difference was observed between the two groups in terms of operation time, time to first flatus, time to first defecation, time to first liquid intake, time to ambulation, postoperative hospital stay, postoperative complications, admission to intensive care unit, time to discontinuing antibiotics, hospitalization expenses, performance status 1 mo after operation, long-term postoperative gastrointestinal discomfort, decrease in hemoglobin or albumin levels, intraoperative blood transfusion, enterostomy, or American Society of Anesthesiologists score. Two patients in each group had distant metastasis prior to the operation, one patient in the HIV-positive group had liver and lung metastasis, and three patients had only liver metastasis. No readmissions or deaths were recorded within 1 mo in either group. The median follow-up time for both HIV-positive patients and matched controls was 31 mo (2–91). Ten patients (41.7%) died (9 from cancer and 1 from other causes) in the HIV-positive group, while seven (14.6%) died in the control group (6 from cancer and 1 from other causes). CRC patients with HIV infection had a reduced overall survival (26 mo *vs* 37 mo, respectively) and progression-free survival (23.5 mo *vs* 37 mo, respectively) compared with the matched controls. The differences in overall survival ($P = 0.007$) (Figure 1) and progression-free survival ($P = 0.035$) (Figure 2) between the two groups were significant. However, it should be noted that two missing patients were recorded in each group at the

Table 1 Comparison of baseline data before and after propensity score matching

	Before PSM			After PSM		
	HIV-negative (*n* = 363)	HIV-positive (*n* = 24)	*P* value	HIV-negative (*n* = 48)	HIV-positive (*n* = 24)	*P* value
Sex			1			1
Male	211 (58.1)	14 (58.3)		29 (60.4)	14 (58.3)	
Female	152 (41.9)	10 (41.7)		19 (39.6)	10 (41.7)	
Age (yr)	66.3 ± 10.6	63.6 ± 12.0	0.283	64.3 ± 12.4	63.6 ± 12.0	0.808
Tumor			0.466			0.833
Proximal colon	126 (34.7)	7 (29.2)		11 (22.9)	7 (29.2)	
Distal colon	101 (27.8)	5 (20.8)		10 (20.8)	5 (20.8)	
Rectum	136 (37.5)	12 (50.0)		27 (56.2)	12 (50.0)	
Degree of differentiation			0.572			1
Low	36 (9.9)	3 (12.5)		6 (12.5)	3 (12.5)	
Moderate	316 (87.1)	20 (83.3)		40 (83.3)	20 (83.3)	
High	11 (3.0)	1 (4.2)		2 (4.2)	1 (4.2)	
Tumor stage			0.425			1
T1	18 (5.0)	0 (0.0)		0 (0.0)	0 (0.0)	
T2	53 (14.6)	6 (25.0)		13 (27.1)	6 (25.0)	
T3	200 (55.1)	13 (54.2)		25 (52.1)	13 (54.2)	
T4a	73 (20.1)	3 (12.5)		7 (14.6)	3 (12.5)	
T4b	19 (5.2)	2 (8.3)		3 (6.2)	2 (8.3)	

[1]The tumor sites of colorectal cancer were classified as proximal colon (ICD-O3C180-84), distal colon (ICD-O3C185-87), and rectum (ICD-O3C199, C209) according to the International Classification of Diseases in Oncology.
Variables are expressed as median (P25, P75) or *n* (%). PSM: Propensity score matching; HIV: Human immunodeficiency virus; T: Tumor.

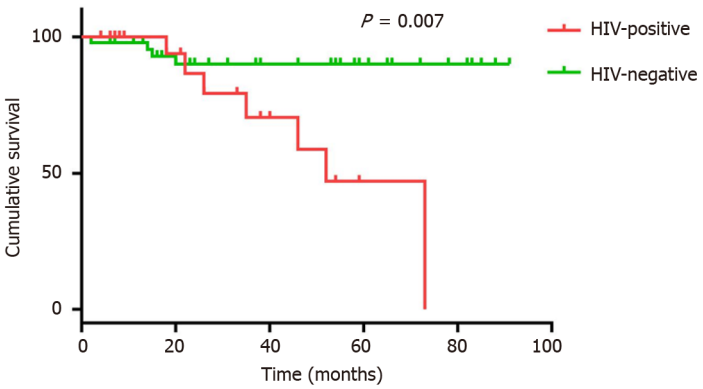

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Figure 1 Overall survival for patients with colorectal cancer with and without human immunodeficiency virus infection. HIV: Human immunodeficiency virus.

postoperative follow-up.

Oncological features

Patients with HIV infection had more lymph node metastases than patients without [1 (0, 3.5) *vs* 0 (0, 0), $P = 0.001$], higher node stage [1 (0, 1.75) *vs* 0 (0,1), $P = 0.005$], as well as higher tumor node metastasis (TNM) stage [3 (2, 3) *vs* 2 (2, 2.75), $P = 0.004$], whereas the harvested lymph nodes, size of the largest lymph node, metastasis, tumor size, microsatellite instability, *RAS* gene mutations, *BRAF* gene mutations, MLH1, MSH2, MSH6, and Ki-67 showed no significant

Table 2 Patient baseline data of the two groups

	HIV-positive (*n* = 24)	HIV-negative (*n* = 48)	*P* value
CRC family history	1 (4.2)	5 (10.4)	0.656
Main comorbidity	8 (33.3)	18 (37.5)	0.729
Hypertension	4 (16.7)	11 (22.9)	0.538
Diabetes mellitus	2 (8.3)	8 (16.7)	0.479
CHD	4 (16.7)	5 (10.4)	0.469
COPD	0	2 (4.2)	0.549
Drinking	6 (25)	16 (33.3)	0.469
Smoking	4 (16.7)	11 (22.9)	0.538
Abdominal surgery history	5 (20.8)	8 (16.7)	0.749
BMI (kg/m^2)	22.06 (19.71, 23.95)	23.02 (21.03, 25.17)	0.074
Chemotherapy	7 (29.2)	30 (62.5)	0.008
Adverse reactions of chemotherapy	2 (28.6)	15 (50)	0.416
Fever[1]	0	0	NA

[1]Recurrent fever before or after surgery.
Variables are expressed as median (P25, P75) or *n* (%). HIV: Human immunodeficiency virus; CRC: Colorectal cancer; CHD: Coronary atherosclerotic heart disease; COPD, Chronic obstructive pulmonary disease; BMI: Body mass index; NA: Not available.

Table 3 Comparison of perioperative serologic indicators between human immunodeficiency virus-positive and -negative patients

	HIV-positive (*n* = 24)	HIV-negative (*n* = 48)	*P* value
Preoperative leukocytes (10^9)	5.36 (3.85, 6.70)	5.92 (4.95, 7.50)	0.049
Postoperative leukocytes (10^9)	6.91 (5.36, 8.84)	8.98 (6.97, 10.89	0.013
Preoperative hemoglobin (g/L)	123.50 (101.25, 139.75)	128.00 (120.00, 140.00)	0.229
Postoperative hemoglobin (g/L)	121.50 (96.00, 127.00)	119.00 (107.25, 125.25)	0.976
Preoperative lymphocytes (10^9)	1.19 (0.77, 1.48)	1.48 (1.18, 1.90)	0.028
Postoperative lymphocyte	0.75 (0.49, 0.98)	0.79 (0.61, 1.07)	0.685
Preoperative albumin (g/L)	43.00 (37.00, 45.00)	41.00 (38.00, 44.00)	0.807
Postoperative albumin (g/L)	32.00 (28.00, 36.00)	29.00 (25.00, 34.75)	0.087
CEA (μg/L)	2.27 (1.38, 3.10)	5.44 (2.90, 20.00)	0.012
CA19-9 (U/mL)	13.96 (5.40, 20.85)	15.00 (6.99, 34.68)	0.983

Variables are expressed as median (P25, P75) or *n* (%). HIV: Human immunodeficiency virus; CEA: Carcinoembryonic Antigen; CA19-9: Carbohydrate antigen 199.

differences. No cases with positive margins were recorded in either group (Table 5). Table 6 shows the number of metastatic lymph nodes, node stage, and TNM stage in patients at different tumor stages.

DISCUSSION

To our knowledge, no studies have yet reported any differences in postoperative pathological features between patients with a combination of HIV infection and CRC and patients with CRC alone at the same tumor stage and tumor site. In this study, after matching factors that may affect lymph node metastasis in CRC using PSM, by comparing the oncological characteristics, surgical safety, and prognosis of the two groups of patients, we discovered that CRC patients with HIV infection had significantly more lymph node metastases than patients without (Table 5). This disparity may be related to the immunosuppression observed in patients with HIV infection. In addition, patients with HIV infection had

Table 4 Comparison of surgical outcomes between the two groups

	HIV-positive (*n* = 24)	HIV-negative (*n* = 48)	*P* value
Intraoperative blood loss (mL)	100 (50, 100)	50 (34, 100)	0.046
Operation time (min)	187.50 (151.25, 227.25)	195.00 (144.75, 240.00)	0.77
Time to first flatus (d)	3 (2, 4)	3 (2.25, 6)	0.668
Time to first defecation (d)	3 (1.25, 4.75)	3 (2, 6)	0.257
Time to first liquid intake (d)	2.5 (2, 3)	3 (2.25, 4)	0.064
Time to ambulation (d)	3 (3, 6.25)	3.5 (3, 4)	0.98
Postoperative hospital stay (d)	9 (7, 13.25)	8 (7, 11)	0.655
Postoperative complications	3 (12.5)	5 (10.4)	1.000
Admission to ICU	1 (4.2)	9 (18.8)	0.149
Time to stopping antibiotics (days)	2 (1, 2.75)	2 (1, 3.75)	0.679
Hospitalization expenses (thousand yuan)	78.7 (65.3, 88.6)	81.4 (67.5, 134.1)	0.173
PS at 1 mo after operation	1 (1, 1)	1 (1, 1)	0.48
Long-term postoperative gastrointestinal discomfort	8 (33.3)	12 (25)	0.457
Decrease in hemoglobin (g/L)	11 (0.5, 18.75)	12 (4, 22)	0.385
Decrease in albumin (g/L)	9.28 (4.75, 13.28)	12 (7, 15)	0.071
Intraoperative blood transfusion	1 (4.2)	1 (2.1)	1.000
Enterostomy	7 (29.2)	10 (20.8)	0.433
Readmission within 1 mo	0	0	NA
Death within 1 mo	0	0	NA
ASA score	3 (2, 3)	2 (2, 3)	0.713

Variables are expressed as median (P25, P75) or *n* (%). HIV: Human immunodeficiency virus; ICU: Intensive care unit; PS: Performance status; ASA: American Society of Anesthesiologists; NA: Not available.

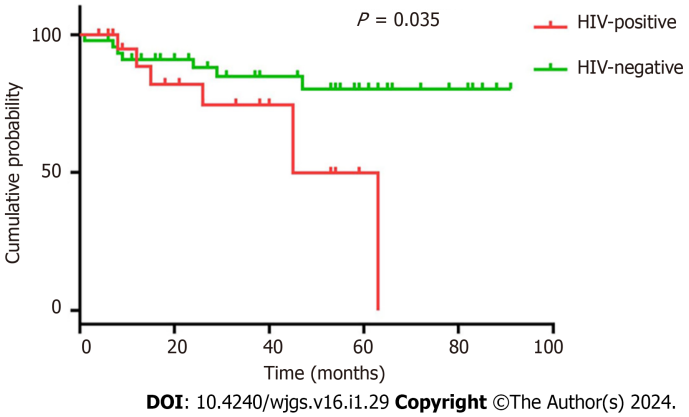

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Figure 2 Progression-free survival for patients with colorectal cancer with and without human immunodeficiency virus infection. HIV: Human immunodeficiency virus.

higher node stage and TNM stage than patients without. Regarding surgical outcomes, although patients with HIV infection had more intraoperative blood loss than patients without, the difference in the decrease in hemoglobin levels between the two groups was not significant. The significant increase in intraoperative blood loss in patients with HIV infection may be etiologically related to AIDS-defining illnesses, other comorbidities, lifestyle, and etiologies related to underlying HIV infection[12,13], while intraoperative blood loss was the expected value for the attending surgeon. Therefore, we concluded that the surgical safety of radical CRC surgery in patients with HIV infection was not worse than that of patients without. However, the overall survival and progression-free survival were shorter in patients with HIV infection.

Table 5 Oncological characteristics of patients in the two groups

	HIV-positive (*n* = 24)	HIV-negative (*n* = 48)	*P* value
Number of metastatic lymph nodes	1 (0, 3.5)	0 (0, 0)	0.001
Node stage	1 (0, 1.75)	0 (0, 1)	0.005
Harvested lymph nodes	13 (10, 15.75)	14.5 (11.25, 18)	0.223
Size of largest lymph node	0.85 (0.525, 1.45)	0.8 (0.5, 1)	0.318
Metastasis	2 (8.3)	2 (4.2)	0.597
TNM stage	3 (2, 3)	2 (2, 2.75)	0.004
Tumor size (cm)	3.75 (2.5, 5)	4 (3, 5)	0.497
Margin	0	0	NA
MSI	1 (11.1)	1 (6.3)	1
RAS gene mutation	3 (37.5)	13 (76.5)	0.087
BRAF gene mutation	0	1 (5.8)	1
MLH1	14 (82.4)	35 (92.1)	0.359
MSH2	16 (94.1)	37 (97.4)	0.527
MSH6	16 (94.1)	37 (97.4)	0.527
Ki-67 (%)	70 (60, 80)	60 (50, 80)	0.159

Variables are expressed as median (P25, P75) or *n* (%). HIV: Human immunodeficiency virus; MSI: Microsatellite instability; TNM: Tumor-Node-Metastasis; RAS: Rat sarcoma; BRAF: Serine/threonine protein kinase B-raf; MLH1: MutL homologue 1; MSH: Melanocyte-stimulating hormone; Ki-67: Antigen identified by monoclonal antibody Ki-67; NA: Not available.

Table 6 The number of metastatic lymph nodes, node stage, and tumor node metastasis stage in patients at different tumor stages

	T2 (*n* = 19)	T3 (*n* = 38)	T4a (*n* = 10)	T4b (*n* = 5)
Number of metastatic lymph nodes				
HIV-positive	1 (0, 1.25)	1 (0, 3.5)	0 (0, -)	6 (4, -)
HIV-negative	0 (0, 0)	0 (0, 0)	0 (0, 3)	1 (0, -)
Node stage (0/I/II)				
HIV-positive	2/4/0	5/5/3	2/0/1	0/0/2
HIV-negative	10/3/0/0	18/4/3	5/1/1	1/2/0
TNM stage (I/II/III/IV)				
HIV-positive	2/0/4/0	0/5/8/0	0/2/1/0	0/0/0/2
HIV-negative	11/0/2/0	0/20/4/1	0/5/2/0	0/0/2/1

Variables are expressed as median (P25, P75) or *n*. HIV: Human immunodeficiency virus; T: Tumor; TNM: Tumor-Node-Metastasis.

The CEA levels of CRC patients with HIV infection were lower than those of patients without. Normal and cancerous tissues produce approximately the same amount of CEA[14,15], with healthy adults excreting approximately 50–70 mg of CEA daily in their feces[14]. Most of the CEA produced by the human body is excreted through the intestine. CEA has been indicated to function in innate immunity[16,17] and to prevent microorganisms from invading the intestinal epithelial cells[17]. However, owing to immune deficiency, the intestinal mucosa of people with HIV infection has decreased resistance to intestinal flora, resulting in a greater release of CEA into the intestine to resist microorganisms. Conversely, blood CEA levels decrease[16,17].

The incidence of CRC in China has increased from 17.1/100000 in 2013 to 26.4/100000 in 2020[8,18]; thus, we estimated that the total incidence rate of CRC in China in the last 10 years was 220/100000. Regarding HIV infection, approximately 64000 patients with AIDS survived, and 21000 died in our region as of October 2022. Therefore, we estimated that approximately 140 patients with AIDS and CRC would have been diagnosed in our region over the past 10 years. Admittedly, this estimation method is inaccurate, as we did not consider the influence of AIDS on the incidence of CRC and the different incidences of CRC in different regions of China. However, as we were unable to access data on HIV-positive

patients with CRC in our region, we used this rough method for estimation.

According to our hospital data, 65 cases of HIV-positive patients with colorectal adenocarcinoma were recorded during the study period; considering that some patients were not treated, we believe that our hospital admitted more than half of the patients with HIV infection and CRC in our province, which is a relatively high proportion. Although the sample size of the HIV-positive group was only 24, which was limited by the stringent inclusion criteria and low incidence of AIDS, we believe that the sample size of our study is relatively large compared to those previously published in the literature. The prior study by Wasserberg *et al*[19] included only 11 HIV-positive patients with CRC, some of whom did not undergo surgery. Another study[20] comparing the clinical presentation and prognosis of patients with and without HIV infection included 27 patients with HIV infection and CRC, of whom four HIV-positive patients underwent surgery. Thus, our series of 24 postoperative patients represents the largest study of patients with HIV infection and CRC reported in the literature to date.

Whether HIV infection increases the risk of CRC remains controversial. Most studies suggest that HIV infection decreases immunity even though HARRT increases life expectancy in patients with HIV infection, leading to an increased risk of malignancy[6,7,21,22]. Some studies have reported no difference in CRC prevalence between patients with and without HIV infection[23]. Conversely, some have suggested that patients with HIV infection have a lower risk of CRC [24]. Reinhold *et al*[21] previously discovered that patients with HIV infection were less likely to undergo CRC screening tests than uninfected patients. This may account for the lower risk of CRC reported by some studies in patients with HIV infection.

In addition, similar to the report of Suneja *et al*[25,26], we observed that patients with HIV infection were less likely to undergo chemotherapy than patients without. Differences in access to cancer treatment may partially explain the shorter survival of patients with HIV infection and cancer. Suneja *et al*[25,26] suggested that many treatment providers may believe that patients with HIV infection are in poorer organismal condition, meaning that they will be less tolerant of treatment, and less likely to adhere to treatment regimens than patients without, thus reducing their chances of receiving systemic therapy. In addition, the lack of specific treatment guidelines for patients with HIV infection and cancer is an important reason for the low proportion of patients with HIV infection receiving systemic therapy[26]. From the patient's perspective, those with HIV infection may be more reluctant to receive systemic therapy for oncology because of concerns about the side-effects of chemotherapy, an inadequate understanding of the need for cancer treatment, or the burden of the dual management of cancer and HIV infection[25]. However, there may be additional medical reasons why patients with HIV infection and CRC have a worse long-term prognosis than those without. Further high-quality studies are needed to explore these reasons.

Available data suggest that CRC patients with HIV infection are more severely ill and younger than those without[9]. In one study, Berretta *et al*[20] compared the clinical presentation and outcomes of 27 CRC patients with HIV infection and 54 age- and sex-matched CRC controls and concluded that patients with HIV infection had poorer performance status and unfavorable Dukes stages. Further, Bini *et al*[9] published the results of a screening colonoscopy study in which the prevalence of colon cancer was assessed in 136 asymptomatic CRC patients with HIV infection who were ≥ 50 years old and 272 asymptomatic uninfected controls with CRC matched by age, sex, and CRC family history. The authors discovered that the prevalence of neoplastic lesions was significantly higher in patients with HIV infection than in controls, even after adjusting for potential confounding variables. In the present study, although we eliminated the age difference after PSM, patients with HIV infection still had significantly more metastatic lymph nodes than patients without (Table 5), while overall survival and progression-free survival were significantly shorter in patients with HIV infection than in those without (Figures 1 and 2). This result is consistent with the findings of Berretta *et al*[20].

André *et al*[27] and Berretta *et al*[28] both concluded that the combination of HAART did not increase the toxicity of FOLFOX4. Currently, the advantages of immunotherapy are being gradually explored. Patients with HIV infection have reduced immunity, regardless of the CD4+ T-cell count; thus, because of the fear of increased HIV viral replication and increased toxicity in the presence of T-cell activation[29], they are usually excluded from trials of immune checkpoint inhibitors, and we currently lack data on the efficacy of immunotherapy in this population. The safety and efficacy of immunotherapy for HIV-infected patients with malignancies remain unclear. The phase 1 trial by Uldrick *et al*[30] revealed that PD-1 monoclonal antibodies are safe for use in patients with HIV infection taking HAART with CD4+ T-cell counts above 100 cells/μL. In addition, the results of Cao *et al*[31] demonstrated that PD-L1/PD-1 interactions may induce an immune environment favorable for tumor development.

Chemotherapy and immunotherapy have a better safety profile during CRC treatment in patients with well-controlled HIV infection; however, caution should be exercised when treating patients with more severe disease and advanced immunosuppression. Notably, HAART with prophylaxis for opportunistic infections should be administered during treatment, and patients should be closely monitored for CD4+ T-cells and serum viral levels. Nonetheless, the reasons for poorer CRC prognoses in patients with HIV infection are unclear, with more advanced diagnosis, inadequate treatment [32], and decreased immune function being possibilities .

Although this was a retrospective study, we used PSM to reduce the differences in baseline data between the two patient groups and to minimize the impact of baseline differences on the outcomes. This allowed better comparison of the postoperative oncological characteristics, surgical safety, and prognosis of patients with and without HIV infection who had CRC at the same tumor stage and site treated by radical resection. Therefore, we believe that the methodology of our study is scientific and that the conclusions are reliable and meaningful. However, we were unable to obtain specific data on AIDS-related symptoms and preoperative or postoperative HAART treatment. As mentioned earlier, patients with HIV infection are more reluctant to receive postoperative adjuvant therapy for malignancies. In addition, standard treatment protocols may not be possible in patients with poorly controlled HIV infection. Therefore, clinicians should direct their attention towards providing patients with prompt treatment, and research should be directed at the rapid development of appropriate treatments. Moreover, the treatment process should be monitored. We hope that more in-

depth studies will be conducted to focus on the efficacy and safety of adjuvant therapy in malignant tumors, to further clarify the interactions of HIV with malignant tumors, and to develop more appropriate treatment plans.

This study had some limitations which should be mentioned. First, although our study had a larger sample size than most AIDS-related clinical studies, the sample size of this study is small compared to that of studies examining the relationship between common diseases and CRC, as it was limited by the low prevalence of AIDS. Second, we did not analyze the relationship between the severity of HIV infection and the prognosis of CRC in the HIV-positive group. Third, because of the small sample size of the two groups of patients with different tumor stages (Table 6), their differences could not be compared. Fourth, we did not specifically analyze the differences in the regimen and cycles of chemotherapy treatments between the two groups of patients. Studies with larger sample sizes are required to further reveal the impact of HIV infection on the oncologic characteristics, prognosis, and safety of surgery in CRC.

CONCLUSION

Compared to CRC patients without HIV infection, HIV-positive patients with CRC with the same stage and site have a higher number of lymph node metastases and worse postoperative long-term survival; however, surgical risks are not increased. Overall, patients with HIV infection and CRC have a worse prognosis. Therefore, clinicians should focus on treating this population more aggressively and should explore standard treatment options for them. We look forward to further studies on HIV-associated malignancies.

ARTICLE HIGHLIGHTS

Research background

Human immunodeficiency virus (HIV) infection may accelerate the progression of colorectal cancer (CRC). Given the prolonged life expectancy and increased risk of CRC among patients with HIV infection, the prognosis and pathological features of CRC in this population should be examined. This study aimed to compare the differences in oncological features, surgical safety, and prognosis between CRC patients with and without HIV infection.

Research motivation

Differences in oncological features and prognoses between HIV-positive and -negative patients at the same stage and site have rarely been reported.

Research objectives

To compare the oncological characteristics, surgical safety, and prognoses between HIV-positive and -negative patients at the same stage and site.

Research methods

In this study, after matching the two patient groups for factors that may affect lymph node metastasis in CRC using propensity score matching (PSM), we compared the oncological characteristics, surgical safety, and prognosis of the two groups of patients. Then, Fisher's exact, Chi-square, and Mann–Whitney *U* tests were applied to conduct statistical analyses on the demographic characteristics, basic preoperative profile, preoperative HIV treatment, perioperative serological indicators, surgical outcomes, oncological characteristics, and survival of the two groups of patients.

Research results

Compared to patients without HIV infection, patients with HIV infection were more reluctant to receive chemotherapy. Clinically, this group of patients had fewer preoperative and postoperative leukocytes, fewer preoperative lymphocytes, lower carcinoembryonic antigen levels, more intraoperative blood loss, more metastatic lymph nodes, higher node stage, higher tumor node metastasis stage, shorter overall survival, and shorter progression-free survival. These findings suggest that the willingness and appropriate treatment of HIV-positive patients with CRC need more attention.

Research conclusions

Compared to CRC patients without HIV infection, HIV-positive patients with CRC at the same stage and site have a higher number of lymph node metastases and worse postoperative long-term survival; however, the risk of surgery is not increased.

Research perspectives

The reasons that fewer CRC patients with HIV infection receive chemotherapy need to be explored. Appropriate treatments for this patient group should be developed.

ACKNOWLEDGEMENTS

The authors are grateful to all their colleagues who helped prepare this article. We thank Yi Xiao for his diligence in data entry. The authors have not applied any AI tools.

FOOTNOTES

Co-first authors: Fu-Yu Yang and Fan He.

Author contributions: Yang FY contributed to the conception and design of the study; Qian K provided the study materials and patients; Yang FY and He F wrote the first draft of the manuscript; Chen DF and He F collected and assembled the data; He F, Woraikat S, Tang CL, and Li Y contributed to the manuscript modification; all authors contributed to the manuscript writing and revision, and approved the submitted version. The reasons for designating Yang FY and He F as co-first authors are twofold. First, the research was performed as a collaborative effort, and the designation of co-first authorship accurately reflects the distribution of responsibilities and burdens associated with the time and effort required to complete the study and the resultant paper. This also ensures effective communication and management of post-submission matters, ultimately enhancing the paper's quality and reliability. Second, Yang FY and He F contributed efforts of equal substance throughout the research process. The choice of these researchers as co-first authors acknowledges and respects this equal contribution, while recognizing the spirit of teamwork and collaboration of this study. In summary, we believe that designating Yang FY and He F as co-first authors is fitting for our manuscript as it accurately reflects our team's collaborative spirit, equal contributions, and diversity.

Supported by General Plan of the Future Medical Youth Innovation Team Development Support Plan of Chongqing Medical University, No. 03030299QC-W0007.

Institutional review board statement: This study was reviewed and approved by the Medical Ethics Committee of Chongqing Medical University (No. K2023-019). The study was carried out in accordance with the Declaration of Helsinki.

Informed consent statement: Informed consent has been waived by the Research Ethics Committee.

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

Data sharing statement: The original anonymous dataset is available on request from the corresponding author at 3069443005@qq.com.

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

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S-Editor: Lin C
L-Editor: Wang TQ
P-Editor: Yu HG

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World Journal of Gastrointestinal Surgery

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World J Gastrointest Surg 2024 January 27; 16(1): 40-48

DOI: 10.4240/wjgs.v16.i1.40

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

Laparoscopic *vs* open surgery for gastric cancer: Assessing time, recovery, complications, and markers

Yun-Yao Lu, Yun-Xiao Li, Meng He, Ya-Li 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, C, C
Grade D (Fair): 0, D
Grade E (Poor): 0

P-Reviewer: Buchert M, Australia; Kang SY, South Korea; Gaetano Gallo, Italy; Arun Prasad, India

Received: September 5, 2023
Peer-review started: September 5, 2023
First decision: September 14, 2023
Revised: September 22, 2023
Accepted: November 8, 2023
Article in press: November 8, 2023
Published online: January 27, 2024

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Abstract

BACKGROUND

Gastric cancer (GC) is one of the most common cancers worldwide. Morbidity and mortality have increased in recent years, making it an urgent issue to address. Laparoscopic radical surgery (LRS) is a crucial method for treating patients with GC; However, its influence on tumor markers is still under investigation.

AIM

To determine the effects of LRS on patients with GC and their serum tumor markers.

METHODS

The data of 194 patients treated at Chongqing University Cancer Hospital between January 2018 and January 2019 were retrospectively analyzed. Patients who underwent traditional open surgery and LRS were assigned to the control (n = 90) and observation groups (n = 104), respectively. Independent sample t-tests and χ^2 tests were used to compare the two groups based on clinical efficacy, changes in tumor marker levels after treatment, clinical data, and the incidence of postoperative complications. To investigate the association between tumor marker levels and clinical efficacy in patients with GC, three-year recurrence rates in the two groups were compared.

RESULTS

Patients in the observation group had a shorter duration of operation, less intraoperative blood loss, an earlier postoperative eating time, and a shorter hospital stay than those in the control group ($P < 0.05$). No significant difference was observed between the two groups regarding the number of lymph node dissections ($P > 0.05$). After treatment, the overall response rate in the control group was significantly lower than that in the observation group ($P = 0.001$).

Furthermore, after treatment, the levels of carbohydrate antigen 19-9, cancer antigen 72-4, carcinoembryonic antigen, and cancer antigen 125 decreased significantly. The observation group also exhibited a significantly lower incidence rate of postoperative complications compared to the control group ($P < 0.001$). Additionally, the two groups did not significantly differ in terms of three-year survival and recurrence rates ($P > 0.05$).

CONCLUSION

LRS effectively treats early gastric cancer by reducing intraoperative bleeding, length of hospital stays, and postoperative complications. It also significantly lowers tumor marker levels, thus improving the short-term prognosis of the disease.

Key Words: Laparoscopic radical surgery; Gastric cancer; Serum tumor markers; Prognosis; Recurrence; Intraoperative bleeding

Core Tip: Laparoscopic radical surgery (LRS) is an effective treatment option for early gastric cancer (GC). Compared with open surgery, LRS offers shorter operation times, less intraoperative blood loss, quicker postoperative recovery, and fewer complications. LRS also contributes to a better short-term prognosis and significantly reduces the levels of tumor markers, such as carbohydrate antigen 19-9, carbohydrate antigen 72-4, carcinoembryonic antigen, and carbohydrate antigen 125. Even in patients with advanced GC, LRS can lower the incidence of postoperative complications and contribute to favorable long-term prognosis.

Citation: Lu YY, Li YX, He M, Wang YL. Laparoscopic *vs* open surgery for gastric cancer: Assessing time, recovery, complications, and markers. *World J Gastrointest Surg* 2024; 16(1): 40-48
URL: https://www.wjgnet.com/1948-9366/full/v16/i1/40.htm
DOI: https://dx.doi.org/10.4240/wjgs.v16.i1.40

INTRODUCTION

Gastric cancer (GC), a malignancy affecting the gastrointestinal tract, stands as a leading cause of cancer-related fatalities worldwide[1]. According to statistics, > 400000 people in China suffer from GC annually. GC accounts for > 20% of total mortality caused by malignant tumors, with increasing annual incidence and mortality rates[2]. The disease often has no obvious clinical symptoms in the early phase and is easily confused with chronic diseases such as gastritis; therefore, most patients are diagnosed in the progressive stage. Early GC usually refers to a tumor with lesions confined to the mucosa or submucosa, with no direct relationship with lesion diameter or lymph node metastasis[3].

Factors such as precancerous lesions, *Helicobacter pylori* infection, poor lifestyle and dietary habits, and regional environmental factors have strong associations with GC development[3]. Measures such as improving eating habits, maintaining a good lifestyle, regular stomach examinations, and awareness of hereditary factors can help lower the risk of developing GC[4]. Further, factors such as tumor location, pathology, and biological behaviors impact the prognosis of patients with GC. Early radical surgery has the potential to enhance prognosis and prolong survival over 3–5 years[5].

Currently, radical surgery is the primary treatment choice for GC, especially in cases of early-stage GC[5]. Commonly adopted surgical methods include open and laparoscopic surgeries. Open surgery can effectively remove tumors at metastatic sites, resulting in a better prognosis; however, it is associated with significant trauma, which is not conducive to postoperative recovery[6,7]. Recently, local, and foreign general surgeons have extensively adopted advanced laparoscopic surgical technology[8]. With significant advantages in cutting off blood vessels and dissecting lymph nodes, laparoscopic radical surgery (LRS) can reduce surgical trauma and provide a higher anatomical resolution for surgeons [9]. Further, LRS may somewhat lower the risk of postoperative complications in patients with GC[10]. Accordingly, it is considered an effective and promising treatment method.

Tumor markers refer to substances produced during tumor development and progression, whose levels are used to judge their presence and stage of progression[11]. Tumor markers are crucial for tumor-based early screening, diagnosis, treatment effect evaluation, and disease monitoring. However, the effect of LRS on tumor marker levels is still under investigation.

This study aimed to determine the effects of LRS on serum levels of tumor markers in patients with GC, and hence provide a reference for clinical efficacy evaluation.

MATERIALS AND METHODS

General data

Data from 355 patients with GC treated at the Chongqing University Cancer Hospital between January 2018 and January 2019 were retrospectively analyzed.

Inclusion criteria: (1) All patients confirmed gastric cancer by pathological examination; (2) Patients with complete relevant data during hospitalization; (3) Patients who met the indications for surgical treatment; (4) Patients with a Karnofsky function score ≥ 60 points; and (5) Patients who understood the study and agreed to participate in it voluntarily.

Exclusion criteria: (1) Patients with other tumor-related diseases; (2) Patients with immune system diseases; (3) Patients with severe liver or kidney dysfunction; (4) Patients with mental disorders; and (5) Patients unable to communicate normally.

A total of 194 patients who met the inclusion criteria were enrolled. Patients who underwent traditional open surgery and LRS were assigned to the control (n = 90) and observation groups (n = 104), respectively.

Collection of clinical indexes

The clinical and laboratory examination data of the patients were collected using our hospital's laboratory information system. Clinical data included sex, age, body mass index (BMI), American Society of Anesthesiologists (ASA) classification score, history of abdominal surgery, and medical history. General information included operation time, intraoperative blood loss, number of lymph node dissections, postoperative complications, postoperative eating time, length of hospital stays, and recurrence rates within 3 years. Laboratory indicators included carbohydrate antigen 19-9 (CA19-9), carbohydrate antigen 72-4 (CA72-4), serum carcinoembryonic antigen (CEA), and carbohydrate antigen 125 (CA125).

Evaluation criteria for efficacy

Markedly effective: After treatment, symptoms such as pain disappeared completely, without complications during the perioperative period, and the tumor was completely removed, with negative cancer cell biopsy lasting for > 1 mo.

Effective: Clinical symptoms were alleviated without complications during the perioperative period, and the tumor shrank by 50%, with negative cancer cell biopsy lasting for ≤ 1 mo.

Outcome measures

Comparison of treatment efficacies and tumor marker level alterations post-treatment between the two groups. Comparative analysis of clinical and general data of the two groups, along with a comparison of the incidence of postoperative complications. Investigation of the association between tumor markers and clinical efficacy by comparing the three-year recurrence rates in the two groups.

Statistical analyses

Based on the retrieved literature on the efficacy of surgery for gastric cancer patients (80% for open surgery and 95% for minimally invasive surgery), we can estimate that approximately 73 patients would be needed in each group while maintaining statistical significance ($\alpha = 0.05$) and sufficient statistical efficacy (80%). This estimate is based on theoretical differences, and in practice a larger sample size may be needed to compensate for the possibility of data loss or follow-up failure. Therefore, the actual sample size may be adjusted according to the specifics of the clinical trial (*e.g.*, feasibility of patient recruitment, expected lost-to-follow-up rate, etc.). Specifics are collected according to the actual clinical situation.

SPSS 26.0 (IBM, Armonk, NY, Unted States) and GraphPad Prism 9 (GraphPad Software, San Diego, California, Unted States) software were used for data analysis. Counting data were described as rates (percentages), and inter-group comparisons were performed using the χ^2 test. Measurement data are described as mean ± SD, and inter-group comparisons were conducted using the independent-sample t-test. Receiver operating characteristic curves were drawn to analyze the levels of the tumor markers in predicting clinical efficacy. A significance level of $P < 0.05$ was chosen to indicate statistical significance.

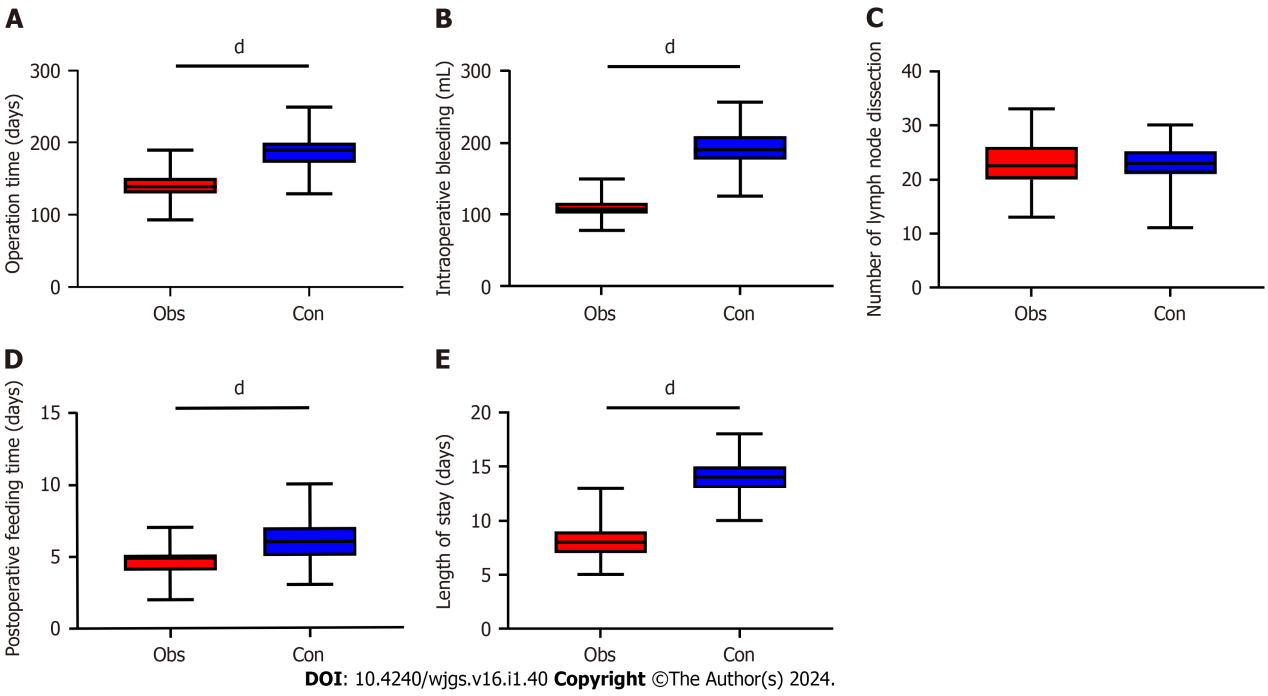
RESULTS

Clinical data

Based on the comparison of clinical data, the control and observation groups did not differ significantly in sex, age, BMI, ASA score, history of abdominal surgery, or medical history ($P > 0.05$, Table 1).

General data

Duration of operation, intraoperative blood loss, number of lymph node dissections, postoperative eating time, and length of hospital stay in the two groups were recorded. The patients in the observation group experienced a shorter duration of operation, less intraoperative blood loss, earlier postoperative eating time, and shorter length of hospital stay than those in the control group ($P < 0.05$, Figure 1). However, the number of lymph node dissections did not significantly differ between the two groups ($P > 0.05$).



DOI: 10.4240/wjgs.v16.i1.40

Figure 1 Comparison of general data of patients before and after operation. A-E: The factors compared were Operation time (A); intraoperative blood loss (B); number of lymph node dissections (C); postoperative eating time (D); and length of hospital stay (E). $^{d}P < 0.0001$.

Clinical efficacy

Based on evaluated clinical efficacy in the two groups, the patients in the control group showed a significantly lower overall response rate than those in the observation group ($P = 0.001$; Table 2).

Changes in tumor marker levels

Tumor marker (CA19-9, CA72-4, CEA, and CA125) levels were compared between the two groups. Before treatment, the two groups had similar levels of CA19-9, CA72-4, CEA, and CA125 ($P>0.05$), which decreased significantly after treatment ($P < 0.001$); tumor marker levels in the observation group were lower than those in the control group ($P < 0.001$, Figure 2).

Statistical analysis of postoperative complications

Statistical analysis of the postoperative complications in the two groups revealed a lower incidence of postoperative complications in the observation group than in the control group ($P < 0.001$; Table 3).

Comparison of recurrence rates in the patients

Three-year follow-up showed that recurrence rates were comparable between the two groups, with the observation group at 20% and the control group at 22%. Thus, no significant difference was found ($P > 0.05$, Table 4).

DISCUSSION

For early GC, surgical treatment is mainly performed in clinical practice[12]. Open surgery can directly remove the focus lesion; however, it results in higher incidence of complications owing to large trauma, more intraoperative bleeding, long recovery time, poor prognosis, complex tissue structure around the stomach, difficult operation procedure, and long exposure time of the organs[13,14]. Therefore, developing a surgical method with less trauma, quick recovery, and minimal impact on immunity is of great practical importance. Laparoscopic surgery is minimally invasive and has become a commonly adopted method for treating GC after several years of development[15]. This study is the first to compare the effects of open and laparoscopic surgeries in patients. Here, patients in the observation group had a shorter duration of operation, less intraoperative blood loss, earlier postoperative eating time, and shorter length of hospital stay with a higher overall response rate than those in the control group; however, the two groups did not significantly differ in the number of lymph node dissections. These results imply that LRS shortens the duration of operation, reduces intraoperative blood loss, and accelerates postoperative recovery of gastrointestinal function. According to Kim *et al*[16], found that, patients who underwent LRS had a shorter recovery duration and a near-ideal surgical effect, consistent with the results of this study. This may be possible because treating GC using LRS guided by an endoscope enables surgeons to observe the anatomical structure of the stomach and its surrounding tissues clearly, allowing for quick and accurate separation of the anatomical level and cleaning of more lymph nodes. In addition, laparoscopic surgery is minimally

Table 1 Clinical data

Factors	Control group (*n* = 90)	Observation group (*n* = 104)	χ^2 value	*P* value
Sex			0.335	0.562
Male	59	64		
Female	31	40		
Age (yr)			0.533	0.465
≥ 60	48	50		
< 60	42	54		
BMI (kg/m^2)			0.359	0.548
≥ 25	25	33		
< 25	65	71		
ASA score			2.300	0.129
Phase II	44	35		
Phase III	56	69		
History of abdominal surgery			1.218	0.269
Yes	12	20		
No	78	84		
Medical history				
Hypertension	28	35	0.142	0.706
Diabetes mellitus	19	27	0.627	0.428

Table 2 Clinical efficacy evaluation

Group	Control group (*n* = 90)	Observation group (*n* = 104)	χ^2 value	*P* value
Markedly effective	40 (44.44)	70 (67.31)	10.656	0.001
Effective	32 (35.56)	34 (32.69)		
Ineffective	18 (20.00)	5 (4.81)		
Total effective rate	72 (20.00)	99 (95.19)		

Table 3 Complications

Group	Control group (*n* = 90)	Observation group (*n* = 104)	χ^2 value	*P* value
Subcutaneous emphysema	8	1	13.36	< 0.001
Incision infection	4	3		
Ileus	4	2		
Seroperitoneum	5	2		
Anastomotic leakage	5	1		
Total incidence rate	26 (28.89%)	9 (8.65%)		

invasive, shortening the operational duration of laparotomy and abdominal closure and reducing abdominal nerve and muscle injury, as well as mechanical traction injury of abdominal organs. Intraoperative blood loss is lower and postoperative pain is milder, promoting postoperative gastrointestinal function recovery. In addition, in this study, the observation group had a lower incidence of postoperative complications than the control group, which was mainly due to lower trauma and stress response after LRS.

Tumor markers are biological substances associated with tumor growth, development, and metastasis. They mainly include proteins, enzymes, genes, antigens, and hormones produced by tumor cells or surrounding tissues, which can be detected in the blood, urine, tissue, and other body fluids[17]. Tumor markers have important clinical applications in

Table 4 Comparison of recurrence and survival rates

Group	Control group (n = 90)	Observation group (n = 104)	χ^2 value	P value
3-year survival rate	64 (71.11)	73 (69.23)	0.081	0.775
3-year recurrence rate	14 (15.56)	18 (17.31)	0.107	0.743

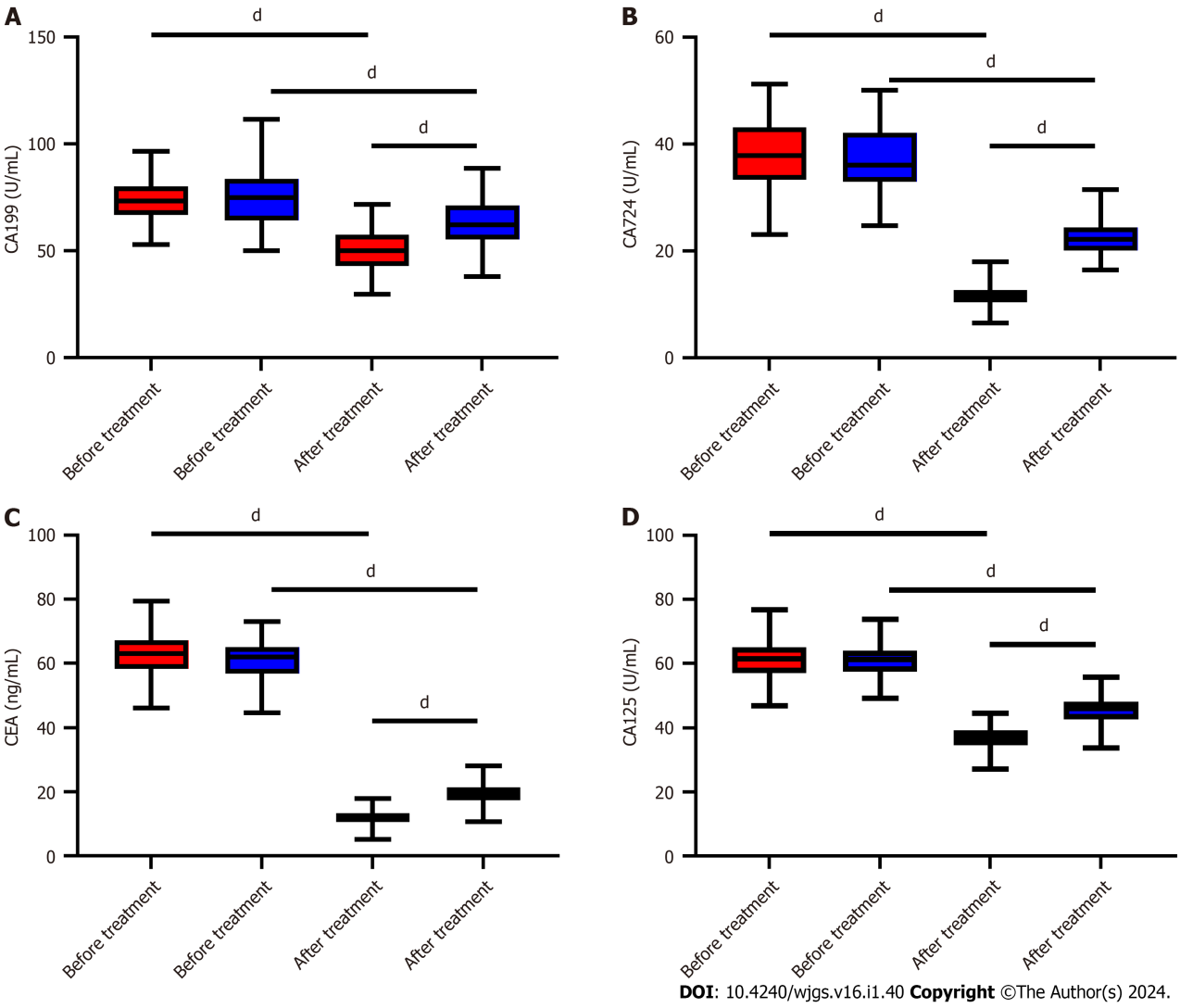


Figure 2 Changes in the levels of tumor markers in patients before and after treatment. A-D: The markers whose levels before and after treatment were compared include: CA19-9 (A); CA72-4 (B); CEA (C); and CA125 (D). CA19-9: Carbohydrate antigen 19-9; CA72-4: Carbohydrate antigen 72-4; CEA: Serum carcinoembryonic antigen; CA125: Carbohydrate antigen 125. $^{d}P < 0.0001$.

many areas, such as early screening, diagnosis, efficacy monitoring, and prognosis evaluation[18]. CA19-9 is a glycoprotein tumor marker present in trace amounts or absent in healthy people. In cases of digestive tract infections or tumors, CA19-9 levels increase, which are closely associated with GC progression[19]. CA72-4 is a high-molecular-weight glycoprotein antigen sensitive to most malignant gastrointestinal tumors; it is commonly adopted as a marker of these tumors[20]. CEA is an acidic protein. After metabolism, tumor cells break away from the surface and enter blood circulation[21,22]. CA-125 is not a specific tumor marker but is related to diagnosis, efficacy evaluation, and prognosis of GC. Increased serum levels of CA-125 in some patients with GC are associated with disease progression and metastasis [23]. After treatment, changes in CA-125 levels may reflect treatment efficacy and improvement or deterioration of the disease condition. In this study, after treatment, CA19-9, CA72-4, CEA, and CA125 levels in the enrolled patients notably decreased. The reduction was significantly more pronounced in the observation group compared to the control group, indicating that LRS was more effective in treating GC. This may be because laparoscopic surgery can effectively remove focus lesions and lymphoid tissue, thus reducing the secretion of tumor-related markers.

Finally, we performed a statistical analysis of survival and recurrence rates in the two groups. The results revealed no significant differences in three-year survival and recurrence rates between the two groups. In patients with advanced GC, LRS can lower the incidence of postoperative complications and contribute to a favorable long-term prognosis. However,

this study has some limitations. First, in this single-center study, the number of samples was greatly reduced after screening, which may have introduced bias in the result analysis. Second, we could not perform long-term follow-up on the patients due to the retrospective nature of the study. Therefore, we hope to perform further experiments with more participants to validate our conclusions.

CONCLUSION

In summary, LRS is effective in the treatment of early-stage GC, and can reduce intraoperative bleeding, length of stay, and complications, contribute to a good short-term prognosis, and greatly lower tumor marker levels. To further validate these findings, future research with long-term follow-up and a larger sample size should be conducted.

ARTICLE HIGHLIGHTS

Research background

Gastric cancer (GC) is a common malignancy with increasing incidence owing to lifestyle changes. This study compared the outcomes of open surgery and laparoscopic radical surgery (LRS), two different surgical techniques used to treat early-stage GC.

Research motivation

The need to find an effective and less invasive surgical method with less trauma, quick recovery, and minimal impact on immunity motivated this study.

Research objectives

The primary objectives of this study were to compare the effects of open surgery and LRS on operation time, intraoperative blood loss, postoperative recovery, length of hospital stay, complications, and tumor marker levels in patients with GC.

Research methods

A comparative study was conducted on two groups of patients: one group underwent open surgery and the other, LRS. Surgical time, intraoperative blood loss, postoperative eating time, length of hospital stays, overall response rate, incidence of complications, tumor marker levels (carbohydrate antigen 19-9, cancer antigen 72-4, carcinoembryonic antigen, and cancer antigen 125), and survival and recurrence rates were compared.

Research results

Patients in the LRS group experienced shorter operation times, less intraoperative blood loss, earlier postoperative eating times, and shorter hospital stays, with a higher overall response rate, lower incidence of complications, and significantly decreased tumor marker levels compared with those in the open surgery group. However, no notable differences in three-year survival and recurrence rates were observed between the two groups.

Research conclusions

LRS is an effective treatment for early-stage GC. It offers several advantages over open surgery, including reduced intraoperative bleeding, shorter hospital stays, fewer complications, and lower levels of tumor markers. Even in advanced GC, LRS can reduce postoperative complications and contribute to a favorable long-term prognosis.

Research perspectives

Despite the promising results, the study has limitations, such as a reduced number of samples and a lack of long-term follow-up due to its retrospective nature. Future studies with larger sample sizes and longer follow-up periods are warranted to validate these findings.

FOOTNOTES

Co-first authors: Yun-Yao Lu and Yun-Xiao Li.

Co-corresponding authors: Ya-Li Wang and Meng He.

Author contributions: Lu YY designed and performed the research and wrote the manuscript; Wang YL designed the study and supervised the report; Li YX designed the study and participated in the analysis; He M provided clinical advice and supervised the report; All authors were involved in the critical review of the results and have contributed to, read, and approved the final manuscript. Lu YY and Li YX contributed equally to this work and are the first co-authors. Wang YL and He M contributed equally to this study and are co-corresponding authors. There are two reasons for designating Lu YY and Li YX as co-first authors, and Wang YL and He M as co-corresponding authors. First, the research was performed as a collaborative effort, and the designation of co-first authors and co-

corresponding authors accurately reflects the distribution of responsibilities and burdens associated with the time and effort required to complete the study and the resultant paper. This also ensures effective communication and management of post-submission matters, ultimately enhancing the paper's quality and reliability. Second, they contributed efforts of equal substance throughout the research process. The choice of these researchers as co-first authors and co-corresponding authors acknowledges and respects this equal contribution, while recognizing the spirit of teamwork and collaboration of this study. In summary, we believe that designating Lu YY and Li YX as co-first authors, and Wang YL and He M as co-corresponding authors is fitting for our manuscript as it accurately reflects our team's collaborative spirit and equal contributions.

Institutional review board statement: The study was reviewed and approved by the Ethics Committee of the Chongqing University Cancer Hospital (Approval No. CZLS2023170-A).

Informed consent statement: The authors have applied for exemption from obtaining patients' informed consent.

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

Data sharing statement: The statistical data used in this study can be obtained from the corresponding author upon request.

Country/Territory of origin: China

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S-Editor: Lin C
L-Editor: A
P-Editor: Xu ZH

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World J Gastrointest Surg 2024 January 27; 16(1): 49-58

DOI: 10.4240/wjgs.v16.i1.49

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

Single-incision laparoscopic transabdominal preperitoneal repair in the treatment of adult female patients with inguinal hernia

Xiao-Jun Zhu, Jing-Yi Jiao, Hui-Min Xue, Peng Chen, Chang-Fu Qin, Peng 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: Gopal SV, Australia; Sultan AAEA, Egypt

Received: August 23, 2023
Peer-review started: August 23, 2023
First decision: November 21, 2023
Revised: December 9, 2023
Accepted: January 4, 2024
Article in press: January 4, 2024
Published online: January 27, 2024

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Abstract

BACKGROUND

Women have a 3% lifetime chance of developing an inguinal hernia, which is not as common in men. Due to its cosmetic benefits, single-incision laparoscopic transabdominal preperitoneal (SIL-TAPP) inguinal hernia repair is becoming increasingly popular in the management of inguinal hernia in women. However, there are no studies comparing the safety and applicability of SIL-TAPP repair with conventional laparoscopic transabdominal preperitoneal (CL-TAPP) inguinal hernia repair for the treatment of inguinal hernia in women.

AIM

To compare the outcomes of SIL-TAPP and CL-TAPP repair in adult female patients with inguinal hernia and to estimate the safety and applicability of SIL-TAPP repair in adult female inguinal hernia patients.

METHODS

We retrospectively compared the clinical information and follow-up data of female inguinal hernia patients who underwent SIL-TAPP inguinal hernia repair and those who underwent CL-TAPP inguinal hernia repair at the Affiliated Hospital of Nantong University from February 2018 to December 2020 and assessed the long-term and short-term outcomes of both cohorts.

RESULTS

This study included 123 patients, with 71 undergoing SIL-TAPP repair and 52 undergoing CL-TAPP repair. The two cohorts of patients and inguinal hernia charac-

teristics were similar, with no statistically meaningful difference. The rate of intraoperative inferior epigastric vessel injury was lower in patients in the SIL-TAPP cohort (0, 0%) than in patients in the CL-TAPP cohort (4, 7.7%) and was significantly different ($P < 0.05$). In addition, the median [interquartile range (IQR)] total hospitalization costs were significantly lower in patients in the SIL-TAPP cohort [$3287 (3218-3325)] than in patients in the CL-TAPP cohort [$3511 (3491-3599)]. Postoperatively, the occurrence rate of trocar site hernia was lower in the SIL-TAPP cohort (0, 0%) than in the CL-TAPP cohort (4, 7.7%), and the median (IQR) cosmetic score was significantly higher in the SIL-TAPP cohort [10 (10-10)] than in the CL-TAPP cohort [9 (9-10)].

CONCLUSION

SIL-TAPP repair did not increase the incidence of intraoperative and postoperative complications in female inguinal hernia patients. Moreover, female inguinal hernia patients who underwent SIL-TAPP repair had a lower probability of trocar site hernia and inferior epigastric vessel injury than female inguinal hernia patients who underwent CL-TAPP repair. In addition, female inguinal hernia patients who underwent SIL-TAPP repair reported a more aesthetically pleasing postoperative abdominal incision. Therefore, SIL-TAPP repair is a better option for the treatment of inguinal hernias in women.

Key Words: Single-incision; Groin hernia; Female; Inguinal hernia; Laparoscopic transabdominal preperitoneal inguinal hernia repair

Core Tip: This study is the first to compare the outcomes of single-incision laparoscopic transabdominal preperitoneal (SIL-TAPP) and conventional laparoscopic transabdominal preperitoneal (CL-TAPP) repair in adult female patients with inguinal hernia. We found that women who underwent SIL-TAPP repair had a lower chance of postoperative trocar site hernia and inferior epigastric vessel injury than those who underwent CL-TAPP repair, which is different from previous reports. Moreover, the results demonstrate the safety and applicability of SIL-TAPP repair in the treatment of adult female patients.

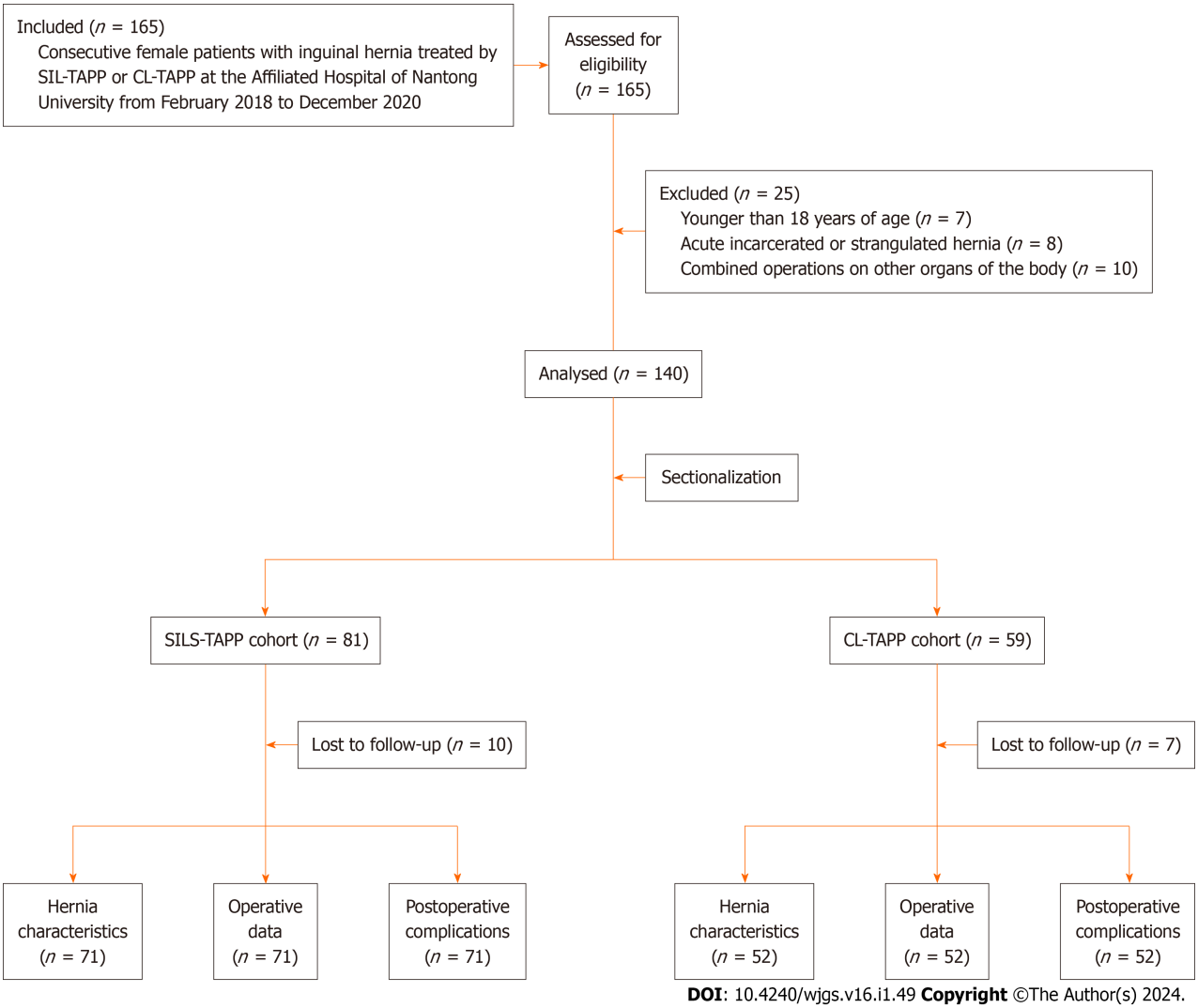
Citation: Zhu XJ, Jiao JY, Xue HM, Chen P, Qin CF, Wang P. Single-incision laparoscopic transabdominal preperitoneal repair in the treatment of adult female patients with inguinal hernia. *World J Gastrointest Surg* 2024; 16(1): 49-58
URL: https://www.wjgnet.com/1948-9366/full/v16/i1/49.htm
DOI: https://dx.doi.org/10.4240/wjgs.v16.i1.49

INTRODUCTION

An inguinal hernia (also called a groin hernia) is an extra-abdominal hernia formed when an intra-abdominal organ protrudes towards the body surface through a congenital or acquired defect in the groin region. The cause of inguinal hernia is mainly weakness of the muscles and tissues in the inguinal region. Causes of inguinal hernias include persistent coughing, smoking, being overweight, and straining while urinating or defecating[1]. Inguinal hernia is not common in men, and women have a 3 percent chance of developing an inguinal hernia in their lifetime[2]. In addition, femoral hernias occur most often in women and most often require surgery.

An inguinal hernia will not improve on its own, and surgery is often needed when a patient develops symptoms of a groin hernia[3]. Tension-free groin hernia repair is now the primary option for groin hernia treatment[4]. Tension-free groin hernia repair includes open groin hernia repair surgery and laparoscopic groin hernia repair surgery. Compared to open groin hernia repair, laparoscopic groin hernia repair is more minimally invasive, and patients experience less postoperative abdominal incision pain and a shorter time to return to normal life[5-8]. Laparoscopic groin hernia repair allows for the use of the posterior approach, which is of particular significance. Using the posterior approach has one benefit: it allows for accurate identification of the groin hernia and the placement of a larger and more stable mesh[9]. As a result, laparoscopic groin hernia repair has become the primary method of treatment for groin hernia over open surgery. To ensure minimal invasiveness, single-incision laparoscopic groin hernia repair is gradually being applied for the treatment of clinical groin hernia patients. Single-incision laparoscopic groin hernia repair further reduces pain, and the abdominal incision is more aesthetically pleasing after single-incision laparoscopic groin hernia surgery compared to conventional laparoscopic surgery, so it is preferred by many patients, especially female patients with aesthetic concerns.

However, there is a lack of comparative studies between single-port laparoscopic groin hernia repair and conventional laparoscopic groin hernia repair to investigate the safety and applicability of single-incision laparoscopic groin hernia repair in adult female patients with groin hernia. Therefore, we conducted a single-centre retrospective study to evaluate the safety and applicability of single-incision laparoscopic transabdominal preperitoneal (SIL-TAPP) repair in female patients by comparing the clinical data of female patients who underwent SIL-TAPP and conventional laparoscopic transabdominal preperitoneal (CL-TAPP) repair and by analysing the long-term and short-term outcomes of both cohorts.



DOI: 10.4240/wjgs.v16.i1.49

Figure 1 Flow chart for patient selection and study. SIL-TAPP: Single-incision laparoscopic transabdominal preperitoneal inguinal hernioplasty; CL-TAPP: Conventional laparoscopic transabdominal preperitoneal inguinal hernioplasty; SILS-TAPP: Single-incision laparoscopic transabdominal preperitoneal inguinal hernioplasty.

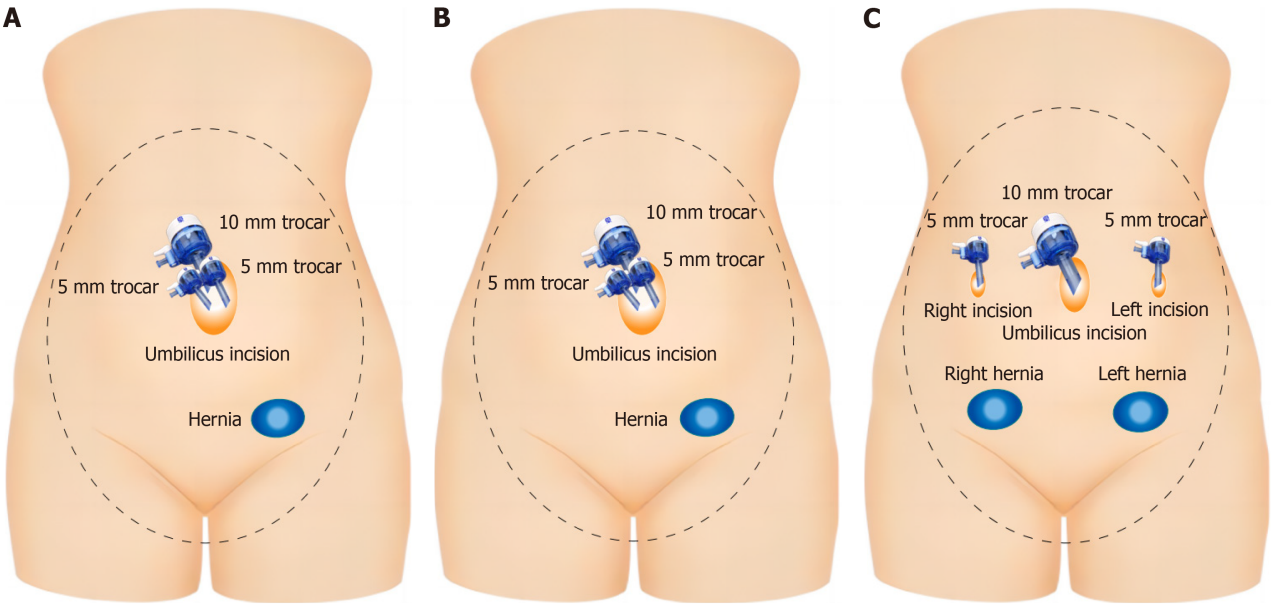
MATERIALS AND METHODS

Research design and patients

Our study retrospectively explored a dataset between February 2018 and December 2020 in the hernia follow-up system. The dataset consisted of prospectively recorded data of 165 female groin hernia patients who underwent SIL-TAPP or CL-TAPP repair at the General Surgery Department of the Affiliated Hospital of Nantong University. These following factors could prevent participation: (1) Being under 18 years old; (2) having an acute and incarcerated inguinal hernia; and (3) having hernia repair combined with other surgeries. Ultimately, 140 patients (81 patients in the SIL-TAPP cohort and 59 patients in the CL-TAPP cohort) were eligible for the study. During follow-up, 17 patients (10 patients in the SIL-TAPP cohort and 7 patients in the CL-TAPP cohort) were lost to follow-up. We ultimately collected data from 123 patients, comprising 71 patients in the SIL-TAPP cohort and 52 patients in the CL-TAPP cohort (Figure 1). The study was conducted with the informed consent of all the patients. All procedures in this study were performed by the same surgeon.

Surgical techniques

After routine disinfection of the abdomen and groin with a towel, we disinfected the navel 2-3 times with an alcohol cotton ball. In SIL-TAPP repair, we generally made a longitudinal incision of approximately 2 cm in the umbilicus and placed one 10 mm trocar and two 5 mm trocars (Figure 2A), and in CL-TAPP repair, one 10-mm trocar was placed at the umbilical opening and one 5-mm trocar was placed on each side of the umbilicus (Figure 2B and C). With the hernia site rotated upwards, the patient was positioned in the reverse Trendelenburg position. The surgical incision was made from the inner umbilical crease to the anterior superior iliac spine at a distance of 2-3 cm from the top of the internal ring aperture (Figure 3A). Then, the preperitoneal space was accessed by separating the top and bottom edges of the peritoneal flap. The lateral edge of the hernia sac was dissected to the midpoint of the iliopsoas muscle and further to the Bogros space. Starting at the middle of the inferior epigastric vessel, the transversalis fascia and the bladder were dis-



DOI: 10.4240/wjgs.v16.i1.49

Figure 2 Schematic of trocar placement. A: Trocar placement in single-incision laparoscopic transabdominal preperitoneal inguinal hernioplasty repair; B: Trocar placement in unilateral Conventional laparoscopic transabdominal preperitoneal inguinal hernioplasty (CL-TAPP) repair; C: Trocar placement in bilateral CL-TAPP repair.

sected to gain access to the Retzius space. The exposure was widened to the pubic symphysis from the pectineal ligament, extending medially through the median line and out to the inner edge of the hernia sac. The hernia sac was then divided (Figure 3B). The hernia sac was completely removed to the apex after separation, if possible. If the hernia sac was extensive and adherent to the adjacent tissue, it was incised, and the distal tip was opened. The round ligament of the uterus was usually preserved. The hernia sac was dissected towards the midline, and both sides of the bilateral hernia were joined. A 10 cm × 15 cm mesh was selected for implantation in the preperitoneal cavity to overlie the separation area described above (Figure 3C). For direct hernias and indirect hernias with sac diameters greater than 4 cm, we usually fix the mesh with a staple gun after placement, while the mesh is not usually fixed for other types of inguinal hernias. We recommend the use of 4-0 V-lock sutures for continuous suturing of the peritoneum, laterally to medially with no knots (Figure 3D). After completion of the suture, the suture was cut without leaving a residual end to avoid bowel injury and obstruction. If there was high peritoneal tension, the remaining end of the suture was clamped with titanium clamps. Finally, all trocars were removed, and the abdominal incisions were closed. For the midline longitudinal incision of the umbilicus, the suture was usually divided into two layers. First, the umbilical fascia layer was sutured continuously with 1-0 v-lock sutures, and then the midpoint of the standing flap at the umbilical ring was sutured with an absorbable protein line. Both ends were sutured intradermally, and the rest were sutured intermittently. After blood was cleaned with gauze, the standing flap was pushed back to the umbilical fossa to achieve a perfect repair.

Follow up

All patients underwent a physical examination in the outpatient clinic at 1 wk and 1 mo postoperatively to determine whether they had recovered well or whether short-term complications including seroma, haematoma, *etc.*, had occurred. In addition, patients returned to the hospital every 6 mo for physical examination and CT to determine whether there were long-term complications, such as trocar hernia and recurrence, had occurred. Patients were followed up by telephone to rate the cosmesis of the postoperative abdominal incision.

Statistical analysis

All statistical procedures were conducted using SPSS version 26 (IBM). We express distributions of continuous variables using the median and interquartile range (IQR) and tested them using the Mann-Whitney *U* test. We used the chi-squared test to test categorical variables and percentages. Statistical differences were indicated by *P* values less than 0.05.

RESULTS

Between February 2018 and December 2020, a total of 123 patients participated in this study, of whom 71 underwent SIL-TAPP repair and 52 underwent CL-TAPP repair. The characteristics of the adult female patients in our study and their groin hernias are summarized in Table 1. The median (IQR) age of the patients in the SIL-TAPP cohort and the patients in the CL-TAPP cohort was 46 (41-53) and 47 (42-53) years, respectively, with no meaningful difference ($P > 0.05$). The median body mass index (IQR) was 22.46 (20.93-22.95) kg/m^2 and 22.35 (21.76-23.06) kg/m^2 for patients in the SIL-TAPP

Table 1 Patients and inguinal hernias characteristics

Variables	SILS-TAPP (*n* = 71)	CL-TAPP (*n* = 52)	Total (*n* = 123)	*P* value
Age, median (IQR), yr	46 (41-53)	47 (42-53)	46 (42-53)	0.393
ASA, *n* (%)				0.396
I	44 (62)	38 (73.1)	82 (66.7)	
II	21 (29.6)	10 (19.2)	31 (25.2)	
III and IV	6 (8.5)	4 (7.7)	10 (8.1)	
BMI, median (IQR), kg/m^2	22.46 (20.93-22.95)	22.35 (21.76-23.06)	22.43 (21.58-22.95)	0.486
Number of hernias, *n* (%)				0.320
Unilateral	62 (87.3)	42 (80.8)	104 (84.6)	
Bilateral	9 (12.7)	10 (19.2)	19 (15.4)	
Type of hernias, *n* (%)				0.961
Direct	10 (14.1)	6 (11.5)	16 (13)	
Indirect	57 (80.3)	44 (84.6)	101 (82.1)	
Femoral	2 (2.8)	1 (1.9)	3 (2.4)	
Mixed	2 (2.8)	1 (1.9)	3 (2.4)	
Site of hernias, *n* (%)				0.231
Left	30 (42.3)	25 (48.1)	55 (44.7)	
Right	33 (46.5)	17 (32.7)	50 (40.7)	
Bilateral	8 (11.3)	10 (19.2)	18 (14.6)	
Primary/recurrent hernias, *n* (%)				0.240
Primary	69 (97.2)	48 (92.3)	117 (95.1)	
Recurrent	2 (2.8)	4 (7.7)	6 (4.9)	
Size of internal inguinal ring, *n* (%)				0.162
< 2 cm	39 (54.9)	20 (38.5)	59 (48)	
2-4 cm	24 (33.8)	26 (50)	50 (40.7)	
> 4 cm	8 (11.3)	6 (11.5)	14 (11.4)	
Previous lower abdominal surgery, *n* (%)				0.338
Yes	8 (11.3)	9 (17.3)	17 (13.8)	
No	63 (88.7)	43 (82.7)	106 (86.2)	

SIL-TAPP: Single-incision laparoscopic transabdominal preperitoneal inguinal hernioplasty; CL-TAPP: Conventional laparoscopic transabdominal preperitoneal inguinal hernioplasty; IQR: Interquartile range; BMI: Body mass index; ASA: The American Society of Anesthesiologists classification.

and CL-TAPP cohorts, res-pectively, which was also not significantly different ($P > 0.05$). In addition, hernia characteristics, including the type of hernia and the location and size of the hernia ring, were similar in both cohorts. A history of lower abdominal operation was reported by 8 (11.3%) patients in the SIL-TAPP cohort compared to 9 (17.3%) patients in the CL-TAPP cohort, but there was no difference between the two cohorts.

Table 2 shows the intraoperative and hospitalization periods of the two cohorts of patients. The median (IQR) operative time was 32 (29-35) minutes and 33.5 (30-39.5) minutes for patients in the SIL-TAPP and CL-TAPP cohorts, respectively, with no meaningful difference ($P > 0.05$). Moreover, there was no meaningful difference between the two cohorts in terms of intraoperative nerve injury, adjacent organ injury, pain in the groin area within 24 h postoperatively or length of hospital stay. However, no patients in the SIL-TAPP cohort had intraoperative inferior epigastric vessel injury, while 4 (7.7%) patients in the CL-TAPP cohort had inferior epigastric vessel injury, with a significant difference between the two cohorts ($P < 0.05$). All four cases of injury to the inferior epigastric artery occurred at the time of trocar placement on both sides, one on the left and three on the right. In addition, the median (IQR) hospitalization cost of patients in the CL-TAPP cohort was $3511 (3491-3559), which was significantly higher than that of the patients in the SIL-TAPP cohort [$3287 (3218-3325)], and there was a meaningful difference ($P < 0.001$).

Table 2 Surgery and hospitalization information

Variables	SILS-TAPP (*n* = 71)	CL-TAPP (*n* = 52)	Total (*n* = 123)	*P* value
Operating time, median (IQR), min	32 (29-35)	33.5 (30-39.5)	33 (30-36)	0.073
Vascular injury caused by trocar, *n* (%)	0 (0)	4 (7.7)	4 (3.3)	0.030
Intraoperative nerve injury in the inguinal region, *n* (%)	2 (2.8)	1 (1.9)	3(2.4)	1.000
Intraoperative adjacent organ injury, *n* (%)	0 (0)	0 (0)	0 (0)	1.000
Postoperative pain within 24 h (VAS score > 3), *n* (%)	6 (8.5)	5 (9.6)	11 (8.9)	1.000
Postoperative hospital stays, median (IQR), d	1 (1-2)	1 (1-2)	1 (1-2)	0.918
Hospitalization costs (USD)	3287 (3218-3325)	3511 (3491-3559)	3375 (3277-3508)	< 0.001

SIL-TAPP: Single-incision laparoscopic transabdominal preperitoneal inguinal hernioplasty; CL-TAPP: Conventional laparoscopic transabdominal preperitoneal inguinal hernioplasty; IQR: Interquartile range; VAS: Visual analogue scale.

Table 3 Postoperative complications and cosmetic scores

Variables	SILS-TAPP (*n* = 71)	CL-TAPP (*n* = 52)	Total (*n* = 123)	*P* value
Seroma, *n* (%)	4 (5.6)	1 (1.9)	5 (4.1)	0.395
Recurrence, *n* (%)	0 (0)	2 (3.8)	2 (1.6)	0.177
Mesh infection, *n* (%)	0 (0)	0 (0)	0 (0.0)	1.000
Trocar site hernia, *n* (%)	0 (0)	4 (7.7)	4 (3.3)	0.030
Chronic pain, *n* (%)	3 (4.2)	4 (7.7)	7 (5.7)	0.455
Labia majora edema, *n* (%)	3 (4.2)	1 (1.9)	4 (3.3)	0.637
Abnormal sensation in the perineal area, *n* (%)	1 (1.4)	0 (0)	1 (0.8)	1.000
Uterine prolapse, *n* (%)	0 (0)	0 (0)	0 (0)	1.000
Fertility abnormalities, *n* (%)	0 (0)	0 (0)	0 (0)	1.000
Cosmetic scores (on a scale of 1-10), median (IQR)	10 (10-10)	9 (9-10)	10 (9-10)	< 0.001

SIL-TAPP: Single-incision laparoscopic transabdominal preperitoneal inguinal hernioplasty; CL-TAPP: Conventional laparoscopic transabdominal preperitoneal inguinal hernioplasty; IQR: Interquartile range.

Table 3 demonstrates the postoperative complications as well as cosmetic scores of the two cohorts of patients. Among the patients, trocar site hernia was seen in 4 (7.7%) patients in the CL-TAPP cohort, whereas it was not seen in the patients in the SIL-TAPP cohort, and there was a meaningful difference ($P < 0.05$). There was no meaningful difference between the two cohorts in terms of postoperative complications such as seroma, patch infection, chronic pain, labia majora oedema, sensory abnormalities in the perineal area, uterine prolapse, fertility abnormalities and recurrence. The cosmetic score was 10 (10-10) for patients in the SIL-TAPP cohort and 9 (9-10) for patients in the CL-TAPP cohort, and the cosmetic score of the patients in the SIL-TAPP cohort was meaningfully better than that of patients in the CL-TAPP cohort ($P < 0.001$).

DISCUSSION

With the development of modern surgical concepts, doctors and patients are paying increasing attention to quality of life after surgery[10]. To reduce the physical pain and psychological burden associated with surgery, surgeries are now becoming more minimally invasive, and this is also true of groin hernia repair surgery[11]. Single-incision laparoscopic groin hernia repair results in less surgical trauma and a faster recovery for the patient[12]. Previous studies have shown that single-incision laparoscopic groin hernia repair is safe and feasible[13]. However, because groin hernias occur more often in male patients, previous reports lack separate studies in female patients. In addition, we know that the outcome of hernia repair in female patients is significantly different from that in male patients[14-16]. Therefore, we included all female patients with inguinal hernia as a way to research the safety and applicability of single-incision laparoscopic groin

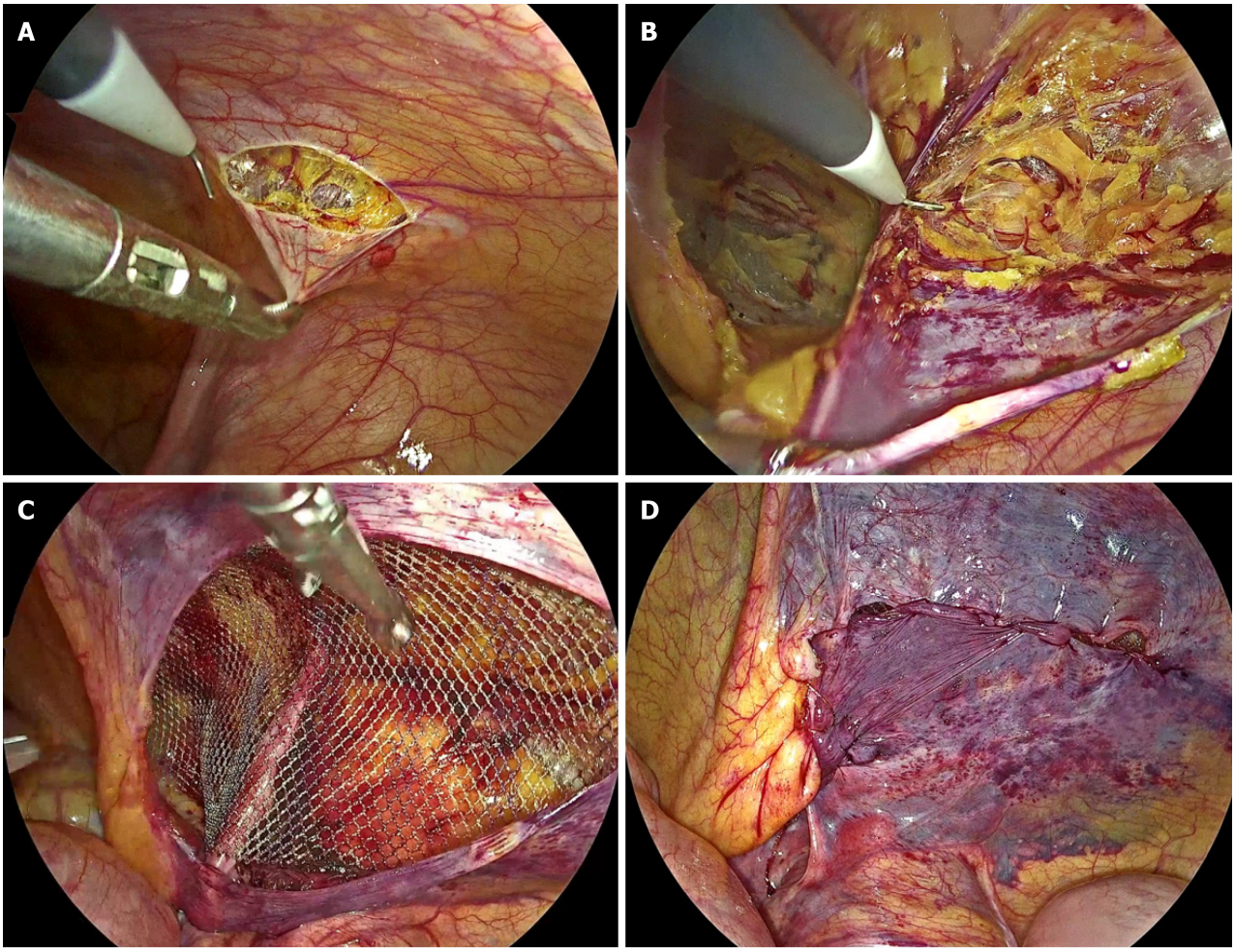


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Figure 3 Photographs of some surgical details. A: At the level of 2-3 cm along the upper margin of the inner ring opening, the peritoneum was cut from the medial umbilical fold to the anterior superior iliac spine; B: The hernia sac was disposed of; C: The mesh was placed and unfolded fully; D: The peritoneum was sutured continuously.

hernia repair in female patients with inguinal hernia. Because of the broader surgical indications for TAPP repair, we chose to compare the results of SIL-TAPP and CL-TAPP repair in female patients[17].

In many studies, the operative time of SIL-TAPP repair was much longer than that of CL-TAPP repair due to the absence of the "chopstick effect" and the "operating triangle" caused by the single incision, as well as the greatly increased difficulty of peritoneal suture under a single incision[18]. However, our study, as well as our previous study, showed that after overcoming the learning curve, there was no statistically meaningful difference in the surgery time between the SIL-TAPP and CL-TAPP cohorts, which did not lead to complications associated with the long operative time[13].

In a retrospective study that included 3100 traditional multiport laparoscopic tension-free groin hernia repairs, the rate of damage to the inferior epigastric vessels was 0.47%[19]. The body surface projection of the inferior epigastric vessels is the midpoint of the groin ligament towards the umbilicus, and traditional multiport laparoscopic groin hernia repair carries the potential for damage to the inferior epigastric vessels during puncture of the trocar on both sides. In contrast, SIL-TAPP repair does not require blind puncture of the trocar on both sides of the umbilicus as the operative hole; therefore, our research found that no patients in the SIL-TAPP cohort suffered any injuries to the inferior epigastric vessels during surgery, whereas four patients (7.7%) in the CL-TAPP cohort suffered intraoperative inferior epigastric vessel injuries, and the difference between the two cohorts was statistically significant ($P < 0.05$).

It is well known that female groin hernia patients are more likely to develop chronic pain after groin hernia repair[16,20], so the occurrence rate of postoperative chronic pain is also an important indicator for evaluating the feasibility of groin hernia repair surgery. In our study, three patients (4.2%) in the SIL-TAPP cohort experienced postoperative chronic pain in the inguinal area, compared with four patients (7.7%) in the CL-TAPP cohort, which shows that the occurrence rate of postoperative chronic pain in the SIL-TAPP cohort was lower than that in the CL-TAPP cohort, suggesting that SIL-TAPP repair is more conducive to improving the postoperative quality of life of female inguinal hernia patients.

Abdominal trocar site hernia often presents as an abdominal incisional mass or bulge, which greatly affects patients' quality of life and causes a very significant psychological burden, especially in female patients. Previous studies have shown that single-incision laparoscopic surgery carries a higher risk of trocar site hernia in patients than conventional multiport laparoscopic surgery[21]. To compare the trocar site hernia incidence between patients in the SIL-TAPP cohort and the CL-TAPP cohort, we followed up the patients in both groups and determined whether they had trocar site

hernias by physical examination and CT. Through follow-up, we found that four (7.7%) patients in the CL-TAPP cohort developed trocar site hernias, whereas there were no trocar site hernias in the SIL-TAPP cohort, and the difference between the two cohorts was statistically significant ($P < 0.05$). Therefore, we conclude that SIL-TAPP repair does not increase the incidence of trocar site hernia in patients but rather decreases it, and this result supports SIL-TAPP repair as a better option for female patients.

As mentioned earlier, the invisibility and cosmetic nature of the incision is also an important indicator improving the postoperative quality of life and reducing the postoperative psychological burden in female patients. Unlike the single-incision laparoscopic groin hernia repair surgery in many previous studies, our SIL-TAPP repair surgery involves a completely transumbilical approach, and the postoperative umbilical incision is completely hidden in the umbilical fossa folds, making the surgical incision completely invisible to the patient after recovery. The results indicated that patients in the SIL-TAPP cohort had a cosmetic score of 10 (10-10), and those in the CL-TAPP cohort had score of 9 (9-10), and patients in the SIL-TAPP cohort had a significantly higher cosmetic score than patients in the CL-TAPP cohort ($P < 0.001$). Concealed incisions resulted in higher confidence and a higher postoperative quality of life in female patients.

However, our research has several limitations. First, this study retrospectively compared patients who underwent SIL-TAPP and CL-TAPP repair. In addition, our sample size was not large enough. Therefore, further studies are needed to validate our ideas.

CONCLUSION

Our findings suggest that female inguinal hernia patients who underwent SIL-TAPP repair had a lower probability of trocar site hernia and inferior epigastric vessel injury than those who underwent CL-TAPP repair. Furthermore, patients who underwent SIL-TAPP repair reported a more cosmetically pleasing postoperative abdominal incision, making SIL-TAPP repair a better option for female inguinal hernia patients.

ARTICLE HIGHLIGHTS

Research background

Single-incision laparoscopic transabdominal preperitoneal (SIL-TAPP) inguinal hernia repair is becoming increasingly popular for the treatment of inguinal hernia in women due to its cosmetic benefits. However, there is no comparative study of SIL-TAPP *vs* conventional laparoscopic transabdominal preperitoneal (CL-TAPP) inguinal hernia repair to illustrate the safety and applicability of SIL-TAPP repair in the treatment of inguinal hernia in female patients. Therefore, a comparative study of SIL-TAPP and CL-TAPP repair in the treatment of inguinal hernia in women is urgently needed and important.

Research motivation

The aim was to compare intraoperative conditions, postoperative complication rates and cosmetic outcome scores of SIL-TAPP *vs* CL-TAPP repair in the treatment of inguinal hernia in women.

Research objectives

The safety and applicability of SIL-TAPP repair in the treatment of inguinal hernia in women was analysed by comparing the intraoperative and postoperative data of SIL-TAPP repair and CL-TAPP repair in the treatment of inguinal hernia in women.

Research methods

We ultimately obtained clinical data for a total of 123 patients (71 who underwent SIL-TAPP repair and 52 who underwent CL-TAPP repair) who participated in this study between February 2018 and December 2020. The safety and applicability of SIL-TAPP repair in the treatment of female inguinal hernia patients was analysed by comparing the hernia characteristics, intraoperative conditions, postoperative complication rates and postoperative cosmetic scores between the two groups.

Research results

SIL-TAPP repair did not increase the incidence of intraoperative and postoperative complications in female inguinal hernia patients. Moreover, female inguinal hernia patients who underwent SIL-TAPP repair had a lower probability of trocar site hernia and inferior epigastric vessel injury than female inguinal hernia patients who underwent CL-TAPP repair. In addition, female inguinal hernia patients who underwent SIL-TAPP repair reported a more aesthetically pleasing postoperative abdominal incision.

