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ABOUT COVER

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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*.

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REVIEW

Recent advances in computerized imaging and its vital roles in liver disease diagnosis, preoperative planning, and interventional liver surgery: A review

Paramate Horkaew, Jirapa Chansangrat, Nattawut Keeratibharat, Doan Cong Le

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Abstract

The earliest and most accurate detection of the pathological manifestations of hepatic diseases ensures effective treatments and thus positive prognostic outcomes. In clinical settings, screening and determining the extent of a pathology are prominent factors in preparing remedial agents and administering appropriate therapeutic procedures. Moreover, in a patient undergoing liver resection, a realistic preoperative simulation of the subject-specific anatomy and physiology also plays a vital part in conducting initial assessments, making surgical decisions during the procedure, and anticipating postoperative results. Conventionally, various medical imaging modalities, *e.g.*, computed tomography, magnetic resonance imaging, and positron emission tomography, have been employed to assist in these tasks. In fact, several standardized procedures, such as lesion detection and liver segmentation, are also incorporated into prominent commercial software packages. Thus far, most integrated software as a medical device typically involves tedious interactions from the physician, such as manual delineation and empirical adjustments, as per a given patient. With the rapid progress in digital health approaches, especially medical image analysis, a wide range of computer algorithms have been proposed to facilitate those procedures. They include pattern recognition of a liver, its periphery, and lesion, as well as pre- and postoperative simulations. Prior to clinical adoption, however, software

must conform to regulatory requirements set by the governing agency, for instance, valid clinical association and analytical and clinical validation. Therefore, this paper provides a detailed account and discussion of the state-of-the-art methods for liver image analyses, visualization, and simulation in the literature. Emphasis is placed upon their concepts, algorithmic classifications, merits, limitations, clinical considerations, and future research trends.

Key Words: Computer aided diagnosis; Medical image analysis; Pattern recognition; Artificial intelligence; Surgical simulation; Liver surgery

Core Tip: Computerized imaging has a vital role in modern liver disease diagnosis and therapeutic intervention, including surgery. The scheme generally involves four elements, *i.e.*, preprocessing, segmentation, modeling and simulation, and software development. This paper describes and discusses how this progressive multidisciplinary technology assists physicians, radiologists, and surgeons in carrying out their tasks effectively and efficiently, hence improving the posttherapeutic outcomes of patients diagnosed with liver diseases.

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INTRODUCTION

It is estimated that there are 20 million new cancer cases worldwide and 10 million cancer-related deaths every year[1]. Among these cases, liver cancer is the third leading cause of cancer death. In 2020, 905700 people globally were diagnosed with liver cancer, and 830200 people died from the disease. Scientists have estimated that in 2040, approximately 1.4 million people will be diagnosed with the disease, while 1.3 million people will die from it[2].

The vital function of the liver is filtering blood flow from the digestive tract before circulating the blood back to the rest of the body. Consequently, the liver is subject to various diseases, *e.g.*, fascioliasis, cirrhosis, hepatitis, and alcoholic liver disease[3]. In particular, cancer is associated with increases in both the number and size of abnormal cells. If diagnosed early, it can be treated by interventional radiology, chemotherapy, radiation therapy, or a combination thereof. Among these treatments, liver surgery removing the tumors is efficient in preventing their recurrence and prolonging the life expectancy of the patient, especially those in primary and secondary stages[4]. Liver surgery is a complex and challenging procedure that requires comprehensive knowledge of the liver anatomy, blood supply, and tumor locations and characteristics. Consequently, preoperative imaging is necessary for its planning.

In recent years, there have been significant advancements in diagnostic and interventional imaging technologies, including the use of software equipped with artificial intelligence (AI), to enhance the accuracy of preoperative imaging. This comprehensive review, therefore, aims to offer an in-depth exploration of the latest progress and applications of imaging techniques. In particular, it highlights their pivotal role in improving the outcomes of diagnoses, preoperative planning, and interventional liver surgeries. The main topics discussed in the remainder of this paper cover liver segmentation, diagnostic imaging, preoperative planning and simulation, surgical and therapeutic intervention, and finally software as a medical device.

LIVER SEGMENTATION

The functional anatomy of a liver is considered in terms of its dual blood supply, as well as its venous and biliary drainage systems. It is divided into four sectors by the three hepatic veins, each of which drains into the inferior vena cava (IVC) and runs within its scissurae. This nomenclature system was famously described by Couinaud in 1957 and later amended at the Brisbane meeting in 2000. Its primary advantage is enabling anatomical resection of this seemingly almost asymmetrical organ. With this classification, each liver subdivision is self-contained in its artery and portal venous supply and biliary drainage[5,6].

Couinaud scheme

According to the Couinaud classification[5], the liver is divided into eight functionally independent segments, each of which has its own vascular in- and outflows, as well as biliary drainage (Figure 1). There are three major planes that divide the liver vertically: The right hepatic vein plane divides the right hepatic lobe into anterior and posterior segments; the middle hepatic vein divides the liver into right and left lobes; and the umbilical plane running from the falciform

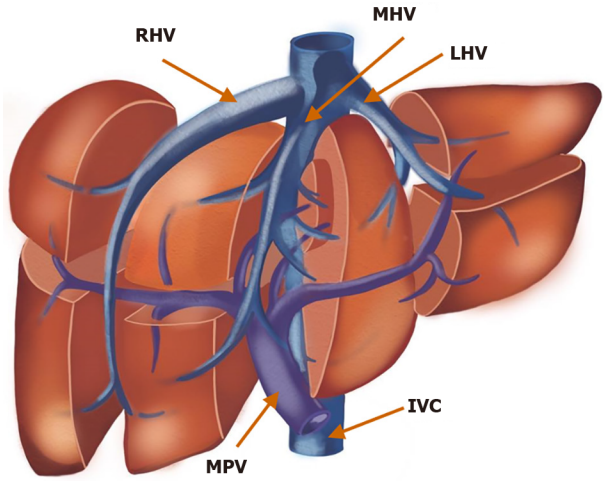

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Figure 1 Segmental anatomy according to the Couinaud classification. RHV: Right hepatic vein; MHV: Middle hepatic vein; LHV: Left hepatic vein; MPV: Main portal vein; IVC: Interior vena cava.

ligament to the IVC divides the left lobe into medial and lateral parts. The portal vein divides the liver into superior and inferior segments.

Image analyses of the liver

Diagnosis, treatment, and prognosis of diseases of the liver involve defining its anatomical boundary as well as characterizing its pathologies, typically from computed tomography (CT) and magnetic resonance (MR) images. On an image plane, a liver is described by closed contours separating itself from the background. Conventionally, physicians must mentally reconstruct the whole liver and relevant structure in 3-dimension (3D) while navigating through its tomographic planes. However, recent advances in computing technology have enabled virtual 3D reconstruction, modeling, and simulation of the organ *in vivo*[7,8].

With these technologies, physicians can accurately calculate the hepatic volumetry. In addition, visualization of a 3D liver can also help locate its arteries, veins, and biliary tracts and, hence, determine its functional segments. In surgical planning, the spatial relationship between tumors and hepatic vasculature with a 3D model increases the precision of proposal resection over that with a 2D counterpart by up to 31%[9]. Last but not least, the use of such a model also reduces time and strain during surgical planning and intervention[10].

Modeling a liver from medical images first involves delineating its boundary from other connective tissues and adjacent organs[11]. One of the key challenges is that, as a complex organ, the liver comprises not only its parenchyma but also an extensive vascular network, as well as lesions in pathological cases. In addition, despite recent advances in tomographic imaging[12], liver images remain contaminated with noise of various distributions, depending on the modality. These problems call for the development of effective preconditioning and robust image analysis algorithms. This section, therefore, investigates state-of-the-art methods, as well as their features, limitations, and challenges. These approaches include data preprocessing and fully automatic and semiautomatic segmentation methods.

Data preprocessing

Medical images are often degraded by noise and artifacts during acquisition. Depending on their model assumptions, various noise reduction strategies are applied prior to image analyses[13]. The perturbation function due to noise is normally random and hence unknown, except for only their distribution. Therefore, in medical imaging, the most frequently assumed distribution models include Gaussian, Poisson, and Rician distributions for charge couple device, X-ray, CT, and MR images, respectively. However, directly applying an inverse filter to reduce noise and possibly other inherent artifacts could adversely affect smaller features or abate anatomical boundaries, such as vasculature, calcification, and connective tissue. Instead, several applications adopt structural adaptive anisotropic[14], spatial frequency or wavelet[15], blind deconvolution[16], regularized diffusion[17] filters or, much more recently, those based on machine learning (ML) or AI models, *e.g.*, convolutional neural networks (CNNs)[18,19].

On measuring their performance, the peak signal-to-noise ratio (PSNR) and structural similarity (SSIM) are often considered. However, a recent study[20] revealed that although visual quality is clearly improved with advanced filters, correlations between PSNR and SSIM and application-specific performance, such as classification (*i.e.*, based on area under the curve), are not clearly present. In fact, fine tuning neural network parameters to a particular noise model is recommended.

In practice, to balance complexity and intended analysis, a trivial anisotropic diffusion filter has been applied to denoise a T1-weighted MR image of a liver while enhancing its border[21] prior to 3D surface generation. Meanwhile, in some other studies, the least commitment principle[22] has been adopted with no preprocessing of an image other than adjusting its windows and levels, but taking noise into account during subsequent analyses[23]. Once preconditioned, a series of cross-sectional images proceeds to the next stage, in which the liver, its peripherals, and lesions are separated.

Fully automatic segmentation

Since liver pixels appear very similar to those of other nearby organs, existing automatic schemes thus rely on auxiliary information, *e.g.*, data-driven appearance models or empirical understanding of its morphology[23]. Accordingly, its main advantage is low inter- and intraobserver variability due to manual intervention. Recent extensive surveys on the topic are found in the literature[24,25]. Several early works were developed and validated based on a public dataset called SLIVER07[26]. They contained 3D CT liver images of 20 and 10 subjects for training and testing, respectively. These images had 512 × 512 pixels at 0.56 to 0.86 mm^2 in-plane resolution and covered 64 to 502 slices with spacing between 0.7 mm and 5 mm. Another recent dataset is 3D-IRCADb[27]. It contains CT images of 20 patients, three thirds of which contain hepatic tumors. Their voxel size and resolution are similar to those of its predecessor. Furthermore, each image is labeled with not only pathologies but also segmentation challenges. Based on these datasets, a number of computerized methods were proposed to delineate a liver and benchmarked. Examples of the recent results are summarized in Table 1 [28-34]. Note that these studies may employ different accuracy metrics, *e.g.*, volumetric overlap error or dice similarity.

The most promising approach in this category is one based on modeling from pretrained data, both statistically[26,30,33,35-37] and using CNNs[34,38-40]. The former iteratively deforms a liver model to fit underlying imaging features while imposing anatomically plausible constraints found in the training, *e.g.*, the active appearance model. The latter learns from some segmented livers, their spatial architecture, and the relationship among their convolutional features, cascaded through a deep network, and fuses them with weighted nonlinear functions. Subsequently, pixels of an unseen image proceed through the same network and are labeled accordingly, resulting in the final segmentation. However, these methods require sufficiently large prelabeled samples and hence a substantial amount of computing power for model learning.

Semiautomatic segmentation

It is evident that various factors, *e.g.*, nearby organs such as the stomach, pancreas, duodenum, and heart, as well as artifacts due to implants, could have adverse effects on segmentation quality. Currently, it remains challenging to incorporate computable elements to automatically address this issue. Therefore, user interaction is often involved but kept to a minimum, *i.e.*, at initialization[23,41], during the process[42,43], in final adjustment[23], or with a combination thereof. The recent works are summarized in Table 2[21,28,41,43-46].

At varying degrees of interaction, many methods can achieve reasonable accuracy without previously trained liver data. For instance, trivial thresholding with K-means clustering has been applied to CT angiography to separate the liver from the kidneys and ribs[47]. Similar methods automatically set these thresholds by learning the pattern of abdominal histograms[48,49] or that of textures[50]. However, they often require prior knowledge of the anatomy for initialization and postprocessing, *e.g.*, manual editing or morphological operators, to remove oversegmented regions. Instead of defining pixel membership by thresholds, many researchers have expanded a region of interest accumulatively from seeding points. They then have exploited different strategies to control new inclusions, *e.g.*, convex hulls[51], binary morphology and anatomical constraints[52], significant differences in boundaries[44,53], and anatomical priors[42].

In addition to region-based approaches, delineating contours around a liver has also attracted considerable interest. Initially, the active contour model and its variants were explored[54,55] based on gradient and curvature and later extended to the level set[43,56-59]. By these methods, starting contours were specified by a user or estimated by other segmentations. They were then implicitly driven by gradient and embedding surface curvature. Unlike its counterparts, any aberration would be regularized by geometric continuity on the hypersurface. Empirical and anatomical knowledge, *e.g.*, distance to centroid, nominal contrast, and segmental and anatomical markers, were translated to computable conditions to assert the evolution of these contours.

Another approach poses the segmentation problem as that of graph optimization[60]. In liver imaging, the deviation of intensity at a pixel from a predefined distribution and its gradient strength are formulated as region and boundary cost functions, respectively[61]. Similar functions are obtained from texture images and supervoxels[32] or constrained by statistically trained shape[45] and intensity[32] models or initialized by CNN[46]. It was shown that automation of the remaining steps was possible if anatomical constraints (*e.g.*, vena cava and tumor) were imposed for postprocessing[62].

DIAGNOSTIC IMAGING

It has been discussed previously that although the liver and its vasculature are clearly presented to a radiologist in medical images, mentally extracting them requires substantial knowledge and expertise regarding hepatic anatomy and physiology. Therefore, automating this process with algorithmic codes remains an open research challenge. Similarly, diagnosing a hepatic disease involves assessing liver damage and characterizing its lesions based on their vascularity and composition, as well as their implications on adjacent vessels[63,64]. A range of radiological and computerized imaging techniques can be utilized and are summarized as follows.

Anatomy of the vasculature

Arterial anatomy: Hepatobiliary surgery, liver transplantation procedures, and endovascular treatments can all benefit from information on anatomical variations in hepatic arteries. The existence of such variations may call for adjustment of surgical procedures to avoid unintentional vascular damage, hemorrhage, and biliary problems.

The Michels classification[65] and its modification by Hiatt *et al*[66] are the most frequently used categories for describing hepatic arterial variations in the literature. Approximately 55%-60% of people have the classic pattern of the common hepatic artery branching from the celiac artery, with the hepatic artery normally splitting off into the right and

Table 1 Selected fully automatic liver segmentation algorithms[28]

Ref.	Key techniques	Dataset	Accuracy
Kumar *et al*[29], 2013	Region growing	Proprietary	98% ± 1%
Chen *et al*[30], 2012	AAM, graph cut	SLIVER07	93.5% ± 1.8%
Huang *et al*[31], 2016	Template matching (SBLDA)	3D-IRCADb	92.16% ± 2.95%
Wu *et al*[32], 2016	Linear clustering, graph cut	SLIVER07	75.2%-71.4%
Mohamed *et al*[33], 2017	Bayesian model	Proprietary	95.5%
Zheng *et al*[34], 2022	DL (CNN, C-LSTM)	SLIVER07	82.5% ± 7.7%

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Table 2 Selected semiautomatic liver segmentation algorithms[28]

Ref.	Key techniques	Dataset	Accuracy
Chen *et al*[44], 2009	Quasi-Monte Carlo	Proprietary	NA
Yang *et al*[41], 2014	Level set	SLIVER07	78.9%
Liao *et al*[45], 2016	Graph cut	SLIVER07	94.2% ± 3.3%
Lu *et al*[46], 2017	3D CNN, graph cut	3D-IRCADb	90.64% ± 3.34%
Chartrand *et al*[43], 2017	Deformable model	SLIVER07	92.38% ± 1.35%
Le *et al*[23], 2021	Mixture model, graph cut	SLIVER07	92.2% ± 1.5%

NA: Not available. Citation: Le DC, Chansangrat J, Keeratibharat N, Horkaew P. Symmetric Reconstruction of Functional Liver Segments and Cross-Individual Correspondence of Hepatectomy. *Diagnostics* 2021; 11: 852. Copyright ©The Author(s) 2021. Published by MDPI. The authors have obtained the permission for data using (Supplementary material).

left hepatic arteries to supply the entire liver. Replaced and accessory left or right hepatic arteries are the most often found anatomical variants. In cases of transarterial embolization of traumatic liver injury or embolization of liver tumors, if the bleeding point or arterial feeders cannot be demonstrated on conventional hepatic angiogram, searching for these possible anatomical variants is crucial. Another example is when left hepatectomy is performed in a patient with a replaced or accessory left hepatic artery, ligation of the left hepatic artery at its origin in the left gastric artery is needed.

Although the anatomical variant classification has been widely accepted, not all variants are surgically significant. Furthermore, the course of the hepatic artery and its topographic relationship to the surrounding structures, such as the portal vein and bile ducts, are not taken into consideration[67].

Portal vein anatomy: There are numerous variations in the portal vein branching patterns. The classic anatomy, which is found in approximately 65% of patients, consists of the main portal vein branching into the right and left portal veins at the porta hepatis. The right portal vein later subdivides into anterior and posterior branches. Found in approximately 35% of patients, the two most common variants are trifurcation of the portal vein trunk and a right posterior branch as the first branch of the portal vein trunk, with the latter being more common and known as the Z-type pattern[68,69].

Hepatic vein anatomy: Accurate perception of the hepatic vein anatomy before liver surgery is crucial. Inadvertent injury of the hepatic veins leads to a higher risk of bleeding and functional loss of the hepatic segment with a compromised venous outflow. Generally, there are three hepatic veins: The right hepatic vein drains segments V, VI, and VII, the middle hepatic vein drains segments IV, V, and VIII, and the left hepatic vein drains segments II and III. The classic anatomy of the hepatic veins, which form a common trunk between the left and middle hepatic veins, is found in approximately 65%-85% of patients[70,71].

Biliary anatomy: The normal biliary anatomy found in approximately 58% of the population comprises the right hepatic duct draining the right hepatic lobe and the left hepatic duct draining the left hepatic lobe. The right hepatic duct divides into the right posterior sectional duct, coursing in a horizontal plane and draining segments VI and VII; the right anterior sectional duct, coursing in a vertical plane, drains segments V and VIII. The left hepatic duct divides into the left superior sectional duct and drains segment IVa, and the left inferior sectional duct drains segments II, III, and IVb[72]. The caudate lobe usually drains into the proximal left or right hepatic duct.

Preoperative evaluation of liver tumors

Generally, 20%-30% of patients have synchronous hepatic disease, while hepatic metastasis occurs in more than 50% of colorectal cancer patients[73]. Primary liver tumors, such as hepatocellular carcinoma (HCC), mass-forming cholangiocarcinoma, hepatic adenoma, or focal nodular hyperplasia, as well as liver metastasis, have distinct cellular components and, hence, unique imaging appearances. As such, they can be characterized by means of CT and MRI.

To date, the only treatment associated with long-term survival for both HCC and colorectal liver metastasis is surgical resection. Imaging studies are essential for identifying potential surgical candidates. Specifically, for the best outcome in the resection procedure, all lesions need to be removed, while a sufficient functioning liver must be preserved. One of the major challenges is that because metachronous hepatic metastasis can occur in over 50% of patients with colorectal cancer [74,75], the imaging sensitivity should be sufficiently high to detect these lesions. Although CT is available worldwide and enables evaluation of extrahepatic disease and vascular structures, the modality has some limitations. These include an inferior ability to delineate the tumor margin, to perform tissue characterization, and to detect and characterize small lesions and associated radiation. Alternatively, MRI with hepatocyte-specific agents is currently the most accurate imaging modality to identify hepatic disease in patients with colorectal cancer[76-78]. Despite its sensitivity, additional metastatic foci can be found intraoperatively in up to 25% of patients after MRI[79,80]. Another drawback of MRI is that in patients with coexisting benign focal liver lesions, such as hemangioma, an ill-defined heterogeneous echoic nodule could lead to confusion during surgery. To resolve the ambiguity, contrast-enhanced ultrasound has increasingly been adopted intraoperatively as a complement. Table 3 summarizes the existing research related to the sensitivity of focal liver tumor detection[63,78,81-83].

Computer-aided diagnosis

The anatomy of both the liver and its peripherals has been extensively explored in the medical literature, and the most common patterns have been firmly established. Despite the highly deformable structure and large intersubject variability of this organ, it has been continually demonstrated that computerized methods can be applied to extract relevant objects with reasonable degrees of accuracy[24,26]. Thus far, pathological manifestations can result in irregular appearances of the interconnecting parts, undermining their merits in clinical and surgical practice[4]. In fact, with the recent advances in ML and AI, research focus has now been particularly directed toward identifying, delineating, and characterizing lesions from tomographic images. Prominent works in the field are summarized and discussed here.

ML algorithms have been widely employed in segmenting the tumoral liver. After a seed point was estimated within a lesion, fuzzy C-means (FCM) was used to expand the coverage toward its margin[29]. Likewise, a watershed was applied to CT images to extract supervoxels with similar characteristics. Subsequently, tumors were identified from the liver and other objects by merging those subregions with FCM and K-means clustering using their textural information[50], *i.e.*, pixel intensities, directional derivative, local binary pattern, and local differences. Based on 22 trained and 22 tested instances, the highest classification accuracies of 95.64% to 98.88% were reported. K-means clustering was applied to approximate liver contours, which were later refined by Graph-Cut[62]. Once the vena cava had been detected and other segments had been discarded by anatomical templates, tumors were extracted by cavity filling. Note, however, that this assumption failed to identify those on the liver boundary. For percutaneous radiofrequency ablation (RFA) to remove inoperable primary or metastatic tumors, the ablation zone was first determined by max-flow min-cuts of a 3D spherical graph expanded from a seed point[84]. It was later automated by using FCM to extract the ablation zone and then cyclic morphology to refine one[85].

Meanwhile, with rapid development in AI and CNNs in particular, a number of network architectures have been adopted for diagnosing tumoral livers. Li *et al*[38] used 2D and 3D DenseUNets to extract within-slice features and to learn their spatial relationships between slices, respectively. The results from both networks were finally fused to produce labels of both liver and tumor pixels. Despite relatively high benchmark scores (*i.e.*, 93.7%), their models took 30 h in total for training with only limited series. Another example[86] applied a simple 3D U-Net to first extract the liver. Super pixel blocks of tumors were localized by a multiscale candidate generation method. The exact regions of these candidates were defined and then refined by a 3D fractal residual network and active contour, which reached a 67% accuracy during evaluation. It was pointed out in another study that a main drawback of data-driven AI is the imbalanced proportion between healthy livers and those with pathologies[87]. As a result, many existing dice loss (DL) models tend to predict lesions as part of the liver or backgrounds. To address this issue, they tried to assemble cascade U-ResNets, each trained with a different loss function, *i.e.*, weighted cross entropy, DL, weighted DL, Teverskry loss (TL), and weighted TL. With ensemble learning, tumors could be segmented with a 75% accuracy, compared to the approximately 65%-70% accuracy obtained by competing networks. The same accuracy of 74.5% was achieved by a 2.5D fully CNN whose loss function consisted of cross-entropy, a similarity coefficient, and a novel boundary loss function[88]. The latter was prescribed based on the boundary between segmented objects by means of logical morphology. Alternatively, using a two-stage densely connected network, where a liver was first localized by an encoder-decoder CNN, tumors were detected with attention modules at a 72.5% accuracy[89].

Since these methods recognize tumors by their features, implicitly learned by examples, the irregularities found on the boundaries of lesions are not precisely traced, while adjacent lesions are sometimes merged. Thus, postprocessing by another empirical model or manual processing by radiologists is often needed. In fact, some studies have shown that, as a baseline, even skilled human raters could achieve only a 78% accuracy.

Table 3 Sensitivity (in percent) of focal liver tumor detection

Ref.	CT	MRI	CEUS
Langella *et al*[81], 2019	-	75.1	94.5
Huf *et al*[82], 2017	-	91.4	90
Niekel *et al*[83], 2010	83.6	88.2	-
Kessel *et al*[78], 2012	69.9	85.7	-
Yang *et al*[63], 2010	83.2	-	-

CT: Computed tomography; MRI: Magnetic resonance imaging; CEUS: Contrast-enhanced ultrasound.

PREOPERATIVE PLANNING AND SIMULATION

Conducting a virtual liver resection prior to the live procedure is highly beneficial. For example, the right portal pedicle divides into anterior and posterior branches, each of which further splits into two segments (*i.e.*, V and VIII, and VI and VII, respectively). The left portal pedicle has a longer and more horizontal extrahepatic course. This allows the surgeon access and exposure to the relevant areas, for instance, during biliary system reconstruction. Moreover, segmental branches arise from the left portal pedicle supplying segments II, III, and IV. The ligamentum venosum, a fibrous remnant of the ductus venosum in the fetus, which connects the left portal vein to the left hepatic vein at the IVC, serves as a distinctive landmark for gaining access to the left portal pedicle and the left hepatic vein, whose terminating discharge is often merged with the middle hepatic vein and thus can be challenging to identify and control during a left hepatectomy.

Upon estimating potential risks of the surgical procedure, liver cirrhosis and portal hypertension (which are usually associated with liver cancer, particularly HCC), must be diagnosed preoperatively. To this end, multidisciplinary teams consider any evidence of advanced cirrhosis or inadequate liver function while devising an appropriate management plan, *e.g.*, by using the Child-Pugh scoring system[90,91]. Specifically, for patients having cirrhosis and meeting certain criteria, liver resection and transplantation address an underlying field change that predisposes the parenchyma to tumor recurrence. Options for patients who are not candidates for those procedures include RFA, microwave ablation, transarterial chemoembolization, and other locoregional therapies[92].

Liver volumetry and future liver remnant

Surgical resection is a primary curative treatment for patients with primary and metastatic liver tumors. Unfortunately, fewer than 25% of patients are suitable for surgery[93,94]. With a better understanding of hepatic anatomy and surgical technique refinements, the extent of liver sections that can be surgically removed is expanding. However, a tendency toward more aggressive liver resections in patients with preexisting liver disease requires thorough evaluation of hepatic function, especially the amount and quality of the postoperative future liver remnant (FLR).

It has been established that an inadequate liver volume following surgery is a robust, independent predictor of postoperative hepatic dysfunction and complications[95]. Generally, the FLR per total liver volume (TLV) ratio must be 25%-30% to minimize postoperative complications[96,97]. Patients with hepatotoxic chemotherapy or hepatic steatosis should have an FLR ratio of greater than 30%, whereas those with cirrhosis should maintain an above 40% ratio. Likewise, in living donor transplantation, the donor's liver volume has to be 30%-35% more than that of the recipient[98], or 40% in cases with hepatic disease[99].

Computerized imaging for FLR

Volumetric CT has currently become the gold standard for determining whether hepatectomy can be performed[100]. To this end, computer software is employed to reconstruct a 3D liver and estimate the ratio of FLR to nontumorous TLV. Normally, the latter is measured directly by CT. Alternatively, it may be estimated from the patient's body surface area [101]. These methods are called mTLV and eTLV, respectively. It was found in some studies[4,102] that eTLV could identify cases where mTLV was previously underestimated. In addition, there have been a number of recent advancements in automated liver volumetry by medical image computing.

Unlike image segmentation, where whole liver boundaries are traced on an underlying volumetric image, functional segmentation or resection involves estimating its composition of independently functional segments, each of which has its own vascular in- and outflow, according to Couinaud's scheme. MeVis LiverAnalyzer™ (MeVis Medical Solution, Germany) and Synapse Vincent™ (Fujifilm, Japan) are currently standard software programs for virtual liver resection that rely on the surgeon's judgment[103]. Common practice involves the user's interactive tracing of the segments with respect to their major vascular tracks. Not only are individual experiences and skills needed, but the process is also tedious and time-consuming, as well as inducing large inter- and intraobserver variability. Meanwhile, many novel imaging algorithms have also been continuously developed to assist or complement this task and have rapidly become an emerging area of investigation.

Provided that portal and hepatic veins are extracted, liver segments are defined with respect to voxel distances to specific branches[104,105], voxel projections onto vascular intersections[106], or categorical search by Voronoi diagram

[107-109]. However, these methods suffer from computationally intensive voxel sorting. Moreover, the topology of voxel aggregation is neither validated nor rectified. Alternatively, to accelerate computation and ensure surgically plausible resection, an extracted liver volume is first converted to a surface and subdivided, based on vasculature and salient anatomical landmarks, by differential geometry[110-115]. Thus far, manual correction is often inevitable. Otherwise, additional anatomical constraints, *e.g.*, from a statistically trained deformable atlas[116], are necessary.

Unfortunately, not every method was able to segment all eight Couinaud segments nor was it always validated on the same liver dataset. Thus, a recent study[115] compared some prominent algorithms only according to their volumetric ratios, *i.e.*, at lobe and sectional levels. The average values are listed in Table 4[11,106,108,112,113,115]. Since these methods rely on accurate extraction of the hepatic vasculature and liver boundary, future directions worth exploring are advanced pattern recognition (PR) of the gastrointestinal structures and integration of other imaging modalities.

Once the resection is made, removal of pathological segments could be planned, and FLR could hence be estimated. One of the most widely utilized 3D software programs in preoperative liver surgery is Synapse Vincent™ (Fujifilm, Japan)[103]. It helps automate liver segmentations and their volumetric assessment. However, with recent surgical techniques, liver resection is no longer limited to only right hepatectomy. Several surgical plans have been devised or tailored for an individual, *i.e.*, patient-specific strategies. Therefore, FLR should be resilient to variations in such planning. In addition, other volumetric assessments are also equally important posttherapy, *e.g.*, graft regeneration after transplantation and responses to cancer treatment[117].

Liver function

In addition to resected volumetry, liver function also needs to be evaluated. In fact, technical limitations of resection and its safety have been exceeded by continually developed procedures, aiming at increasing FLR in patients with insufficient liver volume by utilizing its regeneration in response to blood flow, also known as flow modulation. Among the most often chosen procedures is portal vein embolization (PVE), where the portal vein on the opposite side of the FLR has a catheter radiologically inserted and is then embolized with vascular plugs, coils, particles, or glue[117]. Consequences of a diseased liver parenchyma in terms of liver function may be analyzed by biopsy, performed on the living donor liver prior to transplantation[118]. In patients who may need PVE to enhance the FLR ratio, these anatomical and functional criteria are also relevant, given the proper context. Comprehensive assessment of liver conditions is required prior to any therapy because livers with such as cirrhosis and steatosis, for instance, demand a significantly greater FLR than a healthy liver[119].

The indocyanine green (ICG) clearance test, asialoglycoprotein receptor scintigraphy using 99mTc-galactosyl human serum albumin, and serum hyaluronic acid level assessment are prominent methods that can be used to evaluate the residual liver's ability to function[120,121]. Injection of ICG, a tricarbocyanine dye, causes it to bond with albumin and be carried throughout the body *via* the circulatory system. Elimination of ICG occurs solely through biliary excretion. Thus, serum blood tests or an optical sensor on the finger can reveal the excretion level. ICG levels in the blood should be below 10% at 15 min after injection (ICG-R15). Therefore, blood samples taken at 5-min intervals postinjection can be analyzed to determine the plasma disappearance rate of ICG (ICGK), which is calculated by using linear regression of the plasma ICG concentration[122].

Although there is accurate automated anatomical liver volumetry and identification of its biomarkers, there is currently no computer software with biomarker mapping that can precisely delineate the area of residual functioning liver. A multidisciplinary approach is therefore recommended to determine both the liver volume and function. The selection of the surgical plane, feasibility of resection, visualization of the tumor and its extent, *etc.*, all rely on maintaining an ongoing interaction between the surgeon and radiologist, as well as reliable, though probably not the most precise, imaging software.

Postoperative risk assessment

The risk of postoperative hepatic failure is substantially associated with the extent of liver resection. Although this is logical and simple to assess, the volume of the liver that remains present is more indicative and must be precisely determined. Additionally, because the segmental anatomy and its volume significantly vary among patients, only determining the segmental numbers is inconclusive. Specifically, the right side of the liver accounts for more than half of the TLV in most people, but its variations extend from 49% to 82%, while those of the left side range from 17% to 49% [123]. Therefore, a formal radiologic volumetric assessment is necessary to ensure accurate FLR, especially when planning a major liver resection.

SURGICAL AND THERAPEUTIC INTERVENTION

CT or MRI is typically performed to characterize lesions and devise preoperative planning[21]. Consequently, FLR is estimated from the planned resection outlines by sequential marking on respective cross-sectional images, given slice thickness and voxel dimensions. It has been shown that both the intended and actual FLR as well as their actual surface and volumes are highly correlated radiographically[124,125]. As such, additional tests are not required during the procedure.

For patients with an insufficient FLR who are being considered for hepatic resection, FLR augmentation by PVE *via* interventional radiography is most widely used. With this procedure, the portal vein (with or without segment IV branches) is embolized. Usually, the procedure is performed with percutaneous vascular access[117]. Subsequently, those who exhibit more than 2.0% growth per week on repeated volumetry have no risk of liver failure during the periop-

Table 4 Average proportion (in percent) of functional segment groups[115]

Ref.	Lobe level		Sectional level		Anterior	Posterior
	Left	Right	Lateral	Medial		
Huang *et al*[106], 2008	39	61	14.1	24.7	39.3	21.9
Ruskó *et al*[112], 2013	32	68	12.2	20	40.2	27.6
Chen *et al*[108], 2016	45	55	26.7	18.1	23.3	32
Butdee *et al*[113], 2017	40	60	17.9	22.1	29.4	30.6
Le *et al*[11], 2021	32	68	13.3	19.2	30	37.5

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erative phase following hepatectomy[126].

Liver resection

An anatomic resection involves the removal of a Couinaud segment by selective ligation of the main HPV and portal triad. With this approach, there is a higher chance of obtaining disease-free margins because it resects areas distal to the tumor that are at risk for vascular micrometastasis. Alternatively, nonanatomic resection or parenchymal transection disregards those segmental planes; it is often employed for benign tumors, debulking treatment, or when attempting to preserve the residual parenchyma. A microscopic margin negative (R0) resection must be performed to minimize local recurrence. It has been shown that a resection margin of 1 cm or smaller is safe[127].

Standard anatomic hepatectomy involves controlling both vascular inflow and outflow prior to parenchymal transection. Accordingly, removal can be performed without affecting adjacent hepatic segments. Generally, intraoperative ultrasonography is utilized to determine the presence of vascular structures and to assess the location and size of the tumor as well as their relation to the surrounding vasculature.

Minimally invasive surgery

The development of computerized imaging techniques to further enhance minimally invasive liver surgery has rapidly progressed[128,129]. For instance, near-infrared fluorescence is adopted in laparoscopic and robotic camera systems, allowing the identification of different preoperatively injected dyes (*e.g.*, indocyanine green). This contrast agent propagates through the biliary tree while illuminating the structure after being metabolized mostly by hepatocytes. Recently, this modality has been exploited to differentiate between well- and inadequately-perfused hepatic parenchyma to guide parenchymal dissection following vascular control[130-132].

Computer-assisted surgery

It has been established that computer-based 3D reconstruction of liver tumors could improve the accuracy of their localization and the precision of surgical planning[9]. Thus far, 2D/3D image reviewing during surgery on a traditional picture archiving and communication system in the operating room has been found to be distracting. Therefore, real-time localization of lesions and the identification of arteries and biliary structures by using intraoperative ultrasonography are usually preferred. Nevertheless, similar to what was pointed out in another survey on tumor surgery[133], the need for additional port sites to interpret 2D images and hence to mentally recreate the 3D anatomy with respect to the orientations of ultrasound probes has restricted its wider adoption in minimally invasive surgery.

Currently, an augmented reality (AR) endoscopic overlay of the patient-specific anatomy with associated virtual reality (VR) models has attracted considerable attention as it could increase the surgical efficiency in real-time with intelligent operative guidance[134-136]. With this approach, 3D reconstructed data can be precisely overlaid onto the operated area. Effectively, cognitive strain conventionally imposed on the surgeon could be lessened. For uterine myomectomy, it has been shown that spatial recognition based on AR could improve the localization accuracy[137].

To adopt VR and AR in hepatobiliary surgery, one has to confront the technical challenges of continuously coregistering the computer-generated models to a mobile liver with significant tissue deformation. To address this issue, a recent study[28], for example, applied conformal parameterization to an extracted liver surface. With this technique, the triangle mesh of genus-0 of the surface was mapped onto its topological homeomorphism[138]. Given a set of landmarks on a liver surface, representing the resection paths according to Couinaud's definition, a deformation that bijectively maps a liver and its section onto another instance with minimal distortion could be realized. However, since the liver is morphologically diverse, it was suggested that localized alignment should be the focus. In fact, to ensure physiologically plausible correspondence within or across subjects, statistical deformable models[30,43] are incorporated. Additionally, clinical management aspects, *e.g.*, tumor board evaluations, preoperative strategy, and intraoperative access, also need to be considered.

SOFTWARE AS A MEDICAL DEVICE

Since the early 1990s, Digital Imaging and Communication in Medicine (DICOM) developed by the American College of Radiology and the National Electrical Manufacturers Association has been a gold standard for archiving, transferring, and presenting imaging data among acquiring and processing devices[139] in radiological practices[140]. It features a unique structural content[141], consisting of not only an imaging matrix and its encoding but also relevant medical data, *e.g.*, patient information and study details, as well as a scanning protocol. In a typical liver examination, for instance, its DICOM structure contains a series of multislice CT images in the axial direction, covering the upper abdomen, and each image is numbered and labeled with physical geometry, thickness, and resolution, and perhaps suggested window-level settings. This information is vital for accurately reconstructing a whole 3D liver for diagnostic and intervention purposes. Hence, most current medical image computing software does support this standard by default. In addition, the Neuroimaging Informatics Technology Initiative (NIfTI)[142] has been specifically designed and developed by neuroimaging scientists to resolve physical orientation objects within a brain image. Nonetheless, this data format is also adopted in other fields, where geometric information is needed.

Presently, computer software has increasingly been integrated into digital platforms that serve medical purposes. Software that is a medical device in its own right is called Software as a Medical Device (SaMD)[143]. It is to be distinguished from software in a medical device and that used in manufacturing or maintaining a medical device. Specifically, the International Medical Device Regulators Forum (IMDRF) defines SaMD as "software intended to be used for one or more medical purposes (*e.g.*, to make clinical decisions) that performs these purposes without being part of a hardware medical device." With its unique features, a working group by IMDRF as the representative of regulators worldwide developed a common framework aiming to support innovation and timely access by both patients and providers to safe and effective SaMD.

In liver imaging, SaMD, regardless of its computing platforms, may be used for diagnoses both *in vivo* and *in vitro*, prevention, screening or monitoring, and treatment or alleviation of liver diseases. A manufacturer who intends to make SaMD available for use under their name would be subject to regulations, not only throughout its software engineering life cycle (*e.g.*, ISO/IEC 14764:2006 Software Engineering) but also postmarket surveillance and any subsequent updates, in which risk identification and countermeasures are established[144].

To maintain regulatory compliance, the roles of an SaMD and its deployment in clinical environments must be declared. Its recommendation for intended uses (*i.e.*, diagnosing or treating a disease and informing or driving clinical management) with potential adverse consequences (*i.e.*, critical, serious, and nonserious situations or conditions) must be classified. Most importantly, software evaluation (according to established protocols)[145], clinical evaluations, and relevant evidence must be attached. Finally, its linguistic design and instructions must conform to standard medical terms. Other considerations include technology and sociotechnical system, environment, and information security with respect to safety.

CONCLUSION

This paper has provided an extensive review on computerized imaging in both current and emerging clinical practices and when integrated with state-of-the-art algorithms. The vital roles of this modality include the diagnosis of liver disease and its curative planning, treatment, and surgical intervention. It has been demonstrated in the recent literature that, depending on the data condition, prior knowledge, and amount of user interaction involved, various computer algorithms yield reasonable diagnostic and simulation accuracies. Nonetheless, it is worth noting that while these algorithms perform particularly well for functional segment classification of normal or slightly pathological livers, their performance on hepatic lesion characterization remains to be much further improved.

Although ML and AI strategies have rapidly become the main players in liver imaging and thus far have exhibited promising results, it remains challenging to acquire sufficiently large and heterogeneous datasets with labeled ground truth for training. This issue has been partly addressed in many less critical applications by using, for instance, big and crowdsourced data.

Finally, with advances in medical imaging, many computer algorithms will be adopted and implemented in SaMD. Therefore, researchers, digital health manufacturers, and physicians should be made aware of relevant regulatory requirements and guidelines to ensure the safety of patients.

FOOTNOTES

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MINIREVIEWS

Diagnosis and treatment of post-cholecystectomy diarrhoea

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Abstract

The incidence of cholecystitis is relatively high in developed countries and may usually be attributed to gallstones, the treatment for which involves complete surgical removal of the gallbladder (cholecystectomy). Bile acids produced following cholecystectomy continue to flow into the duodenum but are poorly absorbed by the colon. Excessive bile acids in the colon stimulate mucosal secretion of water and electrolytes leading, in severe cases, to diarrhoea. Bile acid diarrhoea (BAD) is difficult to diagnose, requiring a comprehensive medical history and physical examination in combination with laboratory evaluation. The current work reviews the diagnosis and treatment of BAD following cholecystectomy.

Key Words: Cholecystitis; Gallstones; Bile acids; Colon; Bile acid diarrhoea

Core Tip: The incidence of cholecystitis is relatively high in developed countries, the treatment for which involves complete surgical removal of the gallbladder. Bile acids produced following cholecystectomy are poorly absorbed by the colon. Excessive bile acids in the colon stimulate mucosal secretion of water and electrolytes leading, in severe cases, to diarrhoea. The current work reviews the diagnosis and treatment of bile acid diarrhoea following cholecystectomy.

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INTRODUCTION

The incidence of diarrhoea after cholecystectomy is extremely high, affecting 57.2%[1-3] of patients in a multimedical center study in which only a small proportion of post-cholecystectomy patients were investigated and for which there was a time delay in diagnosis. The true prevalence of bile acid diarrhoea (BAD) after cholecystectomy may be much higher and clinicians need to raise awareness of this treatable disease which seriously impacts patient quality of life[4-6]. Post-cholecystectomy diarrhoea (PCD) may be multifactorial[2]. No storage of bile acids is possible following cholecystectomy, resulting in the slow release of unconcentrated bile into the small intestine. Postprandial gastrointestinal reflex causes large-scale movement of bile from the small intestine to the colon, resulting in biliary acid-mediated diarrhoea[1,6-8]. Indeed, the frequency of bowel movement may change from a pre-operative once a day to a post-operative 4-5 times per day. The risk of postoperative diarrhoea depends on age, weight, and sex[2]. One review published in the US has estimated that, of the 750000 cases of cholecystectomy per annum, 5%-12% are followed by diarrhoea[9]. A prospective study which assessed 93 patients in two years before and after surgery found that eight had recurrent watery diarrhoea during the two years following cholecystectomy[10].

DIAGNOSIS OF BAD

BAD is more common among patients with chronic watery diarrhoea and prior cholecystectomy[11,12] and diagnosis requires a comprehensive medical history and examination (including digital rectal examination) in combination with laboratory assessments, including total blood count, catabolic status, C-reactive protein level, faecal occult blood test, faecal lactoferritin test, white blood cell smear test, and microbiological assessment[13]. Laboratory confirmation of BAD remains a challenge. Five diagnostic tools are available: (1) ^{14}C cholesterol choline and breath test; (2) ^{75}Selenium homocholic acid taurine (SeHCAT) test[12,14-18]; (3) serum measurements of C4 and FGF19[18]; (4) 48-h faecal bile acid test[18-20]; and (5) the bile acid chelator trial[18,21-23] (Figure 1).

The British Society of Gastroenterology Guidelines for Chronic Diarrhoea Investigation recommend endoscopy and the SeHCAT test as the first-line diagnostic modality[24]. Currently, clinicians pay insufficient attention to the diagnosis of diarrhoea after cholecystectomy and approximately 10%-30% of BAD patients are misdiagnosed with irritable bowel syndrome (IBS-D)[5,25-27]. The SeHCAT test allows differentiation between PCD and IBS-D[28]. The 48-h faecal bile acid test is the alternative to the SeHCAT test and may reduce healthcare utilization and costs in patients with chronic non-bloody, unexplained diarrhoea[19].

TREATMENT AND MANAGEMENT OF BAD

Cholecystectomy has an effect on bile concentration and excretion and changes the circulation of bile acids between the liver and intestine. The orthodox explanation for altered intestinal function refers to the loss of gallbladder fluid storage and changes in bile acid metabolism. In particular, the concentration of deoxycholic acid in the faeces increases, which enhances rectal sensitivity, causing an urge to defecate[29]. The accompanying physiological changes expose therapeutic targets for the post-cholecystectomy syndrome. BAD is usually regarded as incurable[17,28,30], and the chronic condition may be treated by drugs targeted to bile acid receptors and transporters or which aim to change bile acid pools. The diarrhoea is considered difficult to treat and is only reduced in half of cases, significantly affecting quality of life. Long-term follow-up is thus necessary, accompanied by adjustment of treatment methods and the development of new approaches[12] (Table 1).

Bile acid sequestrant trial

The Canadian Association of Gastroenterology clinical practice guidelines recommend bile acid sequestrants (BAS) as the first-line treatment for BAD[31,32]. For patients with suspected or confirmed BAD, a BAS trial (BAST), initially with cholestyramine, is suggested. However, the BAST must be carefully managed to avoid under- or over-treatment[33]. BAS, such as cholestyramine, colestipol, and colesevelam, bind bile acids secreted into the intestine to reduce damage to intestinal tissues. Cholestyramine was the first BAS used to treat BAD in 1972, and Hoffman and Poley found favourable results in patients following resection of the small intestine. A study of eight patients with PCD, defined as more than four loose stools in a 24-h period for 1 to 20 years, included six subjects with elevated stool bile acids and stool weight greater than 200 g/24 h. Treatment with 4 to 16 g/d oral cholestyramine reduced the number of daily bowel movements within 72 h. Diarrhoea recurred in all patients after cessation of cholestyramine treatment[28,32]. A meta-analysis of the medical records of 291 patients with chronic watery diarrhoea tested by the SeHCAT test including 74 patients with a previous cholecystectomy[11] and a multi-centre study across three sites in the United Kingdom[5] found that 60%-70%

Table 1 Treatment of post-cholecystectomy bile acid diarrhoea

Treatment	Target	Limited
Bile acid sequestrant trial	Bile acids secreted into the intestine are bound to reduce damage to intestinal tissues	Poorly tolerated due to stomach pain, bloating, flatulence, nausea and vomiting
Bile acid receptor agonists	Receptor agonists reduce bile acid synthesis to relieve symptoms of diarrhoea	Potent FXR agonists may have adverse side effects
Glucagon-like peptide 1 receptor agonist	Slows upper gastrointestinal motility and increases small intestine transit time	Further clinical trials and follow-up required
Intestinal microbiota	Increased bile acid binding, excretion in faeces, and hepatic synthesis *via* an FGF-dependent mechanism after probiotic administration	Not intended to target the entire intestinal microbial community as a therapeutic approach
Ursodeoxycholic acid	Reduces mucosal cytokine levels, inhibiting release of antimicrobial peptides and preventing apoptosis.	LCA metabolism may be required to allow full pharmacological effects of ursodeoxycholic acid
Anti-diarrhoeal agents	Inhibit intestinal secretion and peristalsis, slowing intestinal transit and allowing increased fluid reabsorption to alleviate diarrheal symptoms	High doses or abuse may cause cardiotoxicity
Dietary therapy	Vegetable dietary fiber prevents gastrointestinal diarrhea by reducing gastric emptying	May respond to a reduction of dietary cholesterol and fats

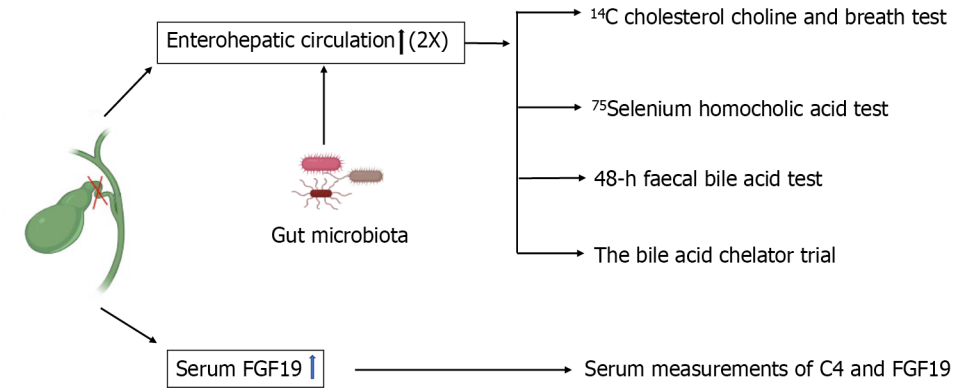

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Figure 1 Five diagnostic tools for bile acid diarrhoea.

of patients discontinue cholestyramine and colestipol within 5 years due to adverse reactions, including constipation, excessive diarrhoea, stomach pain, bloating, flatulence, and nausea and vomiting. Colesevelam is often better tolerated and results in firmer stools but may be less effective in improving stool frequency than colestyramine. In addition, colesevelam may be prohibitively expensive in countries such as Spain. The need for superior BAD treatments is clear and the colon release preparation of bile glycol, A3384, has been shown to be well-tolerated and effective in clinical trials.

Bile acid receptor agonist therapy

Sequestrants bind and remove excessive bile acids to reduce colon secretion but the primary causes of bile acid production remain unresolved[34]. The farnesoid X receptor (FXR) is highly expressed in the intestine and liver[35-38] and receptor agonists reduce bile acid synthesis to relieve symptoms of diarrhoea. Both FXR and Takeda G-protein receptor 5 are bile acid receptors on the nucleus and cell surface and have been considered to participate in the mechanisms by which bile acids regulate physiological functions since 2000. FXR has since been assigned roles in the extrahepatic metabolism of cholesterol, lipid, and glucose. FXR agonists are under development for treatment of liver and intestinal diseases and have excellent potential as anti-diarrheal drugs due to inhibition of calcium- and cyclic adenosine monophosphate-dependent chloride secretion by the colonic epithelium. The impact of FXR agonists on fluid and electrolyte transport by colonic epithelial cells gives these drugs a broader efficacy than preexisting treatments while generating fewer side effects[39]. Walters *et al*[37] have proposed that FXR agonists that influence the fibroblast growth factor 15/19 (FGF15/19) pathway may alleviate cholestatic liver injury and diarrhoea. A reduction of FGF19 synthesis by the ileum would lead to impaired feedback inhibition of hepatic CYP7A1 in the liver and increased bile acid synthesis, reflected by increased C4 Levels. It is the excessive production of bile acids by the liver which are secreted into the small intestine and exceed the reabsorption capacity of the ileum that allows bile acids to enter the colon and cause diarrhoea. Many agonists, including GW4064, PX-102, LJN452, and Ec001, have been developed and INT-747 obberic acid (OCA) was approved by the United States Food and Drug Administration (FDA) for clinical use in 2016. OCA has been shown to be 100 times more potent as an FXR agonist than goose deoxycholic acid[40]. OCA is often combined with ursodeoxycholic acid (UDCA) to treat primary biliary cholangitis and other liver diseases, such as non-alcoholic steatohepatitis and primary sclerosing cholangitis. A recent phase II clinical trial at Imperial College London demonstrated that OCA

improved serum FGF19 Levels and decreased C4 and faecal bile acids, reducing diarrheal symptoms in BAD patients. OCA inhibited colonic fluid secretion and reduced bile acid biosynthesis, decreasing the flow of bile acids into the colon [41]. FXR agonists also have the potential for the treatment of inflammatory diseases and reduced FXR expression was found in intestinal epithelial cells of patients with inflammatory bowel disease (IBD). This finding suggests that changes in bile acid synthesis and FXR expression may be involved in the dysregulation of the immune response and development of inflammatory diseases, such as IBD, an observation that merits further study. A 2-wk clinical study of patients with primary and secondary bile acid malabsorption (BAM)-induced diarrhoea had improved stool frequency, stool morphology, and total diarrhoea index with increased FGF19 and decreased C4 and faecal bile acids after treatment with OCA[42]. However, potent FXR agonists may have adverse side effects, such as lowering HDL levels, and receptors must be carefully selected to achieve the desired treatment effects.

Glucagon-like peptide 1 receptor agonist: Liraglutide

Liraglutide is a commonly used drug for type 2 diabetes and obesity. It also has utility as second-line antisecretory therapy for BAD after cholecystectomy. Liraglutide delays gastric emptying and inhibits duodenal and small intestine motility[43-45]. The peptide glucagon-like peptide 1 (GLP-1) is known to slow upper gastrointestinal motility and increase small intestine transit time, which may enhance the passive resorption of bile acids from the gut to the bloodstream and reduce bile acid flow to the colon[46]. GLP-1 receptor agonist therapy has been reported to reduce cholecystokinin (CCK)-induced gallbladder emptying[47,48] and a study of liraglutide confirmed its safety for pancreatitis but indicated an increased risk of cholelithiasis[49]. However, this adverse effect does not apply to post-cholecystectomy patients. A clinical trial at the Center for Clinical Metabolic Research at Copenhagen University Hospital compared the efficacy of liraglutide and colesevelam in reducing defecation frequency in BAD patients and indicated the superiority of liraglutide[50]. Furthermore, case reports exist of two patients who experienced total remission of BAD symptoms after liraglutide treatment[46]. GLP-1 receptor agonists have also been shown to have beneficial effects on outcomes and mortality for patients with cardiovascular and chronic kidney disease[51-57]. Post-cholecystectomy patients experience mild disturbances in glucose homeostasis and slight deterioration in postprandial blood glucose, GLP-1, and insulin and glucagon concentrations[58]. Cholecystectomy has been reported to be associated with an increased diabetes risk[59]. Therefore, we consider liraglutide to be very suitable for BAD patients with additional benefits for those who also suffer from diabetes, cardiovascular disease, chronic kidney disease, or more than one of these conditions. Furthermore, treatment of PCD with liraglutide may prevent the development of type 2 diabetes. However, contrary views have been recorded previously. Smits *et al*[60] reported the results of a clinical trial in which liraglutide was found to be a cause of BAD. Further clinical trials and follow-up regarding the application of liraglutide for BAD are required.

Treatment targeting the intestinal microbiota

The changes in bowel habits and loss of bile acids during BAD following cholecystectomy may cause changes in the gut microbiota in some patients[61,62]. However, a controlled study in South Korea in which stool samples were collected from 39 gallstone patients and 26 healthy controls found that cholecystectomy did not affect the gut microbiome 3 mo after surgery, although an elevated relationship between microbes in the gallstone patients after surgery was found by network analysis. We suggest that PCD is a delayed postoperative complication that requires long-term follow-up data to determine changes in the gut microbiome[61]. Previous studies have used microbial metabolomics to demonstrate differences between post-cholecystectomy patients and healthy controls, raising the question of whether the gut microbiome could be targeted as a treatment for BAD[3,63-65]. The increasing scrutiny of probiotics in basic and clinical research has illustrated the potential health benefits that may follow sufficient dosages of these sterilized living microorganisms. Unlike drugs, probiotics may be taken by healthy subjects to reduce the risk of developing disease or to optimize physiological functions. Probiotics survive transit through stomach acid and bile, successfully reaching the small intestine and colon. A recent study has demonstrated increased BA binding, excretion in faeces, and hepatic synthesis *via* an FGF-dependent mechanism after probiotic administration. Thus, a beneficial effect of BA on the gut microbiome and systemic metabolism is indicated. Treatment of post-cholecystectomy patients with probiotics to enhance intestinal microecology improves gut microbiome balance through an impact on Bacteroidetes and Firmicutes levels. A healthy gut microbiome balance has the effect of suppressing the growth of opportunistic pathogens and promoting intestinal microecology. *Lactobacillus plantarum* (pCBH1) is a genetically engineered strain which overexpresses bile salt hydrolase and degrades glycodeoxycholic acid and taurodeoxycholic acid *in vitro*. It has the potential to reduce bile acids in BAD patients. Genetic engineering of microbial strains allows the targeting of pathogenic molecules or metabolic pathways of interest, rather than affecting the entire intestinal microbial community and may represent a superior form of BAD treatment. Intestinal dysbiosis may play a key role in PCD, exposing therapeutic targets for this disorder[66].

UDCA

UDCA from bear bile has been used in traditional Chinese medicine for hundreds of years to treat a range of diseases, including liver and intestinal disorders. In Western medicine, UDCA has been used for many years to treat liver diseases, especially primary biliary cholangitis, and as a bile acid replacement therapy to reduce bile acid toxicity in patients with deficient bile acid synthesis, gallstone dissolution, and digestive diseases[67,68]. Its potential for the prevention of primary sclerosing cholangitis and IBD has also been investigated. UDCA has shown therapeutic efficacy in treating a variety of extrahepatic diseases, including IBD, in clinical and preclinical studies[69] and UDCA or taurine conjugated derivatives have demonstrated pharmacological effects in reducing disease severity, mucosal cytokine levels, and the release of antimicrobial peptides and preventing apoptosis in animal models of IBD. UDCA also inhibited activation of

and release of pro-inflammatory cytokines by mucosal immune cells. However, the UDCA metabolite LCA is considered the most toxic of the colonic bile acids and it may be necessary for LCA metabolism to take place to allow the full pharmacological effects of UDCA[70]. Clearly, much work is still needed to elucidate the relationship among UDCA, its metabolites, the microbiome, and mucosal inflammatory responses.

Anti-diarrhoeal agents

Loperamide is a synthetic phenylpiperidine derivative approved by the FDA in 1976 for the treatment of diarrhoea. Loperamide inhibits intestinal secretion and peristalsis, slowing intestinal transit and allowing increased fluid reabsorption to alleviate diarrheal symptoms. Diphenoxylate–atropine is a combination treatment for acute and chronic diarrhoea symptoms[71] but exposure to high doses during use and abuse may cause cardiotoxicity[72,73].

Dietary therapy

PCD may respond to a reduction of dietary cholesterol, fats, and animal protein and eggs and an increase in dietary fruit and vegetables[74-77]. Vegetable dietary fiber can prevent gastrointestinal diarrhea by reducing gastric emptying, improving intestinal barrier function, increasing epithelial cell regrowth, and increasing colonic fluid and electrolyte uptake[78,79].

PROSPECTS

The last two decades has seen great progress in the understanding of the role of bile acids in modulating the intestinal epithelium in health and disease. There has been corresponding interest from the pharmaceutical industry in the utilization of bile acids for the treatment of enteric and parenteral diseases. The discovery of novel bile acid receptors has driven an appreciation of the sensing of luminal bile acid characteristics by intestinal epithelial cells with the resulting activation of molecular pathways. Understanding of the endogenous and exogenous factors that influence bile acid pool size and composition has increased but there remain many unknown areas.

An ideal therapeutic approach would involve a gut-specific FXR activator to alleviate bile enterostasis by inducing FGF19 and reducing hepatic bile acid synthesis. Side effects of hepatic FXR activation would thus be avoided. However, whereas the main site of FGF19 secretion into bile was found to be the gallbladder mucosa, FGF19 is also an endocrine hormone which exerts metabolic effects on distant tissues. FGF19 has a pro-mitogenic function and a concern is potential tumorigenic activity. Long-term treatment of diarrhoea with FXR agonists requires consideration of this possible side effect. A clearer understanding of the regulation of cellular signalling pathways involved in bile acid synthesis, transport, and metabolism is required to avoid bile acid toxicity in the gut and liver. In addition to selective enterohepatic circulating FXR modulators, genetic and metabolic pathway-specific FXR modulators may be possible therapeutic strategies to treat cholestasis and metabolic diseases.

Liraglutide has utility as a second-line treatment for PCD associated with diabetes, metabolic syndrome, and obesity. It is an effective anti-diarrhoea treatment but remains too expensive to be used as a first-line anti-diarrhoea treatment alone.