Research conclusions

SIL-TAPP repair is safe and feasible for the treatment of female inguinal hernia patients and will be a preferred option for female inguinal hernia patients.

Research perspectives

In the future, multicentre studies with larger samples are needed to analyse the safety and applicability of SIL-TAPP repair.

FOOTNOTES

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Author contributions: Zhu XJ, Jiao JY, Xue HM, Qin CF and Wang P conceived, designed and refined the study protocol; Zhu XJ, Jiao JY and Chen P were involved in the data collection; Zhu XJ, Jiao JY, Qin CF and Wang P analyzed the data; Zhu XJ and Jiao JY drafted the manuscript; All authors were involved in the critical review of the results and have contributed to, read, and approved the final manuscript. Zhu XJ and Jiao JY contributed equally to this work as co-first authors. Qin CF and Wang P contributed equally to this work as co-corresponding authors. The reasons for designating Zhu XJ and Jiao JY as co-first authors / Qin CF and Wang P as co-corresponding authors are threefold. First, the research was performed as a collaborative effort, and the designation of co-first and co-corresponding authorship accurately reflects the distribution of responsibilities and burdens associated with the time and effort required to complete the study and the resultant paper. This also ensures effective communication and management of post-submission matters, ultimately enhancing the paper's quality and reliability. Second, the overall research team encompassed authors with a variety of expertise and skills from different fields, and the designation of co-first and co-corresponding authors best reflects this diversity. This also promotes the most comprehensive and in-depth examination of the research topic, ultimately enriching readers' understanding by offering various expert perspectives. Third, the choice of these researchers as co-first and co-corresponding authors acknowledges and respects this equal contribution, while recognizing the spirit of teamwork and collaboration of this study. In summary, we believe that designating Zhu XJ and Jiao JY as co-first authors/Qin CF and Wang P as co-corresponding authors of is fitting for our manuscript as it accurately reflects our team's collaborative spirit, equal contributions, and diversity.

Supported by Wu Jieping Medical Foundation, No. 320.6750.18396; Nantong "14th Five-Year" Science and Education to Strengthen Health Project, General Surgery Medical Key Discipline, No. 42; and Nantong Municipal Commission of Health and Family Planning, No. MS2022005.

Institutional review board statement: The study was reviewed and approved by the Affiliated Hospital of Nantong University Institutional Review Board (Approval No. 2023-K117-01).

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

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

Data sharing statement: The datasets generated during and/or analysed during the current study are available from the corresponding author upon reasonable request.

Country/Territory of origin: China

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S-Editor: Lin C
L-Editor: A
P-Editor: Xu ZH

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World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2024 January 27; 16(1): 59-66

DOI: 10.4240/wjgs.v16.i1.59

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

Computerized tomography-guided therapeutic percutaneous puncture catheter drainage-combined with somatostatin for severe acute pancreatitis: An analysis of efficacy and safety

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Specialty type: Gastroenterology and hepatology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Carli ALE, Australia; Tsilidis KK, United Kingdom

Received: October 30, 2023
Peer-review started: October 30, 2023
First decision: November 8, 2023
Revised: December 6, 2023
Accepted: December 18, 2023
Article in press: December 18, 2023
Published online: January 27, 2024

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Abstract

BACKGROUND

Severe acute pancreatitis (SAP), a condition with rapid onset, critical condition and unsatisfactory prognosis, poses a certain threat to human health, warranting optimization of relevant treatment plans to improve treatment efficacy.

AIM

To evaluate the efficacy and safety of computerized tomography-guided therapeutic percutaneous puncture catheter drainage (CT-TPPCD) combined with somatostatin (SS) in the treatment of SAP.

METHODS

Forty-two SAP patients admitted to The Second Affiliated Hospital of Fujian Medical University from June 2020 to June 2023 were selected. On the basis of routine treatment, 20 patients received SS therapy (control group) and 22 patients were given CT-TPPCD plus SS intervention (research group). The efficacy, safety (pancreatic fistula, intra-abdominal hemorrhage, sepsis, and organ dysfunction syndrome), abdominal bloating and pain relief time, bowel recovery time, hospital stay, inflammatory indicators (C-reactive protein, interleukin-6, and procalcitonin), and Acute Physiology and Chronic Health Evaluation (APACHE) II score of both groups were evaluated for comparison.

RESULTS

Compared with the control group, the research group had a markedly higher total effective rate, faster abdominal bloating and pain relief and bowel recovery,

shorter hospital length of stay, fewer complications, and lower posttreatment inflammatory indices and APACHE-II scores.

CONCLUSION
CT-TPPCD in combination with SS is effective for SAP patients, which can reduce complications, accelerate symptom resolution, inhibit inflammation, and improve patient condition, with promising prospects for clinical promotion.

Key Words: Computerized tomography guidance; Therapeutic percutaneous puncture catheter drainage; Somatostatin; Severe acute pancreatitis; Efficacy and safety

Core Tip: Severe acute pancreatitis (SAP) is a severe acute manifestation of pancreatitis, which may lead to disease deterioration due to local and systemic infections. Therefore, an effective and safe intervention method is urgently needed to optimize the management of SAP patients. This study suggests that computerized tomography-guided therapeutic percutaneous puncture catheter drainage combined with somatostatin for SAP patients has high clinical efficacy and safety, providing a novel option for the clinical management optimization of such patients.

Citation: Zheng XL, Li WL, Lin YP, Huang TL. Computerized tomography-guided therapeutic percutaneous puncture catheter drainage-combined with somatostatin for severe acute pancreatitis: An analysis of efficacy and safety. *World J Gastrointest Surg* 2024; 16(1): 59-66
URL: https://www.wjgnet.com/1948-9366/full/v16/i1/59.htm
DOI: https://dx.doi.org/10.4240/wjgs.v16.i1.59

INTRODUCTION

Pancreatitis, an inflammatory disease occurring in the pancreatic tissue, is classified as either acute or chronic and is associated with high morbidity and mortality, imposing a socioeconomic burden[1,2]. The pathogenesis of this disease involves early protease activation, activation of nuclear factor kappa-B-related inflammatory reactions, and infiltration of immune cells[3]. Severe acute pancreatitis (SAP) is a serious condition involving systemic injury and subsequent possible organ failure, accounting for 20% of all acute pancreatitis cases[4]. SAP is also characterized by rapid onset, critical illness and unsatisfactory prognosis and is correlated with serious adverse events such as systemic inflammatory response syndrome and acute lung injury, threatening the health of patients[5,6]. Therefore, timely and effective therapeutic interventions are of great significance for improving patient prognosis and ensuring therapeutic effects.

Somatostatin (SS), a peptide hormone that can be secreted by endocrine cells and the central nervous system, is involved in the regulatory mechanism of glucagon and insulin synthesis in the pancreas[7]. It has complex and pleiotropic effects on the gastrointestinal tract, which can inhibit the release of gastrointestinal hormones and negatively modulate the exocrine function of the stomach, pancreas and bile, while exerting a certain influence on the absorption of the digestive system[8,9]. SS has shown certain clinical effectiveness when applied to SAP patients and can regulate the severity of SAP and immune inflammatory responses, and this regulation is related to its influence on leukocyte apoptosis and adhesion[10,11]. Computerized tomography-guided therapeutic percutaneous puncture catheter drainage (CT-TPPCD) is a surgical procedure to collect lesion fluid and pus samples from necrotic lesions and perform puncture and drainage by means of CT image examination and precise positioning[12]. In the research of Liu *et al*[13], CT-TPPCD applied to patients undergoing pancreatic surgery contributes to not only good curative effects but also a low surgical risk. Baudin *et al*[14] also reported that CT-TPPCD has a clinical success rate of 64.6% in patients with acute infectious necrotizing pancreatitis, with nonfatal surgery-related complications found in only two cases, suggesting that this procedure is clinically effective and safe in the treatment of the disease.

In light of the limited studies on the efficacy and safety of SS plus CT-TPPCD in SAP treatment, this study performed a relevant analysis to improve clinical outcomes in SAP patients.

MATERIALS AND METHODS

Patient information

Forty-two SAP patients admitted to The Second Affiliated Hospital of Fujian Medical University between June 2020 and June 2023 were selected. In addition to routine treatment, 20 patients in the control group received SS treatment, and the rest 22 patients in the research group received CT-TPPCD plus SS intervention. The inclusion criteria were as follows: Diagnosis of SAP[15]; presence of seroperitoneum and intraperitoneal abscess as indicated by imaging examination;

presence of symptoms such as nausea, vomiting and abdominal pain; treatment-naive SAP patients; no contraindications to the medication used in this study; and complete medical records. The exclusion criteria were as follows: Malignant tumors, autoimmune disease, cardiovascular disorders, coagulation dysfunction, *etc.*; mental illness; previous history of abdominal surgery; severe organ dysfunction; serious abnormality of basic gastrointestinal function; and lactating or pregnant women.

Methods

Both groups received routine treatment, primarily including fasting, anti-infection, maintenance of water and electrolyte balance, pain relief, and reduction of gastrointestinal hypertension. In addition, the control group was treated with SS intravenously, with the SS dose gradually adjusted according to the patient's condition.

Based on the above measures, the research group was supplemented with CT-TPPCD. First, the patient was examined with a CT. The feasibility of catheter drainage was indicated by the presence of peripancreatic effusion, pancreatic necrosis, a pseudocyst, and local infection. A puncture was performed after precise positioning by CT, routine disinfection, and local anesthesia. Focal fluid and pus samples from necrotic lesions were collected. A disposable abdominal cavity drain catheter was then placed, and a common drainage bag was inserted after successful indwelling. After checking and confirming normal drainage, the patient's skin was sutured and the drainage tube was secured to complete the procedure. The collected samples were immediately sent for examination and bacterial culture, and bacterial drug sensitivity tests were performed.

Endpoints

Statistics on efficacy, adverse events [pancreatic fistula (PF), intra-abdominal hemorrhage (IAH), sepsis, and organ dysfunction syndrome], postoperative abdominal bloating and pain relief, bowel recovery time, hospital length of stay, inflammatory indices [C-reactive protein (CRP), interleukin-6 (IL-6) and procalcitonin (PCT)], and Acute Physiological and Chronic Health Evaluation (APACHE) II score were collected for comparative analyses. Among them, the efficacy is assessed as follows: Cure refers to the disappearance of clinical symptoms and signs and the return of laboratory indicators and imaging tests to normal; improvement is indicated by relieved clinical symptoms and signs and an incomplete recovery from complications such as infection, inflammation and false abscess shown by auxiliary examination; if the patient's clinical symptoms and signs did not improve or worsen, it was considered ineffectiveness. Second, CRP, IL-6, and PCT were all determined by enzyme-linked immunosorbent assays (ELISAs). Before detection, 5 mL of fasting elbow venous blood was extracted from each patient, and the serum was separated as a sample for detection. Finally, APACHE-II, including acute physiology (the sum of Glasgow Coma Scale score and various physiological variable scores, with a score range of 0-60), age (0-6 points), and chronic health subscales (0-5 points), was used to evaluate physical health status; on a scale of 0-71, the score is directly proportional to the severity of SAP.

Statistical treatment

The GraphPad Prism 7.0 software package was used for data analyses, and the level of statistical significance was $P < 0.05$. Categorical variables [described as the number of samples (percentage), *n* (%)] and continuous variables (represented by SD ± SEM) were compared by the χ^2 test and the independent sample *t* test, respectively.

RESULTS

General information

The two groups were similar in age, sex, course of disease, body mass index, classification of intra-abdominal hypertension, type of pancreatitis, and other general data ($P > 0.05$) (Table 1).

Efficacy of the two groups

The efficacy was comparatively analyzed to evaluate the effect of the two treatments on the therapeutic efficacy of SAP patients. The total effective rate was 90.91% in the research group, which was significantly higher than the 65.00% in the control group ($P < 0.05$) (Table 2).

Safety of the two groups

Adverse events were counted in both groups to assess the impact of the two treatments on patient safety. The total incidence of adverse events such as PF, IAH, sepsis, and organ dysfunction syndrome was 22.73% in the research group and 55.00% in the control group, with a significant intergroup difference ($P < 0.05$) (Table 3).

Abdominal bloating and pain relief time, bowel recovery time, and hospital stay of the two groups

The abdominal bloating and pain relief time, bowel recovery time, and hospital stay of both groups were recorded to evaluate the influence of the two treatments on SAP patients' recovery. The research group was found to have significantly faster abdominal bloating and pain relief and bowel recovery and shorter hospital stays than the control group ($P < 0.05$) (Figure 1).

Table 1 General information

Indicators	Control group (*n* = 20)	Research group (*n* = 22)	χ^2/t	*P* value
Age	37.20 ± 8.76	36.68 ± 10.61	0.172	0.864
Sex			0.877	0.349
Male	15 (75.00)	19 (86.36)		
Female	5 (25.00)	3 (13.64)		
Course of disease (h)	6.00 ± 2.49	6.82 ± 2.72		
BMI (kg/m^2)	21.76 ± 2.54	22.58 ± 2.68		
Intra-abdominal hypertension			0.479	0.787
I	12 (60.00)	13 (59.09)		
II	5 (25.00)	7 (31.82)		
III	3 (15.00)	2 (9.09)		
Types of pancreatitis			0.557	0.757
Hyperlipidemic pancreatitis	16 (80.00)	18 (81.82)		
Biliary	3 (150.00)	2 (9.09)		
Alcoholic	1 (5.00)	2 (9.09)		

BMI: Body mass index.

Table 2 Efficacy of the two groups

Indicators	Control group (*n* = 20)	Research group (*n* = 22)	χ^2	*P* value
Cure	8 (40.00)	12 (54.55)		
Improvement	5 (25.00)	8 (36.36)		
Ineffectiveness	7 (35.00)	2 (9.09)		
Effective rate	13 (65.00)	20 (90.91)	4.177	0.041

Table 3 Safety of the two groups

Indicators	Control group (*n* = 20)	Research group (*n* = 22)	χ^2	*P* value
Pancreatic fistula	3 (15.00)	1 (4.55)		
Intra-abdominal hemorrhage	3 (15.00)	2 (9.09)		
Sepsis	2 (10.00)	1 (4.55)		
Organ dysfunction syndrome	3 (15.00)	1 (4.55)		
Total	11 (55.00)	5 (22.73)	4.627	0.032

Inflammatory indices of the two groups

The effects of the two treatments on the serum inflammatory response of SAP patients were assessed by measuring CRP, IL-6, and PCT levels by ELISA. The levels of the above inflammatory factors were not significantly different between the groups before treatment ($P > 0.05$). CRP, IL-6 and PCT all decreased significantly after treatment ($P < 0.05$), with lower levels in the research group than in the control group ($P < 0.05$) (Figure 2).

APACHE-II scores in the two groups

The APACHE-II score was tested in both groups to compare the effects of the two treatment modalities on disease severity in SAP patients. The pretreatment APACHE-II score was similar between the two groups ($P > 0.05$). A marked reduction in the APACHE-II score was observed in both groups after treatment ($P < 0.05$), with an even lower score in the research group ($P < 0.05$) (Figure 3).

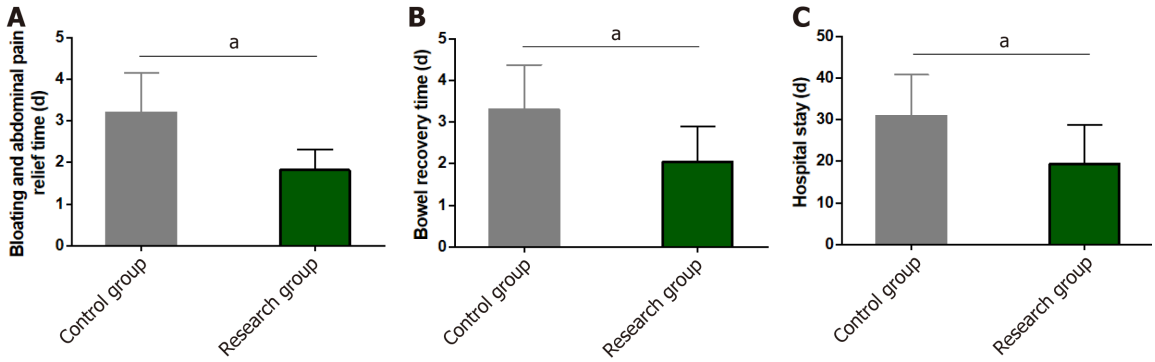

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Figure 1 Abdominal bloating and pain relief time, bowel recovery time, and hospital stay of the two groups. A: Abdominal bloating and pain relief time in the two groups; B: Bowel recovery time in the two groups; C: Hospital stay in the two groups. [a]*P* < 0.01.

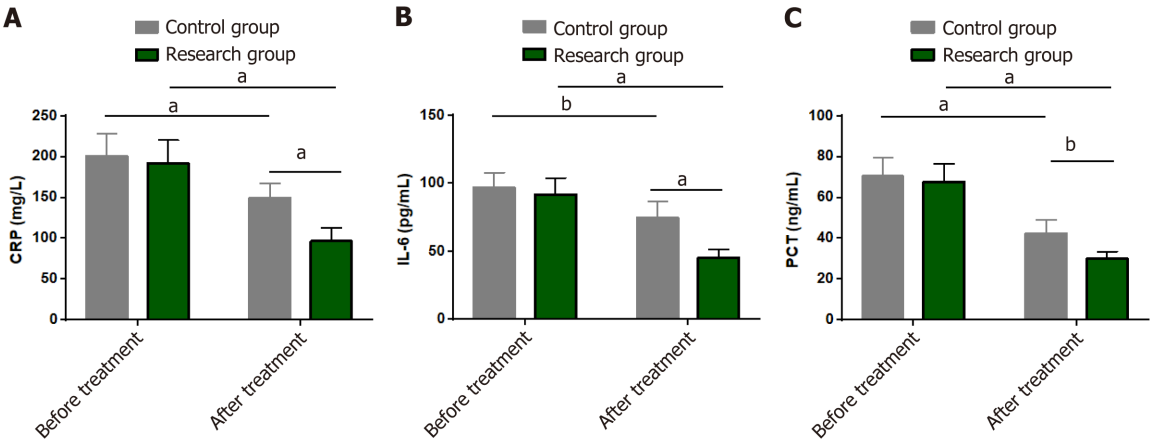

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Figure 2 Inflammation indices of the two groups. A: C-reactive protein in both groups; B: Interleukin-6 in both groups; C: Procalcitonin in both groups. [a]*P* < 0.01; [b]*P* < 0.05. CRP: C-reactive protein; IL-6: Interleukin-6; PCT: Procalcitonin.

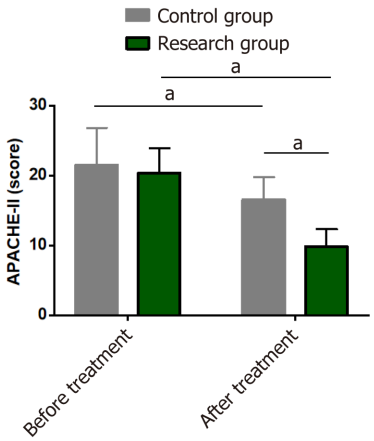

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Figure 3 Acute Physiology and Chronic Health Evaluation-II scores of the two groups. [a]*P* < 0.01. APACHE: Acute Physiology and Chronic Health Evaluation.

DISCUSSION

Pancreatitis, a condition in which the pancreas itself digests abnormally, is mainly manifested by damage to the pancreatic tissue by trypsin, causing dysfunction of glands and distal organs and systems[16]. SAP is a severe acute manifestation of pancreatitis that causes rapid and serious harm to the body once it breaks out[17]. The pathological process of SAP has been shown to involve intestinal barrier dysfunction, which in turn leads to the accelerated development of local and systemic infectious complications[18,19]. Therefore, an effective and safe intervention method is urgently needed to optimize the management of SAP patients.

Our research results showed a significantly higher total effective rate in the research group (90.91%) compared with the control group (65.00%), suggesting that SS plus CT-TPPCD is beneficial for therapeutic effect enhancement. The therapeutic mechanism of SS in SAP is related to its inhibition of insulin and glucagon secretion, which reduces the secretion of the pancreas and gallbladder and favors gastrointestinal absorption and nutritional function[20,21]. After statistical analysis of the incidence of PF, IAH, sepsis and organ dysfunction, the total incidence of the above adverse events was found to be markedly lower in the research group (22.73%) than in the control group (55.00%), indicating that SS plus CT-TPPCD can better guarantee the postoperative safety of SAP patients. Ai *et al*[22] reported that CT-TPPCD reduced mortality and the risk of inflammation-related complications in SAP patients, similar to our research results. In the study by Ganaie *et al*[23], CT-TPPCD is also shown to be clinically effective and safe for SAP pancreatic effusion management, both in patients with coinfection and symptomatic pancreatic effusion. The effects of the two treatments on patient postoperative recovery were evaluated from the aspects of abdominal bloating and pain relief time, bowel recovery time, and hospital stay. It was found that the research group had significantly better performance in the above aspects, suggesting that SS plus CT-TPPCD is conducive to promoting postoperative recovery in SAP patients. On the other hand, CRP is a protein that reflects the acute stage of a disease and is abnormally elevated in the setting of infection, tissue damage, *etc*[24]. IL-6, as an acute-phase reactive lymphocyte factor, not only activates the body's defense response and immunosuppression but also predicts the severity of SAP[25]. While PCT, an inflammatory factor closely related to secondary organ injury, is also associated with systemic inflammatory response syndrome[26]. Therefore, the above three inflammatory indices were detected to evaluate the influence of the two treatments on SAP patients. The research group showed markedly reduced- posttreatment CRP, IL-6, and PCT levels that were lower than the pretreatment levels and those of the control group, demonstrating the ability of SS plus CT-TPPCD to effectively inhibit serum inflammatory reactions in SAP patients. Previous evidence has shown that the downregulation of CRP, IL-6 and PCT levels can reflect treatment effectiveness in SAP patients, consistent with our findings[27]. Huang *et al*[28] also pointed out that lowering IL-6 levels was helpful to prevent SAP. Finally, the APACHE-II score of the research group decreased significantly after treatment and was lower than that of the control group, indicating that SS plus CT-TPPCD can significantly inhibit disease severity in SAP patients.

CONCLUSION

In summary, CT-TPPCD combined with SS is effective and safe in the treatment of SAP, which not only accelerates postoperative abdominal bloating and pain relief and intestinal recovery but also inhibits disease progression and improves patient health by reducing the levels of inflammatory indicators such as CRP, IL-6 and PCT. Our findings can provide a new choice for the clinical management optimization of SAP patients.

ARTICLE HIGHLIGHTS

Research background

Severe acute pancreatitis (SAP) accounts for 20% of all acute pancreatitis cases and poses a more serious threat to human health, so it is necessary to provide timely intervention to patients to improve their outcomes and ensure a certain therapeutic effect.

Research motivation

In view of the limited studies on the efficacy and safety of somatostatin (SS) combined with computerized tomography-guided therapeutic percutaneous puncture catheter drainage (CT-TPPCD) in the treatment of SAP, this study aims to supplement the gaps in this area and provide reliable clinical guidance.

Research objectives

To analyze the efficacy and safety of CT-TPPCD combined with SS in the treatment of SAP.

Research methods

Forty-two SAP patients were included, including 20 cases (control group) treated with SS intervention and 22 cases (research group) with CT-TPPCD + SS intervention. Comparative analyses were conducted from the following perspectives: Efficacy, safety (pancreatic fistula, intraperitoneal hemorrhage, sepsis, and organ dysfunction syndrome), abdominal bloating and pain relief time, intestinal recovery time, length of hospital stay, inflammatory indicators (C-

reactive protein, interleukin-6, and procalcitonin), and Acute Physiology and Chronic Health Evaluation (APACHE) II score.

Research results

The research group showed a higher total effective rate than the control group, with faster relief of abdominal bloating and pain and intestinal recovery, shorter length of hospital stay, and fewer adverse events, all with statistical significance. In addition, lower levels of inflammation indexes and APACHE II scores were determined in the research group after treatment, significantly lower than the baseline and those of the control group.

Research conclusions

CT-TPPCD plus SS is highly effective and safe in the treatment of SAP patients, contributing to fast inhibition of patients' disease and effective alleviation of serum inflammatory responses, which is worthy of clinical promotion.

Research perspectives

The negative impact of SAP on patients should not be underestimated, and it is necessary to improve clinical efficacy from the perspective of treatment optimization. This study proposes that SS combined with CT-TPPCD is significantly superior to SS alone in the treatment of SAP, which is of great significance for improving the clinical outcome of SAP patients and provides new clinical basis and insights.

FOOTNOTES

Author contributions: Zheng XL, and Huang TL designed the research and wrote the first manuscript; Zheng XL, Li WL, Lin YP, and Huang TL contributed to conceiving the research and analyzing data, conducted the analysis and provided guidance for the research; all authors reviewed and approved the final manuscript.

Supported by 2022 Fujian Medical University Qihang Fund General Project Plan, No. 2022QH1120.

Institutional review board statement: This study was approved by the Ethic Committee of The Second Affiliated Hospital of Fujian Medical University. Fuyi Fuer Ethics Review No. (322).

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

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

Data sharing statement: All data and materials are available from the corresponding author.

Country/Territory of origin: China

ORCID number: Ting-Long Huang 0009-0009-8514-5156.

S-Editor: Fan JR
L-Editor: A
P-Editor: Zhang YL

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World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2024 January 27; 16(1): 67-75

DOI: 10.4240/wjgs.v16.i1.67

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

Impact of open hepatectomy on postoperative bile leakage in patients with biliary tract cancer

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Specialty type: Gastroenterology and hepatology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Mita E, Japan; Sharma R, United Kingdom

Received: October 26, 2023
Peer-review started: October 26, 2023
First decision: November 8, 2023
Revised: November 9, 2023
Accepted: December 20, 2023
Article in press: December 20, 2023
Published online: January 27, 2024

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Abstract

BACKGROUND

Bile leakage is a common and serious complication of open hepatectomy for the treatment of biliary tract cancer.

AIM

To evaluate the incidence, risk factors, and management of bile leakage after open hepatectomy in patients with biliary tract cancer.

METHODS

We retrospectively analyzed 120 patients who underwent open hepatectomy for biliary tract cancer from February 2018 to February 2023. Bile leak was defined as bile drainage from the surgical site or drain or the presence of a biloma on imaging. The incidence, severity, timing, location, and treatment of the bile leaks were recorded. The risk factors for bile leakage were analyzed using univariate and multivariate logistic regression analyses.

RESULTS

The incidence of bile leak was 16.7% (20/120), and most cases were grade A (75%, 15/20) according to the International Study Group of Liver Surgery classification. The median time of onset was 5 d (range, 1-14 d), and the median duration was 7 d (range, 2-28 d). The most common location of bile leakage was the cut surface of the liver (70%, 14/20), followed by the anastomosis site (25%, 5/20) and the cystic duct stump (5%, 1/20). Most bile leaks were treated conservatively with drainage, antibiotics, and nutritional support (85%, 17/20), whereas some required endoscopic retrograde cholangiopancreatography with stenting (10%, 2/20) or percutaneous transhepatic cholangiography with drainage (5%, 1/20). Risk factors for bile leakage include male sex, hepatocellular carcinoma, major hepatectomy, blood loss, and blood transfusion.

CONCLUSION
Bile leakage is a frequent complication of open hepatectomy for biliary tract cancer. However, most cases are mild and can be conservatively managed. Male sex, hepatocellular carcinoma, major hepatectomy, blood loss, and blood transfusion were associated with an increased risk of bile leak.

Key Words: Open hepatectomy; Bile leak; Biliary tract cancer; Risk factors; Management; Complication

Core Tip: Bile leakage is a common complication of open hepatectomy for biliary tract cancer; however, it can be managed conservatively in most cases. The incidence of bile leak was 16.7% and was primarily grade A according to the liver surgery classification. The most common site was the cut surface of the liver. Treatment involved conservative measures such as drainage and antibiotics, with some cases requiring endoscopic or percutaneous intervention. Male sex, hepatocellular carcinoma, major hepatectomy, blood loss, and blood transfusion were identified as risk factors for bile leakage. Awareness of these factors can help optimize management strategies and reduce the occurrence of bile leaks.

Citation: Wu G, Li WY, Gong YX, Lin F, Sun C. Impact of open hepatectomy on postoperative bile leakage in patients with biliary tract cancer. *World J Gastrointest Surg* 2024; 16(1): 67-75
URL: https://www.wjgnet.com/1948-9366/full/v16/i1/67.htm
DOI: https://dx.doi.org/10.4240/wjgs.v16.i1.67

INTRODUCTION

Biliary tract cancer is a rare but aggressive malignancy originating from the epithelium of the intrahepatic or extrahepatic bile ducts or the gallbladder[1,2]. The incidence and mortality rates of biliary tract cancer vary widely according to the geographic region, with the highest rates occurring in Asia and Eastern Europe[3]. The primary treatment for biliary tract cancer is surgical resection, which offers a chance for cure and long-term survival[4,5]. However, surgery for biliary tract cancer is often complex and challenging, especially when employing major hepatectomy or hilar dissection[6].

Bile leakage is a common and serious complication of hepatectomy for biliary tract cancer[7,8]. It can cause abdominal pain, fever, infection, biloma formation, delayed wound healing, prolonged hospital stays, increased morbidity and mortality, and impaired quality of life. The reported incidence of bile leak after hepatectomy ranges from 3% to 27% depending on the definition, diagnosis, and classification criteria[9]. Several risk factors for bile leakage after hepatectomy have been identified, including the tumor location, extent of resection, operative time, blood loss, liver function, biliary pressure, surgical techniques, and drainage management[10].

Bile leakage is diagnosed based on clinical signs and symptoms, biochemical tests, imaging studies, and endoscopic or percutaneous interventions[11]. Treatment depends on the severity, timing, location, and source of bile leakage[11]. The International Study Group of Liver Surgery (ISGLS) has proposed a classification system for bile leak after hepatectomy based on the clinical impact and the need for therapeutic interventions[12]. According to this system, bile leaks can be classified into three grades: grade A, bile leaks that do not require any change in the initial treatment plan; grade B, bile leaks that require a change in the initial treatment plan but can be managed without laparotomy; and grade C, bile leaks that require laparotomy.

Open hepatectomy is a conventional surgical approach for biliary tract cancer that allows direct visualization and manipulation of the liver and bile ducts. However, open hepatectomy is associated with a higher risk of bile leakage than laparoscopic or robotic hepatectomy. This is because of the larger cut surface of the liver, longer operative time, and greater blood loss[13]. Therefore, it is important to evaluate the effect of open hepatectomy on postoperative bile leakage in patients with biliary tract cancer and identify optimal management strategies for this complication[14].

We retrospectively analyzed 120 patients who underwent open hepatectomy for biliary tract cancer at our institution from February 2018 to February 2023. We aimed to assess the incidence, risk factors, and management of bile leak after open hepatectomy for biliary tract cancer and to provide suggestions for improving surgical outcomes.

MATERIALS AND METHODS

Study design and population

This retrospective cohort study was conducted at a tertiary referral center. We reviewed the medical records of 120 patients who underwent open hepatectomies for biliary tract cancer from February 2018 to February 2023. Biliary tract cancer was defined as a malignant tumor arising from the intrahepatic or extrahepatic bile ducts or the gallbladder. Diagnosis of biliary tract cancer was confirmed by histopathological examination of the resected specimens. The inclusion criteria were age ≥ 18 years, performance status 0-2, Child-Pugh class A or B, no evidence of distant metastasis, no

previous history of liver surgery or liver transplantation, and no concomitant extrahepatic bile duct resection. The exclusion criteria included incomplete medical records, conversion to laparoscopic or robotic hepatectomy, intraoperative death, or postoperative death within 30 d. The Institutional Review Board approved the study protocol and waived the requirement for informed consent owing to the retrospective nature of the study.

Surgical procedure

All patients underwent open hepatectomy under general anesthesia, performed by experienced hepatobiliary surgeons. The type and extent of hepatectomy were determined based on liver function and remnant liver volume as well as on the location, size, and number of tumors. The surgical approach was either a right or bilateral subcostal incision, with or without midline extension. The Pringle maneuver was performed intermittently or continuously to minimize the blood loss. The liver parenchyma was transected using an ultrasonic dissector or Cavitron ultrasonic surgical aspirator. The intrahepatic bile ducts were identified and ligated using clips or sutures. The cut surface of the liver was treated with fibrin glue or an argon beam coagulator to prevent bile leakage and bleeding. A closed suction drain was placed near the cut surface of the liver before closing the abdomen.

Postoperative management

All patients were transferred to the intensive care unit after surgery and closely monitored for vital signs, fluid balance, hemoglobin levels, liver function, coagulation profile, and drain output. The drain fluid was routinely checked for bilirubin levels on postoperative day three. Bile leak was diagnosed when the bilirubin level in the drain fluid was three times higher than the serum level. The management of bile leakage was based on the ISGLS classification and clinical condition of the patient. Grade A bile leaks were managed using conservative measures such as drainage, antibiotics, and nutritional support. Grade B bile leaks were managed using endoscopic or percutaneous interventions such as endoscopic retrograde cholangiopancreatography (ERCP) with stenting or percutaneous transhepatic cholangiography (PTC) with drainage. Grade C bile leaks were managed using laparotomy and surgical repair.

Data collection and analysis

The following data were collected from the medical records: demographic characteristics, preoperative liver function test results, tumor characteristics, type and extent of hepatectomy, operative time, blood loss and transfusion, postoperative complications, length of hospital stay, and mortality. The primary outcome measure was bile leakage after open hepatectomy for biliary tract cancer. Secondary outcomes were risk factors, management, and bile leak outcomes. Data were analyzed using SPSS software (version 25.0; IBM Corp., Armonk, NY, United States). Continuous variables are expressed as mean ± SD or median (range), and categorical variables are expressed as number (percentage). Univariate analysis was performed using Student's *t*-test or the Mann-Whitney *U* test for continuous variables and the chi-squared test or Fisher's exact test for categorical variables. Multivariate logistic regression analysis was performed to identify independent risk factors for bile leakage. Statistical significance was set at $P < 0.05$.

RESULTS

Patient characteristics and operative details

This study included 120 patients who underwent open hepatectomies for biliary tract cancer from February 2018 to February 2023. Baseline characteristics and operative details of the patients are shown in Table 1. The mean age was 62.3 ± 10.4 years, and 68 (56.7%) patients were male. The most common tumor type was intrahepatic cholangiocarcinoma (n = 54, 45%), followed by gallbladder cancer (n = 36, 30%) and extrahepatic cholangiocarcinoma (n = 30, 25%). The most common type of hepatectomy was right hemihepatectomy (n = 48, 40%), followed by left hemihepatectomy (n = 24, 20%), and segmentectomy (n = 18, 15%). The mean operative time was 312.5 ± 87.6 min, and the mean blood loss was 712.5 ± 345.6 mL. Blood transfusions were required in 36 patients (30%).

Table 1 Patient characteristics and operative details

Patient demographics and characteristics	Value
Age (yr)	62.3 ± 10.4
Sex (male/female)	68/52
Body mass index (kg/m^2)	24.5 ± 3.2
ASA score (I/II/III)	12/84/24
Child-Pugh class (A/B)	108/12
MELD score	8.7 ± 2.4
Albumin (g/L)	38.6 ± 4.5

Total bilirubin (μmol/L)	17.5 ± 6.8
INR	1.05 ± 0.08
Platelet count (× 10^9/L)	198.5 ± 76.4
Tumor type, *n* (%)	
Intrahepatic cholangiocarcinoma	54 (45)
Gallbladder cancer	36 (30)
Extrahepatic cholangiocarcinoma	30 (25)
Tumor size (cm)	6.3 ± 1.5

ASA: American Society of Anesthesiologists; MELD: Model for End-Stage Liver Disease; INR: International normalized ratio.

Postoperative complications and outcomes

Postoperative complications and patient outcomes are shown in Table 2. The overall morbidity rate was 38.3% (46/120) and the most common complications were bile leakage (16.7%, 20/120), wound infections (10%, 12/120), and ascites (8.3%, 10/120). The median length of hospital stay was 12 d (range, 7-35 d). The mortality rate was 1.7% (2/120); both deaths were due to liver failure.

Table 2 Postoperative complications and outcomes, *n* (%)

Complication type	Value
Morbidity	46 (38.3)
Bile leak	20 (16.7)
Wound infection	12 (10)
Ascites	10 (8.3)
Liver failure	4 (3.3)
Bleeding	3 (2.5)
Sepsis	2 (1.7)
Cholangitis	2 (1.7)
Pulmonary embolism	1 (0.8)
Mortality	2 (1.7)
Length of hospital stay (d)	12 (7-35)

Incidence and characteristics of bile leak

Of the 120 patients, 20 (16.7%) developed bile leak after open hepatectomy for biliary tract cancer. Patient characteristics are shown in Table 3. The median time of bile leak onset was 5 d (range, 1-14 d), and the median duration was 7 d (range, 2-28 d). According to the ISGLS classification, most bile leaks were grade A (75%, 15/20), followed by grades B (20%, 4/20) and C (5%, 1/20). The most common location of bile leakage was the cut surface of the liver (70%, 14/20), followed by the anastomosis site (25%, 5/20) and the cystic duct stump (5%, 1/20).

Management and outcomes of bile leak

The management and outcomes of patients with bile leakage are presented in Table 4. Most bile leaks (85%, 17/20) were treated conservatively with drainage, antibiotics, and nutritional support. Four patients (20%) required endoscopic or percutaneous interventions such as ERCP with stenting (*n* = 2) or PTC with drainage (*n* = 2). One patient (5%) required relaparotomy and surgical repair because of a grade C bile leak with biliary peritonitis. The outcomes of bile leak management were favorable in most cases, with resolution in 18 patients (90%). Two patients (10%) experienced persistent bile leakage and required long-term drainage.

Risk factors for bile leak

Univariate and multivariate analyses of risk factors for bile leakage are shown in Table 5. The univariate analysis revealed that male sex, hepatocellular carcinoma, major hepatectomy, blood loss, and blood transfusion were significantly associated with bile leakage. Multivariate analysis confirmed that these factors were independent risk factors, with odds ratios of 2.6, 3.1, 4.2, 2.7, and 3.4, respectively.

Table 3 Characteristics of bile leak

Bile leak details	Value
Time of onset (d)	5 (1-14)
Duration (d)	7 (2-28)
ISGLS grade, *n* (%)	
A	15 (75)
B	4 (20)
C	1 (5)
Location, *n* (%)	
Cut surface of liver	14 (70)
Anastomosis site	5 (25)
Cystic duct stump	1 (5)

ISGLS: International Study Group of Liver Surgery.

Table 4 Management and outcomes of bile leak, *n* (%)

Management and outcome	Value
Management	
Conservative	17 (85)
Endoscopic	2 (10)
Percutaneous	2 (10)
Surgical	1 (5)
Outcome	
Resolution	18 (90)
Persistence	2 (10)

DISCUSSION

This study evaluated the effect of open hepatectomy on postoperative bile leakage in patients with biliary tract cancer and found that the incidence of bile leakage was 16.7%. This value is consistent with previous reports[10]. Most bile leaks were mild and could be managed conservatively, while some required endoscopic or percutaneous interventions, and only one required laparotomy and surgical repair.

The risk factors for bile leakage are male sex, hepatocellular carcinoma, major hepatectomy, blood loss, and blood transfusion[15]. Bile leakage is a common and serious complication of hepatectomy for biliary tract cancer and can cause significant morbidity and mortality[8]. The pathogenesis of bile leak is multifactorial and involves technical, anatomical, physiological, and pathological factors[10]. Technical factors include the surgical technique, extent of resection, type of anastomosis, and use of drainage[16,17]. Anatomical factors include variations in the bile ducts, the presence of accessory ducts or ducts of Luschka, and tumor location[18]. Physiological factors include biliary pressure, liver function, and coagulation status[19,20]. Pathological factors include the type and stage of the tumor, presence of inflammation or fibrosis, and response to chemotherapy or radiotherapy[5]. Bile leakage is diagnosed based on clinical signs and symptoms, biochemical tests, imaging studies, and endoscopic or percutaneous interventions[21].

The most common symptom of bile leakage is abdominal pain accompanied by fever, jaundice, or ascites[22]. Biochemical tests measure the bilirubin level in the drain or peritoneal fluid and are considered diagnostic if the bilirubin is three times higher than the serum bilirubin level. Imaging studies include ultrasonography, computed tomography, magnetic resonance cholangiopancreatography, and hepatobiliary iminodiacetic acid scans, which reveal the presence and location of bile leaks or biloma[23]. Endoscopic or percutaneous interventions include ERCP or PTC, which can not only confirm the diagnosis but also provide therapeutic options such as stenting or drainage[9,20].

The treatment of bile leakage depends on its severity, timing, location, and source of the bile leak. The ISGLS classification provides a useful guide for the management of bile leaks based on the clinical impact and the need for therapeutic interventions[6]. In general, grade A bile leaks can be managed conservatively with drainage, antibiotics, and nutritional support, whereas grade B and C bile leaks may require endoscopic or percutaneous interventions or even laparotomy and surgical repair[24]. Endoscopic interventions include ERCP with stenting or sphincterotomy, which can

Table 5 Risk factors for bile leak

Variables	Univariate analysis results	Multivariate analysis results
Age (> 60 yr)	OR 1.4, 95%CI: 0.6-3.2, $P = 0.42$	
Sex (male)	OR 3.1, 95%CI: 1.2-7.9, $P = 0.02$	OR 2.6, 95%CI: 1.1-6.8, $P = 0.03$
BMI (> 25 kg/m^2)	OR 1.3, 95%CI: 0.6-3.0, $P = 0.51$	
ASA score (> II)	OR 1.8, 95%CI: 0.8-4.3, $P = 0.16$	
Child-Pugh class (B)	OR 1.5, 95%CI: 0.5-4.7, $P = 0.47$	
MELD score (> 10)	OR 1.7, 95%CI: 0.7-4.1, $P = 0.24$	
Albumin (< 35 g/L)	OR 1.9, 95%CI: 0.8-4.5, $P = 0.14$	
Total bilirubin (> 20 μmol/L)	OR 1.6, 95%CI: 0.7-3.8, $P = 0.27$	
INR (> 1.1)	OR 1.4, 95%CI: 0.6-3.3, $P = 0.44$	
Platelet count (< 150 × 10^9/L)	OR 1.2, 95%CI: 0.5-2.8, $P = 0.66$	
Tumor type (HCC)	OR 4.3, 95%CI: 1.8-10.5, $P < 0.01$	OR 3.1, 95%CI: 1.4-7.2, $P < 0.01$
Tumor size (> 5 cm)	OR 1.9, 95%CI: 0.9-3.9, $P = 0.09$	
Type of hepatectomy (major)	OR 5.6, 95%CI: 2.3-13.7, $P < 0.01$	OR 4.2, 95%CI: 1.9-9.4, $P < 0.01$
Blood loss (> 1000 mL)	OR 3, 95%CI: 1.2-7.4, $P = 0.02$	OR 2.7, 95%CI: 1.2-6.3, $P = 0.02$
Blood transfusion (yes)	OR 4, 95%CI: 1.6-10, $P < 0.01$	OR 3.4, 95%CI: 1.5-7.8, $P < 0.01$

ASA: American Society of Anesthesiologists; MELD: Model for End-Stage Liver Disease; INR: International normalized ratio; HCC: Hepatocellular carcinoma.

reduce biliary pressure and divert bile flow to the duodenum, thereby facilitating bile leak healing[25]. Percutaneous interventions include the drainage or embolization of PTCs, which can decompress the biliary system and occlude the leaking duct. Surgical interventions, including suture repair, omental patches, and hepaticojejunostomy, can restore biliary continuity and prevent further leakage[26].

The management of bile leaks should be individualized according to the patient's condition, availability of expertise and resources, and the potential risks and benefits of each intervention. The goal of treatment is to resolve bile leaks with minimal morbidity and mortality.

Despite the valuable insights provided by this study, we acknowledge several limitations. First, the retrospective nature of the study may have introduced selection and information bias. Patients were selected based on specific inclusion criteria, and data were collected from medical records, which may not capture all the nuances of clinical presentations and interventions. Second, this study was conducted at a single tertiary referral center, which may limit the generalizability of the findings to other settings or populations. Third, the sample size of 120 patients, while substantial for rare conditions, may still be too small to detect subtle associations or allow for the generalization of results across a broader patient population with biliary tract cancer. Additionally, relevant variables that could influence the incidence of bile leakage, such as the exact surgical technique used or the surgeon's experience, were not assessed. Lastly, the lack of long-term follow-up data limits the ability to evaluate the impact of bile leakage on long-term outcomes, such as cancer recurrence or long-term survival. Future prospective studies with larger sample sizes and multicenter collaborations are needed to validate our findings and further refine the risk stratification of bile leakage after open hepatectomy for biliary tract cancer.

CONCLUSION

In conclusion, this study demonstrated that open hepatectomy for biliary tract cancer is associated with a high incidence of bile leakage, which can be challenging. However, most bile leaks are mild and can be managed conservatively, while some require endoscopic or percutaneous interventions and rarely require surgical repair. Male sex, hepatocellular carcinoma, major hepatectomy, blood loss, and blood transfusion are risk factors for bile leakage. Further studies are needed to explore optimal strategies for preventing and treating bile leakage after open hepatectomy for biliary tract cancer.

ARTICLE HIGHLIGHTS

Research background

Bile leakage is a common and significant complication of open hepatectomy, a surgical procedure performed to treat biliary tract cancer. Bile leaks are characterized by the drainage of bile from the surgical site or drain or the formation of a biloma (a localized collection of bile), as observed on imaging scans. This complication can lead to various adverse outcomes including infection, abscess formation, sepsis, delayed wound healing, and prolonged hospital stay. Therefore, understanding the incidence, risk factors, and management strategies of bile leaks is crucial to improve patient outcomes and reduce the burden on the healthcare system.

Research motivation

Bile leakage is a significant complication of open hepatectomy for the treatment of biliary tract cancer. However, few studies have focused on the incidence, risk factors, and management of these complications. Therefore, this study aimed to address this knowledge gap by conducting a comprehensive analysis of 120 patients who underwent open hepatectomy for biliary tract cancer. The motivation for this study lies in the need to better understand the frequency, associated risk factors, and effective management strategies of bile leaks. By identifying these factors, healthcare professionals can improve patient outcomes, reduce complications, and optimize treatment approaches in patients undergoing open hepatectomy for biliary tract cancer.

Research objectives

Evaluate the incidence of bile leak after open hepatectomy for biliary tract cancer. Identify the risk factors associated with bile leakage in this patient population. Investigate the management strategies employed for bile leaks, including conservative approaches and interventional procedures. Assess the severity, timing, location, and duration of bile leaks following open hepatectomy. Determine the association between specific risk factors, such as male sex, hepatocellular carcinoma, major hepatectomy, blood loss, and blood transfusion, and the occurrence of bile leaks. By achieving these objectives, the study aimed to provide valuable insights into the incidence, risk factors, and management of bile leak complications after open hepatectomy for biliary tract cancer, ultimately contributing to improved patient care and surgical outcomes.

Research methods

Study population: Patient data from open hepatectomy for biliary tract cancer (February 2018 to February 2023) were retrospectively analyzed. Data Collection: Information on bile leak complications (incidence, severity, timing, location, and treatment) was obtained from patient records and charts. Bile Leak Definition: Defined as bile drainage or presence of biloma observed on imaging. Statistical Analysis: Univariate and multivariate logistic regression analyses were used to assess the risk factors (sex, hepatocellular carcinoma, major hepatectomy, blood loss, and transfusion). Utilizing existing data allows for cost-effective investigations, while statistical analyses enhance understanding. These findings provide insights into bile leak management and may improve the care of patients undergoing open hepatectomy.

Research results

Bile leak occurred in 16.7% (20/120) of patients who underwent open hepatectomy for biliary tract cancer. Most cases were grade A, with a median onset time of 5 d and duration of 7 d. The cut surface of the liver was the most common site of leakage (70%). Conservative treatment was successful in 85% of cases, while 10% required endoscopic retrograde cholangiopancreatography (ERCP) with stenting and 5% required percutaneous transhepatic cholangiography (PTC) with drainage. Male sex, hepatocellular carcinoma, major hepatectomy, blood loss, and blood transfusion were identified as risk factors for bile leak.

Research conclusions

This study provides new insights into the incidence, risk factors, and management of bile leak after open hepatectomy for biliary tract cancer. It highlights that bile leakage is a common complication, with an incidence rate of 16.7%. This study identified male sex, hepatocellular carcinoma, major hepatectomy, blood loss, and blood transfusion as significant risk factors for bile leakage. This suggests that conservative management, including drainage, antibiotics, and nutritional support, is effective in most cases. The study also mentioned the use of ERCP with stenting or PTC with drainage as alternative treatment options.

Research perspectives

Future studies should focus on developing strategies to reduce the incidence of bile leakage after open hepatectomy for biliary tract cancer. Investigating the use of advanced imaging techniques for early detection and assessment of bile leaks could improve patient outcomes. Additionally, the potential of minimally invasive surgical techniques and perioperative interventions to reduce the risk of bile leakage warrants further investigation. Long-term follow-up studies are needed to evaluate the effects of bile leak on patient survival and quality of life. Collaborative efforts are necessary to establish standardized guidelines and protocols for the prevention, diagnosis, and management of bile leakage in clinical practice.

FOOTNOTES

Author contributions: Wu G and Sun C proposed the concept of this study; Li WY contributed to data collection; Wu G and Gong YX drafted the first draft; Lin F contributed to the formal analysis of this study; Sun C conducted guidance research, methodology, and visualization; all authors participated in the study, validated the study, and jointly reviewed and edited the manuscript.

Institutional review board statement: This study has been approved by the Clinical Research Project Ethics Review of the Medical Ethics Committee of the Second Affiliated Hospital of Harbin Medical University, with the Ethics Review Approval Document (No. KY2023-111).

Informed consent statement: All study participants or their legal guardians provided written informed consent before study enrollment.

Conflict-of-interest statement: All authors declare that there are no conflicts of interest.

Data sharing statement: No additional data are available.

Country/Territory of origin: China

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S-Editor: Gong ZM
L-Editor: A
P-Editor: Yu HG

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World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2024 January 27; 16(1): 76-84

DOI: 10.4240/wjgs.v16.i1.76

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

Clinical observation of gastrointestinal function recovery in patients after hepatobiliary surgery

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Specialty type: Gastroenterology and hepatology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Chen Y, United States; Lee HS, South Korea

Received: October 30, 2023
Peer-review started: October 30, 2023
First decision: November 8, 2023
Revised: November 21, 2023
Accepted: December 28, 2023
Article in press: December 28, 2023
Published online: January 27, 2024

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Abstract

BACKGROUND

The liver is an important metabolic and digestive organ in the human body, capable of producing bile, clotting factors, and vitamins.

AIM

To investigate the recovery of gastrointestinal function in patients after hepatobiliary surgery and identify effective rehabilitation measures.

METHODS

A total of 200 patients who underwent hepatobiliary surgery in our hospital in 2022 were selected as the study subjects. They were divided into a control group and a study group based on the extent of the surgery, with 100 patients in each group. The control group received routine treatment, while the study group received targeted interventions, including early enteral nutrition support, drinking water before gas discharge, and large bowel enema, to promote postoperative gastrointestinal function recovery. The recovery of gastrointestinal function was compared between the two groups.

RESULTS

Compared with the control group, patients in the study group had better recovery of bowel sounds and less accumulation of fluids in the liver bed and gallbladder fossa ($P < 0.05$). They also had shorter time to gas discharge and first meal ($P < 0.05$), higher overall effective rate of gastrointestinal function recovery ($P < 0.05$), and lower incidence of postoperative complications ($P < 0.05$).

CONCLUSION
Targeted nursing interventions (early nutritional support, drinking water before gas discharge, and enema) can effectively promote gastrointestinal function recovery in patients undergoing hepatobiliary surgery and reduce the incidence of complications, which is worthy of promotion.

Key Words: Liver and gallbladder patients; Gastrointestinal function; Postoperative recovery

Core Tip: The liver is an important metabolic and digestive organ in the human body, capable of producing bile, clotting factors, and vitamins. The bile duct mainly functions in the secretion and excretion of bile. This study was conducted in a retrospective manner. After undergoing the same surgical procedure, the patients in the control group received routine treatment and management, including relevant examinations of the liver and gallbladder, evaluation of the stage of disease development, and dietary guidance to maintain the balance of various bodily functions.

Citation: Zeng HJ, Liu JJ, Yang YC. Clinical observation of gastrointestinal function recovery in patients after hepatobiliary surgery. *World J Gastrointest Surg* 2024; 16(1): 76-84
URL: https://www.wjgnet.com/1948-9366/full/v16/i1/76.htm
DOI: https://dx.doi.org/10.4240/wjgs.v16.i1.76

INTRODUCTION

The liver, a vital organ involved in metabolism and digestion, plays a crucial role in the production of bile, clotting factors, and vitamins. The primary function of the bile duct is the secretion and excretion of bile[1]. Liver and gallbladder diseases, such as hepatitis, cirrhosis, and gallstones, are commonly observed conditions affecting these organs. The etiology of liver and gallbladder diseases often involves bacterial infections, excessive alcohol consumption, smoking, obesity, and irregular dietary patterns[2,3].

Liver and gallbladder diseases are prevalent surgical conditions in contemporary clinical practice in China. The primary treatment for these diseases involves surgical removal of the affected lesions or the unblocking of obstructed areas, which has demonstrated favorable efficacy. Notably, liver and gallbladder surgery is distinguished by prolonged operation durations, substantial blood loss, and the utilization of multiple postoperative drainage tubes[4-6]. Liver and gallbladder surgery is distinguished by prolonged operation duration, substantial blood loss, and the utilization of multiple postoperative drainage tubes[4-6]. Furthermore, factors such as patient stress response, pain, and hypoxemia have the potential to readily induce postoperative gastrointestinal dysfunction, inflammatory reactions, immune suppression, among other complications[7]. Simultaneously, a significant proportion of surgical procedures necessitate the administration of general anesthesia, encompassing the liver, gallbladder, pancreas, spleen, intestines, and other organs, all of which exhibit intricate associations with major blood vessels[8]. The anatomical structures are complex, and careless surgical manipulation can easily cause damage to the blood vessels. Clinical studies have shown that factors such as traction during surgery and general anesthesia can result in poor postoperative gastrointestinal function recovery in patients, which not only affects the patients' recovery outcomes but also their quality of life. Additionally, due to the large surgical incision, patients need to use pain pumps, further exacerbating gastrointestinal dysfunction[9]. For example, common clinical manifestations include cessation of flatulence and bloating, which require surgical intervention for treatment. Therefore, developing effective methods to promote the recovery of gastrointestinal function in patients is of great importance in clinical practice[10].

Many clinical reports have indicated that early enteral nutrition support therapy has a positive impact on the recovery of gastrointestinal function in patients undergoing liver and gallbladder surgery[11-13]. Research has shown that early enteral nutrition support is crucial. Within 24 h after surgery, providing scientific enteral nutrition support to patients is key to accelerating the recovery of physiological function and status post-surgery[14]. It can protect the gastrointestinal mucosa, effectively improve the patients' gastrointestinal function, and is also the most effective nutritional support method after surgery[15]. Therefore, this study aims to analyze the clinical effects of comprehensive treatment (early enteral nutrition support, enema, *etc.*) on the recovery of gastrointestinal function, including diet, flatulence, and bowel movements, in patients undergoing liver and gallbladder surgery. The purpose is to provide necessary interventions and guidance in the clinical setting to help patients regain gastrointestinal function as quickly as possible.

MATERIALS AND METHODS

General information

This study was conducted in a retrospective manner. A total of 200 patients with liver and gallbladder diseases admitted

to our hospital in 2022 were selected, all of whom underwent surgical treatment. They were randomly divided into a control group and a study group, with 100 patients in each group. The control group received routine treatment methods, while the study group received comprehensive treatment based on routine treatment methods. Both groups of patients underwent surgery performed by the same experienced doctor.

Inclusion criteria: (1) Diagnosed with surgical diseases of the liver and gallbladder based on physical signs, medical history, and laboratory examination results, meeting the requirements for surgical treatment of liver and gallbladder diseases; (2) Normal mental thinking and unobstructed communication; (3) Aware and voluntarily participated in the study, including understanding the content and risks involved; (4) Complete clinical data; and (5) Clear consciousness, normal thinking, and ability to communicate normally.

Exclusion criteria: (1) Concurrent malignancy; (2) Poor nutritional status and poor compliance; and (3) serious organ diseases.

Methods

After undergoing the same surgical procedure, the patients in the control group received routine treatment and management, including relevant examinations of the liver and gallbladder, evaluation of the stage of disease development, and dietary guidance to maintain the balance of various bodily functions. The main contents included postoperative fluid supplementation, correction of electrolyte imbalances, routine nutritional support, preoperative intestinal preparation, strict fasting, routine postoperative anti-infection treatment, and parenteral nutrition support.

The patients in the study group were provided with a comprehensive treatment approach, which included routine treatment methods as well as specific targeted interventions designed to facilitate the recovery of postoperative gastrointestinal function. They underwent routine cardiovascular, pulmonary, and brain function examinations, as well as liver and kidney function and electrolyte testing. If there were concurrent conditions such as hypertension, diabetes, or insufficient lung function, assistance from the corresponding departments was requested for consultation and treatment, ensuring that the coexisting diseases were controlled and the patients were able to tolerate the surgery. The specific measures included: (1) Detailed explanation of the surgical purpose and method to the patient before surgery to reduce their fear; placement of a nasogastric tube during surgery to closely monitor the patient's body temperature, with temperature measurements taken every 30 min to maintain a temperature of 36 °C or above; immediate notification of the anesthesiologist and surgeon if any abnormalities were discovered to prevent excessively low body temperature from affecting the pharmacokinetics of drugs in the body and reduce the occurrence of postoperative incision infection and cardiovascular complications; (2) Early postoperative rehabilitationogastric tube immediately after surgery, promoting gastrointestinal function-related activities for patients after 6 h postoperatively to exercise their chewing ability, and encouraging patients to chew gum to promote the secretion of digestive juices; (3) Early enteral nutrition support, such as administering pantoprazole orally and prophylactic antibiotics tailored to the patient's actual condition and type of disease, with enhanced assessment of the patient's underlying diseases, infection risks, and pain levels; when using anti-inflammatory drugs such as glucocorticoids, consideration should be given to the patient's actual situation and cautious use of drugs; (4) Enema using Da Cheng Qi Decoction once daily, stopping the enema after rectal gas is passed; and (5) Water intake and injection of Xinsideming at the acupuncture point of Zusanli before gas discharge after surgery. Throughout the treatment period, oral care was provided twice daily, including oral hygiene and moistening the lips with a disinfectant cotton swab to avoid adverse symptoms such as intestinal adhesions.

Observation indicators

Observation indicators mainly include detailed records of clinical symptoms and signs of two groups of patients before and after surgery, routine blood, urine, and stool tests, as well as electrolyte and blood routine tests. Liver and kidney function tests showed no abnormalities. The recovery of gastrointestinal function, restoration time of bowel sounds, time of passing gas, and time of first meal for patients were also observed.

Postoperative recovery criteria are as follows: (1) The recovery of gastrointestinal function is divided into three levels: Obvious effect, effective, and ineffective. Obvious effect: No abdominal pain, bloating, or diarrhea after surgery, normal anal gas discharge, and no complications; effective: Significant improvement in gas discharge function, improvement in clinical symptoms such as abdominal pain and bloating, slight diarrhea, and no other complications; ineffective: Failure to meet the above criteria or aggravation of the condition. The overall effectiveness rate = rate of obvious effect + rate of effectiveness; and (2) Postoperative recovery of gastrointestinal function and prognosis nutrition index: Restoration time of bowel sounds, time of first bowel movement, time of first gas discharge, and time of first meal.

Complications

The occurrence of related complications in the two groups was recorded, including oral ulcers, cracked lips, belching, and investigating the presence of hepatic and gallbladder effusion. The effusion was mainly classified as long diameter > 2 cm, long diameter ≤ 2 cm, and no effusion.

Statistical methods

The recorded data of the two groups were classified and summarized. Analysis was performed using SPSS 20.0 statistical software. Measurement data were expressed as (mean ± SD), and *t*-test was used for comparison. Count data were expressed as percentages (%), and χ^2 test was used for intergroup rate comparison. A difference with $P < 0.05$ was considered statistically significant.

RESULTS

Comparison of baseline characteristics of patients: The baseline data of age, gender, and body mass index of the two groups were compared, and no statistically significant differences were found ($P > 0.05$ for all; Table 1).

Postoperative gastrointestinal function recovery

Comparison of bowel sounds recovery time, gas discharge time, and first feeding time between two groups of patients. Compared to the control group, the research group had significantly shorter bowel sounds recovery time, gas discharge time, first defecation time, time to get out of bed, and first feeding time ($P < 0.001$; Table 2).

Overall therapeutic effectiveness

Comparison of treatment effectiveness between the two groups: After treatment, the overall effective rate of the research group was 98.00%, significantly higher than the overall effective rate of 68.00% in the control group, and the difference between the groups was significant ($P < 0.001$; Table 3).

Comparison of hospital stay duration between the two groups of patients

The research group had a shorter time for catheter removal, postoperative hospital stay, and postoperative pain score compared to the control group, and the differences were statistically significant ($P < 0.001$; Table 4).

Comparison of postoperative complications between the two groups

Comparison of postoperative complications between the two groups of patients. The total incidence rate of postoperative complications in the research group was 5.00%, significantly lower than the 34.00% in the control group, and the difference was statistically significant ($P < 0.001$; Table 5).

Comparison of prognosis nutritional index in the two groups of patients

The nutritional index for prognosis in the research group was significantly higher than that in the control group, and the difference between the two groups was statistically significant ($P < 0.001$; Table 6).

DISCUSSION

Presently, there is a gradual rise in the prevalence of liver and gallbladder diseases, and surgical interventions have proven to be an efficacious approach for managing liver diseases[16]. Nonetheless, post-surgery, patients may experience a decline in gastrointestinal function to a certain degree. This decline can manifest as clinical symptoms like abdominal pain and distension, which not only diminish their quality of life but also pose a potential risk to their overall well-being, particularly for individuals who develop deep vein thrombosis in the lower extremities[17]. The efficacy of early nutritional therapy in delivering nutritional support to patients with liver and gallbladder diseases has been substantiated, rendering it a more appropriate treatment modality[18]. In addition to that, early enteral nutrition support can significantly reduce the amount of intravenous fluid administration, thus reducing the incidence of diseases and effectively protecting the gastrointestinal mucosa, promoting recovery, and improving the quality of life[19]. Compared to other methods of nutrition support, early enteral nutrition support has certain advantages as it is relatively simple to implement and allows for customizing treatment plans based on the patients' own conditions, effectively improving treatment compliance and enhancing the recovery of gastrointestinal function. Many patients with liver and gallbladder diseases undergo surgery. If the gastrointestinal function does not recover in a timely manner, they may experience difficulties in defecation, bloating, and other symptoms, which can also affect wound healing and even lead to wound infection. Therefore, it is crucial for doctors to take appropriate postoperative measures to help patients restore gastrointestinal function after surgical treatment of liver and gallbladder diseases. Research has shown that early enteral nutrition support can effectively overcome the disadvantages of surgical treatment, such as intestinal dysbiosis and intestinal mucosal atrophy. Additionally, early enteral nutrition support can accelerate the body's metabolic function[20-25].

In this study, we used a treatment method targeting the recovery of gastrointestinal function in the study group. The study group received early enteral nutrition support, and the average nutritional index of the patients significantly improved, indicating its positive effect in the recovery of gastrointestinal function after surgery. After postoperative treatment, the overall effective rate of the study group patients was significantly higher than that of the control group, and the incidence of postoperative adverse reactions was low, which was beneficial for the patients' postoperative recovery. In addition, early nutrition support for patients with liver and gallbladder diseases also needs to be tailored to the individual's specific situation, including adjustment of the temperature of the nutrition solution and the infusion rate of the nutrients. At the same time, nursing staff should strengthen communication with patients, provide psychological counseling, and alleviate or eliminate any negative psychological reactions of patients (including anxiety and nervousness), allowing patients to maintain a positive mentality, thereby effectively improving their immune system and promoting rapid recovery of gastrointestinal function. After the surgery, patients need to take some oral medications to promote gastrointestinal motility, relieve symptoms such as gastric bloating and vomiting, accelerate the recovery of gastrointestinal function, and accelerate wound healing. This study aims to explore the effects of different treatments on the recovery of gastrointestinal function in patients with liver and gallbladder diseases after surgery. The control group

Table 1 Comparison of clinical data of the two groups of patients

Index	Study group (*n* = 100)	Control group (*n* = 100)	χ^2/t	*P* value
Gender (*n*)			0.022	0.883
Male	65	35		
Female	64	36		
Age (yr)	48.8 ± 4.5	49.5 ± 5.8	0.639	0.524
BMI (kg/m^2)	21.50 ± 3.12	22.01 ± 2.85	1.207	0.229
Surgical type (*n*)			0.088	0.993
Biliary-intestinal anastomosis	33	34		
Hepatic lobectomy	32	31		
Pancreaticoduodenectomy	19	18		
Pancreaticocaudectomy	16	17		
Complications (*n*)			0.795	0.672
Diabetes	4	5		
Hypertension	18	14		
Hyperlipidemia	9	11		
Smoking history (*n*)			0.189	0.664
Yes	16	18		
No	29	27		
Drinking history (*n*)			0.179	0.673
Yes	20	22		
No	25	23		

Table 2 Comparison of bowel sounds recovery time, gas discharge time, and first feeding time in two groups of patients (mean ± SD)

Index	Study group (*n* = 100)	Control group (*n* = 100)	*t*	*P* value
Feeding time (h)	32.15 ± 6.01	45.38 ± 5.63	16.065	< 0.001
Defecation time (h)	41.15 ± 9.46	55.38 ± 11.03	9.793	< 0.001
Bowel sound recovery time (h)	28.86 ± 8.46	47.71 ± 10.27	14.167	< 0.001
Anal first exhaust time (h)	39.14 ± 9.51	49.91 ± 8.53	8.431	< 0.001
First out of bed time (d)	2.16 ± 1.03	3.27 ± 1.62	5.782	< 0.001

Table 3 Comparison of overall therapeutic effectiveness between the two groups [*n* (%)]

Index	Study group (*n* = 100)	Control group (*n* = 100)	χ^2	*P* value
Remarkable	73 (73.00)	40 (40.00)		
Effective	25 (25.00)	28 (28.00)		
Invalidity	2 (2.00)	32 (32.00)		
Total effective rate	98 (98.00)	68 (68.00)	31.892	< 0.001

received routine treatment, while the study group received a special treatment plan to promote gastrointestinal function recovery. Special attention should be paid to the process of early nasogastric tube nutrition support in patients, adjusting the infusion rate based on different symptoms observed in patients, and providing psychological guidance to ensure patient compliance and promote effective recovery of gastrointestinal function. According to the results of this study, it was found that the recovery time for eating, defecation, bowel sounds, and flatulence in the study group patients were significantly shorter than those in the control group patients ($P < 0.001$). The overall effective rate of the control group

Table 4 Postoperative hospitalization status and pain analysis in the two groups (mean ± SD)

Index	Study group (*n* = 100)	Control group (*n* = 100)	*t*	*P* value
Duration of hospitalization (d)	7.24 ± 0.81	12.16 ± 0.93	39.893	< 0.001
Postoperative pain score (s)	2.03 ± 0.15	3.85 ± 1.02	17.653	< 0.001
Catheter removal time (d)	2.16 ± 0.31	3.97 ± 0.52	29.898	< 0.001

Table 5 Comparison of postoperative complications between the two groups [*n* (%)]

Index	Study group (*n* = 100)	Control group (*n* = 100)	χ^2	*P* value
Intestinal obstruction	2 (2.00)	6 (6.00)		
Stomatitis	1 (1.00)	8 (8.00)		
Belch	1 (1.00)	9 (9.00)		
Chapstick	1 (1.00)	11 (11.00)		
Overall incidence rate	5 (5.00)	34 (34.00)	26.788	< 0.001

Table 6 Comparison of nutritional index before and after intervention in the two groups of patients (mean ± SD)

Index	Study group (*n* = 100)	Control group (*n* = 100)	*t*	*P* value
Before intervention	32.15 ± 3.83	31.95 ± 3.28	0.397	> 0.05
After intervention	48.72 ± 2.51	35.63 ± 3.16	32.437	< 0.001

treatment was 98.00%, significantly higher than the 68.00% of the control group (P < 0.001). This indicates that specific treatment methods targeting gastrointestinal function recovery played a crucial role.

In addition, some studies have suggested abdominal massage as an important method to promote gastrointestinal peristalsis after liver and gallbladder surgery[26]. The mechanism is similar to traditional Chinese medicine's "massage", stimulating abdominal blood supply to restore gastrointestinal function. This study did not involve the application of abdominal massage in patients undergoing liver and gallbladder surgery. In future research, abdominal massage can be in postoperative care for patients and evaluate its clinical application effects. Integrating traditional Chinese medicine with Western medicine is also a focus of future research, combining scientific nursing and drug treatment with traditional Chinese medicine to observe its promoting effect on postoperative recovery[27,28].

This study has some limitations that cannot be ignored. Firstly, it is important to acknowledge that this study was conducted at a single-center, which means that the findings might not be fully representative of the broader population. Additionally, the small sample size used in this study limits the generalizability of the results and increases the likelihood of random variations impacting the outcome. It is crucial to consider that potential heterogeneity among the participants, such as demographic factors or underlying health conditions, could influence the observed effects. Therefore, it is essential to exercise caution and avoid overgeneralizing the conclusions drawn from this study.

CONCLUSION

In summary, comprehensive treatment is beneficial for the recovery of gastrointestinal function in patients undergoing liver and gallbladder surgery. Targeted interventions such as early nutritional support, postoperative enema, and rehabilitation training can shorten the recovery time of gastrointestinal function, improve immunity and resistance, reduce the risk of postoperative complications, help patients discharge from the hospital earlier, and have important clinical significance. It is worth promoting and popularizing.

ARTICLE HIGHLIGHTS

Research background

The etiology of hepatobiliary disease primarily stems from bacterial infection, excessive alcohol consumption and tobacco use, obesity, dietary irregularities, and various other contributing factors.

Research motivation
The motivation indicated notable enhancements in the duration of recovery for eating, defecation, bowel sounds, and flatulence. Additionally, patients displayed a favorable psychological perspective, which effectively bolstered their immune system and expedited the restoration of gastrointestinal function.

Research objectives
The objective is to offer essential interventions and guidance within the clinical setting in order to facilitate the prompt restoration of gastrointestinal function for patients.

Research methods
The participants were categorized into control and study groups based on the extent of surgical intervention.

Research results
The patient exhibited favorable recuperation of gastrointestinal function subsequent to the surgical procedure.

Research conclusions
The implementation of specific nursing interventions, such as early nutrition support, pre-exhaustion water intake, and enema administration, has been found to be highly effective in facilitating the recovery of gastrointestinal function in patients undergoing hepatobiliary surgery. Moreover, these interventions have demonstrated the potential to significantly decrease the occurrence of complications.

Research perspectives
The implementation of early enteral nutrition support therapy has been found to have a beneficial effect on the restoration of gastrointestinal function in individuals undergoing surgical interventions for hepatobiliary disorders.

FOOTNOTES

Co-first authors: Hua-Jun Zeng and Jing-Jing Liu.

Author contributions: Zeng HJ and Liu JJ designed the research; Yang YC, Zeng HJ and Liu JJ performed the research; Yang YC, Zeng HJ and Liu JJ contributed new reagents/analytic tools; Yang YC, Zeng HJ and Liu JJ analyzed the data; Zeng HJ and Liu JJ wrote the paper.

Institutional review board statement: This study protocol was approved by the Beijing Fengtai Hospital.

Informed consent statement: All the families have voluntarily participated in the study and have signed informed consent forms.

Conflict-of-interest statement: The authors declared no conflict of interest existing in this paper.

Data sharing statement: Data generated from this investigation are available upon reasonable quest from the corresponding author.

Country/Territory of origin: China

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S-Editor: Gong ZM
L-Editor: A
P-Editor: Xu ZH

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World J Gastrointest Surg 2024 January 27; 16(1): 85-94

DOI: 10.4240/wjgs.v16.i1.85

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

Predictive value of machine learning models for lymph node metastasis in gastric cancer: A two-center study

Tong Lu, Miao Lu, Dong Wu, Yuan-Yuan Ding, Hao-Nan Liu, Tao-Tao Li, Da-Qing Song

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: Cheng C, China; Lee KS, South Korea

Received: September 14, 2023
Peer-review started: September 14, 2023
First decision: November 17, 2023
Revised: November 24, 2023
Accepted: December 21, 2023
Article in press: December 21, 2023
Published online: January 27, 2024

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Abstract

BACKGROUND

Gastric cancer is one of the most common malignant tumors in the digestive system, ranking sixth in incidence and fourth in mortality worldwide. Since 42.5% of metastatic lymph nodes in gastric cancer belong to nodule type and peripheral type, the application of imaging diagnosis is restricted.

AIM

To establish models for predicting the risk of lymph node metastasis in gastric cancer patients using machine learning (ML) algorithms and to evaluate their predictive performance in clinical practice.

METHODS

Data of a total of 369 patients who underwent radical gastrectomy at the Department of General Surgery of Affiliated Hospital of Xuzhou Medical University (Xuzhou, China) from March 2016 to November 2019 were collected and retrospectively analyzed as the training group. In addition, data of 123 patients who underwent radical gastrectomy at the Department of General Surgery of Jining First People's Hospital (Jining, China) were collected and analyzed as the verification group. Seven ML models, including decision tree, random forest, support vector machine (SVM), gradient boosting machine, naive Bayes, neural network, and logistic regression, were developed to evaluate the occurrence of lymph node metastasis in patients with gastric cancer. The ML models were established fo-

llowing ten cross-validation iterations using the training dataset, and subsequently, each model was assessed using the test dataset. The models' performance was evaluated by comparing the area under the receiver operating characteristic curve of each model.

RESULTS
Among the seven ML models, except for SVM, the other ones exhibited higher accuracy and reliability, and the influences of various risk factors on the models are intuitive.

CONCLUSION
The ML models developed exhibit strong predictive capabilities for lymph node metastasis in gastric cancer, which can aid in personalized clinical diagnosis and treatment.

Key Words: Machine learning; Prediction model; Gastric cancer; Lymph node metastasis

Core Tip: The purpose of this study was to explore the performance of machine learning based models for the risk assessment of lymph node metastasis in patients with gastric cancer. We used seven different methods to analyze our data. After training, the algorithm with the highest average area under the receiver operating characteristic curve was selected as the optimal algorithm.

Citation: Lu T, Lu M, Wu D, Ding YY, Liu HN, Li TT, Song DQ. Predictive value of machine learning models for lymph node metastasis in gastric cancer: A two-center study. *World J Gastrointest Surg* 2024; 16(1): 85-94
URL: https://www.wjgnet.com/1948-9366/full/v16/i1/85.htm
DOI: https://dx.doi.org/10.4240/wjgs.v16.i1.85

INTRODUCTION

Gastric cancer is one of the most common malignant tumors in the digestive system, ranking sixth in the world in incidence and fourth in mortality[1]. At present, gastric cancer typically is managed with comprehensive treatment that includes surgery. However, the overall 5-year survival rate remains below 50%[2]. In the Tumor-Node-Metastasis staging system of the American Joint Committee on Cancer, N represents the number of lymph node metastases, which is itself an independent factor in predicting the overall survival rate of gastric cancer patients[3]. However, there are some difficulties in the exploration of lymph nodes in patients with gastric cancer, such as multiple regional lymph nodes located in the abdominal cavity, which are not easy to explore preoperatively. In addition, 42.5% of metastatic lymph nodes in gastric cancer belong to nodule type and peripheral type, restricting the application of imaging diagnosis[4,5].

Artificial intelligence refers to the ability of machines to independently replicate typical human intellectual processes [6]. Artificial intelligence has various applications in the medical field, encompassing image processing, computer vision, machine learning (ML), artificial neural networks (ANNs), and convolutional neural networks (CNNs). ML can assist physicians in interpreting clinical data through the computer-aided diagnostic (CAD) system. The CAD can be categorized into three stages: Feature recognition, feature extraction, and clinical reasoning. It is feasible to feed variables related to gastric cancer lymph node metastasis into the system and develop a risk model for lymph node metastasis of gastric cancer using a more advanced ML-based algorithm[7,8]. ML algorithms play crucial roles in assisting diagnosis and predicting prognosis by processing a large amount of complex medical data[9,10]. A clinical prediction model can be proposed and optimized through the training dataset, and subsequently examined through the external validation dataset to determine its external validity and adaptability to other patients[11,12]. The clinical utility of ML within the realm of artificial intelligence is increasingly attracting clinicians' attention, and it is also applied to help diagnose and treat various clinical diseases, including gastric cancer.

MATERIALS AND METHODS

Study subjects

A total of 369 patients who underwent radical gastrectomy at the Department of General Surgery of the Affiliated Hospital of Xuzhou Medical University (Xuzhou, China) from March 2016 to November 2019 were enrolled as the training group, and 123 patients who underwent radical gastrectomy at the Department of General Surgery of Jining First People's Hospital (Jining, China) were enrolled as the verification group. The inclusion criteria were as follows: (1) Newly diagnosed gastric cancer patients with complete medical records; (2) radical resection for primary gastric cancer was performed in either of the two hospitals, and lymph node metastasis was confirmed by imaging and pathology; and (3)

no anti-tumor therapy, such as radiotherapy or chemotherapy, was performed preoperatively. The exclusion criteria were: (1) Combination with other malignant tumors; (2) preoperative complications of other infectious diseases, blood system diseases, autoimmune diseases, and other diseases that could affect inflammatory indicators; (3) recently or currently receiving anti-inflammatory or immunosuppressive therapy; (4) preoperative blood transfusion treatment; (5) severe liver and kidney dysfunction; and (6) incomplete clinical data (Figure 1).

Observational indicators

Clinical data, such as patient name, age, gender, and other clinicopathological data, including routine blood parameters, tumor location, maximum tumor diameter, depth of invasion, and the presence or absence of lymph node metastasis, were collected from all patients. Blood samples were collected in the morning on an empty stomach on the day after admission to determine neutrophil count, platelet count, monocyte count, and lymphocyte count using the Sysmex XE-2100 Automatic Blood Analyzer. Carcinoembryonic antigen (CEA) level in the blood was also measured. The pan-immune-inflammation value (PIV) and CEA level were utilized to establish clinical prediction models. PIV was calculated as (neutrophil count × platelet count × monocyte count)/lymphocyte count.

Statistical analysis

Continuous variables are expressed as the mean ± SD, and categorical variables are presented as percentages. LR was employed to identify the independent risk factors associated with lymph node metastasis in gastric cancer patients. This analysis allowed for the calculation of odds ratios (ORs) and their corresponding 95% confidence intervals. An OR greater than 1 indicated that the variable was a positive risk factor affecting the outcome, while an OR less than 1 suggested that the variable was a negative risk factor influencing the outcome. Statistical significance was defined as a P value of less than 0.05. The statistical analyses and modeling procedures were carried out using SPSS 20.0 software (IBM, Armonk, NY, United States) and R-Studio 25.0 software (R Foundation for Statistical Computing, Vienna, Austria). Several packages were utilized to train models and draw relevant graphs, with the caret package applied for training and validating ML models. In addition to the fundamental linear model (linear LR), seven ML models were fitted, including LR, random forest (RF), gradient boosting machine (GBM), decision tree (DT), support vector machine (SVM), naive Bayes (NB), and multi-layer perceptron (MLP), as illustrated in Figure 2.

The training dataset was combined with the validation dataset, and seven ML algorithms were employed to establish prediction models. LR is a classification algorithm designed to establish a relationship between a feature and the probability of a specific outcome. Rather than using LR for estimating class probability, it employs S-shaped functions for modeling[13,14]. DT is primarily utilized for classification tasks. It begins at the root node to split the dataset based on the most informative feature, creating decision points that segment the data into distinct classes[15]. RF is an extension of the DT method and functions as an ensemble approach. It generates multiple DTs, with the majority vote from these trees determining the final class prediction of the model[16,17]. MLP is an ML algorithm inspired by biological neural networks. ANNs consist of interconnected nodes that communicate through connections[18,19]. SVM classifies data by defining boundaries that separate classes. The optimization process aims to maximize the margin between these class boundaries. While SVM generally outperforms LR, its computational complexity may lead to longer training time during model development[20,21]. GBM is a boosting technique that serves as a numerical optimization algorithm for constructing additive models that minimize loss functions[22,23]. NB is a straightforward classification algorithm that calculates the probability of each category's occurrence given the item to be classified. The item is assigned to the category with the highest probability[24,25].

Performance evaluation of the models involved various metrics, including accuracy, recall, and other indicators. The primary indicator for predicting binary classification results was the area under the receiver operating characteristic curve (AUC). This metric varies from 0 to 1, with higher values signifying a superior performance. Additionally, for models with two outcomes, the area under the accuracy-recall curve was utilized, illustrating the trade-off between true accuracy and positive predictive value, and the F1 score, defined as the harmonic mean of recall and accuracy. The models underwent 10-fold cross-validation on the training dataset and then assessed for their performance on the test dataset. According to the optimal model, a network estimator was developed to facilitate disease prediction using patient data. This estimator enables surgeons to assess the risk of lymph node metastasis in gastric cancer patients.

RESULTS

Baseline clinical data in the training group and verification group

The comparison of clinical data between the two groups is presented in Table 1. Gender, age, tumor location, and surgical method exhibited no significant differences between the two groups ($P > 0.05$). In the training dataset, the proportion of patients with total gastrectomy, neurovascular invasion, and maximum tumor diameter > 5 cm was significantly higher in patients with lymph node metastasis than in those without ($P < 0.05$). In the verification dataset, the number of patients who were aged > 60 years old and had neurovascular invasion and maximum tumor diameter > 5 cm was significantly greater in patients with lymph node metastasis than in those without ($P < 0.05$).

The results of Mann-Whitney U test revealed that there were no statistically significant differences in the depth of infiltration, PIV, or CEA level between the two groups ($P > 0.05$). It was found that the depth of infiltration and CEA level in patients with lymph node metastasis were significantly higher than those in patients without ($P < 0.05$). In the training dataset, the infiltration depth, PIV, and CEA level in patients with lymph node metastasis were significantly greater than those in patients without ($P < 0.05$).

Table 1 Comparison of clinical data between the two groups

Clinical data	Training set		$t/Z/\chi^2$	*P* value	Validation set		$t/Z/\chi^2$	*P* value
	No lymph node metastasis (*n* = 141)	Lymph node metastasis (*n* = 228)			No lymph node metastasis (*n* = 51)	Lymph node metastasis (*n* = 72)		
Gender			1.017	0.313			1.126	0.289
Male	99 (70.2)	171 (75.0)			33 (64.7)	53 (73.6)		
Female	42 (29.8)	57 (25.0)	0		18 (35.3)	19 (26.4)		
Age (yr)			0.015	0.901			4.729	0.030
≤ 60	64 (45.4)	105 (46.1)			27 (52.9)	24 (33.3)		
> 60	77 (54.6)	123 (53.9)			24 (47.1)	48 (66.7)		
Mode of operation			7.816	0.005			3.578	0.059
Partial gastrectomy	113 (80.1)	152 (66.7)			43 (84.3)	50 (69.4)		
Total gastrectomy	28 (19.9)	76 (33.3)			8 (15.7)	22 (30.6)		
Tumor invasion depth			-11.022	< 0.001			-7.114	< 0.001
T1	61 (43.3)	13 (5.7)			30 (58.8)	4 (5.6)		
T2	42 (29.8)	22 (9.6)			13 (25.5)	13 (18.1)		
T3	21 (14.9)	64 (28.1)			6 (11.8)	27 (37.5)		
T4	17 (12.1)	129 (56.6)			2 (3.9)	28 (38.9)		
Tumor site			0.716	0.699			0.392	0.822
Gastric body	24 (17.0)	32 (14.0)			18 (35.3)	22 (30.6)		
Gastric antrum	73 (51.8)	126 (55.3)			26 (51.0)	38 (52.8)		
Gastric cardia	44 (31.2)	70 (30.7)			7 (13.7)	12 (16.7)		
Nerve or vascular invasion			128.649	< 0.001			54.772	< 0.001
No	108 (76.6)	39 (17.1)			42 (82.4)	11 (15.3)		
Yes	33 (23.4)	189 (82.9)			9 (17.6)	61 (84.7)		
Maximum tumor diameter			38.634	< 0.001			8.323	0.004
≤ 5 cm	122 (86.5)	126 (55.3)			46 (90.2)	49 (68.1)		
> 5 cm	19 (13.5)	102 (44.7)			5 (9.8)	23 (31.9)		
PIV	132.00 (80.73, 226.80)	190.72 (106.49, 311.44)	-3.606	< 0.001	149.43 (91.73, 217.49)	173.59 (102.20, 274.73)	-1.586	0.113
CEA	2.47 (1.53, 3.58)	2.90 (1.82, 6.87)	-3.189	0.001	2.65 (1.47, 3.95)	4.91 (1.97, 9.02)	-2.331	0.020

PIV: Pan-immune-inflammation value; CEA: Carcinoembryonic antigen.

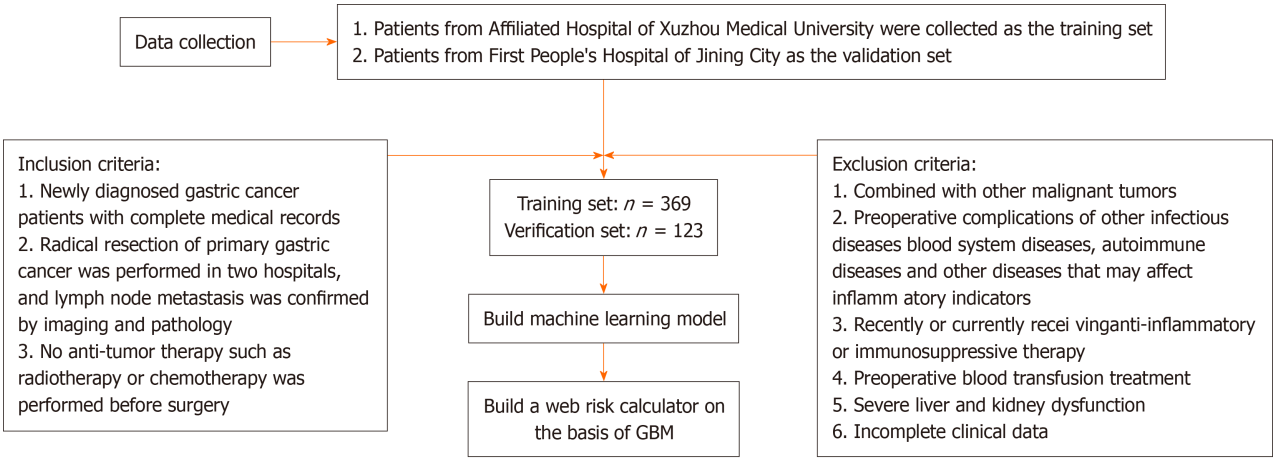
Evaluation of predictive performance of each model

In order to compare the predictive performance of the seven ML-based models, this study employed ten-fold cross-validation and utilized the AUC value, validated on the test dataset, as the primary metric for assessing their performance. As shown in Table 2 and Figure 2, the GBM model exhibited the best performance in predicting the occurrence of lymph node metastasis in gastric cancer patients, with an average AUC of 0.927. In this study, a web-based online estimator, along with feature importance (Figure 3) and Shapley Additive Explanations (SHAP) summary plot (Figure 4), was developed based on the GBM model. Feature importance enables the visualization of the model's internal results, highlighting the significance of specific variables within the model. Utilizing the optimal GBM model, we have developed a web-based risk calculator (https://gastric.shinyapps.io/gbm4Lymph). By entering the clinical characteristics of patients with gastric cancer and lymph node metastasis, healthcare professionals can predict the risk of lymph node development in these patients (Figure 5).

Table 2 Prediction performance evaluation of each model

Model	AUC	Accuracy	Kappa	Sensitivity (recall rates)	Specificity
DT	0.824	0.821	0.638	0.806	0.843
RF	0.923	0.854	0.702	0.847	0.882
SVM	0.721	0.585	0.000	0.750	0.547
GBM	0.927	0.870	0.734	0.875	0.863
NB	0.914	0.821	0.640	0.861	0.843
MLP	0.907	0.837	0.665	0.882	0.824
LR	0.898	0.821	0.636	0.806	0.882

AUC: Area under the receiver operating characteristic curve; DT: Decision tree; RF: Random forest; SVM: Support vector machine; GBM: Gradient boosting machine; NB: Naive bayes; LR: Logistic regression; MLP: Multi-layer perceptron.



DOI: 10.4240/wjgs.v16.i1.85

Figure 1 Flow chart. GBM: Gradient boosting machine.

DISCUSSION

As a result of the limited early detection of gastric cancer, over 50% of patients are diagnosed at advanced stages or with metastasis. At present, surgery is the main method for the treatment of gastric cancer, and lymph node metastasis is regarded as the main factor affecting the stage, grade, and survival rate of gastric cancer[26,27]. Therefore, early prediction of the occurrence of lymph node metastasis is vital. To date, several scholars have concentrated on lymph node metastasis in gastric cancer, while few studies have developed tools to provide accurate predictions. Therefore, the development of precise predictive models is essential to facilitate collaborative decision-making for clinicians and patients. The continuous advancement of artificial intelligence in the field of clinical research has led to the introduction of innovative approaches.

ML represents an evolving frontier in the field of medicine, drawing substantial resources to connect computer science and statistical analysis with medical challenges. ML has the capacity to effectively handle extensive, diverse, and intricate medical data. Consequently, the implementation of ML techniques in medicine is widely regarded as the cornerstone of future endeavors in biomedical research, personalized medicine, and computer-aided diagnosis[28,29]. Specifically, the operational framework of ML involves development of algorithms to execute numerous tasks, refining the algorithms iteratively to optimize performance. Ultimately, this process yields a model that establishes connections between multiple variables and target outcomes. In the present study, clinical data were collected, and ML algorithms were employed to develop a model for assessing the risk of lymph node metastasis in gastric cancer. By leveraging multiple variables, clinicians can employ this AI-driven approach to select more efficacious treatment strategies[30-33].