Examination of faecal samples indicates that post-cholecystectomy patients have significant gut microflora differences compared with controls but gut microbiome changes could not be accurately correlated with the time after cholecystectomy during the current review. Studies are underway to elucidate the association between cholecystectomy and changes to the intestinal microbiota at 3 mo, 1 year, and 5 years after surgery. A study of signalling by bile acids as intermediaries between host and gut microbes and the integration and transduction of signals into biological responses is planned and may expose novel therapeutic targets for diarrhoea.

The apical sodium-dependent bile acid transporter (ASBT) has a theoretical role in hepatic and intestinal bile acid circulation with the potential to influence liver disease. Several ASBT inhibitors are under development, although none has so far been FDA-approved. These small-molecule inhibitors lower plasma LDL levels and have shown therapeutic promise for chronic constipation in preclinical and clinical studies.

CONCLUSION

Finally, the influence of diet should be stressed. Patient follow-up after surgery indicates that diarrhoea is often linked to diet, particularly to the consumption of greasy foods. A diet low in fat and animal protein may alleviate PCD.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Cohort Study

Trans-anal endoscopic microsurgery for non- adenomatous rectal lesions

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Abstract

BACKGROUND

Trans-anal endoscopic microsurgery (TEM) enables a good visualization of the surgical field and is considered the method of choice for excision of adenomas and early T1 rectal cancer. The rectum and retro-rectal space might be the origin of uncommon neoplasms, benign and aggressive, certain require radical trans-abdominal surgery, while others can be treated by a less aggressive approach. In this study we report outcomes in patients undergoing TEM for rare and non-adenomatous rectal and retro-rectal lesions over a period of 11 years.

AIM

To report outcomes in patients undergoing TEM for rare and non-adenomatous rectal and retro-rectal lesions over a period of 11 years.

METHODS

Between January 2008 to December 2019 a retrospective analysis was completed for all patients who underwent TEM for non-adenomatous rectal lesion or retro-rectal mass in our institution. Patients were discharged once diet was well tolerated and no complications were identified. They were evaluated at 3 wk post operatively, then at 3-mo intervals for the first 2 years and every 6 mo depending on the nature of the final pathology. Clinical examination and rectoscopy were performed during each of the follow-up visits.

RESULTS

Out of 198 patients who underwent TEM during the study period, 18 had non-

adenomatous rectal or retro-rectal lesions. Mean age was 47 years. The mean size of the lesions was 2.9 mm, with a mean distance from the anal margin of 7.9 cm. Mean surgical time was 97.8 min. There were no intra-operative neither late post-operative complications. Mean length of stay was 2.5 d. Mean patient follow-up duration was 42 mo.

CONCLUSION

TEM allows for reduced morbidity given its minimally invasive nature. Surgeons should be familiar with the technique but careful patient selection should be considered. It can be used safely for uncommon rectal and selected retro-rectal lesions without compromising outcomes. We believe that it should be reasonably considered as one of the surgical methods when treating rare lesions.

Key Words: Trans-anal endoscopic microsurgery; Rectal lesions; MicrosurgeryTrans-anal endoscopic microsurgery; Rectal lesions; Microsurgery

Core Tip: Trans-anal endoscopic microsurgery allows for reduced morbidity given its minimally invasive nature. Surgeons should be familiar with the technique but careful patient selection should be considered. It can be used safely for uncommon rectal and selected retro-rectal lesions without compromising outcomes. We believe that it should be reasonably considered as one of the surgical methods when treating rare lesions.

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INTRODUCTION

Trans-anal endoscopic microsurgery (TEM) is a surgical method which is capable of resecting lesions up to 20 cm[1-3]. It enables for excellent access, visualization of the surgical field and for precise[4] full-thickness excision of rectal lesions. Today, TEM is considered the method of choice for excision of adenomas and early T1 rectal cancer[5]. The rectum, as well as the retro-rectal space, can be the origin of a heterogeneous group of uncommon neoplasms[6] that range from aggressive malignancies to benign lesions that are almost always symptomatic[7-11]. The treatment of this rare and heterogeneous group of lesions varies depending on the location and nature of the lesions; accordingly, certain lesions require radical trans-abdominal surgery, while others can be treated by a less aggressive approach.

Since being introduced in 1984[6], indications for the use of TEM have expanded beyond benign adenomas and early rectal cancer. Today, several studies suggest that TEM can also be an effective method for excision of uncommon lesion of the rectum and retro-rectal space[2,7,8,12,13]. The objective of this study is to report outcomes in patients undergoing TEM for rare and non-adenomatous rectal and retro-rectal lesions over a period of 11 years.

MATERIALS AND METHODS

Retrospective analysis was completed for all patients who underwent TEM procedure for non-adenomatous rectal lesion or retro-rectal mass at the Hasharon Hospital, Rabin Medical Center from January 2008 to December 2019.

Data was collected from medical records including patient demographics, tumor location, dimension, preoperative histology if present, and indications for surgery. Additionally, data regarding operative findings, post-operative outcomes and post-operative complications were also collected. The local Institutional review board at Rabin Medical Center approved this retrospective study with a waiver of informed consent.

Prior to surgery, all patients underwent an evaluation protocol for TEM. This protocol included a full colonoscopy with biopsy and rigid proctoscopy to assess the tumor size. Distance from the anal verge and location of the rectal or retro-rectal lesion were identified. Endorectal ultrasound was performed in certain cases. Preparation for surgery in TEM patients included mechanical bowel preparation, preoperatively, and prophylactic antibiotics.

The original Richard Wolf equipment was used to perform the procedure, and the procedure was performed according to the standard technique described by Buess *et al*[1]. Patients were placed in a prone jackknife or lithotomy position depending on the tumor location. When located within the rectal wall the tumor was removed by fullthickness excision with a 1 cm margin. Specimens were pinned and marked for orientation by the surgeon.

Closing methods of large rectal defects were completed by approximation of defect edges by interrupted sutures. Full thickness transverse suturing technique was implemented using absorbable sutures. In the case of peritoneal entry, the

closure of the defect was done in two layers with separate closure of the peritoneum when feasible.

For retro-rectal lesions; a transverse incision of the bulge of the rectal wall was made. The mass was extracted after being dissected within the retro-rectal space from the rectal wall, perirectal and presacral tissues. The rectal opening was closed in the same fashion as described above.

Patients resumed oral intake of liquid and soft diet on post-operative day one; with full diet being subsequently advanced, once tolerated. Pain management included oral dipyrone or paracetamol, with opioids ordered as needed. Patients were discharged once diet was well tolerated and no complications were identified.

Patients were evaluated at 3 wk post operatively. Follow ups were completed at 3-mo intervals for the first 2 years and then every 6 mo depending on the nature of the final pathology. Clinical examination and rectoscopy were performed during each of the followup visits.

RESULTS

Out of 198 patients who underwent TEM during the study period, 18 (9%) had non-adenomatous (non-carcinomas or adenomas) rectal or retro-rectal lesions. Mean age was 47 years (27–81).

The pre-operative diagnoses of these lesions are detailed in Table 1 and include 3 patients with clinical and radiological findings suspicious of gastrointestinal stromal tumor (GI) (GIST), 3 patients with neuroendocrine tumors (NET), 1 patient with leiomyosarcoma, 2 patients with submucosal lipoma, 4 patients with indeterminate pathology and 5 patients with retro-rectal lesions without histological diagnosis.

The mean size of the lesions described was 2.9 mm (1-6 mm), with a mean distance from the anal margin of 7.9 cm (5-13 cm). Regarding the locations of the lesions in the rectal wall; 10 lesions were in the posterior wall, 4 were in the anterior wall, 3 in lateral position, and 1 patient had circular stenosis of rectum. Mean surgical time was 97.8 minutes (50-200). There were no intra-operative complications.

Peritoneal cavity entry occurred during fullthickness excision of lateral rectal wall mass with indeterminate pathology, therefore, an additional laparoscopy was required to visualize the suture line of the rectal wall and to perform an anastomotic leak test. In the postoperative period, 1 patient had urinary retention. Another patient presented with rectal bleeding, which was self-limiting and required no intervention or blood transfusion.

Mean length of stay was 2.5 d (1-4). No late postoperative complications were observed. The final pathologies (detailed in Table 1) of the specimens confirmed the diagnosis. These included tailgut cysts without malignancy, GIST lesions, and indeterminate lesions identified as follows: 1 lesion of endometrioma, a solitary rectal ulcer (SRU), a cloacogenic polyp, and 1 lesions found to be fibrotic tissue within the anastomosis without malignancy. Mean patient follow-up duration was 42 mo (14-80): All patients were disease free, except for the patient with the leiomyosarcoma who died due to lung metastasis at 37 mo following intervention.

DISCUSSION

TEM is a minimal invasive technique that has been proven to be an alternative for radical surgery aimed at rectal adenomas and early rectal cancer[14-18]. TEM can also, arguably, give the same surgical advantages for non-adenomatous rare lesions, unless these lesions are easily reached by instrumentation[19-23].

Although GIST lesions are the most common mesenchymal-derived neoplasm of the GI tract, rectal GIST lesions remain rare[12]. Surgical resection with negative margins is the recommended treatment for non-metastatic rectal GIST lesions. Given that nodal harvest is not necessary to cure GIST, local excision was proposed for these lesions[13].

TEM is an effective approach for the resection of rectal GIST due to the minimally invasive approach and rate of anal sphincter preservation[14]. Such advantages as shorter operating time, decrease blood loss, enhanced recovery, and low complication rate should be highlighted. Among our 3 GIST patients, we illustrated successful excision without perioperative complications and disease free without recurrence (local or distal) at 6 year follow-up.

NET lesions of the rectum are rare, and often present as asymptomatic incidental findings. Therapeutic recommendations remain controversial. ENETS guideline[15] recommend local treatment for rectal NET between 10 mm and 20 mm, followed by radical surgery, if local resection is incomplete. Therefore, the optimal local treatment procedure should combine highest local R0 rate with lowest possible complication rate. Studies using TEM for treatment of rectal NET lesions achieved very high R0 rate and conclude that TEM is a safe and effective procedure as long as the resection margins are negative[16-18].

In our cohort, the 3 NET patients had free surgical margins. Excisions were completed without complications or need for more invasive surgery. Of note, 1 patient did develop lung metastases at 1 year follow-up.

Rectal lipomas are rare benign lesions and mostly arise from the sub-mucosa. Patients may be asymptomatic or present with rectal bleeding, constipation and/or tenesmus[19]. In our cohort, both lipomas were submucosal. One presented with tenesmus and the other had rectal bleeding prior to diagnosis. Both patients had no recurrence at 5 and 7 years follow-up, respectively.

Retro-rectal or presacral lesions are rare and a homogeneous group of lesions with about two thirds of them being congenital. Most of these are cystic and benign. 10% are of neurogenic origin, 5%-10% are of bone origin and about 15% are from other origins, including metastasis. Surgical approach may be abdominal, posterior or combined. TEM facilitates the excision of the lesion in almost any place retro-rectally[20,21]. There are several series that illustrate use of TEM for excision of retro-rectal/pre-sacral cysts with excellent outcomes and complete excision of the lesions. In our cohort, all 5

Table 1 Study cohort

No	Age (yr)	Preop diagnosis	Final pathology	Size	Distance	Location	Op time	LOS
1	62	GIST	GIST	3	6	Post	65	2
2	58	NET	NET	1	8	Post	60	3
3	28	Indeterminate pathology	Solitary rectal ulcer	3	10	Ant	65	2
4	58	GIST	GIST	1.5	5	Rt post	90	2
5	66	Retro-rectal mass	Tailgut cyst	3	7	Post	110	2
6	54	Retro-rectal mass	Tailgut cyst	4	8	Post	150	3
7	40	NET	NET	1.5	9	Post	100	1
8	45	Retro-rectal mass	Tailgut cyst	3	7	Post	100	3
9	68	Submucosal lesion	Lipoma	6	8	Post	150	3
10	72	Leiomyosarcoma	Leiomyosarcoma	4	6	Ant	95	3
11	48	Retro-rectal mass	Tailgut cyst	2	6	Rt post	100	2
12	80	Indeterminate pathology	Rectal stenosis		7	Circ	50	2
13	54	GIST	GIST	2	11	Ant	50	3
14	25	Indeterminate pathology	Cloacogenic polyp	4	7	Lt	60	2
15	52	Indeterminate pathology	Endometrioma	4	13	Rt	200	4
16	74	Submucosal lesion	Lipoma	3	7	Lt	120	3
17	44	NET	NET	1	10	Rt ant	90	3
18	42	Retro-rectal mass	Tailgut cyst	3	7	Post	105	3

LOS: Mean length of stay; NET: Neuroendocrine tumor; GIST: Gastrointestinal stromal tumor.

retro-rectal lesions were identified as cysts. Complete excision with closure of the rectal defect was performed in all patients. None had abscess or fistula formation.

TEM is an effective treatment of anastomotic rectal stenosis. It has been described as an alternative to both abdominal resection of the anastomotic area and endoscopic dilatation[22]. In our cohort we describe a patient with rectal stenosis as a result of a mid-rectal anastomosis following anterior resection. We illustrated the use of TEM as a successful approach for anastomotic resection of the fibrotic ring and re-suturing. Rectal bleeding was noted on the 4th post-operative day, although was self-limiting with no need for blood transfusion. At 3-year follow up, the patient was asymptomatic and reported marked improvement quality of life.

Extra-pelvic endometriosis can affect the rectum and account for 15% of intestinal presentations. Our endometrioma patient had a a solitary lesion in the upper rectum without pre-operative pathological diagnosis. TEM was performed with peritoneal entry requiring additional laparoscopy to ensure closure of the intraperitoneal rectum.

SRU syndrome (SRUS) is an uncommon chronic disorder with a wide range of endoscopic findings, clinical presentations and characteristic histopathological features. There is no clear consensus regarding SRUS management, because of its poorly understood pathogenesis and frequent association with various pelvic floor disorders. TEM technique may provide a safe and effective way for full thickness excision of the rectal wall with a 1-cm margin. TEM, as a surgical approach, allows for rectal resection with clear and detail view, specifically for rectal lesions such as SRUS[23].

Rectal leiomyosarcoma is an uncommon malignant tumor, accounting for less than 0.1% of all rectal malignancies[24]. While leiomyosarcoma can occur at any age, it predominantly affects individuals in their 5th and 6th decades of life, with a higher incidence in men.

Surgical intervention remains the primary treatment approach for anorectal leiomyosarcoma. Radical surgical approaches, such as anterior resection or abdominoperineal resection, are preferred over wide local excision in terms of local control. Of note, survival rates do not significantly differ between the two surgical modalities[25]. Neoadjuvant radiotherapy may enhance local control following resection. However, both local and distant recurrence are common and can manifest years after the initial resection. Unfortunately, the prognosis for anorectal leiomyosarcoma is generally poor, with reported 5-year survival rates ranging from 20% to 40%[26].

The histopathological characteristics associated with a poor prognosis include high mitotic activity, intra-tumoral necrosis, and larger tumor size. Moreover, efforts should be made to avoid positive margins during surgical resection, as they independently predict local recurrence[27].

Differential diagnosis that should be considered: fibromatoses, schwannomas, and GIST. An accurate diagnosis is of paramount importance for establishing the treatment modalities. Superficial biopsy specimens may not accurately represent the entire tumor mass, possibly leading to misdiagnosis of leiomyosarcomas. Therefore, full-thickness resection

of the tumor is the best diagnostic modality for precise diagnosis. Additionally, lymph node metastasis is rare in leiomyosarcomas (as reported in previous studies). Thus, lymphadenectomy is not warranted unless preoperative imaging reveals enlarged regional lymph nodes[26,28]. This data provides support for the roll of full-thickness local excision by TEM as a definitive surgical treatment for selected cases.

In our study, the patient who had rectal leiomyosarcoma died 4 years following surgery due to distant lung metastasis disease. No evidence of local recurrence was appreciate during the follow up period.

A cloacogenic polyp of the rectum, also known as a cloacogenic glandular polyp, is a rare type of benign polyp that originates from the cloacal remnants in the rectum. It is considered a developmental anomaly. The cloaca is a common channel during embryonic development that receives waste products from the gastrointestinal, urinary, and reproductive systems before they are expelled from the body[29].

Cloacogenic polyps typically occur in the lower rectum and are composed of glandular tissue resembling the lining of the cloaca. They are usually small in size and asymptomatic, but can occasionally cause rectal bleeding or mucus discharge. Cloacogenic polyps are generally benign, but in rare cases, they may exhibit dysplasia or progress to malignancy. Diagnosis of cloacogenic polyps is made through endoscopic examination, where the polyp's distinct glandular appearance can be visualized. Treatment typically involves complete removal of the polyp through endoscopic or surgical resection[30].

TEM is a safe and effective technique for removing such polyps that are not amenable for endoscopic resection. However, regular follow-up is recommended to monitor for recurrence or any potential malignant transformation, although the risk of malignancy is considered low.

In our study we had 1 patient with this type of pathology who was treated by TEM. No recurrence was observed during the follow up period.

CONCLUSION

It can be argued that TEM allows for reduced morbidity given its minimally invasive nature. Surgeons should be familiar with the technique but careful patient selection should be considered. TEM can be used safely for uncommon rectal and selected retro-rectal lesions without compromising outcomes. We believe that TEM should be reasonably considered as one of the surgical methods when treating rare lesions.

Limitations

The limitation of this is study is the low power, given small sample size.. Although TEM as a surgical modality, has a potential benefit, no solid conclusion can be made from this study alone. Additional research is necessary, with more extensive and diverse sample size, to expand upon the findings of this study.

ARTICLE HIGHLIGHTS

Research background

Trans-anal endoscopic microsurgery (TEM) is a surgical method which is capable of resecting lesions up to 20 cm. It enables for excellent access, visualization of the surgical field and for precise full-thickness excision of rectal lesions.

The rectum, as well as the retro-rectal space, can be the origin of a heterogeneous group of uncommon neoplasms that range from aggressive malignancies to benign lesions that are almost always symptomatic. The treatment of this rare and heterogeneous group of lesions varies depending on the location and nature of the lesions; accordingly, certain lesions require radical trans-abdominal surgery, while others can be treated by a less aggressive approach.

Research motivation

Several studies suggest that TEM can also be an effective method for excision of uncommon lesion of the rectum and retro-rectal space.

Research objectives

The objective of this study is to report outcomes in patients undergoing TEM for rare and non-adenomatous rectal and retro-rectal lesions over a period of 11 years.

Research methods

Retrospective analysis was completed for all patients who underwent TEM procedure for non-adenomatous rectal lesion or retro-rectal mass from January 2008 to December 2019. The original Richard Wolf equipment was used to perform the procedure, and the procedure was performed according to the standard technique described specimens were pinned and marked for orientation by the surgeon. Patients resumed oral intake of liquid and soft diet on post-operative day one; with full diet being subsequently advanced, once tolerated. Patients were discharged once diet was well tolerated and no complications were identified.

Patients were evaluated at 3 wk post operatively. Follow ups were completed at 3 mo intervals for the first 2 years and then every 6 mo depending on the nature of the final pathology. Clinical examination and rectoscopy were performed

during each of the followup visits.

Research results

Out of 198 patients who underwent TEM during the study period, 18 (9%) had non-adenomatous (non-carcinomas or adenomas) rectal or retro-rectal lesions. Mean age was 47 years (27–81). The mean size of the lesions described was 2.9 mm (1-6 mm), with a mean distance from the anal margin of 7.9 cm (5-13 cm). Regarding the locations of the lesions in the rectal wall; 10 lesions were in the posterior wall, 4 were in the anterior wall, 3 in lateral position, and 1 patient had circular stenosis of rectum. Mean surgical time was 97.8 min (50-200). There were no intra-operative complications. Mean length of stay was 2.5 d (1-4). No late postoperative complications were observed. The final pathologies (detailed in Table 1) of the specimens confirmed the diagnosis. Mean patient follow-up duration was 42 mo (14-80): All patients were disease free, except for the patient with the leiomyosarcoma who died due to lung metastasis at 37 mo following intervention.

Research conclusions

It can be argued that TEM allows for reduced morbidity given its minimally invasive nature. Surgeons should be familiar with the technique but careful patient selection should be considered. TEM can be used safely for uncommon rectal and selected retro-rectal lesions without compromising outcomes. We believe that TEM should be reasonably considered as one of the surgical methods when treating rare lesions.

Research perspectives

Additional research is necessary, with more extensive and diverse sample size, to expand upon the findings of this study.

FOOTNOTES

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

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ORIGINAL ARTICLE

Retrospective Study

Effects of cytoreductive surgery combined with hyperthermic perfusion chemotherapy on prognosis of patients with advanced gallbladder cancer

Jin-Xiu Wu, Rong Hua, Xiang-Ji Luo, Feng Xie, Li Yao

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Abstract

BACKGROUND

Gallbladder cancer (GC) is a common malignant tumor and one of the leading causes of cancer-related death worldwide. It is typically highly invasive, difficult to detect in the early stages, and has poor treatment outcomes, resulting in high mortality rates. The available treatment options for GC are relatively limited. One emerging treatment modality is hyperthermic intraperitoneal chemotherapy (HIPEC). HIPEC involves delivering heated chemotherapy directly into the abdominal cavity. It combines the strategies of surgical tumor resection and localized chemotherapy administration under hyperthermic conditions, aiming to enhance the concentration and effectiveness of drugs within the local tumor site while minimizing systemic toxicity.

AIM

To determine the effects of cytoreductive surgery (CRS) combined with HIPEC on the short-term prognosis of patients with advanced GC.

METHODS

Data from 80 patients treated at the Punan Branch of Renji Hospital, Shanghai Jiao Tong University School of Medicine between January 2018 and January 2020 were retrospectively analyzed. The control group comprised 44 patients treated with CRS, and the research group comprised 36 patients treated with CRS combined

with HIPEC. Then, the survival time and prognostic factors of the two groups were compared, as well as liver and kidney function indices before and six days after surgery. Adverse reactions and complications were recorded in both groups.

RESULTS

The baseline data of the research and control groups were similar ($P > 0.05$). Six days after surgery, the alanine aminotransferase, aspartate aminotransferase, total bilirubin, and direct bilirubin levels significantly decreased compared to the preoperative levels in both groups ($P < 0.05$). However, the values did not differ between the two groups six days postoperatively ($P > 0.05$). Similarly, the postoperative creatinine and blood urea nitrogen levels were significantly lower than the preoperative levels in both groups ($P < 0.05$), but they did not differ between the groups six days postoperatively ($P > 0.05$). Furthermore, the research group had fewer postoperative adverse reactions than the control group ($P = 0.027$). Finally, a multivariate Cox analysis identified the tumor stage, distant metastasis, and the treatment plan as independent factors affecting prognosis ($P < 0.05$). The three-year survival rate in the study group was higher than that in the control group ($P = 0.002$).

CONCLUSION

CRS combined with HIPEC lowers the incidence of adverse reactions and improves survival in patients with advanced GC.

Key Words: Gallbladder diseases; Chemotherapy, Cancer, Regional Perfusion; Gallbladder neoplasms; Prognosis; Regression analysis; Survival rate

Core Tip: This study explores the potential benefits of combining cytoreductive surgery with hyperthermic intraperitoneal chemotherapy in treating gallbladder cancer (GC). Our results show that this combined approach may increase the median overall survival and three-year survival rates, and may decrease the incidence of postoperative complications. While the results are promising, this represents a step forward in GC treatment and suggests a possible new therapeutic strategy that warrants further investigation.

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INTRODUCTION

The incidence of gallbladder cancer (GC) ranks first among all biliary tract tumors and is frequently observed in female patients. Additionally, cholecystolithiasis with chronic inflammation is a comorbidity considered a high-risk factor for GC [1]. With symptoms similar to those of biliary colic and chronic cholecystitis, GC can easily go undiagnosed or misdiagnosed. Moreover, this type of cancer is strongly invasive and develops rapidly; therefore, patients often have middle- or late-stage disease at diagnosis[2]. Approximately 30% of patients with GC in China complain of gallstones, inflammation, or polyps at the time of diagnosis, and some patients are unexpectedly diagnosed with GC on pathological examination after cholecystectomy in the hospital[3].

Surgical resection is the only curative treatment for GC. However, GC is highly malignant, can easily invade adjacent organs, and has a high lymph node metastasis rate and poor adjuvant treatment effect. Therefore, the prognosis is usually unfavorable, and the overall five-year survival rate is < 5%[4]. In cases of tumor recurrence, systemic therapy can be selected based on pathological characteristics to prolong survival time[5]. Therefore, close postoperative follow-up is crucial. Reoperation may not be ideal for patients with recurrent or metastatic GC. Traditional systemic chemotherapy has many side effects; therefore, it is crucial to choose postoperative adjuvant therapies with mild side effects and good curative effects[6,7].

Many years of research have resulted in hyperthermic intraperitoneal chemotherapy (HIPEC), a relatively new technology that has become crucial for treating intra-abdominal tumors[8]. After more than 40 years of clinical application and the continual development of perfusion technology, the consensus is that HIPEC significantly affects peritoneal cavity metastasis in patients with digestive tract tumors[9]. Existing level I evidence shows that HIPEC can treat and prevent peritoneal implantation of malignant peritoneal tumors and reduce the incidence of peritoneal metastasis[10]. Over time, HIPEC has been gradually applied to the gastrointestinal tract, gynecological tumors, and other fields, and its clinical efficacy and safety have been widely recognized[11]. Most studies on gynecological malignant tumors, especially advanced ovarian cancer[12], have reported good curative effects; thus, HIPEC has become the first-line treatment for gynecological malignant tumors. Since GC has a high degree of malignancy and metastasis rate, it

requires further postoperative consolidation or adjuvant therapy to prolong survival and improve the patient's quality of life[11]. Currently, postoperative adjuvant therapy is mainly systemic chemotherapy; however, some patients experience many intolerable side effects, compromising their quality of life. HIPEC for gastrointestinal and gynecological malignant tumors has delivered good results; therefore, we speculate that it is feasible to adopt HIPEC as an auxiliary treatment after GC surgery. The curative effects of HIPEC after GC surgery need to be clarified. Therefore, this study analyzed the short-term effects of cytoreductive surgery (CRS) combined with HIPEC in patients with advanced GC to provide a new, alternative treatment plan.

MATERIALS AND METHODS

Participant source

Data from 122 patients with advanced GC treated at the Punan Branch of Renji Hospital, Shanghai Jiao Tong University School of Medicine between January 2018 and January 2020 were analyzed retrospectively. Our hospital's medical ethics committee approved this study.

Inclusion and exclusion criteria

The inclusion criteria were patients: (1) With confirmed GC through postoperative pathology; (2) With tumor, node, metastasis (TNM) stage III or IV disease; (3) Between 18 and 80 years old; (4) Who had not received radiotherapy, chemotherapy, and other adjuvant therapies before surgery; (5) Without abnormalities of the heart, lung, brain, kidney, or other important organs; and (6) With a Karnofsky Performance Scale score of ≥ 70 points[13].

The exclusion criteria were patients: (1) With TNM stage I or II disease; (2) With abnormalities in the heart, lung, brain, liver, kidney, or other important organs; (3) With severe abdominal adhesion; (4) With other malignant tumors; (5) With blood system diseases or blood coagulation insufficiency; (6) With intestinal obstruction; (7) With cachexia; and (8) Who had received chemotherapy, radiotherapy or other adjuvant therapy after surgery.

Participant screening

Eighty patients who met these requirements were screened based on their electronic medical records. Among them, 44 patients treated with CRS were enrolled in the control group, and 36 patients treated with CRS combined with HIPEC were enrolled in the research group.

Clinical data collection

Clinical data of the patients were collected, including age, sex, tumor stage, degree of differentiation, comorbidities, tumor size, lymph node metastasis, nerve invasion, distal metastasis, and vascular invasion. In addition, changes in liver function indices before and after surgery were collected.

Outcome measures

The primary outcome measures were survival time and prognosis. The secondary outcome measures were comparisons of the clinical data between the two groups, including indices related to liver and kidney function before surgery and six days after surgery. Adverse reactions and complications were also recorded in both groups.

Follow-up

Re check the patient in the outpatient department according to the doctor's suggestion, or follow up the patient through telephone communication after discharge. The patients were followed up at 1, 2, 3, 6, 9, 12, 18, 24, 30 and 36 mo after operation. Patients who could not return to the hospital on time or regularly were followed up by telephone, and the circumstances of their recent situation were noted. This study followed each patient for three years or until death.

Statistical analyses

All statistical analyses were performed with SPSS version 26.0 (IBM SPSS Inc., Chicago, United States). Measurement data are presented as means ± SD. All data were subjected to normality tests and analyzed using independent-sample *t*-tests. Countable data were analyzed using χ^2 tests. Survival time was analyzed based on the follow-up results, and the survival rates of the two groups were compared using the log-rank method. Survival curves of the two groups were plotted using the Kaplan-Meier method. Multivariate Cox regression analysis was performed to identify independent risk factors affecting patient prognosis. *P*-vales of < 0.05 were considered significant.

RESULTS

Baseline data

The research and control groups had similar baseline data ($P > 0.05$, Table 1).

Table 1 Baseline data

Factors		Control group (n = 44)	Research group (n = 36)	χ^2 value	P value
Age	< 60 yr	17	19	1.600	0.205
	≥ 60 yr	27	17		
Gender	Male	18	18	0.661	0.416
	Female	26	18		
Tumor staging	Stage III	21	15	0.293	0.587
	Stage IV	23	21		
Differentiation degree	Low	24	12	3.600	0.057
	Moderate	20	24		
Comorbid stones	Yes	39	29	1.014	0.313
	No	5	7		
Tumor size	< 5 cm	25	22	0.150	0.698
	≥ 5 cm	19	14		
Lymph node metastasis	Yes	37	29	0.171	0.678
	No	7	7		
Nerve invasion	Yes	27	20	0.275	0.599
	No	17	16		
Distant metastasis	Yes	30	23	0.163	0.686
	No	14	13		
Vascular invasion	Yes	22	16	0.245	0.620
	No	22	20		

Liver function indices before and after surgery

Liver function-related indices were compared between the two groups before and six days after surgery. The alanine aminotransferase, aspartate aminotransferase, total bilirubin, and direct bilirubin levels were significantly lower after surgery than before surgery in both groups ($P < 0.05$, Figure 1). However, after surgery, the levels did not differ between the two groups ($P > 0.05$, Figure 1).