In this study, in addition to some clinicopathological data, hematological indicators, namely, immunoinflammatory factors (PIV and CEA), were utilized to develop the prediction models. PIV is a novel blood-based biomarker that integrates different subsets of peripheral blood immune cells, neutrophils, platelets, monocytes, and lymphocytes. As PIV has the potential to comprehensively represent patients' immunity and systemic inflammation, it may potentially serve as a robust predictor in advanced cancer patients undergoing cytotoxic chemotherapy, immunotherapy, and targeted therapy. It has been previously demonstrated that PIV is mainly dependent on neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, and other indicators in predicting cancer prognosis[34,35]. CEA is a

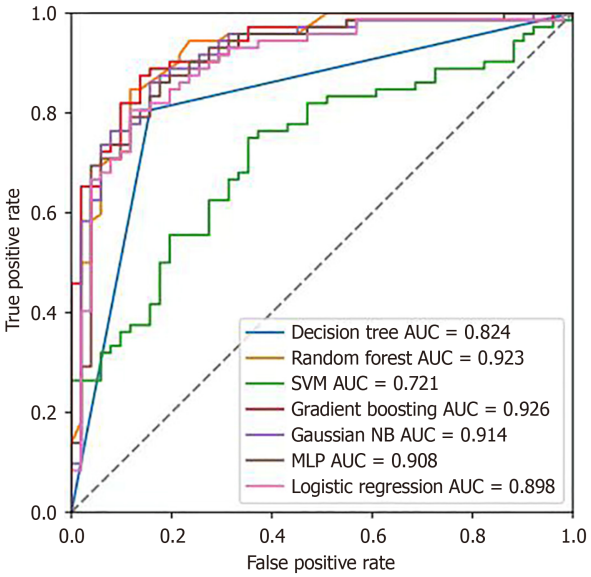


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Figure 2 Prediction performance evaluation of each model. SVM: Support vector machine; AUC: Area under the receiver operating characteristic curve; MLP: Multi-layer perceptron.

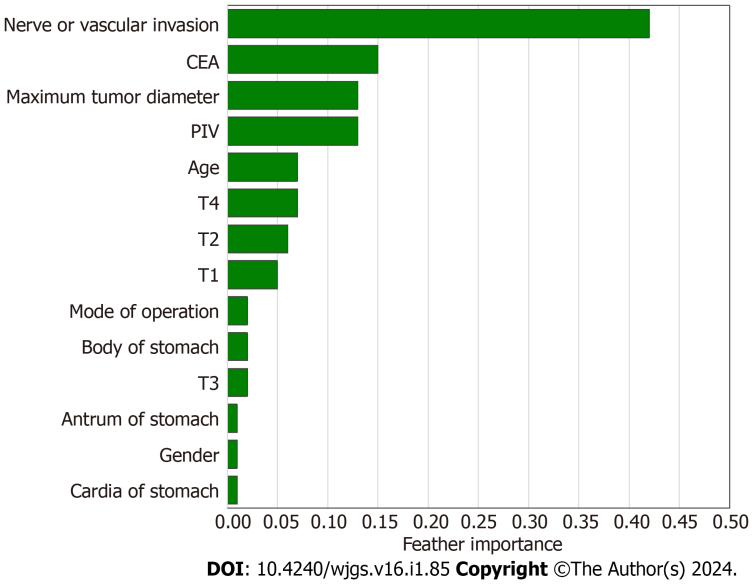

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Figure 3 Feature importance. SHAP: Shapley Additive Explanations; CEA: Carcinoembryonic antigen; PIV: Pan-immune-inflammation value.

widely used serum tumor marker in clinical practice, particularly in the early screening of various types of cancer, and elevation of its elevation is also regarded as an independent risk factor for poor prognosis of gastric cancer[36]. Development of a model based on combination of clinicopathological data with hematological suggestions can better reflect the physiological and pathological changes of patients with gastric cancer during the disease, making the model more representative.

Using ML, seven models were established for comparative analysis, utilizing the AUC as the benchmark for assessment. The outcomes are summarized as follows: The AUC for the DT model was 0.824, the RF model yielded an AUC of 0.923, the AUC for SVM was 0.721, and the GBM model demonstrated an AUC of 0.927. The NB model's AUC stood at 0.914, while the NNET model's AUC reached 0.907. The results of the seven models indicated that the GBM model displayed the most reliable performance, while SVM exhibited the least promising results. Furthermore, a feature importance table was developed based on the highly effective GBM model, which highlighted that factors, such as nerve or vascular invasion, CEA level, maximum tumor diameter, PIV, age, and tumor site, were significant contributors to the occurrence of lymph node metastasis.

Using the best-performing GBM model, feature importance assessment was conducted. This analysis highlighted the significance of specific indicators within the model, providing new insights into the model's structure. To understand the relationship between the direction of lymph node metastasis in gastric cancer and the importance of its main predictors, a

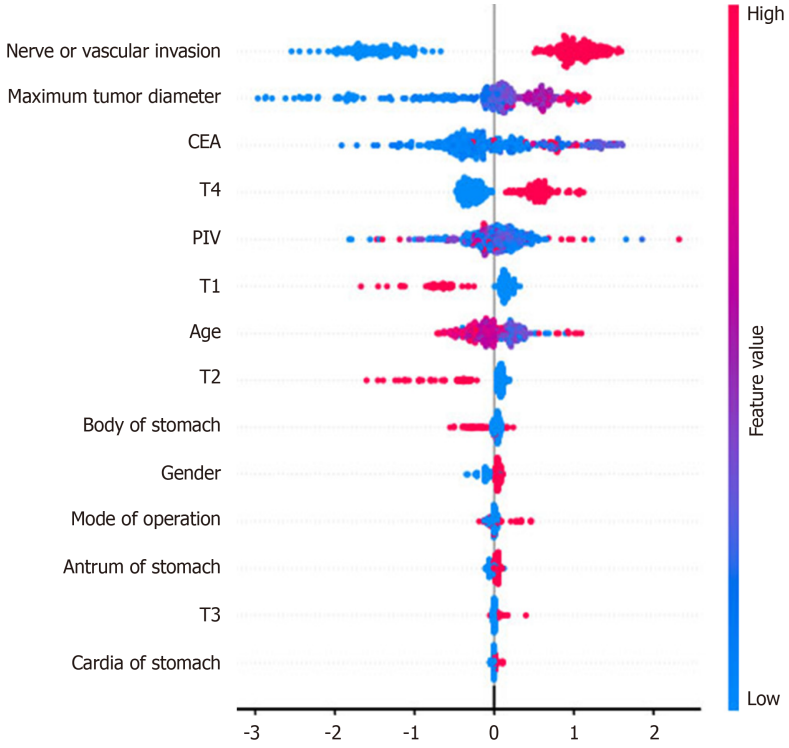

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Figure 4 Shapley Additive Explanations summary plot. SHAP: Shapley Additive Explanations; CEA: Carcinoembryonic antigen; PIV: Pan-immune-inflammation value.

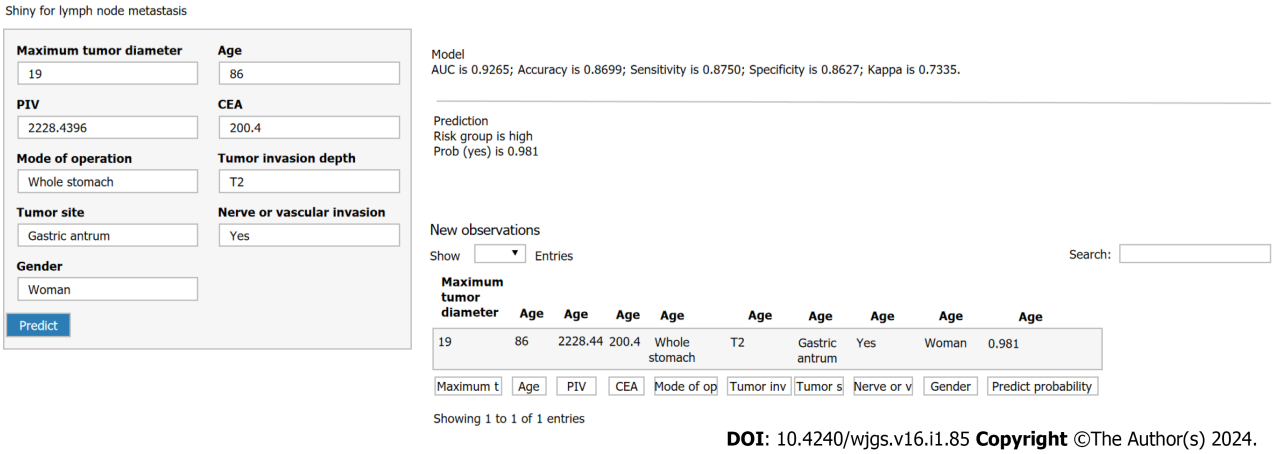

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Figure 5 Web risk calculator. SHAP: Shapley Additive Explanations; CEA: Carcinoembryonic antigen; PIV: Pan-immune-inflammation value.

SHAP summary plot was drawn. This method was utilized to explain the predictions of ML models. SHAP-Beeswarm diagrams, a common visualization tool in SHAP method, display the effect of each feature on the predicted results. The horizontal axis of the plot represents the SHAP value, indicating the contribution of each feature to the predicted result, while the vertical axis represents the feature name. Each data point in the diagram represents a sample, with its horizontal position indicating the sample's influence on the prediction result. Data points closer to the left side of the graph negatively impact the result, while those closer to the right side positively impact the result. The vertical position of the data point represents the feature name, with each feature having a corresponding vertical position.

According to the optimal GBM model, a web-based risk calculator was developed. By inputting patients' clinical characteristics, it can directly predict the probability of lymph node metastasis in patients with gastric cancer. This tool is user-friendly and straightforward, making it accessible for healthcare practitioners. It serves as a valuable resource in diagnosis and treatment, providing significant support for clinicians.

CONCLUSION

In summary, based on the clinicopathological data of 492 gastric cancer patients in two centers, ML algorithms were utilized to establish clinical models and conduct cross-validation, and AUC values were finally compared to draw conclusions. In addition to SVM, other ML models have exhibited promising accuracy and reliability, as well as better predictive value for gastric cancer lymph node metastasis. Among them, GBM outperformed the others, with the highest predictive value and accuracy. This study demonstrated that ML could reveal the potential of clinical data to reflect disease conditions, thereby assisting clinicians in evaluating patients' conditions and making more informed treatment decisions.

ARTICLE HIGHLIGHTS

Research background

Gastric cancer is one of the most common malignant tumors of the digestive system, ranking sixth in incidence and fourth in mortality worldwide. Machine learning (ML) represents an evolving frontier in the field of medicine, drawing substantial resources to connect computer science and statistical analysis with medical challenges. ML has the capacity to effectively handle extensive, diverse, and intricate medical data. Consequently, the implementation of ML techniques in medicine is widely regarded as the cornerstone of future endeavors in biomedical research, personalized medicine, and computer-aided diagnosis.

Research motivation

Using machine learning-based models to predict lymph node metastasis of gastric cancer is helpful to individualized diagnosis and treatment of gastric cancer patients.

Research objectives

Based on the clinicopathological data of 492 gastric cancer patients in two centers, we used ML algorithms to establish clinical models and conduct cross-validation, and finally compared the area under the receiver operating characteristic curve to draw conclusions. In addition to support vector machine, other ML models have good accuracy and reliability, and have better predictive value for gastric cancer lymph node metastasis. Among them, gradient boosting machine (GBM) has the best performance and the highest predictive value and accuracy. Through this study, ML can dig out the ability of clinical data to reflect disease, which can help clinicians evaluate patients' conditions and make better treatment decisions.

Research methods

Seven machine algorithm models were built with data from two centers, and then their performance was evaluated. Based on GBM model, a web-based online estimator and Shapley Additive Explanations summary plot were established.

Research results

ML can tap into the ability of clinical data to reflect disease, which can help clinicians assess patients' conditions and make better treatment decisions.

Research conclusions

ML algorithms have been used to establish an optimal prediction model for lymph node metastasis in gastric cancer, which is helpful for clinical risk stratification and individualized diagnosis and treatment of gastric cancer patients.

Research perspectives

In the future, multi-center data are needed to verify the external applicability of our model.

FOOTNOTES

Co-first authors: Tong Lu and Miao Lu.

Author contributions: Lu T and Wu D designed the study and wrote the manuscript; Li TT and Ding YY analyzed the data; Liu HN collected the data; Lu M and Song DQ revised the manuscript; Lu T and Lu M designed the study and wrote the article; Wu D and Ding YY analyzed the data; Li T and Song DQ revised the article; Lu M is one of the co-first authors of this paper. Lu T and Lu M contributed equally to this work as co-first authors. The research was performed as a collaborative effort, and the designation of co-first authors authorship accurately reflects the distribution of responsibilities and burdens associated with the time and effort required to complete the study and the resultant paper. This also ensures effective communication and management of post-submission matters, ultimately enhancing the paper's quality and reliability. Lu T and Lu M contributed efforts of equal substance throughout the research process. The choice of these researchers as co-first authors acknowledges and respects this equal contribution, while recognizing the spirit of teamwork and collaboration of this study.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of the Affiliated Hospital of Xuzhou Medical University and Jining First People's Hospital.

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: We have no financial relationships to disclose.

Data sharing statement: No additional data are available.

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S-Editor: Qu XL
L-Editor: Wang TQ
P-Editor: Xu ZH

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World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2024 January 27; 16(1): 95-102

DOI: 10.4240/wjgs.v16.i1.95

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

Post-operative morbidity after neoadjuvant chemotherapy and resection for gallbladder cancer: A national surgical quality improvement program analysis

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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: Yang L, China; Zhang CW, China

Received: September 23, 2023
Peer-review started: September 23, 2023
First decision: November 9, 2023
Revised: November 27, 2023
Accepted: December 18, 2023
Article in press: December 18, 2023
Published online: January 27, 2024

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Abstract

BACKGROUND

Gallbladder cancer is the most common malignancy of the biliary tract. Neoadjuvant chemotherapy (NACT) has improved overall survival by enabling R0 resection. Currently, there is no consensus of guidelines for neoadjuvant therapy in gallbladder cancer. As investigations continue to analyze the regimen and benefit of NACT for ongoing care of gallbladder cancer patients, we examined American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database to determine if there was higher morbidity among the neoadjuvant group within the 30-day post-operative period. We hypothesized patients who underwent NACT were more likely to have higher post-operative morbidity.

AIM

To investigate the 30-day post-operative morbidity outcomes between patients who received NACT and underwent surgery and patients who only had surgery.

METHODS

A retrospective analysis of the targeted hepatectomy NSQIP data between 2015 and 2019 was performed to determine if NACT in gallbladder cancer increased the risk for post-operative morbidity (bile leak, infection rate, rate of converting to open surgery, *etc.*) compared to the group who only had surgery. To calculate the odds ratio for the primary and secondary outcomes, a crude logistic regression

was performed.

RESULTS

Of the 452 patients, 52 patients received NACT prior to surgery. There were no statistically significant differences in the odds of morbidity between the two groups, including bile leak [odds ratio (OR), 0.69; 95% confidence interval (95%CI): 0.16-2.10; P = 0.55], superficial wound infection (OR, 0.58; 95%CI: 0.03-3.02; P = 0.61), and organ space wound infection (OR, 0.63; 95%CI: 0.18-1.63; P = 0.61).

CONCLUSION

There was no significant difference in the risk of 30-day post-operative morbidity between the NACT and surgery group and the surgery only group.

Key Words: Gallbladder cancer; Neoadjuvant chemotherapy; Radical cholecystectomy; National Surgery Quality Improvement Program; Postoperative outcome

Core Tip: In this retrospective study, we utilized the National Surgery Quality Improvement Program database to assess the post-operative morbidity of neoadjuvant chemotherapy (NACT) for gallbladder cancer. While the role of NACT for gallbladder cancer is being investigated, surgeons should be mindful of the potential complications patients receiving NACT may be at risk for post-operatively. Our study revealed that NACT was not associated with increased post-operative morbidity, such as bile leaks or wound infections. Although there were no increased complications, NACT should be carefully evaluated for each individual patient due to the inherent side effects of chemotherapy.

Citation: Kim M, Stroever S, Aploks K, Ostapenko A, Dong XD, Seshadri R. Post-operative morbidity after neoadjuvant chemotherapy and resection for gallbladder cancer: A national surgical quality improvement program analysis. *World J Gastrointest Surg* 2024; 16(1): 95-102

URL: https://www.wjgnet.com/1948-9366/full/v16/i1/95.htm

DOI: https://dx.doi.org/10.4240/wjgs.v16.i1.95

INTRODUCTION

Gallbladder cancer is the sixth most common gastrointestinal malignancy in the United States with an incidence of 1.13 cases per 100000[1]. Current guidelines recommend cholecystectomy for stage T1a and radical cholecystectomy (cholecystectomy, segment IVb and V liver resection, regional lymphadenectomy) for T1b or greater. Neoadjuvant chemotherapy (NACT) may be considered for locoregional advanced disease to prevent rapid progression of the cancer and improve rates of R0 and R1 resection[2]. There are currently no consensus guidelines in regards to neoadjuvant therapy for gallbladder cancer.

There have been few clinical studies that have looked into the effects of neoadjuvant therapy, including chemotherapy and radiation, for gallbladder cancer to determine survival benefit and rate for curative resections[3-6]. A 2019 review of six retrospective and two prospective studies showed that of the 40% (approximately 189 out of 474 patients) of patients who had received neoadjuvant therapy, 92.5% had R0 resections and the median overall survival for those patients ranged from 18.5 to 50.1 months[6]. Since the studies that were reviewed lacked comparison between the treatments, the authors of the review concluded that there was not sufficient data to support the use of neoadjuvant therapy for gallbladder carcinoma[1]. The debate whether NACT is beneficial is ongoing and there is a current trial[7] in place to further study the overall survival benefit of NACT for gallbladder carcinoma. Although, post-operative complications are not the focus of these studies and the prevalence of these complications are not fully documented, it would be beneficial for surgeons to be aware of the possible complications in the post-operative setting and whether NACT impacts the patients' overall recovery. From the clinical studies that have been reviewed, the most commonly documented post-operative complication is bile leak[4,8].

The goal of this study was to use the American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQIP) data to identify post-operative morbidities in the setting of NACT as opposed to those who had undergone surgery upfront and determine if there is a significant risk difference between the two groups. This data may assist surgeons in determining whether NACT would be beneficial for their patients prior to undergoing surgery with regards to perioperative morbidity.

MATERIALS AND METHODS

A retrospective analysis of the ACS NSQIP participant use data files was performed. These files include data from participating institutions across the United States based on a robust sampling strategy described previously[9]. Procedure-targeted hepatectomy data files for 2015-2019 were obtained. We included all patients 18 years and older with a diagnosis of gallbladder cancer and excluded patients that underwent emergent surgery, had viral hepatitis B and/or C, or unknown hepatitis status.

The primary outcome for this study was bile leakage within 30 d of surgery. Secondary outcomes were blood transfusion, on ventilator greater than 48 h, length of intensive care unit stay, readmission within 30 d, superficial incisional wound infection, organ space wound infection, secondary intervention, conversion rate to open, and need for biliary reconstruction.

Numerous covariates and potential confounders were included in our analyses. We included demographic variables including age, sex, race, and ethnicity. The following comorbidities: diabetes, history of smoking within one year of surgery, history of hypertension requiring medication, steroid use for chronic condition, and greater than 10 percent loss of body weight in the last six months.

We also included procedure-specific variables including placement of a biliary stent prior to surgery and cancer staging. Pre-operative laboratory values for serum albumin, total bilirubin, blood urea nitrogen, serum creatinine, and international normalized ratio were also examined.

Statistical methods

Statistical analyses were performed using R (R Foundation for Statistical Computing, Vienna, Austria) and StataSE version 16 (StataCorps LLC, College Station, Texas). Missing data was accommodated with listwise deletion in crude and multivariable analyses. We calculated descriptive statistics using mean ± SD for continuous variables and number with percentage for categorical variables. To determine group differences given exposure group, we used Fisher's exact test (cell counts less than 5), Pearson's χ^2 test (cell counts greater than 5), and Wilcoxon rank sum test for non-normally distributed continuous variables.

Model-building strategies were used to determine the difference in the odds of bile leakage given exposure NACT while adjusting for potential confounders. We performed crude logistic regression for all variables with bile leakage as the outcome, only including variables that were statistically significantly associated with the outcome in the final multivariable model ($P < 0.05$ established *a priori*). Crude logistic regression was performed for all secondary dichotomous outcomes and Poisson regression for length of stay. There were no statistically significant differences in secondary outcomes given exposure to NACT. Thus, we did not perform any further testing on these outcomes.

Post hoc analyses

Bivariate analyses were performed to further explore the association between NACT and selected outcomes by tumor stage. We independently assessed differences in outcomes given exposure to NACT in stage T2 patients, then again in stage T3/T4 patients. We used Pearson's chi-squared test and Fisher's exact test for dichotomous outcomes and Wilcoxon rank sum test for length of stay. Again, we selected $\alpha = 0.05$ for these analyses.

RESULTS

After exclusions, we included 452 patients in our sample (Table 1). Seventy percent of patients were tumor stage II, III, or IV though approximately 17% had unknown T stage. Nodal stage was equally distributed across all categories, and the majority were either M0/Mx or had unknown metastasis. The majority of patients did not undergo NACT (88.5%), and there were no statistically significant differences across exposure group for any of the covariates except pre-operative total bilirubin ($P < 0.01$), which is not clinically meaningful.

Ten percent of patients had bile leakage with only three of those patients having had NACT. On univariate logistic regression, the odds of bile leakage were not statistically significantly different given age, sex, race, ethnicity, diabetes status, smoking, steroid use for a chronic condition, or > 10% loss of body weight in the last six months ($P > 0.05$).

There was a statistically significant difference in the odds of bile leakage among patients with a biliary stent placed preoperatively [odds ratio (OR) = 3.66, 95% confidence interval (95%CI) = 1.73, 7.41, $P < 0.01$]. There was no statistically significant difference in the odds of bile leakage for nodal stages 1/2 or Nx/unknown compared to N0 ($P > 0.05$), nor was there a difference for metastasis stage 1 or unknown compared to M0/Mx ($P > 0.05$).

Based on these results, we included NACT and pre-operative placement of a biliary stent in our multivariable logistic regression model. We also included race and ethnicity, as they are commonly hypothesized confounders, and pre-operative bilirubin, which was different across exposure groups. We found there was not a statistically significant difference in the odds of bile leakage among patients who received NACT after controlling for potential confounders (OR = 0.69, 95%CI = 0.16, 2.10, $P = 0.55$).

The median length of stay for all patients regardless of exposure group was five hospital days. Few patients required post-operative mechanical ventilation greater than 48 h (1.3%), while the most common outcome was biliary reconstruction (19.2%). Of note, 21.2% of patients who had NACT required a blood transfusion within 72 h of surgery.

Table 1 Descriptive statistics for patients in the National Surgical Quality Improvement Program hepatectomy targeted dataset diagnosed gallbladder cancer, 2015-2019, *n* (%)

Characteristic	No neoadjuvant chemotherapy (*n* = 400)	Neoadjuvant chemotherapy (*n* = 52)	*P* value
Sex			0.72
Female	267 (59.1)	36 (8.0)	
Male	133 (29.4)	16 (3.5)	
Race			0.70
White	241 (53.3)	35 (7.7)	
Black or African American	38 (8.4)	4 (0.9)	
Asian	30 (6.6)	5 (1.1)	
Other	2 (0.5)	0 (0)	
Unknown/Not reported	89 (19.7)	8 (1.8)	
Ethnicity			0.19
Not Hispanic	293 (64.8)	41 (9.1)	
Hispanic	39 (8.6)	7 (1.6)	
Unknown/not reported	68 (15.0)	4 (0.9)	
Diabetes	93 (20.6)	8 (1.8)	0.20
History of smoking	43 (9.5)	3 (0.7)	0.26
Dyspnea	19 (4.2)	2 (0.4)	1.00
History of chronic obstructive pulmonary disease	19(4.2)	2 (0.4)	1.00
History of congestive heart failure	3 (0.7)	0 (0.0)	1.00
Hypertension requiring medication	238 (52.7)	24 (5.3)	0.07
Steroid use for chronic condition	9 (2.0)	2 (0.4)	0.37
> 10% loss body weight in last 6 mo	19 (4.2)	5 (1.1)	0.18
Biliary stent (Yes)	46 (10.3)	6 (1.3)	0.97
T (tumor) stage			0.91
T0 & T1	43 (9.5)	6 (1.3)	
T2	140 (31.0)	17 (3.8)	
T3 & T4	136 (30.1)	21 (4.7)	
Tx & Unknown	68 (15.0)	7 (1.5)	
N/A	13 (2.9)	1 (0.2)	
N (node) stage			0.24
N0	147 (32.5)	14 (3.1)	
N1 & N2	122 (27.0)	23 (5.1)	
Nx & unknown	115 (25.5)	14 (3.1)	
N/A	16 (3.5)	1 (0.2)	
M (metastasis) stage			0.61
M0/Mx	224 (50.0)	34 (7.5)	
M1	21 (4.6)	3 (0.7)	
Unknown	95 (21.0)	9 (2.0)	
N/A	60 (13.3)	6 (1.3)	
	Mean (SD)	Mean (SD)	

Age	67.0 (10.6)	64.6 (9.1)	0.07
Pre-operative serum albumin	3.9 (0.6)	3.9 (0.5)	0.65
Pre-operative total bilirubin	0.8 (1.2)	0.4 (0.2)	< 0.01
Pre-operative BUN	15.0 (6.0)	16.1 (6.8)	0.33
Pre-operative serum creatinine	0.9 (0.3)	0.9 (0.3)	0.45
Pre-operative INR	1.0 (0.1)	1.0 (0.1)	0.66

P values are the result of Chi-square, Fisher's exact, and Wilcoxon rank sum test. INR: International normalized ratio of prothrombin time; BUN: Blood urea nitrogen; N/A: Note available.

Secondary outcomes and Post hoc analyses

On univariate logistic regression, there were no statistically significant differences in the odds of any of the secondary outcomes given exposure to NACT (Table 2). The hospital length of stay also did not differ significantly on Poisson regression ($P = 0.12$). Patients with stage T2 cancer that underwent NACT did not experience a bile leakage following surgery. There were no significant differences in the other outcomes given NACT among patients with T2 cancer either ($P > 0.05$).

Approximately 20% of patients with stage T3/T4 gallbladder cancer experienced a bile leakage following surgery. However, there was not a statistically significant difference given exposure to NACT (Fisher's exact test, $P = 0.37$). Only two patients in that group experienced a bile leakage. Similar to stage T2, there were no statistically significant differences in any of the other outcomes among stage T3/T4 patients given exposure to NACT.

DISCUSSION

According the to the National Comprehensive Cancer Network guidelines, NACT is considered in patients with gallbladder cancer if there is locoregional advanced disease or if a patient has an unresectable disease. There is no preferred regimen for NACT since there is limited clinical data to define a standard regimen[2]. Patients who undergo NACT have commonly received gemcitabine and cisplatin. This regimen proved to have significant survival benefit in advanced biliary cancer and therefore has been implemented in patients with gallbladder cancer[10].

The goal of surgery for gallbladder cancer is to obtain R0 resection for potential curative treatment[11]. Clinical trials have shown that NACT improves rates of R0 resection in locally advanced gallbladder cancer[1,4,5]. Compared to R0 resection, R1 resection has worse survival[12,13]. Patients with R1 resection may undergo adjuvant therapy for improved survival benefit[11,14-16].

De Savornin Lohman *et al*[17] evaluated the survival benefit of re-resection after incidentally found gallbladder cancer. They found that there was overall survival benefit with re-resection; however, prognosis was affected by the presence of residual disease and lymph node metastasis despite clear resection margins. Lundgren *et al*[18] also found similar results in improved survival in re-resection for pT2 and pT3 incidental gallbladder cancer and residual disease impaired survival. With residual disease, surgeons must consider if additional surgery should be performed. Further resection may not have added benefit since residual disease can be clinical equivalent to distant metastatic disease[19] and patients are at risk for further peri-operative morbidity with major hepatectomy and pancreatoduodenectomy[20-22]. The intended benefit of NACT is to improve overall survival by achieving R0 resection and to avoid further resection. However, NACT does have its own risks and complications. Aside from the direct side effects of chemotherapy, there are concerns chemotherapy can complicate surgery and increase risks for peri-operative morbidities. NSQIP allows us to evaluate potential peri-operative complications within thirty days of surgery.

The primary outcome evaluated in our study was post-operative bile leak as this was a well-documented complication in clinical studies that evaluated survival impact of NACT in gallbladder cancer[4,8]. The treatment for the bile leaks included maintaining the drain placed during surgery or percutaneous drainage. The secondary outcomes that were evaluated were readmission within thirty days of discharge, superficial incisional wound infection, organ space wound infect, and the need for secondary intervention. In our study, we found that there was no statistical significance of any of these complications between the NACT and upfront surgery group.

Although our data may provide reassurance that NACT is safe to use for the appropriate patient population without having concerns for complications in the immediate post-operative period, this data is limited by the power of the study. The power of our study is low, as there were 452 patients diagnosed with gallbladder cancer and 52 patients had undergone NACT. With a larger study sample, there could be a statistically significant difference between the NACT group and upfront surgery group indicating that NACT could increase post-operative complications. Another limitation is the definition of a bile leak. NSQIP defines a bile leak as clinical diagnosis or persistent drainage that may have required maintenance of drain on or after post operative day 3, requiring percutaneous or operative intervention, or spontaneous wound drainage. The definition does not indicate if bilirubin levels were measured to prove a bile leak. A third limitation of this study are that the ACS NSQIP Targeted Hepatectomy dataset does not capture the specific details in regards to timing of chemotherapy, the chemotherapy regimen, duration of treatment, or if patients completed a full course of treatment. The data also only captures perioperative outcomes thirty days from the index operation.

Table 2 Odds ratios for 30-day postoperative complications among patients with gallbladder cancer who underwent neoadjuvant chemotherapy (*n* = 411[1])

Primary outcome[2]	Odds ratio	95% confidence Interval	*P* value
Post-operative bile leak	0.69	0.16, 2.10	0.55
Secondary outcomes[3]			
Required blood transfusion	1.80	0.83, 3.61	0.11
On the ventilator > 48 h	3.96	0.54, 20.83	0.12
Length of ICU stay	1.09	0.97, 1.22	0.12
Readmission	0.68	0.23, 1.64	0.44
Superficial incisional wound infection	0.58	0.03, 3.02	0.61
Organ space wound infection	0.63	0.18, 1.63	0.39
Required secondary intervention	0.41	0.10, 1.17	0.15
Conversion rate to open	1.67	0.47, 4.67	0.37
Need for biliary reconstruction	1.15	0.54, 2.27	0.70

[1]Patients with missing data were omitted from analysis.
[2]Adjusted odds ratio with the model including the primary predictor (neoadjuvant chemotherapy) and potential confounders (race, ethnicity, placement of a biliary stent, and preoperative bilirubin).
[3]Unadjusted odds ratios.
Comparison group is patients having surgery for gallbladder cancer without neoadjuvant chemotherapy. ICU: Intensive care unit.

Despite these limitations, our study provides additional information and insight into the use of NACT. As further clinical trials evaluate the effect of NACT, this study should be re-evaluated to determine potential significant complications of the use of NACT in gallbladder cancer and within the post-operative period.

CONCLUSION

Gallbladder cancer is a rare and aggressive cancer when it is diagnosed late. Randomized controlled clinical trials are needed to validate the routine use of NACT in gallbladder cancer irrespective of their stage at presentation. Although our study shows that NACT does not increase post-operative morbidity, additional data on NACT for gallbladder cancer is needed to better understand the effect of NACT on 30-day post-operative morbidity. Until further information is available, surgeons will need to carefully evaluate the benefit and risks of NACT for patients undergoing surgical intervention.

ARTICLE HIGHLIGHTS

Research background

Gallbladder cancer is the most common malignancy of the biliary tract. There are no consensus guidelines in regards to the use of neoadjuvant chemotherapy (NACT) for gallbladder cancer. Until a standardized regimen and guidelines are implemented, surgeons need to be aware of the potential effects of NACT on post-operative outcomes.

Research motivation

NACT is recommended based on clinical and pathological findings. Physicians need to carefully tailor the management of gallbladder cancer to the individual patient. By being aware of the benefits and risks of NACT both pre-operative and post-operatively, physicians can make informed decisions regarding its use in gallbladder cancer.

Research objectives

The objective of the study was to investigate the 30-day post-operative morbidities associated with NACT in gallbladder cancer.

Research methods

We performed a retrospective analysis using the National Surgery Quality Improvement Program database between 2015 and 2019. Patients with gallbladder cancer were identified and divided the patients into two cohorts based on their NACT

status.

Research results

Compared to the upfront surgery group, patients who underwent chemotherapy and surgery for gallbladder cancer did not experience worse outcome. There were no statistically significant post-operative morbidities.

Research conclusions

While there were no differences in the 30-day post-operative morbidities between the two cohorts, the benefits and risks of NACT should be carefully considered for patients, taking into account the potential side effects of chemotherapy.

Research perspectives

Further research on the effects of NACT for gallbladder cancer needs to be conducted. When more clinical data is available, the post-operative morbidities associated with NACT can be further evaluated.

FOOTNOTES

Author contributions: Kim, M, Aploks K, Ostapenko A, Dong X, and Seshadri R contributed to the conceptualization of the project; Kim M, Stroever S, Aploks K, Ostapenko A, Dong X, and Seshadri R contributed to the methodology and validation of the data; Stroever S conducted the formal statistical analyses; Kim, M, Aploks K, Ostapenko A prepared the original manuscript; Kim, M, Aploks K, Ostapenko A, Dong X, and Seshadri R contributed to the final draft revision and edition; Dong X, and Seshadri R supervised the project.

Institutional review board statement: Ethical review and approval was not required for this study since the data used was de-identified and obtained from a participant use file.

Informed consent statement: This study is a retrospective review that utilized only de-identified patient data from the American College of Surgeons National Surgical Quality Improvement Program.

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

Data sharing statement: Data was obtained with the permission from the American College of Surgeons NSQIP database. NSQIP data can be obtained at https://www.facs.org/quality-programs/data-and-registries/acs-nsqip/.

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S-Editor: Lin C
L-Editor: A
P-Editor: Zhang YL

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World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2024 January 27; 16(1): 103-112

DOI: 10.4240/wjgs.v16.i1.103

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

Risk factors for recurrence of common bile duct stones after surgical treatment and effect of ursodeoxycholic acid intervention

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Specialty type: Gastroenterology and hepatology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Knospe L, Germany; Shimamura Y, Japan

Received: November 3, 2023
Peer-review started: November 3, 2023
First decision: November 16, 2023
Revised: November 29, 2023
Accepted: January 2, 2024
Article in press: January 2, 2024
Published online: January 27, 2024

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Abstract

BACKGROUND

Endoscopic retrograde cholangiopancreatography (ERCP) is an accurate diagnostic method for choledocholithiasis and treatment option for stone removal. Additionally, ursodeoxycholic acid (UDCA) can dissolve cholesterol stones and prevent their development and reappearance by lowering the cholesterol concentration in bile. Despite these treatment options, there are still patients who experience stone recurrence.

AIM

To analyze the risk factors for choledocholithiasis recurrence after ERCP retrograde cholangiopancreatography and the effect of UDCA intervention.

METHODS

The clinical data of 100 patients with choledochal stones who were hospitalized at the Yixing People's Hospital and underwent ERCP for successful stone extraction between June 2020 and December 2022 were retrospectively collected. According to the post-ERCP treatment plan, 100 patients were classified into UDCA (n = 47) and control (n = 53) groups. We aimed to assess the clinical efficacy and rate of relapse in the two patient populations. We then collected information (basic demographic data, clinical characteristics, and serum biochemical indicators) and determined the factors contributing to relapse using logistic regression analysis. Our secondary goal was to determine the effects of UDCA on liver function after ERCP.

RESULTS

Compared to the control group, the UDCA group demonstrated a higher clinical effectiveness rate of 92.45% *vs* 78.72% (P < 0.05). No significant differences were observed in liver function indices, including total bilirubin, direct bilirubin, gamma-glutamyl transpeptidase, alanine aminotransferase, alkaline phosphatase, and aspartate aminotransferase, between the two groups before treatment. After

treatment, all liver function indices were significantly reduced. Comparing the control *vs* UDCA groups, the UDCA group exhibited significantly lower levels of all indices (55.39 ± 6.53 *vs* 77.31 ± 8.52, 32.10 ± 4.62 *vs* 45.39 ± 5.69, 142.32 ± 14.21 *vs* 189.63 ± 16.87, 112.52 ± 14.25 *vs* 149.36 ± 15.36, 122.61 ± 16.00 *vs* 171.33 ± 22.09, 96.98 ± 10.44 *vs* 121.35 ± 11.57, respectively, all $P < 0.05$). The stone recurrence rate was lower in the UDCA group (13.21%) in contrast with the control group (44.68%). Periampullary diverticula (OR: 6.00, 95%CI: 1.69-21.30), maximum stone diameter (OR: 1.69, 95%CI: 1.01-2.85), stone quantity >3 (OR: 4.23, 95%CI: 1.17-15.26), and positive bile culture (OR: 7.61, 95%CI: 2.07-27.91) were independent factors that influenced the relapse of common bile duct stones after ERCP ($P < 0.05$). Furthermore, postoperative UDCA was identified as a preventive factor (OR: 0.07; 95%CI: 0.08-0.09).

CONCLUSION

The intervention effect of UDCA after ERCP for common bile duct stones is adequate, providing new research directions and references for the prevention and treatment of stone recurrence.

Key Words: Endoscopic retrograde cholangiopancreatography; Recurrence; Ursodeoxycholic acid; Common bile duct stones; Clinical effective rate; Risk factors

Core Tip: Choledocholithiasis is a common biliary disorder that can be treated by endoscopic retrograde cholangiopancreatography. However, postoperative recurrence of bile duct stones is a common complication. Ursodeoxycholic acid (UDCA) is used to treat biliary disorders mainly by lowering cholesterol saturation, facilitating bile flow, and reducing inflammation. Through these actions, UDCA improves symptoms, prevents and treats gallstone formation, and promotes biliary health in patients with biliary tract disorders.

Citation: Yuan WH, Zhang Z, Pan Q, Mao BN, Yuan T. Risk factors for recurrence of common bile duct stones after surgical treatment and effect of ursodeoxycholic acid intervention. *World J Gastrointest Surg* 2024; 16(1): 103-112
URL: https://www.wjgnet.com/1948-9366/full/v16/i1/103.htm
DOI: https://dx.doi.org/10.4240/wjgs.v16.i1.103

INTRODUCTION

In recent years, the occurrence of choledocholithiasis has increased, causing serious discomfort and health risks for patients. Choledocholithiasis is mainly treated through endoscopic lithotomy or traditional open surgery[1,2]. Endoscopic retrograde cholangiopancreatography (ERCP) for stone extraction is favored by patients due to the lower risk of trauma [3,4]. However, after stone removal *via* ERCP, the postoperative stone recurrence rate is between 4% to 25%[5], which presents difficulties for both clinicians and patients.

Numerous studies have been conducted on stone recurrence; however, the causes of and risk factors for recurrence have not been well characterized. Ursodeoxycholic acid (UDCA) has been proposed as a treatment for stone recurrence. UDCA is a drug that dissolves cholesterol stones and prevents stone formation and recurrence by lowering the cholesterol concentration in bile[6]. Chen *et al*[7] showed that postoperative application of UDCA after percutaneous hepatic perforation balloon dilatation for choledocholithiasis is a feasible and effective treatment modality. UDCA has been shown to reduce cholesterol levels in the bile and promote the dissolution and elimination of stones. Therefore, we analyzed the effect of UDCA after ERCP in patients with common bile duct stones and screened high-risk individuals for factors that may contribute to relapse in order to alleviate the suffering caused by stone recurrence and improve the prognosis.

MATERIALS AND METHODS

Patient characteristics

The clinical records of a cohort comprising 100 patients with choledochal stones who were hospitalized at Yixing People's Hospital and underwent ERCP for successful stone extraction between June 2020 and December 2022 were retrospectively collected. According to the post-ERCP treatment plan, 100 patients were classified into UDCA ($n = 47$) and control ($n = 53$) groups. Inclusion criteria: (1) Those who fulfilled the diagnostic criteria of choledocholithiasis and whose diagnosis was confirmed by computerized tomography (CT) or abdominal ultrasonography; (2) those who had not taken other medications for the treatment of choledocholithiasis in the last month; and (3) those whose age was ≥ 18 years old. Exclusion criteria: (1) People with combined acute cholangitis, biliary pancreatitis, severe cardiopulmonary insufficiency, or other contraindications to surgery without ERCP; (2) people with a previous history of pancreaticoduodenal or

gastrointestinal anastomosis and other surgical procedures to change the normal structure of the bile ducts; (3) people with biliary ductal abnormalities, pancreatic tumors, and duodenal papilloma tumors detected in the ERCP; (4) individuals within the study population who exhibit drug allergies or whose clinical data are incomplete; and (5) pregnant and lactating women.

Concrete method

ERCP: The patients underwent standard fasting protocols that included restriction of solid food and water intake before the operation and a clean enema 2 h in advance on the day of the operation. The day before the operation, the doctor explained in detail to the patients and their families their conditions, the benefits and possible risks of the operation, and relevant precautions during the perioperative period.

First, the patient was given 10% lidocaine for local anesthesia of the oral pharynx. The endoscope was inserted through the mouth and gradually passed through the esophagus and stomach, eventually reaching the duodenum. During this process, physicians observed and evaluated the morphology and lesions in the bile and pancreatic ducts. Subsequently, a fine guidewire was carefully inserted using an endoscope and guided into the bile and pancreatic ducts. Subsequently, a certain dose of muscle relaxant was injected to relax the sphincter. Once the sphincter relaxed, a special contrast agent was injected into the bile and pancreatic ducts. Distribution and flow of the contrast agent in the ducts were recorded using a PHILIPS BV Pulsera C-arm (Royal Philips, Dutch). This helped determine the structure of the ducts and detect any abnormalities. Based on the imaging results, doctors could perform various therapeutic procedures, such as stone removal, duct dilation, and placement of biliary stents. Finally, after confirming the absence of stones through another imaging procedure, the doctor slowly withdrew the endoscope from the intestine and concluded the procedure. Throughout the process, the doctor closely monitored the patient's vital signs and promptly managed potential complications.

Control group: The control group was administered the routine postoperative treatment, including oral anti-inflammatory choleretic tablets, 1.5 g per dose, three times a day. Aspirin tablets (0.5 g) were orally administered three times daily for 4 wk.

UDCA group: The UDCA group received the same treatment as the control group as well as underwent combination therapy, including the use of UDCA capsules. The UDCA capsules were administered orally at a dose of 25 mg once daily for 4 wk.

Observation indicators: Main outcome

Clinical effects: Evaluation criteria: the treatment was considered markedly effective if the imaging examination of the bile duct showed no evident dilation, there were no obvious residual stones, and clinical symptoms such as jaundice, high fever, chills, and upper abdominal colic were noticeably relieved. The treatment was considered effective if the imaging examination showed no dilation of the bile duct, there was a small amount of residual stones, and some improvement in clinical symptoms such as jaundice, high fever, chills, and upper abdominal colic. The treatment was considered ineffective if the imaging examination showed residual stones and clinical symptoms, such as jaundice, high fever, chills, and upper abdominal colic, did not improve after treatment.

Rate of relapse: Postoperative follow-up was conducted on all patients at intervals of 3-6 mo until June 2023. If the following conditions occurred, stone relapse was considered: (1) During the follow-up period, if patients began to experience symptoms of acute biliary disease, such as fever, jaundice, and right upper quadrant pain, and the recurrence of common bile duct stones was confirmed through abdominal ultrasound, CT, Magnetic resonance cholangiopancreatography (MRCP), or other imaging examinations; and (2) in patients without typical clinical symptoms but suspected of having small stones, endoscopic ultrasonography was used to determine stone relapse.

Analysis of risk factors: We collected information including age, gender, presence of jaundice, presence of hypertension, diabetes, biliary conditions (history of biliary surgery, common bile duct diameter, periampullary diverticulum), stone characteristics (maximum stone diameter, number of stones), laboratory tests [preoperative white blood cell count (WBC), procalcitonin (PCT), total bilirubin (TBiL), direct bilirubin (DBiL), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), *etc.*], and bile culture results as predictive variables.

Secondary outcome

Recovery of liver function: A 5-milliliter aliquot of venous blood was collected from the patient in the morning while fasting, both before and after treatment. The blood collection tube was centrifuged (speed of 3000 r/min, radius of 10 cm) for 10 min, and the upper layer of serum was taken after centrifugation, and serum TBiL, DBiL, IBiL, AST, ALT, GGT were detected by PUZS-300X automatic analyzer (Nanjing Plan Medical Equipment Co., Ltd., Nanjing, Jiangsu Province, China). The analyzer was used to detect serum TBiL, DBiL, IBiL, AST, ALT, and GGT levels.

Statistical analysis

Data were analyzed using SPSS 23.0. (IBM Corporation, Armonk, New York, NY, United States). The age, common bile duct diameter, maximum stone diameter, and laboratory test results were described using mean ± SD or median (P_{25}, P_{75}). Subsequently, we used a *t*-test or non-parametric Mann-Whitney *U* test to compare the differences between the two groups for continuous variables. Sex, the presence or absence of jaundice and hypertension, and diabetes were expressed

as constituent ratios. The differences in rates between the two groups were compared using the chi-square test or Fisher's exact test. Logistic regression analysis was used to analyze risk factors. Statistical significance was defined as a two-sided *P* value of < 0.05.

RESULTS

Clinical characteristics

The 100 patients included were 39-73 years old with a median (P_{25}, P_{75}) of 53.00 (48.00, 60.00) years old, and included 44 males (44.0%) and 56 females (56.0%). The descriptive characteristics of the participants are presented in Table 1.

Clinical effect analysis

In comparison to the control group, the UDCA group demonstrated a higher clinical effectiveness rate of 92.45%, with statistically significant differences ($P < 0.05$; Table 2).

Liver function index analysis

No significant differences were observed in the liver function indices and TBiL, DBiL, GGT, ALT, ALP, and AST levels between the two patient populations before treatment ($P > 0.05$). After treatment, all liver function indices significantly reduced. Moreover, the UDCA group exhibited significantly lower levels of these indices than the control group ($P < 0.05$) (Table 3).

Rate of relapse stones

There were 7 cases (13.21%) of recurrence in the UDCA group and 21 cases (44.68%) in the control group, with statistically significant differences in the recurrence rate between the two groups ($P < 0.05$; Figure 1).

Univariate analysis

The non-recurrent and recurrent groups included parapapillary diverticulum, number of stones, positive bile culture, postoperative treatment, common bile duct diameter, and maximum stone diameter, with statistically significant differences ($P < 0.05$; Table 4).

Multivariate logistic regression analysis

The characteristics in Table 5 with $P < 0.05$ were used as independent variables, and recurrence (no *vs* yes) after ERCP was the dependent variable. Periampullary diverticula (OR: 6.00, 95%CI: 1.69-21.30), maximum stone diameter (OR: 1.69, 95%CI: 1.01-2.85), stone quantity > 3 (OR: 4.23, 95%CI: 1.17-15.26), and positive bile culture (OR: 7.61, 95%CI: 2.07-27.91) were independent factors that influenced the relapse of common bile duct stones after ERCP ($P < 0.05$). Furthermore, postoperative UDCA was identified as a preventive factor (OR: 0.07; 95%CI: 0.08-0.09). The results of the logistic regression analysis are presented in Table 6.

DISCUSSION

The incidence of common bile duct stones has gradually increased in recent years, rising from 8% to 20%[8]. Since its introduction, ERCP, a minimally invasive procedure with low risk, fast recovery, high success rate, and lower cost than traditional surgery, has gradually replaced traditional open surgery for the treatment of choledocholithiasis[9]. However, ERCP may damage liver function and slow its recovery of liver function after surgery, leading to cholestasis and stone recurrence. Routine postoperative liver protection and anti-infection treatments can reduce harm caused by surgery; however, their effect on preventing stone recurrence is not obvious. Therefore, the use of drugs to prevent stone recurrence during the postoperative period may have good long-term efficacy.

In this study, the prophylactic use of UDCA after ERCP achieved an ideal therapeutic effect with a clinical efficacy rate of 92.45%, and TBiL, DBiL, GGT, ALT, ALP, and AST levels were reduced, demonstrating an adequate hepatoprotective effect. UDCA is a dihydroxy bile acid extracted from bear-bile powder. It has the ability to enhance liver detoxification, improve liver function, protect liver cells, inhibit liver cell apoptosis, and regulate immune response in the body[10,11]. UDCA also promotes bile secretion, reduces cholesterol synthase activity, inhibits hepatic synthesis of cholesterol, reduces the amount of cholesterol in bile, and depolymerizes free cholesterol crystals in bile to a microcolloid state that is dissolved in bile[12]. UDCA inhibits the binding of lipids to hydrophobic bile acids on the granular membrane of hepatocytes, thus preventing bile acids from attacking the liver, reducing cytochrome release from mitochondria, and decreasing the permeability of mitochondrial cells, which protect hepatocytes and prevent apoptosis[11,13]. Choi *et al*[14] and Mulliri *et al*[15] found that prophylactic UDCA in patients undergoing gastric or bariatric surgery prevented gallstone formation and ensured clinical benefits while reducing the burden of late cholecystectomy. Lee *et al*[1] recommended the postoperative use of UDCA to prevent recurrence in children with small or large numbers of gallstones treated with cholecystectomy. Thus, UDCA may be a new treatment strategy for reducing the likelihood of recurrence. This is reflected in the results of this study. However, there is insufficient evidence regarding the improvement in liver function.

Table 1 Patient characteristics

Variable		Total (*n* = 100)	Control (*n* = 47)	UDCA (*n* = 53)
Age (yr), median (P_{25}, P_{75})		53.00 (48, 60)	51 (47, 60)	54 (48.5, 60)
Gender, *n* (%)	Male	44 (44)	21 (44.68)	23 (23.40)
	Female	56 (56)	26 (55.32)	30 (56.60)
Jaundice, *n* (%)	Yes	27 (27)	12 (25.53)	15 (28.30)
	No	73 (73)	35 (74.47)	38 (71.70)
Hypertension, *n* (%)	Yes	25 (25)	12 (25.53)	14 (26.42)
	No	75 (75)	35 (74.47)	39 (73.58)
Diabetes, *n* (%)	Yes	32 (32)	14 (29.79)	18 (33.96)
	No	68 (68)	33 (70.21)	35 (66.04)
History of biliary tract surgery, *n* (%)	Yes	14 (14)	6 (12.77)	8 (15.09)
	No	86 (86)	41 (87.23)	45 (84.91)
Parapillary diverticulum, *n* (%)	Yes	36 (36)	23 (48.94)	13 (24.53)
	No	64 (64)	24 (51.06)	40 (75.47)
No. of stones, *n* (%)	≤ 3	49 (49)	25 (53.19)	24 (45.28)
	> 3	51 (51)	22 (46.81)	29 (54.72)
Bile culture positive, *n* (%)		37 (37)	20 (42.55)	17 (32.08)
Common bile duct diameter (mm), median (P_{25}, P_{75})		14.00 (13.00, 16.00)	15.0 (13.0, 16.0)	14.0 (12.0, 16.0)
Maximum stone diameter (mm), median (P_{25}, P_{75})		13.00 (12.00, 15.00)	13.0 (12.0, 15.0)	13.0 (11.5, 14.5)
ERCP time (min), median (P_{25}, P_{75})		64.00 (61.00, 68.00)	63 (61, 67)	64 (61, 71)
WBC (10^9/L, mean ± SD)		6.60 ± 0.96	6.24 ± 1.24	6.60 ± 0.97
PCT (ng/mL), median (P_{25}, P_{75})		0.18 (0.12, 0.27)	0.17 (0.12, 0.25)	0.18 (0.13, 0.28)

UDCA: Ursodeoxycholic acid; ERCP: Endoscopic retro-grade cholangiopancreatography; WBC: White blood cell; PCT: Procalcitonin.

Table 2 Comparison of clinical efficacy between control and ursodeoxycholic acid groups

Group	Efficacious	Effective	Ineffective	χ^2 value	*P* value
Control, *n* (%)	16 (34.04)	21 (44.68)	10 (21.28)	3.990	0.048
UDCA, *n* (%)	22 (41.51)	27 (50.94)	4 (7.55)		

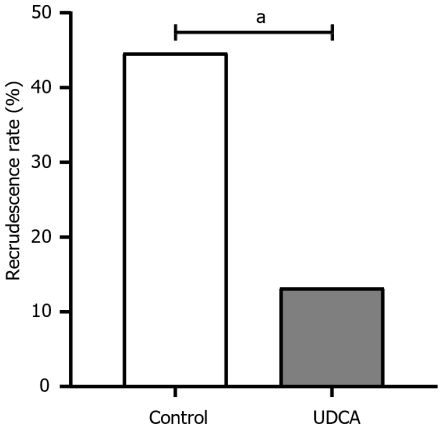
UDCA: Ursodeoxycholic acid.

The rate of relapse stones was lower in the UDCA group (13.21%) in contrast with the control group (44.68%) after ERCP. This finding supports the observations made in previous studies. In our study, parapapillary diverticulum was significantly associated with the recurrence of choledocholithiasis which is consistent with previous studies[16,17]. It is possible that the papilla located within the diverticulum interferes with the normal functioning of the duodenal papilla. As a result, compression occurs in the lower segment of the common bile duct and dilation occurs in the upper segment, which may lead to increased biliary pressure or biliary spasm and consequent obstruction of bile outflow, increasing the risk of stone recurrence. The presence of large stones causes dilatation of the common bile duct and reduces smooth muscle fiber retraction. Thus, bile excretion is difficult, and bile is prone to cholestasis and bacterial infections[18], inducing stone formation. Deng *et al*[16] found that the risk of common bile duct stone recurrence after ERCP was 1.599 times higher for patients with stone diameter ≥ 10 mm compared to those with stone diameter < 10 mm. A study involving 1148 patients found that stone diameter > 12 mm was more likely to recur[19]. Although multiple studies have established that common bile duct diameter increases the risk of common bile duct stone recurrence, predictive cut-offs are controversial. In our study, we observed that mean maximum stone diameter was a significant risk factor for stone recurrence after ERCP. Unfortunately, the cutoff value was not analyzed further. In addition, stones > 3 in diameter were a risk factor for choledochal stone recurrence after ERCP. Multiple stones are not easily removed, and recurrent choledocholithiasis can eventually develop due to negligence of the surgeon or the inability to detect small residual

Table 3 Comparison of liver function indexes between control and ursodeoxycholic acid groups

Group	*n*	TBiL (μmon/L, mean ± SD)		DBiL (μmon/L, mean ± SD)		GGT (U/L, mean ± SD)	
		Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Control	47	96.65 ± 11.24	77.31 ± 8.52	63.74 ± 7.45	45.39 ± 5.69	328.65 ± 20.45	189.63 ± 16.87
UDCA	53	98.63 ± 11.42	55.39 ± 6.53	63.36 ± 7.96	32.10 ± 4.62	330.25 ± 20.64	142.32 ± 14.21
t value		0.872	-14.532	-0.251	-12.896	0.388	-15.217
P value		0.385	< 0.001	0.803	< 0.001	0.699	< 0.001
		ALT (U/L, mean ± SD)		ALP (U/L, mean ± SD)		AST (U/L, mean ± SD)	
		Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Control	47	274.63 ± 25.41	149.36 ± 15.36	256.66 ± 24.12	171.33 ± 22.09	201.32 ± 16.35	121.35 ± 11.57
UDCA	53	268.54 ± 21.23	112.52 ± 14.25	262.36 ± 25.78	122.61 ± 16.00	201.11 ± 15.47	96.98 ± 10.44
t value		-1.306	-12.440	1.139	-12.733	-0.066	-11.072
P value		0.195	< 0.001	0.257	< 0.001	0.947	< 0.001

TBiL: Total bilirubin; DBiL: Direct bilirubin; GGT: Gamma-glutamyl transferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; AST: Aspartate aminotransferase; UDCA: Ursodeoxycholic acid.



DOI: 10.4240/wjgs.v16.i1.103

Figure 1 Recurrence of stones in the two groups. [a]*P* < 0.05. UDCA: Ursodeoxycholic acid.

stones *via* CT. However, results from Akay *et al*[20] differ from ours. Akay *et al*[20] reported that the recurrence rate after endoscopic treatment of common bile duct stones is associated with a wide common bile duct (≥ 10 mm), but not with the number of stones. Therefore, the findings are inconclusive and require further investigation.

In this study, positive bile bacterial culture was found to be a significant risk factor. The specific mechanism is not yet clear, but we speculate that it may be related to the biological activity of intestinal microecology. Biliary tract bacteria may induce an inflammatory response and promote stone formation through changes in KEGG metabolic pathway activity. Alternatively, biliary tract bacteria synthesize many enzymes that participate in bile metabolism, increasing free bilirubin, fatty acids, and other organic components and inducing stone formation[21]. However, there have been few studies on biliary bacterial microorganisms and stone recurrence, which can be supplemented in the future.

Although the risk factors for stone relapse have been extensively studied, we also evaluated UDCA as a preventive factor. The main cause of stone formation is an imbalance in bile composition, resulting in increased cholesterol and decreased bile acid concentrations. Correcting the imbalance in bile composition is a key measure in preventing stone recurrence. UDCA has high solubility, cytoprotective effects, and membrane stability without biotransformation, and can inhibit the absorption of cholesterol in the intestinal tract and reduce cholesterol levels[12,22]. In addition, UCDA can act as a bile transporter that promotes bile acid secretion and reabsorption by increasing hydrophilic bile acids, thus improving endogenous bile acid excretion[23,24]. In conclusion, UDCA can correct the bile composition, effectively alleviate the indications for postoperative cholestasis, and reduce the stone recurrence rate.

This study has some limitations, such as a potentially small sample size, which limits the generalizability of the results. The study may not have accounted for all the possible confounding factors, which could impact the results. The limited follow-up duration may affect the assessment of long-term recurrence rates and intervention effects. Further research with larger sample sizes and rigorous study designs is needed to confirm and expand upon these findings.

Table 4 Univariate analysis of recurrence of common bile duct stones after endoscopic retro-grade cholangiopancreatography

Variables		Non-recurrent group (*n* = 72)	Recurrent group (*n* = 28)	χ^2 value	*P* value
Age (yr, mean ± SD)		54.64 ± 6.62	51.43 ± 8.74	-1.983	0.050
Gender, *n* (%)	Male	31 (43.06)	13 (46.43)	0.093	0.760
	Female	41 (56.94)	15 (53.57)		
Jaundice, *n* (%)	Yes	19 (26.39)	8 (28.57)	0.049	0.825
	No	53 (73.61)	20 (71.43)		
Hypertension, *n* (%)	Yes	18 (25.00)	8 (28.57)	0.134	0.715
	No	54 (75.00)	20 (71.43)		
Diabetes, *n* (%)	Yes	27 (37.50)	5 (17.86)	3.575	0.059
	No	45 (62.50)	23 (82.14)		
History of biliary tract surgery, *n* (%)	Yes	12 (16.67)	2 (7.14)	1.519	0.218
	No	60 (83.33)	26 (92.86)		
Parapillary diverticulum, *n* (%)	Yes	18 (25.00)	18 (64.29)	13.504	< 0.001
	No	54 (75.00)	10 (35.71)		
No. of stones, *n* (%)	≤ 3	46 (63.89)	11 (39.29)	4.979	0.026
	> 3	26 (36.11)	17 (60.71)		
Bile culture positive, *n* (%)		19 (26.39)	18 (64.29)	12.421	< 0.001
Postoperative treatment, *n* (%)	Control	26 (36.11)	21 (75.00)	12.240	< 0.001
	UDCA	46 (63.89)	7 (25.00)		
Common bile duct diameter(mm), median (P_{25}, P_{75})		14.00 (12.00, 15.00)	16.00 (14.00, 17.00)	-3.265	0.001
Maximum stone diameter(mm), median (P_{25}, P_{75})		12.00 (11.25, 13.75)	15.00 (12.00, 16.00)	-3.599	< 0.001
ERCP time (min, mean ± SD)		63.93 ± 5.12	65.82 ± 5.33	1.640	0.140
WBC (× 10^9/L, mean ± SD)		6.45 ± 1.05	6.38 ± 1.27	-0.290	0.772
PCT (ng/mL), median (P_{25}, P_{75})		0.18 (0.12, 0.27)	0.18 (0.12, 0.28)	-0.088	0.930
TBiL (μmon/L, mean ± SD)		97.85 ± 10.95	97.32 ± 12.43	-0.211	0.833
DBiL (μmon/L, mean ± SD)		64.13 ± 7.64	62.02 ± 7.76	-1.234	0.220
GGT (U/L, mean ± SD)		330.90 ± 19.82	325.88 ± 21.99	-1.102	0.273
ALT (U/L, mean ± SD)		272.31 ± 22.87	269.09 ± 24.88	-0.617	0.538
ALP (U/L, mean ± SD)		259.81 ± 25.79	259.36 ± 23.50	-0.079	0.937
AST (U/L, mean ± SD)		201.12 ± 16.02	201.44 ± 15.55	0.089	0.929

ERCP: Endoscopic retro-grade cholangiopancreatography; UDCA: Ursodeoxycholic acid; WBC: White blood cell; PCT: Procalcitonin; TBiL: Total bilirubin; DBiL: Direct bilirubin; GGT: Gamma-glutamyl transferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; AST: Aspartate aminotransferase.

CONCLUSION

We retrospectively studied patients who underwent ERCP for choledocholithiasis, with a special emphasis on the use of UDCA. The main findings of this study were as follows: (1) Prophylactic use of UDCA after ERCP helps reduce intrahepatic bile stasis, promotes hepatic function recovery, and effectively reduces the rate of stone recurrence; and (2) Parapapillary diverticulum, number of stones > 3, positive bile culture, and maximum stone diameter are independent correlates of increased recurrence rates after ERCP in patients with choledochal stones. Postoperative UDCA level was found to be a preventive factor.

Future research directions could include the following aspects: (1) Further exploration of other potential factors that may influence the recurrence of common bile duct stones (CBDS), such as the patients' lifestyles, genetic factors, *etc*.; (2) Investigation of new intervention measures to reduce the recurrence rate after endoscopic treatment of CBDS, such as the

Table 5 Variable assignment description

Variables	Assignment
Parapillary diverticulum	0 = no, 1 = yes
No. of stones	0 = ≤ 2, 1 = > 3
Bile culture positive	0 = no, 1 = yes
Postoperative treatment	0 = UDCA, 1 = control
Common bile duct diameter	Original value
Maximum stone diameter	Original value

UDCA: Ursodeoxycholic acid.

Table 6 Multivariate logistic regression analysis comparing the non-recurrent group *vs* recurrent groups

Variables	*β*	*SE*	Wald χ^2	*P* value	*OR* (95%CI)
Parapillary diverticulum	1.792	0.646	7.692	0.006	6.003 (1.692-21.303)
No. of stones > 3	1.443	0.654	4.863	0.027	4.233 (1.174-15.263)
Bile culture positive	2.029	0.663	9.357	0.002	47.606 (2.073-27.910)
Postoperative UDCA	-1.287	0.628	4.199	0.040	0.072 (0.080-0.094)
Maximum stone diameter	0.527	0.265	3.957	0.047	1.694 (1.008-2.847)
Constant	-8.895	2.360	14.211	< 0.001	-

UDCA: Ursodeoxycholic acid.

use of UDCA for intervention; (3) Study the optimal retreatment strategies for patients with recurrent CBDS to improve treatment outcomes and reduce recurrence rates; (4) Comparison of the effectiveness of different treatment methods, such as endoscopic treatment and surgical treatment, in terms of recurrence rates and complications; and (5) Further research on the pathogenesis of common bile duct stones is needed to better prevent and treat this disease.

ARTICLE HIGHLIGHTS

Research background

Endoscopic retrograde cholangiopancreatography (ERCP) is a commonly used modality for the treatment of choledocholithiasis, with a stone clearance rate of up to 95%; however, the recurrence rate has not decreased. Ursodeoxycholic acid (UDCA) is a postoperative drug used to prevent stone recurrence; however, its effectiveness is yet to be explored. Therefore, this study focused on biliopancreatic surgery to investigate the interventional effect of UDCA after ERCP for choledocholithiasis and analyze the risk factors for recurrence.

Research motivation

Recurrence of choledocholithiasis after ERCP brings pain to patients; therefore, this paper retrospectively analyzes the intervention effect of UDCA after ERCP for choledocholithiasis and the risk factors of recurrence, in order to provide a new research direction and reference for the prevention and treatment of stone recurrence.

Research objectives

To analyze the intervention effect of the prophylactic use of UDCA after ERCP and the influencing factors of postoperative recurrence, and to explain the mechanism of action.

Research methods

The clinical records of 100 cases after ERCP were retrospectively selected, the therapeutic effects of non-UDCA and UDCA after ERCP and their effects on liver function were evaluated, and the rate of relapse within the two patient populations was compared. The risk factors for relapse were determined.

Research results

The clinical efficacy rates were 92.45% in UDCA group and 78.72% in control groups. The factors associated with recurrence after ERCP for choledochal stones included parapapillary diverticulum, number of stones > 3, positive bile culture, postoperative UDCA, and maximum stone diameter.

Research conclusions

The administration of UDCA to patients with common bile duct stones following ERCP can enhance liver function recovery and effectively decrease relapse.

Research perspectives

Future studies should explore the relevant mechanisms of action of UDCA treatment and construct a risk prediction model to evaluate its clinical benefits.

FOOTNOTES

Author contributions: Yuan WH designed and wrote the paper; Yuan T designed the research and supervised the report; Zhang Z, Pan Q and Mao BN designed the research and contributed to the analysis; all authors have approved the manuscript.

Institutional review board statement: The study was reviewed and approved by the Institutional Review Board of Yixing People's Hospital.

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

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

Data sharing statement: The clinical data used in this study can be obtained from the corresponding author upon request.

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

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World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2024 January 27; 16(1): 113-123

DOI: 10.4240/wjgs.v16.i1.113

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

Clinical efficacy of modified Kamikawa anastomosis in patients with laparoscopic proximal gastrectomy

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

P-Reviewer: Weiss H, Austria

Received: October 12, 2023
Peer-review started: October 12, 2023
First decision: December 15, 2023
Revised: December 20, 2023
Accepted: January 10, 2024
Article in press: January 10, 2024
Published online: January 27, 2024

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Abstract

BACKGROUND

With the increasing incidence of proximal gastric cancer, laparoscopic proximal gastrectomy has been applied. However, reflux esophagitis often occurs after traditional esophagogastric anastomosis. In order to solve this problem, several methods of digestive tract reconstruction have emerged, but the most satisfying method remains to be discussed. Therefore, we modified traditional Kamikawa anastomosis to investigate the appropriate digestive tract reconstruction in laparoscopic proximal gastrectomy.

AIM

To discuss the clinical efficacy of modified Kamikawa anastomosis in laparoscopic proximal gastrectomy.

METHODS

A retrospective case series was adopted. Clinicopathological data were collected from 26 patients who underwent laparoscopic proximal gastrectomy and modified Kamikawa anastomosis at our hospital from January 2020 to September 2022. The operation conditions, postoperative recovery, postoperative complications, and follow-up data were collected and analyzed.

RESULTS

All the patients were successfully operated on without conversion to laparotomy. The duration of operation and digestive tract reconstruction were 203.500 (150-224) min and 87.500 (73-111) min, respectively. The intraoperative amount of bleeding was 20.500 mL ± 0.696 mL. The time of postoperative first flatus, the first postoperative fluid intake, and the postoperative length of stay were 2 (1-3) d, 4 (3-5) d, and 9 (8-10) d, respectively. All the patients were followed up for 12-23 months. The body mass index at 6 and 12 months after surgery were 22.577 kg/m^2 ± 3.098 kg/m^2 and 22.594 kg/m^2 ± 3.207 kg/m^2, respectively. The nutrition risk

screening 2002 score, the patient-generated subjective global assessment score, and the gastroesophageal reflux disease scale score were good at 6 and 12 months after surgery. Reflux esophagitis and anastomotic stenosis were not observed in any of the patients during their 12-month postoperative gastroscopy or upper gastrointestinal tract visits. All the patients exhibited no tumor recurrence or metastasis.

CONCLUSION
The modified Kamikawa anastomosis is safe and feasible for laparoscopic proximal gastrectomy and has good antireflux effects and nutritional status.

Key Words: Modified Kamikawa anastomosis; Laparoscopy; Proximal gastrectomy; Antireflux

Core Tip: The study retrospectively analyzed clinicopathological data of patients who underwent laparoscopic proximal gastrectomy and modified Kamikawa anastomosis. According to our research, modified Kamikawa anastomosis in laparoscopic proximal gastrectomy is safe, feasible and shows good antireflux effect.

Citation: Wu CY, Lin JA, Ye K. Clinical efficacy of modified Kamikawa anastomosis in patients with laparoscopic proximal gastrectomy. *World J Gastrointest Surg* 2024; 16(1): 113-123
URL: https://www.wjgnet.com/1948-9366/full/v16/i1/113.htm
DOI: https://dx.doi.org/10.4240/wjgs.v16.i1.113

INTRODUCTION

The incidence of proximal gastric cancer (PGC) has recently increased and has thereby attracted increased amounts of attention from surgeons[1]. A national survey in Korea showed that the incidence of PGC in Korea increased from 11.2% to 16.0% in 2014[2]. The traditional treatment for PGC is total gastrectomy. However, with the development of medicine and improvements in the detection rate of early gastric cancer (GC), maximal preservation of gastric function has become a new requirement for radical excision of tumors. Therefore, proximal gastrectomy for preserving gastric function has emerged. Proximal gastrectomy for early GC does not affect patients' long-term survival and can effectively improve their postoperative nutritional status. Nevertheless, reflux esophagitis occurring after traditional esophagogastric anastomosis has an incidence as high as 21.8%-71.6% and significantly affects patients' postoperative quality of life (QOL)[3]. Several gastrointestinal reconstruction methods after proximal gastrectomy have emerged, including tubular esophagogastric anastomosis, esophagogastric lateral anastomosis, double-channel anastomosis, and interposed jejunum[4]. Although these techniques effectively decrease the incidence of postoperative reflux, they are accompanied by nearly hidden dangers involving operation difficulties or anastomotic complications[5]. Therefore, ensuring surgical safety and patient postoperative QOL has become the focus of domestic and foreign research.

In 1998, Kamikawa *et al*[6] reported of a new esophagogastric double-flap technique, also known as Kamikawa anastomosis, for digestive tract reconstruction. This method is indicated for patients with PGCs and an expected residual stomach volume greater than 50%. Kamikawa anastomosis has been highly recommended by domestic and foreign scholars due to its good antireflux effects and low incidence of postoperative anastomotic leakage[7,8]. However, its application in China is still in its infancy. The traditional Kamikawa anastomosis operation is complicated, and the possibility of anastomotic stenosis occurring after the operation significantly limits the popularization of this procedure[9]. Therefore, we modified the traditional Kamikawa anastomosis procedure by improving the surgical procedure to ensure the antireflux effect. In this study, the clinical efficacy of modified Kamikawa anastomosis in laparoscopic proximal gastrectomy was explored by retrospectively analyzing the clinicopathological data of patients who underwent laparoscopic proximal gastrectomy and modified Kamikawa anastomosis in our department from January 2020 to September 2022.

MATERIALS AND METHODS

Study subjects

The retrospective case series method was adopted in this study. Clinicopathological data were collected from 26 patients who underwent laparoscopic proximal gastrectomy and modified Kamikawa anastomosis at our hospital from January 2020 to September 2022. The patients and their families signed informed consent forms. The clinicopathological characteristics of the patients are shown in Table 1.

Table 1 Clinicopathological characteristics

Item	Value
Age (mean ± SD, yr)	68.846 ± 1.352
Sex	
Male	22
Female	4
Tumor location	
Esophagogastric junction	3
Upper stomach	23
Maximum tumor diameter (mean ± SD, cm)	2.069 ± 0.164
Histological grade	
Poor	6
Moderately	10
Well	10
Tumor stage	
T stage	
T1	15
T2	11
BMI (mean ± SD, kg/m^2)	22.623 ± 3.103
NRS2002 score [M (range)]	2 (1-2)
PG-SGA score [M (range)]	1(1-3)

Measurement data with a skewed distribution are represented as M (range). BMI: Body mass index; NRS: Nutrition risk screening; PG-SGA: Patient-generated subjective global assessment.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) PGC confirmed through pathological examination *via* gastroscopic biopsy before the operation; (2) a tumor diameter < 4 cm; (3) a clinical stage of cT1-2N0M0 according to preoperative enhanced computed tomography (CT) and endoscopic ultrasonography; (4) no distant metastasis before the operation; and (5) lacked a history of abdominal operation.

The exclusion criteria were as follows: (1) A dentate line involved in the tumor; (2) had received neoadjuvant therapies before the operation; (3) had severe cardiopulmonary dysfunction and poor nutritional status and could not tolerate the operation; (4) had complications related to other malignant tumors; and (5) lacked complete clinicopathological data.

Operation methods

In this study, all the operations were performed by the same group of surgeons. The patients were placed in the supine split-leg position, with the head side positioned slightly taller than the rest of the body. After the administration of anesthesia, skin preparation and draping were performed. The surgeons stood on the left side of the patient, and the surgical assistants stood on the right side of the patient. The camera holder was positioned between the legs of the patient. In addition, the five-hole method was adopted. A 12 mm trocar was inserted below the umbilicus as an observation hole to establish pneumoperitoneum, with the pressure maintained at 12-15 mmHg (1 mmHg = 0.133 kPa). A 12 mm trocar and a 5 mm trocar were inserted 2 cm below the costal margin on the left anterior axillary line and 2 cm above the umbilicus on the left midclavicular line as operation holes, respectively. A 5 mm trocar was inserted at the corresponding parts on the right as operation holes. The location and size of the tumor, the degree of infiltration of the tumor, and its relationship with peripheral organ tissues were probed by using a laparoscope.

Laparoscopic proximal gastrectomy and modified Kamikawa anastomosis were performed. First, the falciform ligament was cut. The left deltoid ligament and part of the omentum were separated. The left external lobe of the liver was dissociated, displaced, and placed over the right lobe of the liver by cutting the falciform ligament. The liver was fixed and suspended with a purse suture to enable external puncture. The proximal stomach was dissociated, and the D1+ lymph nodes were dissected in accordance with the Japanese GC treatment guidelines (5th edition)[10] and the Japanese classification of gastric carcinoma (3rd edition)[11]. The tumor was located *via* intraoperative endoscopy. The esophageal hiatus was opened, and the esophagus was fully dissociated, exposed, and severed. The posterior wall at 5 cm from the esophageal stump was marked with gentian violet. The stomach was removed through a small subxiphoid

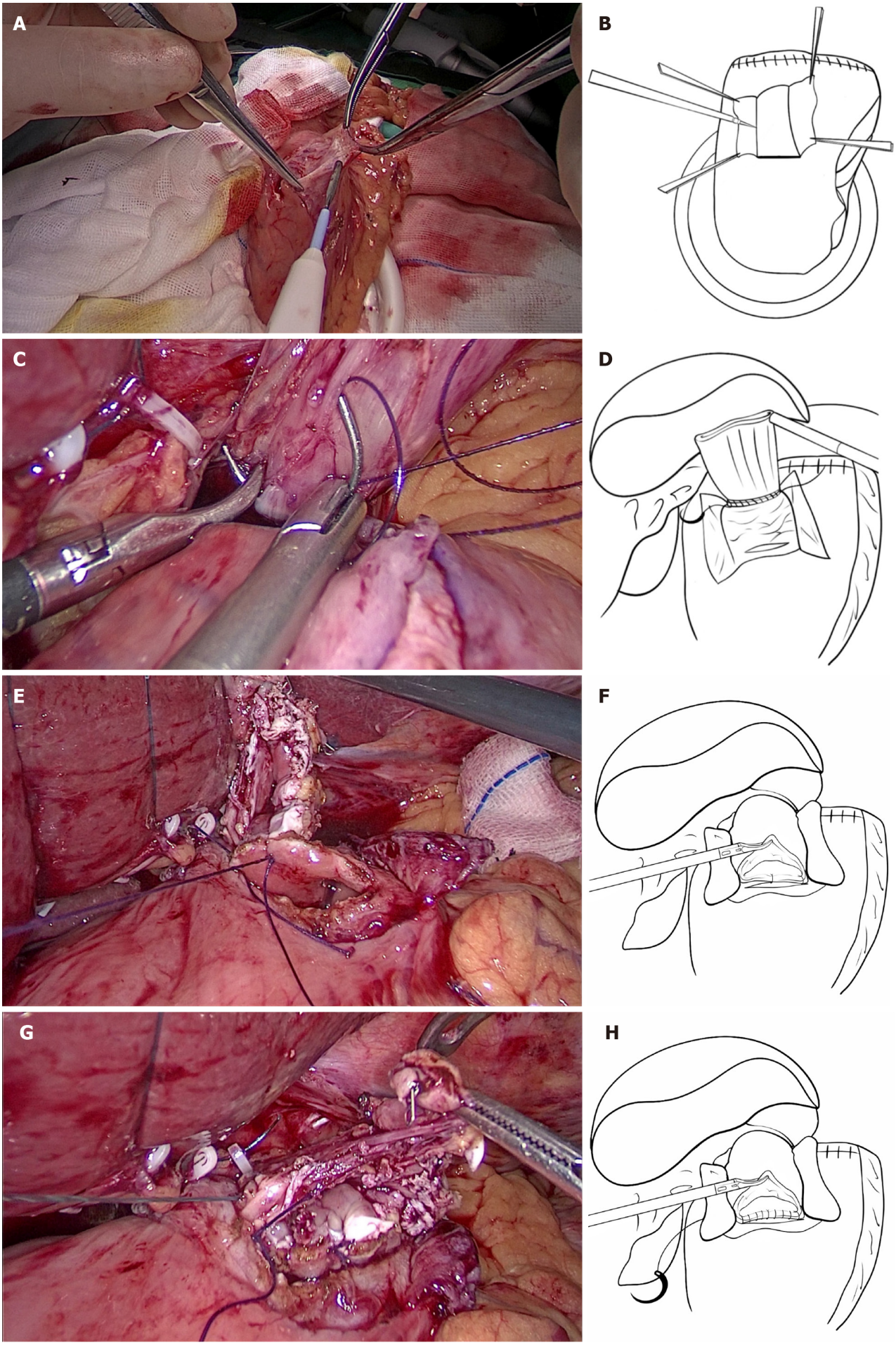
incision. Afterwards, the proximal stomach was severed with a linear cutting stapler 3 cm from the distal end of the tumor, and intermittent sutures were applied to the gastric stump for reinforcement. The intraoperative incisal edge was sent for rapid frozen-section pathological examination. Subsequently, gentian violet was used to mark the anterior wall of the residual stomach (approximately 1.5 cm from the upper incisal edge) near the lesser curvature of the stomach with a 2.5-3.0 cm × 3.5 cm I-shaped mark. The width of the seromuscular flap matched the diameter of the esophagus. Additionally, the superior border of the seromuscular flap was parallel to the upper incisal edge of the residual stomach. Anatomical separation between the submucosa and muscularis layers was performed by using an electrotome along the mark to prepare the seromuscular flap. Care was taken to protect the integrity of the seromuscular flap and gastric mucosa. At this point, a surgical assistant applied upward vertical traction to the muscle flap to close it. The surgeon subsequently used an electrotome to completely dissect the submucosal layer from the mucosa to create the seromuscular flap (Figure 1A and B). The submucosa and mucosa were cut off at the lower margin of the seromuscular flap anastomosis, and the width of the cut was equivalent to that of the esophagus. The gastric remnant was returned to the abdominal cavity after establishing the pneumoperitoneum. The esophagus was pulled under laparoscopic guidance. The right wall of the lower esophageal stump was cut with an electric shovel, and the gastric tube was extended for guidance. The region that was marked with gentian violet at the lower esophagus and the superior border of the seromuscular flap was continuously sutured and fixed with a 3-0 laparoscopic line with an arc of 5/8 (Figure 1C and D). The esophageal stump was reopened with an ultrasound knife. The posterior wall of the esophageal stump opening and the superior border of the anastomotic stoma were first fixed by placing two interrupted sutures on the left and in the middle (Figure 1E and F). A 3-0 barbed suture was then used for continuous suturing of the full thickness of the posterior wall of the esophageal stump opening and the gastric mucosa and submucosa at the superior border of the anastomotic stoma starting from the left part and proceeding to the right edge (Figure 1G and H). The suture needle was threaded into the mucosa of the anterior esophageal wall and threaded out at the adventitia for subsequent suturing of the seromuscular flap. A second 3-0 barbed continuous suture was used to suture the full thickness of the anterior wall of the esophageal stump opening and the stomach at the inferior border of the anastomotic stoma starting from the left part and proceeding to the right edge (Figure 1I and J). The reserved barbed suture was threaded out at the placenta percreta at the lower right corner of the seromuscular flap. The lower ends of the seromuscular flap on both sides were crossed and fixed on the anterior gastric wall below the midpoint of the anastomotic stoma. The reserved barbed suture was used to stitch from the right side to the intersection of the seromuscular flaps on both sides and then upward to the left side of the Y-shaped collar of the seromuscular flap at the anastomotic stoma and esophagus. Similarly, another barbed suture was used to stitch the right side of the Y-shaped collar of the seromuscular flap at the anastomotic stoma and the esophagus to cover the anastomotic stoma. Subsequently, the blood supply in the seromuscular flap was observed (Figure 1K and L). The anastomotic stoma was examined *via* a gastroscope to check for anastomotic stenosis. Finally, irrigation and hemostasis were laparoscopically performed. A drainage tube was placed behind the anastomotic stoma, and the incision was sutured to complete the operation.

The following points are the main modifications of the original Kamikawa anastomosis that was performed by the author's center: (1) The left extrahepatic lobe was separated and suspended, thus reducing the blockage, and ensuring a good view and easy operation. Additionally, the operation requires no extra instrumentation, is simple and practicable, and does not cause any trauma to the liver; (2) as the width of the esophagus is commonly 2.5-3.0 cm, the width of the I-shaped seromuscular flap is changed to 2.5-3.0 cm to match the diameter of the esophagus and consequently lower the incidence of anastomotic stenosis; (3) the posterior wall of the esophageal stump opening and the superior border of the anastomotic stoma were first fixed by placing two interrupted sutures on the right and in the middle. When the posterior wall of the esophageal stump opening and the superior border of the anastomotic stoma are fixed, subsequent sutures are easier and less likely to shift and cause postoperative anastomotic stenosis; (4) continuous sutures (including the suture of the posterior wall of the esophageal stump, the anastomotic stoma, and the seromuscular flap) were used to improve the feasibility of the operation, thus preventing tedious interrupted suturing and reducing the duration of the operation; (5) after proximal gastric resection, the blood supply to the incisional margin is poor. A seromuscular muscle flap positioned close to the incisal margin may lead to postoperative ischemia and elicit the antireflux effect. During our operation, the superior border of the I-shaped seromuscular flap was parallel to the upper incisal edge of the gastric remnant to ensure that the seromuscular flap was close to the lesser curvature side of the stomach with a better blood supply, thus improving the blood supply in the seromuscular flap and allowing it to produce the anti-reflux effect; and (6) an angle is formed after traditional Kamikawa anastomosis, whereas the pseudofornix reconstructed by our modified method on the left side of the esophagus is larger and has a better antireflux effect. A detailed diagram illustrating these modifications is shown in Figure 2. Attention should be given to the tension of the seromuscular flap. When the tension is too high during the folded suture of the seromuscular flap, the flap may be directly and obliquely sutured to the esophageal wall to reduce tension and prevent postoperative anastomotic stenosis.

Observation indicators and evaluation criteria

Observation indicators: The following indicators were used in this study: (1) Intraoperative conditions: Duration of operation, digestive tract reconstruction, and intraoperative amount of bleeding; (2) postoperative conditions: time of postoperative first flatus, first fluid intake, length of stay (LOS), and postoperative complications (such as ileus, lymphatic fistula, abdominal hemorrhage, anastomotic stoma hemorrhage, anastomotic stenosis, anastomotic fistula, pulmonary infection, and incisional wound infection); and (3) follow-up: Postdischarge nutritional status, symptoms of esophageal reflux, reflux esophagitis, anastomotic stoma conditions, and tumor recurrence and metastasis.

Evaluation criteria: Postoperative complications were evaluated by using the Clavien-Dindo grading standard[12]. Body mass index (BMI), nutrition risk screening (NRS) 2002 score, and patient-generated subjective global assessment (PG-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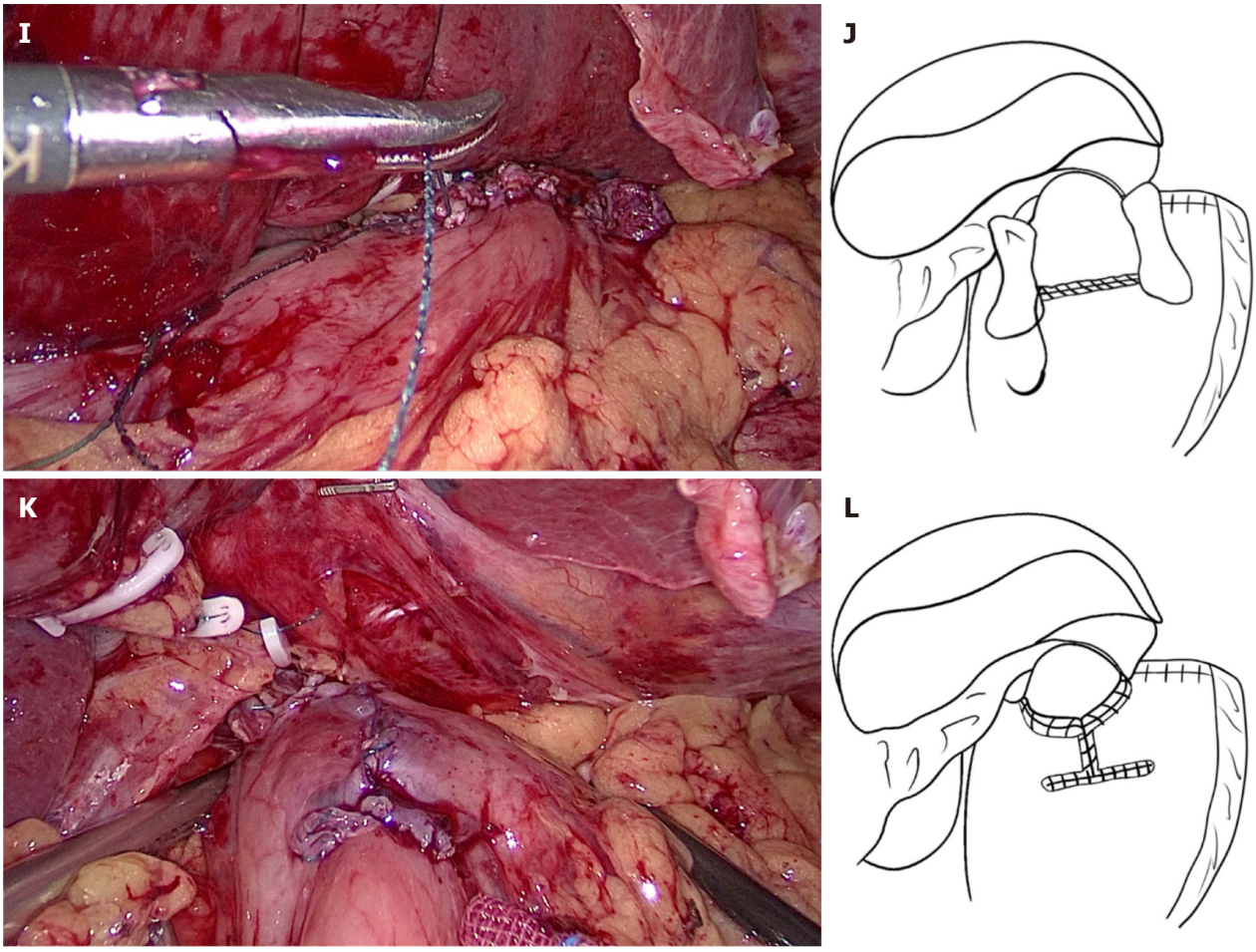

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Figure 1 Laparoscopic proximal gastrectomy and modified Kamikawa anastomosis were performed. A and B: The surgeon used an electrotome to completely dissect the submucosal layer from the mucosa to create the seromuscular flap; C and D: The region marked with gentian violet at the lower esophagus and the superior border of the seromuscular flap was continuously sutured and fixed with a 3-0 laparoscopic line with an arc of 5/8; E and F: The posterior wall of the esophageal stump opening and the superior border of the anastomotic stoma were first fixed by placing two interrupted sutures on the left and in the middle; G and H: A 3-0 barbed suture was used for continuous suturing of the full thickness of the posterior wall of the esophageal stump opening and the gastric mucosa and submucosa at the superior border of the anastomotic stoma, starting from the left part and proceeding to the right edge; I and J: A second 3-0 barbed continuous suture was used to suture the full thickness of the anterior wall of the esophageal stump opening and the stomach at the inferior border of the anastomotic stoma, starting from the left part and proceeding to the right edge; K and L: The blood supply in the seromuscular flap was observed.