Renal function indices before and after surgery

The renal function-related indices were compared between the two groups before and six days after surgery. The creatinine and blood urea nitrogen levels were significantly lower after surgery than before surgery in both groups ($P < 0.05$, Figure 2). However, after surgery, the levels did not differ between the two groups ($P > 0.05$, Figure 2).

Adverse reactions

The research group has notably fewer adverse reactions than the control group after surgery ($P = 0.027$, Table 2).

Prognostic factors

Patient survival was analyzed by Cox regression analysis; the univariate analysis identified the treatment plan, tumor stage, lymph node metastasis, distant metastasis, and vascular invasion as factors affecting prognosis ($P < 0.05$, Table 3). However, the multivariate analysis only identified the tumor stage, distant metastasis, and treatment plan as independent prognostic factors ($P < 0.05$, Table 4).

The relationship between prognostic indicators and patient survival

In the final analysis of the study, Cox regression analysis was performed to examine prognostic indicators related to patient outcomes. The results indicated that patients with stage III tumors, no distal metastases and those who received CRS had significantly higher 3-year survival rates compared to their respective control groups ($P < 0.01$, Figure 3).

DISCUSSION

GC has an extremely low incidence (less than 4%); however, its five-year survival rate does not exceed 5%[14]. Most

Table 2 Adverse reaction statistics

Group	Abdominal distension	Seroperitoneum	Jaundice	Infection	Total occurrence
Control (n = 44)	4	4	4	2	14
Study (n = 36)	2	1	0	1	5
χ^2 value	-	-	-	-	4.869
P value	-	-	-	-	0.027[a]

[a]$P < 0.05$.

Table 3 Univariate Cox regression analysis results

Factors	β	SE	χ^2 value	P value	HR	95%CI	
						Lower limit	Upper limit
Age	0.111	0.253	0.195	0.659	1.118	0.681	1.834
Sex	-0.308	0.255	1.460	0.227	0.735	0.446	1.211
Tumor staging	1.212	0.271	19.953	< 0.001[b]	3.360	1.974	5.719
Differentiation degree	0.255	0.251	1.026	0.311	1.290	0.788	2.111
Comorbid stones	0.126	0.360	0.122	0.727	1.134	0.560	2.296
Tumor size	-0.218	0.254	0.739	0.390	0.804	0.489	1.322
Lymph node metastasis	1.380	0.469	8.650	0.003[a]	3.976	1.585	9.977
Nerve invasion	0.345	0.257	1.794	0.180	1.411	0.853	2.336
Distant metastasis	1.143	0.308	13.73	< 0.001[b]	3.135	1.713	5.739
Vascular invasion	0.797	0.260	9.360	0.002[a]	2.218	1.332	3.696
Treatment plan	0.740	0.262	7.960	0.005[a]	2.095	1.253	3.503

[a]$P < 0.01$.
[b]$P < 0.001$.
CI: Confidence interval; HR: Hazard ratio; SE: Standard error.

Table 4 Multivariate Cox regression analysis results

Factors	β	SE	χ^2 value	P value	HR	95% CI	
						Lower limit	Upper limit
Distant metastasis	0.802	0.319	6.309	0.012	2.230	1.193	4.171
Lymph node metastasis	0.449	0.509	0.777	0.378	1.566	0.578	4.247
Distant metastasis	0.900	0.312	8.289	0.004[a]	2.459	1.333	4.536
Vascular invasion	0.440	0.273	2.599	0.107	1.552	0.909	2.65
Treatment plan	1.068	0.282	14.377	< 0.001[b]	2.908	1.675	5.05

[a]$P < 0.01$.
[b]$P < 0.001$.
CI: Confidence interval; HR: Hazard ratio; SE: Standard error.

patients have middle- or late-stage disease at the first visit; thus, their survival time does not exceed one year[15]. Surgical resection is the only treatment option for GC. A simple cholecystectomy is feasible in the early stages without obvious metastasis[16]. However, surgery is more complicated for patients with metastasis regardless of the stage; if the imaging examination determines that the tumor is resectable and there are no absolute surgical contraindications, then organs with a possible correlation with tumor invasion should also be resected to ensure complete resection of the tumor[17]. In these cases, extended CRS of the GC, including the gallbladder, tumor, adjacent organs, lymph nodes, ligaments, and bile

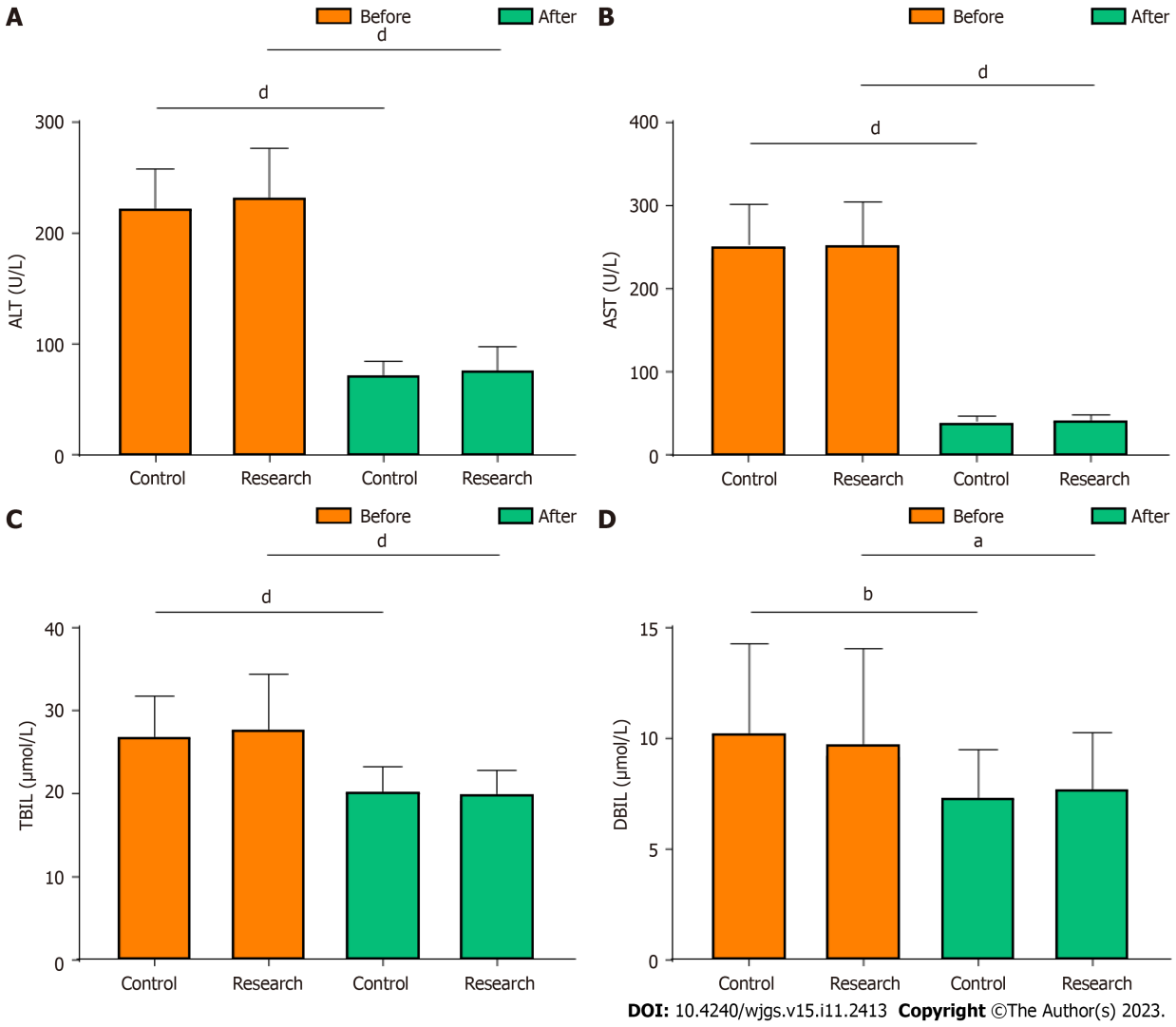

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Figure 1 Liver function indices before and after surgery. A: Alanine aminotransferase; B: Aspartate aminotransferase; C: Total bilirubin; D: Direct bilirubin concentrations before (orange) and after (green) surgery. [a]*P* < 0.05; [b]*P* < 0.01; [d]*P* < 0.0001. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; TBIL: Total bilirubin; DBIL: Direct bilirubin.

duct, is required. Additionally, the lymph nodes around the bile duct, portal vein, and duodenum should be resected as much as possible[4]. However, less than 10% of patients undergo tumor resection through surgery, and nearly 50% have lymph node metastasis[18].

During surgery, instruments may touch cancer cells at the margin, causing them to fall off and form an implantation metastasis[19]. Additionally, tumor dissection can sometimes increase intraperitoneal spread and growth of GC cells owing to their aggressive invasion and adhesion or growth variation. Systemic chemotherapy is frequently administered to patients with unresectable tumors or surgical contraindications. However, the effect of radiotherapy and chemotherapy in most advanced-stage patients is poor; it may prolong progression-free survival, but the five-year survival rate for those with malignant biliary tumors remains at less than 5%[20]. Furthermore, intravenous chemotherapeutic drugs do not easily infiltrate the abdominal cavity; therefore, their effect on tumors is not ideal[21]. Consequently, even if the tumor can be surgically removed, most GCs still progress and metastasize after surgery, highlighting the importance of finding an adjuvant therapy to improve prognosis.

HIPEC is a novel method that combines chemical and physical therapy[22]. This treatment takes advantage of the destructive effect of high temperature on tumor cells, killing them by adding heated chemotherapy drugs into the abdominal cavity[23]. Additionally, high temperatures promote the diffusion of chemotherapy drugs, so the drugs act on tumor cells more effectively. HIPEC treatment can also involve continuous washing through a power pump to increase the probability of contact between the chemotherapeutic drugs and tumor cells. As a result, the chemotherapeutic drugs are maintained at an effective concentration and produce stronger lethality. Compared with intravenous chemotherapy, HIPEC treatment alleviates adverse reactions and improves patient tolerance, delivering a more effective treatment for malignant abdominal tumors[24]. Therefore, HIPEC therapy is a safe and effective treatment suitable for malignant abdominal tumors. In the present study, the incidence of adverse reactions was notably lower in the research group than in the control group. However, liver and kidney function did not differ between the two groups after treatment. Nonetheless, considering this study's small sample size and short observation time, observing and analyzing more cases is

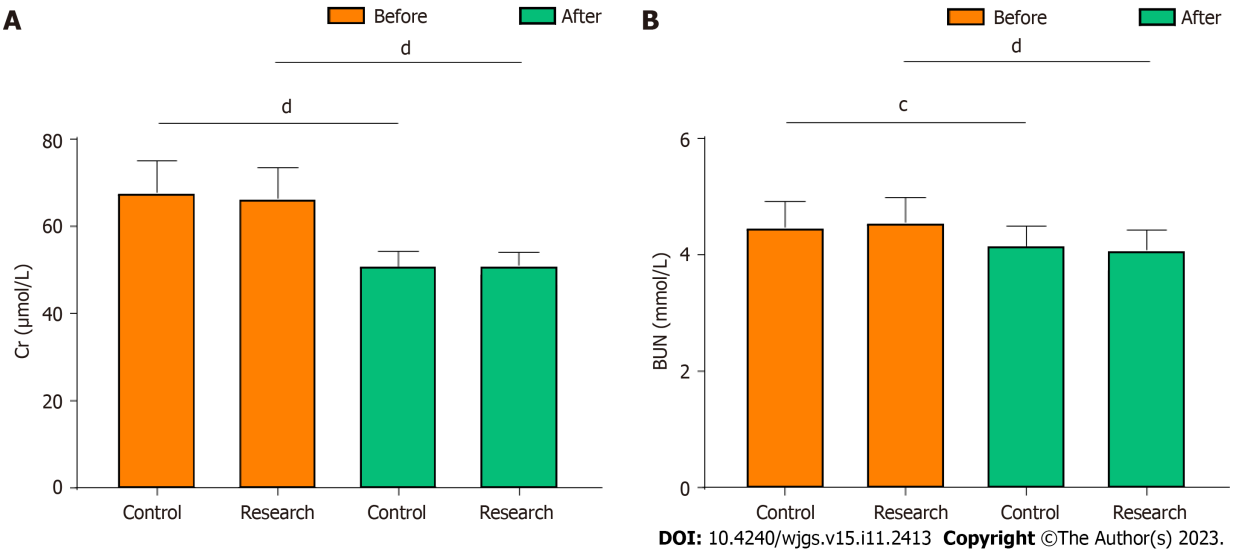

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Figure 2 Renal function markers before and after surgery. A: Creatinine; B: Blood urea nitrogen concentrations before (orange) and after (green) surgery. $^{c}P < 0.001$, $^{d}P < 0.0001$. Cr: Creatinine; BUN: Blood urea nitrogen.

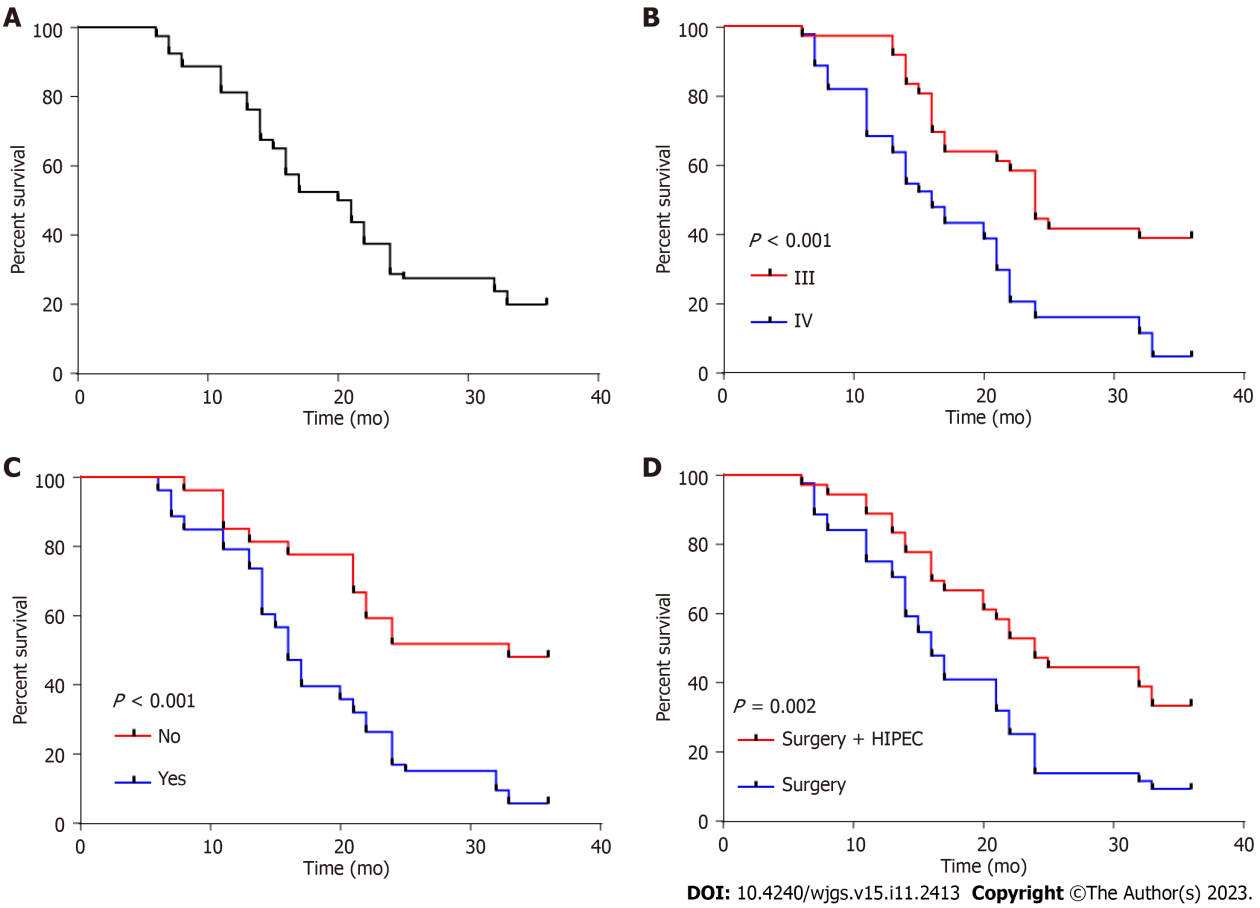

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Figure 3 Three-year survival curves of independent prognostic factors. A: Overall survival; B: Tumor stage; C: Distant metastasis; D: Treatment plan. HIPEC: Hyperthermic intraperitoneal chemotherapy.

necessary.

Finally, we analyzed the prognostic factors affecting three-year patient survival. The tumor stage, distant metastasis, and treatment plan were independent factors affecting prognosis. Many reports have suggested a correlation between tumor stage, distant metastasis, and prognosis in patients with advanced GC[19,25,26]. This study found that CRS combined with HIPEC improves the survival time, indicating that this combination is safe and effective.

Although this study confirmed that CRS combined with HIPEC improves the survival time of patients with advanced GC, there are some limitations. First, this was a single-center study with limited data, which may have resulted in bias in the analysis. Second, this study did not obtain long-term follow-up data from the patients. Therefore, whether the surgical plan affects the long-term prognosis requires further verification. We hope to conduct a prospective study with a longer follow-up period to improve our conclusions.

CONCLUSION

In summary, CRS combined with HIPEC decreases the incidence of adverse reactions and improves survival in patients with advanced GC. Although our study shows the encouraging results of CRS-HIPEC treatment for GC treatment, however, we understand that as a new therapeutic strategy, the long-term impact and efficacy of it need to be verified by further clinical studies.

ARTICLE HIGHLIGHTS

Research background

Gallbladder cancer (GC) is one of the most deadly malignancies worldwide, with a high incidence of peritoneal metastasis, leading to poor prognosis. Despite advances in systemic chemotherapy, survival outcomes remain unsatisfactory. Cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) has been proposed as a promising approach to improve survival and reduce postoperative complications; however, its benefits and risks remain under investigation.

Research motivation

The primary research question was: Is CRS combined with HIPEC efficient and safe for managing GC? The key issues for resolution are the benefits and risks of this combined approach, including its effect on survival rates and postoperative complications compared with CRS. Addressing these questions is paramount to providing evidence-based guidance for clinicians for GC management; it could also potentially revolutionize the treatment paradigm and improve survival rates and quality of life for these patients. Moreover, it opens avenues for further research to optimize CRS-HIPEC protocols and identify patient subgroups that could benefit the most from this approach.

Research objectives

The main objective of this study was to evaluate the efficacy and safety of CRS combined with HIPEC for managing GC. We aimed to comprehensively understand the impact of CRS-HIPEC on survival rates and postoperative complications, which is crucial for future research as it informs clinical decision-making and establishes a foundation for refining treatment protocols.

Research methods

This study employed a retrospective analysis of the medical records of patients with GC treated with CRS-HIPEC. This method allows for a thorough examination of patient outcomes and treatment complications. Additionally, this study includes a comparative analysis of patients receiving CRS, highlighting the novel aspects of the CRS-HIPEC approach.

Research results

CRS-HIPEC significantly improved the survival rates of patients with GC. This study also highlighted an increased risk of certain postoperative complications. These results contribute to the field by providing empirical evidence for the efficacy and safety of CRS-HIPEC.

Research conclusions

CRS-HIPEC significantly improves survival rates but with certain risks. Furthermore, the results of this study underscore the need for personalized patient selection to maximize benefits and minimize complications.

Research perspectives

Future research should focus on optimizing CRS-HIPEC protocols and developing criteria for patient selection, which would enhance the benefits of this approach and mitigate the potential risks. Prospective, randomized controlled trials are also needed to corroborate these findings.

FOOTNOTES

Author contributions: Wu JX, Yao L, and Hua R designed the manuscript; Wu JX performed the study and wrote the manuscript; Yao L supervised the report writing; Hua R contributed to the analysis; Luo XJ and Xie F supervised the report.

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Informed consent statement: All study participants and their legal guardians provided written informed consent.

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ORIGINAL ARTICLE

Retrospective Study

Effect of laparoscopic sleeve gastrectomy on related variables of obesity complicated with polycystic ovary syndrome

Xiao-Tao Wang, Yi-Sen Hou, Hao-Liang Zhao, Jian Wang, Chen-Hao Guo, Jie Guan, Zhi-Gan Lv, Peng Ma, Jian-Li Han

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Peer-review model: Single blind

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Grade B (Very good): 0
Grade C (Good): C, C
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Abstract

BACKGROUND

Polycystic ovary syndrome (PCOS) is closely related to obesity, and weight loss can significantly improve the metabolic, endocrine and reproductive functions of obese individuals with PCOS. However, the efficacy of laparoscopic sleeve gastrectomy (LSG) for obesity with PCOS are unclear.

AIM

The purpose of the study was to investigate the effect of LSG on related variables in obese patients with PCOS.

METHODS

A retrospective analysis was performed on 32 obese patients with PCOS who received LSG treatment at the Third Hospital of Shanxi Medical University from 2013 to 2020. The changes in anthropometric indices, insulin, testosterone, estradiol, follicle stimulating hormone (FSH), luteinizing hormone (LH), menstrual cycle and LH/FSH ratio before and 1 mo, 3 mo, 6 mo and 12 mo after the operation were statistically analyzed.

RESULTS

At 1 mo, 3 mo, 6 mo and 12 mo after surgery, the anthropometric indices, such as body weight and body mass index, of all patients were lower than those before the operation. The percentage excess weight loss (EWL%) at 1 mo, 3 mo, 6 mo and

1 year of follow-up were 25, 40, 46 and 65, respectively. The PCOS-related indices, such as insulin, testosterone, estradiol, follicle stimulating hormone (FSH), luteinizing hormone (LH) and menstrual cycle, were improved to varying degrees. During the 1-year follow-up, the average serum testosterone decreased from preoperative 0.72 ng/mL to 0.43 ng/mL ($P < 0.05$), average fasting insulin level (9.0 mIU/mL, preoperative 34.2 mil, LH level, 4.4 mIU/mL, preoperative 6.1 mIU/mL). The level of FSH (3.8 U/L, 4.8 U/p0.05) and the ratio of LH/FSH (0.7, 1.3/p0.05) were more relieved than those before surgery. During the postoperative follow-up, it was found that the menstrual cycle of 27 patients (nasty 27) returned to normal, and 6 patients (18%) who intended to become pregnant became pregnant within 1 year after surgery.

CONCLUSION

The weight loss effect of LSG is obvious and affirmative, and the endocrine index of obese patients with PCOS is also improved to some extent, although the mechanism is not clear. Laparoscopic sleeve gastrectomy is expected to become a backup choice for patients with polycystic ovaries in the future.

Key Words: Laparoscopic sleeve gastrectomy; Polycystic ovary syndrome; Hyperandrogenism; Insulin resistance

Core Tip: The clinical data of 32 obese patients with polycystic ovary syndrome (PCOS) after laparoscopic sleeve gastrectomy were retrospectively analyzed, and the changes in PCOS after laparoscopic sleeve gastrectomy were analyzed.

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INTRODUCTION

The World Health Organization (WHO) confirms that obesity is a 21st century epidemic that can lead to hormonal imbalances, such as polycystic ovary syndrome (PCOS)[1-3]. PCOS is a common endocrine disease in young women, with a prevalence rate of 5%-18%[4-5]. The widely accepted mechanisms include insulin resistance leading to hyperinsulinemia, stimulating ovarian sheath cells to produce androgen, which is characterized by hypomenorrhea and hyperandrogenemia, and an increased risk of gynecological diseases such as hirsutism, infertility, and ovarian and endometrial cancer[6-8]. The incidence of PCOS in obese women is as high as 50%.

PCOS is closely related to obesity, and an increase in obesity will enhance the severity and expression of the PCOS phenotype. Current data suggest that weight loss is associated with metabolic, endocrine and reproductive improvements in obese women with PCOS. In addition to significant weight loss, bariatric surgery can also lead to recovery of the hypothalamic-pituitary axis, normal menstruation, improvement of hirsutism, reduction of cardiovascular risk, and improvement of fertility[9]. At present, the methods of weight loss are complex and diverse. The two most common types of bariatric surgery are laparoscopic sleeve gastrectomy (LSG) and laparoscopic Roux gastric bypass (LRYGB)[10]. LRYGB is found to be superior in long-term remission of dyslipidemia and hypertension while LSG is relatively low difficulty, small changes to the original structure of the human body and few postoperative complications [11]. Laparoscopic sleeve gastrectomy has been the most commonly performed bariatric procedure since 2014 and continues to steadily increase in number and percentage of all bariatric procedures year after year[12]. In this study, the clinical data of 32 obese patients with PCOS after laparoscopic sleeve gastrectomy were retrospectively analyzed, and the changes in PCOS after laparoscopic sleeve gastrectomy were analyzed.

MATERIALS AND METHODS

General information

The clinical data of 32 patients who were diagnosed with obesity complicated with polycystic ovary syndrome and underwent laparoscopic sleeve gastrectomy in the Department of Weight Loss and Metabolic Surgery of the Third Hospital of Shanxi Medical University from January 2013 to December 2020 were reviewed. Body weight, fasting insulin, testosterone, estrogen, FSH, LH and other endocrine and metabolic indices were statistically analyzed before the operation and 1 mo, 3 mo, 6 mo and 12 mo after the operation. The inclusion criteria were as follows: (1) The diagnosis of obesity was clear, and there were surgical indications according to the guidelines; (2) according to the guidelines, the diagnosis of polycystic ovary syndrome was clear; (3) the patient signed informed consent for the operation and successfully completed laparoscopic sleeve gastrectomy; and (4) there were no postoperative complications or secondary

operations. Exclusion criteria: (1) Polycystic ovary received surgical treatment or nearly 2 mo of treatment; (2) choose other methods of weight loss; and (3) morbid obesity.

Surgical method

After successful anesthesia, the supine split leg position was taken, the skin 1.0 cm was cut along the navel, the visible Trocar was punctured into the abdomen once, and 1.2 cm Trocar was placed on the right side of the umbilical 10 cm; the left clavicle line of 10 cm was disposed into 5 mm Trocar, and a Kirschner needle was placed under the xiphoid process to block the left lobe of the liver, and the omentum tissue was cut off along the great curvature of the stomach, close to the gastric wall, up to 1.5 cm on the left side of the His angle of the cardia, and down to the pyloric 4 cm; a gastric tube approximately 1.2 cm in diameter was placed through the mouth. Close to the pylorus 5 cm, close to the gastric tube, the gastric tissue on the large curved side was resected so that the residual gastric cavity was tubular at approximately 100 mL. Inverted thorns can be absorbed by purse sutures to strengthen the seromuscular layer. The specimen was removed, and it was confirmed that there was no blood oozing or bleeding. The abdomen was closed, and the operation was ended.

Observation index

Body weight-related parameters [body weight, body mass index (BMI), percentage excess weight loss (EWL%)] and polycystic ovary syndrome-related parameters [fasting insulin, testosterone, estrogen, FSH, LH, menstrual cycle and LH/FSH ratio] were measured before and 1, 3, 6 and 12 mo after the operation.

Statistical methods

SPSS 23.0 statistical software was used. The measurement data in accordance with the normal distribution are expressed as the mean ± standard deviation (mean ± SD), and the counting data are expressed as n (%). The related indices before and after the operation were compared by paired sample t tests, and $P < 0.05$ was considered statistically significant.

RESULTS

Between January 2013 and December 2020, 32 obese women with PCOS participated in the study and underwent surgery without intraoperative or postoperative complications. The baseline information of 32 patients were shown in Table 1. The average age of the sample was 33.78 ± 7.31 years old. The body weight and BMI decreased significantly at 1, 3, 6 and 12 mo after the operation (mean preoperative = 41.22 kg/m^2; postoperative mean = 28.98 kg/m^2). The patient's body mass and BMI were basically stable at 1 year after the operation. See Table 2 and Figure 1.

During the postoperative period, the average level of estradiol increased (mean preoperatively = 81.1 PG/dL; postoperative mean = 89.2 pg/dL), and the difference was not statistically significant. The average serum testosterone decreased from 0.72 ng/mL to 0.43 ng/mL ($P = 0.05$), and the insulin level decreased significantly after the operation (preoperative value = 34.2 mIU/mL; postoperative insulin level = 9.0 mIU/mL). After the operation, the level of FSH decreased (mean before the operation = 4.8 U/L, average after the operation = 3.8 U/L), and the difference was not statistically significant. At the same time, the level of LH decreased significantly after the operation ($P < 0.05$) (mean preoperative = 6.1 U/L; postoperative mean = 4.4 U/L). The average LH/FSH ratio decreased after the operation (1.3 before and after the operation). The preoperative average value was greater than 1, indicating that the level of LH was higher than that of FSH. On the other hand, after surgical treatment, it was found that the average ratio was less than 1, indicating that the average FSH level after bariatric surgery was higher than that of LH. The decrease in the LH/FSH ratio was statistically significant ($P = 0.05$). The menstrual cycle of 27 patients (nasty 27, 84%) returned to normal, and 6 patients (18%) who intended to become pregnant became pregnant within 1 year after the operation. See Table 3.

DISCUSSION

According to the clinical research and theoretical basis of PCOS for many years, China's Diagnostic Criteria of Polycystic Ovary Syndrome[13] points out that oligomenorrhea or amenorrhea is a necessary diagnostic condition. In addition, hyperandrogenaemia and/or clinical manifestations and ultrasound polycystic ovaries are nonessential conditions, and one of them can diagnose polycystic ovary syndrome[14]. Clinical hyperandrogenism can be detected by the serum testosterone index. Normal serum testosterone in females is generally below 0.68 ng/L. If it exceeds 0.7 ng/L, it can be diagnosed as hyperandrogenemia. The symptoms can be characterized by exuberant hair growth, male characteristics, oligomenorrhea or amenorrhea. High serum androgen levels directly inhibit follicle stimulating hormone secretion and eventually lead to infertility. The indices of FSH and LH in patients with polycystic ovary syndrome are higher than normal to varying degrees. The ratio of LH/FSH can also be used as an important index for the diagnosis of polycystic ovary syndrome. The pathogenesis of PCOS is not clear, and genetic, environmental and other factors interact with each other. The widely accepted theory is that hyperandrogenemia and hyperinsulinemia caused by insulin resistance are its characteristics. In this study, insulin was also used as an important indicator to evaluate the remission of PCOS[15].