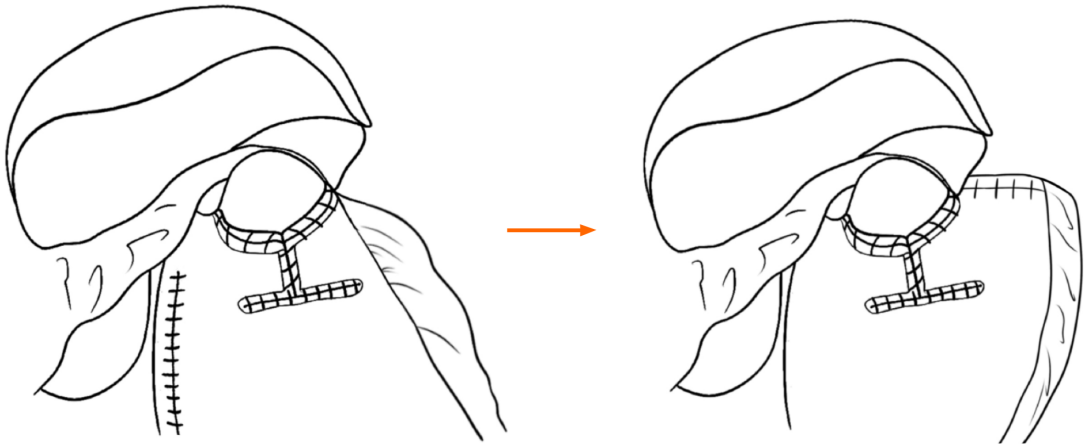

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Figure 2 Our modifications compared with traditional Kamikawa anastomosis.

SGA) score were used to evaluate their nutritional status[13]. The gastroesophageal reflux disease (GERD) scale was used to grade the symptoms of esophageal reflux[14]. Reflux esophagitis was diagnosed by using gastroscopy. The Los Angeles grading standard was adopted to evaluate the severity of the disease[15]. The conditions of the anastomotic stoma were examined by using upper gastrointestinal angiography.

Follow-up methods

The patients were followed up by using outpatient visits, telephone calls, and WeChat to determine their nutritional status, symptoms of esophageal reflux, reflux esophagitis, conditions of anastomotic stoma, and tumor recurrence and metastasis. The follow-up was conducted every three months after surgery and ended in September 2023.

Statistical analysis

SPSS 26.0 software was used for statistical analysis. Descriptive statistics were adopted. Measurement data with a skewed distribution are represented as M (range), and the rank-sum test was used for comparisons between groups. Normally distributed data are represented as mean ± SD, and a *t* test was used for comparisons between groups. $P < 0.05$ was considered to indicate statistical significance.

RESULTS

Clinicopathological characteristics

A total of 26 patients (22 males and 4 females) were included, and the average age was 68.846 years ± 1.352 years. The other characteristics are included in Table 1.

Intraoperative conditions

All 26 patients were successfully operated on without conversion to laparotomy. The duration of the operation was 203.500 (150-224) min. The duration of digestive tract reconstruction was 87.500 (73-111) min. The intraoperative amount of bleeding was 20.500 ± 0.696 mL (Table 2).

Postoperative conditions

The duration of postoperative first flatus was 2 (1-3) d. The duration of the first postoperative fluid intake was 4 (3-5) d. The postoperative LOS was 9 (8-10) d. Among the 26 patients, one patient had a postoperative pulmonary infection, and the Clavien-Dindo grade was 2. The patient's condition improved after conservative treatments, such as anti-infection treatment, oxygen inhalation, and atomization. The remaining 25 patients had no postoperative complications (Table 2).

Follow-up

All 26 patients were followed up for 12-23 months. The median follow-up period was 13 months. The BMIs of the 26 patients at 6 and 12 months after surgery were 22.577 kg/m^2 ± 3.098 kg/m^2 and 22.594 kg/m^2 ± 3.207 kg/m^2, respectively. The NRS2002 scores at 6 and 12 months after surgery were 2 (1-2) points and 2 (1-2) points, respectively; additionally, the PG-SGA scores at 6 and 12 months after surgery were 1 (1-3) point and 1 (1-3) point, respectively. Moreover, the GERD scale scores at 6 and 12 months were 3 (2-4) points and 3 (2-4) points, respectively. There were no significant differences in BMI, NRS2002 score, and PG-SGA score before or after surgery ($P > 0.05$). Reflux esophagitis was not found in any of the patients during their 6-month postoperative gastroscopy. No anastomotic stenosis was observed in any patient during 12-month postoperative upper gastrointestinal angiography. Furthermore, no patients experienced tumor recurrence or metastasis (Table 3).

DISCUSSION

According to the Japanese 5th edition of the Guidelines for the Treatment of GC[10], proximal gastrectomy can be performed for early PGC when more than half of the stomach volume can be preserved after R0 resection. However, due to the specificity of the anatomical site, the original physiological structure and function at the esophagogastric junction are lost after proximal gastrectomy. Therefore, the proper procedure for digestive tract reconstruction is still controversial. In 1988, the Japanese scholars Aikou *et al*[16] first reported that two-channel anastomosis was indicated for digestive tract reconstruction in most proximal gastrectomy patients, especially for those who had extremely small gastric remnants and impaired glucose tolerance, as well as those who were not qualified for esophagogastric anastomosis. However, the risk of postoperative anastomotic fistula is high because the operation is complicated and involves a large number of anastomotic stomata. Additionally, the extensive use of linear cutting staplers also increases the cost. In 1993, Kameyama *et al*[17] first proposed the use of the interposition jejunum for digestive tract reconstruction in proximal gastrectomy. An antireflux barrier is constructed by taking advantage of the tolerance and natural peristalsis of the digestive juice from the jejunum itself. However, this procedure is also complicated and may cause postoperative emptying disorders[18]. The length of the interposition jejunum segment is also difficult to control; specifically, if it is too long, then it will affect postoperative gastroscopy, and if it is too short, then it will affect the postoperative antireflux effect. In 1998, Shiraishi *et al*[19] proposed tubular gastrosophageal anastomosis, which allows food to pass quickly to

Table 2 Intraoperative and postoperative conditions

Item	Value
Duration of operation [M (range), min]	203.500 (150-224)
Duration of digestive tract reconstruction [M (range), min]	87.500 (73-111)
Intraoperative amount of bleeding (mean ± SD, mL)	20.500 ± 0.696
Time of postoperative first exhaust [M (range), d]	2 (1-3)
Time of the first postoperative fluid intake [M (range), d]	4 (3-5)
Postoperative LOS [M (range), d]	9 (8-10)
Postoperative complications	-
Pulmonary infection	1
Others	0

Measurement data with a skewed distribution are represented as M (range). LOS: Length of stay.

Table 3 Follow-up

Follow-up period [M (range), m]	16 (12-23)
BMI 6 months after the surgery (mean ± SD, kg/m^2)	22.577 ± 3.098
BMI 12 months after the surgery (mean ± SD, kg/m^2)	22.594 ± 3.207
NRS2002 score 6 months after the surgery [M (range)]	2 (1-2)
NRS2002 score 12 months after the surgery [M (range)]	2 (1-2)
PG-SGA score 6 months after the surgery [M (range)]	1 (1-3)
PG-SGA score 12 months after the surgery [M (range)]	1 (1-3)
GERD scale score 6 months after the surgery [M (range)]	3 (2-4)
GERD scale score 12 months after the surgery [M (range)]	3 (2-4)
Reflux esophagitis	0
Anastomotic stenosis	0
Recurrence or metastasis	0

Measurement data with a skewed distribution are represented as M (range). BMI: Body mass index; NRS: Nutrition risk screening; PG-SGA: Patient-generated subjective global assessment; GERD: Gastroesophageal reflux disease.

prevent food retention and has a good antireflux effect. The tubular stomach is long and can be lifted to the mediastinum. This approach is particularly suitable for patients with a relatively high incisal edge of the esophagus. However, the risk of postoperative hemorrhage and gastric fistula increases because of the long incisal edge after gastric wall cutting. Yamashita *et al*[20] designed a reconstruction method (also known as side overlap anastomosis) for accessing the digestive tract *via* esophagogastric wall anastomosis after laparoscopic proximal gastrectomy. This approach can effectively reduce the reflux of food and digestive juice after surgery. Side overlap anastomosis was completed by using a linear cutting stapler. A wide anastomotic stoma can effectively reduce postoperative anastomotic stenosis. This procedure is easy to perform, and the duration of the operation is short. However, its application is relatively limited because of the need to preserve the long abdominal segment of the esophagus and large gastric remnant. In 2016, Muraoka *et al*[21] first used Kamikawa anastomosis for proximal gastrectomy. No patient had reflux esophagitis after the operation. In the same year, Kuroda *et al*[7] reported on Kamikawa anastomosis under laparoscopy and verified its safe and feasible clinical efficacy for proximal gastrectomy. As reported by Shoji *et al*[9], the incidence of postoperative anastomotic stoma-associated complications decreases after the application of Kamikawa anastomosis in proximal gastrectomy. Additionally, the incidence of reflux esophagitis is effectively decreased *via* this approach. According to a multicenter Japanese retrospective study, the incidence of reflux esophagitis 1 year after surgery was only 6% among 464 patients who underwent proximal gastrectomy and Kamikawa anastomosis *via* gastroscopy[8]. The anastomotic stoma from Kamikawa anastomosis is manually sutured; therefore, the cost is low. However, this approach involves a complicated process and has high surgical requirements, particularly for laparoscopic suturing; moreover, it takes more time to perform than other digestive tract reconstruction methods. If the seromuscular flap is improperly made, such as

when the width of the seromuscular flap is too short or the suture of the anastomotic stoma is too tight, then anastomotic stenosis will occur. Therefore, the abovementioned factors limit the popularization of this operation.

With these modifications, the technique has become more feasible than the traditional operation. Compared with the traditional approach, the improved Kamikawa anastomosis in this study can reduce the duration of operation to approximately 50%[22]. In the improved Kamikawa anastomosis, the lower esophagus and anastomotic stoma are embedded within an appropriate seromuscular flap that is made at the anterior wall of the gastric remnant. When increased intragastric pressure is applied to the lower esophagus, double flaps can generate counterpressure and close the esophagus above the anastomotic stoma, thus effectively preventing reflux. Moreover, the risk of operative anastomotic fistula is reduced because the sole anastomotic stoma is covered by the seromuscular flap. The matching of the width of the I-shaped seromuscular flap with the width of the esophagus can avoid the anastomotic stenosis caused by the mismatch of the width after reconstruction. Moreover, the modified seromuscular flap is close to the lesser curvature side of the stomach and provides a better blood supply to avoid postoperative anastomotic stenosis or anastomotic fistula caused by ischemia. No anastomotic stenosis was observed in any patient as examined by using upper gastrointestinal angiography. Therefore, improved Kamikawa anastomosis can prevent anastomotic stenosis. The operation was successful in 26 patients, the postoperative recovery was good, and no complications (such as anastomotic fistula or anastomotic stenosis) occurred, thus indicating that the modified Kamikawa anastomosis was safe and feasible. During the follow-up, upper gastrointestinal angiography and gastroscopy demonstrated no reflux or esophagitis in any patient, thus indicating that the improved Kamikawa anastomosis has a good antireflux effect. The postoperative nutritional indices and scores of all the patients were satisfactory, thus indicating that good nutritional status and QOL can be obtained after proximal gastrectomy.

CONCLUSION

According to the preliminary analysis of 26 patients at the author's center, laparoscopic proximal gastrectomy and modified Kamikawa anastomosis are safe and feasible approaches with good postoperative recovery. The expected antireflux effect can be achieved, and good nutritional status can be maintained. This was a retrospective study with a small sample size. The long-term efficacy of these regimens must be further observed and verified by multicenter clinical studies with large sample sizes.

ARTICLE HIGHLIGHTS

Research background

The incidence of reflux esophagitis after proximal gastrectomy is high, and the proper reconstruction of digestive tract is still controversial.

Research motivation

To explore the appropriate digestive tract reconstruction method in laparoscopic proximal gastrectomy to reduce the occurrence of postoperative reflux while ensuring the safety and feasibility of the operation.

Research objectives

To explore the clinical efficacy of modified Kamikawa anastomosis in laparoscopic proximal gastrectomy.

Research methods

We retrospectively collected clinicopathological data of patients who underwent laparoscopic proximal gastrectomy and modified Kamikawa anastomosis. The intraoperative conditions, postoperative conditions and follow-up were analyzed.

Research results

The operation of 26 patients was successful and the postoperative recovery was good. No reflux esophagitis and anastomotic stenosis were found in all patients during postoperative follow-up, and their nutritional status was satisfactory.

Research conclusions

The modified Kamikawa anastomosis in laparoscopic proximal gastrectomy shows satisfactory antireflux effect and is safe and feasible during operation. We can use this procedure in laparoscopic proximal gastrectomy.

Research perspectives

A multicenter prospective study should be performed to verify our modified method.

FOOTNOTES

Co-first authors: Chu-Ying Wu and Jian-An Lin.

Author contributions: Wu CY and Lin JA contributed equally to the study; Wu CY contributed to data curation, original draft preparation, project administration, and funding acquisition; Lin JA contributed to software, writing, review, and editing; Kai Y contributed to conceptualization, supervision, and funding acquisition; all authors have read and agreed to the published version of the manuscript.

Supported by the Fujian Medical University Sailing Fund General Project, No. 2022QH1117; and Key Clinical Specialty Discipline Construction Program of Fujian, Fujian Health Medicine and Politics, No. [2022]884.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of the Second Affiliated Hospital of Fujian Medical University (Approval No. 2022219).

Informed consent statement: The requirement for informed consent was waived by the Ethics Committee considering the retrospective design of the study.

Conflict-of-interest statement: All authors report no conflicts of interest.

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

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S-Editor: Chen YL
L-Editor: A
P-Editor: Zheng XM

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World J Gastrointest Surg 2024 January 27; 16(1): 124-133

DOI: 10.4240/wjgs.v16.i1.124

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

Clinical effect of laparoscopic radical resection of colorectal cancer based on propensity score matching

Yang Liu, Xian-Xue Wang, Yu-Lin Li, Wen-Tao He, Hong Li, Hua 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): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Schulman AR, United States; Tortora G, Italy

Received: November 21, 2023
Peer-review started: November 21, 2023
First decision: December 5, 2023
Revised: December 16, 2023
Accepted: December 28, 2023
Article in press: December 28, 2023
Published online: January 27, 2024

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Abstract

BACKGROUND

The incidence of colorectal cancer (CRC) is increasing annually. Laparoscopic radical resection of CRC is a minimally invasive procedure preferred in clinical practice.

AIM

To investigate the clinical effect of laparoscopic radical resection of CRC on the basis of propensity score matching (PSM).

METHODS

The clinical data of 100 patients who received inpatient treatment for CRC at Changde Hospital, Xiangya School of Medicine, Central South University (The First People's Hospital of Changde City) were analyzed retrospectively. The control group included patients who underwent open surgery (n = 43), and those who underwent laparoscopic surgery formed the observation group (n = 57). The baseline information of both groups was equipoised using 1 × 1 PSM. Differences in the perioperative parameters, inflammatory response, immune function, degree of pain, and physical status between the groups were analyzed.

RESULTS

Thirty patients from both groups were successfully matched. After PSM, baseline data showed no statistically significant differences between the groups: (1) Perioperative parameters: The observation group had a longer surgery time, less intraoperative blood loss, earlier first ambulation and first anal exhaust times, and

shorter gastric tube indwelling time than the control group; (2) Inflammatory response: 24 h after surgery, the levels of interleukin-6 (IL-6), C-reactive protein (CRP), and tumor necrosis factor-α (TNF-α) between groups were higher than preoperatively. IL-6, CRP, and TNF-α levels in the observation group were lower than in the control group; (3) Immune function: At 24 h after surgery, counts of CD4-positive T-lymphocytes ($CD4^+$) and $CD4^+$/CD8-positive T-lymphocytes ($CD8^+$) in both groups were lower than those before surgery, whereas $CD8^+$ was higher than that before surgery. At 24 h after surgery, both $CD4^+$ counts and $CD4^+/CD8^+$ in the observation group were higher than those in the control group, whereas $CD8^+$ counts were lower; (4) Degree of pain: The visual analog scale scores in the observation group were lower than those in the control group at 24 and 72 h after surgery; and (5) Physical status: One month after surgery, the Karnofsky performance score in the observation group was higher than that in the control group.

CONCLUSION

Laparoscopic radical resection of CRC has significant benefits, such as reducing postoperative pain and postoperative inflammatory response, avoiding excessive immune inhibition, and contributing to postoperative recovery.

Key Words: Colorectal cancer; Laparoscopic; Open surgery; Inflammatory reaction; Immune function; Propensity score

Core Tip: Clinical data from 100 patients who underwent radical resection for colorectal cancer were retrospectively analyzed to compare the clinical effects of open and laparoscopic surgeries in terms of perioperative parameters, inflammatory response, immune function, degree of pain, and physical status.

Citation: Liu Y, Wang XX, Li YL, He WT, Li H, Chen H. Clinical effect of laparoscopic radical resection of colorectal cancer based on propensity score matching. *World J Gastrointest Surg* 2024; 16(1): 124-133
URL: https://www.wjgnet.com/1948-9366/full/v16/i1/124.htm
DOI: https://dx.doi.org/10.4240/wjgs.v16.i1.124

INTRODUCTION

Colorectal cancer (CRC) is a common cancer of the digestive system with high incidence and mortality[1]. There would be approximately 1.93 million new cases of CRC and 940000 deaths worldwide in 2020, representing 10% and 9.4% of global cancer morbidity and mortality, respectively[2]. However, early symptoms of CRC remain unclear. Growing tumors can cause abdominal pain, changes in stool characteristics, bloody stools, and other symptoms. At this time, the disease often progresses to the middle and late stages, and its prognosis is poor[3]. Currently, the treatment for CRC is largely based on surgery. Early surgical resection, blocking tumor progression, and avoiding post-diffusion metastasis are key to improving the prognosis of patients with CRC.

Traditional open surgery can effectively remove lesions but has the disadvantages of much trauma, slow recovery of postoperative function, and many complications[4]. Laparoscopic surgery has recently become increasingly popular. It can achieve complete resection of lesions and promote rapid recovery of patients after surgery, while reducing surgical side injuries[5]. However, laparoscopic surgery is complicated, and the anatomy of the colon and rectum increases its difficulty[6]. The application of laparoscopic radical resection of CRC remains controversial at the present clinical stage. Therefore, the clinical data of 100 patients with CRC were retrospectively analyzed in this study, and propensity score matching (PSM) was used to balance confounding variables between the observation group and the control group to control confounding bias and reduce the bias[7]. The aim of this study was to explore the clinical effects of laparoscopic radical resection for CRC, and to provide a reference for the selection of clinical surgical modalities.

MATERIALS AND METHODS

Patient characteristics

The clinical data of 100 patients who received inpatient treatment for CRC between January 2022 and March 2023 at Changde Hospital, Xiangya School of Medicine, Central South University (The First People's Hospital of Changde City) were analyzed retrospectively. Inclusion criteria were: (1) First diagnosed as CRC by histopathological examination; (2) Age ≥ 18 years old; (3) Tumor-node-metastasis (TNM) stage of the tumor was I-III; and (4) Received radical surgical resection, open surgery or laparoscopic surgery. Exclusion criteria were as follows: (1) Previous history of abdominal surgery; (2) Perforation, bleeding, acute intestinal obstruction, and other acute surgeries; (3) Combined with other malignant tumors or malignant tumor history; (4) Combined with major organ dysfunction; (5) Pregnant and lactating

women; and (6) Missing the data required for this study.

Operative method

Open surgery: Lithotomy position after general anesthesia. The size and position of the incision was confirmed based on the size and position of the lesion. First, a normal abdominal examination was performed to determine the location of the tumor and its proximal tissues and organs. The upper and lower regular and corresponding mesenteric vessels of the tumor were first ligated, and the intestinal canal was freed. The tumor was removed and intestinal tubes at each end of the tumor and its corresponding mesentery were fitted. Lymph node dissection, intestinal anastomosis, abdominal cavity irrigation, lining drainage, and abdominal cavity closure were completed.

Laparoscopic surgery: Lithotomy position after general anesthesia. Laparoscopic access was established by opening 3–5 small holes (5–10 mm) in the abdominal wall and introducing the laparoscopic and surgical instruments. A 5 cm incision was made in the abdominal wall, based on the location of the lesion, to remove the tumor tissue. A CO_2 pneumothorax was established, and the intraperitoneal condition was investigated. The mesenteric arterial and peripheral connective tissues were isolated. The tumor, appropriate intestinal tubes at each end of the tumor, and corresponding mesentery were removed, and the lymph nodes were dissected. Colorectal anastomosis was performed, bowel ducts were rationalized, the abdominal cavity was irrigated, internal drainage was performed, instruments were withdrawn, and the abdominal cavity was closed.

Data collection

Data were collected from patients through the hospital information system, including baseline data such as age, sex, body mass index (BMI), tumor diameter, lesion location, and the American Society of Anesthesiologists (ASA) grade.

(1) Perioperative parameters such as surgery duration, intraoperative blood loss, number of lymph node dissections, first ambulation time, bowel sound recovery time, first anal exhaust time, gastric tube indwelling time, and complication rate were compared between the groups; (2) Inflammatory response: Five milliliters of venous blood was collected after fasting preoperatively and 24 h postoperatively. After centrifugation, the levels of interleukin-6 (IL-6), C-reactive protein (CRP), and tumor necrosis factor-α (TNF-α) were determined using an enzyme-linked immunosorbent assay; (3) Immune function: Blood samples were collected as described above. CD4-positive T-lymphocytes ($CD4^+$) and CD8-positive T-lymphocytes ($CD8^+$) counts were quantified using a flow cytometer and companion kit (BD FACSCalibur; Becton, Dickinson And Company., United States); (4) Degree of pain: The visual analog scale (VAS) was used to evaluate the degree of pain preoperatively and 24 h and 72 h postoperatively. The VAS score is 0–10, with a higher score indicating more intense pain; and (5) Physical status: The Karnofsky performance score (KPS) was used to evaluate the physical status preoperatively, and 1 month and 3 mo postoperatively. The KPS can be divided into 11 grades from disease-free (100 points) to death (0 points), with higher scores indicating better conditions.

Statistical analysis

R software (R 4.1.3; Bell Laboratories., Auckland, New Zealand) was used for the PSM. The nearest neighbor matching method and the caliper matching method were used. When the caliper value was set to 0.2, age, tumor diameter, lesion location, and ASA were matched at a ratio of 1 × 1 between groups, and the standardized mean difference (SMD) was applied to evaluate the matching effect. SMD < 0.1 can was considered as a good matching effect. SPSS software (version 26.0; IBM Corp., Armonk, NY, United States) was used for data processing and analysis. Quantitative data according to the Gaussian distribution was described as mean ± standard (mean ± SD), the paired sample *t*-test was applied to compare within groups and the independent sample *t*-test to compare among groups. Quantitative continuous data that did not conform to the Gaussian distribution are shown as median (M) and interquartile range [M (P25-P75)], and the Mann–Whitney U test was applied for comparison. Categorical data were expressed as numbers and percentages, *n* (%), and the chi-square test was applied for comparison. Statistical significance was set at $P < 0.05$.

RESULTS

Patient baseline data

Among the 100 patients in the study, 43 who underwent open surgery were included in the control group, and 57 who underwent laparoscopic surgery were included in the observation group. There were statistically significant differences in age, tumor diameter, lesion location, and ASA between the groups (Table 1).

Patient baseline data after PSM

Sixty patients were successfully matched after 1:1 PSM. The SMD for age, tumor diameter, lesion location, and ASA classification were 0.014, 0.090, 0.092, and 0.035, respectively, which can be considered a good matching effect. After PSM, there were no significant differences between the groups in terms of age, sex, BMI, underlying disease, tumor diameter, TNM stage, histological type, lesion location, or ASA classification (Table 2).

Comparison of the perioperative parameters

There were no significant differences between the groups in the number of lymph node dissections, bowel sound recovery time, or rate of complications ($P > 0.05$). The observation group had a longer surgery time, lesser intraoperative blood loss, earlier first ambulation time, shorter first anal exhaust time, and shorter gastric tube indwelling time than the

Table 1 Patients' baseline data

Data	Control group (*n* = 43)	Observation group (*n* = 57)	$t/\chi^2/Z$	*P* value
Age (yr, mean ± SD)	56.44 ± 7.48	52.37 ± 11.71	2.116	0.037
Sex, *n* (%)			0.220	0.887
Male	24 (55.81)	31 (54.39)		
Female	19 (44.19)	26 (45.61)		
BMI (kg/m^2, mean ± SD)	22.06 ± 1.50	22.41 ± 1.61	1.102	0.273
Underlying disease, *n* (%)				
Hypertension	11 (25.58)	19 (33.33)	0.701	0.402
Diabetes	14 (35.56)	10 (17.54)	3.029	0.082
CHD	8 (18.60)	12 (21.05)	0.092	0.762
Tumor diameter (cm, mean ± SD)	3.93 ± 0.48	3.70 ± 0.52	2.188	0.031
TNM stage, *n* (%)			1.142	0.254
I	20 (46.51)	32 (56.14)		
II	17 (39.53)	21 (36.84)		
III	6 (13.95)	4 (7.02)		
Histological type, *n* (%)			0.256	0.968
Adenocarcinoma	17 (39.53)	25 (43.86)		
Mucinous adenocarcinoma	12 (27.91)	14 (24.56)		
Squamous cell carcinoma	9 (20.93)	11 (19.30)		
Other	5 (11.63)	7 (12.28)		
Tumor location, *n* (%)			8.501	0.037
Rectum	20 (46.51)	24 (42.11)		
Descending colon	13 (30.23)	7 (12.28)		
Ascending colon	6 (13.95)	11 (19.30)		
Sigmoid flexure	4 (9.30)	15 (26.32)		
ASA grade, *n* (%)			2.026	0.043
I	18 (41.86)	14 (24.56)		
II	16 (37.21)	22 (38.60)		
III	6 (13.95)	15 (26.32)		
IV	3 (6.98)	6 (10.53)		

BMI: Body mass index; CHD: Coronary heart disease; TNM: Tumor node metastasis; ASA: American Society of Anesthesiologists.

control group (Table 3).

Comparison of the postoperative inflammatory indexes

There were no differences between groups in the levels of IL-6, CRP, and TNF-α preoperatively ($P > 0.05$). At 24 h after surgery, the IL-6, CRP, and TNF-α levels of both groups were higher than preoperatively, and those in the observation group were lower than the control group (Table 4).

Comparison of the postoperative immune indexes

$CD4^+$ counts and $CD4^+/CD8^+$ in both groups were lower postoperatively and $CD8^+$ counts were higher 24 h after surgery. The observation group had higher $CD4^+$ counts and $CD4^+/CD8^+$ and lower $CD8^+$ counts than the control group at 24 h after surgery (Table 5).

Comparison of the postoperative VAS scores

Before surgery, the average VAS score of the control group was (3.90 ± 0.55) and the observation group was (3.40 ± 1.67),

Table 2 Baseline data of patients after propensity score matching

Data	Control group (*n* = 30)	Observation group (*n* = 30)	$t/\chi^2/Z$	*P* value
Age (year, mean ± SD)	54.97 ± 7.54	54.83 ± 11.52	0.053	0.958
Sex, *n* (%)			0.067	0.795
Male	17 (56.67)	16 (53.33)		
Female	13 (43.33)	14 (46.67)		
BMI (kg/m^2, mean ± SD)	22.11 ± 1.54	22.01 ± 1.62	0.237	0.814
Underlying disease, *n* (%)				
Hypertension	7 (23.33)	10 (33.33)	0.739	0.390
Diabetes	10 (33.33)	5 (16.67)	2.222	0.136
CHD	7 (23.33)	4 (13.33)	0.445	0.505
Tumor diameter (cm, mean ± SD)	3.86 ± 0.48	3.81 ± 0.56	0.347	0.730
TNM stage, *n* (%)			0.701	0.483
I	15 (50.00)	17 (56.67)		
II	12 (40.00)	12 (40.00)		
III	3 (10.00)	1 (3.33)		
Histological type, *n* (%)			0.842	0839
Adenocarcinoma	11 (36.67)	13 (43.33)		
Mucinous adenocarcinoma	10 (33.33)	7 (23.33)		
Squamous cell carcinoma	6 (20.00)	6 (20.00)		
Other	3 (10.00)	4 (13.33)		
Tumor location, *n* (%)			4.149	0.246
Rectum	12 (40.00)	17 (56.67)		
Descending colon	9 (30.00)	3 (10.00)		
Ascending colon	6 (20.00)	6 (20.00)		
Sigmoid flexure	3 (10.00)	4 (13.33)		
ASA grade, *n* (%)			0.008	0.994
I	12 (40.00)	10 (33.33)		
II	10 (33.33)	15 (50.00)		
III	5 (16.67)	2 (6.67)		
IV	3 (10.00)	3 (10.00)		

BMI: Body mass index; CHD: Coronary heart disease; TNM: Tumor node metastasis; ASA: American Society of Anesthesiologists.

with no significant differences between groups ($P > 0.05$). At 24 h after surgery, the average VAS score of the control group was (5.07 ± 1.44) and the observation group was (4.13 ± 0.73). At 72 h after surgery, the average VAS score of the control group was (3.93 ± 0.45) and the observation group was (3.20 ± 0.85). The VAS scores in the observation group were significantly lower than those in the control group at 24 h and 72 h after surgery (Figure 1).

Comparison of the postoperative KPS

Before surgery, the average KPS of the control group was (60.67 ± 12.30) and the observation group was (62.00 ± 9.61). The average KPS of the control group was (65.00 ± 6.82) and the observation group was (69.67 ± 7.18) one month after surgery. The average KPS of the control group and the observation group was (69.00 ± 8.45) and (70.67 ± 6.915) respectively, three months after surgery. Preoperatively and three months after surgery, there were no significant differences in KPS scores among the groups ($P > 0.05$). The observation group had a higher KPS score than the control group one month after surgery (Figure 2).

Table 3 Comparison of perioperative parameters between the two groups

Parameters	Control group (*n* = 30)	Observation group (*n* = 30)	*t*	*P* value
Surgery time (min, mean ± SD)	157.70 ± 14.14	203.13 ± 20.07	10.138	< 0.001
Intraoperative blood loss (mL, mean ± SD)	172.07 ± 26.94	131.93 ± 21.84	6.338	< 0.001
Number of lymph nodes dissected (piece, mean ± SD)	17.73 ± 2.48	17.17 ± 3.08	0.786	0.435
First ambulation time (h, mean ± SD)	47.60 ± 5.37	38.73 ± 6.76	5.626	< 0.001
Bowel sounds recovery time (h, mean ± SD)	67.80 ± 8.06	65.97 ± 6.61	0.963	0.339
First anal exhaust time (h, mean ± SD)	78.33 ± 16.01	67.73 ± 18.20	2.396	0.020
Gastric tube indwelling time, d, M (P25-P75)	4.00 (4.00, 5.00)	3.50 (3.00, 4.00)	4.621	< 0.001
Rate of complications, *n* (%)	5 (16.67)	3 (10.00)	0.144	0.704

M: Median

Table 4 Comparison of postoperative inflammatory indexes between the two groups

Group	IL-6 (ng/L)		CRP (mg/L)		TNF-α (ng/L)	
	Preoperative	24 h after surgery	Preoperative	24 h after surgery	Preoperative	24 h after surgery
Control group (*n* = 30)	8.49 ± 1.23	16.68 ± 4.22[a]	4.96 ± 1.22	21.24 ± 4.32[a]	24.81 ± 3.36	49.37 ± 7.58[a]
Observation group (*n* = 30)	9.06 ± 1.68	13.78 ± 2.34[a]	5.34 ± 1.41	18.96 ± 3.56[a]	23.92 ± 4.07	43.62 ± 5.68[a]
t	1.501	3.294	1.099	2.235	0.920	3.326
P value	0.139	0.002	0.276	0.029	0.361	0.002

[a]*P* < 0.05, compared with the same group before surgery.
Data are shown as mean ± SD. IL-6: Interleukin-6; CRP: C-reactive protein; TNF-α: Tumor necrosis factor-α.

Table 5 Comparison of postoperative immune indexes between the two groups

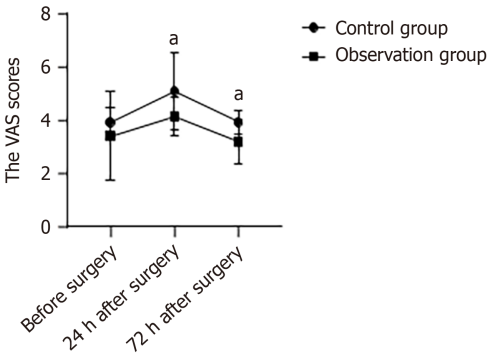
Group	$CD4^+$ (%)		$CD8^+$ (%)		$CD4^+/CD8^+$	
	Preoperative	24 h after surgery	Preoperative	24 h after surgery	Preoperative	24 h after surgery
Control group (*n* = 30)	44.80 ± 6.32	32.17 ± 4.78[a]	27.00 ± 3.46	33.40 ± 3.41[a]	1.69 ± 0.36	0.97 ± 0.19[a]
Observation group (*n* = 30)	44.23 ± 5.74	36.13 ± 4.97[a]	26.10 ± 4.67	31.53 ± 2.99[a]	1.76 ± 0.45	1.15 ± 0.18[a]
t	0.364	3.150	0.848	2.254	0.625	3.736
P value	0.718	0.003	0.400	0.028	0.535	< 0.001

[a]*P* < 0.05, compared with the same group before surgery.
Data are shown as mean ± SD. $CD4^+$: CD4-positive T-lymphocytes; $CD8^+$: CD8-positive T-lymphocytes.

DISCUSSION

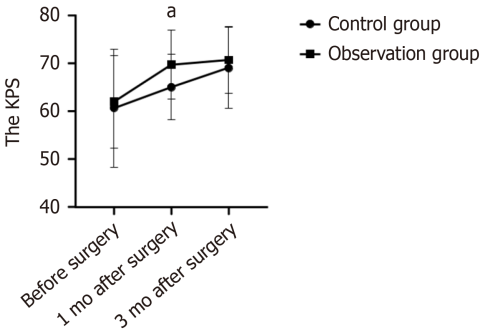
The etiology of CRC is complex and is linked to diet, digestive tract diseases, lifestyle, genetics, and other factors. The long-term interaction of these factors affects the intestinal peristaltic ability and increases the contact time between carcinogens and the intestine, thus continuously stimulating the intestinal mucosal cells, causing them to proliferate out of control and eventually form tumor tissues[6]. With an improvement in living conditions, changes in dietary structure and mode of life have caused a significant increase in the morbidity of CRC, and the age of onset has gradually become lesser[8]. Currently, CRC is generally treated based on the principle of clearing the tumor and lymph nodes, and inhibiting the transfer and invasion of cancer cells[9].

Surgery is the only curative treatment for CRC[10]. Open radical resection for CRC has a long history of clinical application. An abdominal opening can be used to observe the abdominal cavity and locate the intestinal segment of the lesion, and resection of the tumor and the affected intestinal segment can be completed under direct vision to achieve complete removal of the tumor[11]. However, open surgery, with its long incisions and extensive lymph node dissection, is prone to a strong stress response. In addition, the risk of infection increases with a long exposure time of the abdominal



DOI: 10.4240/wjgs.v16.i1.124

Figure 1 Comparison of the visual analogue scale scores between the two groups. VAS: Visual analogue scale. [a]*P* < 0.05



DOI: 10.4240/wjgs.v16.i1.124

Figure 2 Comparison of the Karnofsky performance score between the two groups. KPS: Karnofsky performance score. [a]*P* < 0.05

cavity, which affects the recovery of the body after surgery[12]. Recently, laparoscopic surgery has become increasingly popular for treating CRC. The magnification of laparoscopic images broadens the surgical domain and helps surgeons more clearly identify important structures, such as blood vessels, nerves, and ureters, facilitating delicate surgical manipulation. Laparoscopic surgery results in a smaller wound, which avoids prolonged exposure of the abdominal cavity to air and reduces the damage to the body caused by invasive surgery to a certain extent[13,14]. However, laparoscopy has not been completely developed and laparoscopic surgery is difficult[15]. Most current studies comparing the efficacy of open surgery and laparoscopic surgery for CRC are retrospective analyses, and confounding factors are generally unevenly distributed, thus affecting the reliability of the conclusions. In 1983, Rosenbaum and Rubin[16]. proposed PSM, a subject matching method to reduce confounding effects and balance the difference between the observation group and the control group. This could achieve a balance among the confounding factors through a post-randomization process, thus minimizing the bias in the estimation of the treatment effects[17,18].

We collected clinical data of 43 patients who underwent open radical resection and compared them with those of 57 patients who underwent laparoscopic radical resection for CRC. After 1:1 PSM, 60 patients were matched successfully. By comparing perioperative parameters, we found that open radical resection and laparoscopic radical resection for CRC had similar clinical effects, including the number of lymph nodes removed, bowel sound recovery time, and incidence of complications. Laparoscopic radical resection of CRC results in a longer surgery time, less intraoperative blood loss, earlier time to get out of bed and first anal exit, and shorter time to remove the stomach tube. Considering that the visual field of laparoscopic surgery has a planar structure, the surgeon needs to use an instrument to sense the location of the lesion, which enhances the difficulty of the procedure to a certain extent, thus prolonging the surgery time. VAS scores 24 and 72 h postoperatively were significantly lower in patients who underwent laparoscopic radical response for CRC, and they also had a higher KPS one month after surgery. At three months after surgery, there were no significant differences in the KPS scores between the groups. These results confirmed that laparoscopic surgery can reduce early postoperative pain and contribute to early physical recovery.

Invasive surgery can easily induce a stress response, mainly manifested as excessive expression of inflammatory factors[19]. On the one hand, the production of large amounts of inflammatory cells can increase the incidence of postoperative infection; on the other hand, it can directly affect the surgical outcome[20]. IL-6 and TNF-α are typical pro-inflammatory factors, which are important mediators that trigger and initiate inflammatory responses. CRP levels can be markedly elevated post-trauma. The results of our study showed that patients receiving laparoscopic radical resection of CRC had lower levels of IL-6, CRP, and TNF-α at 24 h after surgery. This indicates that laparoscopic surgery may reduce the early postoperative inflammatory response compared to open surgery. This is consistent with the results reported by Chen *et al*[10]. At the same time, surgical trauma can also cause the temporary inhibition of immune function[21]. $CD4^+$ T cells are helper cells and induce T cells with anti-tumor effects, $CD8^+$ T cells are inhibitory T cells that inhibit the immune

reaction, and $CD4^+/CD8^+$ is an important marker reflecting the body's immune regulation efficacy[22]. The results of our study showed that patients who underwent laparoscopic radical resection for CRC had higher $CD4^+$ counts and $CD4^+/CD8^+$ ratios and lower $CD8^+$ counts than patients who underwent open surgery. This suggests that laparoscopic surgery can avoid excessive immunosuppression compared with open surgery. Strong postoperative inflammatory responses and immunosuppression can lead to delayed healing, which is detrimental to the postoperative recovery.

Although PSM was used to eliminate the influence of some confounding factors and increase the reliability of the study results, there are still some limitations: (1) This study has a retrospective design with a low level of evidence; (2) The number of cases included in the study was small, and the research data were all from the same institution; (3) Based on a single-center retrospective study, in addition to demographic and pathological characteristics, there are still some confounding factors regarding the treatment differences, such as chemoradiotherapy regimen and tumor metastasis; and (4) Lack of long-term observation data. Future studies with large sample sizes and high-quality randomized controlled trials are still needed to confirm this.

CONCLUSION

Our results indicated that laparoscopic radical resection of CRC has significant benefits such as reducing postoperative pain and postoperative inflammatory response, avoiding excessive immune inhibition, and contributing to postoperative recovery.

ARTICLE HIGHLIGHTS

Research background

Currently, there is some debate about the merits of laparoscopic surgery of colorectal cancer (CRC).

Research motivation

The advantages of laparoscopic surgery for CRC require further validation through additional studies and data.

Research objectives

Exploring the advantages of laparoscopic radical resection *vs* open surgery for CRC.

Research methods

Data from 43 patients with CRC who underwent open surgery and 53 who underwent laparoscopic surgery were compared retrospectively, and differences between the groups were analyzed using 1:1 propensity score matching equilibrium treatment.

Research results

Compared with open surgery, laparoscopic radical resection of CRC showed better early inflammatory, immune, and pain indicators, and better physical status one month after surgery.

Research conclusions

Laparoscopic radical resection of CRC can reduce postoperative pain and postoperative inflammatory responses, prevent excessive immune inhibition, and contribute to postoperative recovery.

Research perspectives

To analyze the early clinical effects of laparoscopic radical resection for CRC.

FOOTNOTES

Author contributions: Liu Y designed and performed the research and wrote the paper; Chen H designed the research and supervised the report; Wang XX and Li H designed the research and organized the data; Li YL and He WT designed the research and contributed to the analysis. All authors approved the manuscript.

Supported by Scientific Research Project of Hunan Provincial Health Commission, No. 202204114103.

Institutional review board statement: The study was reviewed and approved by the Changde Hospital, Xiangya School of Medicine, Central South University (The First People's Hospital of Changde City) Institutional Review Board, Approval No. 2021-265-02.

Informed consent statement: All patients have signed informed consent forms.

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

Data sharing statement: The clinical data used in this study can be obtained from the corresponding author upon request at 229chenhua@sina.com.

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S-Editor: Li L
L-Editor: A
P-Editor: Li L

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World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2024 January 27; 16(1): 134-142

DOI: 10.4240/wjgs.v16.i1.134

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

Different timing for abdominal paracentesis catheter placement and drainage in severe acute pancreatitis complicated by intra-abdominal fluid accumulation

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Specialty type: Gastroenterology and hepatology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Sherf-Dagan S, Israel; Suesstrunk J, Switzerland

Received: November 10, 2023
Peer-review started: November 10, 2023
First decision: November 22, 2023
Revised: November 28, 2023
Accepted: December 15, 2023
Article in press: December 15, 2023
Published online: January 27, 2024

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Abstract

BACKGROUND

Non-surgical methods such as percutaneous drainage are crucial for the treatment of patients with severe acute pancreatitis (SAP). However, there is still an ongoing debate regarding the optimal timing for abdominal paracentesis catheter placement and drainage.

AIM

To explore the influence of different timing for abdominal paracentesis catheter placement and drainage in SAP complicated by intra-abdominal fluid accumulation.

METHODS

Using a retrospective approach, 184 cases of SAP complicated by intra-abdominal fluid accumulation were enrolled and categorized into three groups based on the timing of catheter placement: group A (catheter placement within 2 d of symptom onset, n = 89), group B (catheter placement between days 3 and 5 after symptom onset, n = 55), and group C (catheter placement between days 6 and 7 after symptom onset, n = 40). The differences in progression rate, mortality rate, and the number of cases with organ dysfunction were compared among the three groups.

RESULTS

The progression rate of group A was significantly lower than those in groups B and groups C (2.25% *vs* 21.82% and 32.50%, $P < 0.05$). Further, the proportion of patients with at least one organ dysfunction in group A was significantly lower than those in groups B and groups C (41.57% *vs* 70.91% and 75.00%, $P < 0.05$). The mortality rates in group A, group B, and group C were similar ($P > 0.05$). At postoperative day 3, the levels of C-reactive protein (55.41 ± 19.32 mg/L *vs* 82.25 ± 20.41 mg/L and 88.65 ± 19.14 mg/L, $P < 0.05$), procalcitonin (1.36 ± 0.51 ng/mL *vs* 3.20 ± 0.97 ng/mL and 3.41 ± 0.98 ng/mL, $P < 0.05$), tumor necrosis factor-alpha (15.12 ± 6.63 pg/L *vs* 22.26 ± 9.96 pg/L and 23.39 ± 9.12 pg/L, $P < 0.05$), interleukin-6 (332.14 ± 90.16 ng/L *vs* 412.20 ± 88.50 ng/L and 420.08 ± 87.65ng/L, $P < 0.05$), interleukin-8 (415.54 ± 68.43 ng/L *vs* 505.80 ± 66.90 ng/L and 510.43 ± 68.23ng/L, $P < 0.05$) and serum amyloid A (270.06 ± 78.49 mg/L *vs* 344.41 ± 81.96 mg/L and 350.60 ± 80.42 mg/L, $P < 0.05$) were significantly lower in group A compared to those in groups B and group C. The length of hospital stay in group A was significantly lower than those in groups B and group C (24.50 ± 4.16 d *vs* 35.54 ± 6.62 d and 38.89 ± 7.10 d, $P < 0.05$). The hospitalization expenses in group A were also significantly lower than those in groups B and groups C [2.70 (1.20, 3.55) ten-thousand-yuan *vs* 5.50 (2.98, 7.12) ten-thousand-yuan and 6.00 (3.10, 8.05) ten-thousand-yuan, $P < 0.05$). The incidence of complications in group A was markedly lower than that in group C (5.62% *vs* 25.00%, $P < 0.05$), and similar to group B ($P > 0.05$).

CONCLUSION

Percutaneous catheter drainage for the treatment of SAP complicated by intra-abdominal fluid accumulation is most effective when performed within 2 d of onset.

Key Words: Abdominal paracentesis catheter drainage; Timing; Severe acute pancreatitis; Intra-abdominal fluid; Application value

Core Tip: This study investigated the application value of different timing of abdominal puncture catheter drainage in patients with severe acute pancreatitis (SAP) complicated by abdominal effusion. The aim of this analysis to provide clinicians with more precise guidance to optimize treatment strategies and improve the quality of life of SAP patients. The results showed that percutaneous catheter drainage was most effective in the treatment of SAP complicated with abdominal effusion when applied within 2 d of disease onset.

Citation: Chen R, Chen HQ, Li RD, Lu HM. Different timing for abdominal paracentesis catheter placement and drainage in severe acute pancreatitis complicated by intra-abdominal fluid accumulation. *World J Gastrointest Surg* 2024; 16(1): 134-142
URL: https://www.wjgnet.com/1948-9366/full/v16/i1/134.htm
DOI: https://dx.doi.org/10.4240/wjgs.v16.i1.134

INTRODUCTION

Acute pancreatitis is typically caused by the abnormal activation of digestive enzymes within the pancreas. Under normal circumstances, the pancreas secretes digestive enzymes, which are activated before entering the small intestine to help break down fats, proteins, and carbohydrates in food[1]. However, in patients with acute pancreatitis, these digestive enzymes undergo abnormal activation within the pancreas. This leads to the digestion of pancreatic tissue itself and can trigger a series of inflammatory reactions that rapidly spread to surrounding tissues and organs. This cascade of events can result in the occurrence of systemic inflammatory response syndrome and, in severe cases, can lead to organ failure and patient death[2]. According to global statistics, the annual incidence of acute pancreatitis falls between 13 to 45 cases per 100000 people, with approximately 15% of patients progressing to severe acute pancreatitis (SAP)[3]. SAP, as a severe form of acute pancreatitis, is characterized by rapid progression, a higher incidence of complications, and a higher mortality rate, necessitating urgent medical intervention and treatment[4]. While minimally invasive surgery can effectively remove necrotic tissue in SAP, it can be challenging to completely clear necrotic tissue during the early stages of SAP due to the difficulty in accurately distinguishing between normal and necrotic pancreatic tissue. This can affect the surgical outcome[5]. Therefore, in order to effectively control infection in patients and avoid surgical risks, non-surgical methods such as percutaneous drainage are crucial for the treatment of patients with SAP. However, there is still ongoing debate regarding the optimal timing for abdominal paracentesis catheter placement and drainage. Given this background, the aim of the present study was to explore the application value of different timing for abdominal paracentesis catheter placement and drainage in SAP complicated by intra-abdominal fluid accumulation. This study aims to provide more precise guidance for clinicians, optimizing treatment strategies, and improving the quality of life for SAP patients.

MATERIALS AND METHODS

Basic data of the study subjects

Using a retrospective research method, a total of 184 patients with SAP complicated by intra-abdominal fluid accumulation treated at our hospital from August 2022 to July 2023 were enrolled in this study. Inclusion criteria: (1) Diagnosis of SAP in accordance with the criteria outlined in the "Chinese Guidelines for the Diagnosis and Treatment of Acute Pancreatitis"[6], confirmed through imaging studies such as computed tomography with pelvic/abdominal fluid accumulation of ≥ 100 mL; (2) admission to the hospital within 72 h of symptom onset; (3) adult patients; (4) underwent abdominal paracentesis catheter placement and drainage; and (5) completely available of clinical data. The exclusion criteria were: (1) Patients with a history of abdominal surgery; (2) a history of chronic pancreatitis; (3) secondary acute pancreatitis caused by drugs, surgery, and malignant tumors; and (4) concurrent blood system diseases, infectious diseases, and other serious diseases. Patients were divided into different groups according the puncture time point, as follows: Group A (puncture ≤ 2 d), group B (puncture 3-5 d), and group C (puncture 6-7 d), with 89, 55, and 40 cases, respectively.

Treatment methods

All patients underwent abdominal paracentesis catheter drainage (APD). Puncture procedure: An ultrasound device was used to scan the patient's abdomen to determine the location and optimal puncture point for intra-abdominal fluid. Then, local infiltration anesthesia was applied using 4% lidocaine around the puncture site. The operator then employed the Seldinger technique to complete the puncture and utilized an 8 F catheter (from Shenzhen Cooper Business Trading Co., Ltd.) for drainage. A sterile drainage bag was connected to ensure unobstructed drainage. After 3 to 5 d of drainage, another abdominal ultrasound examination was performed to assess the status of intra-abdominal fluid. If the ultrasound suggested that intra-abdominal fluid was still present, the catheter was replaced with a larger diameter catheter to improve drainage efficiency.

Criteria for catheter removal: The drainage catheters were removed when the patient's symptoms and signs significantly improved, and the drainage volume gradually decreased to less than 10 mL continuously for ≥ 2 d, and abdominal ultrasound examination does not detect residual fluid.

Step-up therapy for SAP: When SAP patients experienced worsening symptoms, increased organ failure, or the presence of free gas around the pancreas despite initial treatment with APD, ultrasound-guided percutaneous catheter drainage (PCD) was considered. If the patient's condition did not significantly improve after PCD treatment, and symptoms continue to worsen with no improvement in organ failure, further intervention with endoscopic necrosectomy may be necessary.

Check methods

Before and after treatment, 3 mL of peripheral fasting venous blood was collected from the patients. After centrifugation at a speed of 3600 revolutions per minute for 12 min, enzyme-linked immunosorbent assays with reagent kits from R and D Systems were used to detect interleukin-6 (IL-6) and interleukin-8 (IL-8). Procalcitonin (PCT), C-reactive protein (CRP), and tumor necrosis factor-alpha (TNF-α) were detected using electrochemiluminescence assays, with reagent kits from Roche Diagnostics. Serum amyloid A (SAA) was measured using the scattering turbidity method, with reagent kits from Beckman Coulter.

Observation indicators

The advanced rate (calculated as advanced cases/total cases × 100%, with advanced cases defined as patients who underwent PCD within 4 wk of hospitalization according to the ascending ladder treatment plan), mortality, organ failure, hospitalization time and hospitalization expenses, as well as serum CRP, PCT, TNF-α, IL-6, IL-8 and SAA levels before and after treatment were collected.

Statistical processing

SPSS 22.0 software was used for all analyses. Normally distributed quantitative data are expressed as (mean ± SD), while non-normally quantitative distributed data are expressed as M (Q25, Q75). Count data are represented as *n* (%). For intergroup comparisons, analysis of variance, the Mann-Whitney U test, or χ^2 test is employed. The significance level was set at $\alpha = 0.05$.

RESULTS

Comparison of general clinical data among the patient groups

Gender, age, acute physiology and chronic health evaluation II score at admission, and etiology showed no significant differences between groups A, B, and C ($P > 0.05$, Table 1)

Comparison of progression rate, mortality rate, and organ dysfunction among the groups

The rate of progression to organ failure and the proportion of patients with ≥ 1 organ dysfunction in group A was significantly lower than those in groups B and C ($P < 0.05$). The rates of progression and the proportion of patients with ≥ 1 organ dysfunction were comparable between groups B and C ($P > 0.05$). The mortality rates were comparable between all the groups ($P > 0.05$). These results are summarized in Table 2.

Table 1 Comparison of general clinical data among the groups of patients

Groups	Cases	Gender		Age (yr)	APACHE II score at admission (points)	Etiology		
		Male	Female			Alcoholic	Biliary diseases	Hyperlipidemia
Group A	89	55 (61.80)	34 (38.20)	60.58 ± 8.84	15.65 ± 2.15	29 (32.58)	38 (42.70)	22 (24.72)
Group B	55	30 (54.55)	25 (45.45)	59.87 ± 9.22	15.90 ± 2.09	18 (32.73)	22 (40.00)	15 (27.27)
Group C	40	24 (60.00)	16 (40.00)	61.15 ± 9.03	15.43 ± 2.11	12 (30.00)	18 (45.00)	10 (25.00)
F/χ^2		0.753		0.243	0.581	0.301		
P value		0.686		0.785	0.560	0.990		

APACHE: Acute physiology and chronic health evaluation.

Table 2 Comparison of progression rate, mortality rate, and organ dysfunction among the groups

Groups	Cases	Progression rate (%)	Case fatality rate (%)	Number of organ failure	
				0	≥ 1
Group A	89	2 (2.25)	1 (1.12)	52 (58.43)	37 (41.57)
Group B	55	12 (21.82)[a]	2 (3.64)	16 (29.09)	39 (70.91)[a]
Group C	40	13 (32.50)[a]	4 (10.00)	10 (25.00)	30 (75.00)[a]
χ^2		23.371	5.948	18.309	
P value		< 0.001	0.051	< 0.001	

[a]*P* < 0.05 *vs* group A.

Comparison of serum indicators among the groups

At 3 d post-operation, the CRP, PCT, TNF-a, IL-6, IL-8, and SAA levels in groups A, B, and C significantly decreased compared to pre-operation ($P < 0.05$). However, the levels of CRP, PCT, TNF-α, IL-6, IL-8, and SAA in group A were significantly lower than those in groups B and C at this timepoint ($P < 0.05$). There was no significant difference in the levels of CRP, PCT, TNF-α, IL-6, IL-8, and SAA between groups B and C ($P > 0.05$). Results are presented in Table 3.

Comparison of length of hospital stay and hospitalization costs among the groups

The length of hospital stay and hospitalization costs in group A were both significantly lower than in groups B and C ($P < 0.05$). The length of hospital stay and hospitalization costs were similar between groups B and C ($P > 0.05$). The results are presented in Table 4.

Comparison of complications among the groups

The complication rate in group A was significantly lower than that in group C ($P < 0.05$), and similar to that group B ($P > 0.05$). The complication rates were similar between group B and group C ($P > 0.05$) (Table 5).

DISCUSSION

Acute pancreatitis is a disease characterized by acute inflammation of the pancreatic tissue, and within it, SAP represents an extreme manifestation of acute pancreatitis[7-9]. SAP is a critical condition often associated with widespread inflammation of the pancreas and surrounding tissues. Additionally, the release of inflammatory factors triggers a severe systemic inflammatory response, leading to multi-organ dysfunction, including the cardiovascular system, respiratory system, and kidneys[10-12]. In the early stages of SAP (within the first 24 h after onset), patients often exhibit a phenomenon known as pancreatitis-associated ascitic fluid (PAAF). This is primarily due to increased capillary permeability around the pancreas caused by inflammation and cellular damage. This increased permeability leads to the leakage of fluid from blood vessels into the surrounding tissues, resulting in the formation of ascitic fluid within the abdominal cavity[13-15]. Through abdominal ultrasound examination, the accumulation of fluid within the abdominal cavity, known as abdominal ascites, can be clearly observed. In this situation, PCD serves as a direct and rapid therapeutic approach, effectively removing the accumulated PAAF from the abdominal cavity. This helps reduce intra-abdominal pressure, prevent further exacerbation of the inflammatory response, and decrease the occurrence of complications[16-18]. While this treatment strategy can effectively prevent the pathological and physiological damage caused by

Table 3 Comparison of serum indicators among the groups

Groups	Cases	CRP (mg/L)		PCT (ng/mL)		TNF-α (pg/L)		IL-6 (ng/L)		IL-8 (ng/L)		SAA (mg/L)	
		Preoperative	Postoperative 3 d	Preoperative	Postoperative 3 d	Preoperative	Postoperative 3 d	Preoperative	Postoperative 3 d	Preoperative	Postoperative 3 d	Preoperative	Postoperative 3 d
Group A	89	130.87 ± 32.21	55.41 ± 19.32	9.95 ± 2.94	1.36 ± 0.51	35.46 ± 10.41	15.12 ± 6.63	550.45 ± 80.24	332.14 ± 90.16	630.51 ± 77.16	415.54 ± 68.43	557.97 ± 82.40	270.06 ± 78.49
Group B	55	128.87 ± 30.41	82.25 ± 20.41[a]	10.10 ± 2.73	3.20 ± 0.97[a]	37.80 ± 11.32	22.26 ± 9.96[a]	542.91 ± 84.08	412.20 ± 88.50[a]	634.42 ± 78.20	505.80 ± 66.90[a]	560.43 ± 80.16	344.41 ± 81.96[a]
Group C	40	128.10 ± 31.14	88.65 ± 19.14[a]	10.03 ± 2.85	3.41 ± 0.98[a]	37.15 ± 11.08	23.39 ± 9.12[a]	548.84 ± 81.95	420.08 ± 87.65[a]	629.95 ± 75.43	510.43 ± 68.23[a]	554.18 ± 79.67	350.60 ± 80.42[a]
F value		0.132	53.331	0.048	139.963	0.877	19.559	2.433	20.196	0.055	42.384	0.069	21.354
P value		0.877	< 0.001	0.953	< 0.001	0.418	< 0.001	0.091	< 0.001	0.947	< 0.001	0.934	< 0.001

[a]$P < 0.05$ *vs* group A.

CRP: C-reactive protein; PCT: Procalcitonin; TNF-α: Tumor necrosis factor-alpha; SAA: Serum amyloid A; IL-8: Interleukin-8; IL-6: Interleukin-6.

PAAF, thereby aiding in controlling the severity of SAP and improving patient survival rates, the optimal timing for abdominal puncture remains a subject of debate and a focus of clinical research and discussion[19-21]. Therefore, there is a need for a systematic study to investigate the impact of different timing for PCD on the treatment outcomes and prognosis of patients with SAP complicated by abdominal ascites.

This study's findings indicated that group A had a significantly lower rate of progression and a lower proportion of patients with ≥ 1 organ dysfunction compared to group B and group C. However, there was no significant difference in the mortality rates among group A, group B, and group C. This suggested that early puncture drainage (group A) can significantly reduce the risk of progression and organ dysfunction, whereas there was no significant difference in progression and organ dysfunction rates between the groups with later puncture drainage (group B and group C). However, performing puncture drainage at different time points did not have a significant impact on mortality rates. This study conducted further comparative analysis of inflammatory markers among the three groups of patients. The results showed that, postoperatively, CRP, PCT, TNF-α, IL-6, IL-8, and SAA levels significantly decreased compared to preoperative levels in all three groups. However, the reduction in inflammatory markers in group A was significantly greater than that in groups B and C. This suggests that early abdominal puncture drainage (within 2 d of onset) can more effectively clear inflammatory mediators, reduce organ damage, and prevent the progression of the condition.

The reason for this analysis is that PAAF contains a significant amount of toxic substances such as amylase, endotoxins, pancreatic proenzyme activation peptide, pancreatic enzymes, and free fatty acids. These toxic substances can exacerbate the body's inflammatory response, leading to the release of a series of inflammatory factors such as CRP, PCT, IL-6, *etc*., resulting in an increase in their serum concentrations[21-24]. This implies that PAAF directly promotes the deterioration of the condition in SAP patients. Therefore, for these patients, early abdominal puncture drainage (within 2 d of admission) is crucial. This can rapidly clear harmful substances from the abdominal cavity, alleviate the inflammatory response in SAP, reduce the serum concentrations of various inflammatory factors, and consequently lower the risk of organ dysfunction[25-27]. Comparing the APD performed in groups A, B, and C, this study found that group A had

Table 4 Comparison of length of hospital stay and hospitalization costs among the groups

Groups	Cases	Hospitalization time (d)	Hospitalization expenses (ten thousand yuan)
Group A	89	24.50 ± 4.16	2.70 (1.20, 3.55)
Group B	55	35.54 ± 6.62[a]	5.50 (2.98, 7.12)[a]
Group C	40	38.89 ± 7.10[a]	6.00 (3.10, 8.05)[a]
F/χ^2		114.111	6.644
P value		< 0.001	< 0.001

[a]*P* < 0.05 *vs* group A.

Table 5 Comparison of complications among the groups

Groups	Cases	Pancreatic pseudocyst	Pancreatic abscess	Abdominal infection	Total
Group A	89	2 (2.25)	1 (1.12)	2 (2.25)	5 (5.62)
Group B	55	3 (5.45)	2 (3.64)	3 (5.45)	8 (14.55)
Group C	40	3 (7.50)	3 (7.50)	4 (10.00)	10 (25.00)[a]
χ^2					9.779
P value					0.008

[a]*P* < 0.05 *vs* group A.

better drainage effectiveness. This is because the earlier drainage is performed, the more effectively toxic and harmful substances can be cleared, thereby reducing the inflammatory response, slowing down, or even halting the progression of SAP[28-30]. Therefore, compared to patients who undergo drainage later, those who receive early drainage have a lower progression rate, indicating that their disease is less likely to worsen, leading to better clinical outcomes[31-33].

This study's results indicate that in the treatment of patients with SAP complicated by abdominal ascites, early puncture drainage (group A) significantly reduces hospitalization time and costs. Additionally, it demonstrates a significant advantage in terms of complication rates compared to later drainage. This suggests that choosing early puncture drainage can improve patients' hospitalization conditions and treatment outcomes, reducing the occurrence of complications, and simultaneously lowering healthcare costs. This further highlights the importance and advantages of early puncture drainage in the management of SAP complicated by abdominal ascites[34,35].

This study has several limitations that should be mentioned. Firstly, the retrospective study design and limited sample size in each group may have introduced bias and limit the generalizability of the results. Further, the time of catheter placement was only divided into 3 categories. Thus, the results of this study need to be confirmed by further prospective study with large cohort.

CONCLUSION

When treating patients with SAP complicated by abdominal ascites through abdominal puncture catheter drainage, 2 d after disease onset is the optimal treatment time window to perform drainage.

ARTICLE HIGHLIGHTS

Research background

Severe acute pancreatitis (SAP), a severe form of acute pancreatitis, is characterized by rapid progression, a high incidence of complications, and a high mortality rate among patients. It necessitates urgent medical intervention and treatment. While minimally invasive surgery can effectively remove necrotic tissue in SAP, it can be challenging to completely clear necrotic tissue during the early stages of SAP due to the difficulty in accurately distinguishing between normal and necrotic pancreatic tissue.

Research motivation

Non-surgical methods such as percutaneous drainage are crucial for the treatment of patients with SAP. However, there

is still ongoing debate regarding the optimal timing for abdominal paracentesis catheter placement and drainage.

Research objectives

The aim of this study was to explore the application value of different timing for abdominal paracentesis catheter placement and drainage in SAP complicated by intra-abdominal fluid accumulation. This study aims to provide more precise guidance for clinicians, optimizing treatment strategies, and improving the quality of life for SAP patients.

Research methods

Through a retrospective study design, 184 cases of SAP complicated by intra-abdominal fluid accumulation were selected from patients treated at our hospital from August 2022 to July 2023. These cases were categorized into three groups based on the timing of catheter placement: Group A (catheter placement within 2 d of symptom onset, n = 89), group B (catheter placement between days 3 and 5 after symptom onset, n = 55), and group C (catheter placement between days 6 and 7 after symptom onset, n = 40). Differences in progression rate, mortality rate, and the number of cases with organ dysfunction were then compared between the three groups.

Research results

The progression rate and proportion of patients with at least one organ dysfunction in group A was significantly lower than those in group B and group C. At postoperative day 3, the levels of C-reactive protein, procalcitonin, tumor necrosis factor-alpha, interleukin-6, interleukin-8, and serum amyloid A were significantly lower in group A compared with those observed in groups B and C. The length of hospital stay and hospitalization expenses in group A were also significantly lower than those in groups B and C. The incidence of complications in group A was markedly lower than that in group C, and similar to group B (P > 0.05).

Research conclusions

Percutaneous catheter drainage for the treatment of SAP complicated by intra-abdominal fluid accumulation is more effective when performed within 2 d of onset.

Research perspectives

Prospective study with large cohort is required.

FOOTNOTES

Author contributions: Chen R, Chen HQ, Li RD, and Lu HM designed the research study; Chen R and Chen HQ performed the research; Li RD contributed new reagents and analytic tools; Chen R, Li RD and Lu HM analyzed the data and wrote the manuscript; all authors have read and approve the final manuscript.

Institutional review board statement: The study was reviewed and approved by the Ethics Committee of Chengdu No. 6 People's Hospital.

Informed consent statement: As the study used anonymous and pre-existing data, the requirement for the informed consent from patients was waived.

Conflict-of-interest statement: We have no financial relationships to disclose.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author.

Country/Territory of origin: China

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S-Editor: Qu XL
L-Editor: A
P-Editor: Qu XL

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World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2024 January 27; 16(1): 143-154

DOI: 10.4240/wjgs.v16.i1.143

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

Comparison of different preoperative objective nutritional indices for evaluating 30-d mortality and complications after liver transplantation

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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): 0
Grade E (Poor): 0

P-Reviewer: Sahin TT, Turkey

Received: October 29, 2023
Peer-review started: October 29, 2023
First decision: December 6, 2023
Revised: December 17, 2023
Accepted: January 8, 2024
Article in press: January 8, 2024
Published online: January 27, 2024

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Abstract

BACKGROUND

The nutritional status is closely related to the prognosis of liver transplant recipients, but few studies have reported the role of preoperative objective nutritional indices in predicting liver transplant outcomes.

AIM

To compare the predictive value of various preoperative objective nutritional indicators for determining 30-d mortality and complications following liver transplantation (LT).

METHODS

A retrospective analysis was conducted on 162 recipients who underwent LT at our institution from December 2019 to June 2022.

RESULTS

This study identified several independent risk factors associated with 30-d mortality, including blood loss, the prognostic nutritional index (PNI), the nutritional risk index (NRI), and the control nutritional status. The 30-d mortality rate was 8.6%. Blood loss, the NRI, and the PNI were found to be independent risk factors for the occurrence of severe postoperative complications. The NRI achieved the highest prediction values for 30-d mortality [area under the curve (AUC) = 0.861, $P < 0.001$] and severe complications (AUC = 0.643, $P = 0.011$). Compared to those in the high NRI group, the low patients in the NRI group had lower preoperative body mass index and prealbumin and albumin levels, as well as higher alanine aminotransferase and total bilirubin levels, Model for End-stage Liver Disease

scores and prothrombin time ($P < 0.05$). Furthermore, the group with a low NRI exhibited significantly greater incidences of intraabdominal bleeding, primary graft nonfunction, and mortality.

CONCLUSION

The NRI has good predictive value for 30-d mortality and severe complications following LT. The NRI could be an effective tool for transplant surgeons to evaluate perioperative nutritional risk and develop relevant nutritional therapy.

Key Words: Liver transplantation; Nutritional indicator; Complications; Prognosis; Nutrition assessment

Core Tip: The preoperative nutritional status of liver transplant patients is closely related to prognosis. In this study, we analyzed clinical data from 162 patients to compare the value of different objective nutritional indices in predicting 30-d mortality and complications following liver transplantation. This provides insights for the preoperative assessment of liver transplant prognosis.

Citation: Li C, Chen HX, Lai YH. Comparison of different preoperative objective nutritional indices for evaluating 30-d mortality and complications after liver transplantation. *World J Gastrointest Surg* 2024; 16(1): 143-154
URL: https://www.wjgnet.com/1948-9366/full/v16/i1/143.htm
DOI: https://dx.doi.org/10.4240/wjgs.v16.i1.143

INTRODUCTION

Liver transplantation (LT) is considered to be the most effective and definitive treatment option for patients suffering from end-stage liver disease. These conditions provide these patients with the opportunity not only to survive but also to extend their lifespan significantly. However, the occurrence of posttransplant complications remains prevalent and can greatly influence postoperative prognosis. This can largely be attributed to the compromised preoperative state of liver transplant recipients and the intricate nature of the surgical procedure. Recently, there has been increasing recognition of the critical roles played by preoperative nutrition and immune status in modulating surgical outcomes.

The serum prealbumin concentration, which can objectively reflect nutritional status and is almost unaffected by external supplementation, is an accurate biomarker for assessing the severity of liver disease. It can also be used for preoperative nutritional assessment and risk stratification[1-4]. The controlling nutritional status (CONUT), prognostic nutritional status index (PNI), and nutritional risk index (NRI) are widely used objective indicators for evaluating nutritional status. These indicators are associated not only with cancer-related complications but also with the long-term prognosis of cancer patients[5-10]. However, few studies have investigated the role of these nutritional indices in predicting liver transplant outcomes. Therefore, this study delves into this matter.

MATERIALS AND METHODS

Patient characteristics

This study was approved by the Ethics Committee of the People's Hospital of Guangxi Zhuang Autonomous Region. The inclusion criteria were as follows: (1) First-time liver transplant recipients aged 18-65 years; (2) Organ donation from deceased citizens; and (3) Complete clinical data. The exclusion criteria were: (1) Multiple organ transplants; (2) Severe pneumonia or severe cardiovascular and cerebrovascular diseases before surgery; (3) Receiving marginal livers[11]; or (4) Incomplete follow-up data. This study was approved by the ethics committee of the People's Hospital of Guangxi Zhuang Autonomous Region (KY-ZC-2023-056). All patients provided written informed consent for data analysis before transplantation.

Study design

Before performing a LT, patient demographic information, which include age, sex, body mass index (BMI), and relevant medical history, such as hypertension, diabetes, and hepatitis B, were collected. Additionally, donor age, graft weight, and various laboratory values, such as prealbumin, albumin (ALB), lymphocyte count, alanine aminotransferase (ALT), aspartate aminotransferase, total bilirubin, and creatinine, were collected. The Model for End-Stage Liver Disease (MELD) score, total cholesterol level, type of donor liver, prothrombin time (PT), and platelet count are also important factors to consider. During LT, data such as operating time, anhepatic phase time, total ischemic time, intraoperative blood loss, and intraoperative urine output were collected. After LT, the incidences of pneumonia, abdominal infection, abdominal bleeding, graft rejection, primary graft nonfunction, early graft dysfunction, severe complications (Clavien-Dindo grade ≥

3), bile leakage, biliary stricture and mortality within 30 d were recorded.

Complications above Grade III include various conditions such as portal vein stenosis, portal vein thrombosis, hepatic artery stenosis, hepatic artery thrombosis, bile leakage, bile duct stenosis, retransplantation, pleural effusion requiring thoracentesis, peritoneal effusion requiring peritoneal puncture, intra-abdominal hemorrhage, respiratory failure necessitating extracorporeal membrane oxygenation support, liver insufficiency requiring artificial external liver support, renal failure requiring hemodialysis treatment, intracranial hemorrhage, and mortality.

The CONUT score consists of three components: The serum ALB concentration, total cholesterol concentration, and lymphocyte count[12]. The PNI can be calculated using the formula: ALB (g/L) + 5 × lymphocyte count (× 10^9/mL). The following equation was used to determine the NRI: (1.519 × ALB, g/L) + (41.7 × actual body weight/ideal body weight) [13]. The ideal weight for males and females can be calculated as follows: For males, 2.3 kg per foot is added to a base weight of 50 kg (if height > 5 feet, with 1 foot equal to 30.48 cm); for females, 1.65 kg per foot is added to a base weight of 48.67 kg (if height > 5 feet, with 1 foot equal to 30.48 cm)[14]. If the actual weight exceeds the ideal weight, set the ratio to one[15].

This study aimed to analyze the risk factors associated with severe postoperative complications (Clavien-Dindo grade ≥ 3) and 30-d mortality following LT. Moreover, the researchers compared the effectiveness of the CONUT score, NRI, PNI, and prealbumin concentration as predictors of postoperative complications and mortality after LT using receiver operating characteristic (ROC) curves. Based on the area under the curve (AUC), the most accurate predictive index was identified and utilized to stratify patients into low-risk and high-risk groups using an appropriate cutoff value. Furthermore, the study compared the differences in baseline characteristics and postoperative complications between the two groups.

Postoperative assessment

After transplantation surgery and before discharge, the functionality of the transplant was assessed through routine laboratory tests. Surgical complications are typically diagnosed by evaluating clinical symptoms and conducting diagnostic examinations. These postoperative complications were documented in the patients' medical records. The Clavien-Dindo classification system was employed to assess and classify these complications. In this study, complications classified as Clavien-Dindo III or higher were considered severe. We recorded all adverse reactions, including pneumonia, abdominal infection, abdominal bleeding, graft rejection, primary graft nonfunction, early graft dysfunction, death, biliary leakage, and biliary stricture, in patients after surgery.

Statistical analysis

The statistical analysis was performed using SPSS 23.0 software. Continuous variables are represented using the median, 25th percentile, and 75th percentile, while categorical variables are represented using the frequency. A binary logistic regression model was used for both univariate and multivariate analyses of the entire sample. In the univariate analysis, indicators with a significance level of $P < 0.05$ were included in the multivariate analysis. However, given the existence of multicollinearity between the serum ALB concentration and the NRI, PNI, and CONUT score, the total serum ALB concentration was not incorporated into the multivariate analysis. The diagnostic results of multicollinearity, following the exclusion of ALB, indicated that the values for the variance inflation factor were less than 5. Consequently, no collinearity issues were observed within the model. The predictive values, optimal thresholds, sensitivities, and specificities for complications and mortality were calculated using ROC curves and AUC. MedCalc 10.2 software was used for the Z test, and the Delong test was used to compare the AUC of the different scoring systems. A P value of less than 0.05 was considered to indicate statistical significance.

RESULTS

Patient characteristics

A total of 162 patients were included in the study, including 133 males and 29 females. Fourteen patients (8.6%) died within a 30-d period following LT. The median age of the patients was 53.0 (45.0-57.0) years. The preoperative BMI was recorded as 23.0 (21.1-25.1). Preoperative hypertension was observed in 18 patients, diabetes was present in 22 patients, and 118 patients tested positive for hepatitis B surface antigen (Table 1).

Univariate and multivariate analyses of severe complications and mortality

The factors correlated with the 30-d mortality rate are outlined in Table 2. Univariate analysis revealed that the following factors were significantly correlated with 30-d mortality: BMI, operation time, blood loss, intraoperative urine volume, prealbumin concentration, NRI, CONUT, PNI, ALT, total bilirubin, preoperative MELD score, and PT. The multivariate analysis confirmed that blood loss [odds ratio (OR) = 1.001, 95%CI: 1.000-1.002, $P = 0.034$], the NRI (OR = 0.665, 95%CI: 0.446-0.991, $P = 0.045$), the CONUT (OR = 2.088, 95%CI: 1.016-4.291, $P = 0.045$), and the PNI (OR = 0.920, 95%CI: 0.848-0.997, $P = 0.042$) were risk factors for the 30-d mortality rate (Table 2).

Factors associated with severe complications (Clavien-Dindo grade ≥ 3) included operation time, blood loss, intraoperative urine volume, NRI, PNI, ALB, total bilirubin, preoperative MELD score, and PT. However, the results of the multivariate analysis showed that blood loss (OR = 1.003, 95%CI: 1.001-1.005, $P = 0.004$), the NRI (OR = 0.942, 95%CI: 0.901-0.986, $P = 0.011$), and the PNI (OR = 0.994, 95%CI: 0.989-0.999, $P = 0.013$) were risk factors associated with severe complications (Clavien-Dindo grade ≥ 3; Table 3).

Table 1 Patient characteristics

Characteristics	Total (*n* = 162)
Age, yr	53.0 (45.0-57.0)
Male/female	133/29
BMI	23.0 (21.1-25.1)
Hypertension, yes/no	18/144
Diabetes, yes/no	22/140
HBsAg-positive, yes/no	118/44
Operation time (min)	535.0 (440.0-600.0)
Anhepatic phase (min)	58.0 (47.3-66.0)
Donor age, yr	45.0 (36.0-55.0)
Total ischemia time (min)	305.0 (250.5-372.6)
Graft weight (kg)	1.4 (1.3-1.7)
Split LT/whole LT	20/142
Blood loss (mL)	1750.0 (975.0-3925.0)
Intraoperative urine volume (mL)	2650.0 (1600.0-4000.0)
Prealbumin (mg/L)	95.0 (89.7-101.8)
NRI	95.1 (89.7-101.8)
CONUT	6.0 (4.0-6.0)
PNI	42.6 (38.7-46.4)
ALB (g/L)	37.2 (33.6-40.7)
Lymphocyte count ($\times 10^9$ /mL)	0.9 (0.6-1.5)
Alanine aminotransferase (U/L)	31.0 (19.0-53.3)
Aspartate aminotransferase (U/L)	46.5 (31.0-90.1)
Total bilirubin (μmol/L)	30.8 (15.2-107.2)
Creatinine (umol/L)	71.0 (58.8-85.3)
Preoperative MELD score	12.0 (8.0-22.0)
Total cholesterol (mmol/L)	3.4 (2.2-4.6)
Prothrombin time (s)	16.4 (14.1-20.8)
Platelet ($\times 10^9$/mL)	67.0 (44.0-150.3)
Death, yes/no	14/148

The data are presented as the median (25^{th}-75^{th} percentile) or *n*. BMI: Body mass index; HBsAg: Hepatitis B surface antigen; CONUT: Control nutritional status; PNI: Prognostic nutritional index; NRI: Nutritional risk index; MELD: Model for end-stage liver disease; LT: Liver transplantation; ALB: Albumin.

The value of different preoperative objective nutritional indicators for predicting severe complications and mortality

ROC curve analysis revealed that the NRI, CONUT score, PNI, and prealbumin concentration were significantly associated with 30-d mortality ($P < 0.05$). Among these, the NRI had the highest AUC value (0.861) for prediction (Tables 4 and 5, Figure 1). When the predictive ability of various indicators for severe complications was compared, the NRI, PNI, and prealbumin concentration all showed good predictive value for severe complications ($P < 0.05$). Among them, the NRI exhibited the highest predictive ability (AUC = 0.643; Tables 5 and 6, Figure 2).

Comparison of clinical characteristics and postoperative complications between the high NRI group and low NRI group patients

In terms of clinical characteristics, the high NRI group exhibited a greater BMI, improved liver function, and a lower preoperative MELD score than did the low NRI group. In terms of prognosis, the high NRI group had a significantly lower incidence of postoperative intra-abdominal bleeding, primary graft dysfunction, and 30-d mortality than did the low NRI group ($P < 0.05$). These findings are summarized in Tables 7 and 8.

Table 2 Univariate and multivariate analyses of predictors of 30-d mortality

Variables	Univariable OR (95%CI)	*P* value	Multivariable OR (95%CI)	*P* value
Age	1.054 (0.996-1.114)	0.066		
Male	0.781 (0.204-2.999)	0.719		
BMI	0.772 (0.616-0.967)	0.024	0.720 (0.336-1.542)	0.397
Hypertension	2.418 (0.606-9.648)	0.211		
Diabetes	1.067 (0.222-5.124)	0.936		
HBsAg-positive	0.644 (0.203-2.040)	0.454		
Operation time	1.005 (1.002-1.009)	0.008	1.004 (0.996-1.011)	0.367
Anhepatic phase	1.039 (1.010-1.069)	0.091		
Donor age	1.004 (0.995-1.020)	0.475		
Total ischemia time	1.000 (0.996-1.005)	0.984		
Graft weight	1.002 (0.999-1.004)	0.253		
Split LT	0.938 (0.195-4.503)	0.936		
Blood loss	1.003 (1.001-1.004)	< 0.001	1.001 (1.000-1.002)	0.034
Intraoperative urine volume	0.999 (0.999-1.000)	0.004	0.999 (0.998-1.000)	0.295
Prealbumin	0.988 (0.977-0.999)	0.040	0.975 (0.929-1.023)	0.310
NRI	0.258 (0.082-0.811)	0.020	0.665 (0.446-0.991)	0.045
CONUT	5.756 (1.695-19.540)	0.005	2.088 (1.016-4.291)	0.045
PNI	0.160 (0.051-0.500)	0.002	0.920 (0.848-0.997)	0.042
ALB	0.798 (0.706-0.903)	< 0.001		
Lymphocyte count	0.723 (0.301-1.736)	0.468		
Alanine aminotransferase	1.002 (1.000-1.004)	0.045	1.002 (0.993-1.011)	0.639
Aspartate aminotransferase	1.001 (1.000-1.002)	0.231		
Total bilirubin	1.007 (1.003-1.012)	0.001	1.004 (0.988-1.021)	0.606
Creatinine	1.003 (0.999-1.007)	0.173		
Preoperative MELD score	1.099 (1.042-1.158)	< 0.001	1.003 (0.517-1.946)	0.994
Total cholesterol	0.694 (0.452-1.065)	0.095		
Prothrombin time	1.114 (1.042-1.191)	0.001	0.773 (0.309-1.931)	0.773
Platelet	1.002 (0.997-1.007)	0.432		

BMI: Body mass index; HBsAg: Hepatitis B surface antigen; CONUT: Control nutritional status; PNI: Prognostic nutritional index; NRI: Nutritional risk index; MELD: Model for end-stage liver disease; OR: Odds ratio; LT: Liver transplantation; ALB: Albumin.

DISCUSSION

Early posttransplant mortality is the main factor affecting the overall effectiveness of LT, with most recipients dying within 1 mo after LT. In the current situation of severe shortage of donor livers and an increasing number of patients awaiting for LT, there is an urgent need for ideal risk prediction models to evaluate posttransplantation effectiveness and further determine the patients who are most likely to benefit from LT.

The MELD score is extensively applied in clinical practice and successfully predicts the likelihood of mortality in patients awaiting LT, as well as the risk of mortality after the transplant procedure[16,17]. However, the MELD score itself has limitations, as research has shown that it does not predict perioperative outcomes well in liver cancer patients without cirrhosis[18,19]. In recent years, scholars have shown greater interest in the relationship between nutritional status and post-LT complications. The serum prealbumin concentration serves as a reliable marker of liver synthesis capacity and nutritional status, making it a useful tool for predicting long-term survival in liver cancer patients undergoing liver resection[20]. Recent research has shown that prealbumin also demonstrates significant superiority in predicting complications after LT (AUC = 0.754)[1]. The COUNT score, PNI, and NRI are commonly used inflammatory nutritional indices in clinical practice. The CONUT score is a measure of the immune-nutritional status of patients and has been

Table 3 Factors that predict a Clavien-Dindo grade ≥ 3

Variables	Univariable OR (95%CI)	*P* value	Multivariable OR (95%CI)	*P* value
Age	0.997 (0.968-1.028)	0.852		
Male	0.518 (0.222-1.212)	0.129		
BMI	0.918 (0.819-1.028)	0.138		
Hypertension	1.073 (0.359-3.210)	0.900		
Diabetes	1.044 (0.380-2.868)	0.934		
HBsAg-positive	0.813 (0.377-1.754)	0.598		
Operation time	1.004 (1.001-1.006)	0.004	1.003 (1.000-1.006)	0.078
Anhepatic phase	1.019 (0.999-1.041)	0.069		
Donor age	1.010 (0.998-1.022)	0.113		
Total ischemia time	1.001 (0.999-1.003)	0.350		
Graft Weight	1.065 (0.978-1.158)	0.146		
Split LT	1.515 (0.477-4.812)	0.582		
Blood loss	1.004 (1.002-1.005)	< 0.001	1.003 (1.001-1.005)	0.004
Intraoperative urine volume	0.998 (0.996-1.000)	0.042	0.999 (0.995-1.002)	0.382
Prealbumin	0.995 (0.990-1.001)	0.089		
NRI	0.945 (0.904-0.988)	0.013	0.942 (0.901-0.986)	0.011
CONUT	1.037 (0.984-1.094)	0.169		
PNI	0.856 (0.738-0.994)	0.041	0.994 (0.989-0.999)	0.013
ALB	0.910 (0.848-0.977)	0.009		
Lymphocyte count	1.113 (0.814-1.522)	0.502		
Alanine aminotransferase	1.002 (0.999-1.004)	0.138		
Aspartate aminotransferase	1.000 (1.000-1.001)	0.314		
Total bilirubin	1.004 (1.002-1.006)	< 0.001	1.005 (0.999-1.010)	0.079
Creatinine	1.001 (0.997-1.004)	0.685		
Preoperative MELD score	1.057 (1.020-1.097)	0.003	0.894 (0.763-1.047)	0.165
Total cholesterol	0.886 (0.721-1.088)	0.886		
Prothrombin time	1.075 (1.019-1.134)	0.009	1.075 (0.923-1.252)	0.354
Platelet	1.001 (0.998-1.005)	0.422		

BMI: Body mass index; HBsAg: Hepatitis B surface antigen; CONUT: Control nutritional status; PNI: Prognostic nutritional index; NRI: Nutritional risk index; MELD: Model for end-stage liver disease; LT: Liver transplantation; ALB: Albumin.

Table 4 Values of different preoperative objective nutritional indicators for predicting 30-d mortality

	AUC	Sensitivity	Specificity	95%CI	Optimal threshold value	*P* value
CONUT	0.724	0.58	0.80	0.646-0.794	6	0.015
NRI	0.861	0.70	0.83	0.765-0.958	88	< 0.001
PNI	0.781	0.64	0.80	0.682-0.829	38	0.001
Prealbumin	0.666	0.76	0.60	0.589-0.754	79	0.003

AUC: Area under the curve; CONUT: Control nutritional status; PNI: Prognostic nutritional index; NRI: Nutritional risk index.

Table 5 Comparisons of the area under the curve of various nutritional indicators for predicting severe complications and 30-d mortality

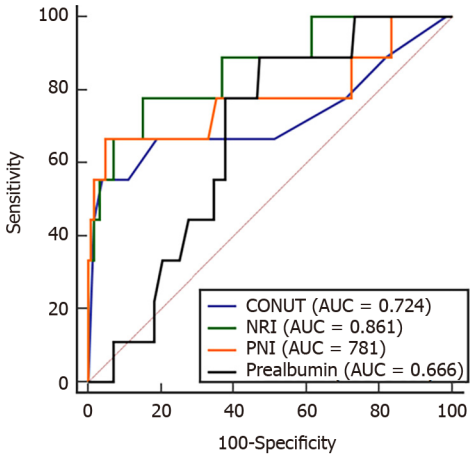
ROC	Severe complications		30-d mortality	
	Z value	*P* value	Z value	*P* value
CONUT *vs* NRI	1.851	0.064	1.550	0.121
CONUT *vs* PNI	1.945	0.051	0.832	0.405
CONUT *vs* Prealbumin	0.818	0.413	0.490	0.623
NRI *vs* PNI	0.749	0.454	1.061	0.288
NRI *vs* Prealbumin	0.582	0.560	2.337	0.019
PNI *vs* Prealbumin	0.176	0.860	1.062	0.288

CONUT: Control nutritional status; PNI: Prognostic nutritional index; NRI: Nutritional risk index; ROC: Receiver operating characteristic.

Table 6 Values of different preoperative objective nutritional indicators for predicting severe complications

	AUC	Sensitivity	Specificity	95%CI	Optimal threshold value	*P* value
CONUT	0.547	0.17	0.96	0.463-0.627	8	0.410
NRI	0.643	0.50	0.72	0.555-0.712	91	0.011
PNI	0.615	0.23	0.94	0.522-0.678	34	0.047
Prealbumin	0.603	0.63	0.61	0.533-0.695	82	0.027

AUC: Area under the curve; CONUT: Control nutritional status; PNI: Prognostic nutritional index; NRI: Nutritional risk index.



DOI: 10.4240/wjgs.v16.i1.143

Figure 1 Receiver operating characteristic curve for the cutoff values of multiple preoperative objective nutritional indicators for predicting postoperative death. CONUT: Control nutritional status; PNI: Prognostic nutritional index; NRI: Nutritional risk index; AUC: Area under the curve.

reported to independently predict the prognosis of various malignant tumors[21]. Among liver transplant patients, those with intermediate to high CONUT scores have a higher incidence of postoperative Clavien-Dindo grade III/IV complications and infections than do those with high CONUT scores[22]. The PNI has a certain role in predicting post-LT renal injury and postliver cancer recurrence[23,24]. The NRI was first introduced in 2005 as an objective nutritional assessment tool that accurately predicts the mortality rate of elderly patients in internal medicine[25]. Subsequent multicenter studies have demonstrated that patients with an NRI of 98 or lower have a 1.5-fold greater risk of postoperative complications following abdominal surgery than patients with an NRI above 98. However, to date, the relationship between the NRI and post-LT complications has not been thoroughly elucidated[26]. Therefore, we further investigated the relationship between nutritional indices and the prognosis of LT patients.