According to the diagnostic criteria of polycystic ovary syndrome, the testosterone index was used as the indication of hyperandrogenism, the insulin index was used as the manifestation of insulin resistance, and oligoovulation showed abnormal gonadotropin secretion, which could be observed by FSH and LH. The changes in related indices in patients with PCOS before and after the operation were analyzed. Anovulation in patients with PCOS is characterized by

Table 1 Baseline information of 32 patients

Characteristic	*n* = 32
Age, yr	33.78 ± 7.31
Marital status	
Unmarried	6 (18.8)
Married	24 (75.0)
Divorced	2 (6.2)
Smoking	4 (12.5)
Alcohol	3 (9.4)

Table 2 Changes of anthropometric indexes before and after operation

Time	Weight (kg)	BMI (kg/m^2)	EWL (%)
Preoperative	113.39 ± 21.25	41.22 ± 6.35	-
1 mo after operation	106.33 ± 20.12[a]	36.78 ± 6.26[a]	25
3 mo after operation	93.36 ± 18.89[a]	33.76 ± 5.81[a]	40
6 mo after operation	85.67 ± 17.47[a]	30.34 ± 5.1[a]	46
12 mo after operation	81.28 ± 14.38[a]	28.98 ± 5.52[a]	65

[a]$P < 0.05$, and at each time point after operation, it was compared with that before operation.
Compared with that before operation. BMI: Body mass index; EWL%: Percentage excess weight loss.

Table 3 Changes of polycystic ovary syndrome related indexes before and after operation

Time	Estradiol (pg/dL)	Testosterone (ng/mL)	Insulin (mIU/mL)	LH (U/L)	FSH (U/L)	LH/FSH
Preoperative	81.1 ± 25.6	0.72 ± 0.32	34.2 ± 16.0	6.1 ± 2.0	4.8 ± 1.6	1.3 ± 0.6
1 mo after operation	83.4 ± 21.2	0.68 ± 0.29[a]	30.3 ± 12.8[a]	6.3 ± 1.8[a]	5.3 ± 2.1	1.1 ± 0.5[a]
3 mo after operation	78.7 ± 18.8	0.57 ± 0.24[a]	24.8 ± 9.2[a]	5.8 ± 2.4[a]	5.5 ± 1.8	1.1 ± 0.5[a]
6 mo after operation	82.6 ± 16.4	0.51 ± 0.25[a]	15.8 ± 6.1[a]	5.5 ± 2.2[a]	5.0 ± 2.5	0.9 ± 0.4[a]
12 mo after operation	89.2 ± 29.3	0.43 ± 0.19[a]	9.0 ± 2.5[a]	4.4 ± 1.9[a]	3.8 ± 2.3	0.7 ± 0.4[a]

[a]$P < 0.05$, and at each time point after operation, it was compared with that before operation.
Compared with that before operation. LH: Luteinizing hormone; FSH: Follicle stimulating hormone.

abnormal secretion of gonadotropin, which is usually characterized by increased serum LH concentration and normal or low FSH, resulting in an increase in the ratio of LH/FSH. Clinically, the ratio is used as an index to predict ovarian reserve function, and an increase in the ratio indicates a decrease in female ovarian reserve function[16]. In this study, there were important changes in gonadotropin secretion after LSG; that is, FSH synthesis increased, and LH synthesis decreased, resulting in the reversal of the LH/FSH ratio. In this way, in addition to the reduction in plasma insulin, it helps to reduce hyperandrogenemia, promote the complete development of antral follicles and is conducive to ovulation. During the return visit, we found that some patients became pregnant within six months after the operation. This study did not evaluate the long-term effects of reproductive parameters such as infertility, but a systematic review published by Dağ *et al*[17] showed that bariatric surgery can significantly improve menstrual irregularity and hirsutism, and fertility may be improved after bariatric surgery. The ovulation process leads to the formation of the corpus luteum and the continuous release of progesterone from the luteal structure, which reduces the risk of endometrial hyperplasia and cancer[13]. Gonadotropin levels show hormonal oscillations during the menstrual cycle, which makes the study of gonadotropin more meaningful by taking the LH/FSH ratio as a variable rather than just focusing on a gonadotropin index. In this study, LH showed a downward trend compared with that before the operation, the change in FSH showed periodic changes, and LH/FSH was significantly improved compared with that before the operation. During the follow-up, it was also found that the menstrual cycle of 27 patients returned to normal, and 6 patients with pregnancy intention (18%) became pregnant within 1 year after the operation. According to the guidelines, women of childbearing age should avoid pregnancy for at least one year after weight loss, mainly because of the patient's own nutritional status and

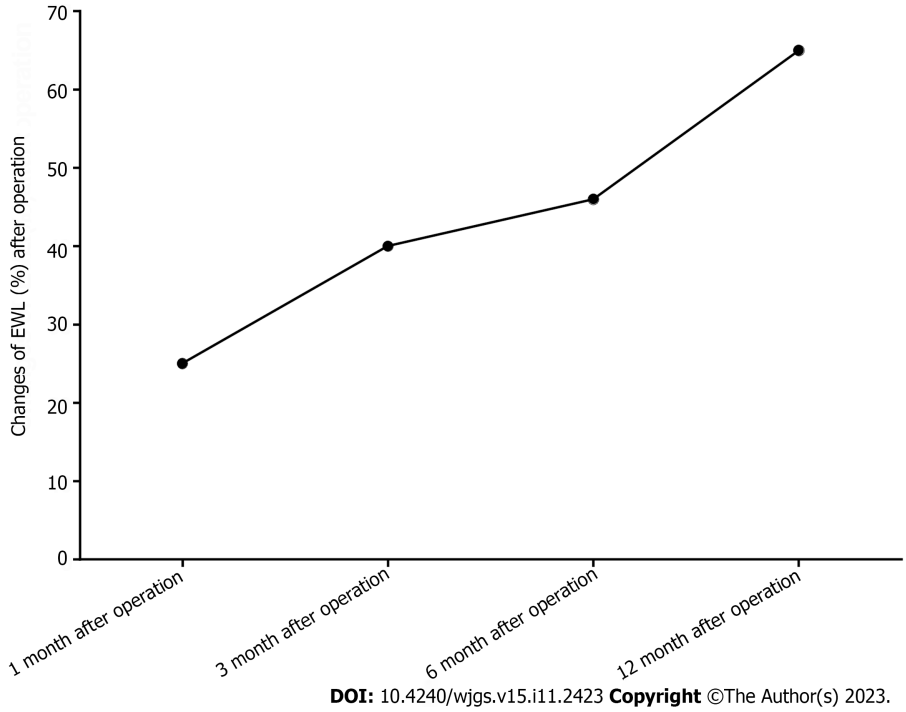

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Figure 1 Changes of percentage excess weight loss after operation.

physical recovery. In this study, some patients became pregnant within 1 year after the operation due to age, family and other factors; that is, laparoscopic sleeve gastrectomy has a definite effect on obesity complicated with polycystic ovary syndrome.

The fasting insulin level reflects compensatory hyperinsulinemia. The diagnostic criterion of insulin resistance is that fasting insulin is greater than or equal to 85 pmol/L, especially in patients with hypertension and obesity. Fat accumulation often weakens the biological activity of insulin and makes the body resistant to insulin. Although the effects of obesity are different, it interferes with the pathophysiology of PCOS and affects insulin resistance and hyperinsulinemia [15]. Hyperinsulinemia stimulates androgen production and maintains abnormal gonadotropin secretion in the pituitary gland. In contrast, weight loss can improve insulin resistance, reduce circulating LH concentration, and increase reproductive potential[18]. In this study, it was observed that the level of serum insulin decreased from 34.2 mIU/mL to 9 mIU/mL, which reflected the improvement of insulin resistance and had a positive effect on the attenuation of androgen, resulting in the secretion of gonadotropin tending to normal. The above results can be explained by the increase in postoperative gastric emptying, which further leads to a decrease in GLP-1-mediated insulin secretion and related auxin-releasing peptide and leptin, thus increasing serum insulin and reducing insulin resistance[19].

In this study, EWL% finally reached 65% and stabilized 12 mo after the operation, and BMI gradually decreased to 28.98 at 12 mo after the operation ($P < 0.05$), which confirmed the significant weight loss effect of LSG. During the postoperative follow-up, it was found that 15 patients with acanthosis nigricans improved to varying degrees. At present, the etiology of acanthosis nigricans is not clear, and it is often associated with abnormal metabolism of hormones and insulin and is often associated with polycystic ovary syndrome. It is undeniable that the improvement of acanthosis nigricans is related to polycystic ovary syndrome. However, the specific mechanism and causality still need to be further studied. Hyperandrogenemia can also show hirsutism, especially in female patients. Although there was no specific score in this study, it was found that the endocrine and metabolic indices gradually stabilized and hirsutism significantly improved during the follow-up.

CONCLUSION

In summary, LSG can improve hyperandrogenaemia and irregular menstruation in obese patients with PCOS, significantly reduce weight loss and improve a series of complications related to PCOS. such as acanthosis nigricans and hirsutism. Laparoscopic sleeve gastrectomy can improve patients' physical, hormonal and reproductive indicators and can be considered part of the treatment of infertility in obese patients. Further research is needed to draw more reliable conclusions.

ARTICLE HIGHLIGHTS

Research background

Polycystic ovary syndrome (PCOS) is a common endocrine disease in young women, with a prevalence rate of 5%-18%. PCOS is closely related to obesity, and an increase in obesity will enhance the severity and expression of the PCOS phenotype.

Research motivation

The efficacy of laparoscopic sleeve gastrectomy (LSG) for obesity with PCOS are still unclear.

Research objectives

The purpose of the study was to investigate the effect of LSG on related variables in obese patients with PCOS.

Research methods

The clinical data of 32 patients who were diagnosed with obesity complicated with polycystic ovary syndrome and underwent laparoscopic sleeve gastrectomy from January 2013 to December 2020 were reviewed. The changes in anthropometric indices, insulin, testosterone, estradiol, follicle stimulating hormone (FSH), luteinizing hormone (LH), menstrual cycle and LH/FSH ratio before and 1 mo, 3 mo, 6 mo and 12 mo after the operation were statistically analyzed.

Research results

The patient's body mass and BMI were basically stable at 1 year after the operation. During the postoperative period, the average level of estradiol increased; the average serum testosterone and the insulin level decreased significantly after the operation. On the other hand, after surgical treatment, it was found that the average ratio was less than 1, indicating that the average FSH level after bariatric surgery was higher than that of LH.

Research conclusions

Laparoscopic sleeve gastrectomy can improve hyperandrogenaemia and irregular menstruation in obese patients with polycystic ovary syndrome, significantly reduce weight loss and improve a series of complications related to polycystic ovary syndrome.

Research perspectives

The impact of laparoscopic sleeve gastrectomy on obese patients with polycystic ovary syndrome's physical, hormonal and reproductive indicators.

FOOTNOTES

Author contributions: Wang XT and Han JL contributed to protocol/project development; Wang XT, Hou YS, Zhao HL, Wang J, Guo CH, and Han JL contributed to data collection or management; Wang XT, Guan J, Lv ZG, Ma P, and Han JL contributed to data analysis; Wang XT, and Han JL contributed to manuscript writing/editing; All authors reviewed the manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Advantage of log odds of positive lymph nodes in prognostic evaluation of patients with early-onset colon cancer

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Abstract

BACKGROUND

Colon cancer (CC) is one of the most common cancers of the digestive tract, the third most common cancer worldwide, and the second most common cause of cancer-related deaths. Previous studies have demonstrated a higher risk of lymph node metastasis (LNM) in young patients with CC. It might be reasonable to treat patients with early-onset locally advanced CC with extended lymph node dissection. However, few studies have focused on early-onset CC (ECC) patients with LNM. At present, the methods of predicting and evaluating the prognosis of ECC patients with LNM are controversial.

AIM

To compare the prognostic values of four lymph node staging indices and establish the best nomogram for patients with ECC.

METHODS

From the data of patients with CC obtained from the Surveillance, Epidemiology, and End Results (SEER) database, data of young patients with ECC (≤ 50 years old) was screened. Patients with unknown data were excluded from the study, while the remaining patients were included. The patients were randomly divided into a training group (train) and a testing group (test) in the ratio of 7:3, while building the model. The model was constructed by the training group and verified by the testing group. Using multiple Cox regression models to compare the prediction efficiency of LNM indicators, nomograms were built based on the best model selected for overall survival (OS) and cause-specific survival (CSS). In

the two groups, the performance of the nomogram was evaluated by constructing a calibration plot, time-dependent area under the curve (AUC), and decision curve analysis. Finally, the patients were grouped based on the risk score predicted by the prognosis model, and the survival curve was constructed after comparing the survival status of the high and low-risk groups.

RESULTS

Records of 26922 ECC patients were screened from the SEER database. N classification, positive lymph nodes (PLN), lymph node ratio (LNR) and log odds of PLN (LODDS) were considered to be independent predictors of OS and CSS. In addition, independent risk factors for OS included gender, race, marital status, primary site, histology, grade, T, and M classification, while the independent prognostic factors for CSS included race, marital status, primary site, grade, T, and M classification. The prediction model including LODDS is composed of minimal Akaike information criterion, maximal concordance indexes, and AUCs. Factors including gender, race, marital status, primary site, histology, grade, T, M classification, and LODDS were integrated into the OS nomogram, while race, marital status, primary site, grade, T, M classification, and LODDS were included into the CSS nomogram. The nomogram representing both cohorts had been successfully verified in terms of prediction accuracy and clinical practicability.

CONCLUSION

LODDS is superior to N-stage, PLN, and LNR of ECC. The nomogram containing LODDS might be helpful in tumor evaluation and clinical decision-making, since it provides an appropriate prediction of ECC.

Key Words: Early-onset colon cancer; Log odds of positive lymph nodes; Lymph node metastasis; Nomogram; Prognosis; Surveillance, Epidemiology, and End Results

Core Tip: Few studies have focused on early-onset colon cancer (ECC) patients with lymph node metastasis. This study compared the prognostic value of four lymph node staging indexes. It is shown that log odds of positive lymph nodes (LODDS) is superior to N-stage, positive lymph nodes, and lymph node ratio of ECC. Subsequently, the nomogram containing LODDS was established and provides an appropriate prediction of ECC, which may be helpful in tumor evaluation and clinical decision-making.

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INTRODUCTION

Colon cancer (CC) is one of the most common cancers of the digestive tract, the third most common cancer in the world, and the second leading cause of cancer-related deaths[1]. Although medical technology and prevention policies in addition to advances in colonoscopy screening and treatment have enabled a reduction in the morbidity and mortality associated with colorectal cancer (CRC) in elderly patients[2], an opposite trend has been observed in young people under the age of 50[3]. The incidence of early-onset CRC (EOCRC), defined as CRC diagnosed before the age of 50 is increasing worldwide. A previously conducted study has reported that about 11% of CRC cases registered in the National Cancer Database had been diagnosed in adults between the ages 18-49 years[4]. Similarly, the latest data from Europe indicates that the incidence of CRC in subjects aged 4-9 years, 1-6 years, and 20-29 years has increased by 30.39%, 40.49%, and 2004.20%, respectively in last seven to nine years[5]. Although the prevalence of CRC is still relatively limited in the younger population (0.12%), the alarming increase in EOCRC patients cannot be ignored[1]. Compared with late-onset CRC, most early-onset CC (ECC) patients tend to ignore the occult incidence of CRC, which leads to a late-stage diagnosis and poor prognosis.

The first choice for the treatment for locally advanced CC is radial resection. Colectomy has been shown to be associated with a greater survival advantage[6], and complete mesocolic excision has become the preferred treatment option for colorectal surgeons[7]. In addition, with the emergence and development of endoscopic technology, CRC surgery is further benefited due to the application of laparoscopy and robot-assisted laparoscopy[8]. With regards to lymph node dissection, there is a consensus that, specimens after radical surgery for CC should contain at least 12 regional lymph nodes in accordance with the recommendations in the NCCN guidelines[9]. However, previously conducted studies have demonstrated that a higher risk of lymph node metastasis (LNM) is observed in young patients with CC[10], because of which extended lymph node dissection might be a more reasonable choice for treating patients

with early-onset locally advanced CC. One of the main causes of poor prognosis and frequent recurrence is LNM. Large population-based cohort studies have demonstrated a high incidence of LNM in patients with ECC. These studies have also indicated that 60% of patients with stages III or IV-ECC develop LNM[11]. Previously conducted studies have considered factors such as the location of the primary tumor, histopathological grade, tumor-node-metastasis (TNM) stage, carcinoembryonic antigen level, and tumor size for evaluating the prognosis[12]. However, studies focusing on ECC patients with LNM are rare. The current methods of predicting and evaluating the prognosis of ECC patients with LNM are controversial[13]. Previous prognostic models ignored a different number of anatomical regional lymph nodes, which could compromise the accuracy of the prognostic predictions. In addition, along with individual differences in the pattern of regional LNM, there is a lack of consensus on the optimum extent of intraoperative lymph node dissection. Therefore, new LNM indicators are urgently required to develop better prognostic nomograms that would enable the prediction of overall survival (OS) and cause-specific survival (CSS) in patients with ECC.

In the past, several scholars have proposed several prognostic factors of lymph nodes including the number of positive lymph nodes (PLN)[14], the number of negative lymph nodes[15,16], and lymph node ratio (LNR) for estimating the prognosis of ECC patients[17-19]. In recent years, the log odds of PLN (LODDS) have proven reliable for many tumor types[20,21]. Some studies have found LODDS to be more efficient in predicting the prognosis of CC patients compared with American joint committee of cancer (AJCC)-N classification and LNR[22-24]. However, prediction of CSS were unexplored in these studies, nor did they further establish clinical prognostic nomograms.

The study analyzed the data of the Surveillance, Epidemiology, and End Results (SEER) database to compare the predictive values of different lymph nodes indicators in ECC patients. Subsequently, establishing a new nomogram including LODDS for predicting OS and CSS, and successfully verifying it on the testing group.

MATERIALS AND METHODS

Data source

Data of CC patients was obtained from the SEER database of the National Cancer Institute program, which is one of the most representative oncology databases. Since the data was downloaded from public databases, ethical approval for this study was exempted. The exclusion criteria for data extraction included: (1) Patients aged < 18 years or > 50 years at the time of diagnosis; (2) Patients with lymph nodes (ELN) and PLN without resection of lymph nodes or unclear lymph nodes examination; (3) Patients with unclear T-stage, N-stage, stage, and grade; and (4) Patients with unclear survival data. Finally, 26922 patients diagnosed with ECC following radical resection of CC were recruited for the study, and they were randomly divided into a training group (n = 18845, 70%) and a testing group (n = 8077, 30%) in a ratio of 7:3 (Figure 1).

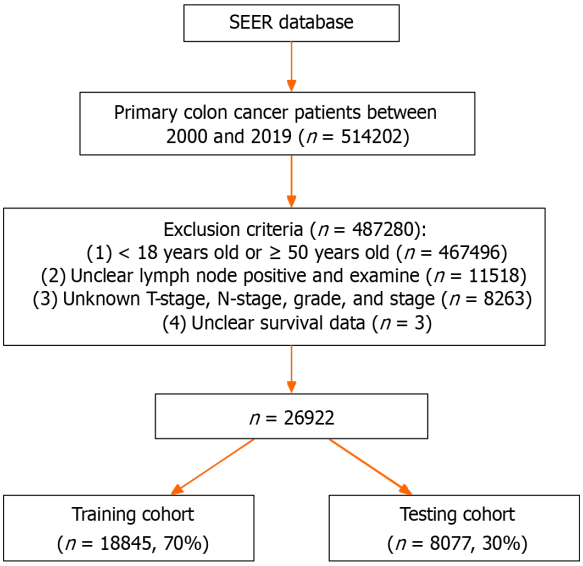

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Figure 1 The flowchart of data collection and grouping for early-onset colon cancer patients. 26922 patients with ECC after radical resection of colon cancer were enrolled and randomly divided into a training group (n = 18845, 70%) and a testing group (n = 8077, 30%).

Measurement of variables

Patient variables including age, sex, primary site and pathology, tumor size and grade, TNM classification, number of regional ELN and PLN, survival time, and status were collected for the study. Race was divided into four subgroups: White, black, other, and unknown. The "Other" subgroup included American Indian, AK Native, Asian, and Pacific Islanders. Marital status was divided into two subgroups, namely married and others/unknown. The primary site was

divided into right colon (transverse colon), left colon, and large intestine (NOS). Histology was divided into three subgroups: Adenomas/adenocarcinomas, cystic/mucinous/serous neoplasms, and others. The grade was divided into four subgroups, namely well, moderate, poor, and undifferentiated. The stage was divided into: Stage 0, stage I, stage II, stage III, and stage IV. T-stage was divided into five subgroups, namely T0, T1, T2, T3, and T4. N-stage was divided into three subgroups: N0, N1, and N2. M-stage was divided into three subgroups: M0, and M1. The size was divided into three subgroups: < 5 cm, ≥ 5 cm, and unknown.

Staging was determined in accordance with the sixth edition of the AJCC staging system. LNR was defined as the ratio of the amount of PLN to ELN. LODDS is determined in accordance with the reaction: log[(PLN + 0.5)/(ELN - PLN + 0.5)]. 0.5 was added to both numerator and the denominator, to avoid division by the zero error. The primary and secondary endpoints are OS and CSS, which have been indicated in the SEER database as "COD to site recording" and "SEER cause-specific death classification", respectively.

Independence and prediction performance comparison of lymph nodes status indicators

Clinicopathological predictors with univariate Cox regression analysis were selected through the "survival" R package of OS and CSS in the training group. Each lymph nodes status factor (including N classification, PLN, LNR, and LODDS), was integrated with other risk variables into a multivariate regression model for further evaluation of the predicted value. The predicted value for the univariate analysis was $P < 0.05$. The above models respectively use the Akaike information criterion (AIC) was employed by the above models as the stop rule, which adopted backward step-by-step selection (through the "MASS" R packet). The model with the minimum AIC was selected as the best model. The prediction efficiencies of these filtering models with different lymph nodes factors were compared by the "risk regression" R package using AIC, bootstrapped concordance index (C-index), and the area under the curve (AUC).

Construction and verification of nomograms

The nomograms, which were developed by integrating variables with the highest precision from the filtering model, were used to predict the OS and CSS in the training group (through the "rms" R package). The C-index, AUC, and calibration plots in the training group and testing group were used to evaluate the efficiency of the nomogram. The "ggDCA" R package was used to evaluate the net income and clinical performance of the nomograms based on a decision curve analysis (DCA) generated in advance.

Survival risk classifiers established by nomograms

The "nomogram formula" R package was used to apply the multivariate Cox regression formula of OS and CSS nomograms formed in the training group to the patients in the two groups. All patients were divided into a high-risk group and a low-risk group based on the total score calculated by the "survminer" R package. The survival differences of OS and CSS between the two risk groups were evaluated using the Kaplan-Meier method.

Statistical analysis

The counting data were expressed as an example (%), and the comparison between groups was conducted using χ^2 test. The measurement data of normal distribution were expressed by mean ± SD, and the comparison between groups was done using the independent sample *t*-test. The measurement data of non-normal distribution were expressed by median (interquartile range), and the comparison between the groups was done with the Mann-Whitney *U* nonparametric test with $P < 0.05$ indicating statistical significance. The R software was used for all statistical analyses.

RESULTS

Patient characteristics and survival

The characteristics of the training group and testing group of the patients have been depicted in Table 1. The median follow-up times of the training group and the testing group in the whole SEER database were 51 mo [95% confidence interval (CI): 21-106] and 50 mo (95%CI: 21-103), respectively. Additionally, there was insignificant difference in the indices of the training group and the testing group ($P > 0.05$).

Prognostic analyses for OS and CSS

Table 2 depicts the detailed results of the univariate Cox regression analysis in the training group. The important risk factors for OS were gender, race, marital status, primary site, histology, grade, T-stage, N-stage, M-stage, PLN, LNR, and LODDS. The important prognostic factors for CSS included race, marital status, primary site, histology, grade, T-stage, N-stage, M-stage, PLN, LNR, and LODDS.

We further generated prognostic models, including different lymph nodes indicators after conducting amultivariate analysis. In short, as evident from Tables 3 and 4, N classification, PLN, LNR, and LODDS are independent risk factors for OS and CSS, respectively. In addition, the independent prognostic factors for OS were gender, race, marital status, primary site, histology, grade, T, and M classification; while the independent risk factors for CSS were race, marital status, primary site, grade, T, and M classification.

Comparison of N classification, PLN, LNR, and LODDS

The comparison of lymph nodes status indicators in the training group is shown in Table 5. The C-index of the filter

Table 1 Clinical and pathologic characteristics of patients with early-onset colon cancer in two cohorts

Characteristics	Overall	Training set	Testing set	*P* value
	n = 26922	*n* = 18845	*n* = 8077	
Age	44.00 (39.00, 47.00)	44.00 (39.00, 47.00)	44.00 (39.00, 47.00)	0.730
LN examined	19.00 (14.00, 27.00)	19.00 (14.00, 27.00)	19.00 (14.00, 27.00)	0.959
LN positive	1.00 (0.00, 4.00)	1.00 (0.00, 4.00)	1.00 (0.00, 4.00)	0.800
LNR	0.03 (0.00, 0.19)	0.03 (0.00, 0.19)	0.03 (0.00, 0.20)	0.851
LODDS	-2.66 (-3.66, -1.29)	-2.66 (-3.61, -1.30)	-2.71 (-3.66, -1.24)	0.881
Survival months	51.00 (21.00, 105.00)	51.00 (21.00, 106.00)	50.00 (21.00, 103.00)	0.169
Gender (%)				0.856
Female	13367 (49.7)	9364 (49.7)	4003 (49.6)	
Male	13555 (50.3)	9481 (50.3)	4074 (50.4)	
Race (%)				0.898
White	19659 (73.0)	13783 (73.1)	5876 (72.7)	
Blake	4050 (15.0)	2829 (15.0)	1221 (15.1)	
Others	2985 (11.1)	2073 (11.0)	912 (11.3)	
Unknown	228 (0.8)	160 (0.8)	68 (0.8)	
Marital status (%)				0.383
Married	15296 (56.8)	10674 (56.6)	4622 (57.2)	
Others/unknown	11626 (43.2)	8171 (43.4)	3455 (42.8)	
Primary site (%)				0.783
Right colon	13053 (48.5)	9139 (48.5)	3914 (48.5)	
Left colon	13342 (49.6)	9330 (49.5)	4012 (49.7)	
Large intestine, NOS	527 (2.0)	376 (2.0)	151 (1.9)	
Histology (%)				0.995
Adenomas/adenocarcinomas	23406 (86.9)	16384 (86.9)	7022 (86.9)	
Cystic/mucinous/serous neoplasms	3324 (12.3)	2326 (12.3)	998 (12.4)	
Others	192 (0.7)	135 (0.7)	57 (0.7)	
Grade (%)				0.055
Well	2775 (10.3)	1992 (10.6)	783 (9.7)	
Moderately	18265 (67.8)	12708 (67.4)	5557 (68.8)	
Poorly	5094 (18.9)	3603 (19.1)	1491 (18.5)	
Undifferentiated	788 (2.9)	542 (2.9)	246 (3.0)	
Stage (%)				0.198
Stage 0	204 (0.8)	136 (0.7)	68 (0.8)	
Stage I	3939 (14.6)	2792 (14.8)	1147 (14.2)	
Stage II	7360 (27.3)	5103 (27.1)	2257 (27.9)	
Stage III	9806 (36.4)	6914 (36.7)	2892 (35.8)	
Stage IV	5613 (20.8)	3900 (20.7)	1713 (21.2)	
T stage (%)				0.437
T0	210 (0.8)	142 (0.8)	68 (0.8)	
T1	2595 (9.6)	1845 (9.8)	750 (9.3)	
T2	2801 (10.4)	1985 (10.5)	816 (10.1)	

T3	15121 (56.2)	10537 (55.9)	4584 (56.8)	
T4	6195 (23.0)	4336 (23.0)	1859 (23.0)	
N stage (%)				0.259
N0	12410 (46.1)	8645 (45.9)	3765 (46.6)	
N1	7886 (29.3)	5576 (29.6)	2310 (28.6)	
N2	6626 (24.6)	4624 (24.5)	2002 (24.8)	
M stage (%)				0.351
M0	21309 (79.2)	14945 (79.3)	6364 (78.8)	
M1	5613 (20.8)	3900 (20.7)	1713 (21.2)	
Size (%)				0.871
< 5 cm	9238 (34.3)	6476 (34.4)	2762 (34.2)	
≥ 5 cm	9179 (34.1)	6434 (34.1)	2745 (34.0)	
Unknown	8505 (31.6)	5935 (31.5)	2570 (31.8)	

LNR: Lymph node ratio; LODDS: Log odds of positive lymph node.