Table 7 Comparation of the clinical characteristics among different nutritional risk index groups

Characteristics	Low NRI (*n* = 30)	High NRI (*n* = 132)	*P* value
Age, yr	53.0 (44.0-56.0)	52.5 (46.0-58.0)	0.587
Male/female	26/4	107/25	0.602
BMI	21.5 (19.0-23.4)	23.3 (21.4-25.4)	0.012
Hypertension, yes/no	4/26	14/118	0.747
Diabetes, yes/no	5/25	17/115	0.563
HBsAg-positive, yes/no	21/9	97/35	0.820
Operation time (min)	540.0 (452.5-650.3)	520.0 (440.0-600.0)	0.344
Anhepatic phase (min)	58.0 (48.5-65.0)	57.0 (47.0-66.0)	0.719
Donor age, yr	46.5 (39.0-59.6)	43.0 (35.1-53.0)	0.651
Total ischemia time (min)	329.5 (271.4-395.0)	286.5(234.7-356.2)	0.323
Graft weight (kg)	1.3 (1.2-1.6)	1.5 (1.4-1.8)	0.409
Split LT/whole LT	2/28	18/114	0.373
Blood loss (mL)	2000.0 (850.0-5000.0)	1650.0 (925.0-3500.0)	0.305
Intraoperative urine volume (mL)	2600.0 (1650.0-3225.0)	2800.0 (1600.0-4000.0)	0.636
Prealbumin (mg/L)	56.0 (33.0-82.0)	109.5 (54.5-172.0)	< 0.001
NRI	83.8 (81.2-85.5)	98.8 (93.1-103.5)	< 0.001
CONUT	8.0 (7.0-9.8)	5.0 (4.0-6.0)	< 0.001
PNI	34.9 (31.7-38.9)	43.7 (40.3-47.6)	< 0.001
ALB (g/L)	29.8 (27.4-31.2)	39.0 (35.6-41.4)	< 0.001
Lymphocyte count (× 10^9/mL)	0.9 (0.5-1.6)	0.9 (0.6-1.4)	0.978
Alanine aminotransferase (U/L)	41.5 (19.8-62.5)	29.5 (19.0-45.8)	0.154
Aspartate aminotransferase (U/L)	64.5 (38.8-126.3)	42.0 (29.3-77.5)	0.008
Total bilirubin (μmol/L)	53.0 (20.4-250.4)	28.4 (14.8-87.8)	0.047
Creatinine (umol/L)	73.0 (57.0-86.3)	70.0 (59.3-85.0)	0.848
Preoperative MELD score	15.0 (11.8-24.8)	11.0 (7.3-20.8)	0.028
Total cholesterol (mmol/L)	2.7 (2.0-4.4)	3.6 (2.3-4.6)	0.050
Prothrombin time (s)	17.8 (16.2-23.4)	15.9 (14.1-20.0)	0.037
Platelet (× 10^9/mL)	63.5 (32.5-143.0)	67.5 (47.0-152.8)	0.386

BMI: Body mass index; HBsAg: Hepatitis B surface antigen; CONUT: Control nutritional status; PNI: Prognostic nutritional index; NRI: Nutritional risk index; MELD: Model for end-stage liver disease; LT: Liver transplantation; ALB: Albumin.

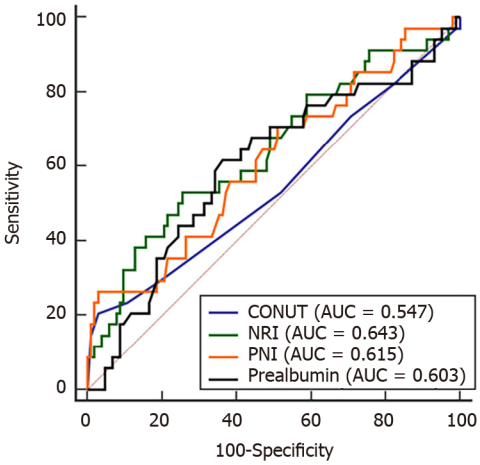
This retrospective analysis revealed that the NRI, PNI, and prealbumin have certain value for predicting 30-d mortality and severe complications in liver transplant recipients, with the NRI having the highest AUC value. The CONUT score can predict 30-d mortality in liver transplant recipients but cannot predict severe postoperative complications. In the multifactorial logistic regression analysis, blood loss, NRI, PNI, and CONUT were independent predictors of 30-d mortality, while blood loss, NRI, and PNI were independent predictors of severe postoperative complications. Based on the optimal cutoff value of the NRI, patients with an NRI > 88 had better preoperative liver function; lower rates of intra-abdominal bleeding (6.1% *vs* 20.0%, $P = 0.025$) and primary graft nonfunction (1.5% *vs* 10.0%, $P = 0.044$); and lower mortality rates (6.1% *vs* 20.0%, $P = 0.025$) than patients with an NRI < 88.

The serum prealbumin concentration has good predictive ability for 30-d mortality and severe complications after LT, consistent with previous findings[1]. The variation in AUC values may be attributed to varying definitions of severe complications. Serum prealbumin is a carrier protein entirely produced by liver cells, and its main physiological function is to transport thyroid hormones and vitamin A, enhancing the body's immune function by promoting lymphocyte maturation [27]. Moreover, due to its short half-life and small amount of interference factors, prealbumin can sensitively reflect liver synthesis function and has high sensitivity and specificity for detecting hepatocyte damage[28,29]. Therefore, the serum prealbumin concentration can be a potential indicator for predicting poor early outcomes after LT.

Table 8 Comparison of postoperative complications between the low nutritional risk index group and the high nutritional risk index group, *n* (%)

	Total (*n* = 162)	Low NRI (*n* = 30)	High NRI (*n* = 132)	*P* value
Pneumonia	37 (22.8)	8 (26.7)	29 (22.0)	0.631
Intra-abdominal infection	20 (12.3)	4 (13.3)	16 (12.1)	0.767
Intra-abdominal bleeding	14 (8.6)	6 (20.0)	8 (6.1)	0.025
Graft rejection	6 (3.7)	2 (6.7)	4 (3.0)	0.308
Primary graft nonfunction	5 (3.1)	3 (10.0)	2 (1.5)	0.044
Early graft dysfunction	4 (2.5)	0 (0.0)	4 (3.0)	1.000
Mortality	14 (8.6)	6 (20.0)	8 (6.1)	0.025
Clavien-Dindo grade ≥ 3	43 (26.5)	12 (40)	31 (23.5)	0.071
Biliary leakage	3 (1.9)	1 (3.3)	2 (1.5)	0.461
Biliary stricture	4 (2.5)	2 (6.7)	2 (1.5)	0.156

NRI: Nutritional risk index.



DOI: 10.4240/wjgs.v16.i1.143

Figure 2 Receiver operating characteristic curve for the cutoff values of multiple preoperative objective nutritional indicators for predicting severe complications. CONUT: Control nutritional status; PNI: Prognostic nutritional index; NRI: Nutritional risk index; AUC: Area under the curve.

We found that the AUC for predicting 30-d mortality was the highest for the NRI, followed by the PNI, CONUT, and prealbumin concentration. Similarly, the AUC for predicting severe complications was the highest for the NRI, followed by the PNI and prealbumin concentration. Although both the NRI and the PNI incorporate the measurement of ALB, the NRI also reflects the degree of weight loss in patients. Malnutrition is prevalent among patients with end-stage liver disease, and the incidence of malnutrition in individuals with decompensated cirrhosis and liver failure ranges from 50% to 90%[30]. Surgical intervention exacerbates liver injury, reduces ALB synthesis, impairs immune function and body repair capacity, increases the likelihood of postoperative complications, and adversely affects survival prognosis in malnourished patients. Recent studies have elucidated the association between sarcopenia and the prognosis of liver transplant recipients[22,31]. These findings indicate that diminished muscle mass is linked to unfavorable outcomes following LT and is a predictive factor for short-term survival. Furthermore, low muscle mass has an equally significant impact on the prognosis of patients with malignancies. In patients with nonmetastatic breast cancer, the overall mortality rate is significantly greater in individuals with sarcopenia (hazard ratio, 1.41; 95%CI, 1.18-1.69)[32]. Similarly, among patients diagnosed with colorectal cancer, those exhibiting sarcopenia have a notably elevated overall mortality rate (hazard ratio, 1.27; 95%CI, 1.09-1.48) compared to that of their counterparts without sarcopenia[33]. This finding suggested a strong association between wasting and unfavorable prognosis. However, the existing evidence is insufficient to establish a definitive link between lymphocyte count and nutritional status. Consequently, the predictive efficacy of the NRI surpasses that of the PNI, highlighting its potential in clinical prognostication. The CONUT score incorporates cholesterol as an indicator. Cholesterol is primarily synthesized in the liver, and its levels indirectly reflect liver synthetic function. Changes in liver function due to cellular damage can lead to alterations in cholesterol levels. Although a small-scale study suggested an association between low cholesterol levels and unsuccessful liver transplant, there is currently

insufficient evidence to support the role of cholesterol in the prognosis following LT[34]. Therefore, these findings may explain why the predictive efficacy of the CONUT score is lower than that of the NRI and PNI.

This study aimed to compare the role of multiple objective nutritional indicators in predicting the prognosis of LT patients, thereby facilitating a comprehensive preoperative nutritional assessment, early identification of malnutrition, timely and appropriate nutritional support for enhancing surgical safety, and reducing the incidence of postoperative complications. This study has several limitations, including the following: (1) The sample size was not large enough; (2) This was a retrospective analysis, and further prospective analysis is needed to clarify the predictive value of different scoring systems for post-LT outcomes; and (3) We analyzed only a portion of the nutritional indicators and did not include all nutritional indicators in our analysis. Despite these limitations, our results still demonstrate the superiority of the NRI as a nutritional indicator for predicting post-LT 30-d mortality and severe complications.

CONCLUSION

This study identified several independent risk factors associated with 30-d mortality, including blood loss, the PNI, the NRI, and the CONUT. The 30-d mortality rate was 8.6%. Blood loss, the NRI, and the PNI were found to be independent risk factors for the occurrence of severe postoperative complications. The NRI achieved the highest predictive values for 30-d mortality (AUC = 0.861, $P < 0.001$) and severe complications (AUC = 0.643, $P = 0.011$). Compared to those in the high NRI group, the patients in the low NRI group had lower preoperative BMIs; prealbumin, and ALT levels; and higher ALT, total bilirubin, MELD score, and PT ($P < 0.05$). Furthermore, the low NRI group exhibited significantly greater incidences of intraabdominal bleeding, primary graft nonfunction, and mortality. In conclusion, the NRI can serve as an effective tool for transplant surgeons to assess perioperative nutritional risk in patients and formulate relevant nutritional interventions.

ARTICLE HIGHLIGHTS

Research background

Nutritional status is closely associated with the prognosis of liver transplantation (LT) patients.

Research motivation

However, few studies have thoroughly investigated the relationship between the preoperative nutritional status of liver transplant recipients and postoperative prognosis. In clinical practice, there is a lack of a simple and effective tool for assessing the nutritional risk of patients during the perioperative period and for predicting the outcomes of LT.

Research objectives

The objective of this study was to compare the value of different preoperative objective nutritional indicators for predicting the 30-d mortality and the incidence of complications following LT.

Research methods

This study conducted a retrospective analysis of clinical data from 162 patients who underwent LT. The present study compared the ability of the serum prealbumin concentration, the controlling nutritional status (CONUT) score, the prognostic nutritional index (PNI), and the nutritional risk index (NRI) to predict the 30-d mortality rate and the incidence of severe complications after LT. This study also aimed to analyze the risk factors associated with the 30-d mortality rate and incidence of severe complications after LT. The area under the receiver operating characteristic curve was used to select the index with the best predictive ability. Patients were then divided into low-risk and high-risk groups based on the optimal cutoff value, and the differences in postoperative complications and mortality rates between the two groups were compared.

Research results

This study identified several independent risk factors associated with 30-d mortality, including blood loss, the PNI, the NRI, and the CONUT. The 30-d mortality rate was 8.6%. Blood loss, the NRI, and the PNI were found to be independent risk factors for the occurrence of severe postoperative complications. The NRI achieved the highest prediction values for 30-d mortality [area under the curve (AUC) = 0.861, $P < 0.001$] and severe complications (AUC = 0.643, $P = 0.011$). Compared to those in the high NRI group, the patients in the low NRI group had lower preoperative body mass index and prealbumin and albumin levels, as well as higher alanine aminotransferase and total bilirubin levels, Model for End-stage Liver Disease scores and prothrombin time ($P < 0.05$). Furthermore, the group with a low NRI exhibited significantly greater incidences of intraabdominal bleeding, primary graft nonfunction, and mortality.

Research conclusions

The NRI has good predictive value for 30-d mortality and severe complications following LT. The NRI could be an effective tool for transplant surgeons to evaluate the perioperative nutritional risk and provide relevant nutritional therapy.

Research perspectives

The purpose of this study was to investigate the predictive value of different objective nutritional indicators before surgery for the outcome of LT.

FOOTNOTES

Author contributions: Li C conceived the study, collected and analyzed the data and drafted the manuscript; Chen HC assisted with the data collection; Lai YH revised the manuscript; and all the authors read and approved the final version to be published.

Supported by The Self-Funded Research Project of the Health Commission of Guangxi Zhuang Autonomous Region, No. Z-A20230045.

Institutional review board statement: The study was reviewed and approved by the Ethics Committee of Guangxi Zhuang Autonomous Region People's Hospital, No. KY-ZC-2023-056.

Informed consent statement: All patients provided written informed consent for data analysis before transplantation.

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

Data sharing statement: No additional data are available.

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S-Editor: Li L
L-Editor: A
P-Editor: Li L

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World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2024 January 27; 16(1): 155-165

DOI: 10.4240/wjgs.v16.i1.155

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

Predictive value of NLR, Fib4, and APRI in the occurrence of liver failure after hepatectomy in patients with hepatocellular carcinoma

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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): 0
Grade E (Poor): 0

P-Reviewer: El-Nabarawi M, Egypt

Received: November 30, 2023
Peer-review started: November 30, 2023
First decision: December 18, 2023
Revised: December 21, 2023
Accepted: January 5, 2024
Article in press: January 5, 2024
Published online: January 27, 2024

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Abstract

BACKGROUND

Neutrophil-lymphocyte ratio (NLR), fibrosis index based on four factors (Fib4), aspartate aminotransferase-to-platelet ratio index (APRI) can be used for prognostic evaluation of hepatocellular carcinoma. However, no study has established an individualized prediction model for the prognosis of hepatocellular carcinoma based on these factors.

AIM

To screen the factors that affect the prognosis of hepatocellular carcinoma and establish a nomogram model that predicts postoperative liver failure after hepatic resection in patients with hepatocellular carcinoma.

METHODS

In total, 220 patients with hepatocellular carcinoma treated in our hospital from January 2022 to January 2023 were selected. They were divided into 154 participants in the modeling cohort, and 66 in the validation cohort. Comparative analysis of the changes in NLR, Fib4, and APRI levels in 154 patients with hepatocellular carcinoma before liver resection and at 3 mo, 6 mo, and 12 mo postoperatively was conducted. Binary logistic regression to analyze the influencing factors on the occurrence of liver failure in hepatocellular carcinoma patients, roadmap prediction modeling, and validation, patient work characteristic curves (ROCs) to evaluate the predictive efficacy of the model, calibration curves to assess the consistency, and decision curve analysis (DCA) to evaluate the model's validity were also conducted.

RESULTS

Binary logistic regression showed that Child-Pugh grading, Surgical site, NLR, Fib4, and APRI were all risk factors for liver failure after hepatic resection in patients with hepatocellular carcinoma. The modeling cohort built a column-line graph model, and the area under the ROC curve was 0.986 [95% confidence in-

terval (CI): 0.963-1.000]. The patients in the validation cohort utilized the column-line graph to predict the probability of survival in the validation cohort and plotted the ROC curve with an area under the curve of the model of 0.692 (95%CI: 0.548-0.837). The deviation of the actual outcome curves from the calibration curves of the column-line plots generated by the modeling and validation cohorts was small, and the DCA confirmed the validity.

CONCLUSION
NLR, Fib4, and APRI independently influence posthepatectomy liver failure in patients with hepatocellular carcinoma. The column-line graph prediction model exhibited strong prognostic capability, with substantial concordance between predicted and actual events.

Key Words: Hepatocellular carcinoma; Hepatic resection; Liver failure; Influencing factors; Columnar graphs

Core Tip: Postoperative liver failure in hepatocellular carcinoma is a serious complication that seriously affects the survival and quality of life of patients. Our work showed that neutrophil-lymphocyte ratio, fibrosis index based on four factors, and aspartate aminotransferase-to-platelet ratio index independently influenced the occurrence of liver failure following hepatectomy in patients with hepatocellular carcinoma. The column-line graph prediction model constructed in this study for the occurrence of liver failure after hepatectomy in patients with hepatocellular carcinoma showed good predictive ability, and the consistency between the predicted and actual events was high. This model has broad potential as a tool to prevent liver failure after hepatectomy in patients with hepatocellular carcinoma.

Citation: Kuang TZ, Xiao M, Liu YF. Predictive value of NLR, Fib4, and APRI in the occurrence of liver failure after hepatectomy in patients with hepatocellular carcinoma. *World J Gastrointest Surg* 2024; 16(1): 155-165
URL: https://www.wjgnet.com/1948-9366/full/v16/i1/155.htm
DOI: https://dx.doi.org/10.4240/wjgs.v16.i1.155

INTRODUCTION

Hepatocellular carcinoma is a common malignant tumor, and its incidence and mortality rates are increasing worldwide [1]. Hepatic resection is a primary treatment for hepatocellular carcinoma; however, postoperative liver failure is a serious complication that severely affects patient survival and quality of life[2,3]. Therefore, an accurate assessment of the risk of developing postoperative liver failure is essential to guide clinical treatment and improve patient prognosis. In recent years, inflammation and fibrosis indices have received extensive attention for prognostic assessment of patients with hepatocellular carcinoma. Neutrophil-lymphocyte ratio (NLR) is the ratio of neutrophils to lymphocytes in the blood and is usually associated with inflammatory responses, infections, tumors, and other diseases[4]. The fibrosis index based on four factors (Fib4) is used to assess the degree of liver fibrosis and is often used to evaluate patients with chronic liver disease; the higher the value, the more severe the degree of liver fibrosis[5]. The aspartate aminotransferase-to-platelet ratio index (APRI) is the ratio of aspartate transaminase (AST) to platelets (PLT) in the blood, and changes in this ratio can offer insights into the liver's state and extent of inflammation[6]. These three indices are commonly used indicators of inflammation and fibrosis and have been shown to be strongly associated with the prognosis of patients with hepatocellular carcinoma. However, few studies have investigated the predictive value of these indicators in the development of postoperative liver failure and their changes. Therefore, this study aimed to investigate the changes in the levels of NLR, Fib4, and APRI in patients with hepatocellular carcinoma after hepatic resection and to establish a corresponding prediction model to assess their predictive ability in the occurrence of postoperative liver failure. It aimed to provide clinicians with a more accurate prognostic assessment tool, enhancing the prevention and therapeutic outcomes of postoperative liver failure while improving the survival rate and quality of life of patients.

MATERIALS AND METHODS

Objects of study

A total of 220 patients with hepatocellular carcinoma who received treatment in our hospital from January 2022 to January 2023 were selected as the study objects, and were divided into a modeling cohort of 154 patients and a model validation cohort of 66 patients according to a ratio of 7:3. The model validation cohort was divided into liver failure group (n = 21) and non-liver failure group (n = 45). The study has been approved by the hospital ethics committee.

Inclusion criteria: (1) Meeting the diagnostic criteria for hepatocellular carcinoma[7]; (2) the age is above 18 years old; (3) the condition is stable and non-life threatening; (4) all patients received hepatectomy; and (5) complete clinical data.

Exclusion criteria: (1) There are other types of liver cancer; (2) complicated with heart, kidney, lung and other important organ dysfunction; (3) there is a mental system disease; (4) combined with malignant tumor; and (5) not all follow-up work was completed.

Methodology

Observation of grouping and prognosis: At the same time, according to whether the patients had liver failure after hepatectomy, the modeling group was divided into liver failure group (n = 53) and no liver failure group (n = 101). The validation cohort was divided into liver failure group (n = 21) and non-liver failure group (n = 45). The outcome was observed, and postoperative liver failure was taken as the end event. Criteria for hepatic failure: Increased international normalized ratios and associated hyperbilirubinemia on or after the 5th d after surgery.

Index observation and method: General data of patients with and without liver failure were collected through electronic medical records of our hospital: Age, gender, body mass index (BMI), smoking history, drinking history, hepatitis B, tumor diameter, cirrhosis, tumor number, Child-Pugh grade of liver function, surgical site, alpha-fetoprotein, and postoperative NLR, Fib4, APRI levels of the two groups were compared to analyze the influencing factors of liver failure in patients with hepatocellular carcinoma after hepatectomy. Build a roadmap prediction model and verify it.

Child-Pugh grading: including the assessment of general condition, ascites, bilirubin, albumin, prothrombin time, *etc.*, with 1-3 points scored and a total of 15 points, of which 5-6 points are graded as grade A, indicating the presence of a small surgical risk; 7-9 points are graded as grade B, indicating the presence of a moderate surgical risk; and ≥ 10 points are graded as grade C, indicating the presence of a large surgical risk.

To analyze the changes of NLR, Fib4 and APRI levels in patients with hepatocellular carcinoma after hepatectomy, as well as their predictive value for the occurrence of postoperative liver failure, and to establish and validate a roadmap prediction model. The formula for calculating NLR: NLR = Neutrophil count/lymphocyte count; the formula for calculating Fib4: Fib4 = (Age × AST)/(PLT × $\sqrt{\text{ALT}}$); APRI calculation formula: APRI = (AST/upper limit normal)/PLT count × 100%.

Statistical analysis

SPSS 26.0 software and R software were used to analyze the data collected in this collection, and all the collected measures were tested for normality by the Shapiro-Wilk method, with $P > 0.05$ for normally distributed data expressed as (mean ± SD) and t-test, and with $P < 0.05$ for non-normally distributed data described as median (quartiles) and Mann-Whitney U test. Collected count data were expressed as (%), χ^2 or Fisher exact test was used for data that were unordered, and Mann-Whitney U test was used for data that were ordered. Univariate and multivariate logistic regression was used to analyze the factors affecting the development of liver failure after hepatectomy in patients with hepatocellular carcinoma, to develop a predictive model for the column-line diagram, and the discriminative power of the validation set and the calibration plot were used to assess the accuracy of the column-line diagram. The area under the patient operating characteristic curve (ROC) (AUC) was used to evaluate the discriminative ability of the column-line diagram. Calibration curves for the model were calculated and the consistency of the model was verified with the Hosmer-Lemeshaw test. Decision curve analysis was also performed to evaluate the discriminative ability of the model. $P < 0.05$ was considered a statistically significant difference.

RESULTS

Baseline clinical features

A total of 220 patients with hepatocellular carcinoma were included, including 154 in the modeling cohort and 66 in the model validation cohort. The mean age of the patients was (53.11 ± 2.58) years, with 124 males (56.36%) and 96 females (43.64%). There were 86 males (55.84%) and 68 females (44.16%) in the modeling cohort. There were 38 males (57.58%) and 28 females (42.42%) in the validation cohort. The baseline data of the modeling cohort and the validation cohort were shown in Table 1. Except for differences in Child-Pugh grade, surgical site and Fib4, there were no statistically significant differences in other general data between the two groups ($P > 0.05$, Table 1).

Comparison of clinical data between the modeling cohort with liver failure and the group without liver failure

There were no significant differences in gender, age, BMI, tumor diameter, resection range and tumor number in the modeling cohort (all $P > 0.05$). There were significant differences in Child-Pugh grade, surgical site, NLR, Fib4 and APRI between the two groups, and the levels of NLR, Fib4, and APRI indexes in the liver failure group were significantly higher than those in the non-liver failure group (all $P < 0.05$, Table 2).

Logistic regression analysis of risk factors for liver failure after hepatectomy in patients with hepatocellular carcinoma

Binary logistic regression analysis with liver failure = 1 and no liver failure = 0 as dependent variables and factors with significant differences in the above univariate analyses as covariates showed that Child-Pugh classification, BCLC stage, NLR, Fib4, and APRI were all risk factors for the development of liver failure after hepatic resection in patients with hepatocellular carcinoma.

Table 1 Baseline data for modeling queues and validation queues, *n* (%) or mean ± SD

Index		Total cases (*n* = 220)	Modeling queue (*n* = 154)	Validation queue (*n* = 66)	χ^2	*P* value
Gender	Male	124 (56.36)	86 (55.84)	38 (57.58)	3.333	0.068
	Female	96 (43.64)	68 (44.16)	28 (42.42)		
Age (yr)		53.11 ± 2.58	53.03 ± 3.98	52.98 ± 3.54	0.088	0.930
BMI (kg/m^2)		21.26 ± 2.07	21.36 ± 2.36	21.28 ± 2.11	0.238	0.812
Smoking history	No	106 (48.18)	74 (48.05)	32 (48.48)	0.222	0.638
	Yes	114 (51.82)	80 (51.95)	34 (51.52)		
Drinking history	No	114 (51.82)	79 (51.30)	35 (53.03)	0.346	0.556
	Yes	106 (48.18)	75 (48.70)	31 (46.97)		
Hepatitis B	No	124 (56.36)	86 (55.84)	38 (57.58)	3.333	0.068
	Yes	96 (43.64)	68 (44.16)	28 (42.42)		
Tumor diameter	< 5 cm	121 (55.00)	85 (55.19)	36 (54.55)	1.757	0.185
	≥ 5 cm	99 (45.00)	69 (44.81)	30 (45.45)		
Liver cirrhosis	No	168 (76.36)	125 (81.47)	43 (65.15)		
	Yes	52 (23.64)	29 (18.83)	23 (34.85)	0.346	0.556
Number of tumors	< 2	114 (51.82)	79 (51.30)	35 (53.03)		
	≥ 2	106 (48.18)	75 (48.70)	31 (46.97)		
Child-Pugh classification	Grade A	111 (50.45)	90 (58.44)	21 (31.82)	26.615	0.000
	Grade B	54 (24.55)	31 (20.13)	23 (34.85)		
	Grade C	55 (25.00)	33 (21.43)	22 (33.33)		
Surgical site	Left half liver	109 (49.55)	87 (56.49)	22 (33.33)	7.312	0.007
	Right half liver	67 (30.45)	33 (21.43)	34 (51.52)	19.842	0.000
	Bilateral hemiliver	44 (20.00)	34 (22.08)	10 (15.15)		
AFP	< 400 μg/L	121 (55.00)	85 (55.19)	36 (54.55)	1.757	0.185
	≥ 400 μg/L	99 (45.00)	69 (44.81)	30 (45.45)		
NLR		5.35 ± 3.23	5.36 ± 3.25	4.49 ± 2.55	1.934	0.054
Fib4		9.76 ± 2.53	9.72 ± 2.36	7.72 ± 3.42	4.999	0.000
APRI		0.58 ± 0.21	0.54 ± 0.22	0.53 ± 0.23	0.305	0.761

AFP: Alpha-fetoprotein; BMI: Body mass index; NLR: Neutrophil-lymphocyte ratio; Fib4: Fibrosis index based on four factors; APRI: Aspartate aminotransferase-to-platelet ratio index.

The logarithm of the odds of liver failure was modeled using the following equation: Log (P) = 2.023 × Child-Pugh grading + 1.269 × surgical site + 0.505 × NLR + 0.569 × Fib4 + 5.254 × APRI - 16.266 (Table 3).

Establishment of a nomogram model for predicting liver failure in patients with hepatocellular carcinoma after hepatectomy

Five independent risk factors (Child-Pugh grade, surgical site, NLR, Fib4, and APRI) were obtained by R software to build a prediction model, and a nomogram model was established (Figure 1). After calibration of the generated nomogram (Figure 2A), the predicted event had a high consistency with the actual event. The area under the ROC curve of the nomogram prediction model was 0.692 (95%CI: 0.548-0.830) (Figure 2B). The decision analysis curve is shown in Figure 2C, where the X-axis represents the threshold probability, the Y-axis represents the net return, and the solid black line represents the net return of the prediction model using the nomogram. The curve shows a high return rate, which further confirms the effectiveness of the nomogram prediction model.

Verification of the nomogram model

Based on the clinical data of patients in the validation cohort (*n* = 66) (Table 4), the ROC curve was used for external

Table 2 Comparison of clinical data between the modeling cohort with liver failure and the group without liver failure, *n* (%) or mean ± SD

Index		Liver failure group (*n* = 53)	No liver failure group (*n* = 101)	χ^2	*P* value
Gender	Male	29 (54.72)	57 (56.44)	0.042	0.838
	Female	24 (45.28)	44 (43.56)		
Age (yr)		52.95 ± 4.20	53.11 ± 3.76	0.241	0.810
BMI (kg/m^2)		21.44 ± 2.06	21.08 ± 2.23	0.977	0.330
Smoking history	No	23 (43.40)	51 (50.50)	0.520	0.471
	Yes	30 (56.60)	50 (49.50)		
Drinking history	No	26 (49.06)	53 (52.48)	0.033	0.857
	Yes	27 (50.94)	48 (47.52)		
Hepatitis B	No	29 (54.72)	57 (56.44)	0.042	0.838
	Yes	24 (45.28)	44 (43.56)		
Tumor diameter	< 5 cm	26 (49.06)	59 (58.42)	1.231	0.267
	≥ 5 cm	27 (50.94)	42 (41.58)		
Liver cirrhosis	No	40 (75.47)	85 (84.16)	0.768	0.381
	Yes	13 (24.53)	16 (15.84)		
Number of tumors	< 2	26 (49.06)	53 (52.48)	0.033	0.857
	≥ 2	27 (50.94)	48 (47.52)		
Child-Pugh classification	Grade A	4 (7.55)	86 (85.15)	102.766	0.000
	Grade B	16 (30.19)	15 (14.85)		
	Grade C	33 (62.26)	0 (0.00)		
Surgical site	Left half liver	4 (7.55)	83 (82.18)	88.726	0.000
	Right half liver	18 (33.96)	15 (14.85)		
	Bilateral hemiliver	31 (58.49)	3 (2.97)		
AFP	< 400 μg/L	26 (49.06)	59 (58.42)	1.231	0.267
	≥ 400 μg/L	27 (50.94)	42 (41.58)		
NLR		8.31 ± 2.52	3.22 ± 1.57	15.406	0.000
Fib4		12.41 ± 4.59	6.45 ± 1.73	11.600	0.000
APRI		0.79 ± 0.25	0.32 ± 0.19	13.044	0.000

AFP: Alpha-fetoprotein; BMI: Body mass index; NLR: Neutrophil-lymphocyte ratio; Fib4: Fibrosis index based on four factors; APRI: Aspartate aminotransferase-to-platelet ratio index.

validation of the ATC risk nomogram, and the results showed that the lower product of the ROC curve was 0.692 (95%CI: 0.548-0.837) (Figure 3A). The slope of the calibration curve of the generated nomogram was close to 1 (Figure 3B), and the result of Hosmer-Lemeshow test was χ^2 = 1.784, P = 0.987. The decision curve shows that the model has a higher net benefit (Figure 3C), suggesting that the nomogram model has better calibration ability in the validation group.

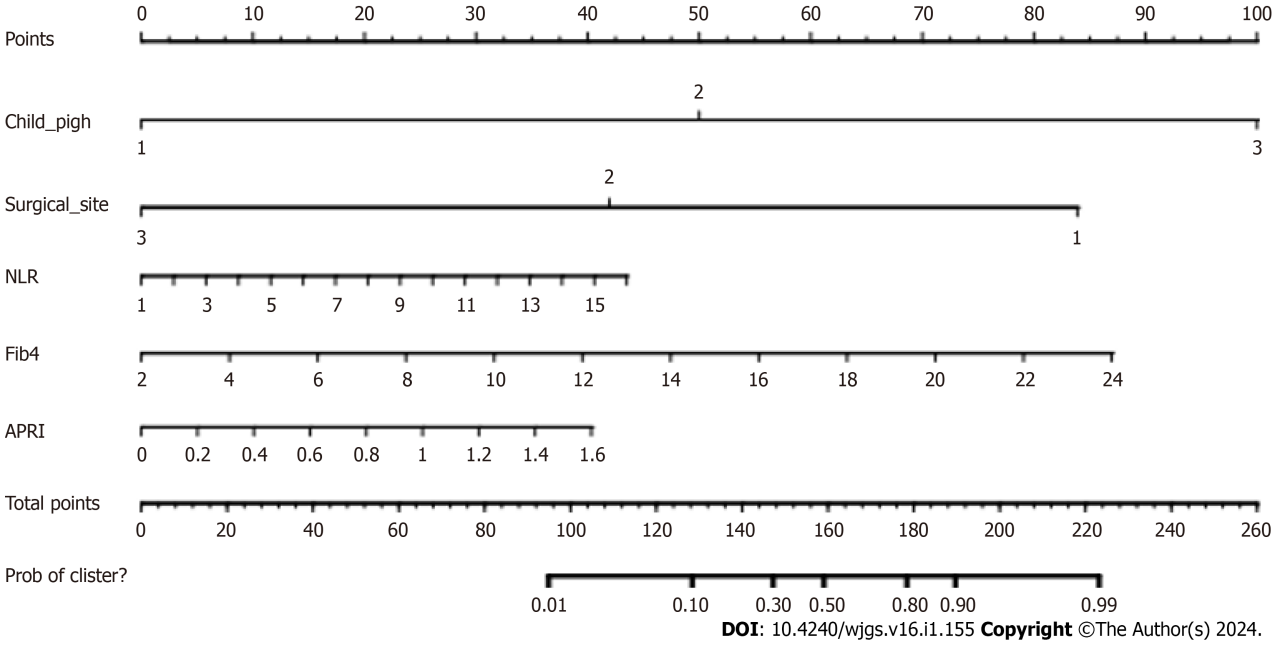
DISCUSSION

In recent years, the safety of hepatic resection has been greatly improved and the perioperative morbidity and mortality rates have been reduced by about 15% with the continuous development of surgical techniques, the widespread use of relevant instruments, and the continuous advancement of intensive care techniques[8]. Liver failure after hepatic resection is a progressive multi-organ failure that occurs in about 10% of patients undergoing major liver surgery and includes mild hepatic impairment (characterized by transient hyperbilirubinemia) and severe hepatic impairment (resulting in multi-systemic insufficiency requiring invasive treatment in the intensive care unit)[9]. As liver function declines, patients experience persistent hyperbilirubinemia and coagulation disorders, which seriously affect their postoperative

Table 3 Logistic regression analysis of risk factors for liver failure after hepatectomy in patients with hepatocellular carcinoma

	B	SE	Wals	*P* value	OR	OR, 95%CI
Child-Pugh classification	2.023	0.942	4.610	0.032	7.559	1.193-47.901
Surgical site	1.269	0.638	3.960	0.047	3.557	1.019-12.416
NLR	0.505	0.211	5.761	0.016	1.658	1.097-2.505
Fib4	0.569	0.283	4.033	0.045	1.766	1.014-3.076
APRI	5.254	2.425	4.694	0.030	191.283	1.650-22174.958
Constant	-16.266	3.824	18.094	0.000	0.000	-

OR: Odd ratio; 95%CI: 95% confidence interval; NLR: Neutrophil-lymphocyte ratio; Fib4: Fibrosis index based on four factors; APRI: Aspartate aminotransferase-to-platelet ratio index.



DOI: 10.4240/wjgs.v16.i1.155

Figure 1 Column line diagram.

prognosis. Based on this, this study focuses on analyzing the factors influencing the occurrence of liver failure after hepatic resection in patients with hepatocellular carcinoma and establishing a column-line graph prediction model.

In this study, patients were divided into modeling cohort and validation cohort, and clinical data of patients were compared. In the modeling cohort, 53 patients (21.90%) with liver failure and 101 patients (78.10%) without liver failure were found, indicating that the prognosis of patients after comprehensive hepatectomy was better. At the same time, by comparing the clinical data of the two groups of subjects in the modeling cohort, it was found that there were significant differences in Child-Pugh grade, surgical site, NLR, Fib4, and APRI between the two groups. Among them, the levels of NLR, Fib4, and APRI indexes in the liver failure group were significantly higher than those in the non-liver failure group, while there were no significant differences in other indexes. Binary logistic regression analysis with liver failure = 1 and no liver failure = 0 as dependent variables and the factors with significant differences in the above univariate analyses as covariates showed that Child-Pugh grading, BCLC staging, NLR, Fib4, and APRI were risk factors for liver failure after hepatic resection in patients with hepatocellular carcinoma. Child-Pugh grading was mainly based on the following five indicators to assess liver function: Total bilirubin level, serum albumin level, prothrombin time, and the presence or absence of ascites and encephalopathy. Higher Child-Pugh grades (B and C) mean poorer liver function and more damage to liver cells, which can result in the liver not being able to perform its functions properly, including synthesizing proteins, detoxifying and metabolizing medications, making the liver unable to efficiently deal with toxins and wastes produced by the body and increasing the risk of liver failure[10]. At the same time, hepatectomy can result in partial removal or damage to the liver, which can affect the function of the liver. The liver has a very important physiological function in the human body, including metabolism, detoxification, synthesis of important proteins, *etc*., so even partial resection may have a certain impact on the body. In addition, after hepatectomy, the remaining liver tissue needs to undertake more functions to maintain normal physiological activities, and if the surgical site is removed too far, the remaining liver tissue may not be able to meet the needs of the body, resulting in an increased risk of liver dysfunction

Table 4 Comparison of clinical data between the validation cohort with liver failure and the cohort without liver failure, *n* (%) or mean ± SD

Index		Liver failure group (*n* = 21)	No liver failure group (*n* = 45)	χ^2	*P* value
Gender	Male	11 (52.38)	27 (60.00)	0.891	0.345
	Female	10 (47.62)	18 (40.00)		
Age (yr)		52.84 ± 2.54	52.76 ± 2.19	0.131	0.896
BMI (kg/m^2)		21.33 ± 2.08	21.29 ± 2.25	0.069	0.945
Smoking history	No	12 (57.14)	20 (44.44)	0.015	0.904
	Yes	9 (42.86)	25 (55.56)		
Drinking history	No	11 (52.38)	24 (53.33)	0.187	0.665
	Yes	10 (47.62)	21 (46.67)		
Hepatitis B	No	11 (52.38)	27 (60.00)	0.891	0.345
	Yes	10 (47.62)	18 (40.00)		
Tumor diameter	< 5 cm	15 (71.43)	21 (46.67)	1.939	0.164
	≥ 5 cm	6 (28.57)	24 (53.33)		
Liver cirrhosis	No	13 (61.90)	30 (66.67)	4.785	0.029
	Yes	8 (38.10)	15 (33.33)		
Number of tumors	< 2	11 (52.38)	24 (53.33)	0.187	0.665
	≥ 2	10 (47.62)	21 (46.67)		
Child-Pugh classification	Grade A	3 (14.29)	18 (40.00)	4.381	0.112
	Grade B	9 (42.86)	14 (31.11)		
	Grade C	9 (42.86)	13 (28.89)		
Surgical site	Left half liver	5 (23.81)	17 (37.78)	25.414	0.000
	Right half liver	6 (28.57)	28 (62.22)		
	Bilateral hemiliver	10 (47.62)	0 (0.00)		
AFP	< 400 μg/L	15 (71.43)	21 (46.67)	1.939	0.164
	≥ 400 μg/L	6 (28.57)	24 (53.33)		
NLR		6.97 ± 3.41	3.33 ± 0.09	7.220	0.000
Fib4		10.54 ± 4.12	6.41 ± 1.99	5.516	0.000
APRI		0.75 ± 0.21	0.43 ± 0.15	7.080	0.000

AFP: Alpha-fetoprotein; BMI: Body mass index; NLR: Neutrophil-lymphocyte ratio; Fib4: Fibrosis index based on four factors; APRI: Aspartate aminotransferase-to-platelet ratio index.

and even liver failure[11]. Neutrophil count reflects the pro-inflammatory state of the body and lymphocyte count reflects the immune state of the body, NLR is the ratio of these two values, a high NLR value implies an increased inflammatory response and immune dysfunction which further promotes liver injury, thus greatly increasing the risk of liver failure after surgery[12]. In addition, patients with liver failure have a dysregulated immune system, which is characterized by systemic inflammation and immune paralysis, leading to bacterial infections[13]. As a result, neutrophils and lymphocytes in the blood of patients with liver failure are generally at a high level, which proves that a high level of NLR is closely related to the development of liver failure, and can be used as a predictive indicator for the development of liver failure. The results suggest that high levels of NLR are closely related to the development of liver failure, and may be used as a predictive indicator of liver failure.

Recently, there has been increasing evidence of the utility of non-invasive liver fibrosis-related markers, such as the Fib4 index[14] with APRI[15]. A study observed the value of Fib4 in the prognosis of patients with hepatic failure, and it was noted in the study that patients with hepatic failure tend to have underlying chronic liver disease and cirrhosis, and that Fib4 can, to a certain extent, reflect the level of liver fibrosis in them[16]. Fib4 is an important indicator for non-invasive and objective evaluation of liver fibrosis and cirrhosis, and its role in liver fibrosis and cirrhosis is even greater, and the degree of fibrosis is positively correlated with the Fib4 value[17]. The same result was also obtained in the study by Zhang *et al*[18] and is similar to the results of the study in this paper. In addition, APRI also affects the occurrence of

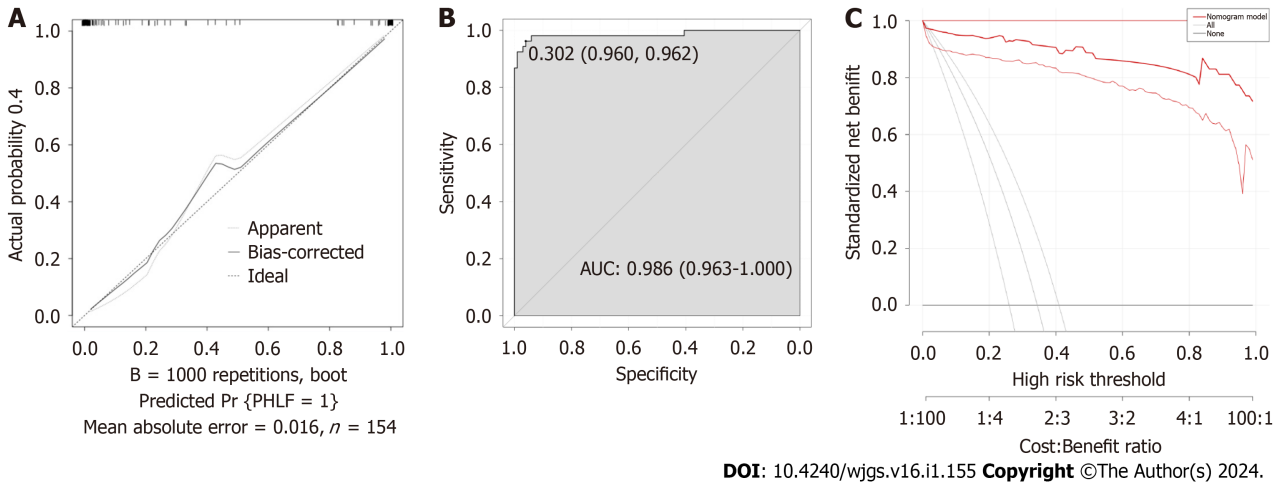


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Figure 2 Modeling queue. A: Modeling queue calibration curves; B: Modeling queue patient work characteristic curve; C: Modeling queue decision analysis curve.

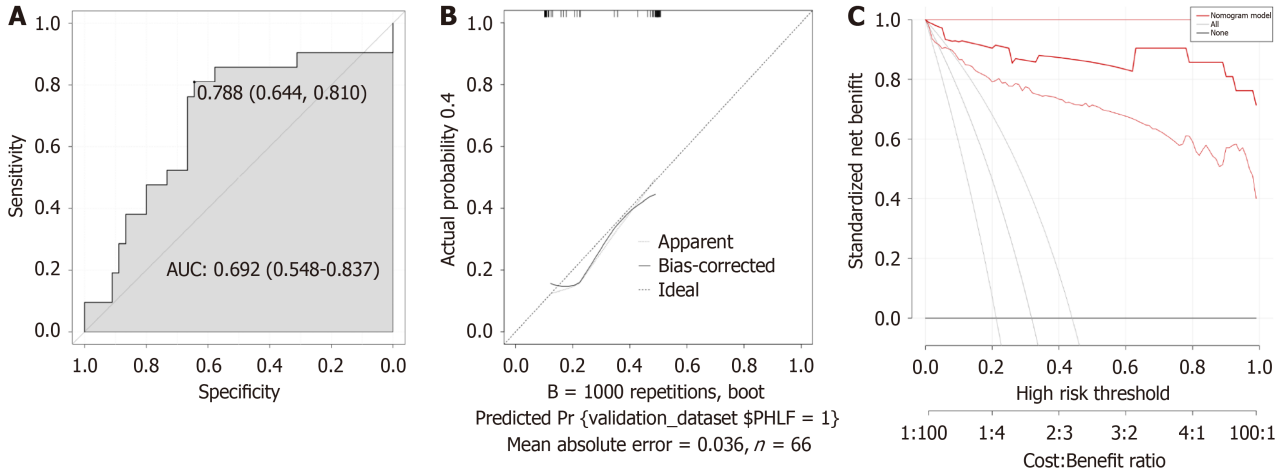

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Figure 3 Verification queue. A: Verification queue patient work characteristic curves curve; B: Verification queue calibration curve; C: Verification queue decision analysis curve.

postoperative liver failure in hepatocellular carcinoma patients undergoing hepatic resection to some extent. Yugawa *et al* [19] showed that APRI was the best independent predictor of liver failure after severe hepatic resection in patients with hepatocellular carcinoma, which was similar to the findings of the present study. Although the Child-Pugh score has long been the most commonly used tool for evaluating liver function in the clinic, the Child-Pugh score relies mainly on the observation and judgment of the patient's symptoms and signs, resulting in possible subjective differences, and can only provide a general risk assessment and cannot accurately predict the occurrence of liver failure. There is a significant correlation between APRI and the degree of fibrosis and hepatic impairment in hepatic histopathology. Among the APRIs, the PLT count is an important factor representing hepatic fibrosis, and a low PLT level has been associated with advanced hepatic fibrosis and liver cirrhosis[20]. In addition, serum AST has a high sensitivity to reflect the presence of liver fibrosis or cirrhosis. Therefore, APRI is more accurate in predicting liver failure after hepatectomy.

In order to clarify the predictive value of NLR, Fib4, and APRI in the occurrence of liver failure after hepatic resection in patients with hepatocellular carcinoma, the present study used the modeling cohort to establish a column-line diagram model, the area under the ROC curve of the column-line diagram prediction model was larger, and the predictive efficacy was better, and the subjects in the validation cohort predicted the probability of the occurrence of liver failure in the validation group by the column-line diagram of , suggesting that has a certain predictive value. In addition, the factors of the model are all patients' medical record data, which are easier to obtain and have higher clinical adaptability. In addition, as can be seen from the validation cohort calibration curve graph, the deviation between the actual outcome curve and the calibration curve is small, indicating that the consistency between the predicted events and the actual events is high. As can be seen from the validation cohort decision analysis curve, the decision analysis curve is located in the upper right corner usually indicates that the model has a high true positive rate and a low false positive rate, which means that this model has a certain degree of accuracy and reliability.

CONCLUSION

In summary, NLR, Fib4, and APRI are all independent influences on the occurrence of liver failure after hepatectomy in patients with hepatocellular carcinoma. The column-line graph prediction model constructed in this study for the occurrence of liver failure after hepatectomy in patients with hepatocellular carcinoma showed good predictive ability, and the consistency between the predicted events and the actual events was high. The model has a broad potential as a tool to prevent the occurrence of liver failure after hepatectomy in patients with hepatocellular carcinoma. As this study is a retrospective analysis with limited clinical data of subjects, the selection of indicators may not be comprehensive enough. At the same time, there are initial differences in the modeling and verification of groups of patients, which may lead to differences in research results. Therefore, a large sample size and multi-indicator analysis can be conducted in the future to establish a more comprehensive prediction model.

ARTICLE HIGHLIGHTS

Research background

Hepatectomy is a common surgical procedure for hepatocellular carcinoma, but liver failure can occur after surgery, which is a serious complication that can be life-threatening to some extent. Therefore, predicting the occurrence of liver failure is very important for postoperative management and patient care. Neutrophil-lymphocyte ratio (NLR), fibrosis index based on four factors (Fib4), aspartate aminotransferase-to-platelet ratio index (APRI) are indicators derived from a simple blood test that reflect liver function and degree of fibrosis. By analyzing the relationship between these indicators and the occurrence of liver failure, we can evaluate their potential value in predicting liver failure and provide a basis for clinical practice.

Research motivation

Hepatectomy is an important treatment for hepatocellular carcinoma, but the occurrence of postoperative liver failure may bring serious complications and risks to patients. Abnormal expressions of NLR, Fib4, and APRI are common in patients with liver failure. However, there are few studies on the predictive value and changes of these indicators in the occurrence of postoperative liver failure.

Research objectives

To analyze the expression differences of NLR, Fib4, and APRI in hepatocellular carcinoma patients with liver failure after hepatectomy and their predictive value in postoperative liver failure, and establish and verify their nomogram prediction models.

Research methods

A total of 220 patients with hepatocellular carcinoma who received treatment in our hospital from January 2022 to January 2023 were retrospectively selected as research objects, and were divided into a modeling cohort of 154 patients and a model validation cohort of 66 patients according to a ratio of 7:3. At the same time, according to whether the patients developed liver failure after hepatectomy, The model group was divided into liver failure group (n = 53 cases) and no liver failure group (n = 101 cases). The model validation cohort was divided into a group with liver failure (n = 21 cases) and a group without liver failure (n = 45 cases). By comparing the general data of patients, binary logistic regression analysis was conducted to analyze the factors affecting the occurrence of liver failure in patients with hepatocellular carcinoma after hepatectomy, the road map prediction model was established and verified, the predictive efficacy of the model was evaluated by patient operating characteristic curve (ROC), the consistency of predicted events with actual events was evaluated by calibration curve, and the effectiveness of the model was evaluated by decision curve analysis.

Research results

Child-Pugh grade, surgical site, NLR, Fib4, and APRI were all risk factors for liver failure in patients with hepatocellular carcinoma after hepatectomy. In addition, in this study, the deviation between the actual result curve and the calibration curve of the nomogram generated by the modeling queue and the verification queue is small, and the consistency between the predicted event and the actual event is high. The validity of the nomogram prediction model is further confirmed in the decision analysis curve of modeling queue and verifying queue prediction model.

Research conclusions

NLR, Fib4, and APRI were all independent factors influencing the occurrence of liver failure in hepatocellular carcinoma patients after hepatectomy, and the further constructed nomogram prediction model of liver failure in hepatocellular carcinoma patients after hepatectomy showed good prediction ability, with high consistency between predicted events and actual events. This model has broad potential as a tool to prevent liver failure in patients with hepatocellular carcinoma after hepatectomy.

Research perspectives

This study is a retrospective analysis with limited clinical data of subjects, and the selection of indicators may not be comprehensive enough. At the same time, there are initial differences in the modeling and validation of groups of patients, which may lead to differences in study results. Therefore, more clinical indicators need to be added for further comprehensive evaluation and a more comprehensive prediction model needs to be established.

FOOTNOTES

Author contributions: Kuang TZ contributed to investigation, software, data curation, formal analysis, and writing-original draft; Xiao M contributed to methodology, supervision, and validation; Liu YF contributed to conceptualization, resources, writing-review, and editing.

Institutional review board statement: The study was reviewed and approved by the Medical Ethics Committee of Ji'an Central People's Hospital. Institutional Review Board (Approval No. 2021-L121201).

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 conflicts of interest to declare.

Data sharing statement: No additional data are available.

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S-Editor: Chen YL
L-Editor: A
P-Editor: Xu ZH

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World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2024 January 27; 16(1): 166-172

DOI: 10.4240/wjgs.v16.i1.166

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

Practical effect of different teaching modes in teaching gastrointestinal surgery nursing

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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): 0
Grade E (Poor): 0

P-Reviewer: Ameli Mojarad M, Iran

Received: December 5, 2023
Peer-review started: December 5, 2023
First decision: December 8, 2023
Revised: December 11, 2023
Accepted: December 20, 2023
Article in press: December 20, 2023
Published online: January 27, 2024

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Abstract

BACKGROUND

With the continuous development and progress of medical technology, the position of surgical nursing in the field of clinical medicine is becoming increasingly prominent. As an important branch of the surgical field, the nursing requirements and difficulty of gastrointestinal surgery are also increasing. In order to improve the teaching quality of nursing care in gastrointestinal surgery, many educators and researchers are actively exploring new teaching methods. Among them, the teaching method case-based learning (CBL), scene-simulated learning (SSL), task-based learning (TBL), combining self-evaluation and training mode is considered as an effective method. This method aims to help students to better master knowledge and skills and improve their comprehensive quality by cultivating their self-evaluation ability.

AIM

To explore the practical effect of CBL-SSL-TBL combined with training mode and student self-assessment in nursing teaching of gastrointestinal surgery.

METHODS

Seventy-one nursing interns in our hospital from December 2020 to December 2021 were selected. According to different teaching modes, they were divided into observation group CBL-SSL-TBL combined with training mode combined with student self-assessment and control group (conventional teaching mode), of which 36 were in observation group and 35 were in control group. The results of operational skills, theoretical knowledge, nursing students' satisfaction, learning effectiveness questionnaire and teaching effect were compared between the two groups.

RESULTS

Compared between the two groups, the operational skills and theoretical knowledge scores of the observation group were higher than those of the control

group, and the difference was statistically significant ($P < 0.05$). Compared between the two groups, the total satisfaction ratio of the observation group was higher than that of the control group, the difference was statistically significant ($P < 0.05$). Compared between the two groups, the observation group was lower than the control group in the questionnaire results of learning efficacy, and the difference was statistically significant ($P < 0.05$). Compared between the two groups, the proportion of thinking ability, subjective initiative and understanding of theoretical knowledge in the observation group was higher than that in the control group, the difference was statistically significant ($P < 0.05$).

CONCLUSION

The use of CBL-SSL-TBL combined with training mode and student self-assessment in gastrointestinal surgery nursing teaching can improve the operational skills of nursing interns, theoretical knowledge and satisfaction scores of nursing students, improve the results of learning efficiency questionnaire and teaching effect, which can be popularized in clinical teaching.

Key Words: Gastrointestinal surgery; Nursing teaching; Teaching model; Practical effect; Learning ability

Core Tip: Clinical practice is the only way for nursing students to combine theory with practice as a qualified nurse. It is also a key period for cultivating nursing interns to develop communication, communication, cognition, emotion and skills. Case-based learning (CBL), scene-simulated learning (SSL), task-based learning (TBL) combines the training mode and the students' self-evaluation teaching mode, which enriches the operation process, takes cases as the guide, and guides nursing interns to self-study and discuss with clinical problems. This teaching mode not only improves the thinking ability of nursing interns, but also improves their self-learning ability and subjective initiative. To this end, this paper discusses the practical effect of CBL-SSL-TBL combined with training mode and students' self-evaluation in teaching gastrointestinal surgical nursing.

Citation: Rong XJ, Ning Z. Practical effect of different teaching modes in teaching gastrointestinal surgery nursing. *World J Gastrointest Surg* 2024; 16(1): 166-172
URL: https://www.wjgnet.com/1948-9366/full/v16/i1/166.htm
DOI: https://dx.doi.org/10.4240/wjgs.v16.i1.166

INTRODUCTION

Clinical practice is the only way for nursing students to combine theory with practice as a qualified nurse. It is also a key period for cultivating nursing interns to develop communication, communication, cognition, emotion and skills[1,2]. However, due to the complexity of medical work and the patients' requirements for safe medical services, there are few opportunities for nursing interns to directly practice operations, and they will also be greatly limited. Especially in the process of emergency disposal of gastrointestinal surgery patients, nursing interns often do not have enough practice opportunities, which affects their learning effect and self-confidence[3,4]. As usual using conventional teaching mode of training for them, but the conventional teaching through lectures, computer teaching, and "cramming" knowledge instill nursing interns lack of gastrointestinal surgery disease nursing knowledge and easy to produce simple fragment memory, ignore the students' enthusiasm, subjective initiative and their own fear of gastrointestinal surgery skills operation cognitive, lead to nursing interns skills and theory appraisal is often not the ideal[5,6]. Case-based learning (CBL), scene-simulated learning (SSL), task-based learning (TBL) combines the training mode and the students' self-evaluation teaching mode, which enriches the operation process, takes cases as the guide, and guides nursing interns to self-study and discuss with clinical problems. This teaching mode not only improves the thinking ability of nursing interns, but also improves their self-learning ability and subjective initiative[7,8]. To this end, this paper discusses the practical effect of CBL-SSL-TBL combined with training mode and students' self-evaluation in teaching gastrointestinal surgical nursing.

MATERIALS AND METHODS

General information

Seventy-one nursing interns practicing in our hospital from December 2020 to December 2021 were selected, according to different teaching modes, were divided as observation group (CBL-SSL-TBL combined with self-evaluation) and control group (conventional teaching mode), among which 36 cases were in the observation group and 35 cases were in the control group. In the observation group, 15 males and 21 females, 18-23 years, mean (20.33 ± 0.23); in the control group, 13

males, 22 females, 18-23 years, mean (20.45 ± 0.31); the two experimental data were comparable ($P > 0.05$).

Inclusion criteria: (1) The experimental data and related data are complete; (2) All nursing interns included in this study are undergraduates; and (3) Researchers who have participated in the whole project; exclusion criteria: (1) Unable to participate in the whole process; and (2) Those who withdraw from the research project. All interns volunteered to practice in the gastrointestinal surgery department of the hospital and gave informed consent to the research project.

Methods

The control group was taught in the conventional mode: Conventional mode teaching is mainly divided into "belt, pass, help", by the nursing teacher of gastrointestinal surgery disease characteristics, diagnosis and treatment method, case data analysis, at the same time with stomach cancer patients nursing teaching, and then their operation demonstration, let the students see, then let the students do, finally correct the problems in students' practice, and knowledge summary.

The observation group adopted CBL-SSL-TBL combined with training mode to combine students' self-assessment: CBL-SSL-TBL combined training mode joint students self-evaluation: (1) With the teacher using multimedia case data, case data with controls, 1 d before inform the basic case data of nursing interns and the main content of the next day of the ward round, the day round by the intern group of cases, when the patients have corresponding complications, nurses should how to deal with? What consequences may patients have? And formulate relevant treatment plans; (2) In the hospital skills training center, each group of students will perform necessary skills such as cardiopulmonary resuscitation, endotracheal intubation, oxygen inhalation, sputum aspiration and intravenous infusion according to the plan formulated by their own, and complete the treatment by using defibrillator, monitor and other equipment. The patient's recovery team is treated successfully, otherwise it fails; and (3) Finally, the indications, contraindications and operation points of relevant skills and operation are explained, and the nursing teacher will make corrections and comments[9].

Observed indicators

Comparison of two groups of general data, including age, comprehensive scores in school, *etc.*

Compare the post-teaching operation skills between the two groups. Operation skills: After the teaching, the teacher set up the simulated cases. The interns collected the medical history, physical examination, preliminary disease diagnosis and treatment plan in the simulated scenario, and completed the operation specified by the teacher, including the use of electrocardiogram machine and the interpretation of the results. Score is scored strictly according to the scoring criteria, with a total score of 100 points[10].

Compare the theoretical knowledge results of the two groups after teaching. Theoretical knowledge score: After the teaching, the teacher will give the questions based on the teaching content, which are divided into two parts: Basic knowledge and case analysis. The total score of the two parts is 100 points. After all the interns, the test papers will be sealed and the papers will be marked uniformly[11].

Compare the satisfaction between the two groups. Satisfaction questionnaire statistics, the full score of 100 points. Satisfied with: 90-100 points; more satisfied with: 60-89 points; dissatisfied with: 59 points or less. Total satisfaction rate = (satisfied + relatively satisfied)/100% of total nursing students. The reliability coefficient was 0.898 and the validity coefficient was 0.854, which met the study requirements[12].

Compare the results of the post-teaching learning efficacy questionnaire between the two groups. There were 4 questions in the questionnaire, including 5 points for "very agree" and 5 points for "very disagree". The lower the score, the higher the learning efficiency. The questionnaire was tested for letter and validity, and the reliability coefficient was 0.898 and the validity coefficient was 0.854, which met the study requirements. Using the classroom recovery mode, the questionnaire recovery rate was 100%[13].

Compare the teaching effect between the two groups. The teaching effect includes the thinking ability, the subjective initiative and the understanding of the theoretical knowledge in detail.

Statistical methods

Analysis by SPSS20.0 software, measurement data described in (± SD), two *t*-test; count data expressed in (%) and χ^2 test; $P < 0.05$ was considered as significant.

RESULTS

General information

Compared with the age and comprehensive school score of the experimental group and the control group, the difference was not statistically significant ($P > 0.05$; Table 1).

Operation skills

In comparison between the two groups, the observation group was higher than the control group, and the difference was statistically significant ($P < 0.05$; Table 2).

Theoretical knowledge achievement

In comparison between the two groups, the theoretical knowledge score of the observation group was higher than that of the control group, and the difference was statistically significant ($P < 0.05$; Table 3).

Table 1 Compares the two groups of general data (mean ± SD)

Group	*n*	Age	Comprehensive results at school
The observation group	36	20.33 ± 0.23	81.20 ± 0.29
The control group	35	20.45 ± 0.31	81.22 ± 0.31
t	-	1.855	0.280
P value	-	0.067	0.779

Table 2 Comparison of post-teaching operational skills (mean ± SD between the two groups)

Group	*n*	Operation skills (points)
The observation group	36	95.17 ± 1.32
The control group	35	87.46 ± 3.32
t	-	12.924
P value	-	< 0.001

Table 3 Compares the post-teaching theoretical knowledge scores between the two groups (mean ± SD)

Group	*n*	Theoretical knowledge (points)
The observation group	36	93.24 ± 0.69
The control group	35	88.97 ± 4.88
t	-	5.197
P value	-	< 0.001

Nursing student satisfaction

In comparison between the two groups, the proportion of total satisfaction in the observation group was higher than that in the control group, and the difference was statistically significant ($P < 0.05$; Table 4).

Results of the learning efficacy questionnaire survey

In the comparison between the two groups, the results of the observation group were low ($P < 0.05$; Table 5).

Teaching effect

By comparison between the two groups, the proportion of the number of thinking ability, subjective initiative and theoretical knowledge in the observation group was higher than that of the control group, and the difference was statistically significant ($P < 0.05$; Table 6).

DISCUSSION

Clinical practice is a process that every medical student must go through before becoming a real doctor or nurse. When encountering problems during the internship, it is more important to answer questions than simple knowledge memory and to master how to solve them[13,14]. For nursing interns, it is extremely difficult to master the knowledge content. This requires the key training of interns' professional knowledge, skills operation, thinking logic and other abilities in the process of teaching teachers[15].

Conventional teaching mode is usually used in gastrointestinal surgery nursing intern teaching work, but the study found that the teaching mode is the knowledge, simple teacher centered, related disease knowledge, it's not interns become active, and professional theoretical knowledge to clinical practical ability transformation process is slow, makes the teaching theoretical knowledge and skills evaluation results often reach the ideal[16,17]. However, a large number of foreign studies show that CBL-SSL-TBL combined with training mode and students' self-assessment to take nursing interns as the main body, which stimulates their desire for independent exploration and learning, and greatly improves the final assessment results[18,19]. However, the results of this paper show that in the comparison between the two groups, the operation skills and theoretical knowledge scores of the observation group were higher than that of the control group, and the difference had statistical significance ($P < 0.05$). Results are consistent with the appeal argument, shows that CBL-SSL-TBL combined with training mode joint students self-evaluation can improve nursing interns

Table 4 Compares the satisfaction of two post-teaching nursing students, *n* (%)

Group	*n*	Very satisfied	More satisfied	Discontent	Total satisfaction
The observation group	36	31 (86.11)	4 (11.11)	1 (2.77)	35 (97.22)
The control group	35	8 (22.85)	19 (54.28)	8 (22.85)	27 (77.14)
t	-	-	-	-	6.463
P value	-	-	-	-	0.011

Table 5 Results of the learning effectiveness questionnaire (mean ± SD)

Group	*n*	Contribute to knowledge understanding	Dare to share your personal opinions	Trust on your ability to deal with patients	Understand the responsibilities and obligations of nurses
The observation group	36	1.33 ± 0.23	1.88 ± 0.28	1.46 ± 0.83	1.03 ± 0.67
The control group	35	2.33 ± 0.73	2.45 ± 0.83	3.33 ± 0.23	2.95 ± 0.33
t	-	7.830	3.899	12.855	15.248
P value	-	< 0.001	< 0.001	< 0.001	< 0.001

Table 6 Compares the post-teaching effects between the two groups, *n* (%)

Group	*n*	Ability of thinking	Subjective initiative	Understanding of the theoretical knowledge
The observation group	36	34 (94.44)	34 (94.44)	35 (97.22)
The control group	35	23 (65.71)	26 (74.28)	25 (71.42)
χ^2	-	9.253	5.508	9.018
P value	-	0.002	0.018	0.002

operation skills and theoretical knowledge, analysis the reason, CBL-SSL-TBL combined with training mode joint students self-evaluation will ask students to cases in advance, and through the scenario simulation based on the real cases, immersive as the core training students' practical ability, integrate the relevant important basic knowledge, at the same time by discussion with other interns, teachers after correction, makes the basic knowledge to deepen fusion, so as to improve the theoretical knowledge and operational skills[20,21].

At the same time, it is reported that CBL-SSL-TBL combined with training mode and students' self-evaluation have been highly recognized by students in gastrointestinal surgery nursing teaching[22,23]. However, the results of this paper show that in the comparison between the two groups, the proportion of total satisfaction in the observation group was higher than that of the control group, and the difference was statistically significant ($P < 0.05$). The results are similar to the above study results, indicating that CBL-SSL-TBL combined with training mode and self-assessment can improve the satisfaction of nursing students. A large number of foreign studies have proved that CBL-SSL-TBL combined with training mode and students' self-evaluation in nursing teaching, which greatly improves the learning effectiveness of nursing interns and improves the teaching effect[24]. As the results of this paper show, Comparison between the two different groups, The result scores of the learning efficacy questionnaire of the observation group were lower than that of the control group, The difference has statistical significance ($P < 0.05$), And the comparison between the two groups, The proportion of thinking ability, subjective initiative, and theoretical knowledge in the observation group was higher than that of the control group, The difference was statistically significant ($P < 0.05$), It shows that CBL-SSL-TBL combined with training mode and students 'self-evaluation can improve nursing, interns' learning effectiveness questionnaire results and teaching effect, Analyzing the reason, CBL-SSL-TBL combined with the training mode and students' self-evaluation mainly through the six steps of "teaching content selection-question raising-data collection-clinical access problem case-scenario simulation-summary" to stimulate the learning motivation of nursing interns, To it from passive to active learning, Indirectly improve the subjective initiative and improve the thinking ability. CBL-SSL-TBL combining training mode and student self-evaluation has certain advantages in the teaching of gastrointestinal surgery nursing, but it also has some limitations. The CBL-SSL-TBL training mode requires a lot of time and energy, which may pose some challenges to the teaching plan and course arrangement.

CONCLUSION

To sum up, the use of CBL-SSL-TBL combined with students' self-evaluation in gastrointestinal surgery nursing teaching can improve the operational skills, theoretical knowledge scores and satisfaction scores of nursing interns, and improve the questionnaire results and teaching effect of learning efficiency, which can be promoted in clinical teaching.

ARTICLE HIGHLIGHTS

Research background

With the continuous development of medical technology, the diagnosis and treatment methods of gastrointestinal surgical diseases are also constantly updated and improved. Therefore, it is essential for gastrointestinal surgical caregivers to continuously learn and update their knowledge and skills.

Research motivation

In order to improve the teaching quality of gastrointestinal surgery nursing.

Research objectives

Application of case-based learning (CBL), scene-simulated learning (SSL), task-based learning (TBL) combining training mode and student self-evaluation in teaching gastrointestinal surgery nursing.

Research methods

According to different teaching modes, they are set as observation group (CBL-SSL-TBL combined with training mode and students' self-evaluation) and control group (conventional teaching mode).

Research results

The operational skills and theoretical knowledge scores of the observation group were higher than those of the control group.

Research conclusions

Through the application of CBL-SSL-TBL teaching method, it can effectively improve the nursing teaching quality of gastrointestinal surgery, and cultivate more high-quality nursing talents.

Research perspectives

The importance of gastrointestinal surgical care.

FOOTNOTES

Author contributions: Rong XJ and Ning Z designed the research; Ning Z contributed new reagents/analytic tools; Rong XJ analyzed the data; Rong XJ and Ning Z wrote the paper.

Institutional review board statement: This study protocol was approved by Medical College in Jiangxi University of Technology, and all the families have voluntarily participated in the study and have signed informed consent forms.

Informed consent statement: All the families have voluntarily participated in the study and have signed informed consent forms.

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

Data sharing statement: Data generated from this investigation are available upon reasonable request from the corresponding author at rongxiaojuan2022@163.com.

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S-Editor: Li L
L-Editor: A
P-Editor: Li L

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World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2024 January 27; 16(1): 173-185

DOI: 10.4240/wjgs.v16.i1.173

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Observational Study

Predictive factors and model validation of post-colon polyp surgery *Helicobacter pylori* infection

Zheng-Sen Zhang

Specialty type: Gastroenterology and hepatology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Bhansali A, India; Rastogi A, India

Received: November 6, 2023
Peer-review started: November 6, 2023
First decision: November 16, 2023
Revised: December 3, 2023
Accepted: December 20, 2023
Article in press: December 20, 2023
Published online: January 27, 2024

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Abstract

BACKGROUND

Recently, research has linked *Helicobacter pylori* (*H. pylori*) stomach infection to colonic inflammation, mediated by toxin production, potentially impacting colorectal cancer occurrence.

AIM

To investigate the risk factors for post-colon polyp surgery, *H. pylori* infection, and its correlation with pathologic type.

METHODS

Eighty patients who underwent colon polypectomy in our hospital between January 2019 and January 2023 were retrospectively chosen. They were then randomly split into modeling (n = 56) and model validation (n = 24) sets using R. The modeling cohort was divided into an *H. pylori*-infected group (n = 37) and an *H. pylori*-uninfected group (n = 19). Binary logistic regression analysis was used to analyze the factors influencing the occurrence of *H. pylori* infection after colon polyp surgery. A roadmap prediction model was established and validated. Finally, the correlation between the different pathological types of colon polyps and the occurrence of *H. pylori* infection was analyzed after colon polyp surgery.

RESULTS

Univariate results showed that age, body mass index (BMI), literacy, alcohol consumption, polyp pathology type, high-risk adenomas, and heavy diet were all influential factors in the development of *H. pylori* infection after intestinal polypectomy. Binary multifactorial logistic regression analysis showed that age, BMI, and type of polyp pathology were independent predictors of the occurrence of *H. pylori* infection after intestinal polypectomy. The area under the receiver operating characteristic curve was 0.969 [95% confidence interval (95%CI): 0.928–1.000] and 0.898 (95%CI: 0.773–1.000) in the modeling and validation sets,

respectively. The slope of the calibration curve of the graph was close to 1, and the goodness-of-fit test was $P > 0.05$ in the two sets. The decision analysis curve showed a high rate of return in both sets. The results of the correlation analysis between different pathological types and the occurrence of *H. pylori* infection after colon polyp surgery showed that hyperplastic polyps, inflammatory polyps, and the occurrence of *H. pylori* infection were not significantly correlated. In contrast, adenomatous polyps showed a significant positive correlation with the occurrence of *H. pylori* infection.

CONCLUSION

Age, BMI, and polyps of the adenomatous type were independent predictors of *H. pylori* infection after intestinal polypectomy. Moreover, the further constructed column-line graph prediction model of *H. pylori* infection after intestinal polypectomy showed good predictive ability.

Key Words: Colon polyps; *Helicobacter pylori*; Risk factors; Pathologic type; Columnar graphic modeling

Core Tip: *Helicobacter pylori* (*H. pylori*) infection is reportedly a risk factor for the development of colonic adenomas, especially progressive or multiple adenomas. However, few studies have examined the risk factors for *H. pylori* infection after therapeutic colon polypectomy and the type of polyp pathology associated with its occurrence. This randomized study evaluated the risk factors for the development of *H. pylori* infections in patients with colon polyps and the relationship between their pathology and the development of *H. pylori* infections.

Citation: Zhang ZS. Predictive factors and model validation of post-colon polyp surgery *Helicobacter pylori* infection. *World J Gastrointest Surg* 2024; 16(1): 173-185
URL: https://www.wjgnet.com/1948-9366/full/v16/i1/173.htm
DOI: https://dx.doi.org/10.4240/wjgs.v16.i1.173

INTRODUCTION

Colonic polyps are tumor-like lesions that grow on the mucosal surface of the colon, usually in the form of protruding or elevated masses or fleshy lesions[1]. They do not invade surrounding tissues and are clinically classified based on their histologic features and susceptibility to malignant transformation. Mainly, there are colorectal adenomatous polyps, inflammatory polyps, and hyperplastic polyps[2]. Colonic adenomatous polyps are abnormal tissues that may develop into colorectal cancer (CC); colonic adenomatous polyps are the most common in clinical practice and carry a higher risk of developing cancer[3]. According to the 2016 United States Guidelines for Follow-up after Colorectal Polypectomy[4], the presence of adenomas that are more than 1 cm in diameter, three or more in number, or that exhibit villous or high-grade intraepithelial neoplasia, along with the occurrence of any of the aforementioned criteria, suggests a high risk of cancer development in colorectal polyp case. To reduce the risk of CC, further development of colonic adenomatous polyps must be inhibited to the greatest extent possible, through prevention and early treatment[5]. In the last decade, *Helicobacter pylori* (*H. pylori*) infection of the stomach has been demonstrated to induce an inflammatory response in the colon through the production of toxins, thereby promoting the development of CC, to some extent[6]. Considering the increasing number of patients with colonic polyps in our country and the large number of *H. pylori* infections, an in-depth understanding of the current status and risk factors for *H. pylori* infections in these patients is essential[7]. A previous study[8] revealed that the development of colon tumors is significantly associated with *H. pylori* infection. Simultaneously, *H. pylori* infection is also identified as a risk factor for the development of colon adenomas, especially progressive or multiple adenomas. Therefore, this study aimed to analyze the risk factors for the development of *H. pylori* infection in patients with colonic polyps, and the relationship between their pathological type and the development of *H. pylori* infection.

MATERIALS AND METHODS

Objects of study

Eighty patients who underwent colon polypectomy at our hospital between January 2019 and January 2023 were retrospectively selected as participants. They were randomly divided into a modeling cohort (n = 56) and a model validation cohort (n = 24) at a ratio of 7:3 using the R language.

Inclusion and exclusion criteria

Inclusion criteria: (1) Participants who met the indications for colonoscopic polypectomy; (2) those who underwent the 14C-urea breath test; (3) had no immune system disease or immune dysfunction; (4) no psychiatric disorders and were able to communicate and interact normally; and (5) had complete clinical data. Participants that met all the above criteria were included in this study.

Exclusion criteria: Participants who met any one of the following criteria were excluded from the study: (1) Participants with a previous history of gastrointestinal disease or colon tumor; (2) those who presented with coagulation disorders after discontinuing oral anticoagulant medication for < 1 wk; and (3) those who were on medication prior to *H. pylori* screening.

Observation of grouping and H. pylori-infection

The modeling cohort was divided into an *H. pylori*-infected group (n = 37) and an *H. pylori*-uninfected group (n = 19) according to whether the patients developed an *H. pylori* infection. Patients were monitored for the occurrence of *H. pylori* infection, which served as the endpoint.

Observation indicators

The general information of the patients was collected through electronic medical records. This included general information [sex, age, body mass index (BMI), exercise, education, smoking and drinking habits, history of hypertension and diabetes mellitus, and heavy diet consumptions] and specialty information (number, size, location, and pathological type of the polyps, and whether they were high-risk adenomas).

We analyzed the risk factors for developing *H. pylori* infection after colon polyp surgery by observing the age, sex, BMI, and exercise of patients in the modeling cohort (*H. pylori*-infected and *H. pylori*-uninfected groups). In addition, we assessed whether or not they smoked, consumed alcohol, suffered from high blood pressure, consumed a heavy diet, and had diabetes mellitus. The number, size, location, and the pathological type of polyps, and the presence of high-risk adenomas, were also assessed. All of the information was used to develop and validate a roadmap prediction model. Finally, the correlation between the different pathological types and the occurrence of *H. pylori* after colon polyp surgery was analyzed.

Statistical analysis

SPSS 26.0 software and R software were used to analyze the data. The collected count data were expressed as cases (%); χ^2 or Fisher exact test was used for unordered data, and the Mann–Whitney U test was used for ordered data. Univariate and multivariate binary logistic regression analyses were used to analyze the factors influencing the development of *H. pylori* infection after colon polyp surgery and to develop a column-line graph prediction model. The discriminative power of the validation set and calibration graphs were used to assess the accuracy of the column-line graphs. The area under the receiver operating characteristic (ROC) curve (AUC) was used to evaluate the discriminative ability of the column diagram. Calibration curves for the model were calculated, and the consistency of the model was verified using the Hosmer–Lemeshow test. Decision curve analysis (DCA) was performed to evaluate the discriminative ability of the model. $P < 0.05$ was considered statistically significant, and correlations were tested using Spearman's test.

RESULTS

Baseline clinical characteristics

A total of 93 patients with severe traumatic brain injury were included in the study: 56 in the modeling cohort and 24 in the validation cohort. All patients were aged 30–72 years at the time of diagnosis; 42 (52.50%) were male and 38 (47.50%) were female. Other baseline information regarding the modeling and validation cohorts is shown in Table 1.

Comparison of clinical data between H. pylori-infected and H. pylori-uninfected groups of patients in the model cohort

There were no statistically significant differences in sex composition, exercise and smoking status, history of hypertension and diabetes mellitus, number of polyps, polyp size, or polyp site in the model cohort ($P > 0.05$). The differences in age, BMI, literacy level, alcohol consumption, polyp pathological type, high-risk adenomas, and heavy diet consumption in the *H. pylori*-infected group were statistically significant when compared with the *H. pylori*-uninfected group ($P < 0.05$; Table 2).

Univariate analysis of the occurrence of H. pylori infection in the model cohort of patients

In the model cohort, *H. pylori* infection was the dependent variable and assigned 1, and its absence was assigned 0. Variables with $P < 0.05$ in the clinical data were included in the univariate analysis. The univariate results showed that age, BMI, literacy level, alcohol consumption, type of polyp pathology, high-risk adenomas, and a heavy diet consumption were all influential factors in the occurrence of *H. pylori* infections after intestinal polypectomy (Table 3).

Multifactorial analysis of the occurrence of H. pylori infection

Variables with $P < 0.05$ in the univariate analysis were included in the binary multivariate logistic regression analysis, which showed that age, BMI, and pathologic type of polyp were independent predictors of the development of *H. pylori*

Table 1 Baseline information for modeling and validation cohorts

Sports event		Total population (*n* = 80)	Modeling queues (*n* = 56)	Validation queue (*n* = 24)
Gender [*n* (%)]	Male	42 (52.50)	30 (53.57)	12 (50.00)
	Female	38 (47.50)	26 (46.43)	12 (50.00)
Age (yr, mean ± SD)		36.15 ± 11.79	36.67 ± 10.00	35.92 ± 13.58
BMI [*n* (%)]		22.42 ± 3.44	22.20 ± 2.32	22.64 ± 4.55
Movement [*n* (%)]	< 1 h/wk	38 (47.50)	27 (48.21)	11 (45.83)
	≥ 1 h/wk	42 (52.50)	29 (51.79)	13 (54.17)
Literacy [*n* (%)]	Primary and below	30 (37.50)	20 (35.71)	10 (41.67)
	Junior high school and secondary school	29 (36.25)	21 (37.50)	8 (33.33)
	Junior college or above	21 (26.25)	15 (26.79)	6 (25.00)
Smoking [*n* (%)]	Be	33 (41.25)	24 (42.86)	9 (37.50)
	Clogged	45 (56.25)	32 (57.14)	13 (54.17)
Alcohol consumption [*n* (%)]	Be	44 (55.00)	31 (55.36)	13 (54.17)
	Clogged	34 (42.50)	25 (44.64)	9 (37.50)
History of hypertension [*n* (%)]	Be	32 (40.00)	22 (39.29)	10 (41.67)
	Clogged	48 (60.00)	34 (60.71)	14 (58.33)
History of diabetes [*n* (%)]	Be	14 (17.50)	10 (17.86)	4 (16.67)
	Clogged	66 (82.50)	46 (82.14)	20 (83.33)
Number of polyps [*n* (%)]	An odd one	38 (47.50)	27 (48.21)	11 (45.83)
	Multi- (faceted, ethnic *etc.*)	42 (52.50)	29 (51.79)	13 (54.17)
Polyp size [*n* (%)]	< 1 cm	33 (41.25)	23 (41.07)	10 (41.67)
	≥ 1 cm	47 (58.75)	33 (58.93)	14 (58.33)
Polyp site [*n* (%)]	Proximal	27 (33.75)	19 (33.93)	8 (33.33)
	Far end	25 (31.25)	18 (32.14)	7 (29.17)
	Whole colon	28 (35.00)	19 (33.93)	9 (37.50)
Type of polyp pathology [*n* (%)]	Adenomatous polyp	35 (43.75)	24 (42.86)	11 (45.83)
	Non-adenomatous polyp	45 (56.25)	32 (57.14)	13 (54.17)
High-risk adenomas [*n* (%)]	Be	23 (28.75)	16 (28.57)	7 (29.17)
	Clogged	57 (71.25)	40 (71.43)	17 (70.83)
Heavy diet [*n* (%)]	Be	46 (57.50)	32 (57.14)	1 4 (58.33)
	Clogged	34 (42.50)	24 (42.86)	10 (41.67)

BMI: Body mass index.

infection after intestinal polypectomy, with the model equation: Logistic = −3.798 – 0.342 × age + 1.222 × BMI − 3.760 × type of polyp pathology (Table 4).

Modeling of a column-line diagram to predict the occurrence of H. pylori infection in patients after colon polyp surgery

The resulting three independent risk factors (age, BMI, and polyp pathology type) were used to construct a prediction model using R software, and subsequent column-line graph model, as shown in Figure 1. The C-statistic of the model was calculated using the R language software as 0.809, with a 95% confidence interval (95%CI) of 0.761–0.890 and a standard error of 0.030 ($P < 0.001$). The C-statistic was calculated using the R language software as 0.818, with a standard error of 0.030 ($P < 0.001$), and the 10000 Bootstrap calculated a C statistic of 0.818. The slope of the generated column-line graph calibration curve was close to 1 (Figure 2), with a goodness-of-fit test of $P > 0.05$ and a high degree of consistency between the predicted and actual events. The area under the ROC curve of the column-line diagram prediction model was 0.969 (95%CI: 0.928–1.000) (Figure 3). The decision analysis curve is shown in Figure 4, where the X-axis indicates the threshold

Table 2 Comparison of clinical data between *Helicobacter pylori*-infected and *Helicobacter pylori*-uninfected groups of patients in the model cohort

Sports event		Hp infection group (n = 37)	Hp uninfected group (n = 19)	χ^2 value	P value
Gender [n (%)]	Male	20 (54.05)	10 (52.63)	0.010	0.920
	Female	17 (45.95)	9 (47.37)		
Age (yr, mean ± SD)			46.58 ± 3.50	4.788	0.000
BMI [n (%)]			20.37 ± 1.65	5.114	0.000
Movement [n (%)]	< 1 h/wk	18 (48.65)	9 (47.37)	0.008	0.928
	≥ 1 h/wk	19 (51.35)	10 (52.63)		
Literacy [n (%)]	Primary and below	16 (43.24)	4 (21.05)	2.348	0.019
	Junior high school and secondary school	15 (40.54)	6 (31.58)		
	Junior college or above	6 (16.22)	9 (47.37)		
Smoking [n (%)]	Be	16 (43.24)	8 (42.11)	0.007	0.935
	Clogged	21 (56.76)	11 (57.89)		
Alcohol consumption [n (%)]	Be	24 (64.86)	7 (36.84)	3.989	0.046
	Clogged	13 (35.14)	12 (63.16)		
History of hypertension [n (%)]	Be	15 (40.54)	7 (36.84)	0.072	0.788
	Clogged	22 (59.46)	12 (63.16)		
History of diabetes [n (%)]	Be	9 (24.32)	1 (5.26)	1.946	0.163
	Clogged	28 (75.68)	18 (94.74)		
Number of polyps [n (%)]	An odd one	17 (45.95)	10 (52.63)	0.225	0.636
	Multi- (faceted, ethnic *etc.*)	20 (54.05)	9 (47.37)		
Polyp size [n (%)]	< 1 cm	15 (40.54)	8 (42.11)	0.013	0.910
	≥ 1 cm	22 (59.46)	11 (57.89)		
Polyp site [n (%)]	Proximal	10 (27.03)	9 (47.37)	2.326	0.313
	Far end	13 (35.14)	5 (26.32)		
	Whole colon	14 (37.84)	5 (26.32)		
Type of polyp pathology [n (%)]	Adenomatous polyp	20 (56.76)	4 (21.05)	5.583	0.018
	Non-adenomatous polyp	17 (27.03)	15 (52.63)		
High-risk adenomas [n (%)]	Be	14 (37.84)	2 (10.53)	4.588	0.032
	Clogged	23 (62.16)	17 (89.47)		
Heavy diet [n (%)]	Be	25 (67.57)	7 (36.84)	4.839	0.028
	Clogged	12 (32.43)	12 (63.16)		

BMI: Body mass index.

probability, the Y-axis indicates the net return, and the black solid line indicates the net return using the column-line diagram prediction model, which shows a higher return and further confirms the effectiveness of the column-line diagram prediction model.

Validation of the column-line diagram model

Based on the validation cohort (n = 24), which was divided into *H. pylori*-infected (n = 16) and *H. pylori*-uninfected (n = 8) groups, the column-line diagram of the risk of *H. pylori* infection was externally validated using an ROC curve, and the lower product of the ROC curve was 0.898 (95%CI: 0.773–1.000) (Figure 5). The slope of the generated calibration curve for the column-line diagram was close to 1 (Figure 6), and the result of the Hosmer-Lemeshow test was, χ^2 =10.609, P = 0.157 > 0.05. The decision curve showed a higher net benefit of the model (Figure 7), suggesting that the calibration of the

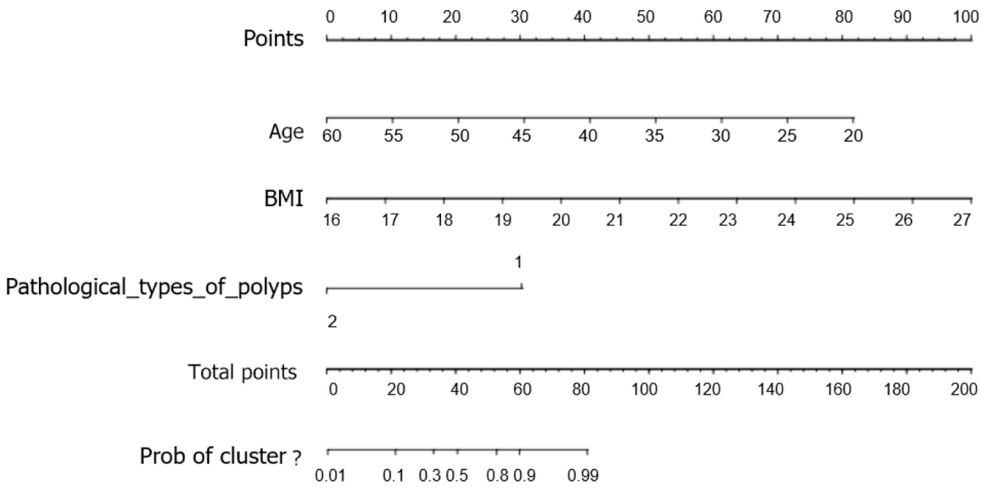
Table 3 Univariate analysis of *Helicobacter pylori*-infected and *Helicobacter pylori*-uninfected groups

Considerations	*B*	*SE*	*Wals*	*P* value	OR	95%CI
Age	-0.169	0.049	12.137	0.000	0.844	0.768-0.929
BMI	0.738	0.216	11.708	0.001	2.093	1.371-3.194
Educational attainment	-0.912	0.393	5.383	0.020	0.402	0.186~0.868
Drinking wine	1.152	0.587	3.850	0.050	3.165	1.001-10.004
Types of polyp pathology	1.484	0.652	5.178	0.023	0.227	0.063-0.814
High-risk adenoma	1.644	0.821	4.010	0.045	5.174	1.035-25.852
Heavy diet	1.399	0.596	5.506	0.019	4.052	1.259-13.038

OR: Odds ratio; 95%CI: 95% confidence interval; BMI: Body mass index.

Table 4 Multifactorial analysis of *Helicobacter pylori*-infected and *Helicobacter pylori*-uninfected groups

considerations	B	SE	*Wals*	*P* value	OR	95%CI
Age	-0.342	0.145	5.574	0.018	0.710	0.535-0.944
BMI	1.222	0.446	7.524	0.006	3.395	1.418-8.130
Types of polyp pathology	-3.760	1.772	4.505	0.034	0.023	0.001-0.750
Constant	-3.798	7.216	0.277	0.599	0.022	-



DOI: 10.4240/wjgs.v16.i1.173

Figure 1 Column-line diagram.

column-line diagram model in the validation group was better.

Analysis of the correlation between different pathology types and the occurrence of H. pylori infection after colon polyps

Three pathologic types were identified in the model cohort of patients with colon polyps. In the *H. pylori*-infected group, these included seven cases of inflammatory polyps, 10 cases of hyperplastic polyps, and 20 cases of adenomatous polyps. In the *H. pylori*-uninfected group, these included five cases of inflammatory polyps, 10 cases of hyperplastic polyps, and four cases of adenomatous polyps. Correlation analysis of the occurrence of different pathological types and *H. pylori* infection after colon polyp surgery was performed. The results of the correlation analysis showed no significant correlation between hyperplastic polyps, inflammatory polyps, and the occurrence of *H. pylori* infection. In contrast, adenomatous polyps showed a significant positive correlation with the occurrence of *H. pylori* infection (Table 5).

Table 5 Correlation between different types of pathology and occurrence of *Helicobacter pylori* infection after colon polyp surgery

		Inflammatory polyp	Hyperplastic polyp	Adenomatous polyp
Helicobacter pylori infection	Correlation coefficient	-0.085	-0.253	0.316
	Sig. (bilateral)	0.532	0.060	0.018

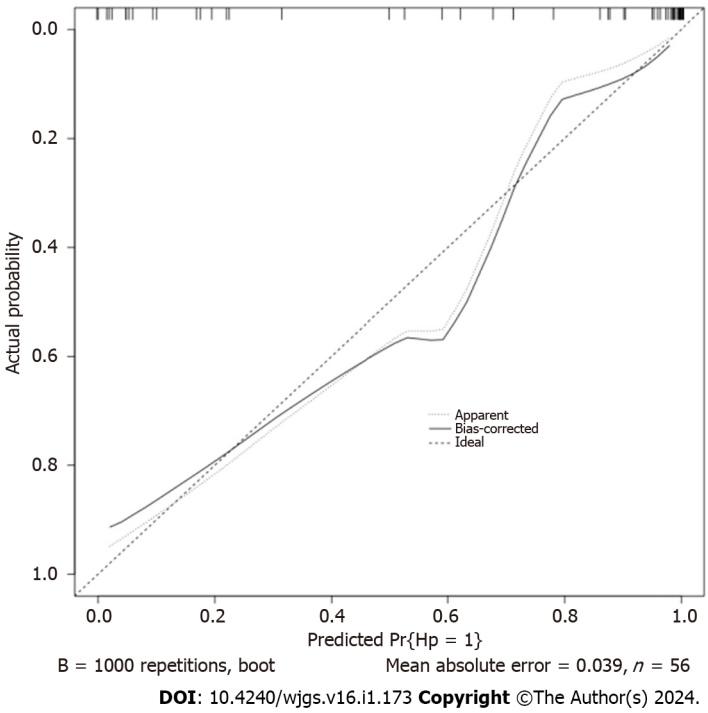


Figure 2 Calibration curves of the column graph prediction model.

DISCUSSION

H. pylori is a bacterium that parasitizes areas such as the stomach or duodenum, and can survive for long periods of time under conditions of little oxygen. It not only has the ability to secrete toxic substances, which contribute to gastrointestinal disorders such as gastric ulcers and gastritis, but also has an impact on the rate of infection[9,10]. *H. pylori* can be detected not only by non-invasive methods such as the urease breath test and serum *H. pylori* antibodies, but also by invasive methods such as biopsy of the gastric mucosa with special staining of the tissue biopsies. Moreover, its important role in the digestive system has been widely recognized[11]. However, few studies have addressed the exact relationship between the three pathological types of colon polyps, namely, adenomatous, inflammatory, and hyperplastic colon polyps, and *H. pylori* infection. Further research is needed to clarify this relationship. Therefore, the present study developed a column-line diagram model focusing on analyzing the factors influencing the occurrence of *H. pylori* infection in patients with gastrointestinal polyps and exploring the correlation between the pathological types of polyps and the occurrence of *H. pylori* infection.

By comparing the clinical data of patients with gastrointestinal polyps, we found that there were statistically significant differences between the *H. pylori*-infected and *H. pylori*-uninfected groups in terms of age, BMI, literacy, alcohol consumption, polyp pathology type, presence of high-risk adenomas, and heavy diets consumption. There were no significant differences in the other indicators. The results of the binary logistic one-way regression analysis assigned a value of 1 to the occurrence of *H. pylori* infection and a value of 2 to the non-occurrence of *H. pylori* infection as the dependent variables. Moreover, the factors with significant differences in the aforementioned clinical data as the covariates, showed that age, BMI, literacy, alcohol consumption, polyp pathology type, high-risk adenomas, and heavy diets consumption were the factors influencing the occurrence of *H. pylori* infection after intestinal polypectomy. Subsequently, we performed a binary logistic regression analysis, of the factors with significant differences in the univariate analysis as covariates and found that age, BMI, and polyp pathology type were independent predictors of the occurrence of *H. pylori* infection after intestinal polypectomy. Among them, younger age is associated with a greater likelihood of developing *H. pylori* infection after intestinal polypectomy. This may be because younger patients, with continuous changes in their social environment, are presented with increasing work and life pressures, which tend to result in lower resistance of their bodies and thus are more susceptible to *H. pylori* infection[12]. Additionally, adolescents tend to favor convenient diets, such as high-fat, high-sugar, and high-salt foods, which subsequently increase the risk of *H. pylori* infection[13]. In contrast, older people have a more regular lifestyle, pay more attention to healthy eating and

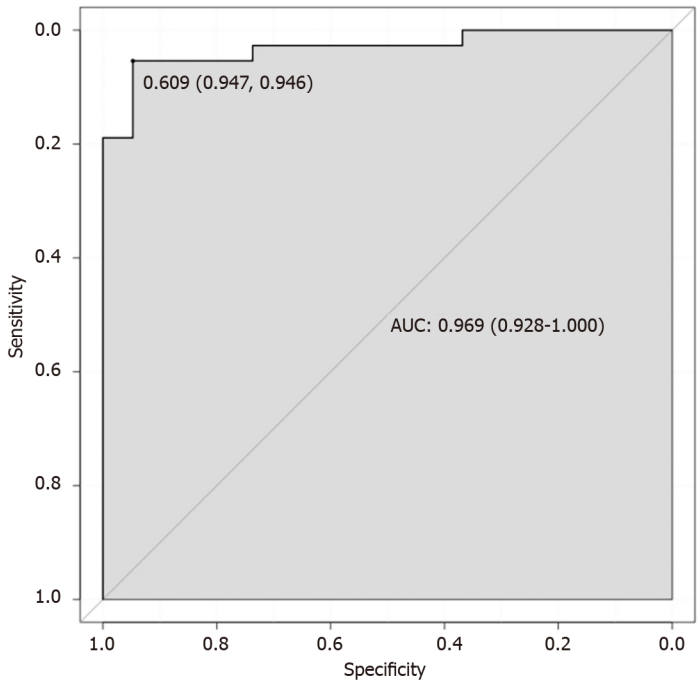


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Figure 3 Receiver operating characteristic curve of the column chart prediction model.

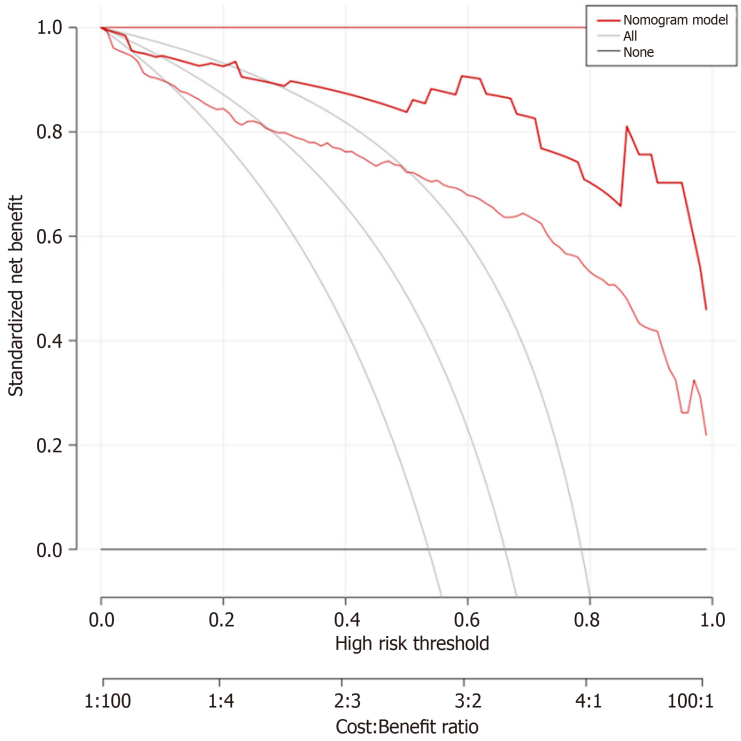

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Figure 4 Decision analysis curve.

living habits, have frequent medical checkups, and follow their doctors' advice. This reduces their likelihood of becoming infected with *H. pylori*[14,15].

In contrast to the age trend, regarding BMI and polyp pathology type, we found that higher BMI is associated with a greater likelihood of *H. pylori* infection after intestinal polypectomy. Thus patients with adenomatous polyps on polyp pathology had a greater likelihood of *H. pylori* infection. It has been reported in the literature[16,17] that this can be because there is an association between BMI and *H. pylori* infection, and that the two factors can interact with each other. Due to the long-term intake of excessively high calories, the immune environment of their organs is changed, which leads

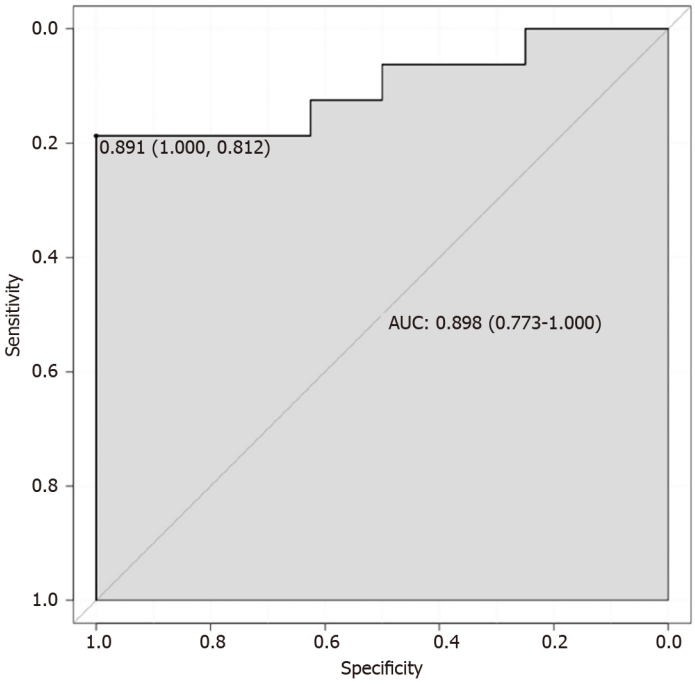

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Figure 5 Verification queue receiver operating characteristic curve.

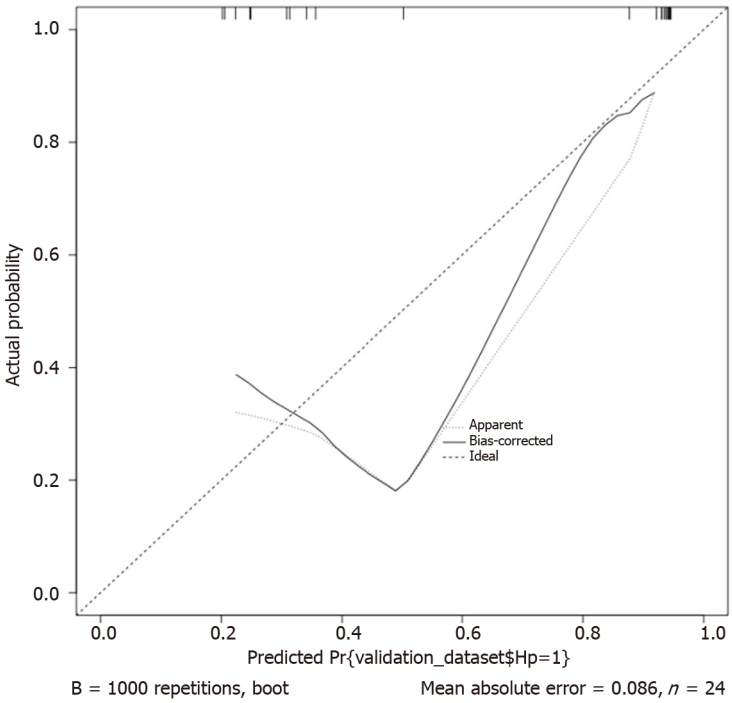

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Figure 6 Verification queue calibration curve.

to the expansion of adipose tissues and the activation of macrophages through the secretion of chemokines, subsequently causing a localized inflammatory response. Consequently, the immune microenvironment of obese patients creates favorable conditions for the survival of *H. pylori*; thus, obese people are more likely to be infected with *H. pylori*. This is similar to the findings of Xie *et al*[18] Additionally, changes in the intragastric microenvironment due to *H. Pylori* may lead to intestinal microecological disorders, further affecting the intestinal microecology of the patients. This may lead to intestinal tumor-like lesions and adenomatous polyps[19]. Thus, adenomatous polyps in patients are often accompanied by *H. pylori* infection. The results of a study by Zhang *et al*[20] showed that the proportion of adenomatous polyps occurring in *H. pylori*-infected populations was significantly higher than that in *H. pylori*-uninfected populations. This is

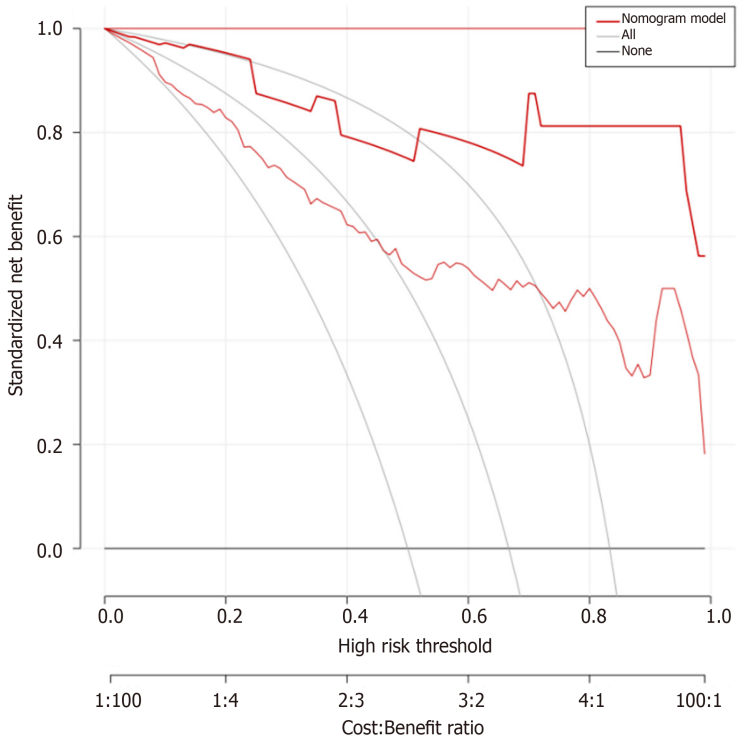

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Figure 7 Verification queue decision analysis curve.

similar to the results of the present study and further supports the findings of the present study.

Additionally, to further clarify the predictive value of age, BMI, and polyp pathology type in the occurrence of *H. pylori* infection after intestinal polypectomy, we utilized the R software to establish a column-line graph model. The C statistic of this model was calculated using the R language software as 0.809, which indicated that the model had a stronger discriminatory ability and was able to distinguish patients with high likelihood to develop *H. pylori* infection. The slope of the calibration curve of the column-line graph it generated was close to 1, and the test of goodness of fit was $P > 0.05$, which showed that the model had a strong calibration ability. The consistency between the predicted events and the actual events was high, and the area under the ROC curve was 0.969 (95%CI: 0.928-1.000). This indicated that the model was more efficacious in predicting the risk of *H. pylori* infection. Furthermore, the AUC value was closer to 1, indicating that the model is more capable of discriminating risk. The decision analysis curve showed a higher yield, further confirming the validity of the column–line graph prediction model. Further external validation ROC curve product under the curve was 0.898 (95%CI: 0.773–1.000), which indicated that the model also performed well in the external validation cohort and had good generalization ability. The slope of the generated column-line graph calibration curve was close to 1, with a Hosmer–Lemeshow test result of $P > 0.05$. Moreover, the decision curve showed a higher net gain of the model, suggesting that the column-line graph model had a better calibration ability in the validation cohort. The column-line diagram model of *H. pylori* infection risk obtained in this study showed good predictive and calibration abilities for both in-sample and out-of-sample validations. According to the visualized form of the column-line diagram, age ≤ 50 years, lower education level, and higher BMI are associated with higher risk of *H. pylori* infection after intestinal polypectomy. Moreover, patients with adenomatous polyps often have *H. pylori* infection. This showed effective clinical discrimination of the high-risk group of *H. pylori* infection after intestinal polypectomy, based on the information of patients in the aforementioned key factors. Therefore, the present study illustrated simple predictors that are favorable for the early prevention of *H. pylori* infection.

CONCLUSION

In conclusion, age, BMI, and polyp pathology of the adenomatous type were independent predictors of *H. pylori* infection after intestinal polypectomy. In addition, the columnar graph prediction model of *H. pylori* infection after intestinal polypectomy showed good predictive ability, which provided assistance in the clinical identification of high-risk groups of *H. pylori* infection after intestinal polypectomy. This is beneficial for the timely prevention of *H. pylori* infection. However, because this study was a retrospective analysis, the sample size was limited, and more clinical indicators should be added for further comprehensive assessment and establishment of a more comprehensive prediction model.

ARTICLE HIGHLIGHTS

Research background

Colon polyps are tumor-like lesions that grow on the surface of the colonic mucosa, usually in the form of a protruding or bulging mass, or meaty lesion. They are abnormal tissue that can develop into colorectal cancer. Considering that the number of patients with colon polyps in our country has been rising and that a large number of *Helicobacter pylori* (*H. pylori*) infections also exist, an in-depth understanding of the current status of *H. pylori* infections in patients with colonic polyps in our country and the risk factors for these infections is necessary.

Research motivation

The development of colon tumors is significantly associated with *H. pylori* infection, of which colonic adenomatous polyps may develop into colon cancer. It is also a risk factor for the development of colonic adenomas, especially progressive or multiple adenomas. However, few clinical studies have investigated the correlation between the pathological types of colonic polyps and *H. pylori* infection.

Research objectives

To investigate the risk factors for the development of *H. pylori* infection after colon polyp surgery, and to establish the relationship between the type of pathology and its occurrence.

Research methods

Eighty patients who underwent colon polypectomy in our hospital from January 2019 to January 2023 were retrospectively selected as participants, and randomly divided into a modeling cohort (n = 56) and a model validation cohort (n = 24) at a ratio of 7:3 using R. Simultaneously, based on whether the patients were infected with *H. pylori*, the modeling cohort was divided into an *H. pylori*-infected group (n = 37) and an *H. pylori*-uninfected group (n = 19). The risk factors for *H. pylori* after colon polyp surgery were analyzed by comparing the age, sex, body mass index (BMI), and exercise status of patients in the modeling cohort (*H. pylori*-infected and *H. pylori*-uninfected groups). In addition, whether or not they smoked, consumed alcohol, suffered from hypertension and diabetes mellitus, and had heavy diets, and the number, size, location, and the pathological type of the polyps, and whether or not they were high-risk adenomas, were also analyzed. A binary logistic regression analysis was used to analyze the factors influencing the occurrence of *H. pylori* infection after colon polyp surgery. A roadmap prediction model was therefore established and validated; receiver operating characteristic was used to evaluate the predictive efficacy of the model; calibration curves were used to assess the consistency between predicted and actual events. DCA curves were also used to evaluate the validity of the model; and finally, the correlation between the different pathological types of colon polyps and the occurrence of *H. pylori* infection was analyzed after colon polyp surgery.

Research results

Age, BMI, and polyp pathology type were independent predictors of *H. pylori* infection after intestinal polypectomy. Additionally, the *H. pylori* infection risk column-line diagram model obtained in this study demonstrated good predictive and calibration abilities for both in-sample and out-of-sample validations. The visualized form of the column-line diagram showed that for age ≤ 50 years, the lower the education level, the higher the risk of *H. pylori* infection after intestinal polypectomy, the higher the BMI, the higher the risk of *H. pylori* infection, and that patients with adenomatous polyps often have *H. pylori* infection. This is conducive to the effective clinical discrimination of patients at high risk of *H. pylori* infection, after intestinal polypectomy, based on the information of the above mentioned key factors. Moreover, the predictors obtained in this study are favorable for the early prevention of *H. pylori* infection.

Research conclusions

Age, BMI, and polyp pathology of the adenomatous type were all independent predictors of *H. pylori* infection after intestinal polypectomy, and the column-line graph prediction model of *H. pylori* infection after intestinal polypectomy showed good predictive ability. This provides assistance in the clinical identification of high-risk groups for *H. pylori* infection after intestinal polypectomy and is conducive to timely prevention.

Research perspectives

This study was a retrospective analysis with a limited sample size, and additional clinical indicators need to be added for further comprehensive assessment and predictive modeling.

FOOTNOTES

Author contributions: Zhang ZS was responsible for the methodology, investigation, software, data curation, formal analysis, writing the original draft and editing, conceptualization, validation.

Institutional review board statement: The study was reviewed and approved by the Ethics Committee of Affiliated Hospital of Shaoxing University (Shaoxing Municipal Hospital (NO.2023-072-01).

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 conflicts of interest to declare.

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

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S-Editor: Lin C
L-Editor: A
P-Editor: Yu HG

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World Journal of Gastrointestinal Surgery

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World J Gastrointest Surg 2024 January 27; 16(1): 186-195

DOI: 10.4240/wjgs.v16.i1.186

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Randomized Controlled Trial

Micro-power negative pressure wound technique reduces risk of incision infection following loop ileostomy closure

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Specialty type: Gastroenterology and hepatology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Komatsu S, Japan

Received: August 22, 2023
Peer-review started: August 22, 2023
First decision: November 20, 2023
Revised: November 30, 2023
Accepted: December 13, 2023
Article in press: December 13, 2023
Published online: January 27, 2024

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Abstract

BACKGROUND

Prophylactic loop ileostomy is an effective way to reduce the clinical severity of anastomotic leakage following radical resection of rectal cancer. Incisional surgical site infection (SSI) is a common complication after ileostomy closure.

AIM

To evaluate the efficacy and safety of the micro-power negative pressure wound technique (MPNPWT) in preventing incisional SSI.

METHODS

This was a prospective, randomized controlled clinical trial conducted at a single center. A total of 101 consecutive patients who underwent ileostomy closure after rectal cancer surgery with a prophylactic ileostomy were enrolled from January 2019 to December 2021. Patients were randomly allocated into an MPNPWT group and a control group. The MPNPWT group underwent intermittent suturing of the surgical incision with 2-0 Prolene and was covered with a micro-power negative pressure dressing. The surgical outcomes were compared between the MPNPWT (n = 50) and control (n = 51) groups. Risk factors for incisional SSI were identified using logistic regression.

RESULTS

There were no differences in baseline characteristics between the MPNPWT (n = 50) and control groups (n = 51). The incisional SSI rate was significantly higher in

the control group than in the MPNPWT group (15.7% *vs* 2.0%, $P = 0.031$). However, MPNPWT did not affect other surgical outcomes, including intra-abdominal complications, operative time, and blood loss. Postoperative hospital stay length and hospitalization costs did not differ significantly between the two groups ($P = 0.069$ and 0.843, respectively). None of the patients experienced adverse effects of MPNPWT, including skin allergy, dermatitis, and pain. MPNPWT also helped heal the infected incision. Our study indicated that MPNPWT was an independent protective factor [odds ratio (OR) = 0.005, $P = 0.025$)] and diabetes was a risk factor (OR = 26.575, $P= 0.029$) for incisional SSI.

CONCLUSION

MPNPWT is an effective and safe way to prevent incisional SSI after loop ileostomy closure.

Key Words: Micro-power negative pressure technique; Ileostomy closure; Incisional surgical site infection; Infection prevention; Postoperative incision

Core Tip: This is the first study to apply the micro-power negative pressure wound technique (MPNPWT) to postoperative incision for incisional surgical site infection (SSI) prevention. The efficacy and safety of MPNPWT in preventing incisional SSI after ileostomy closure were evaluated. Our study showed that MPNPWT significantly reduced the incisional SSI rate to a low level (2.0%). No patients suffered adverse effects with MPNPWT. MPNPWT is an effective and safe way to prevent incisional SSI after loop ileostomy closure.

Citation: Xu DY, Bai BJ, Shan L, Wei HY, Lin DF, Wang Y, Wang D. Micro-power negative pressure wound technique reduces risk of incision infection following loop ileostomy closure. *World J Gastrointest Surg* 2024; 16(1): 186-195
URL: https://www.wjgnet.com/1948-9366/full/v16/i1/186.htm
DOI: https://dx.doi.org/10.4240/wjgs.v16.i1.186

INTRODUCTION

Prophylactic loop ileostomy is an effective way to reduce the clinical severity of anastomotic leakage following radical resection for rectal cancer[1]. Afterward, the digestive tract can be reconstructed through ileostomy closure. Although ileostomy closure is technically easy, it is associated with a non-negligible overall morbidity rate (11%-37%), with incisional surgical site infection (SSI) being the most common[2]. Incisional SSI is responsible for increased pain, longer hospital stays, and higher treatment costs. Surgeons have attempted to implement effective techniques to prevent incisional SSI. For example, purse-string skin closure is used as a substitute for conventional linear skin closure[3], and subcutaneous closedsuction drainage or negative-pressure technology (NPT) has been introduced to achieve adequate drainage[4]. These are valid techniques but have some limitations. Purse-string skin closure results in a circular open incision that requires frequent dressing changes. Applying a subcutaneous suction drain or a negative-pressure system has an adverse effect on patient mobility.

The micro-power negative pressure wound technique (MPNPWT) is a new approach to wound treatment in China[5]. This technique is based on a wound dressing that is made of a special polyvinyl alcohol foam material. When covering the wound, the material is completely sealed with a medical transparent film. Thus, a closed environment is formed at the local wound. Then, this kind of medical, biological material can produce the "siphonic effect" and "pumping effect" through compression, thus generating micro-power negative pressure that can quickly absorb exudates from the wound surface and achieve wound drainage (Figure 1). The micro-power negative pressure dressing can spare frequent dressing changes or an external device. This technique has been successfully applied in wound healing[6-8]. It reduces wound edema and stimulates epithelial cell proliferation and granulation tissue growth, thus shortening wound healing time. However, it is seldom used in the postoperative incisions to prevent incisional SSI. According to our previous experience with MPNPWT in patients with loop ileostomy closure, the postoperative incision could heal satisfactorily.

The primary objective of this prospective, randomized controlled trial (RCT) was to evaluate the efficacy and safety of MPNPWT in preventing incisional SSI after loop ileostomy closure.

MATERIALS AND METHODS

Study design

This was a single-center prospective, RCT conducted at Sir Run Run Shaw Hospital, Hang Zhou, China, between January 2019 and December 2021. The trial was registered at Chinese Clinical Trial Registry (registration number: ChiCTR-2200064827) after approval by the Ethics Committee of Sir Run Run Shaw Hospital, School of Medicine, Zhejiang

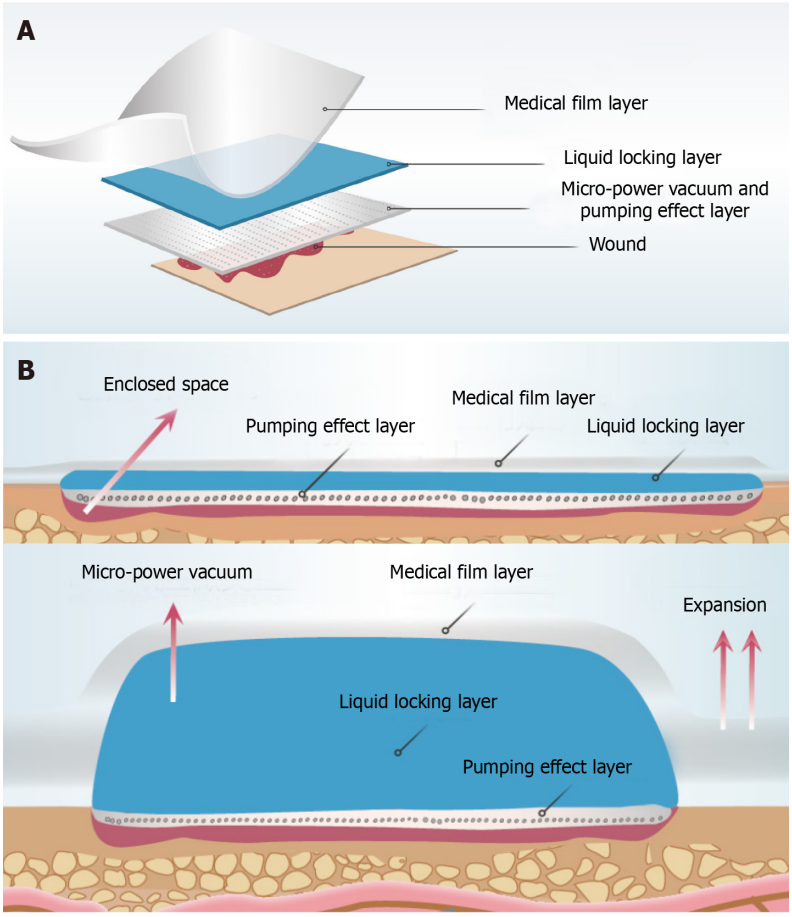

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Figure 1 Composition and working principle of micro-power negative pressure wound technique. A: The wound dressing is made of a special polyvinyl alcohol foam material. The material covers the wound and is sealed by a medical transparent film. In this way, it becomes a three-layer dressing containing a medical film layer, liquid locking layer, and micro-power vacuum and pumping effect layer; B: When exudates are absorbed into the liquid locking layer, the dressing expands, and the medical film layer is elevated. Then the closed space becomes larger and forms a local micro-power vacuum, which exerts negative pressure attraction on the wound and its deep soft tissue.

University (No. 20191217-9). Each participant provided written informed consent prior to study enrollment. This work is reported in line with the CONSORT guidelines.

Patients

Patients were enrolled according to the following inclusion criteria: (1) Age over 18 years; (2) history of radical resection of a rectal tumor with protective loop ileostomy; (3) scheduled to undergo an elective procedure of ileostomy closure; and (4) provision of signed informed consent. The exclusion criteria were as follows: (1) Age < 18 years; (2) loop ileostomy due to other surgeries; (3) end ileostomy; (4) emergency surgery; (5) other surgical procedures performed during the ileostomy period; and (6) no provision of informed consent. Patients can withdraw from the study without any reason or condition. The enrolled patients were randomly assigned to either an MPNPWT or a control group using sealed envelopes.

Sample size

The sample size calculation was based on an unpublished prospective observational study conducted at our center, in which 38 patients were evaluated for incision SSI after ileostomy. The overall incidence of incisional SSI was 10.5%. Incisional SSI occurred in four of the 25 patients (16%) in the control group, while no incisional SSI was observed in 13 patients using MPNPWT (incisional SSI incidence was 0). A total of 44 patients were required in each group to achieve a type I error of 0.05 with a power of 0.8. Assuming a 10% dropout rate, the expected 50 patients were recruited in each arm, with a sample size of 100 patients.

Randomization and blinding

An independent statistician randomly assigned eligible patients in a 1:1 ratio using sequentially sealed envelopes to the control or MPNPWT groups without stratification. Randomization was done after admission to the hospital and before ileostomy closure. The sealed envelopes contained allocations from a computer-generated table of random numbers and were opened before surgery. This study did not permit the use of blinding methods because the application of the

MPNPWT could not be concealed. However, the analysis was done by a blinded statistician.

Surgical procedures

Each patient underwent the same procedure of ileostomy closure at the Department of Colorectal Surgery, Sir Run Run Shaw Hospital. During the operation, the ileum was reconstructed with mechanical side-to-side anastomosis using an easyEndo™ endoscopic linear cutter stapler (60 mm length, blue cartridge). Hand-sewn end-to-end anastomosis can also be chosen. All patients received reinforcement sutures for anastomotic stoma. The fascia of the rectus abdominis muscle was closed using continuous suturing. The subcutaneous tissues were not sutured. The skin was intermittently sutured with 2–0 Prolene in both groups. Needle spacing was 6–8 mm in the control group and 10–12 mm in the MPNPWT group. A micro-power negative pressure dressing (MJ-01B3, Guangdong Meiji Biotechnology Co. Ltd.) was filled on the skin surface of the patients in the MPNPWT group by nurses from the wound care clinic. As displayed in Figure 2, the incision was covered with two pieces of polyvinyl alcohol foam material and then sealed and fixed with a transparent film. The material expanded as it absorbed exudates. The dressing was removed after 72 h. If excessive exudates caused negative pressure failure, the dressing was removed earlier and changed to a new one.

Perioperative and postoperative care

Cefmetazole was administered intravenously as a preoperative prophylactic antibiotic. Etimicin sulfate was injected in patients allergic to penicillin or cephalosporin. Typically, the same antibiotics were used postoperatively until the C-reactive protein dropped below 50 mg/L (usually three continuous days). If there was other evidence of infection, the type and duration of antibiotics were adjusted according to clinical experience. In the experimental group, the micro-power negative-pressure dressing was maintained for 72 h and then changed to a traditional dressing material. The negative pressure dressing should be replaced if there was excessive leakage or if the negative pressure failed within 72 h. In the control group, the traditional dressing material was routinely changed in 72 h. In addition, the dressing was changed whenever it became wet. The stitches were removed 2 wk after surgery in both groups. The patients were followed for 30 d postoperatively. The surgical wounds were routinely monitored by the surgical team for 30 d.

Identification of incisional SSI

The primary outcome of this study was incisional SSI. The infection occurred within 30 d after the operation and involved only the skin or subcutaneous tissue of the incision. It was defined according to the standard of the Center for Disease Control and Prevention (1999)[9], following at least one of the criteria: Purulent drainage, with or without positive culture; laboratory confirmation of the incision exudate; or any one of the following signs or symptoms of infection: Pain or tenderness, localized swelling, and redness or heat.

Statistical analysis

Continuous variables with a normal or non-normal distribution are presented as the mean ± SD or median and 25^{th}–75^{th} percentiles, respectively. Continuous variables were compared using Student's *t*-test or Mann–Whitney *U* test. Categorical variables were compared using Pearson's chi-squared test or Fisher's exact test. Logistic regression was used to detect risk factors for incisional SSI. Statistical significance was set at $P < 0.05$. The data were statistically analyzed using SPSS software (version 25.0.0.2; SPSS Inc., Chicago, IL, United States).

RESULTS

Characteristics of patients

This study enrolled 101 consecutive patients: 51 in the control group and 50 in the MPNPWT group (Figure 3). Table 1 displays no significant differences in the demographic and clinical features of the patients between the two groups. Most enrolled patients were male (65.3%). Most patients were in good health, with an average body mass index within the normal range for Chinese people (18.5–24). The majority had an American Society of Anaesthesiology (ASA) score of 1-2 (96.0%), with normal values of preoperative albumin and hemoglobin. There were no significant differences in the medical history, including hypertension and diabetes, between the two groups. Since a considerable proportion of patients received perioperative chemoradiotherapy, the waiting time until ileostomy closure was almost 6 mo.

Surgical outcomes

We compared the surgical outcomes between the two groups to evaluate the efficacy and safety of MPNPWT. The surgical outcomes did not differ significantly between them (Table 2). These two different surgical procedures shared similar operative time (78.14 ± 20.02 *vs* 81.36 ± 17.64, $P = 0.393$) and blood loss (17.35 ± 4.40 *vs* 19.70 ± 7.45, $P = 0.056$) in the control and MPNPWT groups. Moreover, postoperative intra-abdominal complications, including anastomotic inflammation and bowel obstruction, did not differ significantly between the two groups. No anastomotic leakage or bleeding was observed in either group. The patients complained of no pain or discomfort with a micro-power negative pressure dressing. In addition, in the MPNPWT group, no patients had skin allergy or dermatitis potentially caused by the micro-power negative pressure dressing. The above evidence indicates that MPNPWT is a safe procedure without side effects on ileostomy closure.

Importantly, the incisional SSI rate was significantly lower in the MPNPWT group than in the control group (2.0% *vs* 15.7%, $P = 0.031$). In the MPNPWT group, only one patient developed SSI on postoperative day 5. However, eight

Table 1 Demographic and clinical features of included patients

Variable	Control group (*n* = 51)	MPNPWT group (*n* = 50)	*P* value
Gender, *n* (%)			0.487
Male	34 (66.7)	30 (60.0)	
Female	17 (33.3)	20 (40.0)	
Age (yr)	64.43 ± 9.06	61.66 ± 14.22	0.247
BMI (kg/m^2)	21.82 ± 2.90	22.61 ± 3.06	0.184
Hypertension, *n* (%)	22 (43.1)	19 (38.0)	0.599
Diabetes, *n* (%)	7 (13.7)	8 (16.0)	0.748
ASA score, *n* (%)			0.362
1-2	50 (98.0)	47 (94.0)	
3	1 (2.0)	3 (6.0)	
HB (g/L)	130.78 ± 14.67	132.36 ± 13.32	0.573
Albumin (g/L)	43.10 ± 4.00	43.95 ± 3.75	0.275
Perioperative, *n* (%), CRT	32 (62.7)	27 (54.0)	0.373
Parastomal hernia, *n* (%)	7 (13.7)	5 (10.0)	0.563
Time duration from ileostomy to closure (mo)	6.13 ± 2.45	5.51 ± 2.67	0.232

MPNPWT: Micro-power negative pressure wound technique; BMI: Body mass index; HB: Hemoglobin; CRT: Chemoradiotherapy.

Table 2 Surgical outcomes of included patients

Variable	Control group (*n* = 51)	MPNPWT group (*n* = 50)	*P* value
Operative time (min)	78.14 ± 20.02	81.36 ± 17.64	0.393
Blood loss (mL)	17.35 ± 4.40	19.70 ± 7.45	0.056
Complications, *n* (%)			
Anastomotic inflammation	3 (5.9)	0 (0.0)	0.243
Bowel obstruction	3 (5.9)	5 (10.0)	0.487
Incisional SSI, *n* (%)	8 (15.7)	1 (2.0)	0.031
Postoperative hospital stays (d)	8.51 ± 4.03	7.34 ± 2.06	0.069
Hospitalization costs (yuan)	26168.84 ± 6627.74	26419.4 ± 6019.23	0.843

MPNPWT: Micro-power negative pressure wound technique; SSI: Surgical site infection.

patients in the control group experienced incisional SSI within 9 d after surgery. Three patients underwent MPNPWT after opening the infected incision. The incisions were then cleaned and subsequently closed. In addition, there were 15 patients with a medical history of diabetes. The incisional SSI rate among diabetic patients was lower in the MPNPWT group (1/8) than in the control group (3/7), but the difference was not statistically significant (12.5% *vs* 42.9%, $P = 0.282$). Postoperative hospital stay length and hospitalization cost did not differ significantly between the two groups ($P = 0.069$ and 0.843, respectively).

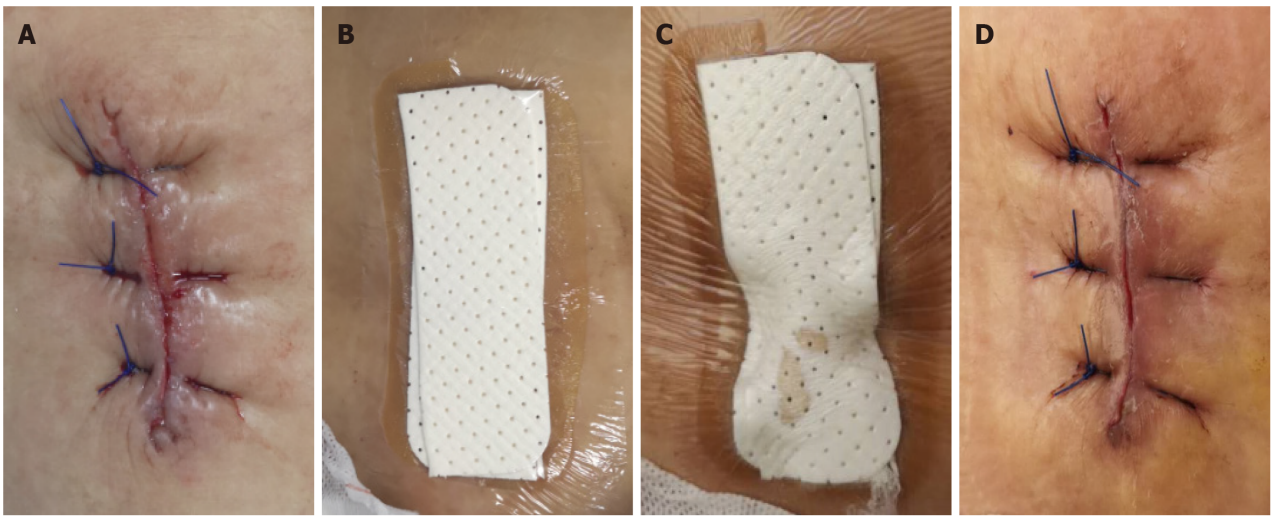
Risk factors for incisional SSI

Logistic regression was performed to identify the risk factors associated with incisional SSI. Table 3 shows that those patients who underwent ileostomy closure with MPNPWT had a significantly lower incisional SSI rate than those who underwent traditional procedures [odds ratio (OR) = 0.110, $P = 0.041$)]. Moreover, patients with diabetes were more likely to suffer incisional SSI (OR = 5.891, $P = 0.017$). Multivariate analysis further confirmed that MPNPWT was an independent protective factor (OR = 0.005, $P = 0.025$) and diabetes was a risk factor (OR = 26.575, $P = 0.029$) for incisional SSI.

Table 3 Logistic analysis of risk factors for surgical site infection

Variable	Univariate		Multivariate	
	OR (95%CI)	*P* value	OR (95%CI)	*P* value
Female gender	0.465 (0.091–2.367)	0.357		
Age (yr)	1.034 (0.965–1.107)	0.343		
BMI (kg/m^2)	1.115 (0.929–1.337)	0.241		
ASA score 3	3.708 (0.345–39.908)	0.28		
Hypertension	3.257 (0.765–13.863)	0.11		
Diabetes	5.891 (1.371–25.311)	0.017	26.575 (1.391–507.694)	0.029
HB (g/L)	0.967 (0.921–1.016)	0.189		
Albumin (g/L)	1.053 (0.883–1.254)	0.567		
MPNPWT	0.110 (0.013–0.913)	0.041	0.005 (0.000–0.515)	0.025
Perioperative CRT	0.880 (0.222–3.492)	0.855		
Blood loss (mL)	1.010 (0.910–1.122)	0.849		
Operative time (min)	1.007 (0.973–1.043)	0.677		

ASA: American Society of Anaesthesiology; MPNPWT: Micro-power negative pressure wound technique; BMI: Body mass index; HB: Hemoglobin; CRT: Chemoradiotherapy; OR: Odds ratio; 95%CI: 95% confidence interval.



DOI: 10.4240/wjgs.v16.i1.186

Figure 2 Incision equipped with micro-power negative pressure wound dressing. A: During the surgery, the incision was intermittently sutured with 2-0 Prolene with a 10-12 mm needle spacing in the micro-power negative pressure wound technique group; B: Then the micro-power negative pressure wound dressing was equipped immediately; C: When exudates were absorbed, they appeared on the the material's surface, and the dressing expanded; D: A clean and dry incision was obtained after removing the material in 72 h.

DISCUSSION

Incisional SSI is the main complication of loop ileostomy closure. In the present study, we introduced a new technique, MPNPWT, to prevent postoperative incision infection after loop ileostomy closure. This technique significantly reduced the incisional SSI rate to a low level (2.0%).

Surgical incisions are classified into four classes. Class I or class II wounds are clean or relatively clean, with an infection risk of < 2% or < 10%, respectively[10]. Although the surgical incision for ileostomy closure is a class II wound, the incisional SSI rate is much higher than those of other intestinal surgeries, ranging from 2% to 40%[11-13]. In this study, the incisional SSI rate in the control group was also higher than 10%. Adequate drainage is the most effective way to deal with an infected or potentially infected incision and can greatly reduce the incisional SSI rate[14]. Current methods for incisional SSI prevention involve increasing drainage, including subcutaneous suction drainage, negative-pressure system, and purse-string skin closure. However, each of these technologies has its limitations.

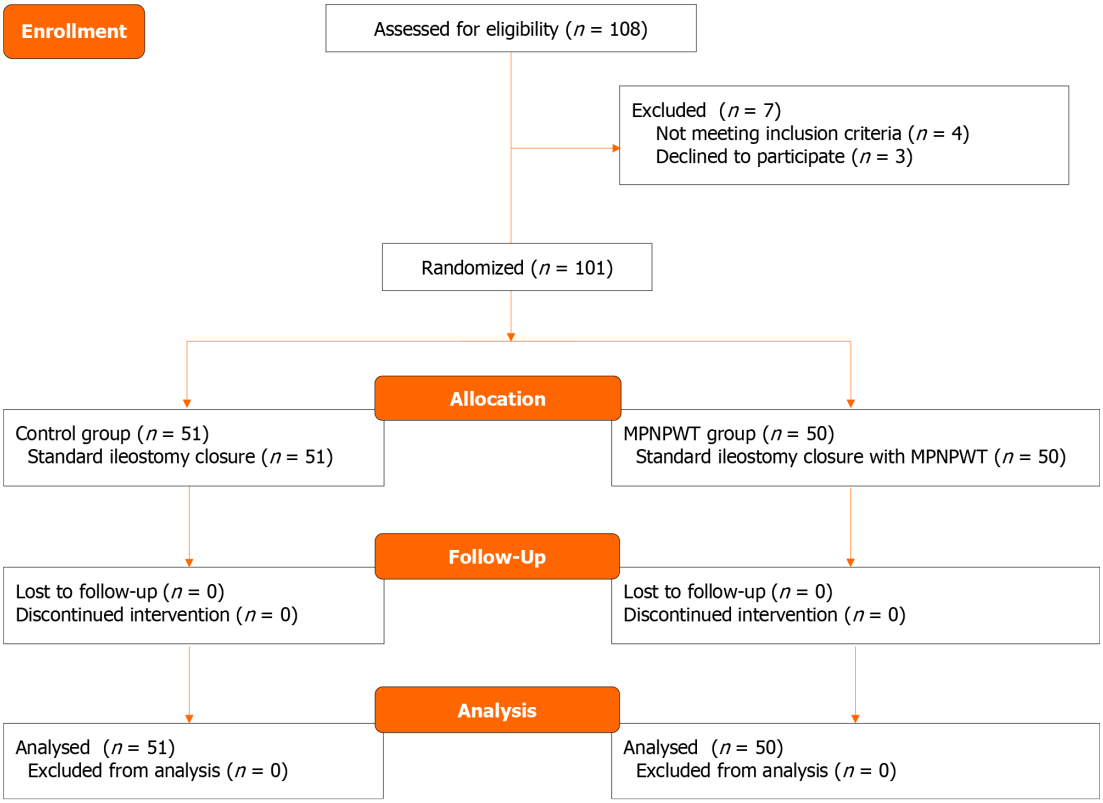


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Figure 3 Consort diagram.

MPNPWT is a new technique that has been improved by the NPT. It does not require the configuration of external negative pressure equipment, whether connected to the wall or portable. The suction efficiency of traditional NPT depends on pressure regulation. If the negative pressure is too low, it may be unable to absorb the effusion effectively, yet if it is too high, it may cause tissue damage. Moreover, high pressure may induce the exfoliation of regenerative cells in the wound[15]. However, MPNPWT uses a special material that produces micro-negative pressure by absorbing exudates rather than a suction device. The material expands when the exudates are absorbed. Then, the medical film is gradually elevated, leading to a larger closed space and local vacuum, resulting in a negative pressure suction effect. The suction mechanism is different from the capillary action caused by the adhesive and cohesive forces interacting between the liquid and the surface. Due to the unique design of the material, the more exudates it absorbs, the more powerful the micro-negative pressure. Obviously, excess exudates can invalidate the negative pressure. Meanwhile, it only maintains a relatively low pressure (–0.1 to –0.3 kPa) that may not cause tissue damage. Consequently, MPNPWT can be used to prevent incisional infection because it works on incisions with exudates. The liquid-locking layer of the material has a high liquid absorption efficiency. According to the test, a material with 7.0 cm × 10 cm × 0.1 cm dimension can absorb and preserve up to 70 mL of liquid[6]. After applying MPNPWT to the incision, the exudate may be quickly absorbed by the liquid-locking layer, thereby keeping the incision clean. In the MPNPWT group, we used 2–0 Prolene to close the incision with a wide needle distance so that the micro-negative pressure could effectively absorb the effusion and create a favorable condition for incision healing.

In this study, the MPNPWT group had a 2.0% incisional SSI rate, which was significantly lower than that of the control group. Moreover, MPNPWT may be superior to other techniques in preventing incision infection[3,13,16-18]. Serracant *et al*[13] inserted contralateral drainage into the subcutaneous space to reduce the incisional SSI rate after loop ileostomy closure, achieving an 8.6% rate in 35 patients. Wierdak *et al*[18] designed a RCT to assess the role of prophylactic negative-pressure wound therapy in preventing wound healing complications. In that study, negativepressure wound therapy reduced the incidence of SSI to 5.71%. Another study by Lee *et al*[3] introduced a purse-string skin closure in which a circular suture was performed on the dermal layer with absorbable sutures. Purse-string skin closure contributed to a significantly lower wound infection rate (5.6%) than conventional linear skin closure. Although the incisional SSI rate may vary among studies, it is presumed that MPNPWT is a more efficient and convenient technique. A recent RCT study recruited patients undergoing reoperative open colorectal resections to investigate the effect of NPT on SSIs[19]. The results indicated that the 30-d SSI rate did not differ significantly between the NPT group and control groups (9.4% *vs* 14.1%, $P = 0.28$). Therefore, that study concluded that NPT was unrelated to a significant reduction in SSI. There were several reasons for this contradictory conclusion. First, the high SSI rate in the NPT group could be explained by the selection criteria that included high-risk factors for SSI. Second, we have noticed that the incision was closed with skin staples in that study. Generally, the needle spacing of skin staples was narrower than that of Prolene, which might lead to poor drainage. Moreover, the narrow needle spacing would cause the epidermis to heal earlier than the subcutaneous

tissue, which might prevent NPT from absorbing exudates. Therefore, our MPNPWT accompanied with wider needle spacing would be more effective for incisional SSI.

Several factors are associated with incisional SSI, such as ASA score and operative time[9]. Diabetes is likely to induce poor wound healing. Our results demonstrated that diabetes was an independent risk factor for incisional SSI. Moreover, MPNPWT could decrease the incisional SSI rate in diabetic patients. Additionally, MPNPWT was appropriate for infected incisions. Patients with MPNPWT spared the trouble of dressing change and suffered less pain than patients with open incisions. Previous studies have confirmed the efficacy of MPNPWT in open wounds such as diabetic foot, open fracture, and burn wounds[6,8]. Notably, MPNPWT is not recommended for wounds with excessive exudates because of the special mechanism of this material.

In our center, we do not choose subcutaneous suction drainage or purse-string skin closure to prevent incisional SSI. We believe that these techniques are cumbersome and increase patient suffering. In contrast, MPNPWT is simple and convenient. It can be performed in a post-anesthesia care unit by a wound care clinic at our center or performed by trained surgeons during the surgery. Furthermore, we confirmed that MPNPWT is safe. Specifically, patients in the MPNPWT group did not suffer from skin allergy, dermatitis, or any pain. In addition, MPNPWT did not affect hospitalization costs (P = 0.843). Moreover, MPNPWT shortened the length of hospital stays to a certain extent, though not significantly. Surgical outcomes such as operative time, hospitalization cost, and length of hospital stay are important factors associated with patient recovery and feelings. Previous studies have often lacked investigations into these aspects. Lee *et al*[3] reported that the median hospitalization period in the purse-string skin closure group was 7 d, which was significantly shorter than that in the linear skin closure group. However, according to our center's experience, it takes longer than 7 d to heal the incision with purse-string skin closure, implying that patients still need dressing changes even after hospital discharge.

The main limitation of this study was that it was a single-center clinical trial with a relatively small sample size. In addition, needle spacing was different between the two groups, which may be a bias when analyzing the effectiveness of MPNPWT. Finally, some other less significant confounders that were not recorded in our study may have introduced bias. A larger multicenter clinical study with a better design should be conducted in the future.

CONCLUSION

As a prospective RCT, our study introduced a novel technique, MPNPWT, to prevent incisional SSI after loop ileostomy closure. MPNPWT reduces the incidence of incisional SSI and helps patients recover during hospitalization.

ARTICLE HIGHLIGHTS

Research background

Although ileostomy closure is technically easy, it is associated with a non-negligible overall morbidity rate (11%-37%), with incisional surgical site infection (SSI) being the most common.

Research motivation

The incisional SSI rate after ileostomy closure is much higher than those of other intestinal surgeries, ranging from 2% to 40%. Incisional SSI is responsible for increased pain, longer hospital stays, and higher treatment costs. Current methods for incisional SSI prevention have limitations. Finding a new approach to prevent incisional SSI is urgent for patients receiving ileostomy closure.

Research objectives

Micro-power negative pressure wound technique (MPNPWT) contains a special material that produces micro-negative pressure by absorbing exudates rather than suction device. It reduces wound edema and stimulates epithelial cell proliferation and granulation tissue growth, thus shortening wound healing time. This study aimed to evaluate the efficacy and safety of MPNPWT in preventing incisional SSI. The results of our study will provide foundation for future application of MPNPWT.

Research methods

This was a single-center, prospective, randomized controlled trial (RCT). An independent statistician randomly assigned eligible patients in a 1:1 ratio using sequentially sealed envelopes to a control group or an MPNPWT group without stratification. Micro-power negative pressure dressing was filled on the skin surface of patients in the MPNPWT group by nurses from wound care clinic.

Research results

MPNPWT significantly reduced incisional SSI rate (2.0%). MPNPWT is a safe technique without any side effect. MPNPWT could also help heal the infected incision.

Research conclusions

Our study introduces a novel technique, MPNPWT, to prevent incisional SSI after loop ileostomy closure. MPNPWT reduces the incidence of incisional SSI after loop ileostomy closure.

Research perspectives

A larger RCT with a larger sample is the direction of the future research.

FOOTNOTES

Author contributions: Xu DY and Bai BJ were responsible for the study conception and design; Shan LN and Wei HY analyzed the data and wrote the manuscript; Lin DF, Wang Y, and Wang D critically revised the article for important intellectual content; all the authors reviewed and approved the final version to be published.

Supported by the Zhejiang Provincial Natural Science Foundation of China, No. LQ20H260002.

Institutional review board statement: The study was reviewed and approval by the Ethics Committee of Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University (No. 20191217-9).

Clinical trial registration statement: The trial was registered at Chinese Clinical Trial Registry at https://www.chictr.org.cn (registration number: ChiCTR2200064827).

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

Conflict-of-interest statement: All authors declare no potential conflicting interests related to this paper.

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

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S-Editor: Lin C
L-Editor: Wang TQ
P-Editor: Zhao S

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World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2024 January 27; 16(1): 196-204

DOI: 10.4240/wjgs.v16.i1.196

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Randomized Controlled Trial

Paravertebral block's effect on analgesia and inflammation in advanced gastric cancer patients undergoing transarterial chemoembolization and microwave ablation

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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: Bessede E, France; Tanabe M, Japan

Received: November 6, 2023
Peer-review started: November 6, 2023
First decision: November 16, 2023
Revised: November 20, 2023
Accepted: December 11, 2023
Article in press: December 11, 2023
Published online: January 27, 2024

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Abstract

BACKGROUND

Transarterial chemoembolization (TACE) combined with microwave ablation (MWA) is an effective treatment strategy for patients with advanced gastric cancer and liver metastasis. However, it may cause severe postoperative pain and inflammatory responses. The paravertebral block (PVB) is a regional anesthetic technique that provides analgesia to the thoracic and abdominal regions.

AIM

To evaluate the effect of PVB on postoperative analgesia and inflammatory response in patients undergoing TACE combined with MWA for advanced gastric cancer and liver metastasis.

METHODS

Sixty patients were randomly divided into PVB and control groups. The PVB group received ultrasound-guided PVB with 0.375% ropivacaine preoperatively,

whereas the control group received intravenous analgesia with sufentanil. The primary outcome was the visual analog scale (VAS) score for pain at 6 h, 12 h, 24 h, and 48 h after the procedure. Secondary outcomes were the dose of sufentanil used, incidence of adverse events, and levels of inflammatory markers (white blood cell count, neutrophil percentage, C-reactive protein, and procalcitonin) before and after the procedure.

RESULTS

The PVB group had significantly lower VAS scores at 6 h, 12 h, 24 h, and 48 h after the procedure compared with the control group ($P < 0.05$). The PVB group also had a significantly lower consumption of sufentanil and a lower incidence of nausea, vomiting, and respiratory depression than did the control group ($P < 0.05$). Compared with the control group, the PVB group had significantly lower levels of inflammatory markers 24 h and 48 h after the procedure ($P < 0.05$).

CONCLUSION

PVB can effectively reduce postoperative pain and inflammatory responses and improve postoperative comfort and recovery in patients with advanced gastric cancer and liver metastasis treated with TACE combined with MWA.

Key Words: Transarterial chemoembolization; Microwave ablation; Paravertebral block; Visual analog scale; Sufentanil; Inflammatory markers

Core Tip: Paravertebral block (PVB) provides effective postoperative analgesia and reduces inflammatory responses in patients undergoing transarterial chemoembolization combined with microwave ablation for advanced gastric cancer and liver metastasis. In a study comparing PVB with intravenous analgesia, the PVB group exhibited lower pain scores, reduced sufentanil consumption, and fewer adverse events. Additionally, the PVB group showed decreased levels of inflammatory markers, indicating improved postoperative comfort and recovery. PVB is a valuable technique for managing pain and inflammation in this patient population.

Citation: Xiong YF, Wei BZ, Wang YF, Li XF, Liu C. Paravertebral block's effect on analgesia and inflammation in advanced gastric cancer patients undergoing transarterial chemoembolization and microwave ablation. *World J Gastrointest Surg* 2024; 16(1): 196-204
URL: https://www.wjgnet.com/1948-9366/full/v16/i1/196.htm
DOI: https://dx.doi.org/10.4240/wjgs.v16.i1.196

INTRODUCTION

Gastric cancer is one of the most common malignancies worldwide and the third leading cause of cancer-related death [1]. Liver metastasis is a common complication of advanced gastric cancer that affects the patient prognosis and quality of life[2]. Transarterial chemoembolization (TACE) combined with microwave ablation (MWA) is a minimally invasive treatment that can achieve local tumor control and prolong the survival of patients with gastric cancer and unresectable liver metastases[3,4]. However, this treatment may induce severe postoperative pain and inflammatory responses, which may affect patient recovery and outcomes[5,6].

The paravertebral block (PVB) is a regional anesthesia technique that provides analgesia to the thoracic and abdominal regions by blocking the spinal nerves in the paravertebral space[7]. PVB has been shown to reduce postoperative pain, opioid consumption, and the side effects of various surgical procedures[8-10]. However, few studies have reported the effect of PVB on postoperative analgesia and the inflammatory response in patients undergoing TACE combined with MWA for advanced gastric cancer and liver metastasis.

Therefore, we conducted a randomized controlled trial to compare the effects of PVB with those of intravenous analgesia on postoperative pain and inflammatory response in these patients. We hypothesized that PVB would reduce postoperative pain and inflammatory responses and improve postoperative comfort and recovery.

MATERIALS AND METHODS

This study was approved by the Ethics Committee of our hospital. Written informed consent was obtained from all patients before enrollment. The study was conducted following the principles of the Declaration of Helsinki.

Patients

We enrolled patients who met the following criteria: (1) Aged 18–75 years; (2) diagnosed with advanced gastric cancer

and unresectable liver metastasis; (3) scheduled for TACE combined with MWA; (4) American Society of Anesthesiologists (ASA) physical status I–III; (5) no contraindications to PVB or intravenous analgesia; (6) no history of allergy to local anesthetics or opioids; (7) no history of coagulation disorders or anticoagulant therapy; (8) no history of chronic pain or opioid use; (9) no history of infection or inflammation in the paravertebral region; and (10) no history of psychiatric disorders or cognitive impairment.

We excluded patients who met any of the following criteria: (1) Conversion to open surgery during the procedure; (2) failure of PVB or intravenous analgesia; (3) occurrence of severe complications during or after the procedure; and (4) withdrawal of consent or loss of follow-up.

Randomization and blinding

We used a computer-generated random number table to randomly assign patients to the PVB or the control group at a 1:1 ratio. The allocation sequence was concealed in sealed opaque envelopes and opened by an independent researcher before the procedure. The patients, anesthesiologists who performed the PVB, radiologists who performed TACE and MWA, and outcome assessors were blinded to the group allocation. The blind method was maintained using a sham PVB procedure for the control group. The control group received an ultrasound-guided needle insertion into the paravertebral space without the injection of a local anesthetic. The patients, anesthesiologists, radiologists, and outcome assessors were blinded to the group allocation and the presence or absence of local anesthetic injections.

Interventions

All patients underwent standard preoperative preparations, including fasting for 8 h and intravenous hydration. Upon arrival at the interventional radiology suite, standard monitoring was performed, including electrocardiography, noninvasive blood pressure measurement, pulse oximetry, and bispectral index. All patients received intravenous midazolam 0.03 mg/kg and dexmedetomidine 1 μg/kg as sedatives before the procedure.

The PVB group underwent ultrasonography-guided PVB with 0.375% ropivacaine before the procedure. The PVB was performed by an experienced anesthesiologist using a linear probe (6-13 MHz) and a 22-gauge, 80-mm needle (Stimuplex® A, B. Braun Melsungen AG, Germany). PVB was performed at the T10-L1 levels on both sides of the spine. The paravertebral space was identified using the loss-of-resistance technique and confirmed by ultrasound visualization of the spread of local anesthetic. Twenty milliliters of 0.375% ropivacaine were injected at each level on each side for a total dose of 150 mg.

The patients in the control group received intravenous sufentanil analgesia before and during the procedures. Sufentanil was administered using a patient-controlled analgesia (PCA) pump (Graseby™ 3400, Smiths Medical International Ltd., United Kingdom) with a bolus dose of 5 μg, a lockout interval of 10 min, and a background infusion of 0.1 μg/kg/h.

TACE, combined with MWA, was performed by two experienced radiologists using standard techniques. A 5-Fr catheter was inserted into the femoral artery and advanced into the celiac trunk or the superior mesenteric artery under fluoroscopic guidance. Selective angiography was performed to identify the arteries feeding the liver metastases. A microcatheter was advanced into the feeding arteries, and a mixture of lipiodol, doxorubicin, and mitomycin C was injected until stasis was achieved. After TACE, MWA was performed using a microwave generator (KY-2000; Kangyou Medical, Nanjing, China) and a 14-gauge antenna (KY-2000-14G-15CM-2.45G; Kangyou Medical). The antenna was inserted into the liver metastases under ultrasound guidance, and ablation was performed until a sufficient safety margin was achieved. This procedure was repeated until all liver metastases had been ablated.

Outcomes

The primary outcome was the visual analog scale (VAS) score for pain at 6 h, 12 h, 24 h, and 48 h after the procedure. The VAS score is a 10-cm horizontal line with anchors at each end representing no pain (score = 0) and the worst pain imaginable (score = 10). Patients were asked to mark their pain intensity on a line, and the score was measured using a ruler.

The secondary outcomes were: (1) The consumption of sufentanil during and after the procedure; (2) the incidence of adverse events, such as nausea, vomiting, respiratory depression (respiratory rate < 8 breaths/min or oxygen saturation < 90%), hypotension (systolic blood pressure < 90 mmHg or decrease > 20% from baseline), bradycardia (heart rate < 50 beats/min or decrease > 20% from baseline), and puncture site hematoma; and (3) the levels of inflammatory markers, including white blood cell (WBC) count, neutrophil percentage (NEUT%), C-reactive protein (CRP), and procalcitonin (PCT), before and after the procedure.

Sufentanil consumption was recorded using a PCA pump during and 48 h after the procedure. Radiologists activated the PCA pump during the procedure according to the patient's pain levels. The PCA pump was activated after the procedure. Sufentanil consumption during the procedure was calculated by subtracting the amount of sufentanil used during anesthesia from the total sufentanil consumption during the procedure. Sufentanil consumption during anesthesia was recorded separately for the control group. The PVB group did not receive sufentanil during anesthesia, and adverse events were recorded through direct observation and patient interviews during and after the procedure until discharge. Inflammatory markers were measured using blood samples obtained preoperatively and 24 and 48 h postoperatively.

Statistical analysis

We calculated that a sample size of 26 patients per group would provide 80% power to detect a difference of 2 points in VAS scores between the two groups with a standard deviation of 2.5 points and a significance level of 0.05. The sample size was increased to 30 patients per group to account for a dropout rate of 10%. Data were analyzed using SPSS software

(version 22.0; IBM Corp., Armonk, NY, United States). The normality of the data was tested using the Kolmogorov-Smirnov test. Categorical data are expressed as frequencies and percentages and compared using the chi-square or Fisher's exact test. Continuous data were expressed as means ± SD and compared using the independent t-test or the Mann-Whitney *U* test. Repeated-measures analysis of variance (ANOVA) or the Friedman test was used to compare the changes in the VAS score and inflammatory markers over time within and between the groups. Statistical significance was set at $P < 0.05$.

RESULTS

Sixty patients were enrolled and randomly assigned into one of two groups. Two patients in the control group were excluded due to conversion to open surgery or failure of intravenous analgesia. The final analysis included 28 and 30 patients in the PVB and control groups, respectively. The baseline patient characteristics are shown in Table 1. The groups did not differ significantly in age, sex, body mass index, ASA of anesthesiologist's physical status, tumor size, number of tumors, or procedure duration.

VAS scores for pain at different time points after the procedure are shown in Table 2. The PVB group had significantly lower VAS scores than that in the control group at all time points ($P < 0.05$). A repeated-measures ANOVA revealed a significant interaction effect between the groups and time ($P < 0.001$), indicating that the difference in the VAS scores between the two groups changed over time.

Sufentanil consumption during and after the procedure is shown in Table 3. The PVB group had a significantly lower consumption of sufentanil than that in the control group during and after the procedure ($P < 0.05$).

The incidence of adverse events during and after the procedure is shown in Table 4. The PVB group had a significantly lower incidence of nausea, vomiting, and respiratory depression than that in the control group ($P < 0.05$). The groups did not differ significantly regarding the incidence of hypotension, bradycardia, or puncture site hematoma between the two groups ($P > 0.05$).

The levels of inflammatory markers before and after the procedure are shown in Table 5. The PVB group had significantly lower WBC count, NEUT%, CRP, and PCT levels than those in the control group at 24 and 48 h after the procedure ($P < 0.05$). Repeated measures ANOVA revealed a significant interaction effect between group and time for all inflammatory markers ($P < 0.001$), indicating that the difference in the inflammatory response between the two groups changed over time.

DISCUSSION

This study revealed that PVB can effectively reduce postoperative pain and inflammatory responses in patients with advanced gastric cancer and liver metastasis treated with TACE combined with MWA and improve postoperative comfort and recovery.

Postoperative pain is a common and distressing symptom in patients undergoing TACE combined with MWA and may affect their quality of life and recovery. Postoperative pain may trigger or exacerbate inflammatory responses, which may increase the risk of infection, organ dysfunction, and poor outcomes. Therefore, adequate postoperative analgesia is essential for these patients.

PVB is a regional anesthetic technique that provides analgesia to the thoracic and abdominal regions by blocking the spinal nerves in the paravertebral space. PVB has several advantages over other analgesic methods, such as intravenous, epidural, and intrathecal analgesia[11]. First, PVB provides effective and long-lasting analgesia without affecting the motor or sensory functions of the lower limbs[12]. Second, PVB can reduce the consumption of opioids and associated side effects such as nausea, vomiting, respiratory depression, pruritus, and constipation[13]. Third, PVB can attenuate stress and inflammatory responses induced by surgery or trauma, which may improve immune function and patient outcomes[14].

In this study, PVB significantly reduced the VAS score for pain at all time points after the procedure compared to that in intravenous analgesia, indicating that PVB provides superior postoperative analgesia for these patients[15]. This is consistent with the findings of previous studies that reported that PVB can reduce postoperative pain in various surgical procedures involving the thoracic or abdominal regions[16]. We observed that PVB significantly reduced the consumption of sufentanil during and after the procedure compared with that in intravenous analgesia, indicating that PVB reduced the need for opioids and their potential side effects[17]. This is consistent with the results of previous studies, indicating that PVB can reduce opioid consumption and side effects during various surgical procedures[18,19].

In addition to postoperative analgesia, we evaluated the effect of PVB on the postoperative inflammatory responses in these patients. We measured the levels of inflammatory markers, including WBC count, NEUT%, CRP, and PCT, before and after the procedure. We identified that PVB significantly reduced the levels of inflammatory markers 24 and 48 h after the procedure compared to that in intravenous analgesia, indicating that PVB attenuated the postoperative inflammatory response in these patients. This is in accordance with previous studies showing that PVB reduces the levels of inflammatory markers during various surgical procedures[20-23]. The mechanism by which PVB reduces the postoperative inflammatory response may be related to its effect on blocking sympathetic nerve activity and modulating the neuroendocrine-immune axis[24].

Table 1 Patients' baseline characteristics

Variable	PVB group (*n* = 28)	Control group (*n* = 30)	*P* value
Age (yr)	56.4 ± 9.2	58.3 ± 8.7	0.42
Sex (male/female)	16/12	18/12	0.72
Body mass index (kg/m^2)	23.5 ± 3.1	24.2 ± 2.9	0.34
ASA physical status (I/II/III)	6/16/6	8/14/8	0.81
Tumor size (cm)	4.6 ± 1.2	4.8 ± 1.3	0.56
Tumor number (single/multiple)	12/16	14/16	0.77
Procedure duration (min)	82.5 ± 15.4	85.3 ± 16.2	0.51

Data are expressed as means ± SD or frequencies. ASA: American Society of Anesthesiologists; PVB: Paravertebral block.

Table 2 Visual analog scale score for pain at different time points after the procedure

Time point	PVB group (*n* = 28)	Control group (*n* = 30)	*P* value
6 h after the procedure	2.1 ± 1.2	4.3 ± 1.4	< 0.001
12 h after the procedure	1.8 ± 1.0	3.7 ± 1.3	< 0.001
24 h after the procedure	1.4 ± 0.9	3.2 ± 1.2	< 0.001
48 h after the procedure	1.1 ± 0.8	2.8 ± 1.1	< 0.001

Data are expressed as means ± SD. PVB: Paravertebral block.

Table 3 Consumption of sufentanil during and after the procedure

Variable	PVB group (*n* = 28)	Control group (*n* = 30)	*P* value
Sufentanil consumption during the procedure (μg)	15.7 ± 4.2	25.3 ± 5.6	< 0.001
Sufentanil consumption after the procedure (μg)	32.1 ± 8.7	48.6 ± 10.4	< 0.001
Total sufentanil consumption (μg)	47.8 ± 11.3	73.9 ± 13.2	< 0.001

Data are expressed as means ± SD. PVB: Paravertebral block.

Table 4 Incidence of adverse events during and after the procedure

Variable	PVB group (*n* = 28)	Control group (*n* = 30)	*P* value
Nausea (%)	7.1	26.7	0.03
Vomiting (%)	3.6	16.7	0.04
Respiratory depression (%)	0	10	0.02
Hypotension (%)	3.6	6.7	0.65
Bradycardia (%)	0	3.3	> 0.99
Puncture site hematoma (%)	0	0	> 0.99

Data are expressed as means ± SD. PVB: Paravertebral block.

Table 5 Levels of inflammatory markers before and after the procedure

Variable	Time point	PVB group (*n* = 28)	Control group (*n* = 30)	*P* value
WBC (× 10^9/L)	Before the procedure	6.8 ± 1.5	7.1 ± 1.6	0.36
	24 h after the procedure	9.4 ± 2.1	12.3 ± 2.7	< 0.001
	48 h after the procedure	8.2 ± 1.8	10.5 ± 2.4	< 0.001
NEUT% (%)	Before the procedure	65.3 ± 8.5	66.7 ± 9.2	0.54
	24 h after the procedure	72.4 ± 7.6	80.5 ± 6.8	< 0.001
	48 h after the procedure	69.2 ± 7.2	76.3 ± 7.4	< 0.001
CRP (mg/L)	Before the procedure	5.2 ± 1.4	5.6 ± 1.6	0.32
	24 h after the procedure	18.7 ± 4.3	26.4 ± 5.9	< 0.001
	48 h after the procedure	14.3 ± 3.8	20.6 ± 5.2	< 0.001
PCT (ng/mL)	Before the procedure	0.12 ± 0.04	0.13 ± 0.05	0.46
	24 h after the procedure	0.28 ± 0.08	0.42 ± 0.11	< 0.001
	48 h after the procedure	0.22 ± 0.07	0.34 ± 0.09	< 0.001

Data are expressed as means ± SD. PVB: Paravertebral block; WBC; White blood cell; NEUT%: Neutrophil percentage; CRP: C-reactive protein; PCT: Procalcitonin.

Reducing the postoperative inflammatory response caused by PVB may have clinical implications for these patients [25]. First, it may reduce the risk of infection, a common complication of TACE combined with MWA[26,27]. Second, it may improve organ function and outcomes in these patients because the postoperative inflammatory response is associated with organ dysfunction and mortality[28]. Third, it may enhance the antitumor effect in these patients because postoperative inflammatory responses are linked to tumor progression and recurrence[29].

This study had certain limitations that should be acknowledged. First, this was a single-center study with a relatively small sample size, which may limit its generalizability and statistical power. Second, the patients were followed up for only 48 h after the procedure, which might not have reflected the long-term effects of PVB on postoperative recovery and outcomes. Third, we did not measure other outcomes that may have been affected by PVB, such as patient satisfaction, quality of life, length of hospital stay, and survival.

CONCLUSION

PVB can effectively reduce postoperative pain and inflammatory responses in patients with advanced gastric cancer and liver metastasis treated with TACE combined with MWA and improve postoperative comfort and recovery. We suggest that PVB should be considered as an alternative or adjunctive analgesic method for these patients. Further studies with larger sample sizes and longer follow-up periods are required to validate our findings.

ARTICLE HIGHLIGHTS

Research background

Transarterial chemoembolization (TACE) combined with microwave ablation (MWA) has emerged as an effective treatment strategy for patients with advanced gastric cancer and liver metastasis. However, this approach often leads to severe postoperative pain and inflammatory responses, impacting patient comfort and recovery. The paravertebral block (PVB) is a regional anesthetic technique known for providing analgesia in the thoracic and abdominal regions. This study aims to evaluate the potential benefits of PVB in terms of postoperative analgesia and inflammatory response in patients undergoing TACE combined with MWA for advanced gastric cancer and liver metastasis. By comparing the outcomes between the PVB group and the control group receiving intravenous analgesia, this research investigates the effectiveness of PVB in reducing pain scores, minimizing sufentanil consumption, decreasing adverse events, and lowering inflammatory marker levels. The findings of this study will shed light on the role of PVB in managing pain and inflammation and improving the postoperative experience and recovery of patients with advanced gastric cancer and liver metastasis treated with TACE combined with MWA.

Research motivation

The treatment of advanced gastric cancer and liver metastasis using TACE combined with MWA has shown promising

results. However, the occurrence of severe postoperative pain and inflammatory responses poses significant challenges in patient management. The PVB technique offers a potential solution by providing effective analgesia to the thoracic and abdominal regions. This study aims to investigate the impact of PVB on postoperative pain and inflammation in patients undergoing TACE combined with MWA for advanced gastric cancer and liver metastasis.

Research objectives

The main objective of this study was to evaluate the effect of PVB on postoperative analgesia and inflammatory response in patients undergoing TACE combined with MWA for advanced gastric cancer and liver metastasis. The specific objectives were to compare the visual analog scale (VAS) scores for pain, the dose of sufentanil used, the incidence of adverse events, and the levels of inflammatory markers between the PVB group and the control group. The significance of realizing these objectives is to contribute to improving postoperative comfort and recovery in patients with advanced gastric cancer and liver metastasis treated with TACE combined with MWA, as well as informing future research in this field.

Research methods

This study used a randomized controlled trial design. Sixty patients undergoing TACE combined with MWA for advanced gastric cancer and liver metastasis were randomly divided into two groups: the PVB group and the control group. The PVB group received ultrasound-guided PVB with 0.375% ropivacaine preoperatively, while the control group received intravenous analgesia with sufentanil. The primary outcome measured was the VAS score for pain at specific time points after the procedure. Secondary outcomes included the dose of sufentanil used, incidence of adverse events, and levels of inflammatory markers before and after the procedure. Statistical analyses were performed to compare the outcomes between the two groups.

Research results

The findings of this study demonstrated that patients in the PVB group had significantly lower VAS scores for pain at 6 h, 12 h, 24 h, and 48 h after the procedure compared to the control group. Additionally, the PVB group showed reduced consumption of sufentanil and a lower incidence of adverse events such as nausea, vomiting, and respiratory depression. Moreover, the PVB group exhibited significantly lower levels of inflammatory markers 24 h and 48 h after the procedure. These results contribute to the understanding of how PVB can effectively alleviate postoperative pain, reduce inflammatory responses, and enhance the comfort and recovery of patients with advanced gastric cancer and liver metastasis treated with TACE combined with MWA. Further research is needed to address any remaining challenges in optimizing the application of PVB in this context.

Research conclusions

That the use of PVB in patients undergoing TACE combined with MWA for advanced gastric cancer and liver metastasis results in effective reduction of postoperative pain and inflammatory responses. Moreover, PVB improves postoperative comfort and enhances recovery. These results support the implementation of PVB as a valuable technique in managing pain and inflammation in this patient population. Further investigations should focus on optimizing the utilization of PVB and exploring its long-term effects on patient outcomes.

Research perspectives

TACE combined with MWA offers promising research prospects for the treatment of advanced cancer and liver metastasis. Further studies can focus on optimizing the technique and dosage of PVB, exploring its long-term impact on patient prognosis, and investigating the potential synergistic benefits when PVB is combined with other analgesic strategies. Additionally, research can investigate the effects of PVB on other aspects such as quality of life, length of hospital stay, and healthcare costs to further evaluate its overall clinical benefits.

FOOTNOTES

Co-first authors: Ying-Fen Xiong and Ben-Zhong Wei.

Author contributions: Xiong YF and Wei BZ proposed the concept of this study; Liu C validated this study; Xiong YF and Wei BZ jointly wrote the first draft; Wang YF contributed to data collection; Li XF contributed to formal analysis; Xiong YF and Wei BZ participated in the survey; Liu C and Li XF contributed to the methods; Wang YF contributed to the visualization of this study. All authors collectively guided the research, reviewed, and edited the manuscript. Xiong YF and Wei BZ have made equal contributions to this work as co-first authors. It has been decided to designate Xiong YF and Wei BZ as co-first authors for three main reasons. Firstly, this study was conducted as a collaborative effort, warranting the designation of co-first authors. The authors accurately reflect the distribution of responsibilities and burdens associated with the time and effort required to complete the research and final manuscript. Designating two co-first authors will ensure effective communication and management of post-submission matters, thereby enhancing the quality and reliability of the paper. Secondly, the co-first authors from the research team possess diverse expertise and skills from different fields, and their designation best reflects this diversity. It also facilitates the most comprehensive and in-depth exploration of the research topic, ultimately enriching readers' understanding by providing various expert perspectives. Thirdly, Xiong YF and Wei BZ have made substantial and equal contributions throughout the research process. Selecting these researchers as co-first authors acknowledges and respects their equal contributions, showcasing the collaborative and teamwork spirit within this study. We believe that designating Xiong YF and Wei BZ as co-first authors is fitting for our manuscript as it accurately reflects the collaborative spirit, equal contributions,

and diversity within our team.

Institutional review board statement: This study has been reviewed and approved by the Medical Ethics Committee of the First Affiliated Hospital of Nanchang University.

Clinical trial registration statement: This study is registered in https://www.researchregistry.com. The registration identification number is Researchregistry9712.

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

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

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

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S-Editor: Lin C
L-Editor: A
P-Editor: Che YX

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World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2024 January 27; 16(1): 205-214

DOI: 10.4240/wjgs.v16.i1.205

ISSN 1948-9366 (online)

META-ANALYSIS

Unraveling the efficacy network: A network meta-analysis of adjuvant external beam radiation therapy methods after hepatectomy

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Specialty type: Gastroenterology and hepatology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Goja S, India

Received: August 28, 2023
Peer-review started: August 28, 2023
First decision: November 24, 2023
Revised: December 9, 2023
Accepted: January 9, 2024
Article in press: January 9, 2024
Published online: January 27, 2024

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Abstract

BACKGROUND

Primary liver cancer is a malignant tumor with a high recurrence rate that significantly affects patient prognosis. Postoperative adjuvant external radiation therapy (RT) has been shown to effectively prevent recurrence after liver cancer resection. However, there are multiple RT techniques available, and the differential effects of these techniques in preventing postoperative liver cancer recurrence require further investigation.

AIM

To assess the advantages and disadvantages of various adjuvant external RT methods after liver resection based on overall survival (OS) and disease-free survival (DFS) and to determine the optimal strategy.

METHODS

This study involved network meta-analyses and followed the PRISMA guidelines. The data of qualified studies published before July 10, 2023, were collected from PubMed, Embase, the Web of Science, and the Cochrane Library. We included relevant studies on postoperative external beam RT after liver resection that had OS and DFS as the primary endpoints. The magnitudes of the effects were

determined using risk ratios with 95% confidential intervals. The results were analyzed using R software and STATA software.

RESULTS

A total of 12 studies, including 1265 patients with hepatocellular carcinoma (HCC) after liver resection, were included in this study. There was no significant heterogeneity in the direct paired comparisons, and there were no significant differences in the inclusion or exclusion criteria, intervention measures, or outcome indicators, meeting the assumptions of heterogeneity and transitivity. OS analysis revealed that patients who underwent stereotactic body radiotherapy (SBRT) after resection had longer OS than those who underwent intensity modulated radiotherapy (IMRT) or 3-dimensional conformal RT (3D-CRT). DFS analysis revealed that patients who underwent 3D-CRT after resection had the longest DFS. Patients who underwent IMRT after resection had longer OS than those who underwent 3D-CRT and longer DFS than those who underwent SBRT.

CONCLUSION

HCC patients who undergo liver cancer resection must consider distinct advantages and disadvantages when choosing between SBRT and 3D-CRT. IMRT, a RT technique that is associated with longer OS than 3D-CRT and longer DFS than SBRT, may be a preferred option.

Key Words: Primary liver cancer; Hepatocellular carcinoma; Network meta-analysis; External beam radiation therapy; Stereotactic body radiotherapy; Intensity modulated radiotherapy

Core Tip: The core focus of this study is the comparative analysis of various adjuvant external beam radiation therapy (RT) methods following hepatectomy based on the network meta-analysis. The key aspects emphasized in the study include the efficacy of different RT methods in terms of disease-free survival and overall survival for postoperative liver cancer patients. The research aims to provide valuable insights for future investigations and clinical applications, potentially influencing the direction of liver cancer treatment.

Citation: Yang GY, He ZW, Tang YC, Yuan F, Cao MB, Ren YP, Li YX, Su XR, Yao ZC, Deng MH. Unraveling the efficacy network: A network meta-analysis of adjuvant external beam radiation therapy methods after hepatectomy. *World J Gastrointest Surg* 2024; 16(1): 205-214

URL: https://www.wjgnet.com/1948-9366/full/v16/i1/205.htm

DOI: https://dx.doi.org/10.4240/wjgs.v16.i1.205

INTRODUCTION

Primary liver cancer is the second leading cause of cancer-related death, and its recurrence has always been an important factor affecting the prognosis of liver cancer patients. Liver resection surgery is currently the preferred treatment for liver cancer, but approximately 70% of patients experience recurrence within 5 years after surgery, severely impacting patient survival time[1,2]. Additionally, a second surgery increases the treatment risk and is influenced by factors such as patient health status, liver function, and liver reserve that further burden patients both physically and mentally and hinder subsequent treatment. Therefore, preventing postoperative recurrence of liver cancer has become an important research topic.

Postoperative adjuvant therapy, including interventional therapy, chemotherapy, and targeted therapy, has been proven effective in preventing liver cancer recurrence after liver resection[3,4]. As an emerging treatment modality relying on technological advances, external beam radiotherapy (EBRT), including stereotactic body radiotherapy (SBRT), intensity-modulated radiotherapy (IMRT)/image-guided radiotherapy (IGRT), volumetric modulated arc therapy (VMAT), and three-dimensional conformal radiation therapy (3D-CRT), features precision and safety and offers significantly better efficacy and safety than traditional radiotherapy. EBRT has recently been considered to achieve curative effects in several early-stage liver cancers and has also been applied as adjuvant therapy after liver resection surgery. However, there are multiple EBRT methods available, and they have not yet become commonly used approaches for postoperative adjuvant treatment of liver cancer. As a result, there is a lack of clarity on which EBRT method is better for preventing recurrence after liver cancer resection, and related research is relatively insufficient. In this study, we aim to use network meta-analysis methods based on the results of current clinical trials to evaluate the advantages and disadvantages of EBRT methods for preventing recurrence after liver resection surgery, thereby providing a reference for future clinical experiments and the selection of clinical treatments.

MATERIALS AND METHODS

This network meta-analysis has been registered in the PROSPERO international database (https://www.crd.york.ac.uk/prospero/). The PROSPERO Registration Number is CRD42023448817. The entire analysis process was conducted in accordance with the PRISMA guidelines, as shown in Supplementary Table 1[5].

Search strategy

As of July 10, 2023, the participants in this study completed the retrieval of all relevant and language-unrestricted literature from PubMed, Embase, the Web of Science, and the Cochrane Library. The search terms used were as follows: "liver cancer", "hepatocellular carcinoma", "radiotherapy", "radiation", "external beam radiotherapy", "EBRT", "radical surgery", "hepatectomy", "postoperative", "recurrence", "stereotactic body radiotherapy", "SBRT", "intensity-modulated radiotherapy", "IMRT", "image-guided radiotherapy", "IGRT", "3-dimensional conformal radiation therapy", "3D-CRT", "volumetric modulated arc therapy", "VMAT", and "proton beam therapy". The participants in this study also cross-checked and supplemented the literature included in this analysis based on relevant published meta-analyses and references cited in reviews to ensure that the retrieved literature met the inclusion criteria and that the search scope was sufficient.

Selection criteria

Study population: Adult hepatocellular carcinoma (HCC) patients diagnosed with primary liver cancer who underwent surgical resection and had negative surgical margins according to postoperative pathology.

Interventions: Only radiation therapy (RT) methods classified as EBRT techniques were considered interventions.

Outcome measures: Two-year disease-free survival (DFS) and 2-year overall survival (OS).

Study design: Randomized controlled trials (RCTs), prospective studies, and retrospective studies that included propensity score matching or controls; the inclusion criteria included the following: (1) RCTs focusing on adjuvant radiotherapy for HCC patients after liver cancer resection; (2) studies reporting the following outcome measures were included: 2-year OS and DFS, with hazard ratio and 95% confidential intervals (95%CI) data; and (3) studies involving patients who underwent liver cancer resection and received only EBRT or no other treatment. The exclusion criteria were as follows: (1) Clinical studies without the specified outcome measures of this study; (2) studies that did not compare adjuvant radiotherapy with no adjuvant radiotherapy or single-arm studies; (3) studies including misdiagnosed or underage patients; (4) studies including HCC patients with positive surgical margins or unclear surgical margins; (5) studies including HCC patients receiving other liver cancer-related treatments in addition to EBRT; and (6) literature published in the form of conference abstracts, research proposals, case reports, or reviews, not representing clinical studies.

Data extraction and quality assessment

The literature search and data extraction for the included studies were conducted by three research participants (Yang GY, He ZW and Tang YC) based on the aforementioned search strategy. Any disagreements were resolved by the fourth research participant (Yao ZC). The following data were extracted from each included study: (1) Study characteristics, publication year, author names, study design, study population, and number of participants; (2) specific radiotherapy methods; and (3) outcome measures, including 2-year DFS and OS. Two researchers assessed the quality of the included RCTs using the Cochrane Collaboration's risk of bias tool. The quality of the non-RCT studies was assessed using the Newcastle-Ottawa Scale, with a score of 0-3 indicating low quality, 3-6 indicating moderate quality, and ≥ 7 indicating high quality. Any disagreements were resolved by the third research participant. An overview of the inclusion and exclusion criteria for the included studies can be found in Supplementary Table 2.

Statistical methods

The software packages "rjags4-14" and "gemt1.0-1" in R software version 4.3.1 (https://www.r-project.org/) and Stata SE version 15.1 were used for conducting network meta-analyses of different intervention measures. The Bayesian network framework was employed to assess the consistency of direct and indirect comparisons, and the Markov chain Monte Carlo model was used to detect model heterogeneity (I^2). An I^2 value less than 50 indicated acceptable heterogeneity and satisfied the assumption of consistency. The convergence of the model was evaluated using region and density plots and Brooks–Gelman–Rubin diagnostic plots. The model was considered to have good convergence when the iteration number reached 20000 and the bandwidth approached 0. The "rank" method was used to generate a ranking plot of the probability of treatment efficacy. The advantages and disadvantages of intervention measures were inferred by calculating the area under the cumulative ranking curve (SUCRA).

RESULTS

Study characteristics

A flowchart of the studies included in this research is presented in Supplementary Figure 1. A total of 735 articles were initially extracted through a preliminary search based on the search strategy. After removal of 149 duplicate articles, the

remaining 104 articles were screened based on their titles and abstracts. Subsequently, 92 articles were excluded for the following reasons: not related to the objective (n = 18); not compare postoperative adjuvant radiotherapy with no adjuvant radiotherapy (n = 46); published as conference abstracts, study protocols, case reports, or reviews (n = 17); and not yet completed (n = 11). Finally, 12 clinical studies were included in this network meta-analysis. The included studies were conducted from 2014 to 2023, and all the research centers were located in China. A total of 1265 patients were included in this study. The NMT approach was used to evaluate the effects of three different external radiotherapy techniques, namely, SBRT[6,7], IMRT[8-12], and 3D-CRT[13-17], on preventing postoperative recurrence of liver cancer, with sample sizes ranging from 9 to 82 patients. The baseline characteristics of the included studies are shown in Supplementary Table 3.

Risk of bias

The specific scoring criteria for the included RCTs in this study can be found in Supplementary Figure 2. Any disagreements were resolved by the third research participant. Due to the current realities of clinical practice, conducting double-blind RCTs with both patients and health care providers is almost impractical. Some randomized trials were open-label, and the proportion of non-RCT studies among the included studies was relatively high. The blinding of participants and the potential risk of bias resulting from the lack of blinding could affect the outcomes. We believe that as long as the sequence of participant enrollment is randomized, the bias risk of participants may be considered relatively low.

Assessment of heterogeneity and transitivity

A total of 12 studies were included in this research, and the trace and density plots can be found in Supplementary Figure 3. The Brooks–Gelman–Rubin diagnostic plots are presented in Supplementary Figure 4, which indicates good convergence of the evaluation model. The heterogeneity analysis is shown in Figure 1. The analysis demonstrated that for OS and DFS, the I2 values of direct comparisons between SBRT, IMRT, 3D-CRT, and no adjuvant radiotherapy were all less than 50%, indicating no significant heterogeneity and meeting the assumption of homogeneity.