Table 2 Univariate Cox regression analyses for predicting overall survival and cause-specific survival in the training cohort

Characteristics	OS		CSS	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Age	1.004 (0.999-1.008)	0.090	1.000 (0.995-1.005)	0.896
Gender	1.096 (1.040-1.156)	0.001[a]	1.058 (0.996-1.123)	0.067
Race	1.050 (1.013-1.090)	0.009[a]	1.073 (1.030-1.118)	0.001[a]
Marital status	1.330 (1.262-1.402)	< 0.001[a]	1.282 (1.208-1.362)	< 0.001[a]
Primary site	0.926 (0.881-0.974)	0.003[a]	0.926 (0.875-0.980)	0.007[a]
Histology	1.501 (1.409-1.599)	< 0.001[a]	1.498 (1.394-1.609)	< 0.001[a]
Grade	1.696 (1.631-1.764)	< 0.001[a]	1.774 (1.698-1.853)	< 0.001[a]
Stage	3.267 (3.149-3.389)	< 0.001[a]	4.102 (3.922-4.290)	< 0.001[a]
T stage	2.258 (2.169-2.350)	< 0.001[a]	2.566 (2.448-2.690)	< 0.001[a]
N stage	2.347 (2.271-2.426)	< 0.001[a]	2.653 (2.552-2.757)	< 0.001[a]
M stage	7.380 (6.988-7.793)	< 0.001[a]	8.790 (8.262-9.351)	< 0.001[a]
LN examined	0.989 (0.987-0.991)	< 0.001[a]	0.988 (0.985-0.991)	< 0.001[a]
LN positive	1.085 (1.082-1.087)	< 0.001[a]	1.088 (1.085-1.090)	< 0.001[a]
LNR	14.557 (13.403-15.811)	< 0.001[a]	17.876 (16.324-19.575)	< 0.001[a]
LODDS	1.562 (1.541-1.584)	< 0.001[a]	1.630 (1.605-1.656)	< 0.001[a]
Size	1.006 (0.970-1.043)	0.759	0.999 (0.959-1.040)	0.955

[a]$P < 0.05$.

OS: Overall survival; CSS: Cause-specific survival; HR: Hazard ratio; CI: Confidence interval; LNR: Lymph node ratio; LODDS: Log odds of positive lymph node.

model containing LODDS was higher than that of N classification, PLN, and LNR; when compared with the above prognostic models. In addition, the selected model containing LODDS has the least AIC. Additionally, the 1-year, 3-year, 5-year, and 10-year AUCs of the selected models, including LODDS, were higher than those of other models. To sum up, the selected model including LODDS is more efficient in the predictions of OS and CSS, and LODDS might be the strongest predictor of N classification, PLN, and LNR.

Table 3 Multivariate Cox regression analyses for predicting overall survival in the training cohort

Characteristics	N-stage		PLN		LNR		LODDS	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Gender	1.131 (1.073-1.193)	< 0.001[a]	1.103 (1.046-1.164)	< 0.001[a]	1.120 (1.062-1.181)	< 0.001[a]	1.120 (1.062-1.181)	< 0.001[a]
Race	1.046 (1.008-1.086)	0.017[a]	1.058 (1.020-1.098)	0.003[a]	1.048 (1.010-1.088)	0.013[a]	1.045 (1.007-1.085)	0.019[a]
Marital status	1.300 (1.233-1.371)	< 0.001[a]	1.289 (1.223-1.360)	< 0.001[a]	1.307 (1.239-1.378)	< 0.001[a]	1.310 (1.243-1.382)	< 0.001[a]
Primary site	0.901 (0.856-0.948)	< 0.001[a]	0.934 (0.888-0.983)	0.008[a]	0.891 (0.847-0.938)	< 0.001[a]	0.873 (0.830-0.919)	< 0.001[a]
Histology	1.184 (1.108-1.264)	< 0.001[a]	1.089 (1.019-1.164)	0.012[a]	1.120 (1.048-1.197)	0.001[a]	1.125 (1.052-1.202)	0.001[a]
Grade	1.256 (1.205-1.309)	< 0.001[a]	1.284 (1.232-1.338)	< 0.001[a]	1.238 (1.188-1.290)	< 0.001[a]	1.230 (1.180-1.281)	< 0.001[a]
T-stage	1.433 (1.373-1.495)	< 0.001[a]	1.485 (1.425-1.549)	< 0.001[a]	1.456 (1.396-1.518)	< 0.001[a]	1.439 (1.380-1.501)	< 0.001[a]
M-stage	4.645 (4.378-4.928)	< 0.001[a]	5.074 (4.783-5.382)	< 0.001[a]	4.484 (4.220-4.764)	< 0.001[a]	4.254 (4.003-4.519)	< 0.001[a]
N-stage	1.636 (1.578-1.697)	< 0.001[a]	/	/	/	/	/	/
PLN	/	/	1.048 (1.044-1.052)	< 0.001[a]	/	/	/	/
LNR	/	/	/	/	4.736 (4.303-5.213)	< 0.001[a]	/	/
LODDS	/	/	/	/	/	/	1.309 (1.288-1.330)	< 0.001[a]

[a]*P* < 0.05.

HR: Hazard ratio; CI: Confidence interval; PLN: Positive lymph node; LNR: Lymph node ratio; LODDS: Log odds of positive lymph node.

Table 4 Multivariate Cox regression analyses for predicting cause-specific survival in the training cohort

Characteristics	N-stage		PLN		LNR		LODDS	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Race	1.066 (1.023-1.111)	0.003	1.080 (1.036-1.126)	< 0.001	1.068 (1.025-1.114)	0.002	1.066 (1.022-1.111)	0.003
Marital status	1.252 (1.178-1.329)	< 0.001	1.240 (1.167-1.317)	< 0.001	1.258 (1.185-1.336)	< 0.001	1.262 (1.189-1.341)	< 0.001
Primary site	0.885 (0.836-0.938)	< 0.001	0.925 (0.873-0.979)	0.008	0.876 (0.826-0.928)	< 0.001	0.858 (0.809-0.909)	< 0.001
Histology	1.155 (1.071-1.245)	< 0.001	1.044 (0.967-1.126)	0.272	1.074 (0.996-1.159)	0.065	1.077 (0.999-1.162)	0.054
Grade	1.270 (1.212-1.331)	< 0.001	1.311 (1.252-1.373)	< 0.001	1.256 (1.200-1.316)	< 0.001	1.244 (1.188-1.303)	< 0.001
T-stage	1.546 (1.471-1.626)	< 0.001	1.609 (1.532-1.690)	< 0.001	1.574 (1.499-1.654)	< 0.001	1.551 (1.477-1.630)	< 0.001
M-stage	5.132 (4.800-5.487)	< 0.001	5.772 (5.399-6.170)	< 0.001	5.017 (4.684-5.373)	< 0.001	4.716 (4.404-5.051)	< 0.001
N-stage	1.783 (1.710-1.860)	< 0.001	/	/	/	/	/	/
PLN	/	/	1.050 (1.046-1.054)	< 0.001	/	/	/	/
LNR	/	/	/	/	5.304 (4.773-5.895)	< 0.001	/	/
LODDS	/	/	/	/	/	/	1.345 (1.321-1.368)	< 0.001

HR: Hazard ratio; CI: Confidence interval; PLN: Positive lymph node; LNR: Lymph node ratio; LODDS: Log odds of positive lymph node.

Construction and validation of nomograms

In this study, the nomogram was based on the selected model containing LODDS in the training group. As a result, the final nomogram for predicting the OS included the gender, race, marital status, primary site, histology, grade, T, M classification, and LODDS in the (Figure 2); while the CSS nomogram included factors such as race, marital status, primary site, grade, T, M classification, and LODDS (Figure 3). The calibration plots of the two groups are shown in the figure, which demonstrates the consistency of predicted observations of OS and CSS with the actual observations. The time-dependent AUC values of the OS nomograms (Figure 4) and CSS (Figure 5) show more stable accuracy and better prediction efficiency. DCA, which has more advantages over AUC, is a new method for evaluating alternative prognostic strategies. The DCA of nomogram is more beneficial compared to the TNM staging system, indicating that it has better clinical application value than TNM staging. The detailed C-index of the nomogram in each group was evaluated along with the 1-year, 3-year, 5-year, and 10-year AUC values. The results demonstrate the reliability and clinical practicability of the prognostic nomograms.

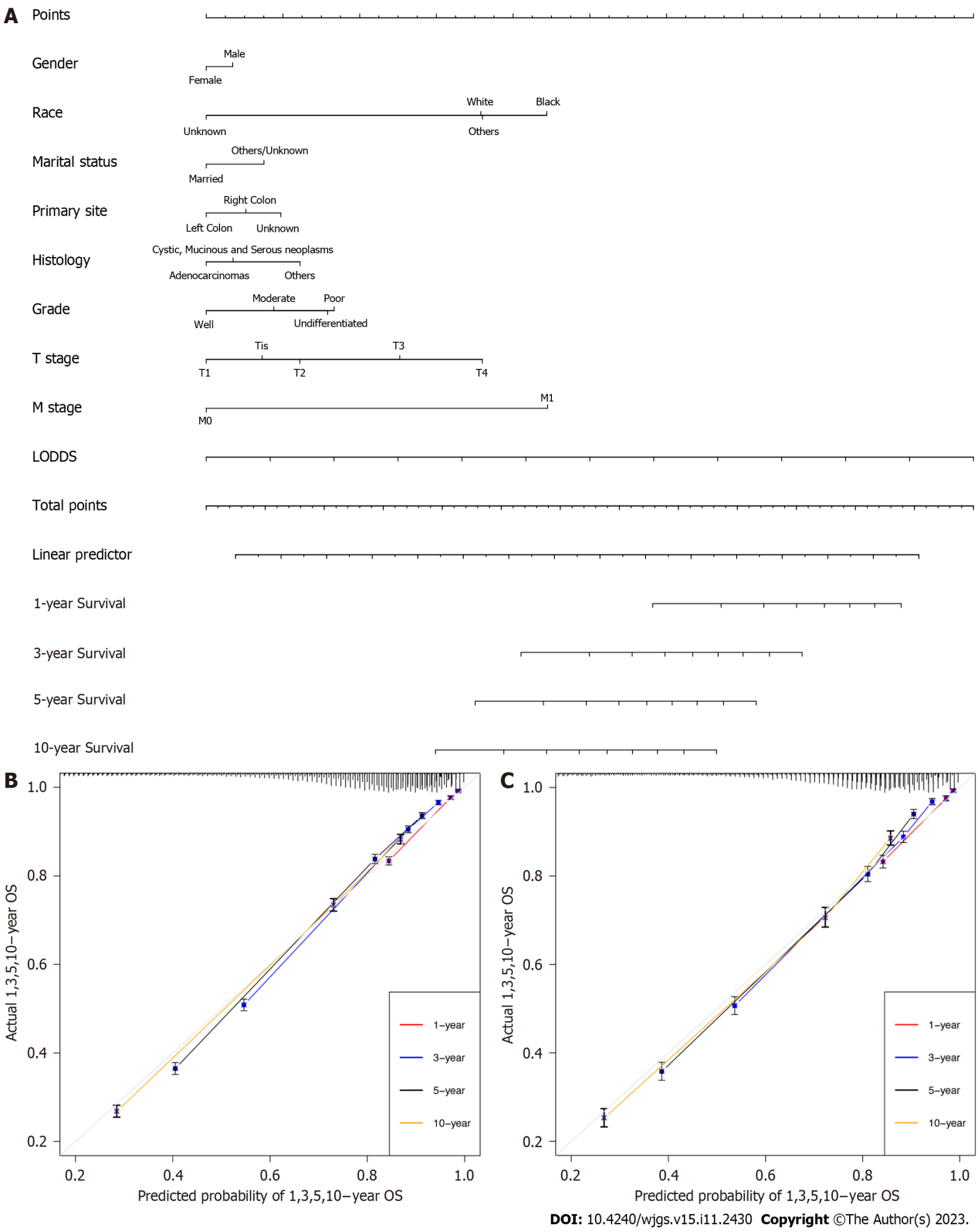

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Figure 2 Nomogram for overall survival of early-onset colon cancer patients. A: Prediction for 1-, 3-, 5- and 10-year overall survival of nomogram; B and C: Calibration plots for 1-, 3- 5- and 10-year in training (B), internal validation (C). LODDS: Log odds of positive lymph node; OS: Overall survival.

Survival risk classifiers based on nomograms

To further verify the performance of the nomogram, the patients were divided based on the total scores calculated by OS and CSS nomograms into high- and low-risk groups. Kaplan-Meier curves demonstrated a significant difference in the survival outcomes of the risk classifiers of OS and CSS between the two cohorts (Figure 6).

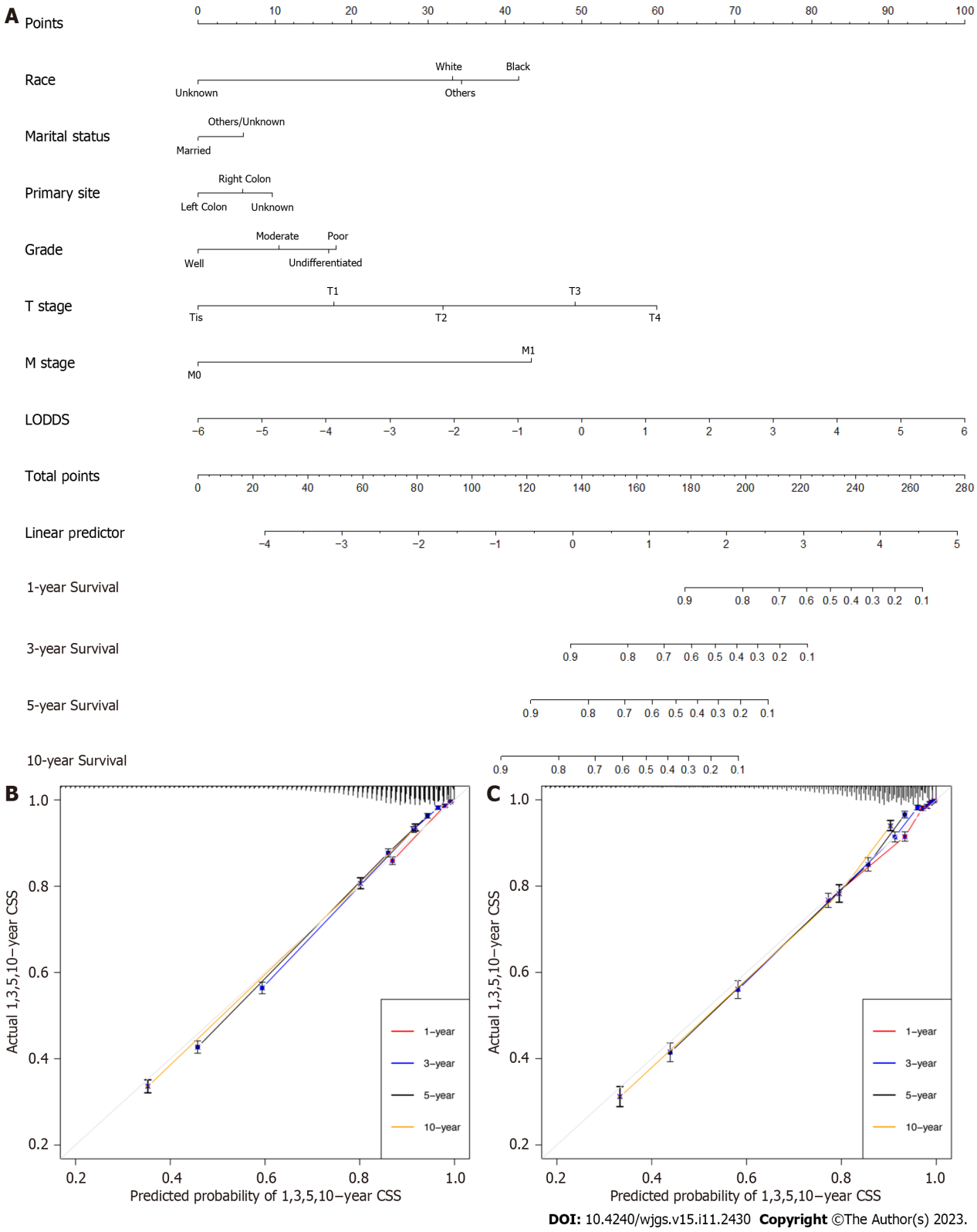

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Figure 3 Nomogram for cause-specific survival of early-onset colon cancer patients. A: Prediction for 1-, 3-, 5- and 10-year cause-specific survival of the nomogram; B and C: Calibration plots for 1-, 3- 5- and 10-year in training (B), internal validation (C). ECC: LODDS: Log odds of positive lymph node; CSS: Cause-specific survival.

DISCUSSION

The screening of CC in the elderly is getting better due to the development and popularity of colonoscopy in recent years. CC is now detected in the early stages of tumorigenesis, enabling early intervention, and subsequently better prognosis for patients. However, studies have indicated that CRC in young patients is more invasive than that in the elderly population[25]. Despite the rapid developments in medical technology, ECC remains a malignant tumor of the digestive

Table 5 Prognostic efficiency of different lymph node status indicators in the training cohort

Endpoint	Filtered model	C-index	AIC	AUC			
				1-yr	3-yr	5-yr	10-yr
OS	N-stage	0.799	96473.30	0.835	0.844	0.842	0.818
	LN-positive	0.796	96726.02	0.835	0.845	0.838	0.811
	LNR	0.802	96299.43	0.840	0.849	0.842	0.817
	LODDS	0.806	96143.26	0.842	0.850	0.845	0.820
CSS	N-stage	0.826	74358.02	0.862	0.871	0.869	0.855
	LN-positive	0.822	74674.34	0.861	0.872	0.863	0.846
	LNR	0.829	74253.59	0.868	0.876	0.870	0.853
	LODDS	0.834	74084.86	0.870	0.877	0.872	0.857

AIC: Akaike information criterion; AUC: Area under the curve; C-index: Concordance index; OS: Overall survival; CSS: Cause-specific survival.

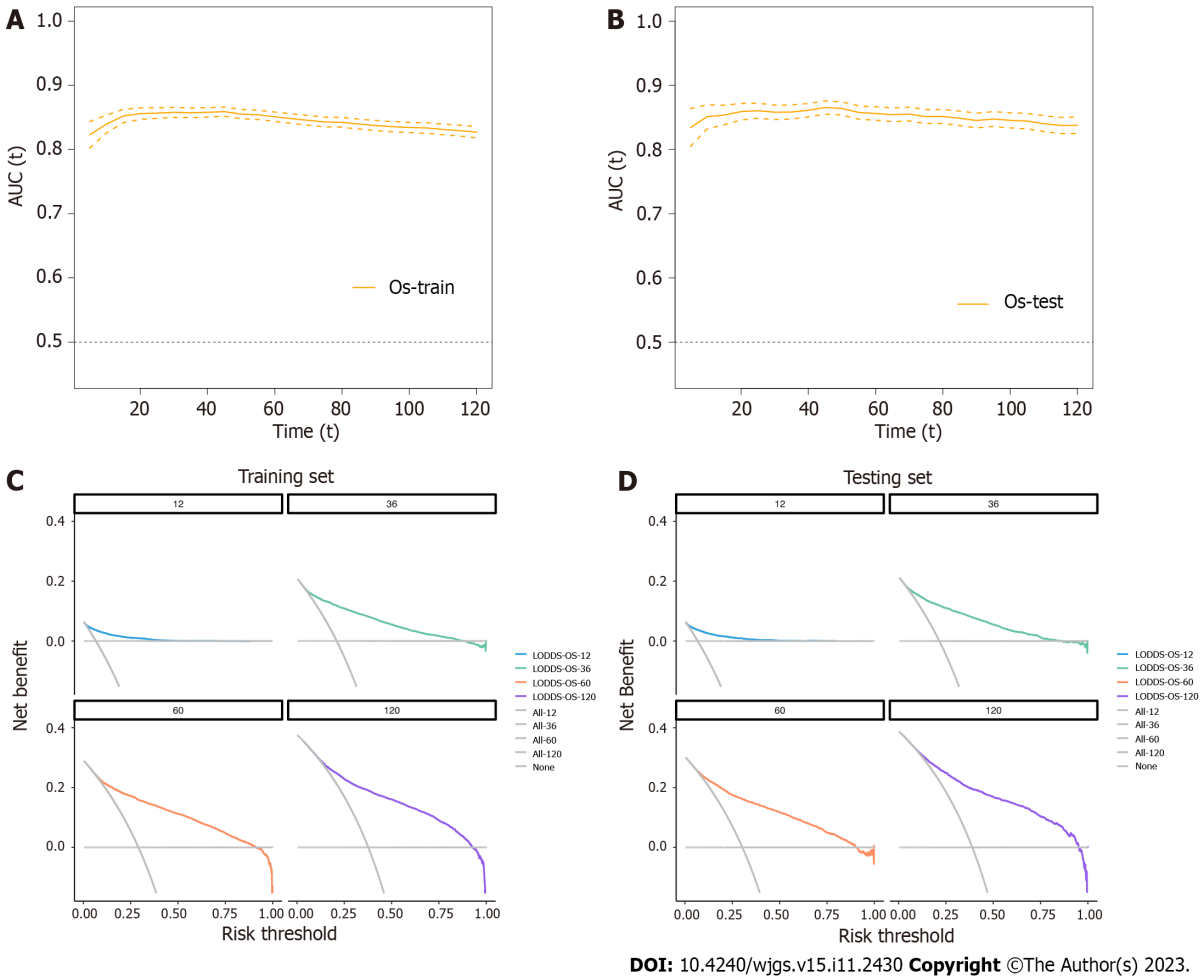

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Figure 4 Evaluation of the nomograms for overall survival of early-onset colon cancer patients with area under the curve and decision curve analysis. A and B: The time-dependent area under the curve for overall survival (OS) in the training (A) and testing (B) cohort; C and D: Decision curves for predicting 1-, 3-, 5- and 10-year OS in training (C) and testing (D) cohort. LODDS: Log odds of positive lymph node; OS: Overall survival; AUC: Area under the curve.

tract and is associated with a poor prognosis because of its location and difficulty in detection. Although the TNM staging system is the most widely used system for prognosis evaluation and determination of the course of treatment for patients with CC, it is associated with several hidden defects limiting its application. Related studies indicate the importance of LNM for the prognosis of ECC[26]; however, the N classification based on the AJCC staging system[27] is not accurate enough to evaluate LNM. Therefore, new lymph nodes status indicators are urgently required to evaluate lymph nodes

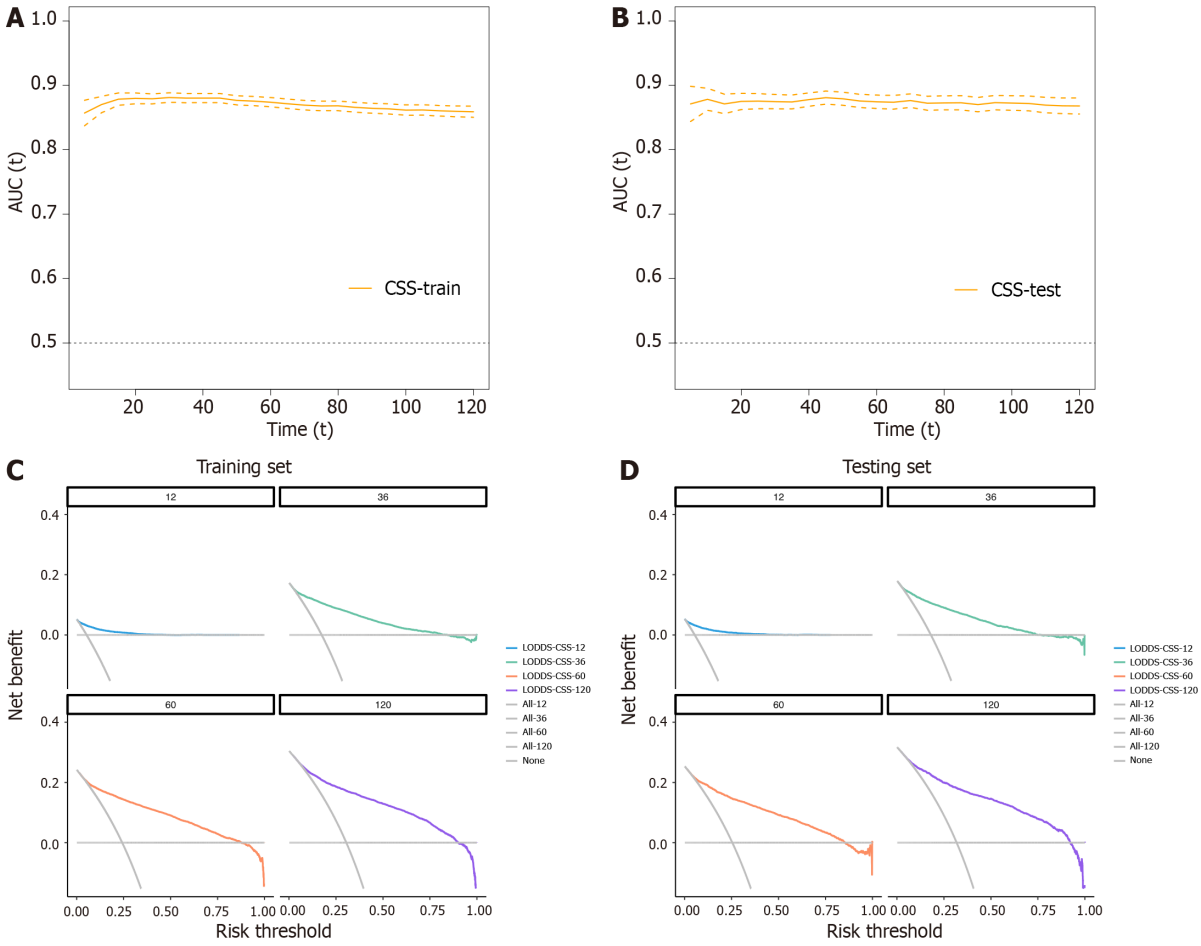

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Figure 5 Evaluation of the nomograms for cause-specific survival of early-onset colon cancer patients with area under the curve and decision curve analysis. A and B: The time-dependent area under the curve for cause-specific survival (CSS) in the train (A) and testing (B) cohort; C and D: Decision curves for predicting 1-, 3-, 5- and 10-year CSS in training (C) and testing (D) cohort. LODDS: Log odds of positive lymph node; CSS: Cause-specific survival; AUC: Area under the curve.

involvement and to stratify ECC patients for individualized treatment.

Several studies have proposed modified lymph nodes state factors including PLN[28], LNR[29], and LODDS[30] to predict the prognosis of ECC patients, but there are no uniform results to confirm, which one is the best. One study has demonstrated the reliability of LODDS in predicting the prognosis of elderly patients with CRC[31]. Our study demonstrated that the four lymph nodes indices are independent prognostic factors of OS and CSS in patients with ECC, and further compared the predictions between N classification, PLN, LNR, and LODDS. The results indicate that the LODDS model can be considered to be the best prognostic model for OS and CSS, since it encompasses minimum AIC, maximum C-index, and AUC, The results indicate that LODDS is better for predicting the prognosis of ECC patients. However, to ensure its clinical applicability, we constructed two nomograms combined with LODDS, using the training group data to predict the OS and CSS of ECC patients, and then verified the accuracy of the nomogram using the testing group data. The calibration curve demonstrates stable linearity and appropriate validity of the nomogram, and the calculated C-index and AUC are the highest in the two groups. With regards to clinical utility, the DCA curve reveals consistently large net benefits of the nomogram over a wide range of thresholds, leading us to trust the satisfactory applicability of the nomogram in predicting the survival of ECC patients. To sum up, our nomogram has better prediction accuracy and clinical effectiveness compared with AJCC and other lymph nodes state systems.

In addition, the risk classifiers of OS and CSS have been established according to the total score of the nomogram, and the patients with ECC have been divided into different risk groups. The results demonstrate the poor survival rate of the two high-risk groups in each cohort. It is worth noting that the high-risk group had a higher matrix score, which was consistent with previous studies on ECC patients.

Although our research has proved that the prediction model including LODDS has obvious advantages in the prediction of OS and CSS, there are still some limitations. First, the presence of some unknown indicators may reduce the predictive ability of the model. Second, use of data from only a single database (SEER) may reduce the credibility of the model. Third, the study was a retrospective study and more prospective and multicenter studies are needed to verify the prognostic value of LODDS. Finally, the details of the surgical approach, such as the degree of lymph nodes anatomy at a specific lymph node level, have not been recorded in detail, and further research is warranted. Despite these limitations, our study has successfully demonstrated better predictive values of LODDS, and included it in the prognostic

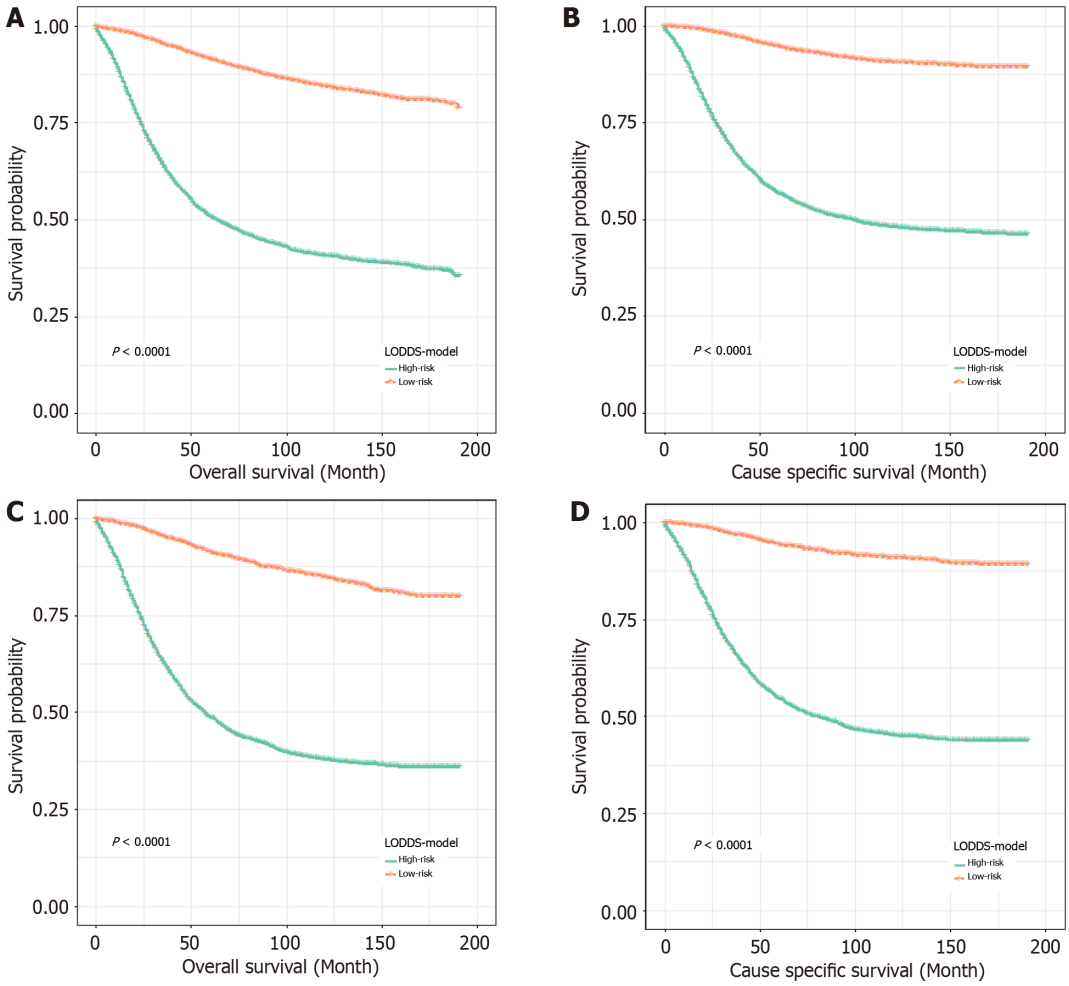

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Figure 6 Kaplan-Meier analyses for early-onset colon cancer patients classified by nomograms. A and B: Kaplan-Meier curves for overall survival (OS) (A) and cause-specific survival (CSS) (B) in the training cohort; C and D: Kaplan-Meier curves for OS (C) and CSS (D) in the testing cohort. LODDS: Log odds of positive lymph node.

nomograms of OS and CSS in patients with ECC for the first time.

CONCLUSION

Our study confirmed that LODDS is more accurate than other LNM indicators in predicting the prognosis of ECC patients and established a new nomogram containing LODDS to predict OS and CSS. The applicability of the nomogram was successfully verified in the testing group. The nomogram can help physicians to design a more accurate treatment plan and personalized follow-up management for ECC patients. It is worthy of further clinical promotion.

ARTICLE HIGHLIGHTS

Research background

Colon cancer (CC) is one of the most common cancers of the digestive tract, the third most common cancer worldwide, and the second most common cause of cancer-related deaths. A higher risk of lymph node metastasis (LNM) in young patients with CC. It might be reasonable to treat patients with early-onset locally advanced CC with extended lymph node dissection. However, few studies have focused on early-onset CC (ECC) patients with LNM.

Research motivation

To compare the predictive values of different LN indicators in ECC patients.

Research objectives
The prognostic values of four lymph node staging indices were compared. And the best nomogram for patients with ECC was established.

Research methods
The patients obtained from the Surveillance, Epidemiology, and End Results database were randomly divided into a training group and a testing group. The model was constructed by the training group and verified by the testing group. Using multiple Cox regression models to compare the prediction efficiency of LNM indicators, nomograms were built based on the best model selected for overall survival (OS) and cause-specific survival (CSS). In the two groups, the performance of the nomogram was evaluated by constructing a calibration plot, time-dependent area under the curve (AUC), and decision curve analysis. Finally, the patients were grouped based on the risk score predicted by the prognosis model, and the survival curve was constructed after comparing the survival status of the high and low-risk groups.

Research results
Log odds of PLN (LODDS) were considered to be independent predictors of OS and CSS. The prediction model including LODDS is composed of minimal Akaike information criterion, maximal concordance indexes, and AUCs. The nomograms of OS and CSS were constructed, which representing both cohorts had been successfully verified in terms of prediction accuracy and clinical practicability.

Research conclusions
LODDS is superior to N-stage, PLN, and LNR of ECC. The nomogram based on LODDS might be helpful in tumor evaluation and clinical decision-making, since it provides an appropriate prediction of ECC.

Research perspectives
The nomogram containing LODDS may be helpful in tumor evaluation and clinical decision-making.

FOOTNOTES

Co-first authors: Heng-Bo Xia and Chen Chen.

Co-corresponding authors: Liang Li and A-Man Xu.

Author contributions: Xia HB, Chen C, and Jia ZX wrote the manuscript and revised the main work, and they contributed equally to this work; Li L and Xu AM designed this study, and they are all the correspondence and contributed equally to this work; Xu AM provided the idea for the article and Li L provided guidance in writing and revising; and all authors contributed to the article and approved the submitted version.

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

Informed consent statement: All the subjects involved have been informed of the purpose and significance of this study, signed the informed consent. This study was performed in line with the principles of the Declaration of Helsinki.

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ORIGINAL ARTICLE

Retrospective Study

Correlation between preoperative systemic immune inflammation index, nutritional risk index, and prognosis of radical resection of liver cancer

Jing Li, Hai-Yan Shi, Min Zhou

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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Abstract

BACKGROUND

Radical surgery is the most commonly used treatment for hepatocellular carcinoma (HCC). However, the surgical effect remains not ideal, and prognostic evaluation is insufficient. Furthermore, clinical intervention is rife with uncertainty and not conducive to prolonging patient survival.

AIM

To explore correlations between the systemic immune inflammatory index (SII) and geriatric nutritional risk index (GNRI) and HCC operation prognosis.

METHODS

This retrospective study included and collected follow up data from 100 HCC. Kaplan–Meier survival curves were used to analyze the correlation between SII and GNRI scores and survival. SII and GNRI were calculated as follows: SII = neutrophil count × platelet count/lymphocyte count; GNRI = [1.489 × albumin (g/L) + 41.7 × actual weight/ideal weight]. We analyzed the predictive efficacy of the SII and GNRI in HCC patients using receiver operating characteristic (ROC) curves, and the relationships between the SII, GNRI, and survival rate using Kaplan–Meier survival curves. Cox regression analysis was utilized to analyze independent risk factors influencing prognosis.

RESULTS
After 1 year of follow-up, 24 patients died and 76 survived. The area under the curve (AUC), sensitivity, specificity, and the optimal cutoff value of SII were 0.728 (95% confidence interval: 0.600-0.856), 79.2%, 63.2%, and 309.14, respectively. According to ROC curve analysis results for predicting postoperative death in HCC patients, the AUC of SII and GNRI combination was higher than that of SII or GNRI alone, and SII was higher than that of GNRI (P < 0.05). The proportion of advanced differentiated tumors, tumor maximum diameter (5–10 cm, > 10 cm), lymph node metastasis, and TNM stage III-IV in patients with SII > 309.14 was higher than that in patients with SII ≤ 309.14 (P < 0.05). The proportion of patients aged > 70 years was higher in patients with GNRI ≤ 98 than that in patients with GNRI > 98 (P < 0.05). The 1-year survival rate of the SII > 309.14 group (compared with the SII ≤ 309.14 group) and GNRI ≤ 98 group (compared with the GNRI > 98 group) was lower (P < 0.05).

CONCLUSION
The prognosis after radical resection of HCC is related to the SII and GNRI and poor in high SII or low GNRI patients.

Key Words: Systemic immune inflammation index; Nutritional risk index; Radical resection; Liver cancer; Prognosis; Correlation

Core Tip: Hepatocellular carcinoma (HCC) has a high incidence and mortality. We evaluated the systemic immune inflammatory index (SII), geriatric nutritional risk index (GNRI), and clinicopathological features of 100 patients undergoing radical HCC resection in this research. We analyzed the correlation between SII, GNRI, and clinicopathological characteristics and addressed the problem of weak prognostic assessment by studying the changes in survival rates of patients undergoing HCC treatment under different levels of SII and GNRI.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the leading type of liver cancer, accounting for 90 percent of all liver tumors[1]. The prevalence and mortality of HCC are increasing annually, posing a significant threat to the health of residents. The onset of HCC is insidious, and the early symptoms are not obvious. Usually, when its clinical symptoms or signs appear, the disease has already progressed to the middle and late stages. The early diagnosis, treatment, and prognosis of HCC have received widespread attention. Clinical treatments for liver cancer are mainly surgical resection, radiofrequency ablation, and percutaneous hepatic arterial chemoembolization. As the primary treatment for resectable liver cancer, surgical resection can prolong the postoperative survival in patients; however, this is still not ideal. Early prognosis prediction and timely individualized therapeutic strategies are crucial for improving patient prognosis. Clinical indicators of prognosis include alpha-fetoprotein, tumor stage, vascular tumor thrombus, and tumor size[2,3]; however, these traditional clinicopathological features have limited predictive value. Recently, the systemic immune inflammatory index (SII) and geriatric nutritional risk index (GNRI) have become the focus of clinical research. They are easy to obtain and have been shown to be good predictors of prognosis of various solid tumors[4-7]. However, we found few reports on the application of the SII or GNRI in predicting the prognosis of HCC despite an urgent need to explore a new and widely used prognostic index of HCC after radical resection. Therefore, to guide clinical practice, we analyzed the clinical data of HCC patients undergoing radical resection with the aim to explore the relationship between the SII and GNRI and prognosis.

MATERIALS AND METHODS

Patients

We screened 100 HCC patients who underwent radical resection in the Liuzhou Hospital of Traditional Chinese Medicine from January 2021 to December 2021. Among the included patients, there were 70 men and 30 women with the age of 68.78 ± 6.69 years old. According to the Child-Pugh classification there were 84 cases of grade A and 16 of grade B. Based on the Barcelona Clinic Liver Cancer staging there were 13 cases of stage 0, 35 of stage A, 42 of stage B, and 10 of stage C.

Inclusion criteria: (1) According to the relevant criteria in the "diagnostic criteria for primary liver cancer[8]", HCC was clinically diagnosed and confirmed by pathology; (2) Age ≥ 60 years; (3) First onset; (4) No preoperative chemoradiotherapy; (5) Patients received radical resection of liver cancer and did not die during the perioperative period; (6) Preoperative SII, GNRI, and clinicopathological features were complete; and (7) Patients could be followed up normally for at least 1 year after surgery, and the clinical data were not missing. The exclusion criteria were as follows: (1) Previous liver surgery; (2) Combination with malignant tumors other than HCC; (3) Combination with other acute or chronic diseases or immune system diseases; (4) A history of drug allergy; and (5) An estimated survival time of < 6 mo.

Collection of research indicators

The preoperative SII, GNRI, and clinicopathological features were obtained from electronic medical record system. SII calculation formula: SII = neutrophil count × platelet count/lymphocyte count[9]. It was determined that there were no infectious diseases, such as pulmonary or urinary tract infections, within 7 d before the radical resection of liver cancer. After special treatment without inhibition and/or promotion of bone marrow growth, the blood routine 3 d before the operation was defined to calculate the SII.

The source of GNRI was as follows: GNRI = [1.489 × albumin (g/L) + 41.7 × actual weight/ideal weight][10]. The ideal weight was calculated according to the Lorenz equation, male: Height − 100 − [(height − 150)/4]; female: Height − 100 − [(height − 150)/2.5]. When the patient's actual weight exceeded the ideal weight, the actual weight/ideal weight ratio was set at 1. GNRI > 98 was considered as normal nutrition, and GNRI ≤ 98 was considered at risk of malnutrition.

The clinicopathological features included sex, age, hepatitis B markers, degree of differentiation, maximum tumor diameter, number of tumors, ascites, lymph node metastasis, TNM stage, capsule integrity, portal vein tumor thrombus, Child-Pugh classification, and alpha-fetoprotein expression.

Postoperative follow-up and survival records

Patients were followed-up by outpatient, telephone, or readmission after the operation, and survival was calculated at the last follow-up. They were followed up every 1 m for 3 mo after the operation, and then every 3 mo for 1 year. The follow-up period ranged from 1 to 12 mo, and the last follow-up was on December 31, 2022.

Methods

All patients underwent conventional radical resection for liver cancer, with 62 undergoing regular hepatectomy and 38 limited hepatectomy. The clinical stage was identified on the basis of the American Cancer Diagnostic Criteria[11], and the degree of differentiation was distinguished in line with histopathological results. For the detection of alpha-fetoprotein, 3 mL of the morning fasting venous blood was centrifuged for 10 min at 3000 r/min. The supernatant was placed in an EP tube and then stored at -20 °C. Serum alpha-fetoprotein expression levels were detected using the cobas e 411 automatic electrochemiluminescence immunoassay analyzer (German Roche, Approval number: China Food and Drug Administration (Jin) Zi 2011 No. 3402843) and the supporting original kit. Alpha-fetoprotein expression > 20 μg/L was positive and ≤ 20 μg/L was negative.

Data processing

Statistical software SPSS 23.0 and Excel 2016 were used for data analysis. The measurement data are presented as x ± s and compared using *t*-tests. The enumeration data are described by the number of cases and rate and analyzed using χ^2 or corrected χ^2 tests. The receiver operating characteristic (ROC) curve was used to observe the area under the curve (AUC) and analyze the efficacy of the SII and GNRI in predicting the death of HCC patients. We used the Kaplan–Meier model for the survival time cohort data and tested it by a log rank approach. Cox regression analysis was applied to analyze the independent risk factors affecting prognosis. Because these were bilateral tests, the statistical test level was $\alpha = 0.05$.

RESULTS

ROC curve analyzing the SII and GNRI for death prediction

In this study, 24 patients died, and 76 survived after 1 year of follow-up. The AUC, sensitivity, specificity, and the optimal cut-off value of SII were 0.728 (95% confidence interval: 0.600-0.856), 79.2%, 63.2%, and 309.14, respectively.

The AUC of the SII combined with the GNRI was higher than that of the SII or GNRI alone. Meanwhile, the AUC of the SII was higher than that of the GNRI ($P < 0.05$) (Table 1, Figure 1). Thus, the combined prediction ability of SII and GNRI is the highest for predicting mortality in patients undergoing radical hepatectomy, and the prediction ability of SII alone is higher than that of GNRI alone.

The preoperative SII and clinicopathological features

There were 47 patients with a SII > 309.14 and 53 with a SII ≤ 309.14. The proportion of well-differentiated tumors, maximum tumor diameter (5–10 cm, > 10 cm), lymph node metastasis, and TNM stage III-IV in patients with SII > 309.14 was higher than that in patients with SII ≤ 309.14 (all $P < 0.05$) (Table 2).

The preoperative GNRI and clinicopathological features

There were 20 patients with a GNRI ≤ 98 and 80 with a GNRI > 9 8. The proportion of patients aged > 70 years was higher in patients with GNRI ≤ 98 than that in patients with GNRI > 98 ($P < 0.05$) (Table 3).

Table 1 Area under the curve of preoperative systemic immune inflammatory index and geriatric nutritional risk index in predicting death in patients undergoing radical resection of liver cancer

Test result variables	AUC	SE	*P* value	95%CI	
				Lower limit	Upper limit
SII	0.728	0.065	0.001[1]	0.600	0.856
GNRI	0.227	0.056	< 0.001[2]	0.117	0.337
SII + GNRI	0.817	0.052	< 0.001[3]	0.715	0.919

[1]$P < 0.05$ vs null hypothesis.
[2]$P < 0.05$ vs null hypothesis.
[3]$P < 0.05$ vs null hypothesis.
AUC: Area under the curve; 95%CI: 95% confidence interval; GNRI: Geriatric nutritional risk index; SII: Systemic immune inflammatory index.

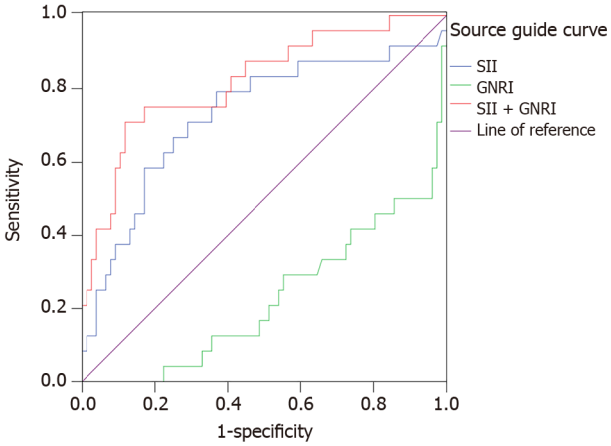

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Figure 1 Receiver operating characteristic curve of preoperative systemic immune inflammatory index and geriatric nutritional risk index predicting death in patients undergoing radical hepatocellular carcinoma surgery. SII: Systemic immune inflammatory index; GNRI: Geriatric nutritional risk index.

The SII, GNRI, and the survival rate

According to the Kaplan–Meier survival curve, the 1-year survival rates of the SII > 309.14 and GNRI ≤ 98 groups were 40.43% (19/47) and 60.00% (12/20), respectively, and those of the SII ≤ 309.14 and GNRI > 98 groups were 9.43% (5/53) and 15.00% (12/80), respectively. Compared with the SII ≤ 309.14 group, the 1-year survival rate of the SII > 309.14 group was lower; compared with the GNRI ≤ 98 group, the 1-year survival rate of the GNRI ≤ 98 group was lower (all $P < 0.05$) (Table 4, Figure 2).

Cox multivariate analysis

Multivariate analysis of prognosis was performed by incorporating the SII, GNRI, and pathological features into the Cox proportional hazard regression model. The SII and GNRI were independent risk factors ($P < 0.05$) (Table 5).

DISCUSSION

The morbidity and mortality associated with HCC are at the forefront of malignant tumor research[12]. Radical resection of liver cancer is one of the main treatment methods and is associated with a high postoperative mortality rate, which can be confusing for surgeons. Tumor progression and invasion depend on the characteristics of tumor cells that are closely related to the tumor microenvironment[13]. Inflammatory cells are an integral part of the tumor microenvironment. These cells, including tumor necrosis factor-α and vascular endothelial growth factor, not only promote the formation of new blood vessels but also regulate the proliferation and invasion of tumor cells and affect their apoptosis[14,15]. In addition, due to factors such as insufficient nutritional intake and high metabolism in tumor cells, the probability of disease-related malnutrition is greatly increased[10], which substantially reduces the prognosis.

We found that the 1-year mortality rate in HCC patients undergoing radical resection was 24%, which was similar to previous studies[16]. The patients were classified into SII > 309.14 and SII ≤ 309.14 groups, and 47% were in the SII >

Table 2 Relationship between preoperative systemic immune inflammatory index and clinicopathological features of patients undergoing radical resection of liver cancer

Indexes	Number of cases	SII		χ^2	*P* value
		> 309.14 (47 cases)	≤ 309.14 (53 cases)		
Gender				0.002	0.965
Male	70	33 (70.21)	37 (69.81)		
Female	30	14 (29.79)	16 (30.19)		
Age				0.047	0.828
≤ 70 yr old	33	15 (31.91)	18 (33.96)		
> 70 yr old	67	32 (68.09)	35 (66.04)		
Hepatitis B markers				0.097	0.755
Negative	27	12 (25.53)	15 (28.30)		
Positive	73	35 (74.47)	38 (71.70)		
Degree of differentiation				4.643	0.031
Middle-low differentiation	55	20 (42.55)	35 (66.04)		
High differentiation	45	27 (57.45)	18 (33.96)		
Maximum tumor diameter				6.807	0.033
5 cm	28	8 (17.02)	20 (37.74)		
5-10 cm	54	27 (57.45)	27 (50.94)		
> 10 cm	18	12 (25.53)	6 (11.32)		
Number of tumors				0.004	0.948
3	13	6 (12.77)	7 (13.21)		
≥ 3	87	41 (87.23)	46 (86.79)		
Ascites				0.846	0.358
No	79	39 (82.98)	40 (75.47)		
Yes	21	8 (17.02)	13 (24.53)		
Lymph node metastasis				8.687	0.003
Yes	38	21 (44.68)	17 (32.08)		
No	62	26 (55.32)	36 (67.92)		
TNM staging				7.517	0.006
I–II	59	21 (44.68)	38 (71.70)		
III–IV	41	26 (55.32)	15 (28.30)		
Envelope Integrity				0.525	0.469
Complete	57	25 (53.19)	32 (60.38)		
Incomplete	43	22 (46.81)	21 (39.62)		
Portal vein tumor thrombus				0.200	0.655
Yes	32	14 (29.79)	18 (33.96)		
No	68	33 (70.21)	35 (66.04)		
Child-Pugh classification				0.424	0.515
A	54	27 (57.45)	27 (50.94)		
B	46	20 (42.55)	26 (49.06)		
Alpha-fetoprotein expression				0.102	0.749
Negative	43	21 (44.68)	22 (41.51)		

Positive	57	26 (55.32)	31 (58.49)

SII: Systemic immune inflammatory index; TNM: tumor node metastasis.

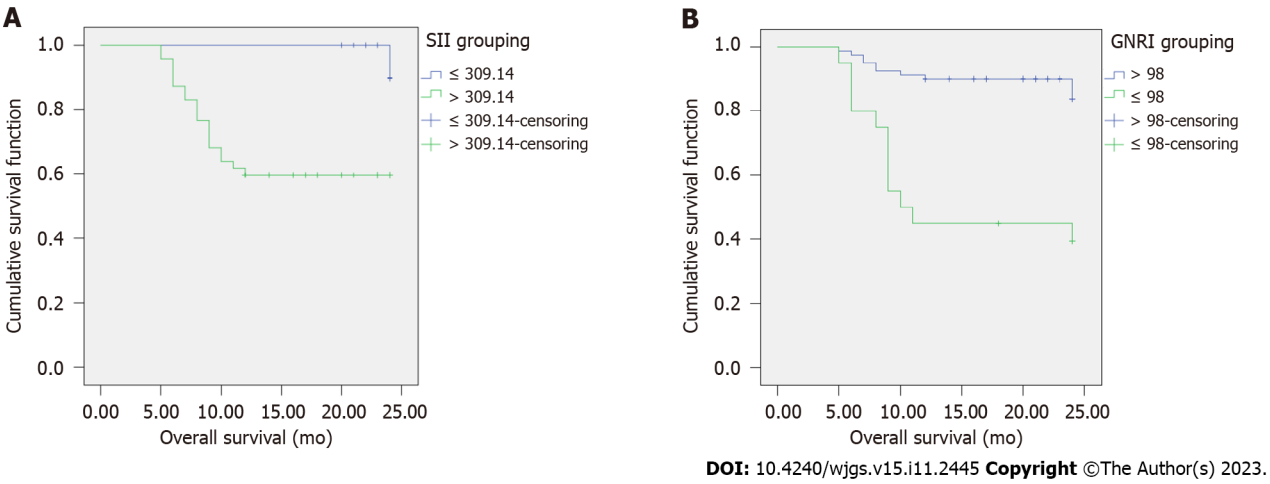

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Figure 2 Kaplan–Meier survival curve of the relationship between systemic immune inflammatory index and geriatric nutritional risk index and survival rate in patients with radical resection of liver cancer. A: The relationship between systemic immune inflammatory index and survival rate; B: The relationship between geriatric nutritional risk index and survival rate. SII: Systemic immune inflammatory index; GNRI: Geriatric nutritional risk index.

309.14 group. Approximately 20% of preoperative patients had abnormal GNRI (GNRI ≤ 98). Further statistical analysis indicated that the SII was related to tumor differentiation, maximum tumor diameter, lymph node metastasis, TNM stage, and other indicators reflecting the degree of malignancy of HCC. Our results showed a relationship between GNRI and age. Statistical analysis confirmed that the SII can be used as an index to evaluate the immune inflammatory state and malignant biological behavior in patients with HCC before radical resection. In addition, the GNRI can be used as an index to reflect nutritional risk and elderly status. Therefore, the SII and GNRI have guiding values for distinguishing high-risk liver cancer. Finally, the survival curve suggested that the survival rate in preoperative SII > 309.14 patients was significantly lower than that in SII ≤ 309.14 patients, and the survival rate in patients with normal GNRI (≤ 98) was significantly lower than that in patients with abnormal GNRI. This suggests that SII and GNRI can be used to estimate the survival status in patients with HCC after radical resection.

Cox multivariate analysis showed that high SII increased the risk of death in patients by approximately 10 times. SII is an efficient inflammatory immune index based on neutrophil, blood plate, and lymphocyte counts. This index comprehensively reflects the immune function and inflammatory responses. An increase in SII indicates an increase in platelets and neutrophils and a decrease in lymphocytes, suggesting that the body is in a state of enhanced inflammatory response and weak immune function[17]. Neutrophils are divided into N1 and N2 phenotypes, and their functions differ. In the early stages of the tumor, the antitumor effect is mainly exerted by the N1 type. In the middle and late tumor stages, the tumor microenvironment promotes the transformation of the N1 neutrophil phenotype into the N2 type and plays a role in promoting tumor development, tumor angiogenesis, and metastasis[18]. Platelets are a mass of cytoplasm shed from mature megakaryocyte cytoplasm in the bone marrow and are important members of the blood clotting system in the body. In recent years, tumors and tumor stromal cells have been found to secrete a large number of thrombogenic and platelet-activating factors. A large amount of angiogenic regulatory proteins in platelets can also promote tumor neovascular angiogenesis, thus participating in the occurrence and development of tumors[19]. Lymphocytes are the main executors of immune functions and participate in antitumor processes. These values reflect the immune functions of the body. Due to the long-term consumption of tumor cells, patients with HCC experience malnutrition and low immunity, and usually have lower lymphocyte counts. Neutrophil and platelet counts were increased, and the lymphocyte count decreased in patients with HCC, which jointly promoted an increase in SII.

The GNRI is a simple, accurate, and objective tool for assessing nutrition-related risks using indicators such as height, weight, and albumin. Changes in its value are accompanied by changes in the development of malignant tumors and overall survival rate in patients[20]. It can predict nutrition-related complications and mortality risk[21]. The GNRI is determined using only serum albumin level, height, and weight. Some scholars have proposed that the GNRI is related to perioperative and postoperative complications, postoperative recurrence, and the overall survival rate in patients with various malignant tumors. It can be used as an important predictor in the prognostic evaluation of gastric, stage I lung, and colorectal cancers[22]. Cox multivariate analysis showed that high GNRI increased the risk of death in patients by approximately 4 times. Serum albumin levels are routinely used to evaluate malnutrition. Scheufele *et al*[23] found that low preoperative serum albumin levels were associated with in-hospital mortality in patients undergoing esophagectomy. Studies have also demonstrated a correlation between preoperative hypoalbuminemia and adverse postoperative clinical outcomes[24]. Height and weight are often used to evaluate the nutritional status of individuals.

Table 3 Relationship between preoperative geriatric nutritional risk index and clinicopathological features of patients undergoing radical resection of liver cancer

Indexes	Number of cases	GNRI		χ^2	*P* value
		≤ 98 (20 cases)	> 98 (80cases)		
Gender				0.298	0.585
Male	70	15 (75.00)	55 (68.75)		
Female	30	5 (25.00)	25 (31.25)		
Age				4.752	0.029
≤ 70 yr old	33	2 (10.00)	31 (38.75)		
> 70 yr old	67	18 (90.00)	49 (61.25)		
Hepatitis B markers				0.257	0.612
Negative	27	4 (20.00)	23 (28.75)		
Positive	73	16 (80.00)	57 (71.25)		
Degree of differentiation				< 0.001	> 0.999
Middle-low differentiation	55	11 (55.00)	44 (55.00)		
High differentiation	45	9 (45.00)	36 (45.00)		
Maximum tumor diameter				0.141	0.932
< 5 cm	28	5 (25.00)	23 (28.75)		
5-10 cm	54	11 (55.00)	43 (53.75)		
> 10 cm	18	4 (20.00)	14 (17.50)		
Number of tumors				0.174	0.677
< 3	10	3 (15.00)	7 (8.75)		
≥ 3	90	17 (85.00)	73 (91.25)		
Ascites				1.221	0.269
No	79	14 (70.00)	65 (81.25)		
Yes	21	6 (30.00)	15 (18.75)		
Lymph node metastasis				0.042	0.837
Yes	38	8 (40.00)	30 (37.50)		
No	62	12 (60.00)	50 (62.50)		
TNM staging				0.056	0.812
I–II	77	15 (75.00)	62 (77.50)		
III–IV	23	5 (25.00)	18 (22.50)		
Envelope Integrity				0.092	0.762
Complete	57	12 (60.00)	45 (56.25)		
Incomplete	43	8 (40.00)	35 (43.75)		
Portal vein tumor thrombus				0.103	0.748
Yes	32	7 (35.00)	25 (31.25)		
No	68	13 (65.00)	55 (68.75)		
Child-Pugh classification				< 0.001	> 0.999
A	60	12 (60.00)	48 (60.00)		
B	40	8 (40.00)	32 (40.00)		
Alpha-fetoprotein expression				0.092	0.762
Negative	43	8 (40.00)	35 (43.75)		

Positive	57	12 (60.00)	45 (56.25)				

GNRI: Geriatric nutritional risk index; SII: Systemic immune inflammatory index.

Table 4 Kaplan-Meier survival curve

Indicators	Number of follow-up cases	1-year survival (rate, %)	Log-rank test	
			χ^2	*P* value
SII			17.706	< 0.001
> 309.14	47	19 (40.43)		
≤ 309.14	53	5 (9.43)		
GNRI			21.624	< 0.001
> 98	80	12 (15.00)		
≤ 98	20	12 (60.00)		

GNRI: Geriatric nutritional risk index; SII: Systemic immune inflammatory index.

Table 5 Cox multivariate analysis of 1-year prognosis in patients undergoing radical resection of liver cancer

Variable	B	SE	Wald	*P* value	RR	95%CI	
						Lower limit	Upper limit
SII	2.345	0.639	13.445	< 0.001	10.429	2.978	36.518
GNRI	1.490	0.532	7.833	0.005	4.438	1.563	12.602
Gender	0.600	0.528	1.291	0.256	1.822	0.647	5.131
Age	0.041	0.025	2.760	0.097	1.042	0.993	1.093
Hepatitis B markers	-0.339	0.527	0.414	0.520	0.713	0.254	2.000
Degree of differentiation	0.072	0.619	0.014	0.907	1.075	0.320	3.617
Maximum tumor diameter	-0.056	0.053	1.091	0.296	0.946	0.852	1.050
Number of tumors	-0.148	0.082	3.275	0.070	0.863	0.735	1.012
Ascites	-0.020	0.554	0.001	0.971	0.980	0.331	2.902
Lymph node metastasis	0.226	0.495	0.209	0.647	1.254	0.475	3.309
TNM staging	-0.478	0.568	0.709	0.400	0.620	0.204	1.886
Envelope Integrity	-0.456	0.493	0.853	0.356	0.634	0.241	1.668
Portal vein tumour thrombus	0.581	0.479	1.470	0.225	1.788	0.699	4.575
Child-Pugh classification	0.321	0.467	0.472	0.492	1.378	0.552	3.440
Alpha-fetoprotein expression	0.095	0.504	0.036	0.851	1.100	0.409	2.955

95%CI: 95% confidence interval; B: Regression coefficient β; GNRI: Geriatric nutritional risk index; RR: Relative ratio; SII: Systemic immune inflammatory index; TNM: Tumor node metastasis.