The evaluators of this study assessed the inclusion and exclusion criteria of the included studies to ensure that the patients involved met the criteria. Additionally, it was ensured that the same radiotherapy methods used in the included studies did not significantly affect treatment variables, such as the number of radiotherapy sessions and radiation dose. In most of the studies, the total radiation dose for patients receiving posthepatectomy adjuvant radiotherapy was above 40 Gy; in more than half of the studies, the 2-year OS rate was above 84.4%, and the 2-year DFS rate was above 71.1%, indicating good generalizability of the included studies. Moreover, all the research centers included in the studies were located in China. No significant differences in patient samples related to etiology were found in the included studies, indicating high geographical consistency and compliance with the assumption of generalizability.

Network meta-analysis

A total of 12 included studies involved 1265 enrolled patients and included three types of posthepatectomy adjuvant external radiotherapy methods. The network geometry plots directly comparing no adjuvant radiotherapy with posthepatectomy adjuvant radiotherapy using SBRT, IMRT, and 3D-CRT are shown in Figure 2. For all direct pairwise comparisons, there was no statistically significant heterogeneity among the included studies. Among the studies related to OS and DFS, two studies compared posthepatectomy SBRT with no adjuvant radiotherapy, five studies compared posthepatectomy IMRT with no adjuvant radiotherapy, and three studies compared posthepatectomy 3D-CRT with no adjuvant.

A comparison of OS and DFS after liver cancer resection and adjuvant radiotherapy in patients with HCC, along with 95%CI, can be found in Tables 1 and 2. The probability histograms for the rankings of OS and DFS according to different adjuvant radiotherapy methods after liver resection are shown in Figure 3. The area under the SUCRA calculations are shown in Figure 4. In terms of OS, patients who underwent SBRT after surgery had longer OS than those who underwent IMRT or 3D-CRT. Patients who underwent IMRT after surgery had a better OS than those who underwent 3D-CRT. Regarding DFS, patients who underwent 3D-CRT after surgery experienced a better preventive effect against HCC recurrence than did patients who underwent SBRT or IMRT. IMRT was more effective than SBRT at prolonging patient DFS. Among the three techniques, SBRT resulted in the longest OS, while 3D-CRT resulted in the longest DFS.

DISCUSSION

Key findings

Based on the high recurrence rates in clinical practice, we explored adjuvant treatment options after liver cancer resection. Compared to invasive treatments such as repeat surgery or ablation, transcatheter arterial chemoembolization, and expensive systemic treatments such as targeted therapy and immunotherapy, as well as chemotherapy with important side effects, external radiotherapy seems to have unique advantages and can serve as a new option for adjuvant therapy. Given the limited specific research on adjuvant radiotherapy methods after liver cancer resection and the lack of a definitive consensus in clinical practice, we chose to evaluate which external RT method was most effective at preventing recurrence after liver cancer surgery through NMT. In this study, we conducted NMT on 1265 patients from 12 clinical studies to assess which external RT method after liver cancer surgery could effectively prevent recurrence. We also selected OS and DFS, which are commonly used to evaluate the efficacy of liver cancer treatments, as the primary

Table 1 Commutatively comparative efficacy of different interventions for overall survival

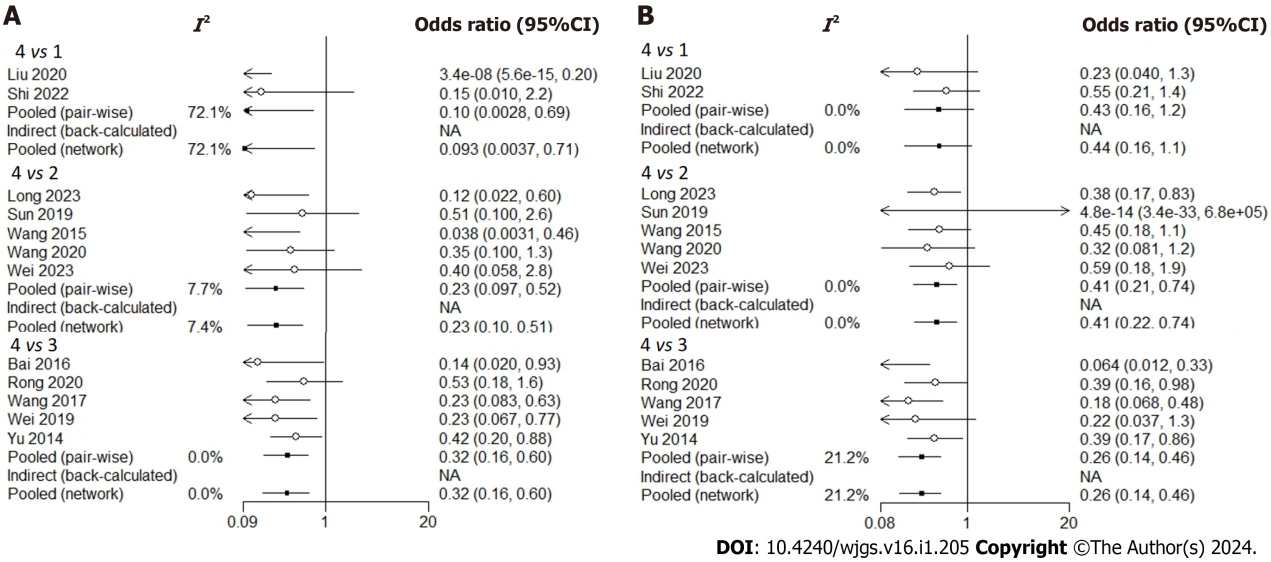
	Log odds ratio (95%CI)			
	SBRT	IMRT	3D-CRT	Surgery
SBRT	-	-0.8913 (-4.685, 1.333)	-1.241 (-4.957, 0.9864)	-2.38 (-6.083, -0.2884)
IMRT	0.8913 (-1.333, 4.685)	-	-0.3267 (-1.379, 0.7683)	-1.475 (-2.325, -0.6613)
3D-CRT	1.241 (-0.9864, 4.957)	0.3267 (-0.7683, 1.379)	-	-1.14 (-1.874, -0.5102)
Surgery	2.38 (0.2884, 6.083)	1.475 (0.6613, 2.325)	1.14 (0.5102, 1.874)	-

95%CI: 95% confidence interval; SBRT: Stereotactic body radiotherapy; IMRT: Intensity modulated radiotherapy; 3D-CRT: 3-dimensional conformal radiation therapy.

Table 2 Commutatively comparative efficacy of different interventions for disease-free survival

	Log odds ratio (95%CI)			
	SBRT	IMRT	3D-CRT	Surgery
SBRT	-	0.07723 (-1.135, 1.230)	0.5162 (-0.6510, 1.697)	-0.8220 (-1.878, 0.1440)
IMRT	-0.07723 (-1.230, 1.135)	-	0.4326 (-0.3994, 1.323)	-0.9057 (-1.545, -0.3127)
3D-CRT	-0.5162 (-4.697, 0.651)	-0.4326 (-1.323, 0.3994)	-	-1.339 (-1.994, -0.7873)
Surgery	0.8220 (-0.1440, 1.878)	0.9057 (0.3127, 1.545)	1.339 (0.7873, 1.994)	-

95%CI: 95% confidence interval; SBRT: Stereotactic body radiotherapy; IMRT: Intensity modulated radiotherapy; 3D-CRT: 3-dimensional conformal radiation therapy.



DOI: 10.4240/wjgs.v16.i1.205

Figure 1 Forest plot diagram of heterogeneity analysis. A and B: Forest plot in direct comparisons for evaluation of overall survival (A) and disease-free survival (B). 1: Stereotactic body radiation therapy; 2: Intensity-modulated radiation therapy 3D; 3: 3-dimensional conformal radiation therapy; 4: Surgery.

outcome measures.

Clinical implications

Unlike previous comparisons between RT and ablation and between RT and interventional therapy, we focused on RT itself. Although we collected almost all clinical studies on adjuvant radiotherapy after liver cancer resection, only 12 studies met the inclusion criteria. Among them, there were only 2 studies on SBRT after liver resection and no clinical studies on VMAT, proton radiotherapy, or IGRT after liver resection. Additionally, no clinical studies comparing different EBRT methods were found. This posed a challenge for our study because it made it difficult for us to construct a perfect network meta-analysis structure for EBRT.

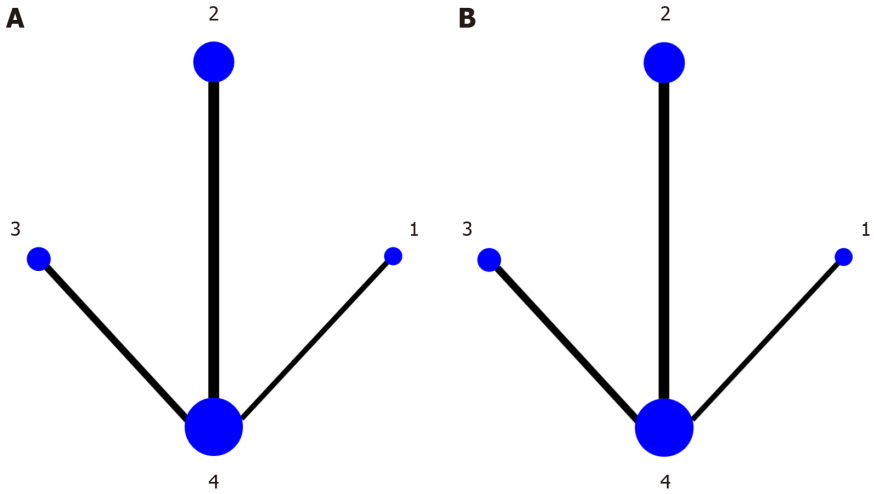


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Figure 2 Network diagram of the four kinds of therapies in the treatment of hepatocellular carcinoma. A and B: Network geometry of all the included radiotherapy methods for overall survival (A) and disease-free survival (B). 1: Stereotactic body radiation therapy; 2: Intensity-modulated radiation therapy 3D; 3: 3-dimensional conformal radiation therapy; 4: Surgery.

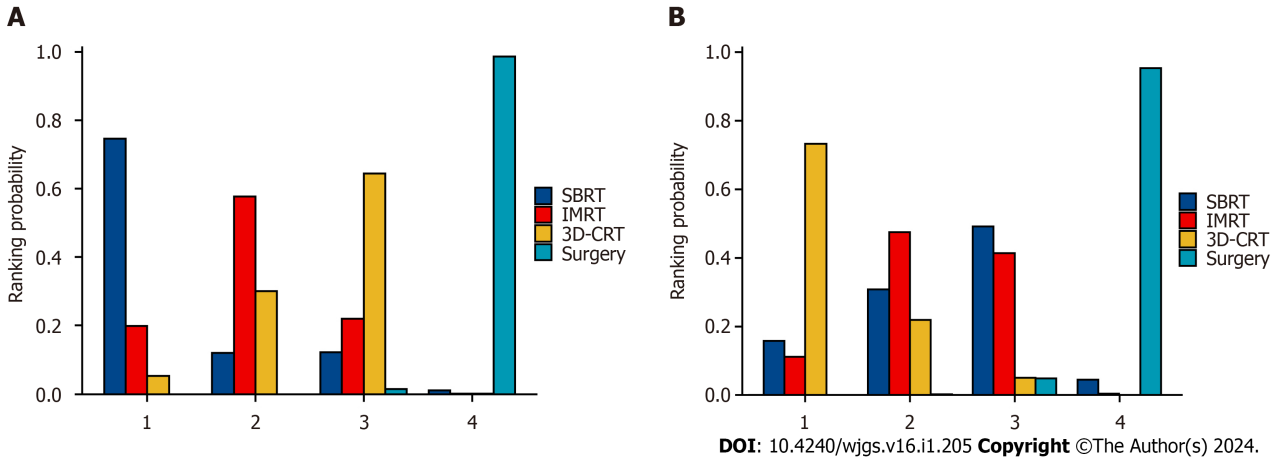

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Figure 3 Probability ranking diagram of each outcome indicator. A and B: Ranking probability histogram of different interventions for overall survival (A) and disease-free survival (B). SBRT: Stereotactic body radiation therapy; IMRT: Intensity-modulated radiation therapy; 3D-CRT: 3-dimensional conformal radiation therapy.

However, we believe this finding reflects the current clinical practice. In recent years, SBRT has been considered an alternative to ablation for achieving local tumor control, but it is rarely used as adjuvant radiotherapy for irregular or extensive liver cancer resection margins. Although IMRT is the most commonly used external radiotherapy method in our country, IMRT did not have overall advantages in terms of OS or DFS compared to the other two methods in this study; moreover, it demonstrated noninferiority in prolonging OS and preventing recurrence in HCC patients. This finding indicates that IMRT may be a good option for extending OS while effectively preventing recurrence. Although 3D-CRT has the greatest advantage in terms of improving DFS, the results of the related analysis on OS in this study were not optimistic for 3D-CRT patients. Similar findings were reported by Jiang *et al*[18], who reported that for patients with unresectable but localized HCC, IMRT was superior to 3D-CRT in terms of treatment response and potential survival. Hou *et al*[19] also reported that IMRT was more effective than 3D-CRT in HCC patients with portal or inferior vena cava tumor thrombus without increasing radiation-related toxic reactions. Chen *et al*[20] reported that IMRT had a better conformal index for the planned target volume than did 3D-CRT, with a lower hot spot (V = 110%). These findings suggest that IMRT, and even IGRT based on advanced guidance techniques, may achieve better treatment outcomes than 3D-CRT, including better prolongation of patient survival. Although new adjuvant 3D-CRT regimens have emerged with the advancement of associated technologies, their effectiveness has not been definitively confirmed.

Strengths and limitations

Previous studies comparing the advantages and disadvantages of adjuvant radiotherapy methods after liver cancer surgery have been extremely limited. This article attempts to fill this research gap and provides some guidance and assistance in selecting the appropriate radiotherapy method after liver cancer resection. This approach is attended by a

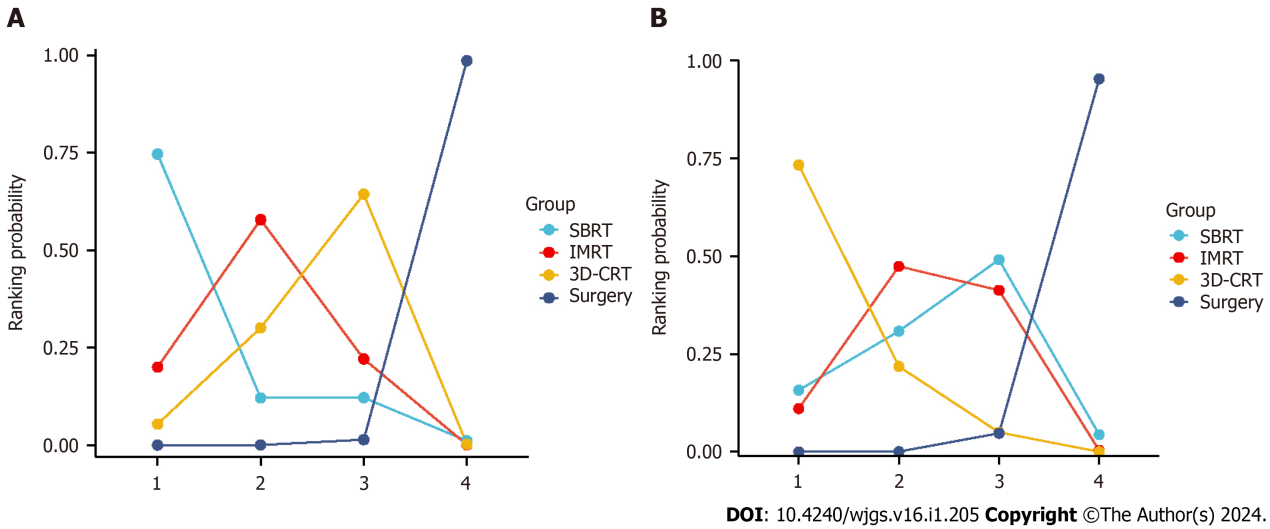

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Figure 4 Area under the cumulative ranking curve. A and B: Cumulative ranking curve of different interventions for overall survival (A) and disease-free survival (B). SBRT: Stereotactic body radiation therapy; IMRT: Intensity-modulated radiation therapy; 3D-CRT: 3-dimensional conformal radiation therapy.

certain degree of novelty. The search strategy of this study was extensive and included all relevant research, without restrictions on language, country, or year. The use of 2-year OS and 2-year DFS as primary outcome measures and the relatively long follow-up period added to the representativeness of the study.

Although every effort was made to include all relevant studies, the limited number of reports on clinical trials, especially RCTs, increased the potential risk of bias in the research findings. The lack of published clinical trials comparing different radiotherapy methods also affected the assessment of the consistency of the studies. We minimized bias through methodological approaches such as study identification, data selection, statistical analysis, and heterogeneity analysis, enhancing the accuracy of the study.

Future studies

As surgical resection is the preferred treatment for liver cancer, the role of RT in the field of liver cancer treatment is still being explored, and its position remains undetermined. Therefore, the use of RT in the clinical treatment of liver cancer is still considered rare and insufficiently effective by some medical practitioners. Currently, when there have been no breakthroughs in surgical approaches or techniques, it is important to find ways to "add value" to liver cancer resection surgery. Numerous basic research studies have demonstrated that RT can influence the epigenetic regulation of liver cancer, apoptosis programming, and even the tumor immune microenvironment[21]. Therefore, postoperative adjuvant RT is not simply a "wider surgical excision" but may also prolong DFS and OS by reshaping the tumor microenvironment, inducing genetic mutations in pericancerous liver cells, and regulating the expression of cellular products through various pathways and mechanisms. Exploring the mechanisms of RT can also provide theoretical feasibility for combining RT with chemotherapy, targeted therapy, and immunotherapy, thus guiding further experimental investigations and clinical practices. Due to the limited number of clinical trials on various combined therapies, including RT, for postoperative liver cancer, we were unable to conduct an in-depth study on the relevant questions. However, we look forward to exploring these questions in the future. Answers to issues such as the synergistic or antagonistic effects of RT with certain drugs, the pathways involved, and the impact on patients may provide new directions and insights for liver cancer treatment.

CONCLUSION

After liver cancer resection in HCC patients, SBRT resulted in the longest OS, while 3D-CRT provided the longest DFS. IMRT, a RT technique associated with longer OS than 3D-CRT and longer DFS than SBRT, may be a good choice of postoperative RT.

ARTICLE HIGHLIGHTS

Research background

Patients with primary liver cancer face a high recurrence rate, impacting prognosis significantly. Research has demonstrated the effectiveness of postoperative adjuvant external radiation therapy (RT) in preventing liver cancer recurrence after resection. However, the varying effects of different RT techniques on postoperative liver cancer recurrence necessitate further exploration and investigation.

Research motivation

This study aims to uncover and compare the efficacy of different adjuvant external beam RT (EBRT) methods after hepatectomy. Ultimately, the goal is to guide future experimental investigations, clinical practices, and potentially identify new directions for liver cancer treatment.

Research objectives

This study conducted a network meta-analysis to evaluate different adjuvant external RT methods following liver resection, focusing on overall survival (OS) and disease-free survival (DFS) to identify the optimal approach.

Research methods

In adherence to PRISMA guidelines, this study utilized network meta-analyses to collect data from qualified studies published before July 10, 2023, from various reputable databases. Specifically, relevant studies pertaining to postoperative EBRT following liver resection with OS and DFS as primary endpoints were included for analysis. The effects were evaluated using risk ratios and 95% confidential intervals, with data analysis performed *via* R and STATA software for comprehensive assessment.

Research results

Inclusive of 1265 patients with hepatocellular carcinoma (HCC) post-liver resection, 12 studies formed the basis of this study. The absence of significant heterogeneity in direct paired comparisons, and consistency in inclusion/exclusion criteria, intervention measures, and outcome indicators, corroborated the assumptions of heterogeneity and transitivity. Findings from the analysis of OS indicated that patients who received stereotactic body radiotherapy (SBRT) after resection exhibited longer OS compared to those who underwent intensity modulated radiotherapy (IMRT) or 3-dimensional conformal RT (3D-CRT). Moreover, the analysis of DFS revealed that patients treated with 3D-CRT after resection had the longest DFS, while those undergoing IMRT post-resection demonstrated longer OS compared to 3D-CRT and longer DFS compared to SBRT.

Research conclusions

When considering RT options after liver cancer resection for HCC patients, IMRT stands out as a preferred choice due to its association with longer OS than 3D-CRT and longer DFS than SBRT.

Research perspectives

The role of RT in liver cancer treatment is currently uncertain, with some practitioners deeming its use rare and insufficiently effective alongside surgical resection. However, basic research shows that RT can influence epigenetic regulation, apoptosis programming, and the tumor immune microenvironment, potentially extending disease-free and OS. Further understanding of RT mechanisms can pave the way for combining it with chemotherapy, targeted therapy, and immunotherapy, offering new directions for clinical practices.

FOOTNOTES

Co-first authors: Gao-Yuan Yang and Zhi-Wei He.

Co-corresponding authors: Zhi-Cheng Yao and Mei-Hai Deng.

Author contributions: Yao ZC, and Deng MH contributed to the study design, formal analysis, and writing – original draft; Yang GY, He ZW, Tang YC, and Yuan F contributed to the literature research; Ren YP and Li YX contributed to the data acquisition and curation; Yang GY, Cao MB, and Su XR contributed to the writing – review and editing; all authors contributed to the article and approved the submitted version. It is worth noting that Yao ZC and Deng MH made equal contributions to the research design and supervision, so they are listed as the co-corresponding authors. Yang GY and He ZW made equal contributions to the collection, organization and analysis of data and the writing of the manuscript, so they are listed as the co-first authors.

Supported by The Science and Technology Plan Project of Guangzhou, No. 202102010171; National Natural Science Foundation Cultivation Project of The Third Affiliated Hospital of Sun Yat-sen University, No. 2020GZRPYMS11; Natural Science Foundation of Guangdong Province, No. 2018A030313641; and CSCO-Roche Joint Cancer Research Fund, No. Y-Roche2019/2-0041.

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

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: China

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S-Editor: Lin C
L-Editor: A
P-Editor: Zheng XM

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World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2024 January 27; 16(1): 215-227

DOI: 10.4240/wjgs.v16.i1.215

ISSN 1948-9366 (online)

META-ANALYSIS

Estimation of Physiologic Ability and Surgical Stress scoring system for predicting complications following abdominal surgery: A meta-analysis spanning 2004 to 2022

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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: Haddadi S, Algeria; Tenreiro N, Portugal

Received: August 31, 2023
Peer-review started: August 31, 2023
First decision: November 9, 2023
Revised: November 24, 2023
Accepted: December 19, 2023
Article in press: December 19, 2023
Published online: January 27, 2024

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Abstract

BACKGROUND

Postoperative complications remain a paramount concern for surgeons and healthcare practitioners.

AIM

To present a comprehensive analysis of the Estimation of Physiologic Ability and Surgical Stress (E-PASS) scoring system's efficacy in predicting postoperative complications following abdominal surgery.

METHODS

A systematic search of published studies was conducted, yielding 17 studies with pertinent data. Parameters such as preoperative risk score (PRS), surgical stress score (SSS), comprehensive risk score (CRS), postoperative complications, post-operative mortality, and other clinical data were collected for meta-analysis. Forest plots were employed for continuous and binary variables, with χ^2 tests assessing heterogeneity (P value).

RESULTS

Patients experiencing complications after abdominal surgery exhibited significantly higher E-PASS scores compared to those without complications [mean difference and 95% confidence interval (CI) of PRS: 0.10 (0.05-0.15); SSS: 0.04 (0.001-0.08); CRS: 0.19 (0.07-0.31)]. Following the exclusion of low-quality studies, results remained valid with no discernible heterogeneity. Subgroup analysis indicated that variations in sample size and age may contribute to heterogeneity in CRS analysis. Binary variable meta-analysis demonstrated a correlation between high CRS and increased postoperative complication rates [odds ratio (OR) (95%CI): 3.01 (1.83-4.95)], with a significant association observed between high CRS and postoperative mortality [OR (95%CI): 15.49 (3.75-64.01)].

CONCLUSION
In summary, postoperative complications in abdominal surgery, as assessed by the E-PASS scoring system, are consistently linked to elevated PRS, SSS, and CRS scores. High CRS scores emerge as risk factors for heightened morbidity and mortality. This study establishes the accuracy of the E-PASS scoring system in predicting postoperative morbidity and mortality in abdominal surgery, underscoring its potential for widespread adoption in effective risk assessment.

Key Words: Estimation of Physiologic Ability and Surgical Stress scoring system; Preoperative risk score; Surgical stress score; Comprehensive risk score; Complications

Core Tip: Excessive surgical stress surpassing the patient's physiological thresholds could precipitate the occurrence of morbidity and mortality following abdominal surgery, especially for resection of liver, pancreas, spleen, and gastrointestinal tract. As a robust evaluation system, Estimation of Physiologic Ability and Surgical Stress scoring system has been widely recognized and adopted over 20 years. Whether the risk prediction score exhibit precise predictive capability of morbidity and mortality in patients undergoing abdominal surgery and provide a favorable evaluation for surgeons? This systematic review will present you with interesting viewpoints.

Citation: Pang TS, Cao LP. Estimation of Physiologic Ability and Surgical Stress scoring system for predicting complications following abdominal surgery: A meta-analysis spanning 2004 to 2022. *World J Gastrointest Surg* 2024; 16(1): 215-227
URL: https://www.wjgnet.com/1948-9366/full/v16/i1/215.htm
DOI: https://dx.doi.org/10.4240/wjgs.v16.i1.215

INTRODUCTION

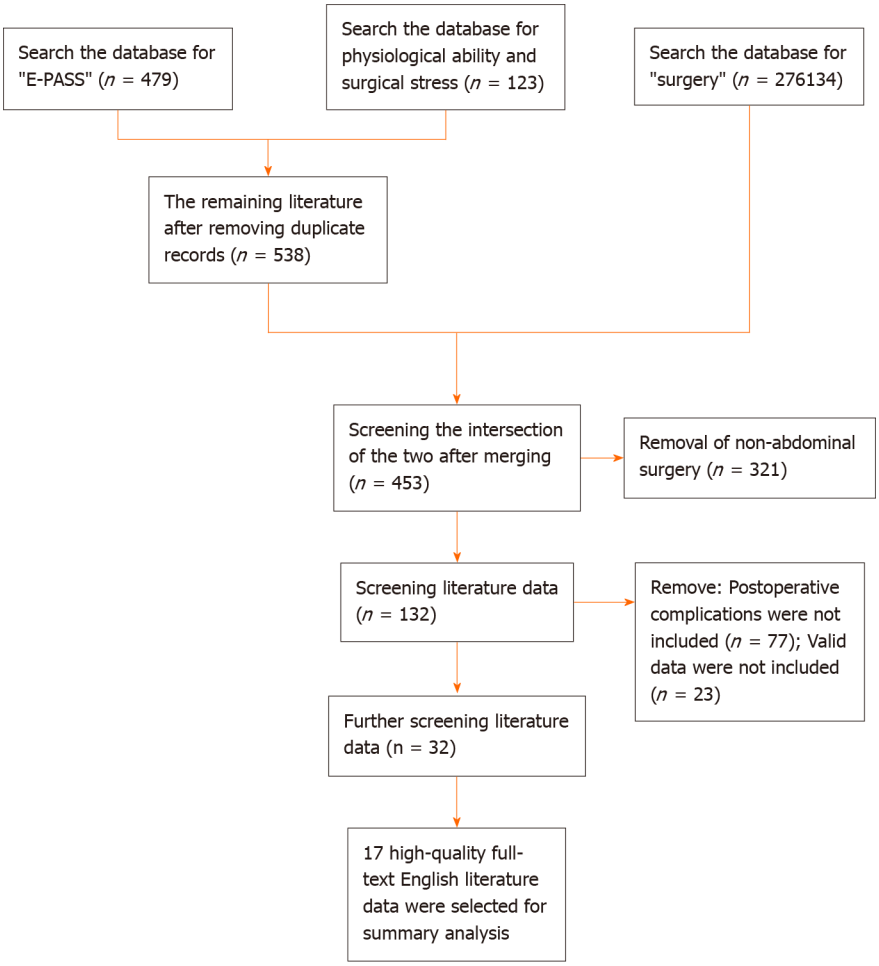
Abdominal surgeries often entail significant visceral trauma, presenting an enduring challenge for clinicians due to the subsequent emergence of postoperative complications. Within the realm of general surgery, the postoperative complication rates vary: Pancreaticoduodenectomy exceeds 40%[1], hepatectomy hovers around 38%[2], gastrectomy ranges from 10% to 15%[3], and colorectal resection is approximately 12%[4]. The incidence of postoperative complications is intricately linked to both patient-specific conditions and the intricacies of clinical treatment processes. Such complications contribute to prolonged hospital stays, escalated hospitalization costs, and, in severe cases, heightened postoperative mortality. Therefore, the effective prediction and assessment of postoperative complications stand as imperative objectives in clinical practice.

Excessive surgical stress surpassing the patient's physiological thresholds can induce sustained damage to vital organs, precipitating postoperative complications across multiple organ systems. The Estimation of Physiologic Ability and Surgical Stress (E-PASS) scoring system, initially introduced by Haga *et al*[5], emerged as a predictive tool for postoperative morbidity and mortality among patients undergoing gastrointestinal surgery. Its utility has since been extensively validated and demonstrated efficacy in risk assessment for various surgical domains, including gastrointestinal surgery[5,6], pancreatic surgery[7,8], colorectal surgery[9], hepatobiliary tumor surgery[6,10,11], vascular surgery[12,13], among others. This study systematically evaluates the correlation between the E-PASS scoring system and the incidence and prognosis of postoperative complications following abdominal surgery. Employing a comprehensive literature search, the study conducts a detailed analysis and synthesis of a substantial body of prior research data.

MATERIALS AND METHODS

Retrieval strategy

In this study, literature data available up to February 2023 were retrieved from six databases including PubMed, Web of Science, EBSCO, Embase, Ovid and Springerlink. The initial search utilized terms such as "E-PASS" or "physiological ability and surgical pressure" (n = 538 of literature obtained), which were subsequently synthesized and cross-referenced with "surgery" (n = 276134). This multi-step approach resulted in the initial selection of 453 studies. The second phase involved meticulous screening, narrowing down the focus to 132 studies by excluding those unrelated to abdominal surgery (n = 321). In the third stage, 23 studies lacking valid data and 77 studies lacking information on postoperative complications were excluded, yielding 32 effective data points. Finally, stringent exclusion criteria were applied to eliminate non-English and non-full-text literature, culminating in the identification of 17 studies with valuable data for analysis (Figure 1).



DOI: 10.4240/wjgs.v16.i1.215

Figure 1 Flow chart of literature retrieval.

Data extraction

The basic data extracted for this study included author information, journal details, publication year, clinical study location (country), number of research institutions, study design (prospective/retrospective), age, sex, surgical site, comprehensive risk score (CRS) truncation value, postoperative complications, postoperative mortality, and E-PASS score. To ensure uniformity, literature data originally presented in median and quartile ranges were transformed into mean and SD values using the methodology devised by Hozo *et al*[14]. Haga *et al*[5] initially proposed the E-PASS score that was elaborated from Asian population, similarly, our analysis was also conducted among Asian patients, excluding regional heterogeneity.

The E-PASS scoring system consists of three parts: The preoperative risk score (PRS), the surgical stress score (SSS), and the CRS. The calculation formula is as follows:

PRS = -0.0686 + 0.00345X_1 + 0.323X_2 + 0.205X_3 + 0.153X_4 + 0.148X_5 + 0.0666X_6, X_1 represents age; X_2 represents the presence (1) or absence (0) of severe heart disease; X_3 represents the presence (1) or absence (0) of serious lung disease; X_4 represents the presence (1) or absence (0) of diabetes; X_5 represents the performance status index (0-4); and X_6 stands for [American Society of Anesthesiologists (ASA)] physiological status scale score (0-5).

SSS = -0.342 + 0.0139X_1 + 0.0392X_2 + 0.352X_3, X_1 represents blood loss/body weight (g/kg); X_2 represents operation time (h); and X_3 represents the range of skin incisions: Laparoscopic surgery (0) or open surgery (1).

CRS = -0.328 + 0.936(PRS) + 0.976(SSS).

The six variables of PRS and the three variables of SSS within the E-PASS scoring system serve as unequivocal indicators, employing identical examination methods. Their standardized nature ensures consistency, precluding any potential impact on the assessment of analysis scales across different countries. Notably, all 17 studies retained for the meta-analysis encompassed patients subjected to both laparoscopic and open surgeries. Given that the SSS score incorporates the variable of skin incisions, the consideration of laparoscopy as a factor is integral in ensuring the feasibility and appropriateness of the evaluation across the diverse studies. Postoperative complications were evaluated according to the Clavien-Dindo (CD) classification[15], which was established in 2004[16] and is a simple and feasible classification system for the severity of postoperative complications. CD categorization is a simple grading of post-operative complications used in common surgery: Grade I is a deviation from the normal postoperative course without any treatment, grade II is a need for medication, grade III is a need for surgery, endoscopic or radiological intervention, grade IV is a life-threatening condition requiring intensive care unit management, and grade V is death. Grade ≥ III is

defined as severe complications[17].

Statistical analysis

In this study, Review Manager Software 5.3 was used for meta-analysis. Continuity variables and binary variables were analyzed using forest plots, and heterogeneity was evaluated by the χ^2 test P value. The random effects model was adopted when the heterogeneity was large ($I^2 \geq 50\%$), and the fixed effects model was adopted when the heterogeneity was small and the homogeneity was considered ($I^2 < 50\%$). For the continuity variable, the mean difference (MD) was selected when the measurement methods or units of the intervention were the same. Heterogeneity tests, P values (validity), and effect scales were analyzed using forest plots, and publication bias was evaluated using funnel plots. The effect size of continuous variables was expressed by the MD and 95% confidence interval (CI), and that of dichotomous variables was expressed by the odds ratio (OR) value and 95%CI. Among the dichotomous variables, risk ratio (RR) for prospective studies and OR for case-control studies were selected. When heterogeneity was high, subgroup analysis was conducted to explore the potential causes of heterogeneity. The literature data are divided into several subgroups according to different attributes, and the subgroup analysis of continuous variables and two categorical variables are analyzed respectively. We affirm that the statistical review of the study was performed by a biomedical statistician and the meta-analysis was based on the PRISMA guidelines.

RESULTS

Summary of general clinical data

By exploring the above six databases, 17 studies that included 12744 patients were identified and quantitatively analyzed. The minimum number of samples was 46, and the maximum number was 2495. Of the 17 studies included, 14 studies were from Japan, and the remaining 3 were from China, Switzerland and Turkey; 3 studies were multicenter studies, and the other 14 were single-center studies; 3 studies were prospective, and the remaining 14 were retrospective; 6 studies involved gastrointestinal surgery, and the remaining 11 involved non-gastrointestinal surgery; 6 studies looked specifically at older adults, while the remaining 11 looked at people of all ages; 7 studies defined CRS = 0.5 as the cutoff value, and the remaining 10 defined different CRS cutoff values (Table 1).

Assessment of risk bias

First, an assessment of risk bias was conducted, which was based on the Cochrane Collaboration's Bias Risk Tool[18] to assess the quality of trials, and it was found that most literature had a little risk bias (Figure 2).

Heterogeneity effect analyses and sensitivity analyses

The E-PASS scoring system was analyzed in patients with or without complications after abdominal surgery (Figure 3).

PRS

The forest plot was further analyzed to evaluate the heterogeneity effect, and the data were divided into a group with postoperative complications and a group without complications. The PRS, SSS and CRS values are shown from top to bottom in order (Figure 3A). In the PRS analysis, a total of 2183 patients participated in 10 studies[11,16,19-26] that reported the relationship between PRS scores and postoperative complications. The mean value of PRS in the group with complications was 0.45, and that without complications was 0.40. Since the data had heterogeneity ($I^2 = 85\% \geq 50\%$, $P < 0.0001$), we used a random-effects model for the meta-analysis. The result [MD (95%CI): 0.04 (0.001-0.08), $P = 0.05$] indicated that PRS scores with postoperative complications increased 0.04% more than those without complications, but this difference was not statistically significant.

The results from the sensitivity analysis using a fixed-effect model after removing two low-quality studies[11,25] confirmed the findings that the overall effect of the two groups had no significant difference, and the result was robust [MD (95%CI): -0.01 (-0.01 to 0.001), $I^2 = 39\%$, $P = 0.20$].

SSS

We used a random-effects model for the SSS meta-analysis (Figure 3B). A total of 2183 patients participated in 10 studies [11,16,19-26] that reported the relationship between SSS scores and postoperative complications. The mean value of SSS in the group with complications was 0.21, and that without complications was 0.12. The forest plot showed that SSS scores with postoperative complications increased 0.1% more than those without complications, and this difference was statistically significant [MD (95%CI): 0.10 (0.05-0.15), $P < 0.0001$].

Since the data had significant heterogeneity ($I^2 = 87\%$), sensitivity analyses were performed by using a fixed-effect model and removing two low-quality studies[16,21]. The results showed that the SSS score in the group with complications was 0.06% higher than that in the group without complications, which was reliable for the homogeneity of the two groups [MD (95%CI): 0.06 (0.04-0.09), $P < 0.0001$, $I^2 = 0$].

CRS

In the CRS analysis, a total of 2279 patients participated in 12 studies[7,11,16,19-27] that reported the relationship between CRS score and postoperative complications (Figure 3C). The mean value of CRS in the group with complications was 0.37, and that without complications was 0.19. Since the studies had heterogeneity ($I^2 = 98\%$), we used a random-effects model

Table 1 Basic information of the included literature

Ref.	Country	Institution	Prescription	Journal	Surgical site	Sample size	Sex (M/F)	Age	Elderly	CRS cutoff
Abe *et al*[19], 2014	Japan	Single-center	Retrospective	*Dig Surg*	Gastrointestinal	73	51/22	66.0 ± 9.0	Yes	0.5
Banz *et al*[20], 2009	Switzerland	Single-center	Prospective	*World J Surg*	Liver	243	131/112	61.0 ± 10.5	No	0.5
Dai *et al*[21], 2022	China	Single-center	Retrospective	*Transl Cancer Res*	Liver	236	199/37	59.73 ± 11.0	No	0.126
Hayashi *et al*[16], 2021	Japan	Single-center	Retrospective	*J Hepatobiliary Pancreat Sci*	Pancreas	343	153/190	71.0 ± 2.3	No	0.5
Kasap *et al*[22], 2022	Turkey	Single-center	Retrospective	*Int Urol Nephrol*	Abdominal	424	248/176	49.1 ± 15.3	No	-0.2996
Kondo *et al*[23], 2020	Japan	Single-center	Retrospective	*J Anus Rectum Colon*	Colorectal	145	72/73	87.8 ± 2.0	Yes	-0.058
Murakami *et al*[24], 2020	Japan	Single-center	Retrospective	*Dig Surg*	Gastrointestinal	136	94/42	80.1 ± 4.01	Yes	0.2802
Nanashima *et al*[11], 2011	Japan	Single-center	Retrospective	*J Surg Oncol*	Liver	188	152/36	65.1 ± 9.5	Yes	0.5
Tominaga *et al*[25], 2016	Japan	Single-center	Retrospective	*Int J Colorectal Dis*	Colorectal	239	118/121	77.86 ± 5.57	Yes	0.2
Yamamoto *et al*[26], 2020	Japan	Single-center	Retrospective	*Dig Surg*	Colorectal	166	91/75	80.2 ± 4.5	Yes	0.05
Hashimoto *et al*[7], 2010	Japan	Single-center	Retrospective	*Surg Today*	Pancreas	46	19/27	63.5 ± 13.4	No	0.43
Koushi *et al*[27], 2011	Japan	Single-center	Retrospective	*Surg Today*	Gastrointestinal	51	30/21	64.1 ± 14.0	No	0.5
Haga *et al*[28], 2004	Japan	Multi-center	Prospective	*Surgery*	Gastrointestinal	5212	2730/2482	65.0 ± 16.2	No	0.5
Kato *et al*[29], 2022	Japan	Multi-center	Retrospective	*Int J Surg*	Colorectal	2407	1377/1030	69.63 ± 11.36	No	-0.025
Nakanishi *et al*[30], 2022	Japan	Multi-center	Retrospective	*Surg Today*	Gastrointestinal	2495	1790/705	67.73 ± 9.996	No	0.4179
Norimatsu *et al*[31], 2022	Japan	Single-center	Prospective	*World J Surg*	Hepatobiliary pancreas	184	118/66	75.8 ± 1.0	Yes	0.049
Oka *et al*[32], 2005	Japan	Single-center	Retrospective	*World J Surg*	Gastrointestinal	156	98/58	62.14 ± 9.29	No	0.5

CRS: Comprehensive risk score.

for the meta-analysis. The result [MD (95%CI): 0.19 (0.07-0.31), $P = 0.002$] indicated that CRS scores with postoperative complications were 0.04% higher than those without complications.

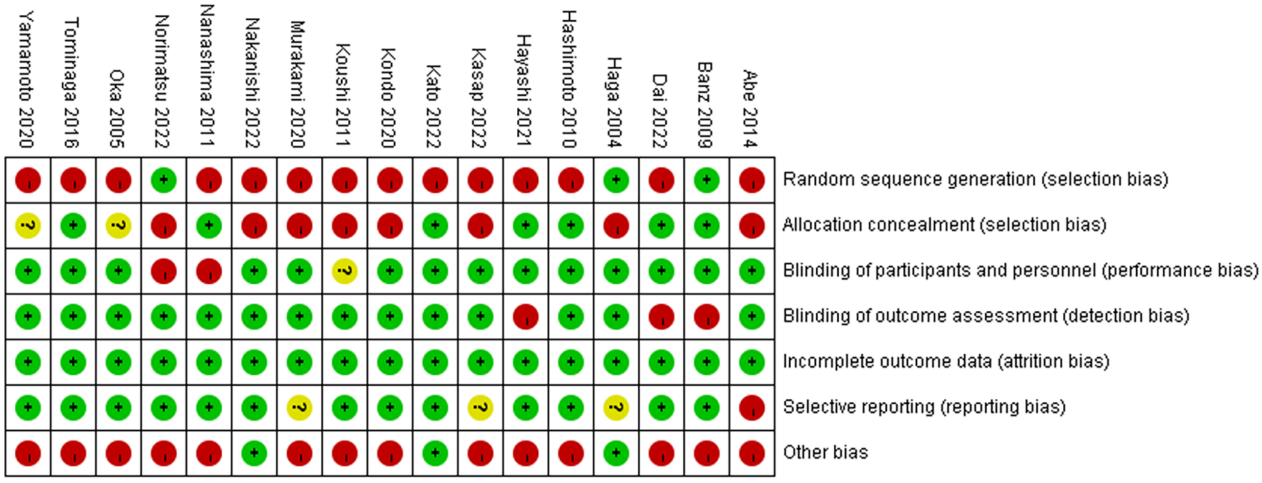
Sensitivity analyses were performed by removing two low-quality studies[7,21]. The results showed that the CRS score in the group with complications was 0.13% higher than that in the group without complications, and the result was robust [MD (95%CI): 0.13 (0.11-0.14), $P < 0.0001$, $I^2 = 27\%$].

Publication bias analysis

While analyzing the forest maps, the funnel maps were compared correspondingly. The data on both sides of the map are not completely symmetrical, and publication bias might exist (Figure 4). After removing low-quality studies in the PRS, SSS, and CRS analyses, it can be seen that the plots were basically symmetrical on both sides, indicating that there was almost no publication bias in the literature (Figure 5).

Subgroup analysis

To explore the source of CRS heterogeneity, a total of 6 subgroups of 12 studies on CRS score were further analyzed, including sample size (< 100, 100-200, ≥ 200); country (Japan, non-Japan); influence factor (< 2.0, ≥ 2.0); operation site (gastrointestinal tract, hepatobiliary pancreas); age (elderly, nonelderly); and CRS cutoff (< 0.5, ≥ 0.5). Subgroup analysis showed that the sample size grouping ($I^2 = 99.6\%$) and the elderly grouping ($I^2 = 97.7\%$) had significant heterogeneity, while the other groups had no significant heterogeneity (Supplementary Figures 1-6). Therefore, the differences in sample



DOI: 10.4240/wjgs.v16.i1.215

Figure 2 Assessment of risk bias in meta-analyses.

size and age may be the source of heterogeneity in the CRS analysis (Table 2).

Comparison of postoperative morbidity and mortality between the high CRS group and the low CRS group

In the further meta-analysis of dichotomous variables, we compared the CRS score with postoperative morbidity and mortality studies. A total of 11194 patients with 10 studies were enrolled in the postoperative morbidity analysis[19-21,23,27-32] (Figure 6A); a total of 10557 patients were enrolled in the postoperative mortality analysis, including 6 studies[21,27-30,32] (Figure 6B).

According to the dichotomous variables analysis, patients with a high CRS score had a higher incidence of postoperative complications [OR (95%CI): 3.01 (1.83-4.95), $P < 0.0001$]. Patients with high CRS scores had a significantly higher incidence of postoperative death, with an OR (95%CI) of 15.49 (3.75- 64.01) ($P = 0.0002$). There was significant heterogeneity between the two groups ($I^2 \geq 50\%$).

The heterogeneity of CRS and complications did not change when one or more articles were removed, while, when one low-quality study was removed[29], the heterogeneity of CRS and mortality meta-analysis immediately became homogeneous [OR (95%CI): 24.94 (14.72-42.25), $P < 0.0001$, $I^2 = 0$]. According to the funnel plot analysis of the two groups, the publication bias of postoperative complications was significantly lower than that of postoperative mortality (Figure 7).

Subgroup analysis of dichotomous variables

The ten studies[19-21,23,27-32] were performed six subgroup analyses as follows: The number of institutions (single-center, multicenter); research time span (retrospective, prospective); sample size (< 200, ≥ 200); influencing factors(< 3.0, ≥ 3.0); operation site (gastrointestinal, nongastrointestinal); and CRS cutoff (< 0.5, ≥ 0.5) (Supplementary Figures 7-12). Subgroup analysis showed that there was no heterogeneity among the groups (subgroup differences $I^2 = 0$), suggesting that the overall heterogeneity was due to certain individual low-quality studies (Table 3).

DISCUSSION

Currently, the common predictive surgical scores include the ASA score, Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity (POSSUM) score, E-PASS scoring system, and so on. Developed in the United Kingdom in 1991[33], the POSSUM system integrates 12 physiological factors and 6 surgical factors, generating Physiological score (P score) and Operative score (O score), respectively. However, both POSSUM and P-POSSUM scores that have complex calculation formulas[16] are acknowledged for their tendency to overestimate postoperative mortality in digestive surgery[34,35]. Additionally, the revised modified E-PASS score, while having not been extensively tested [36], shows reduced accuracy in elderly patients undergoing perihilar cholangiocarcinoma surgery[6]. Comparative analyses have consistently shown that E-PASS scores prove more convenient and effective than POSSUM scores and ASA scores, particularly in the realms of hepatobiliary, pancreatic, and gastrointestinal surgeries. Furthermore, E-PASS scores outperform other scoring models in their predictive accuracy for postoperative complications[16,23,25,28]. Widely recognized as a robust evaluation system, the E-PASS scoring system excels in predicting postoperative complications in abdominal surgery. Its capacity to distinguish patients at high and low risk of hospital death following digestive surgery further underscores its clinical utility.

The E-PASS scoring system incorporates PRS, SSS, and CRS. CRS, a composite of PRS and SSS, enhances the comprehensiveness and accuracy of complications prediction. The E-PASS scoring system necessitates the collection of medical history pertaining to heart disease, lung disease, and diabetes. Meanwhile, it involves the assessment of the ASA

Table 2 Summary of subgroup analysis in comprehensive risk score and comparison with or without postoperative complications

Subgroup	Classification	Studies	MD (95%CI)	Subgroup I^2	Subgroup effect (*P* value)	Subgroup overall I^2
Sample size	< 100	3	0.51 (0.48-0.54)	95%	< 0.0001	99.6%
	100-200	4	0.12 (0.08-0.16)	0	< 0.0001	
	≥ 200	4	0.14 (0.12-0.16)	85%	< 0.0001	
Country	Japan	9	0.19 (0.04-0.34)	98%	0.01	0
	Non-Japan	3	0.18 (0.05-0.31)	88%	0.005	
Influence factor	< 2.0	3	0.19 (0.09-0.28)	92%	< 0.0001	0
	≥ 2.0	9	0.19 (0.02-0.36)	98%	0.03	
Surgical site	Gastrointestinal tract	6	0.13 (0.07-0.19)	57%	< 0.0001	0
	Hepatobiliary pancreas	5	0.24 (0.02-0.46)	99%	0.03	
Age	Elderly	5	0.12 (0.08-0.15)	0%	< 0.0001	97.7%
	Non-elderly	7	0.25 (0.23-0.26)	99%	< 0.0001	
CRS cut-off	< 0.5	7	0.20 (0.03-0.37)	98%	0.02	0
	≥ 0.5	5	0.14 (0.07-0.22)	55%	< 0.0001	

CRS: Comprehensive risk score; MD: Mean difference; CI: Confidence interval.

Table 3 Subgroup analysis of postoperative complications in the high comprehensive risk score group and the low comprehensive risk score group

Subgroup	Classification	Studies	OR (95%CI)	Subgroup I^2	Subgroup effect (*P* value)	Subgroup overall I^2
Institutions quantity	Single-center	7	3.29 (1.83-5.93)	72%	< 0.0001	0
	Multi-center	3	2.57 (1.08-6.10)	99%	0.03	
Time span	Retrospective	7	2.62 (1.75-3.94)	81%	< 0.0001	0
	Prospective	3	3.51 (1.26-9.75)	92%	0.02	
Sample size	< 100	5	3.68 (1.91-7.08)	60%	< 0.0001	0
	≥ 200	5	2.59 (1.32-5.10)	97%	0.006	
Influence factor	< 3.0	5	2.71 (1.61-4.56)	92%	0.0002	0
	≥ 3.0	5	3.25 (1.39-7.58)	64%	0.006	
Operation site	Gastrointestinal	6	3.30 (1.73-6.29)	96%	0.0003	0
	Non-gastrointestinal	4	2.61 (1.12-6.07)	80%	0.03	
CRS cut-off	< 0.5	5	2.54 (1.67-3.84)	82%	< 0.0001	0
	≥ 0.5	5	3.24 (1.45-7.22)	88%	0.004	

CRS: Comprehensive risk score; OR: Odds ratio; CI: Confidence interval.

physiological state rating, along with the retrieval of intraoperative blood loss, preoperative weight, operation time, and surgical incision details. These elements, readily available in medical records, collectively contribute to the effective evaluation of postoperative complication incidence. We believe that each component of the E-PASS can be easily obtained from medical records and directly applied in clinical settings without requiring supplementary calculations.

Numerous prior studies have consistently affirmed the correlation between the E-PASS scoring system and postoperative morbidity and mortality. Nakanishi *et al*[30] posited the E-PASS score as an independent prognostic factor throughout the stages of gastric cancer. Kato *et al*[29] validated a significant association between a high CRS and overall survival and recurrence-free survival in colorectal cancer patient's post-resection, irrespective of disease stage. The CRS score emerges as an indicator of poor prognosis regardless of disease stage. Abe *et al*[19] advocated the superior predictive value of SSS over PRS, emphasizing the importance of maintaining low surgical pressure rather than solely relying on preoperative patient status for evaluation. Murakami *et al*[24] suggested that, compared to open surgery, laparoscopic surgery results in a lower CRS score. Specifically, laparoscopic-assisted surgery exhibits a lower SSS score,

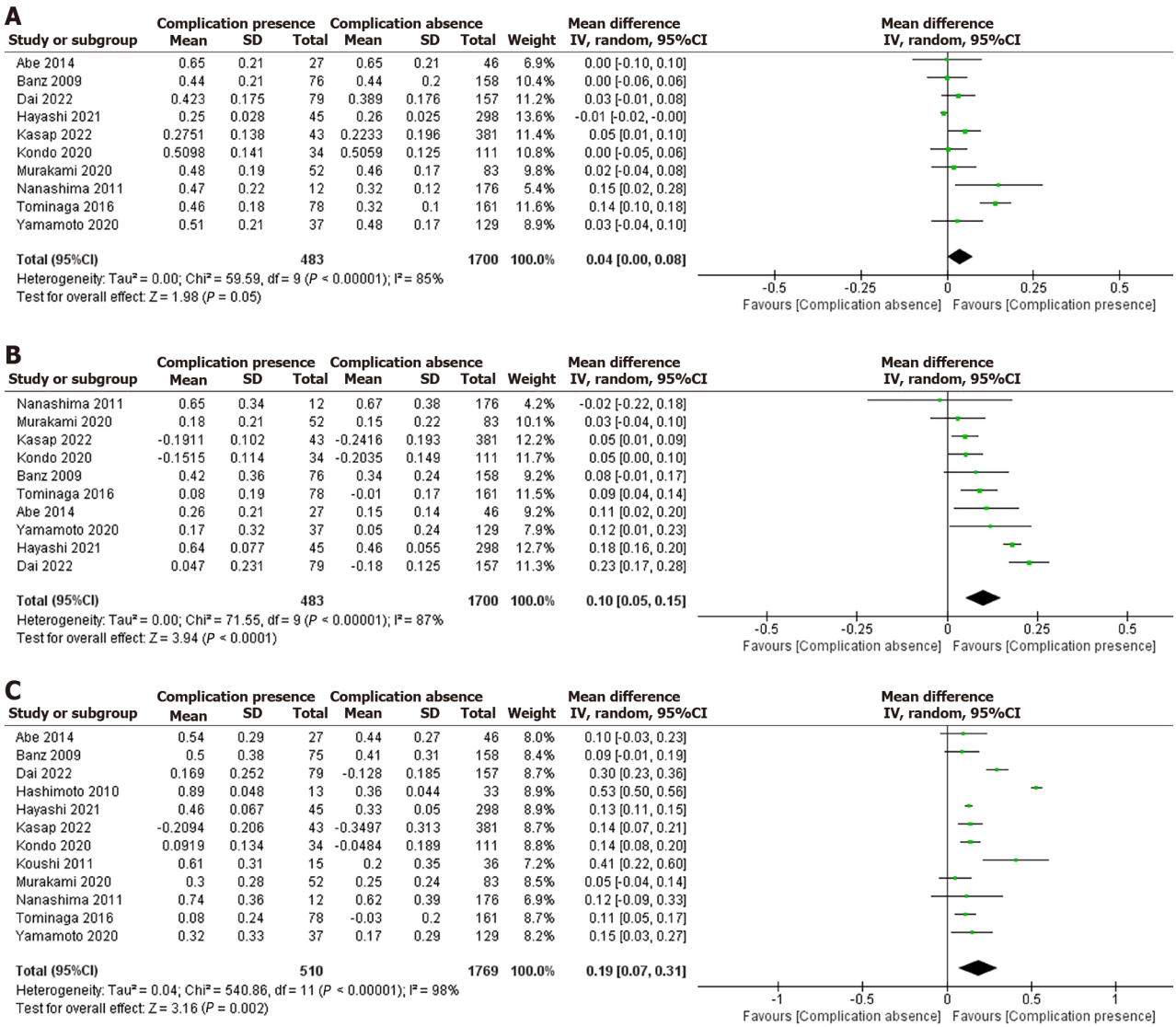


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Figure 3 Forest plot of the Estimation of Physiologic Ability and Surgical Stress scoring system compared with postoperative complications. A: Preoperative risk score; B: Surgical stress score; C: Comprehensive risk score. CI: Confidence interval.

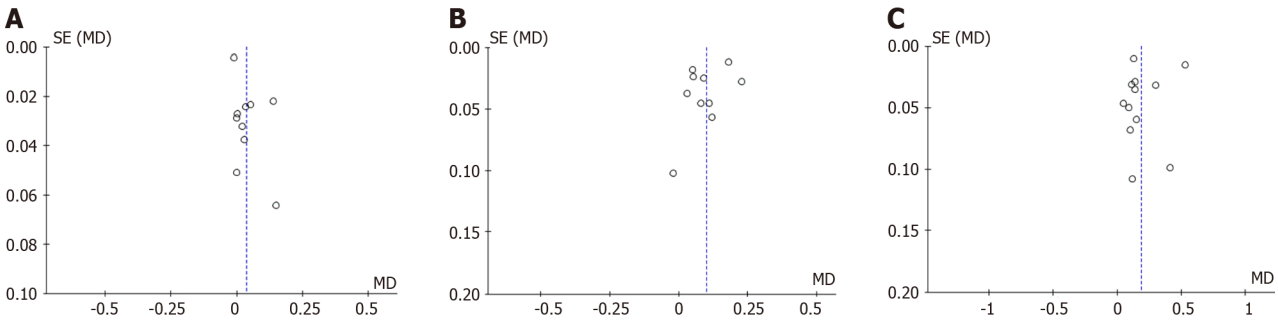

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Figure 4 Funnel plot of random effects model analysis in the Estimation of Physiologic Ability and Surgical Stress scoring system compared with postoperative complications of abdominal surgery. A: Preoperative risk score; B: Surgical stress score; C: Comprehensive risk score.

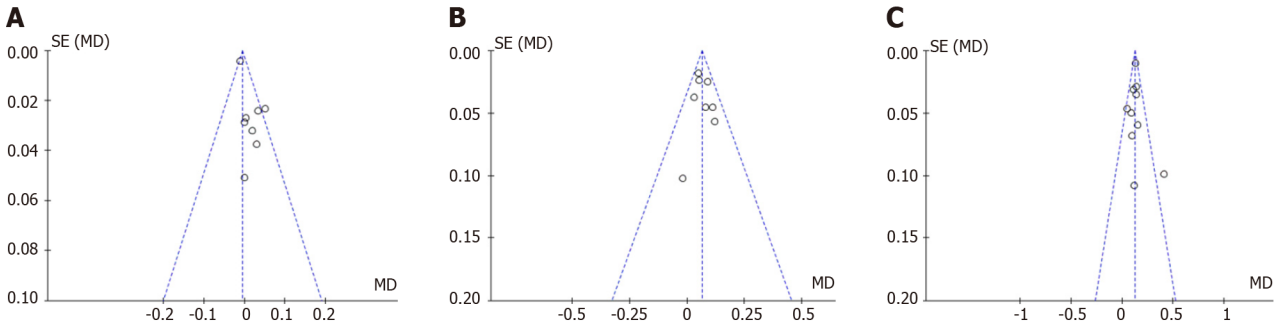

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Figure 5 Funnel plot of fixed effects model analysis in the Estimation of Physiologic Ability and Surgical Stress scoring system compared with postoperative complications of abdominal surgery. A: Preoperative risk score; B: Surgical stress score; C: Comprehensive risk score.

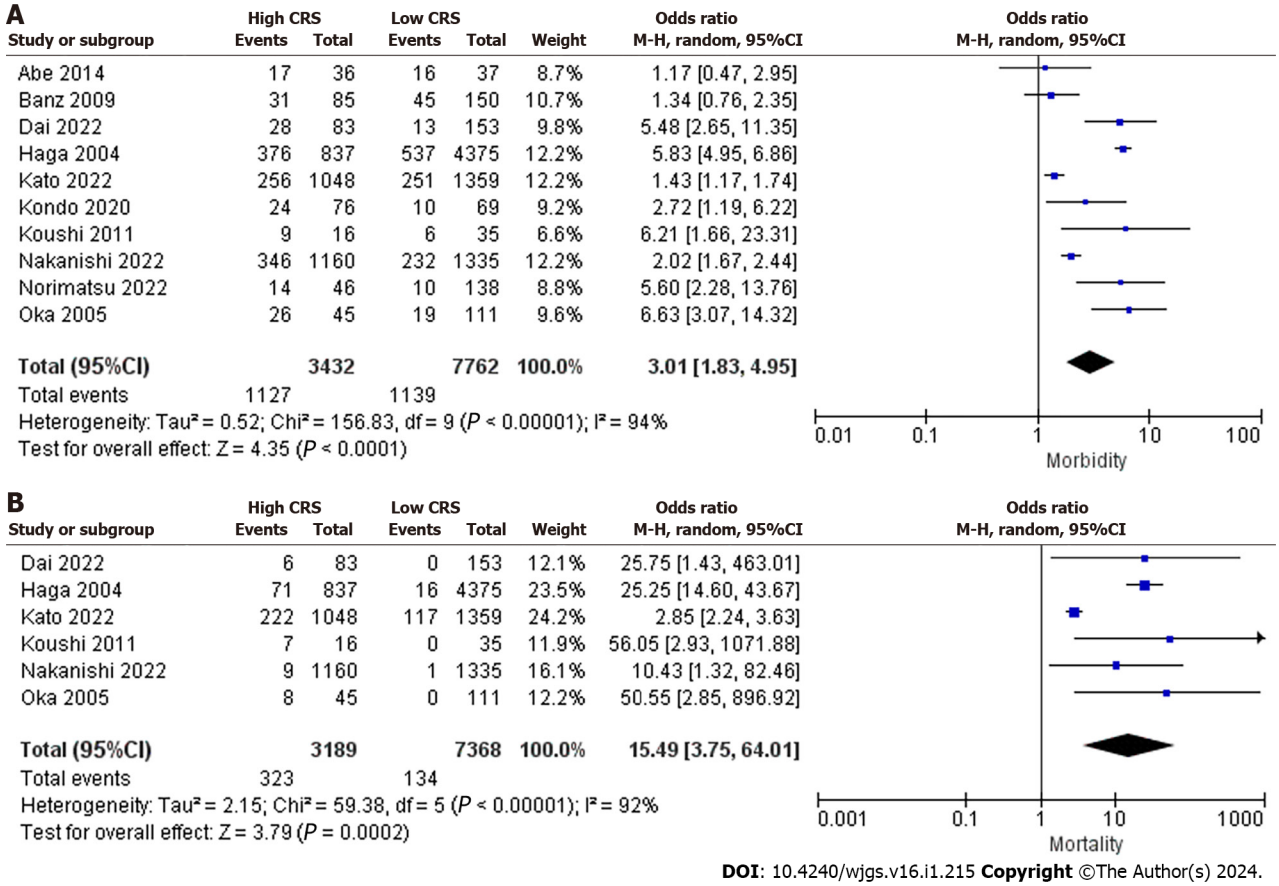

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Figure 6 Forest plot of postoperative complications and mortality in the high comprehensive risk score group and the low comprehensive risk score group. A: Postoperative complication rate; B: Postoperative mortality. CI: Confidence interval; CRS: Comprehensive risk score.

indicating reduced invasive trauma and a diminished postoperative risk compared to open surgery. Consequently, the recommendation for minimizing postoperative complications in abdominal surgery is to opt for minimally invasive treatment. Kondo *et al*[23] proposed that almost all elderly patients undergoing laparoscopic surgery exhibited lower mean CRS scores, attributing this to their baseline low CRS values. Overall, approximately 25% of elderly patients experience mortality attributable to noncancer-related comorbidities within the five-year period surgery[37]. Regardless of age, laparoscopic surgery for abdominal visceral diseases is deemed safe and feasible[38,39]. Recognizing that postoperative pain can contribute to complications such as atelectasis, insufficient ventilation, and reduced mobility[40,41], laparoscopic surgery offers patients distinct advantages. These include reduced postoperative pain due to minimized skin incisions, a corresponding decrease in the incidence of lung complications, and enhanced early activity, thereby promoting postoperative recovery.

One notable limitation of this meta-analysis lies in the predominant utilization of retrospective data in the majority of the included studies. The subgroup analysis of binary variables was conducted in Supplementary Figure 8. Potential bias in the risk prediction can be ignored due to that there was no significant heterogeneity between prospective and

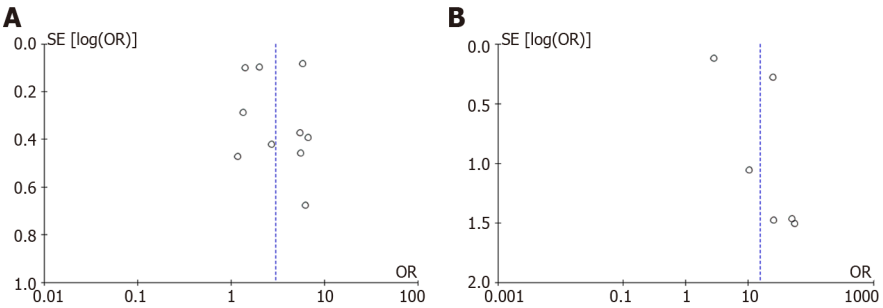

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Figure 7 Funnel plot analysis of postoperative complication rate and mortality in the high comprehensive risk score group and the low comprehensive risk score group. A: Postoperative complication rate; B: Postoperative mortality.

retrospective studies (subgroup differences $I^2 = 0$). Additionally, certain studies relied on the classification of complications based on the severity criteria defined by the Comprehensive Complication Index (CCI), specifically, a CCI score equal to or exceeding 40 points[42]. Such an approach may introduce outcome bias to some extent. Despite these limitations, the meta-analysis boasts several strengths. Firstly, it consolidates and scrutinizes a substantial volume of literature data, encompassing a diverse array of clinical studies. Secondly, the analysis goes beyond previous studies by intricately examining the heterogeneity and efficacy of the E-PASS system through split analysis, sensitivity analysis, and subgroup analysis of each component. This detailed approach enhances the persuasiveness and granularity of the findings. Third, the meta-analysis furnishes a robust directional guide for predicting the postoperative risk associated with the E-PASS scoring system.

CONCLUSION

In summary, the amalgamation of findings from 17 studies indicates a positive correlation between postoperative complications in abdominal surgery and elevated scores in PRS, SSS, and CRS within the E-PASS system. Notably, heightened CRS scores emerge as risk factors associated with an increased incidence of postoperative complications and mortality. The simplicity and practicality of the E-PASS scoring system position it as an effective model for accurately predicting postoperative complications. This endorsement underscores the potential for widespread adoption, offering a valuable tool for enhancing risk assessment after abdominal surgery and furnishing a reliable direction for clinical practice.

ARTICLE HIGHLIGHTS

Research background

Postoperative complications have always been a close concern to surgeons. Numerous studies affirm the simplicity and efficacy of the Estimation of Physiologic Ability and Surgical Stress (E-PASS) scoring system, which demonstrates superior predictive capabilities for postoperative complications in hepatobiliary, pancreatic, and gastrointestinal surgeries compared to alternative models.

Research motivation

How can doctors exhibit precise predictive capability for the risk of morbidity and mortality in patients undergoing abdominal surgery?

Research objectives

The main objective is to present a comprehensive analysis of the E-PASS scoring system's efficacy in predicting postoperative complications following abdominal surgery.

Research methods

A systematic search of published studies was conducted, yielding 17 studies with pertinent data. Preoperative risk score, surgical stress score, comprehensive risk score (CRS), postoperative complications, postoperative mortality, and other clinical data were collected for meta-analysis. Continuity variables and binary variables were analyzed using forest plots, and heterogeneity was evaluated by the χ^2 test P value. Heterogeneity tests, P values (validity), and effect scales were analyzed using forest plots, and publication bias was evaluated using funnel plots. The literature data are divided into several subgroups according to different attributes, and the subgroup analysis of continuous variables and two categorical variables are analyzed respectively.

Research results

Patients experiencing complications after abdominal surgery exhibited significantly higher E-PASS scores compared to those without complications. Subgroup analysis indicated that variations in sample size and age may contribute to heterogeneity in CRS analysis. Binary variable meta-analysis demonstrated a correlation between high CRS and increased postoperative complication rates, with a significant association observed between high CRS and postoperative mortality.

Research conclusions

The E-PASS scoring system is simple and practical to be used as a good model to predict the postoperative complications with accuracy, being expected to popularize effective risk assessment after abdominal surgery.

Research perspectives

We confirmed that the E-PASS scoring system can predict the postoperative morbidity and mortality of abdominal surgery with accuracy, worth to be popularized for effective risk assessment.

FOOTNOTES

Author contributions: Pang TS and Cao LP contributed equally to this work; Pang TS and Cao LP collected the data together; Pang TS designed the study and wrote the manuscript; Cao LP performed the research and analyzed the data; and all authors have read and approve the final manuscript.

Supported by Medical Science and Technology Project of Zhejiang Province of China, No. 2020PY053.

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

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

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S-Editor: Wang JJ
L-Editor: A
P-Editor: Yu HG

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World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2024 January 27; 16(1): 228-238

DOI: 10.4240/wjgs.v16.i1.228

ISSN 1948-9366 (online)

META-ANALYSIS

Role of Oncostatin M in the prognosis of inflammatory bowel disease: A meta-analysis

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Specialty type: Gastroenterology and hepatology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Matsui T, Japan

Received: November 14, 2023
Peer-review started: November 14, 2023
First decision: December 8, 2023
Revised: December 19, 2023
Accepted: December 29, 2023
Article in press: December 29, 2023
Published online: January 27, 2024

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Abstract

BACKGROUND

Oncostatin M (OSM) is a pleiotropic cytokine which is implicated in the pathogenesis of inflammatory bowel disease (IBD).

AIM

To evaluate the prognostic role of OSM in IBD patients.

METHODS

Literature search was conducted in electronic databases (Google Scholar, Embase, PubMed, Science Direct, Springer, and Wiley). Studies were selected if they reported prognostic information about OSM in IBD patients. Outcome data were synthesized, and meta-analyses were performed to estimate standardized mean differences (SMDs) in OSM levels between treatment responders and non-responders and to seek overall correlations of OSM with other inflammatory biomarkers.

RESULTS

Sixteen studies (818 Crohn's disease and 686 ulcerative colitis patients treated with anti-tumor necrosis factor-based therapies) were included. OSM levels were associated with IBD severity. A meta-analysis found significantly higher OSM levels in non-responders than in responders to therapy [SMD 0.80 (0.33, 1.27); P = 0.001], in non-remitters than in remitters [SMD 0.75 (95%CI: 0.35 to 1.16); P < 0.0001] and in patients with no mucosal healing than in those with mucosal healing [SMD 0.63 (0.30, 0.95); P < 0.0001]. Area under receiver operator curve values showed considerable variability between studies but in general higher OSM levels were associated with poor prognosis. OSM had significant correlations with Simple Endoscopic Score of Crohn's disease [r = 0.47 (95%CI: 0.25 to 0.64); P < 0.0001], Mayo Endoscopic Score [r = 0.35 (95%CI: 0.28 to 0.41); P < 0.0001], fecal

calprotectin [r = 0.19 (95%CI: 0.08 to 0.3); P = 0.001], C-reactive protein [r = 0.25 (95%CI: 0.11 to 0.39); P < 0.0001], and platelet count [r = 0.28 (95%CI: 0.17 to 0.39); P < 0.0001].

CONCLUSION
OSM is a potential candidate for determining the severity of disease and predicting the outcomes of anti-tumor necrosis factor-based therapies in IBD patients.

Key Words: Inflammatory bowel disease; Crohn's disease; Ulcerative colitis; Oncostatin M; Prognosis

Core Tip: Higher Oncostatin M (OSM) expression/levels are found to be associated with worse disease outcomes which shows that OSM can be used as a s surrogate marker of poor prognosis in inflammatory bowel disease patients treated with anti-tumor necrosis factor based therapies. Thus, OSM appears to be an attractive biomarker for patient selection and clinical decision-making. However, owing to the presence of heterogeneity in included studies, this evidence should be refined in future studies.

Citation: Yang Y, Fu KZ, Pan G. Role of Oncostatin M in the prognosis of inflammatory bowel disease: A meta-analysis. *World J Gastrointest Surg* 2024; 16(1): 228-238
URL: https://www.wjgnet.com/1948-9366/full/v16/i1/228.htm
DOI: https://dx.doi.org/10.4240/wjgs.v16.i1.228

INTRODUCTION

Inflammatory bowel disease (IBD) is a disease of the gastrointestinal tract with two main types: Crohn's disease, and ulcerative colitis. Crohn's disease can affect any part of the gastrointestinal tract, whereas ulcerative colitis mainly affects the colon. IBD may arise at any age but usually onsets at early adulthood[1]. Primary surgery is required for approximately 32%, 55%, 70%, and 82% of Crohn's disease patients after 5, 10, 15, and 20 years of diagnosis, respectively[2]. It is speculated that an altered immune response to gut flora depending on individual's hereditary variability and environmental influences may be involved in the etiology of IBD. Age at onset, location, behavior, perianal disease in Crohn's disease and disease extent in ulcerative colitis are important determinants of disease condition[3].

There is an increasing trend in the prevalence of IBD. In the United States, the prevalence of IBD has increased from 0.8% (1.8 million) in 1999 to 1.3% (3 million) in 2015[4]. Globally, the prevalence of IBD is rising in newly industrialized countries[5]. Concomitantly, the prevalence rates of pediatric-onset IBD are also increasing even in regions where this disease was not previously reported[6]. IBD is clinically difficult-to-treat disease that affects younger individuals and leads to long-term morbidity. Resistance to therapeutic agents is a hallmark of its management that necessitates personalized medicine research and development. Use of alternative drugs is frequent, but prediction of disease course and response to a particular therapy can profoundly benefit to patients.

IBD is a lifelong incurable disease that alternates with remission and relapse. Management may require 5-aminosalicylates, thiopurines, steroids, and biologics such as antibodies against tumor necrosis factor alpha (TNFα), vedolizumab, ustekinumab *etc.*[7]. TNFα is involved in IBD onset and progression. Anti-TNFα antibody-based drugs including infliximab, adalimumab, certolizumab, and golimumab are the mainstay in the treatment of IBD[8]. However, about 40% of patients do not respond to anti-TNF therapies, and among those who initially respond, several develop resistance to treatment. This necessitates IBD research to focus not only on the development of newer drugs, but also to identify biomarkers that can predict response to a therapy in advance[9].

Oncostatin M (OSM) is a proinflammatory cytokine belonging to the interleukin-6 family. OSM is produced mostly in hematopoietic tissues including T-lymphocytes, monocytes, macrophages, dendritic cells, neutrophils, eosinophils, and mast cells[10]. It is a pleiotropic factor that participates in several organismic processes including hematopoiesis, differentiation, regeneration, and inflammation. On the other hand, several pathological processes including arthritis, ossification, dermatitis, fibrosis, gingivitis, and carcinogenesis are found to have OSM mediation[11]. In colorectal cancer, higher OSM levels are associated with advanced disease and metastasis[12]. One of the major pathological processes in which the involvement of OSM has been found critical is the inflammation of various parts including the joints, skin, lungs, and intestine[10].

The role of OSM in the pathogenesis of IBD was first described in a discovery of single nucleotide polymorphism in OSM receptors[13]. OSM mediates its effects by binding to a glycoprotein called gp130 and this complex then activates the OSM receptor for signaling[14]. OSM is highly expressed in inflamed mucosa of IBD patients in comparison with normal individuals. Elevated OSM levels are also found in serum of IBD patients. Moreover, higher OSM levels are observed in first-degree relatives of multiple-affected families in comparison with normal families[15]. Several studies have evaluated the prognostic role of OSM in IBD patients. However, there are variabilities in the degree of associations between OSM and disease or interventional outcomes. This necessitates a systematic review of this area. The aim of the

present study was to identify studies that evaluated the prognostic role of OSM in IBD patients in order to synthesize the reported outcomes and to perform meta-analyses of statistical indices for seeking up-to-date evidence of the prognostic role of OSM in IBD prognosis.

MATERIALS AND METHODS

Inclusion and exclusion criteria

Studies were included in this meta-analysis if they: (1) Evaluated IBD patients receiving a therapy who were subjected to OSM measurements in serum or tissue; (2) evaluated prognostic role of OSM in predicting disease outcomes and reported statistical indices of this relationship; and (3) reported correlations between baseline OSM and other important indicators of disease. Exclusion criteria were: (1) Studies involving the prognostic role of OSM in combination with other biomarkers; (2) molecular studies not providing any prognostic outcome; (3) molecular studies evaluating a possible role of OSM in IBD therapeutics; (4) preclinical studies; and (5) reviews and congress abstracts.

Literature search

The literature search was conducted in electronic databases (Google Scholar, Ebsco, PubMed, Science Direct, Springer, and Wiley) using the most relevant keywords. Primary search strategy was: Inflammatory bowel disease OR Crohn's disease OR ulcerative colitis AND oncostatin M AND prognosis OR prognostic OR predictor. The literature search encompassed original research articles published in English language from the date of inception of the database till September 2023.

Data analysis

The quality assessment of the included studies was performed with the Newcastle-Ottawa Scale for the Quality Assessment of Observational Studies. Demographic information, disease pathological indices, previous treatments, study design and conduct features, and study outcome data including OSM levels at baseline, OSM levels in association with response, remission, and mucosal healing rates, statistical data depicting the relationship between baseline OSM levels and outcomes of disease, and correlation coefficients between OSM and other variables of IBD etiology were extracted from research articles of the included studies and were organized in datasheets. Important characteristics of the included studies were tabulated, and outcome data were synthesized for use in analyses.

Area under the receiver-operator curve (AUC) values depicting the relationship between OSM and disease indicators including response rate, remission rate, and mucosal healing rate reported by individual studies were tabulated. A meta-analysis of standardized mean differences (SMDs) in OSM levels between responders and non-responders, remitters and non-remitters, and in patients with mucosal healing and no mucosal healing was performed. Correlation coefficients between OSM and other variables of disease etiology reported by the individual studies were first converted to z-scores and were pooled under random-effects model by deriving variance from respective sample sizes. Overall estimates were back transformed into correlation coefficients.

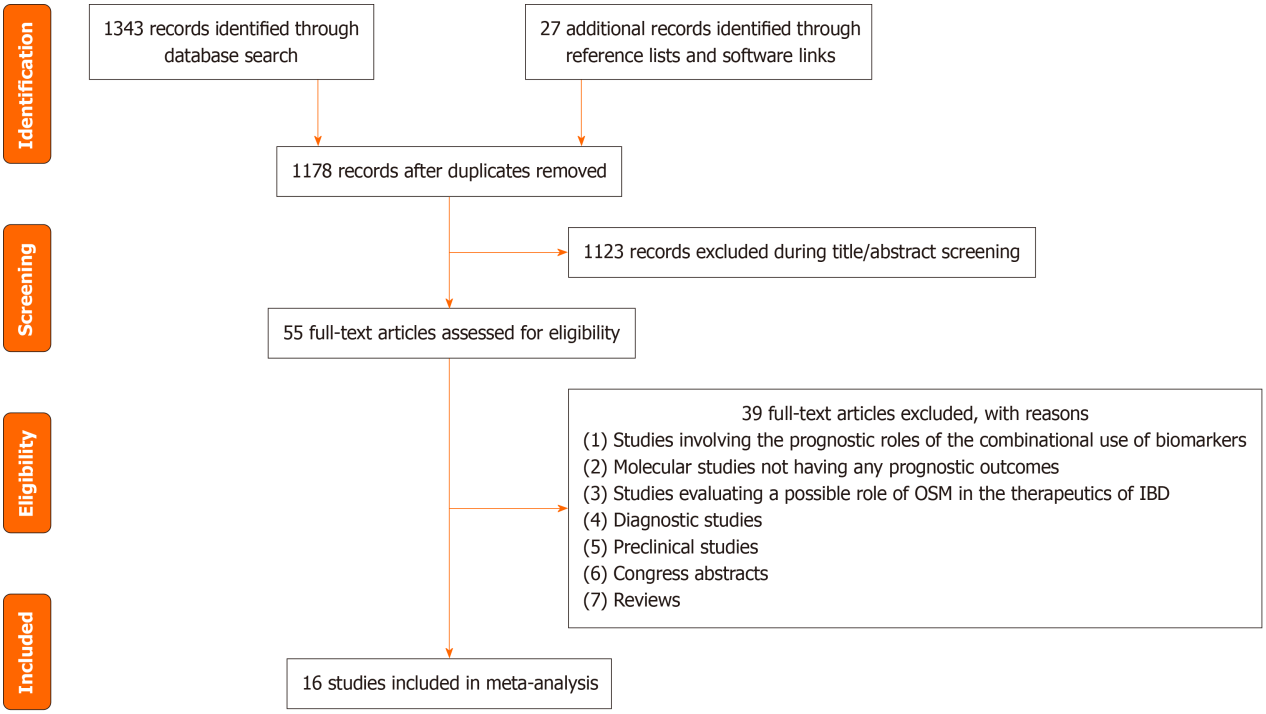
RESULTS

Sixteen studies[16-31] were included in this review (Figure 1). In these studies, 1353 IBD (818 Crohn's disease and 686 ulcerative colitis) patients were evaluated. Important characteristics of the included studies are presented in Supplementary Tables 1 and 2. The quality of these studies was generally good. The lack of unexposed cohort was the main constraint which was observed for 7 studies. One of the included studies was double-blind, randomized, placebo-controlled with high quality. An assessment of the quality of other included studies with the Newcastle-Ottawa Scale is presented in Supplementary Table 3.

OSM levels in patients with Crohn's disease and ulcerative colitis were generally similar. In Cao *et al*[18], fecal OSM levels (mean ± SD; pg/mL) were 7 ± 3 in Crohn's disease and 11 ± 4 in ulcerative colitis patients. In Cao *et al*[19], serum OSM levels (mean ± SD; pg/mL) were 119.4 (range: 34.8 - 240.6) in Crohn's disease and 122.1 (range: 58.7 - 294.9) in ulcerative colitis patients. In Verstockt *et al*[28], OSM expression levels (NPX; OLINK proximity extension technology values) were 6.4 (IQR: 5.5, 7) in Crohn's disease and 6.5 (IQR: 4.35, 4.9) in UC patients. In the study of West *et al*[29], log 2 OSM mRNA expression levels relative to control were 5 (IQR: 4, 8) in Crohn's disease and 5.2 (IQR: 4.5, 7) in ulcerative colitis patients.

However, OSM levels were associated with disease severity. In Cao *et al*[18], fecal OSM levels (mean ± SD; pg/mL) were 7 ± 2 in mild, 8 ± 5 in moderate, and 14 ± 4 in severe IBD cases whereas in Cao *et al*[19], serum OSM levels (mean ± SD; pg/mL) were 10 ± 27 in mild, 220 ± 240 in moderate, and 340 ± 150 in severe IBD cases. Mohamed *et al*[24] reported serum OSM levels to be 109.5 ± 25.5 in mild, 116.2 ± 27.6 in moderate, and 144.8 ± 33.5 in severe IBD cases. In West *et al*[29], OSM expression relative to control was 2 (IQR: 0, 2.2) in mild, 5 (IQR: 4, 5.2) in moderate, and 4 (IQR: 3, 4.5) in severe IBD cases.

A meta-analysis found significantly higher OSM levels in non-responders than in responders to therapy [SMD 0.80 (95%CI: 0.33 to 1.27); $P = 0.001$]. OSM levels were also significantly higher in non-remitters in comparison with remitters [SMD 0.75 (95%CI: 0.35 to 1.16); $P < 0.0001$] and in patients with no mucosal healing than in those with mucosal healing [SMD 0.63 (95%CI: 0.30 to 0.95); $P < 0.0001$; Figure 2]. OSM levels and tissue expression data of all included studies are



DOI: 10.4240/wjgs.v16.i1.228

Figure 1 A flowchart of study screening and selection process. OSM: Oncostatin M; IBD: Inflammatory bowel disease.

presented in Supplementary Table 4.

A synthesis of AUC values of treatment outcomes revealed that anti-TNF treatment had poor outcomes in patients with higher OSM levels in most studies (Tables 1 and 2). AUC values of OSM predicting the response of anti-TNF treatment in IBD patients ranged from 0.56 [95%CI: 0.31 to 0.82] to 0.91 [95%CI: 0.81 to 1.0] whereas the AUC values of OSM in distinguishing between responders and non-responders (including remission and mucosal healing) to anti-TNF therapy ranged from 0.52 to 0.9. Two studies did not report numeric data. Among these, O'Connell *et al*[26], who studied 21 patients with ulcerative colitis, did not find an association of pretreatment colonic OSM expression with the outcomes of infliximab therapy, and Mateos *et al*[21], who studied 22 patients with Crohn's disease, reported that OSM levels measured before induction therapy predicted response to infliximab treatment.

The correlation coefficients between OSM and Simple Endoscopic Score and Mayo Endoscopic Score were 0.47 [95%CI: 0.25 to 0.64] ($P < 0.0001$) and 0.35 [95%CI: 0.28 to 0.41] ($P < 0.0001$) respectively. The correlation coefficients between OSM and fecal calprotectin, C-reactive protein, and platelet count were 0.19 [95%CI: 0.08 to 0.3] ($P = 0.001$), 0.25 [95%CI: 0.11 to 0.39] ($P < 0.0001$), and 0.28 [95%CI: 0.17 to 0.39] ($P < 0.0001$) respectively (Figure 3). The correlation coefficients between OSM and other inflammatory/hematological markers observed in the included studies are given in Supplementary Table 5.

DISCUSSION

OSM has emerged as an important biomarker for determining disease condition and response to anti-TNF therapies in IBD patients. Higher OSM levels are found to be associated with disease severity and therapeutic non-response. AUC values reported by the individual studies showed that higher OSM levels predicted poor response and could be used to distinguish responders from non-responders of anti-TNF therapy. OSM had significant correlations with Simple Endoscopic Score, Mayo Endoscopic Score, fecal calprotectin, C-reactive protein, and platelet count.

Where there is always a need to search for newer drugs, there is also a need to identify markers which can predict the effectiveness of a therapy in advance. Although C-reactive protein is a commonly used marker for predicting response to a therapy, it is non-specific to IBD[16,32,33]. Fecal calprotectin is more important for IBD outcome prediction. Higher FC levels are found to be associated with no response to therapy[34-36]. Cao *et al*[18] found higher AUC value for fecal calprotectin (0.834) than fecal OSM (0.763) in predicting response to anti-TNF therapy. In the meta-analysis of correlation coefficients, we have found a significant correlation between OSM and fecal calprotectin in IBD patients.

It has been observed that OSM predicts therapeutic response better to anti-TNF than to other pharmacological treatments. Bertani *et al*[17] found OSM to be a useful biomarker for predicting response to anti-TNF therapy (AUC 0.91) but not to vedolizumab (AUC 0.56). Verstockt *et al*[28] also found low AUC values for distinguishing remitters from non-remitters after vedolizumab therapy both by serum OSM (0.51) and colonic OSM (0.685). Nishioka *et al*[25] found a relatively higher AUC value for mucosal OSM expression in distinguishing resistant from sensitive patients to anti-TNF therapy (0.83) compared to ustekinumab (0.77).

Table 1 Area under receiver operator curve values for the prediction of treatment outcomes by the Oncostatin M

Ref.	Prognostic association	OSM cutoff	AUC [95%CI]	Sensitivity [95%CI]	Specificity [95%CI]
Bertani *et al*[16], 2020	Prediction of no mucosal healing after anti-TNFα therapy at week 54 by baseline serum OSM	14	0.91 [0.81, 1]	96% [82, 100]	89% [67, 97]
Bertani *et al*[16], 2020	Prediction of no mucosal healing after anti-TNFα therapy at week 54 by serum OSM at week 14		0.83 [0.7, 0.95]		
Bertani *et al*[17], 2022	Prediction of no mucosal healing after anti-TNFα therapy at week 54 by baseline serum OSM	14	0.91 [0.84, 0.99]	91% [78, 97]	90% [75, 97]
Bertani *et al*[17], 2022	Prediction of non-response to vedolizumab therapy at week 54 by baseline serum OSM		0.56 [0.42, 0.7]		
Cao *et al*[18], 2021	Prediction of non-response to infliximab at week 54 by baseline fecal OSM		0.638		
Cao *et al*[18], 2021	Prediction of non-response to infliximab at week 28 by baseline fecal OSM	132	0.763	66.7%	92.5%
Ezirike Ladipo *et al*[21], 2021	Prediction of response to anti-TNF therapy by OSM expression in biopsies	OSM expression in pre-treatment biopsies did not predict response to anti-TNF in a pediatric population			
Mateos *et al*[22], 2021	Prediction of response to infliximab in a calprotectin log drop measurement model	OSM was found to have predicting ability to infliximab response			
Minar *et al*[23], 2019	Prediction of no remission after anti-TNFα therapy at week 12 by baseline serum OSM	144	0.71 [0.52, 0.89]	71%	78%
Minar *et al*[23], 2019	Prediction of non-response to anti-TNFα therapy at week 12 by baseline serum OSM	117	0.69 [0.5, 0.89]		
Mohamed *et al*[24], 2022	Prediction of no remission after anti-TNFα therapy by baseline serum OSM	119	0.56 [0.31, 0.82]	66.7%	54.2%
O'connell *et al*[26], 2022	Prediction of response to infliximab by colonic OSM expression	No association of pretreatment colonic OSM expression with outcomes of Infliximab therapy			
Zhou *et al*[31], 2019	Prediction of the response to PF-00547659 (anti-human mucosal addressin cell adhesion molecule-1) therapy	Baseline OSM expression/levels were unable to predict response			

AUC: Area under receiver operator curve; OSM: Oncostatin M; TNF: Tumor necrosis factor.

Minar *et al*[23] found no association between clinical remission and OSM 3 months after anti-TNF therapy but observed a significant association between OSM and clinical response one year after treatment. They suggested that duration of response evaluation may affect the outcomes. However, Cao *et al*[18] found higher AUC value (0.76) of serum OSM to predict nonresponse at week 28 in comparison with AUC value observed at week 54 of treatment (0.64). Verstockt *et al*[28] found no significant association between serum OSM and endoscopic remission after 6 months of anti-TNF therapy. On the other hand, Bertani *et al*[16,17] and Guo *et al*[20] found significant associations between serum OSM and response to anti-TNF therapy after one year of treatment.

In a transcriptomic gene expression study, Zhou *et al*[31] found that on week 12 of PF-00547659 (anti-human mucosal addressin cell adhesion molecule-1 antibody) treatment the OSM expression and serum levels decreased profoundly from baseline in patients with ulcerative colitis who achieved response, remission, or mucosal healing. Whereas the change in serum OSM levels was 1.4-fold among responders, the change in OSM expression among responders and those achieving mucosal healing was 6.1-fold and 7.4-fold respectively[31]. Verstockt *et al*[28] who found mucosal OSM to predict response to anti-TNF therapy, did not find serum OSM to do the same. In the study of Zhou *et al*[31], baseline OSM expression did not predict therapeutic outcomes. Whether this difference can be attributed to the mechanism of action of drug (PF-00547659 *vs* anti-TNF based therapies) remains to be evaluated. OSM acts synergistically with TNF to promote inflammation in stromal cells and this phenomenon may not be exhibited by the other modulators such as human mucosal addressin cell adhesion molecule-1.

Verstockt *et al*[28] performed immunohistochemical staining on resected tissues and found OSM expression in the macrophages lying in superficial lamina propria as well as in the epithelial granulomas and multinucleated giant cells. In this study, macrophagic OSM expression had a strong correlation with mucosal OSM. OSM expression is found consistently higher in inflamed parts of intestine where it promotes inflammation in gut stromal cells in response to microbial challenges[22]. O'Connell *et al*[26] who studied 21 acute severe ulcerative colitis patients observed a greater degree of immunostaining in the mucosal epithelial cells rather than stromal cells which provides impetus for studying OSM immunostaining in different IBD phenotypes. This study did not find an association between OSM expression levels and response to infliximab used as rescue therapy.

We found that OSM levels were not much different between patients with Crohn's disease and those with ulcerative colitis[19,28,29]. However, Cao *et al*[18] found fecal OSM levels to be significantly higher in patients with ulcerative colitis

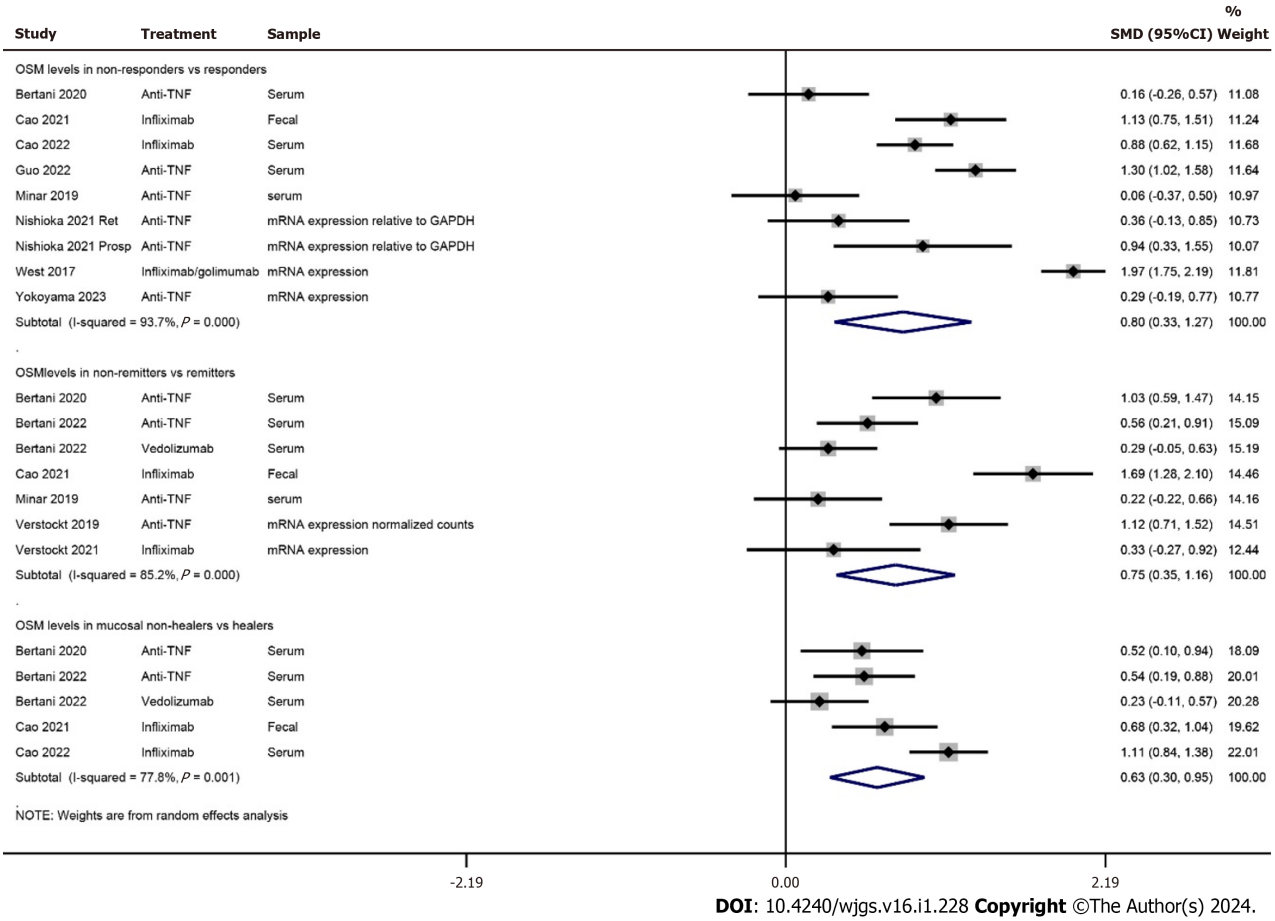
Table 2 Area under receiver operator curve values for identifying/distinguishing treatment response by OSM

Ref.	Prognostic association	OSM cutoff	AUC [95%CI]	Sensitivity [95%CI]	Specificity [95%CI]
Cao *et al*[18], 2021	Identification of mucosal healing after infliximab therapy by fecal OSM		0.702		
Cao *et al*[18], 2021	Identification of clinical remission after infliximab therapy by fecal OSM		0.674		
Cao *et al*[19], 2022	Identification of mucosal healing after infliximab therapy by serum OSM	64.1	0.84 [0.75, 0.91]	81.8%	80.8%
Cao *et al*[19], 2022	Identification of clinical response to infliximab therapy by serum OSM	83	0.90 [0.8, 0.96]	86.4%	87%
Cao *et al*[19], 2022	Identification of clinical remission after infliximab therapy by serum OSM	98.9	0.9 [0.83, 0.95]	82.1%	86.4%
Guo *et al*[20], 2022	Distinction between remitters and non-remitters after 1 year of anti-TNFα therapy in CD patients by serum OSM	169	0.88 [0.79, 0.96]	76% [58, 88]	91% [80, 96]
Guo *et al*[20], 2022	Distinction between remitters and non-remitters after 1 year of anti-TNFα therapy in UC patients by serum OSM	234	0.94 [0.87, 1]	80% [55, 93]	96% [79, 99]
Nishioka *et al* [25], 2021	Distinction between anti-TNFα resistant and sensitive patients by mucosal OSM mRNA		0.83		
Nishioka *et al* [25], 2021	Distinction between ustekinumab resistant and sensitive patients by mucosal OSM mRNA		0.77		
Verstockt *et al* [28], 2021	Distinction between remitters and non-remitters 6 months after surgery by serum OSM		0.80 [0.68, 0.92]		
Verstockt *et al* [28], 2021	Distinction between remitters and non-remitters after anti-TNFα therapy by serum OSM		0.52 [0.44, 0.61]		
Verstockt *et al* [28], 2021	Distinction between remitters and non-remitters after anti-TNFα therapy by colonic OSM		0.74 [0.54, 0.94]		
Verstockt *et al* [28], 2021	Distinction between remitters and non-remitters after vedolizumab therapy by serum OSM		0.51 [0.43, 0.59]		
Verstockt *et al* [28], 2021	Distinction between remitters and non-remitters after vedolizumab therapy by colonic OSM		0.69 [0.53, 0.84]		
West *et al*[29], 2017	Distinction between responders and non-responders to infliximab by mucosal OSM mRNA		0.99	100	91.7
Yokoyama *et al* [30], 2023	Distinction between responders and non-responders to anti-TNFα by mucosal OSM mRNA		0.94		
Yokoyama *et al* [30], 2023	Distinction between CORT-dependent vs non-dependent remission by mucosal OSM mRNA		0.79		
Zhou *et al*[31], 2019	Distinction between responders and non-responders to F-00547659 by change in OSM expression in inflamed tissue		0.88		
Zhou *et al*[31], 2019	Distinction between remitters and non-remitters to F-00547659 by change in OSM expression in inflamed tissue		0.81		
Zhou *et al*[31], 2019	Distinction between mucosal healing and no mucosal healing by F-00547659 therapy by the change in OSM expression during treatment in inflamed tissue		0.83		

AUC: Area under receiver operator curve; OSM: Oncostatin M; TNF: Tumor necrosis factor.

than in Crohn's disease. On the other hand, OSM levels were associated with disease severity as there was an increasing trend of OSM levels from mild, to moderate and severe disease[18,19,24,29]. OSM levels are also found higher in IBD patients in comparison with healthy controls[18,21,24,28]. These outcomes are similar to a study that characterized serum inflammatory protein profile and found a differential regulation of OSM between patients with ulcerative colitis and healthy controls but not between patients with Crohn's disease and ulcerative colitis[37].

Although, most of the studies included herein identified OSM as a potential biomarker of IBD severity and predictor of response to anti-TNF therapies, some studies could not find so. Ezirike Ladipo *et al*[21] who studied 98 children with IBD reported that OSM or OSM receptor expression did not predict response to anti-TNF treatment, although OSM was associated with disease severity. Mohamed *et al*[24] reported that OSM did not have an appreciable ability to predict the response to therapy. O'Connell *et al*[26] also reported that colonic OSM expression was unable to predict infliximab treatment outcomes. Verstockt *et al*[28] reported that serum OSM levels had an AUC value of 0.52 in distinguishing



DOI: 10.4240/wjgs.v16.i1.228

Figure 2 A forest graph showing the outcomes of a meta-analysis of standardized mean differences between responders and non-responders, remitters and non-remitters, and mucosal healers and non-healers of anti-tumor necrosis factor-based therapies in patients with inflammatory bowel disease. OSM: Oncostatin M; TNF: Tumor necrosis factor; SMD: Standardized mean difference.

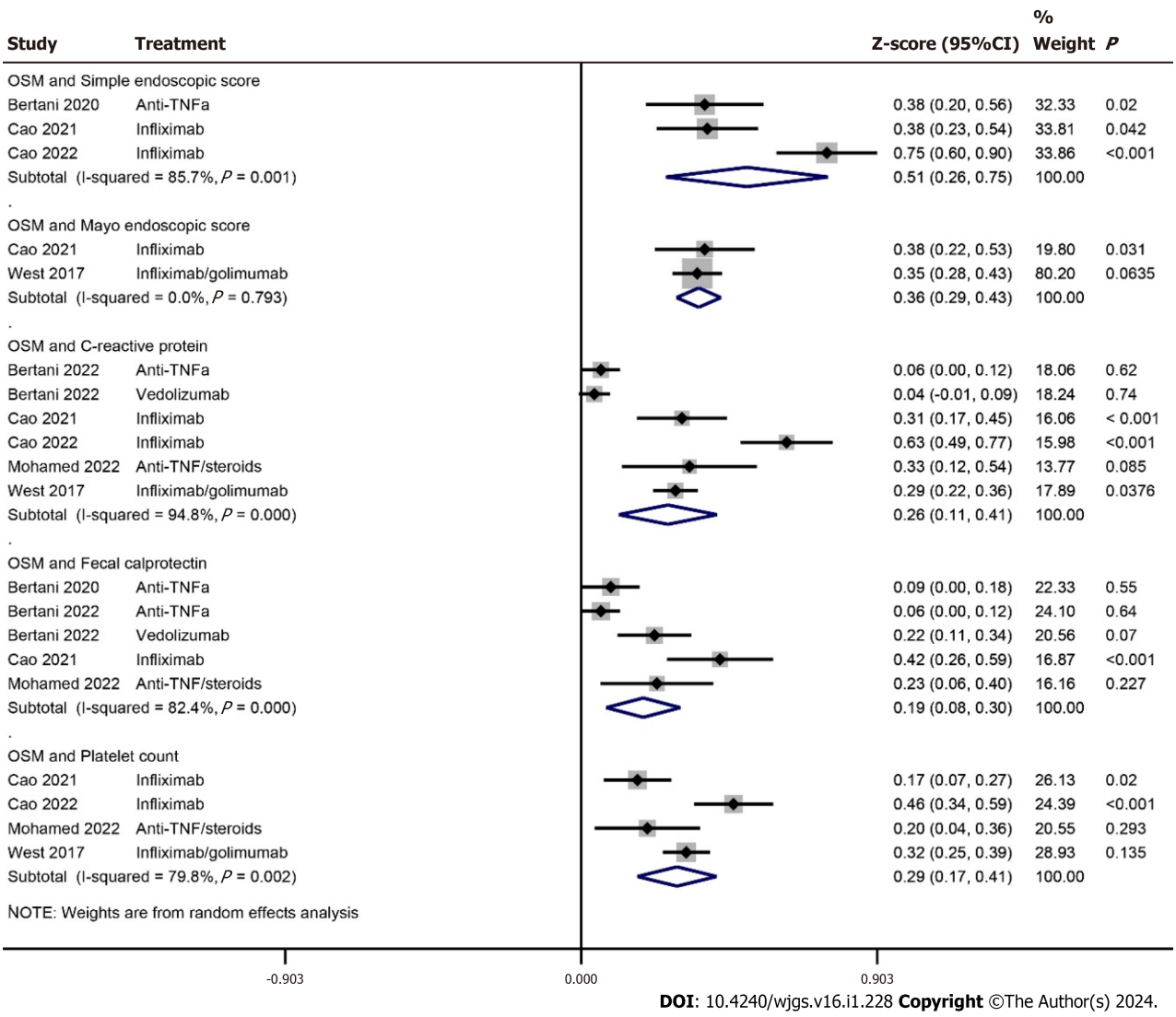
between remitters and non-remitters after anti-TNF therapy. In the study of Zhou *et al*[31], baseline OSM levels were unable to predict response to PF-00547659.

West *et al*[29] reported that among the 64 cytokines evaluated, the OSM and its receptor were most intensely overexpressed in the inflamed mucosa of IBD patients. They suggested that OSM may also be involved in developing resistance to anti-TNF therapies. According to West *et al*[29], haematopoietically derived OSM appears to mediate intestinal pathology by promoting inflammatory behavior in gut-resident stromal cells which is a novel system of leukocyte-stromal cell cross talk that may have relevance in multiple mucosal tissues. Because of its stabilizing interactions with extracellular matrix components, OSM may play a critical role in the etiology of disease. Thus, OSM may act as an inflammatory amplifier and driver of disease chronicity by promoting chemokines, cytokines, and adhesion factor production from intestinal stromal cells.

There are some limitations of this review. There were inconsistencies in the outcome data of individual studies in measuring OSM levels/expression and their numerical presentations due to which not all data could be meta-analyzed. Moreover, in some studies, numerical outcome data were not accompanied by the variance. To account for such constraints, we either performed a meta-analysis of SMDs or tabulated the outcomes systematically. This constraint also precluded us from having a generalized estimate of OSM levels/concentrations. Moreover, for data where meta-analyses were possible, we observed higher statistical heterogeneity. Methodological differences of individual studies could have also played a role in the variabilities observed in this review.

CONCLUSION

Most of the studies attempting to seek relationship between OSM and disease or treatment outcomes have found that higher OSM expression/levels to be associated with worse disease outcomes which shows that OSM can be used as a s surrogate marker of poor prognosis in IBD patients treated with anti-TNF treatments. This makes OSM an attractive biomarker for patient selection and clinical decision-making. However, some studies could not recognize such associations and others found non-significant correlations between OSM and other indicators such as fecal calprotectin, C-reactive protein, and platelets. Therefore, more studies are required to validate present day evidence and to explore the behavior of OSM for IBD treatments other than anti-TNF drugs.



DOI: 10.4240/wjgs.v16.i1.228

Figure 3 A forest graph showing the outcomes of a meta-analysis of correlation coefficients between baseline Oncostatin M and other baseline inflammatory biomarkers/disease indicators. OSM: Oncostatin M; TNF: Tumor necrosis factor.

ARTICLE HIGHLIGHTS

Research background

Oncostatin M (OSM) is a pleiotropic factor that participates in several physiological processes such as hematopoiesis, differentiation, regeneration, and inflammation, and pathological processes such as arthritis, ossification, dermatitis, fibrosis, gingivitis, and carcinogenesis.

Research motivation

Higher OSM levels in patients with inflammatory bowel disease (IBD) provided impetus for reviewing the outcomes of studies that evaluated the prognostic role of OSM in IBD patients.

Research objectives

The objective of this research was to systematically review relevant studies and perform meta-analyses of statistical indices for seeking current evidence about the role of OSM in IBD prognosis.

Research methods

After a literature search in electronic databases, studies were identified for synthesis. Meta-analyses were performed to estimate standardized mean differences in OSM levels between responders and non-responders, and to pool correlations of OSM with other inflammatory biomarkers.

Research results

OSM levels were associated with disease severity and were significantly higher in non-responders, in non-remitters, and

in patients with no mucosal healing after anti-tumor necrosis factor (anti-TNF) therapy. Area under receiver operator curve values showed considerable variability between studies but in general higher OSM levels were associated with poor prognosis. OSM had significant correlations with Simple Endoscopic Score of Crohn's disease, Mayo Endoscopic Score, fecal calprotectin, C-reactive protein, and platelet count.

Research conclusions

OSM can potentially determine IBD severity and can predict the outcomes of anti-tumor necrosis factor-based therapies.

Research perspectives

Future studies may refine the outcomes reported herein. It could also be interesting to explore the role of OSM in achieving response to non-anti-TNF therapies.

FOOTNOTES

Co-first authors: Yue Yang and Kan-Zuo Fu.

Author contributions: Yang Y and Fu KZ wrote the manuscript; Yang Y, Fu KZ, and Pan G collected and analyzed the data; all authors read and approved the final manuscript.

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

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: China

ORCID number: Gu Pan 0009-0009-9248-5714.

S-Editor: Gong ZM
L-Editor: A
P-Editor: Xu ZH

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World J Gastrointest Surg 2024 January 27; 16(1): 239-247

DOI: 10.4240/wjgs.v16.i1.239

ISSN 1948-9366 (online)

CASE REPORT

Endoscopic treatment of extreme esophageal stenosis complicated with esophagotracheal fistula: A case report

Jia-Heng Fang, Wei-Min Li, Cheng-Hai He, Jian-Liang Wu, Yun Guo, Zhi-Chao Lai, Guo-Dong Li

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: Martino A, Italy; Sintusek P, Thailand

Received: October 15, 2023
Peer-review started: October 15, 2023
First decision: November 16, 2023
Revised: November 25, 2023
Accepted: December 12, 2023
Article in press: December 12, 2023
Published online: January 27, 2024

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Abstract

BACKGROUND

At present, there is no unified and effective treatment for extreme corrosive esophageal stenosis (CES) with esophagotracheal fistula (ETF). This case had extreme and severe esophageal stenosis (ES) and ETF after ingesting an enzyme-based chemical detergent, resulting in a serious pulmonary infection and severe malnutrition. Upper gastrointestinal imaging showed that he had an ETF, and endoscopy showed that he had extreme and severe esophageal stricture. This case was complex and difficult to treat. According to the domestic and foreign literature, there is no universal treatment that is low-risk.

CASE SUMMARY

A patient came to our hospital with extreme ES, an ETF, and severe malnutrition complicated with pulmonary tuberculosis 1 mo after the consumption of an enzyme-based detergent. The ES was serious, and the endoscope was unable to pass through the esophagus. We treated him by endoscopic incision method (EIM), esophageal stent placement (ESP), and endoscopic balloon dilation (EBD) by using the bronchoscope and gastroscope. This treatment not only closed the ETF, but also expanded the esophagus, with minimal trauma, greatly reducing the pain of the patient. According to the literature, there are no similar reported cases.

CONCLUSION

We report, for the first time, a patient with extreme CES complicated with ETF, where the endoscope could not be passed through his esophagus but he could be examined by bronchoscopy and treated by EIM, ESP, and EBD.

Key Words: Extreme corrosive esophageal stenosis; Esophagotracheal fistula; Endoscopic incision method; Esophageal stent placement; Endoscopic balloon dilation; Case report

Core Tip: Patients who have extreme corrosive esophageal stenosis (CES) with esophagotracheal fistula (ETF) often suffer a lot and have bad quality of their lives. Currently, there are no clinical evidence-based guidelines, and there is great uncertainty regarding the best treatment approach. We report, for the first time, a patient with extreme CES complicated with ETF, where the endoscope could not be passed through his esophagus but he could be examined by bronchoscopy and treated by endoscopic incision method, esophageal stent placement, and endoscopic balloon dilation.

Citation: Fang JH, Li WM, He CH, Wu JL, Guo Y, Lai ZC, Li GD. Endoscopic treatment of extreme esophageal stenosis complicated with esophagotracheal fistula: A case report. *World J Gastrointest Surg* 2024; 16(1): 239-247
URL: https://www.wjgnet.com/1948-9366/full/v16/i1/239.htm
DOI: https://dx.doi.org/10.4240/wjgs.v16.i1.239

INTRODUCTION

Corrosive esophageal stenosis (CES) is rare but destructive, placing a significant burden on contemporary health systems around the world[1]. Patients who have extreme CES with esophagotracheal fistula (ETF) often suffer from typical chest pain, severe pulmonary infection-related symptoms, malnutrition, *etc.*, which seriously affect the quality of their lives[2]. Because of the rarity of this adverse event, clinicians usually have limited personal experience with it. Currently, there are no clinical evidence-based guidelines, and there is great uncertainty regarding the best treatment approach.

For the treatment of extreme CES with ETF, there is no relevant guidelines or a relatively unified treatment plan in clinical practice. At present, the main clinical treatments for esophageal stenosis (ES) are the endoscopic incision method (EIM), endoscopic balloon dilation (EBD), gastroscope-assisted bougienage, esophageal stent placement (ESP), and local injection of glucocorticoids[3].

Recently, a patient came to our hospital with extreme ES, an ETF, and severe malnutrition complicated with pulmonary tuberculosis 1 mo after the consumption of an enzyme-based detergent. The ES was serious, and the endoscope was unable to pass through the esophagus. We treated him by EIM, ESP, and EBD using the bronchoscope and gastroscope. This treatment not only closed the ETF, but also expanded the esophagus. All treatment events are displayed on the timeline in Figure 1. It solved the problem with minimal trauma and greatly reduced the pain of the patient. According to the literature, there are no similar reported cases.

CASE PRESENTATION

Chief complaints

A 21-year-old man came to the Department of Gastroenterology of our hospital for "having upper gastrointestinal pain with dysphagia after mistakenly consuming an enzyme-based detergent 6 mo ago". The patient developed burning sensation and pain in the the oral, throat, and chest behind the sternum and under the xiphoid process after taking an enzyme-based detergent by mistake on May 5, 2020. The pain score was 8 (total score: 10). Contrast enhanced chest computed tomography (CT) showed infectious lesions in both lungs. Anti-infection treatment was given and the patient was discharged after improvement. On May 25, 2020, the patient had difficulty in swallowing and vomited after eating fluid food. Upper gastrointestinal imaging (UGI) showed that he had CES and pharyngeal fistula (Figure 2), but the patient decided to return to the local hospital for treatment. Gastroscopy was performed in the First Hospital of Lanzhou University on June 1, 2020, which showed that the esophagus was narrow 19 cm away from the incisors, and the endoscope could not pass through. Esophageal scar hyperplasia was noticeable, and it was brittle and prone to bleeding. A gastric tube was placed for enteral nutrition. At 6 mo, the patient's weight had decreased by 15 kg. Finally, the patient came to our hospital for further treatment (November 23, 2021). On admission, continuous enteral nutrition was given since the patient complained of dysphagia and vomiting immediately after eating. He had persistent pain behind the sternum and under the xiphoid process. The pain score was 4 (total score: 10). The patient had shortness of breath, accompanied by cough and expectoration. The sputum was yellow and purulent, which was semisolid and difficult to expectorate.

History of present illness

The patient mistakenly consumed an enzyme-based detergent 6 mo ago.

History of past illness

The patient was healthy in the past.

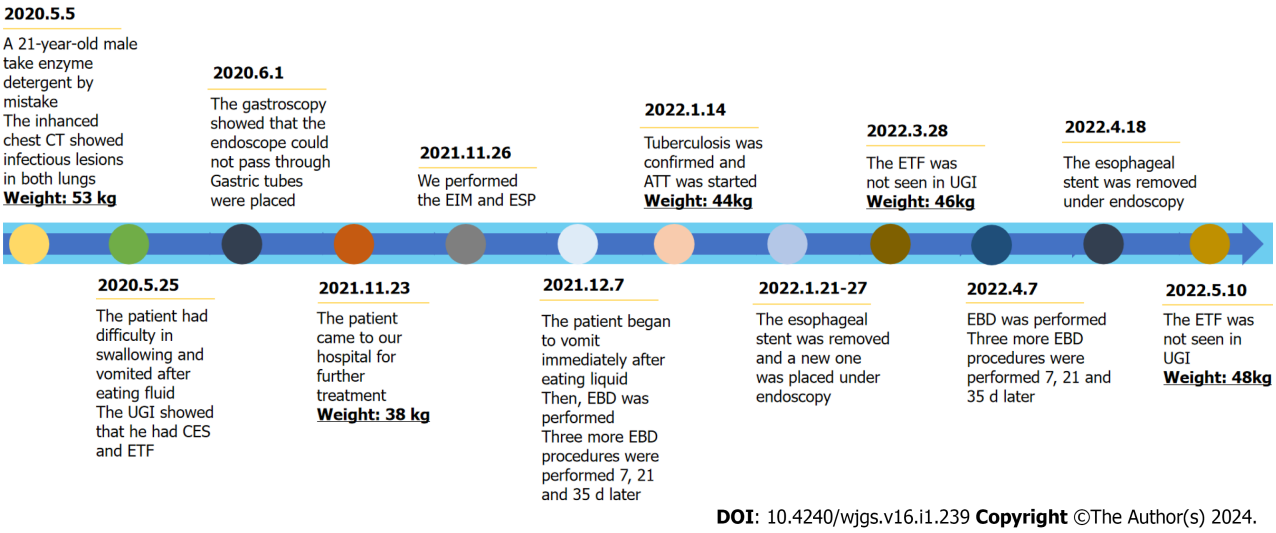
Personal and family history

There was no remarkable personal and family history.

Table 1 The patient's laboratory test results and weight

Laboratory test	Routine blood test			Biochemical test			Tuberculosis related test				Weight (kg)
	Hemoglobin (g/L)	Leucocytes (10^9/L)	High-sensitivity C-reactive protein (mg/L)	Albumin (g/L)	Preal-bumin (g/L)	Apolipo-protein (g/L)	PPD test	Serum tuberculosis antibody	T-spot test	Detection of *Myco-bacterium* DNA	
May 5, 2021	148	15.88	10.52	44.10	0.179	0.59	-	-	-	-	53.0
November 23, 2021	106	7.71	80.81	26.30	0.051	0.63	-	Negative	Negative	-	38.0
November 26, 2021	91	6.60	26.30	33.60	0.149	0.76	-	Negative	Negative	**Positive**	38.5
Janurary21, 2022	112	6.87	9.0	32.40	0.091	0.51	-	Negative	Negative	**Positive**	44.0
May 10, 2022	140	5.29	8.12	39.60	0.218	0.94	-	-	Negative	Negative	47.8

PPD: Purified protein derivative.



DOI: 10.4240/wjgs.v16.i1.239

Figure 1 Treatment timeline. ATT: Antituberculosis therapy; CT: Computed tomography; CES: Corrosive esophageal stenosis; EBD: Endoscopic balloon dilation; EIM: Endoscopic incision method; ESP: Esophageal stent placement; ETF: Esophagotracheal fistula; UGI: Upper gastrointestinal imaging.

Physical examination

The Kubota water swallow test suggested that the patient had grade 5 swallowing function. The trachea was in midline, the breathing sounds in both lungs were not clear, and moist rales could be heard in the left lung. Bowel sounds at a frequency of 3-5 times/min could be heard.

Laboratory examinations

The results are all shown in Table 1.

Imaging examinations

The UGI and endoscopy results are shown in the figures.

FINAL DIAGNOSIS

Extreme ES complicated with an ETF.

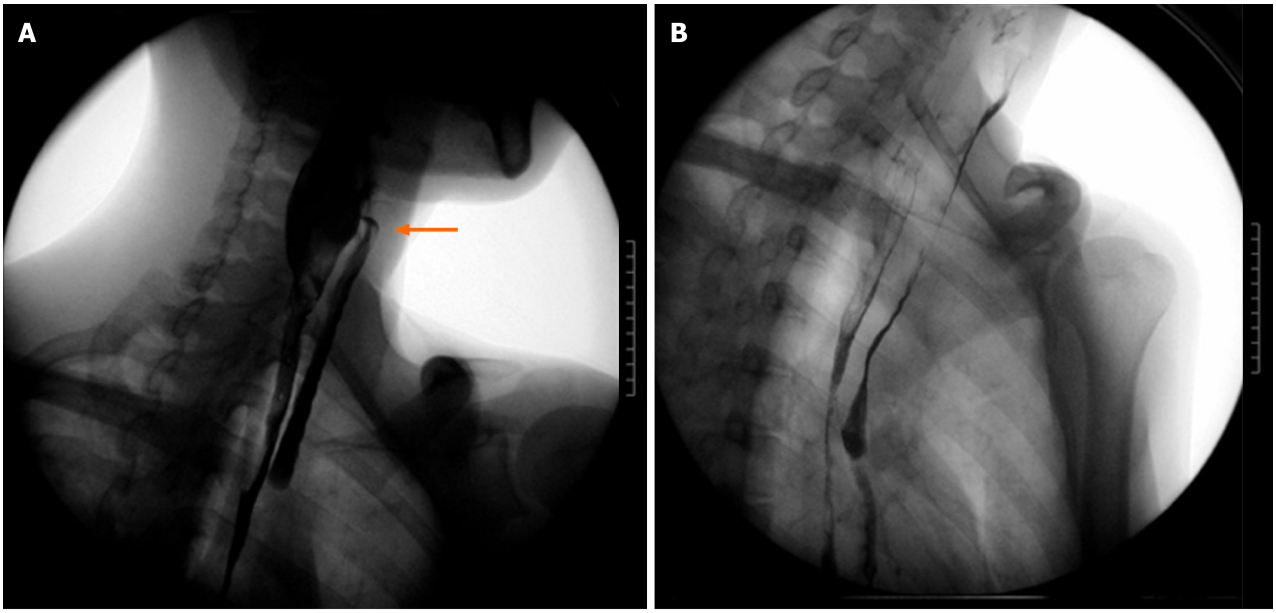


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Figure 2 Upper gastrointestinal imaging showed corrosive esophageal stenosis and pharyngeal fistula. A: Upper gastrointestinal imaging (UGI) indicated that the patient had a pharyngeal fistula (yellow arrow); B: UGI indicated that the patient had total esophageal stenosis.

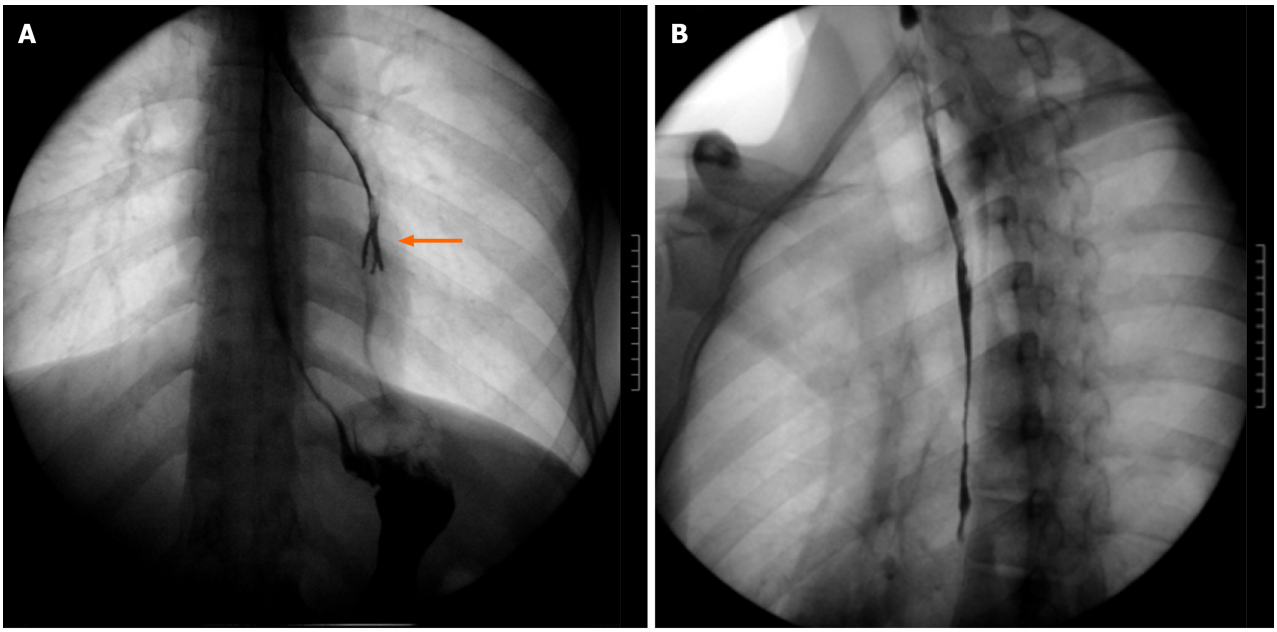

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Figure 3 Upper gastrointestinal imaging at admission. A: Upper gastrointestinal imaging (UGI) indicated that the patient had an esophagotracheal fistula (yellow arrow); B: UGI indicated that the patient had total esophageal stenosis.

TREATMENT

The patient was treated with nutritional support therapy and anti-infection therapy. The test results are shown in Table 1. Contrast-enhanced chest CT showed that the patient had ES. Hypopharyngeal and esophageal injury and partial gas accumulation can be seen. There were pneumonic lesions in both lungs. UGI (Figure 3) showed that the pharyngeal fistula disappeared, the esophageal mucosa was rough and disordered, the esophageal wall was irregular, an ETF appeared, and the fistula was located at the level of the 4th thoracic vertebra. After determining the location of the ETF, relevant surgical contraindications were excluded. On November 26, 2021, bronchoscopy (Olympus BF-260) instead of gastroscopy was used to evaluate the esophagus, which showed that the whole esophagus was narrow and twisted, and three fistulas were found in the upper part of the esophagus (Figure 4A and B). The obvious stenosis part was located 19 cm and 38 cm away from the incisors. The patient's following conditions posed great challenges to the treatment: (1) The patient had total ES combined with ETF. Gastroscope could not be use to assess the condition and treat him; and (2) The

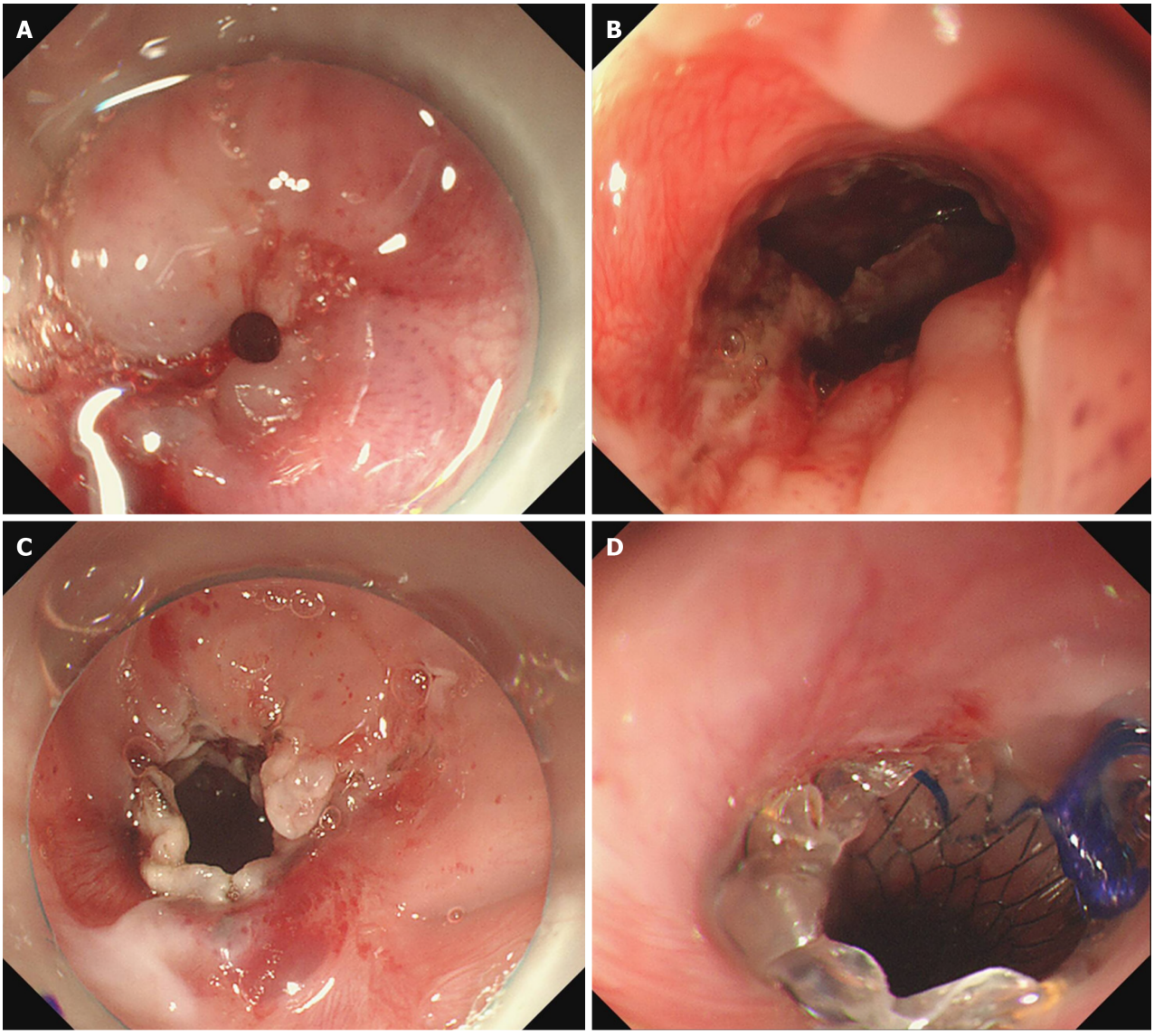

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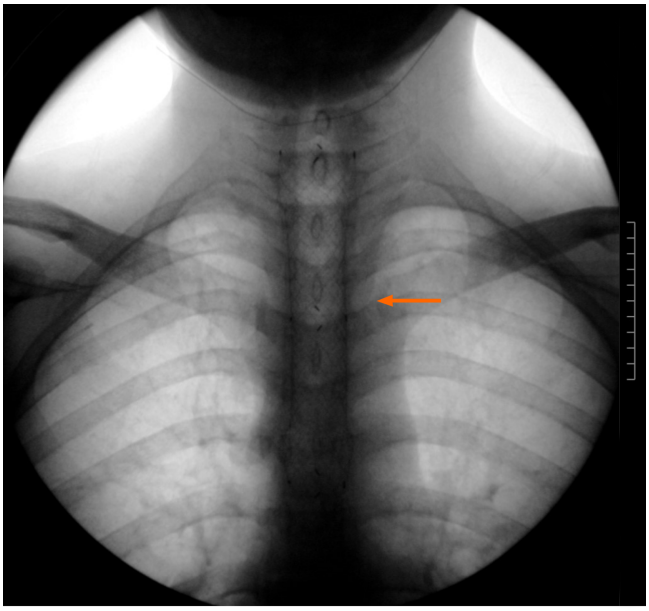
Figure 4 The endoscopic incision method and esophageal stent placement performed at admission. A: The esophageal stenosis part which made the endoscope unable to enter; B: There were fistulas in the patient's esophagus; C: The esophageal lumen increased significantly after treatment by the endoscopic incision method; D: The upper end of the stent after placement.

length of ES in the patient is much longer than that of the existing stent.

We performed EIM with a gastroscope (Olympus GIF-H290Z) at 19 cm (Figure 4C). The bronchoscope was used again to enter the gastric cavity and to insert the guidewire (AG-5043-3545, Hangzhou Honghai Medical Devices Co., Ltd.). After the bronchoscope was withdrawn, the gastroscope was placed to send the esophageal stent pusher (NES-20-120-070, Hangzhou Qianshenghui Science and Technology Ltd.) along the guidewire. Then, we released the covered stent under direct vision of the endoscope. It was found that the release position was good, the upper end was located 17 cm away from the incisors (Figure 4D), the inside of the stent was clear, and there was no obvious bleeding. On the second day after the operation, the patient had minor pharyngeal pain, with no obvious retrosternal pain and no pain under the xiphoid process. He drank fluids and had no discomfort after eating. Esophageal radiography (Figure 5) showed that the esophageal dilation was good, no contrast medium overflow was found, and the cardia opened and contracted regularly and freely. On December 7, 2021, the patient began to vomit immediately after eating liquid food. The vomitus was food. The rating grade of the Kubota water swallow test was 5. Then, EBD was performed with an endoscope (No.: ES128549). The stent was still in place. A narrow esophageal lumen could be seen 38 cm away from the incisors, and the endoscope could not pass through. A guidewire was placed through the narrow part, and a columnar dilatation balloon of the duodenal papilla (BDC-12/55-7/18, Hangzhou Weichuang Medical (Group) Co., Ltd.) was placed along the guidewire. After dilation, the mucosa was torn, and the gastroscope could enter the gastric cavity through the narrow segment. Three more EBD procedures were performed 7, 21, and 35 d later (BDC-12/55-7/18, BDC-15/55-7/18, and BDC-15/55-7/18, Hangzhou Weichuang Medical (Group) Co., Ltd.). The patient could drink fluids or semi-fluids during this period.

During hospitalization, the patient still suffered from cough and expectoration and maintained a low fever every day. Although the laboratory examination results did not support the diagnosis of pulmonary tuberculosis, we used



DOI: 10.4240/wjgs.v16.i1.239

Figure 5 After esophageal stent placement, the stent was in place and esophageal dilation was good.

bronchoscopy to collect bronchial lavage fluid to perform *Mycobacterium tuberculosis* culture. Tuberculosis was confirmed (Table 1) and four-drug antituberculosis therapy (ATT) was started. Finally, the patient's persistent pain behind the sternum and under the xiphoid process, pharyngeal pain, and other discomfort disappeared, the nutritional index increased continuously, and his weight increased by 7 kg. The patient could tolerate the exercise of normal activities, and the quality of his life was greatly improved.

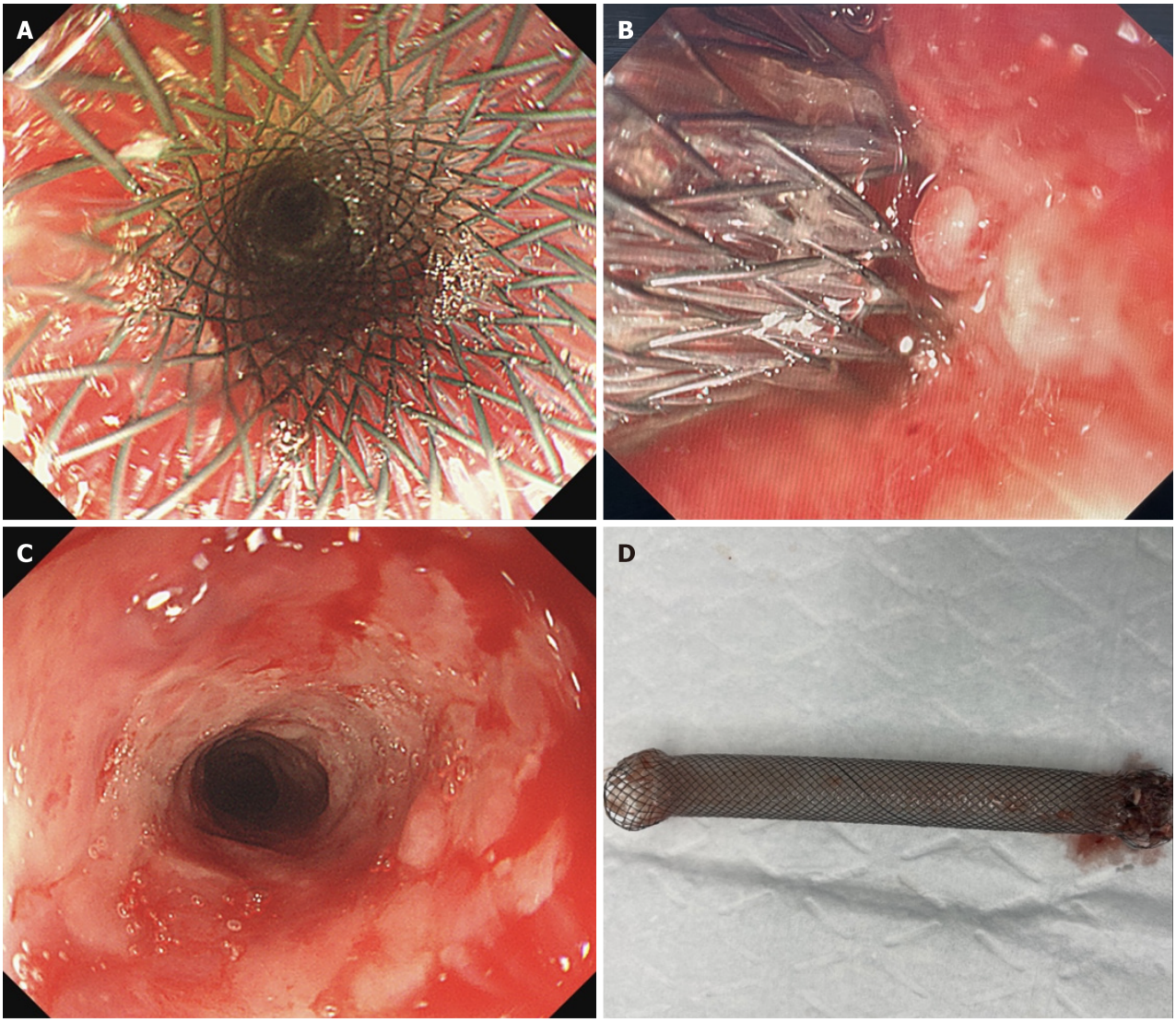
OUTCOME AND FOLLOW-UP

To avoid the implantation of the stent into the esophageal mucosa, we decided to remove the esophageal stent and place a new one. We removed the stent on January 1, 2022. Seven days later, a new stent was placed. The two operations went well, upper esophageal mucosal erosion was found, the esophageal cavity dilated well, and the fistulas disappeared. ES could be seen 36 cm away from the incisors. The patient kept having semi-fluids. Sustained nutritional support and ATT were given. Since UGI showed that the fistula had been blocked, we removed the stent on April 18, 2022 (Figure 6) and four times of EBD was performed since April 7, 2022 to dilate the esophagus. A month later, UGI showed that the fistula was still blocked (Figure 7), but the esophagus was still partially narrow. The patient could have semi-fluids at that time. ETF may recur, and the patient may have to accept EIM, ESP, and EBD in the future.

DISCUSSION

Since the physiological structure of the esophagus is thin and tubular, it is prone to stenosis when subjected to major injuries, such as corrosion and surgery. The incidence of esophageal stenosis is approximately 1.1/100000 cases per year [4]. Chronic ETF is extremely rare and occurs in approximately 3% of patients with chemically CES[1]. The treatment mainly includes the repair of airway defects and esophageal reconstruction, which usually uses staged operation[5,6]. The first stage, as most clinicians think, is endoscopic esophageal dilatation (including EBD and bougienage)[7]. This case is very special for the following reasons: First, the patient was very young. If we chose surgical resection of the whole esophagus, the quality of life would be greatly reduced in the coming decades. Second, endoscopy suggested that the patient's esophagus was entirely narrow with multiple fistulas. The guidewire was very likely to be displaced during the EBD. Even if the dilation were successful, the large balloon pressure could easily tear the fistula mucosa and cause further damage. Considering comprehensively, we immediately performed EIM, which made it possible to expand the esophageal cavity and provide further ESP. As a new technology, EIM shows amazing feasibility and effectiveness.

There is no unified clinical treatment for complex CES. EIM is a new technology developed in recent years that was first used to treat recurrent Schatzki rings. Since 2012, it has gradually replaced EBD to be used to treat complex esophageal anastomotic stenosis[8]. Wu *et al*[9] have shown that EIM for complex ES is safe and can significantly alleviate the clinical symptoms of dysphagia in a short time, but its long-term effect is still uncertain. Li *et al*[10] and Hordijk *et al*[11] believed that EIM benefits patients who have severe and complex benign ES and have fewer side effects. In this case, the total esophageal tube was narrow, there were multiple fistulas in the esophagus, and it was difficult to reach the gastric cavity with the guidewire. We performed EIM for upper ES, which expanded the esophageal cavity and created the



DOI: 10.4240/wjgs.v16.i1.239

Figure 6 The stent was removed finally. A: The stent was in place; B: The stent was being removed; C: After the stent was removed, the esophageal cavity expanded significantly; D: The removed stent.

possibility of subsequent treatments.

As one of the treatments for ES, ESP has many adverse events, such as chest pain, stent displacement or shedding, and tissue embedding. Fuccio *et al*[12] performed a meta-analysis indicating that approximately 28.6% of patients had esophageal stent displacement and 20.6% had adverse events. Therefore, ESP is not recommended as the best treatment for benign ES[3]. For cases of malignant ES complicated with ETF, ESP is the recommended scheme[3]. For the treatment of benign ES combined with ETF, there has been no recommended treatment. The patient faced the following two problems on admission: (1) The patient's esophagus was completely narrow, and the endoscope was unable to pass through; and (2) The patient had stenosis complicated with an ETF. Therefore, we believed that the most appropriate treatment was EIM and ESP. On the one hand, the covered stent can block the ETF and promote self-healing; on the other hand, the covered stent can dilate the narrow esophagus and alleviate the symptoms of dysphagia. There were no adverse events, such as stent displacement or stent insertion. The esophagus was unobstructed after placement, and the fistula was closed after stent removal. It was proven to be a reasonable treatment for benign ES complicated with ETF.

Patients with extreme CES often have to accept EBD dozens of times. They go through a great deal, and the esophagus is easy to tear after operation. The medical cost is also high. The expansion success rate for corrosive stenosis is approximately 50%, which is significantly lower than that for other benign stenoses (75%-80%)[7]. For the stenosis part located below the esophageal stent in this case, considering the tear caused by ordinary balloon dilatation, we used the duodenal papilla columnar expansion balloon to expand the esophagus by dividing segments. We performed this three additional times at 7, 21, and 35 d after the initial EBD. The inner diameter of the balloon increased in turn during each expansion. The patient maintained a liquid and semiliquid diet during this period, without obvious tearing, perforation, bleeding, or other adverse events. For the treatment of lower ES, there are two choices: ESP or ESP after EBD. More clinical studies are needed to prove which one has better safety, efficacy, and economic benefits.

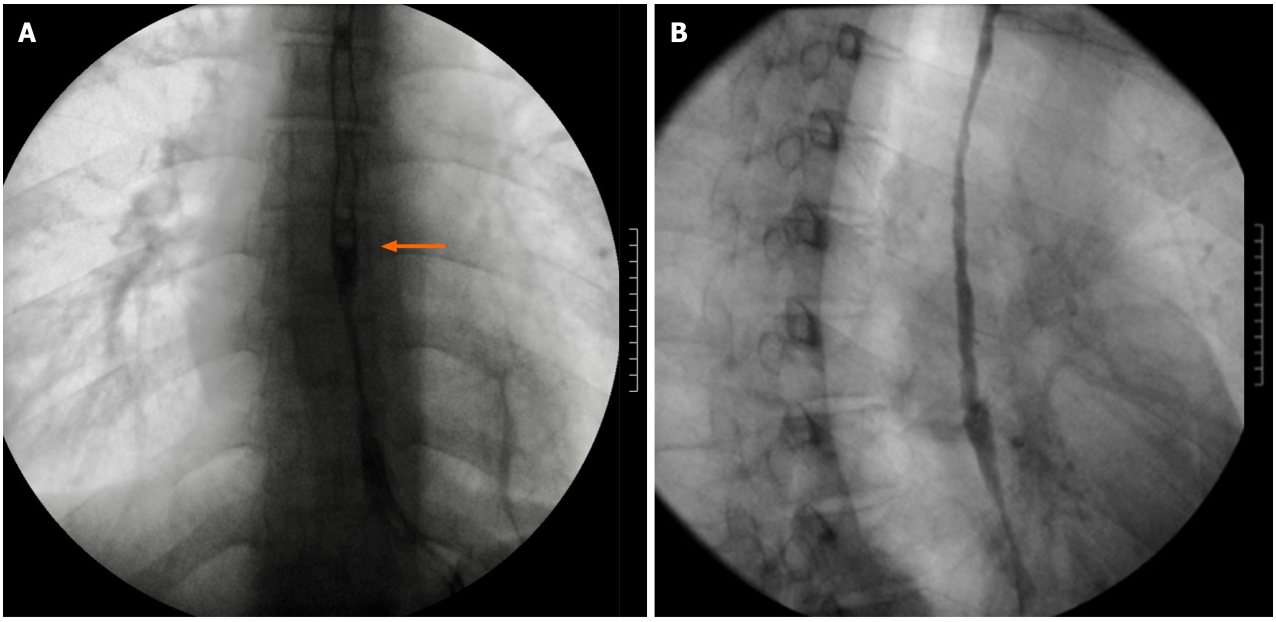


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Figure 7 The fistula was blocked, but the esophagus was partially narrow. A: There was no esophagotracheal fistula; B: The esophagus was partially narrow.

For the treatment of benign ES, Xie *et al*[13] believed that oral administration of glucocorticoids in patients with diabetes, hypertension, infection, tuberculosis, and other patients will lead to aggravation, so it is not recommended. The effect of glucocorticoid injection is ideal, but no drug injection has been proven to be effective for the treatment of chemically CES, and corticosteroids also have no benefits[14]. Enzyme-based chemical detergent could corrode the patient's esophagus, and long-standing tuberculosis infection for more than 2 mo also could lead to an acquired ETF. We believe that ATT is also crucial for the healing of ETF and subsequent recovery, so we used ATT immediately as soon as tuberculosis was confirmed. Khan *et al*[15] cured a patient who had tuberculous fistulas successfully with ATT, which supports our view.

CONCLUSION

Chemical corrosive esophageal injury should be examined by gastroscopy combined with UGI, nasal endoscopy, and even bronchoscopy when necessary. For treatment, EIM, EBD, and ESP should be chosen according to every patient's specific situation. Due to entire CES combined with ETF having a wide range of stenosis, the treatment is extremely difficult. Clinical treatment should be taken under individualized assessment, and combined treatment should be given when necessary. In this case, we used a bronchoscope with a thinner diameter to evaluate and treat ES repeatedly instead of a gastroscope, which was rarely used in clinical practice and achieved a perfect effect. Whether the ETF and ES will recur in this patient remains to be observed.

FOOTNOTES

Author contributions: Li GD performed all surgical treatments; Fang JH prepared the initial draft of the manuscript and revised the manuscript; Li GD and Wu JL critically reviewed and revised the manuscript and provided input on the endoscopic operation aspects of the manuscript; Guo Y, Lai ZC, Li WM, and He CH contributed equally toward the senior authorship of this manuscript; all authors contributed to the article and approved the submitted version.

Informed consent statement: The study was reviewed and approved by Hangzhou Normal University Affiliated Hospital's ethics committee. The patient provided written informed consent for the publication of this case report.

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

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country/Territory of origin: China

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S-Editor: Lin C
L-Editor: Wang TQ
P-Editor: Xu ZH

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World Journal of Gastrointestinal Surgery

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World J Gastrointest Surg 2024 January 27; 16(1): 248-256

DOI: 10.4240/wjgs.v16.i1.248

ISSN 1948-9366 (online)

CASE REPORT

Intestinal tuberculosis with small bowel stricture and hemorrhage as the predominant manifestation: Three case reports

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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): 0
Grade E (Poor): 0

P-Reviewer: Alzerwi NAN, Saudi Arabia

Received: November 20, 2023
Peer-review started: November 20, 2023
First decision: December 11, 2023
Revised: December 24, 2023
Accepted: January 4, 2024
Article in press: January 4, 2024
Published online: January 27, 2024

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Abstract

BACKGROUND

Intestinal tuberculosis is a chronic disease caused by *Mycobacterium tuberculosis* that mainly affects the ileum and cecum. Small bowel tuberculosis, characterized by predominant involvement of the small intestine, is an extremely rare condition with highly atypical clinical presentations, making diagnosis even more challenging.

CASE SUMMARY

We report three cases of small intestinal tuberculosis, two of the patients presented primarily with abdominal pain, and one presented with gastrointestinal bleeding. All patients underwent blood tests and imaging examinations. Small bowel endoscopy (SBE) revealed that the main lesions in these patients were intestinal stenosis or gastrointestinal bleeding caused by small intestinal ulcers. One patient ultimately underwent surgical treatment. Following a complex diagnostic process and comprehensive analysis, all patients were confirmed to have small intestinal tuberculosis and received standard antituberculosis treatment, leading to an improvement in their condition.

CONCLUSION

Patients with SBTs present with nonspecific symptoms such as abdominal pain, weight loss, and occasional gastrointestinal bleeding. Accurate diagnosis requires a thorough evaluation of clinical symptoms and various tests to avoid misdiagnosis and complications.

Key Words: Intestinal tuberculosis; Gastrointestinal hemorrhage; Small bowel endoscopy; Case report

Core Tip: Intestinal tuberculosis is a chronic disease caused by *Mycobacterium tuberculosis* and primarily affects the ileum and cecum. Small bowel tuberculosis (SBT) is rare. We report three cases in which patients with SBTs presented with intestinal stenosis or bleeding. Following a complex diagnostic process involving procedures such as small bowel endoscopy and even surgical intervention, all patients were definitively diagnosed and received standard antituberculosis treatment. SBT manifests primarily with nonspecific symptoms such as abdominal pain, weight loss, and occasional gastrointestinal bleeding. A comprehensive evaluation of clinical symptoms and various examinations including laboratory tests, endoscopy, and pathology, are essential for obtaining an accurate diagnosis.

Citation: Huang G, Wu KK, Li XN, Kuai JH, Zhang AJ. Intestinal tuberculosis with small bowel stricture and hemorrhage as the predominant manifestation: Three case reports. *World J Gastrointest Surg* 2024; 16(1): 248-256
URL: https://www.wjgnet.com/1948-9366/full/v16/i1/248.htm
DOI: https://dx.doi.org/10.4240/wjgs.v16.i1.248

INTRODUCTION

Tuberculosis (TB) is a chronic granulomatous inflammatory disease with diverse clinical presentations and can affect various systems of the body, such as the lungs, bones, lymphatic system, and intestines[1]. The disease is caused by *Mycobacterium tuberculosis*, a gram-positive bacterium with high treatment resistance. Although existing drugs can effectively control this disease, tuberculosis still has high contagiousness and fatality rates globally[1-5]. Intestinal tuberculosis accounts for 1%-3% of all tuberculosis cases, and the intestine is not a commonly affected site of tuberculosis [6]. As a result, this issue has long been overlooked. The terminal ileum and cecum are common areas of involvement due to their rich lymphatic tissue, stagnant intestinal contents, and limited digestive activity[7]. However, intestinal tuberculosis predominantly affecting the small intestine is very rare.

This case series aims to help clinicians understand the rare situation of intestinal tuberculosis with primary clinical manifestations of small intestinal bleeding or stenosis.

CASE PRESENTATION

Chief complaints

Case 1: A 49-year-old male patient presented with persistent complaint of melena for the previous 20 d.

Case 2: A 23-year-old female patient presented with recurrent abdominal pain over a span of 5 months.

Case 3: A 63-year-old female patient presented with recurrent abdominal pain that persisted for 2 years.

History of present illness

Case 1: The patient reported three episodes of melena over the last 20 d, amounting to approximately 300 mL. No obvious precipitating factors were identified, with the patient denying significant abdominal pain or bloating, as well as symptoms of dizziness or palpitations. Upon the patient's presentation to a local hospital, the patient's hemoglobin level was measured at 134 g/L, while computed tomography (CT) scans revealed slight thickening of the colonic wall in the ascending colon. However, both colonoscopy and gastroscopy examinations conducted at that time failed to identify any sites of bleeding.

Case 2: The patient suffered from intermittent abdominal pain of unclear origin, primarily around the umbilicus, over the previous 5 months. The associated symptoms included decreased appetite, weight loss, and fatigue, but no fever. The patient had an average of two well-formed bowel movements per day, without mucus or bloody discharge on the stool surface. One month prior, the patient sought medical attention at a local hospital. Laboratory tests indicated a hemoglobin level of 84 g/L. The chest CT scans were normal, and colonoscopy demonstrated segmental ulcers at the terminal ileum and sigmoid colon, suggestive of Crohn's disease based on pathological findings. The patient received oral glutamine, probiotics, and sulfasalazine for treatment. However, one week prior to the patient's current presentation, her abdominal pain significantly worsened, and her bowel movements increased to 5 times per day.

Case 3: Two years prior, this patient initially presented with recurrent paroxysmal epigastric pain without any clear etiology. These episodes occurred once every 1-2 months and lasted for 4-6 d each. A previous gastrointestinal endoscopy conducted at an external hospital failed to yield any definitive findings. The patient experienced multiple episodes of abdominal pain and sought medical attention at multiple sites. Positron emission (PET)/CT performed three months previously revealed thickening of the intestinal wall in the segment of the small intestine, accompanied by increased fluorodeoxyglucose metabolism. Additionally, multiple hypermetabolic lymph nodes were observed in the perilesional area, left pulmonary hilum, and mediastinum. Subsequently, a mediastinal lymph node biopsy was performed, and the pathological examination suggested a high possibility of tuberculosis infection.

History of past illness

Case 1: The patient had pulmonary tuberculosis during childhood, which was successfully treated. At the age of 24, the patient developed cervical lymph node tuberculosis and underwent surgical removal of the infected lymph nodes.

Case 2: The patient did not report any significant medical conditions.

Case 3: The patient did not report notable illnesses or conditions.

Personal and family history

The personal and family histories of these patients were unremarkable.

Physical examination

Case 1: The patient had a body mass index (BMI) of 19.42 kg/m^2 and displayed pallor of the skin and conjunctiva, with no apparent positive chest or abdominal signs.

Case 2: The patient had a BMI of 18.22 kg/m^2 and had pale conjunctiva and nail beds. Physical examination of the chest and abdomen revealed no specific positive signs.

Case 3: The patient had a BMI of 19.53 kg/m^2 and no apparent positive chest or abdominal signs.

Laboratory examinations

Case 1: Routine blood analysis revealed a hemoglobin level of 106 g/L, with positive fecal occult blood test results. The blood biochemistry and tumor marker levels were found to be within the normal range.

Case 2: The patient's complete blood count showed a hemoglobin level of 101 g/L. Blood biochemistry tests revealed a low albumin level of 20 g/L, an elevated erythrocyte sedimentation rate of 25 mm/h, and a C-reactive protein level of 113 mg/L. Tumor marker, *Clostridium difficile*, Epstein–Barr virus, and cytomegalovirus tests were negative.

Case 3: The patient's complete blood count, blood biochemistry, and tumor marker levels were within the normal range.

Imaging examinations

Case 1: Small bowel endoscopy (SBE) revealed multiple ulcers and stenosis in the middle and distal segments of the ileum. (Figure 1A-C). The affected areas exhibited friable mucosal tissue that was prone to bleeding upon touch. Pathological analysis revealed the predominance of chronic inflammation, along with granuloma formation in the submucosa, muscularis mucosa, and lamina propria (Figure 1D). Both the purified protein derivative (PPD) test and tuberculosis-specific T-cell spot test (T-SPOT) were positive.

Case 2: Computed tomography enterography (CTE) findings revealed the presence of multiple luminal strictures in both the small intestine and colon, as well as segmental thickening of the intestinal wall, consistent with characteristic features of Crohn's disease (Figure 2A and B). The patient's initial presentation suggested a diagnosis of Crohn's disease. However, upon admission, the patient experienced intermittent fever with a maximum temperature of 39 °C. Chest CT revealed interstitial inflammation and infection in both lungs (Figure 2C and D). Her T-SPOT test was remarkably positive (3+), which made a diagnosis of tuberculosis infection of the lungs possible. Although the patient's previous colonoscopy suggested Crohn's disease, it lacked specificity for differential diagnosis. Thus, further investigation is warranted to optimize the pathological basis of this diagnosis. Segmental ulcers were identified throughout the entire ileum and colon during SBE. Larger ulcers extended along the circumference of the intestinal lumen (Figure 2E and F). Pus patches covered the surface of the ulcers. Multiple biopsy samples were obtained from these areas. Pathological examination of the specimens revealed diffuse mucosal inflammation with the formation of multiple granulomas in the lamina propria and submucosa (Figure 2G). Positive acid-fast bacilli (AFB) staining indicated the presence of mycobacteria (Figure 2H). Based on the collective findings, the patient was diagnosed with intestinal tuberculosis.

Case 3: CTE revealed localized thickening of the lower left abdominal small intestinal wall (Figure 3A). During SBE, ileal stenosis and gastric mucosal lesions were identified (Figure 3B). Histopathological examination of the gastric mucosal lesions suggested gastric adenocarcinoma, while the histopathological findings of the ileum and jejunum indicated chronic inflammatory changes. However, the PPD test was positive. Consequently, a curative distal gastrectomy, intra-abdominal lymph node dissection, and partial small bowel resection were performed. The resected small bowel specimen exhibited significant thickening of the intestinal wall, luminal narrowing, and localized mass-like lesions. Pathological examination revealed granuloma formation in all layers of the intestinal wall (Figure 3C). Additionally, the pathology also revealed advanced dysplasia in the gastric mucosa with focal carcinoma in situ, confirming a moderately differentiated gastric adenocarcinoma (T1N0M0) (Figure 3D).

FINAL DIAGNOSIS

In all of these patients, the final diagnosis was intestinal tuberculosis.

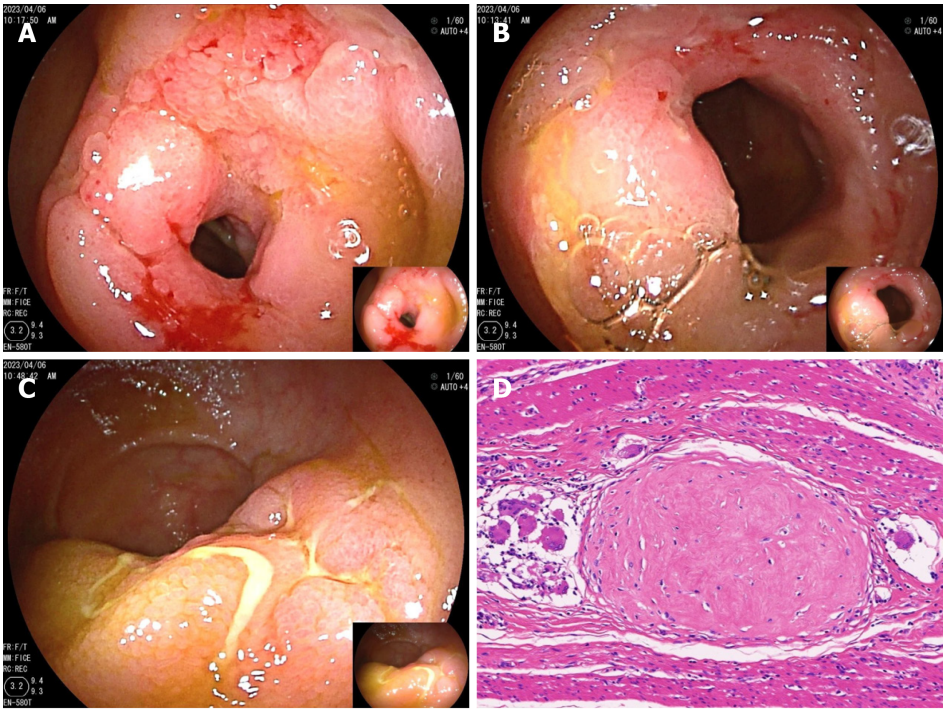

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Figure 1 Small bowel endoscopy and pathology images from case 1. A: A circular ulcer with luminal narrowing and mucosal hyperplasia located in the middle segment of the ileum; B: Another circular ulcer with a narrowing located in the middle segment of the ileum; C: A longitudinal ulcer with mucosal hyperplasia located in the terminal segment of the ileum; D: Histopathological examination by hematoxylin-eosin (200 ×) staining demonstrated the formation of multiple granulomas.

TREATMENT

Case 1

Standard anti-tuberculosis treatment was given.

Case 2

One week after admission, the patient presented with gastrointestinal bleeding. Blood transfusions were administered, and anti-tuberculosis treatment was initiated, leading to a significant improvement in the symptoms compared to those that the patients had previously.

Case 3

Standard anti-tuberculosis treatment was given.

OUTCOME AND FOLLOW-UP

These patients recovered well and follow-up was routinely performed. During the telephone follow-up in the 10th month after discharge, the patients did not develop abdominal pain or other obvious discomfort (Table 1).

DISCUSSION

We report three cases of small bowel tuberculosis (SBT) involving the ileocecal region, which is a typical site affected by this disease. The diagnosis and differentiation of intestinal tuberculosis are challenging, and the confirmation of such cases can be further complicated by atypical lesion sites.

A recent series of studies indicated that the most common clinical features of intestinal tuberculosis are abdominal pain, weight loss and fever[8-13]. Abdominal pain is typically chronic and occurs frequently in the right lower quadrant and periumbilical regions, with the symptoms of case 2. However, in case 3, the abdominal pain was mainly localized in the upper abdomen. Weight loss is also a common symptom among patients with intestinal tuberculosis. Among the three patients we described, all had a BMI less than 20 kg/m^2, which may be attributed to chronic inflammatory processes, reduced nutrient intake, or impaired absorption[14]. Notably, none of the three patients presented with fever, indicating the atypical clinical manifestations of SBTs.

Table 1 Patients' clinical features, management and outcomes

Case/gender	Age at diagnosis	Main clinical features	Examinations for tuberculosis	Features of CTE	Endoscopic appearance	Histopathological examination	Management	Outcome
1/male	49 yr	Melena	PPD (+); TSPOT (+)	Multiple luminal strictures and thickened intestinal walls	Multiple ulcers and stenosis in the small intestine	Multiple granulomas	Standard anti-tuberculosis treatment	No symptoms at the 10th month after discharge
2/female	23 yr	Recurrent abdominal pain	T-SPOT (+)	Multiple luminal strictures and thickened intestinal walls	Segmental ulcers were identified throughout the entire ileum and colon	Multiple granulomas; acid-fast staining detects positive bacteria	Standard anti-tuberculosis treatment	No symptoms at the 10th month after discharge
3/female	63 yr	Recurrent abdominal pain	PPD (+)	Localized thickening of the small intestine with clustering in the lower left abdomen	Ileal stenosis	Multiple granulomas	Standard anti-tuberculosis treatment	No symptoms at the 10th month after discharge

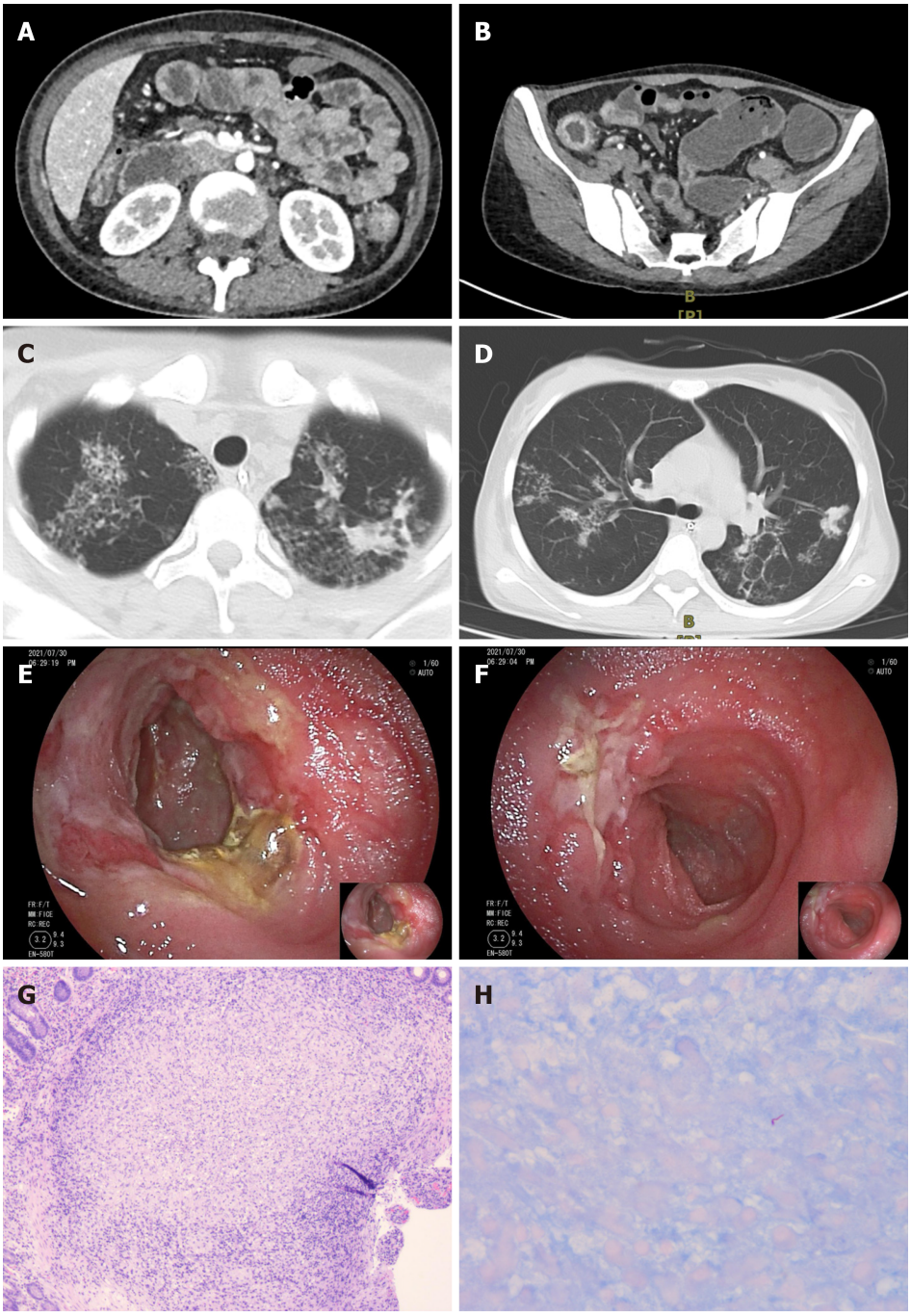
CTE: Computed tomography enterography; PPD: Purified protein derivative test; T-SPOT: Tuberculosis-specific T-cell spot test.

Cases 2 and 3 presented primarily with abdominal pain, while case 1 exhibited small intestine bleeding (SIB) as the main clinical feature. SIB, also known as obscure gastrointestinal bleeding, is commonly caused by malignancies (such as lymphoma), polyposis syndromes, Meckel's diverticulum, inflammatory bowel disease, Dieulafoy's lesions, vascular dilations, or ulcers induced by nonsteroidal anti-inflammatory drugs[15]. There are reports of cases in which colonic tuberculosis has caused significant gastrointestinal hemorrhage[16,17], but SIB attributed to intestinal tuberculosis is extremely rare.

Intestinal tuberculosis is a disease known as the "great mimicker" due to its clinical symptoms, which can mimic various conditions. Currently, endoscopic combined biopsy histopathology is widely regarded as the most important approach for diagnosing intestinal tuberculosis. A meta-analysis study[18] revealed that the relative endoscopic features of intestinal tuberculosis include transverse ulcers, a patulous ileocecal valve, and cecal involvement. Pathology is considered the gold standard for diagnosing intestinal tuberculosis, although its diagnostic efficacy heavily relies on the quality of the endoscopic biopsy specimens. In comparison to the granulomas of Crohn's disease, tuberculous granulomas in the intestine are typically larger (> 200 mm), confluent, and dense (> 5/hpf) and are predominantly distributed in the submucosal layer. The presence of central caseous necrosis allows for a specific diagnosis of intestinal tuberculosis [19,20]. However, due to the typical location of tuberculous granulomas in the submucosal layer, endoscopic biopsies are often sampled too superficially, resulting in a relatively low detection rate of caseous granulomas. Several studies[21,22] have suggested that extensive sampling during endoscopy could be performed to improve the diagnostic rate of tuberculosis, albeit at the cost of an increased biopsy and processing time. In some cases of intestinal tuberculosis, surgical intervention may be necessary to obtain sufficient pathological specimens for a definitive diagnosis. Additionally, interferon-gamma release assays (IGRAs) still hold significant value as a complementary method in the diagnosis of intestinal tuberculosis. A study indicated that the T-SPOT test has a sensitivity of 88% for diagnosing natural Mycobacterium tuberculosis infection, which is significantly greater than the 66% sensitivity of the tuberculin skin test[23]. In recent years, several studies[24,25] have utilized the ratio of visceral fat to subcutaneous fat on CT scans to distinguish between Crohn's disease and intestinal tuberculosis. A cutoff value of 0.63 for the VF/SC ratio demonstrated a high sensitivity of 82% and specificity of 81% in distinguishing intestinal tuberculosis from Crohn's disease.

Traditional examinations such as histopathological examination, AFB, and Mycobacterium tuberculosis culture exhibit high specificity but low sensitivity[26]. Various novel molecular-based approaches, including IGRA, GeneXpert, polymerase chain reaction (PCR), and multiplex PCR, offer high sensitivity but limited specificity, resulting in limited clinical application[26]. In conclusion, an accurate diagnosis of intestinal tuberculosis requires a combination of patient history, physical examination, imaging examination, endoscopy, pathology, and the latest molecular detection methods.

Regarding case 1, the patient had a history of tuberculosis, and both the PPD and T-SPOT results were positive. SBE revealed multiple ulcers and strictures in the small intestine, and histopathological examination revealed granuloma formation in the submucosa, muscularis mucosa, and lamina propria. Considering these findings collectively, a diagnosis of SBT was made. In case 2, the patient was initially misdiagnosed with Crohn's disease, but as the disease progressed, fever and pulmonary symptoms emerged. The chest CT and T-SPOT results suggested the possibility of tuberculosis, and small bowel endoscopic biopsy revealed AFB. The patient was ultimately diagnosed with SBT. For case 3, endoscopy did not reveal any specific findings, which led to doubts about the diagnosis of intestinal tuberculosis. However, CTE revealed thickening of the small intestine wall, suggesting further SBE examination. While identifying ileal stenosis, endoscopic biopsy pathology indicated gastric malignancy. As such, the patient underwent surgical intervention and postoperative pathological examination revealed multiple granulomas throughout the full thickness of the small intestinal wall,



DOI: 10.4240/wjgs.v16.i1.248

Figure 2 Computed tomography, small bowel endoscopy, and pathology images from case 2. A: Computed tomography scan showing multiple strictures in the small intestine; B: CT scan showing multiple strictures and thickening of the colonic wall; C: CT scan showing multifocal patchy opacities in the upper lungs; D: CT scan showing multifocal patchy opacities in both lungs, predominantly in the right middle lobe and left lower lobe; E: An ulcer with purulent exudate and surrounding mucosal hyperplasia was observed at the terminal ileum; F: An ulcer with luminal involvement was observed at the terminal ileum; G: Histopathological examination *via* hematoxylin-eosin staining (100 ×) revealed the presence of multiple granulomas; H: Histopathological examination *via* acid-fast bacilli staining (400 ×) revealed positive bacteria.

confirming the diagnosis of SBT.

Currently, conservative antituberculosis treatment is commonly used for patients with a confirmed diagnosis of SBT. A Cochrane meta-analysis of a randomized controlled trial (328 participants) revealed that patients treated with isoniazid, rifampicin, pyrazinamide, or ethambutol for a shorter duration (6 months) did not have a high rate of recurrence[27]. Additional observational data suggest that in most cases, six months of treatment is sufficient[28,29]. If drug therapy fails to relieve symptoms or if complications such as intestinal obstruction occur, surgical treatment may be considered based on careful evaluation of the patient. In our reported cases, except for case 3 who underwent surgical resection of the intestinal tuberculosis lesion due to gastric malignancy, the main approach was drug therapy, and all the patients achieved satisfactory therapeutic effects.

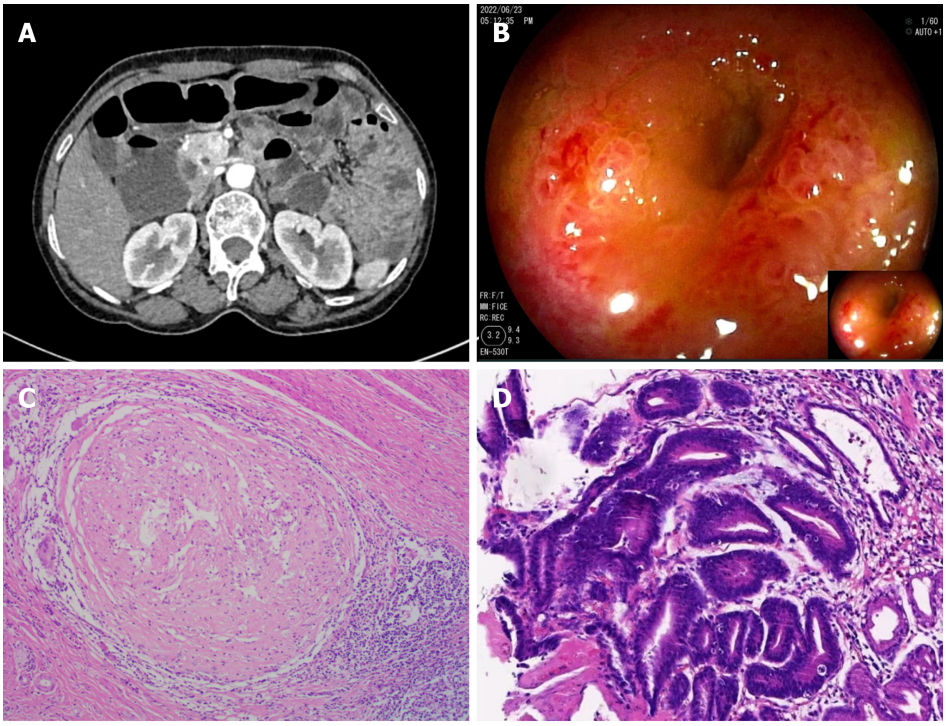


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Figure 3 Computed tomography, small bowel endoscopy, and pathology images from case 3. A: Computed tomography enterography revealed localized thickening of the small intestine with clustering in the lower left abdomen; B: Small bowel endoscopy revealing ileal stenosis; C: Histopathological examination by hematoxylin-eosin staining (100 ×) demonstrated the formation of granulomas; D: Histopathological examination by hematoxylin-eosin staining (200 ×) demonstrated advanced dysplasia in the gastric mucosa and focal carcinoma in situ.

CONCLUSION

In summary, the clinical manifestations of SBT are complex and nonspecific, often presenting as abdominal pain, weight loss, and, occasionally, isolated gastrointestinal bleeding. Purely isolated SBTs are relatively rare, with most cases being associated with pulmonary tuberculosis or extrapulmonary tuberculosis. The diagnosis of intestinal tuberculosis relies on a comprehensive assessment of clinical symptom and the laboratory, radiological, endoscopic, bacteriological, and histopathology findings. Only through a thorough analysis of the disease can we distinguish between true and false cases, thus avoiding misdiagnosis and other potential complications.

FOOTNOTES

Co-first authors: Gang Huang and Kang-Kang Wu.

Author contributions: Huang G and Wu KK contributed to manuscript writing and editing; LI XN contributed to data collection; Kuai JH contributed to conceptualization; Zhang AJ contributed to proofreading and supervision; Huang G and Wu KK contributed equally to this work as co-first authors; All authors have read and approved the final manuscript.

Informed consent statement: Informed written consent was obtained from the patient for publication of this report and any accompanying images.

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

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country/Territory of origin: China

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

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World J Gastrointest Surg 2024 January 27; 16(1): 257-259

DOI: 10.4240/wjgs.v16.i1.257

ISSN 1948-9366 (online)

LETTER TO THE EDITOR

Sarcopenia in cirrhotic patients: Does frailty matter while waiting for a liver transplant?

Xing-Jie Li, Kang He

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): 0
Grade E (Poor): 0

P-Reviewer: Sholkamy A, Egypt

Received: November 10, 2023
Peer-review started: November 10, 2023
First decision: December 4, 2023
Revised: December 7, 2023
Accepted: December 12, 2023
Article in press: December 12, 2023
Published online: January 27, 2024

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Abstract

Sarcopenia reflects patient frailty and should be routinely assessed due to its high prevalence in cirrhotic patients awaiting liver transplants. Pre-transplant nutritional optimization should be tailored for patients with a definitive diagnosis of sarcopenia, therefore improving functional status at transplant and reducing post-transplant mortality. Hepatologists and transplant surgeons should have raised awareness regarding sarcopenia and the reflected frailty that hinder posttransplant outcomes. The policymakers should also take into account when modifying the organ allocation model that sarcopenia or frailty might become a decisive factor in allocating organs for cirrhotic patients, in order to ensure post-transplant survival and quality of life.

Key Words: Sarcopenia; Liver transplant; Organ allocation policy; Cirrhosis; Frailty

Core Tip: Sarcopenia is an independent risk factor for mortality in cirrhotic patients waiting for a liver transplant. It is important to recognize sarcopenia at pre-transplant evaluation, provide supportive management and optimize patient conditions prior to the transplant. Also, the future organ allocation policymakers should take into account that cirrhotic patients with sarcopenia carry a potentially higher mortality than reflected by the current model for end-stage liver disease-Na model and therefore in a more urgent need of a liver transplant.

Citation: Li XJ, He K. Sarcopenia in cirrhotic patients: Does frailty matter while waiting for a liver transplant? *World J Gastrointest Surg* 2024; 16(1): 257-259
URL: https://www.wjgnet.com/1948-9366/full/v16/i1/257.htm
DOI: https://dx.doi.org/10.4240/wjgs.v16.i1.257

TO THE EDITOR

We read with great interest an original research paper by Yin *et al*[1], who performed a retrospective case-control study on patients who received a transjugular intrahepatic portosystemic shunt (TIPS) procedure between January 2020 and June 2021 at their center. It was evidenced that myosteatosis and sarcopenia were associated with a high incidence of overt hepatic encephalopathy in patients after the TIPS procedure[1].

We appreciate and agree with the authors' findings and would like to further investigate into the effects of sarcopenia, a reflection of patient frailty, on cirrhotic patients listed for a liver transplant. By definition, sarcopenia refers to a decline in both quantity and quality of the skeletal muscle, presented clinically with corresponding decline in muscle strength, therefore the ability to carry out physical activity[2]. It is associated with an increased likelihood of adverse outcomes. In cirrhotic patients, the prevalence of sarcopenia range between 30% and 70%, with a higher proportion in males, low body mass index patients and patients with alcoholic liver diseases[3]. The pathogenesis is not clear, but it was postulated that most cirrhotic patients had been suffering from chronic decompensated end-stage liver disease with an altered catabolism, direct myotoxicity from systemic ammonia, poor nutrition status and long-term physical inactivity[4].

A meta-analysis from Tantai *et al*[5] reported an approximately 2-fold higher mortality among all subgroups of cirrhotic patients with sarcopenia, comparing to those who don't[5]. To be noticed, the results also applied to patients with low model for end-stage liver disease (MELD)-Na score, which is a predictor of three-month mortality of cirrhotic patients and the current modality of prioritizing liver allocation. It is calculated based on the parameters of serum creatinine, bilirubin, international normalized ratio and serum sodium, ranging from 6 to 40. However, sarcopenia, as an independent risk factor for mortality in post-transplant patients, has not been integrated into the MELD-Na score, nor has it been accepted as an exception score. In the study by Montano-Loza *et al*[6], a modified MELD-sarcopenia score was proposed[6]. The patients with lower MELD scores particularly benefit from the novel model because they were traditionally deemed of low risk. It requires multicenter study with higher case number to validate a reliable and predictive model and implicate it in the clinical setting, but we do believe sarcopenia should be considered during listing and organ allocation, to prioritize patients who have poor performance status not properly reflected by MELD-Na score.

Therefore, it is of vital importance to recognize sarcopenia at listing and during pre-transplant surveillance. The gold standard for sarcopenia diagnosis is psoas muscle cross-sectional area normalized for stature (cm^2/m^2) at the level of L3 on abdominal computed tomography (CT) scan, also known as the L3 skeletal muscle index, although different cutoffs have been applied in previous studies[3,4]. As abdominal CT scan is routinely performed in cirrhotic patients at transplant evaluation for either cancer screening or anatomical mapping, it enables a qualitative measurement and a definitive diagnosis of sarcopenia concurrently at no additional costs. Once the diagnosis is made, pre-transplant management should be advocated for to optimize those cirrhotic patients for an upcoming transplant, including nutrition clinic visits and physical therapist appointments for individualized counseling if available[7].

As mentioned above, sarcopenia is a reflection of patient frailty. While it may be logistically unrealistic to repeat an abdominal CT scan at every follow-up visit with no other clinical indications, there are various well-developed clinical assessment tools for frailty. The liver frailty index (LFI) is an objective measurement specifically developed for cirrhotic patients, which involves three easily assessed aspects of grip strength, timed chair stands, and balance testing. With a well-established cutoff, LFI significantly improves mortality prediction in cirrhotic patients compared to subjective assessment solely (0.74 *vs* 0.68; $P = 0.02$) and is further implicated with great reproducibility in noncirrhotic populations [8,9].

We would like to emphasize that sarcopenia and frailty are both dynamic processes rather than a static status, in which continuous interval monitoring, documentation, and management could potentially optimize the overall condition of a cirrhotic patient prior to receiving an organ[10].

FOOTNOTES

Author contributions: Li XJ wrote the manuscript; He K designed the study and revised the manuscript.

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

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S-Editor: Li L
L-Editor: A
P-Editor: Li L

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