Yilma *et al*[25] reported that a low body mass index is associated with HCC development and recurrence. Fischer *et al*[26] proposed that overweight and obesity are more conducive to short-term prognosis after major hepatectomy than a normal body mass index. We found that the abnormal GNRI group had higher early postoperative mortality, and early death was a more important factor affecting the overall survival rate in the patients than later death. This also suggests that there is a correlation between the preoperative GNRI and the overall survival rate in patients with HCC after radical resection, with a certain reference value for predicting the prognosis of the disease.

CONCLUSION

In summary, the prognosis of patients with HCC after radical resection is related to the SII and GNRI. The prognosis was poor in patients with a high SII or low GNRI.

ARTICLE HIGHLIGHTS

Research background

The prognostic effect of radical hepatocellular carcinoma (HCC) surgery is not ideal, and clinicians urgently need a reliable evaluation index to guide further clinical interventions.

Research motivation

Prognostic indicators for HCC after radical resection are lacking. The systemic immune inflammatory index (SII) and geriatric nutritional risk index (GNRI) are effective in predicting the prognosis of tumors; however, few attempts have been made to apply them to the prognosis of HCC.

Research objectives

To analyze the relationship between the SII and GNRI and the clinicopathological features in patients undergoing radical HCC resection, we further explored the correlation between the SII and GNRI and mortality and explained the possible causes.

Research methods

This study retrospectively analyzed the SII, GNRI, and clinicopathological data in patients with HCC undergoing radical HCC resection at this research center, analyzed the relationship between the SII and GNRI and clinicopathological features, and further explored the relationship between the SII and GNRI and survival rate.

Research results

The SII > 309.14 group had a 1-year survival rate lower than that of the SII < 309.14 group. The 1-year survival rate was lower in the GNRI > 98 group than that in the GNRI < 98 group ($P < 0.05$).

Research conclusions

After analysis, we put forward the theory of the correlation between SII and GNRI and the mortality of HCC radical operations in China. Using available independent early case reports, the difficult problem of postoperative prognosis assessment was resolved to a certain extent.

Research perspectives

Based on the relationship between the SII and GNRI and the clinicopathological features in patients undergoing radical HCC surgery, the relationship between the SII and GNRI and the postoperative survival rate was further analyzed.

FOOTNOTES

Co-first authors: Jing Li and Hai-Yan Shi.

Author contributions: Li J and Shi HY designed and conducted the research and wrote the manuscript; Zhou 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. Li J and Shi HY contributed equally to this work as co-first authors. The reasons for designating Li J and Shi HY as co-first authors are threefold. First, the research was performed as a collaborative effort, and the designation of co-first authorship accurately reflects the distribution of responsibilities and burdens associated with the time and effort required to complete the study and the resultant paper. This also ensures effective communication and management of post-submission matters, ultimately enhancing the paper's quality and reliability. Second, the overall research team encompassed authors with a variety of expertise and skills from different fields; thus, the designation of co-first 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, Li J and Shi HY contributed efforts of equal substance throughout the research process. The choice of these researchers as co-first authors acknowledges and respects their equal contribution, while recognizing the spirit of teamwork and collaboration on this study. To conclude, we believe that designating Li J and Shi HY as co-first authors is appropriate for our manuscript and accurately reflects our team's collaborative spirit, equal contributions, and diversity.

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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: The authors declare no conflict of interest.

Data sharing statement: Clinical data used in this study can be obtained from the corresponding author.

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Correlation between pre-treatment serum total blood bilirubin and unconjugated bilirubin and prognosis in patients with colorectal cancer

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Abstract

BACKGROUND

Epidemiological studies have found that unconjugated bilirubin (UCB) levels are positively correlated with the incidence of colorectal cancer (CRC). Therefore, bilirubin may also play an important role in the prognosis of CRC.

AIM

To investigate the predictive value of total bilirubin (TBIL) and UCB in the prognosis of patients with CRC.

METHODS

A total of 142 CRC patients were selected as the research subjects in Jingxian Hospital, from October 2014 to May 2021. General and tumour-related clinical data at admission and the overall survival at 3 years after surgery were collected. The optimal cut-off values of TBIL and UCB were determined by receiver operating characteristic curve analysis. Univariate and multivariate Cox regression were used to analyse the effect of bilirubin level on the survival of CRC patients. The Kaplan–Meier method was used to assess the survival time.

RESULTS

The 3-year overall survival rate of CRC patients was significantly higher in the high TBIL (> 13.45 μmol/L) group than in the low TBIL (≤ 13.45 μmol/L) group (76.4% *vs* 37.1%; $P < 0.05$). The 3-year overall survival rate of CRC patients in the high UCB (> 10.75 μmol/L) group was significantly higher than that in the low UCB (≤ 10.75 μmol/L) group (83.3% *vs* 34.2%; $P < 0.05$). Multivariate Cox regression analysis showed that higher TBIL levels were an independent predictor

of better prognosis in CRC patients (hazard ratio = 0.360, 95% confidence interval: 0.159-0.812, P = 0.014).

CONCLUSION
TBIL levels can be used as a prognostic indicator for CRC patients.

Key Words: Bilirubin; Colorectal neoplasms; Prognosis

Core Tip: In this study, we demonstrated that bilirubin levels may be used as a prognostic indicator in colorectal cancer (CRC) patients. Higher total bilirubin (TBIL) and unconjugated bilirubin levels were negatively correlated with 3-year survival in CRC patients. TBIL may be used as a protective prognostic indicator in patients with CRC.

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INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer worldwide and the second leading cause of cancer-related death[1]. The incidence of CRC is higher in men than in women. The CRC burden is expected to increase by 60%, with more than 2.2 million new cancer cases and more than 1.1 million cancer deaths, by 2030[2].

Some studies have reported that bilirubin, a product of haemoglobin catabolism, and particularly unconjugated bilirubin (UCB), has significant anti-inflammatory and anti-oxidant effects and that it plays a role in several oxidative stress-related diseases, including CRC[3]. Epidemiological studies have found that, in men, UCB levels are positively correlated with the incidence of CRC, while they are negatively correlated with the incidence of CRC in women[4,5].

However, clinical data on the relationship between UCB levels and CRC prognosis are lacking. Therefore, this study aimed to investigate the effect of serum total bilirubin (TBIL) and UCB levels on the prognosis of patients with CRC.

MATERIALS AND METHODS

General information

Patients with CRC who attended Jingxian Hospital between October 2014 and May 2021 were selected. The clinical data of 142 study subjects who met the inclusion criteria were retrospectively analysed. Patient inclusion criteria were as follows: (1) Age > 18 years without preoperative antitumor treatment; (2) radical resection of primary CRC; (3) histopathology-confirmed diagnosis of all patients with stage I–III CRC; and (4) complete clinical and pathological data. Patient exclusion criteria were as follows: (1) Colon perforation and peritonitis; (2) history of oncological disease and death from other causes during follow-up; (3) severe cardiovascular disease; (4) primary hepatobiliary diseases that may affect serum bilirubin levels; and (5) incomplete data.

Among the 142 patients finally included, 91 were male and 51 were female, with an average age of (64.11 ± 9.10) years and a follow-up period of (5 to 49 mo). Clinical data of the study subjects at the time of admission were collected by reviewing electronic records. These data included age, sex, smoking status, tumour differentiation, tumour size, tumour location, tumour, node, and metastasis (TNM) staging, and laboratory test data (imaging examination, *etc*). Fasting peripheral blood samples were obtained from patients before surgery to determine TBIL and UCB levels.

Follow-up methods

Patients included in the study were followed up by telephone, or at inpatient or outpatient visits, starting from the time of patient discharge, with a follow-up interval of once every 2 mo. Patient survival and other conditions were followed up until the patient's death or the study endpoint (October 31, 2022).

Statistical analysis

SPSS v22.0 (IBM SPSS Inc., Armonk, NY, United States) was used for statistical analysis of the data. Normally distributed quantitative data are expressed as mean ± SD and were compared between the two groups using t-tests. Quantitative data with a skewed distribution are expressed as median (interquartile interval) and were compared between the two groups using the non-parametric Mann-Whitney U test. Count data were expressed as composition ratios and were compared using the Chi-Square test. Survival curves were plotted using the Kaplan-Meier method and differences in survival between groups were analysed using the log-rank test. A Cox regression model was used to analyse the risk

factors affecting disease prognosis. A *P* value of less than 0.05 was considered statistically significant.

RESULTS

Determination of optimal cut-off values for TBIL and UCB

To determine the optimal cut-off values for TBIL and UCB, the area under the receiver operating characteristic (ROC) curve for prediction of survival in CRC patients was fitted. The area under the ROC curve predicted by TBIL was 0.660 [95% confidence interval (CI): 0.565-0.755; $P = 0.001$], with a sensitivity of 67.9% and specificity of 72.1%. The maximum Youden index value was 0.400 at a cut-off value of 13.45 μmol/L for TBIL for dividing CRC patients into high TBIL (> 13.45 μmol/L) and low TBIL (≤ 13.45 μmol/L) groups. The area under the ROC curve predicted by UCB was 0.735 (95%CI: 0.646-0.82; $P < 0.001$), with a sensitivity of 67.9% and a specificity of 82.0%. The maximum Youden index value was 0.499 at a cut-off value of 10.75 μmol/L for UCB for dividing CRC patients into high UCB (> 10.75 μmol/L) and low UCB (≤ 10.75 μmol/L) groups (Table 1).

Relationship between TBIL level grouping and basic clinical characteristics

The differences between the two groups in the degree of tumour differentiation, presence of lymph node metastasis and pathological TNM stage were statistically significant ($P < 0.05$). However, there were no statistically significant differences ($P > 0.05$) in age, sex, tumour diameter, tumour location, chemotherapy, and smoking ratio (Table 2).

Survival curve analysis of the TBIL and UCB groups

The 3-year overall survival rate was 37.1% (26/70) in the low TBIL group and 76.4% (55/72) in the high TBIL group, which was statistically significantly different ($P < 0.001$). The 3-year overall survival rate was 34.2% (26/76) in the low UCB group and 83.3% (55/66) in the high UCB group, with a statistically significant difference between the two groups ($P < 0.001$), as shown in Figure 1.

Cox regression analysis of factors affecting the prognosis of CRC patients

Cox univariate regression analysis was performed on variables collected in this study that had the potential to affect the prognosis of patients, including age and sex. The analysis showed that the degree of tumour differentiation, tumour diameter, lymph node metastasis, pathological stage, smoking, TBIL, and UCB were associated with prognosis ($P < 0.05$). Variables with statistically significant differences were further included in the multivariate regression analysis. The results showed that the degree of tumour differentiation, lymph node metastasis, and TBIL were risk factors affecting the prognosis of patients ($P < 0.05$), as shown in Table 3.

DISCUSSION

In this study, we demonstrated that bilirubin levels may be used as a prognostic indicator in CRC patients. Higher TBIL and UCB levels were negatively correlated with 3-year survival in CRC. TBIL may be used as a protective prognostic indicator in patients with CRC.

Bilirubin is a product of secondary catabolism of haemoglobin, which is released during the breakdown of aging red blood cells. Bilirubin is present in the circulation mainly in the form of TBIL, direct bilirubin, and UCB[6]. Although abnormally high concentrations of bilirubin are considered harmful, mildly to moderately elevated serum bilirubin concentrations can act as a potent endogenous anti-oxidant with anti-inflammatory, anti-oxidant, and anti-proliferative effects through the process of oxidation of bilirubin itself to biliverdin[7]. Recent evidence suggests that mildly elevated levels of bilirubin, a novel metabolic hormone, may have a protective role in cardiovascular disease and cancer[8]. Several studies have shown a close relationship between serum bilirubin levels and digestive system tumours. Sun *et al*[9] found that low TBIL levels were associated with poor prognosis in gastric cancer, but other studies have shown that high levels of TBIL are a risk factor for poor tumour prognosis[10].

Studies have reported inconsistent results regarding the relationship between circulating bilirubin levels and risk of CRC. In a Mendelian randomization study (67878 cases), TBIL levels were not associated with the risk of CRC[11], which was similar to the findings of a meta-analysis and a prospective survey[12,13]. In an approximately 10-year follow-up study by He *et al*[14], baseline TBIL levels were found to be negatively correlated with the risk of CRC. On the other hand, a nested case-control study by McCullough *et al*[15] found a positive correlation between TBIL levels and the risk of CRC. Although the relationship between bilirubin levels and the risk of CRC remains inconclusive, its potential predictive value for the prognosis of CRC remains a hot topic in the field.

In a prospective study, combining preoperative albumin with bilirubin could predict postoperative complications and overall survival in CRC patients, particularly in stage III patients with tumour metastasis[16]. In the present study, we found that CRC patients with lower levels of TBIL had a worse prognosis and that a lower TBIL level was an independent risk factor for poor survival outcomes in CRC patients, which was consistent with the findings of Sun *et al*[9]. On the other hand, Yang *et al*[17] found that increased TBIL was associated with decreased overall survival in CRC patients. The difference between our study findings and those of Yang *et al*[17] may be related to the inclusion of different study subjects, as their study subjects consisted of stage IV CRC patients, while our study subjects did not include stage IV patients.

Table 1 Determination of optimal cut-off values for total bilirubin and unconjugated bilirubin (%)

	Cut-off (μmol/L)	Sensitivity	Specificity	Jordan index	Area	95%CI
TBIL	13.45	67.9	72.1	0.400	0.660	0.565-0.755
UCB	10.75	67.9	82.0	0.499	0.735	0.646-0.823

TBIL: Total bilirubin; UCB: Unconjugated bilirubin; CI: Confidence interval.

Table 2 Relationship between total bilirubin level grouping and basic clinical characteristics of patients (mean ± SD)

		TBIL ≤ 13.45 μmol/L (*n* = 70)	TBIL > 13.45 μmol/L (*n* = 72)	t/χ^2	*P* value
Age (yr)		65.21 ± 8.33	63.03 ± 9.73	1.437	0.153
TBIL (μmol/L)		10.65 ± 2.11	17.70 ± 4.43	12.163	< 0.001
UCB (μmol/L)		8.81 ± 2.42	13.48 ± 4.10	8.297	< 0.001
Sex	Male	49 (70.0)	42 (58.3)	2.099	0.147
	Female	21 (30.0)	30 (41.7)		
Grade	High	20 (18.6)	26 (36.1)	16.039	< 0.001
	Middle	16 (22.9)	33 (45.8)		
	Low	34 (48.6)	13 (18.1)		
Diameter	< 5 cm	26 (37.1)	38 (52.8)	3.505	0.061
	≥ 5 cm	44 (62.9)	34 (47.2)		
Site	Rectum	26 (37.1)	34 (47.2)	1.508	0.471
	Right	20 (28.6)	18 (25.0)		
	Left	24 (34.3)	20 (27.8)		
Lymph node metastasis	No	27 (38.6)	40 (55.6)	4.108	0.043
	Yes	43 (61.4)	32 (44.4)		
TNM	I	23 (32.9)	34 (47.2)	6.077	0.048
	II	22 (31.4)	25 (34.7)		
	III	25 (35.7)	13 (18.1)		
Smoking	Yes	23 (32.9)	26 (36.1)	0.166	0.683
	No	47 (67.1)	46 (63.9)		
Chemotherapy	Yes	42 (60.0)	38 (52.8)	0.753	0.386
	No	28 (40.0)	34 (47.2)		

T-test for age, total bilirubin, unconjugated bilirubin, χ^2 for gender, degree of tumour differentiation, tumour diameter, tumour location, presence of lymph node metastasis, pathological tumour, node, and metastasis stage, smoking, whether chemotherapy. TBIL: Total bilirubin; UCB: Unconjugated bilirubin; TNM: Tumor, node, and metastasis.

UCB, which is the most active anti-oxidant component of TBIL *in vitro*, comprises a large part of circulating bilirubin [18]. In the present study, lower UCB levels were associated with lower survival rates in CRC patients in univariate, but not in multivariate Cox regression analysis, similar to previous findings[19]. This suggests that UCB, as a prognostic factor, is influenced by other factors and is not suitable as an independent predictor in clinical practice.

In conclusion, our results indicate that circulating TBIL may be used as a prognostic indicator in CRC patients. However, due to the retrospective nature of this study and the small sample size, larger prospective studies are still needed to confirm these findings.

Table 3 Cox regression analysis affecting the prognosis of colorectal cancer patients

Variable		Univariate analysis			Multivariate analysis		
		HR	95%CI	*P* value	HR	95%CI	*P* value
Age (yr)		1.017	0.989-1.046	0.234	-		
Sex	Male						
	Female	0.805	0.468-1.384	0.433	-		
Grade	High	1			1		
	Middle	4.664	1.888-11.521	0.001	2.619	0.939-7.303	0.066
	Low	39.435	16.469-94.427	< 0.001	22.873	7.092-73.769	< 0.001
Diameter	< 5 cm						
	≥ 5 cm	2.287	1.315-3.980	0.003	0.927	0.494-1.741	0.814
Lymph node metastasis	No						
	Yes	17.672	7.815-39.963	< 0.001	9.129	1.157-73.485	0.036
TNM	I	1			1		
	II	7.235	3.023-17.315	< 0.001	0.998	0.121-8.218	0.999
	III	19.778	8.461-46.235	< 0.001	1.124	0.125-10.088	0.917
Smoking	No						
	Yes	2.357	1.424-3.093	0.001	0.800	0.444-1.442	0.458
TBIL (μmol/L)	≤ 13.45						
	> 13.45	0.282	0.160-0.495	< 0.001	0.360	0.159-0.812	0.014
UCB (μmol/L)	≤ 10.75						
	> 10.75	0.178	0.093-0.344	< 0.001	0.986	0.385-2.526	0.977

TBIL: Total bilirubin; UCB: Unconjugated bilirubin; TNM: Tumour, node, and metastasis; CI: Confidence interval; HR: Hazard Ratio.

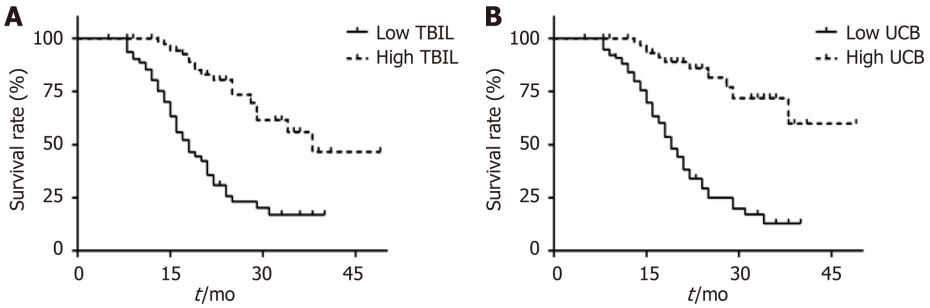

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Figure 1 Survival curve analysis of colorectal cancer patients in the total bilirubin and unconjugated bilirubin groups. A: Colorectal cancer (CRC) patients in the total bilirubin group; B: CRC patients in the unconjugated bilirubin group. TBIL: Total bilirubin; UCB: Unconjugated bilirubin.

CONCLUSION

TBIL levels can be used as a prognostic indicator for CRC patients.

ARTICLE HIGHLIGHTS

Research background

Epidemiological studies have found that unconjugated bilirubin (UCB) levels are positively correlated with the incidence of colorectal cancer (CRC).

Research motivation
Therefore, we speculate that bilirubin may also play an important role in the prognosis of CRC.

Research objectives
To investigate the predictive value of total bilirubin (TBIL) and UCB in the prognosis of patients with CRC.

Research methods
A total of 142 CRC patients were selected as the research subjects in Jingxian Hospital, from October 2014 to May 2021. General and tumour-related clinical data at admission and the overall survival at 3 years after surgery were collected. The optimal cut-off values of TBIL and UCB were determined by receiver operating characteristic curve analysis. Univariate and multivariate Cox regression were used to analyse the effect of bilirubin level on the survival of CRC patients. The Kaplan–Meier method was used to assess the survival time.

Research results
The 3-year overall survival rate of CRC patients was significantly higher in the high TBIL (> 13.45 μmol/L) group than in the low TBIL (≤ 13.45 μmol/L) group (76.4% *vs* 37.1%; $P < 0.05$). The 3-year overall survival rate of CRC patients in the high UCB (> 10.75 μmol/L) group was significantly higher than that in the low UCB (≤ 10.75 μmol/L) group (83.3% *vs* 34.2%; $P < 0.05$). Multivariate Cox regression analysis showed that higher TBIL levels were an independent predictor of better prognosis in CRC patients (hazard ratio = 0.360, 95% confidence interval: 0.159-0.812, $P = 0.014$).

Research conclusions
TBIL levels can be used as a prognostic indicator for CRC patients.

Research perspectives
To investigate the role of TBIL and UCB in the prognosis of patients with CRC.

FOOTNOTES

Author contributions: Ji ZN designed the research; Tong H performed the research; Ji ZN and Xing P contributed new reagents or analytic tools; Tong H analyzed data and wrote the paper.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of Jingxian Hospital in Anhui Province.

Informed consent statement: As the study used anonymous and pre-existing data, the requirement for informed consent from patients was waived.

Conflict-of-interest statement: We have no financial relationships to disclose.

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ORIGINAL ARTICLE

Retrospective Study

Correlation between the expressions of metastasis-associated factor-1 in colon cancer and vacuolar ATP synthase

Miao He, Zuo-Feng Cao, Li Huang, Wen-Juan Zhong, Xue-Ming Xu, Xiao-Li Zeng, Jing Wang

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Abstract

BACKGROUND

Clinical prognosis often worsens due to high recurrence rates following radical surgery for colon cancer. The examination of high-risk recurrence factors post-surgery provides critical insights for disease evaluation and treatment planning.

AIM

To explore the relationship between metastasis-associated factor-1 in colon cancer (MACC1) and vacuolar ATP synthase (V-ATPase) expression in colon cancer tissues, and recurrence rate in patients undergoing radical colon cancer surgery.

METHODS

We selected 104 patients treated with radical colon cancer surgery at our hospital from January 2018 to June 2021. Immunohistochemical staining was utilized to assess the expression levels of MACC1 and V-ATPase in these patients.

RESULTS

The rates of MACC1 and V-ATPase positivity were 64.42% and 67.31%, respectively, in colon cancer tissues, which were significantly higher than in paracancerous tissues ($P < 0.05$). Among patients with TNM stage III, medium to low differentiation, and lymph node metastasis, the positive rates of MACC1 and V-ATPase were significantly elevated in comparison to patients with TNM stage I-II, high differentiation, and no lymph node metastasis ($P < 0.05$). The rate of MACC1 positivity was 76.67% in patients with tumor diameters > 5 cm, notably higher than in patients with tumor diameters ≤ 5 cm ($P < 0.05$). We observed a positive correlation between MACC1 and V-ATPase expression ($r_s = 0.797$, $P < 0.05$). The

positive rates of MACC1 and V-ATPase were significantly higher in patients with recurrence compared to those without ($P < 0.05$). Logistic regression analysis revealed TNM stage, lymph node metastasis, MACC1 expression, and V-ATPase expression as risk factors for postoperative colon cancer recurrence (OR = 6.322, 3.435, 2.683, and 2.421; $P < 0.05$).

CONCLUSION

The upregulated expression of MACC1 and V-ATPase in colon cancer patients appears to correlate with clinicopathological features and post-radical surgery recurrence.

Key Words: Metastasis-associated factor-1 in colon cancer; Vacuolar ATP synthase; Colon cancer; Radical surgery; Recurrence

Core Tip: The abnormal expression of colon cancer metastasis-related factor-1 and vacuolar ATP synthase in colon cancer tissues is related to the clinicopathological characteristics of patients, and is related to the recurrence of colon cancer after radical resection.

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INTRODUCTION

Clinical prognosis often worsens due to high recurrence rates following radical surgery for colon cancer[1,2]. The examination of high-risk recurrence factors post-surgery provides critical insights for disease evaluation and treatment planning[3]. Metastasis-associated factor-1 in colon cancer (MACC1), a metastasis regulation-related factor, fosters epithelial cell invasiveness by increasing stromal infiltration depth, potentially causing metastasis and malignant tumor recurrence[4]. Similarly, the enzyme-binding ATP protease regulator, vacuolar ATP synthase (V-ATPase), regulates ATPase. This action enhances ATPase's binding activity to the tumor cell membrane, thereby optimizing tumor cell energy metabolism and exacerbating abnormal proliferation and division[5]. This study, involved 104 colon cancer patients treated at our hospital, and aimed to comprehensively explore risk factors for recurrence following radical colon cancer surgery. This study focused on the expression of MACC1 and V-ATPase and analyzed the relationship between their expression and the recurrence rate of colon cancer.

MATERIALS AND METHODS

General information

A total of 104 patients with colon cancer treated in our hospital from January 2015 to February 2017 were selected, including 56 males and 48 females. Their age ranged from 40 to 71 years old, with a median age of 54.50 years old.

The inclusion criteria were as follows: (1) Patients confirmed to have colon cancer through pathology from tissue samples; (2) Patients who underwent radical colon cancer surgery at our hospital; and (3) Patients who completed clinical follow-up treatment

The exclusion criteria included: (1) Patients receiving preoperative antitumor treatments such as radiotherapy; (2) Patients with other malignant tumors; and (3) Patients with other severe conditions such as autoimmune and metabolic diseases.

The staging of colon cancer refers to the standards in the TNM staging system for colorectal cancer (7th edition) by the American Joint Committee on Cancer/Union for International Cancer Control. Stage I is T1-2N0M0, Stage II is T3-4bN0M0, Stage III is T1-4bN1-2bM0, and Stage IV is T(any)N(any)M1a-1b[6,7].

Experimental methods

Paraffin sections were prepared, dehydrated, and subsequently incubated with 3% H_2O_2 for 20 min at room temperature. The goat serum was washed with phosphate buffer for 3 times, 5 min each time, and the goat serum diluted with phosphate buffer was blocked for 5 min. After pouring off the serum without washing, 5 mL of primary antibody (sourced from Thermo Fisher China, concentration:1:1000) was added. The mixture was incubated at 37 ℃ for 2 h or refrigerated at 4 ℃ for overnight incubation. It was then washed three times with phosphate buffer, each wash lasting 5 min. Next, 3 mL of biotin fluorescence-labeled secondary antibody (sourced from Thermo Fisher China, concentration:1:2000) was added, followed by a 20-30 min incubation at 37 ℃. After three 5-min phosphate buffer washes,

Table 1 Comparison of metastasis-associated factor-1 and vacuolar ATP synthase expression in colon cancer and paracancerous tissues

Group	Cases	MACC1 positive expression (%)	V-ATPase positive expression (%)
Colon cancer	104	67 (64.42)	70 (67.31)
Paracancerous tissue	104	20 (19.23)	8 (7.69)
χ^2		43.647	78.851
P value		0.000	0.000

MACC1: Metastasis-associated factor-1; V-ATPase: Vacuolar ATP synthase.

Streptavidin/HRP horseradish-labeled streptavidin was added. After incubation at 37 ℃ for another 20-30 min and three more phosphate buffer washes of 5 min each, the enhanced HRP-DAB substrate chromogenic kit (PA110) was used for development. This was followed by rinsing with tap water, restraining, and sealing[8].

Statistical processing

This study adopted SPSS 22.0 software to conduct statistical analysis, used χ^2 test to compare the counting data, and applied logistic regression analysis to implement multivariate analysis. Inspection level a = 0.05.

RESULTS

Comparison of MACC1 and V-ATPase expression in colon cancer and paracancerous tissues

The positive expression rates of MACC1 and V-ATPase in colon cancer tissues were significantly higher than those in paracancerous tissues ($P < 0.05$). See Table 1 for more details.

The Relationship between the expression of MACC1, V-ATPase and clinicopathological features of colon cancer

The positive expression rates of MACC1 and V-ATPase in patients with TNM stage III, medium and low differentiation, and lymph node metastasis were significantly higher than those in patients with stage I-II, high differentiation and no lymph node metastasis ($P < 0.05$); MACC1 positive expression rates of patients with tumor diameter > 5 cm were significantly higher than those of patients with tumor diameter ≤ 5 cm ($P < 0.05$). See Table 2 for more details.

Correlation analysis

The expressions of MACC1 and V-ATPase in colon cancer tissues were positively correlated ($r_s = 0.797$, $P < 0.05$). See Table 3 for more details.

Comparison of the expressions of MACC1 and V-ATPase in colon cancer tissues between patients with postoperative recurrence and patients without postoperative recurrence

As of September 2019, a total of 72 patients had recurrence, and 32 patients had no recurrence; the positive expression rates of MACC1 and V-ATPase in colon cancer tissues of patients with recurrence were significantly higher than those of patients without recurrence ($P < 0.05$), as shown in Table 4.

Multivariate analysis

The study used clinicopathological features of the patients and the expressions of MACC1 and V-ATPase as independent variables, and used the recurrence as the dependent variable for Logistic regression analysis. The analysis results showed that TNM staging, lymph node metastasis, MACC1 expression and V-ATPase expression were risk factors for postoperative recurrence (OR = 6.322, 3.435, 2.683 and 2.421, $P < 0.05$). See Table 5 for more details.

DISCUSSION

The recurrence of colon cancer post-radical surgery is intricately linked to factors such as the excised tumor lesion's completeness, the biological activity of tumor cells, and the self-proliferation traits of residual tumor cells[9,10]. For patients with poorly differentiated tumor cells or in advanced clinical stages, the risk of recurrence may progressively rise post-surgery, correspondingly increasing the mortality rate[11,12]. Currently, reliable indicators to assess the risk of post-surgical recurrence in colon cancer are scarce. While postoperative clinicopathological staging or immunohistochemical indicators can offer some degree of predictability, their reliability remains insufficient. Imaging techniques can aid in predicting recurrence; however, most patients are usually in the intermediate to advanced disease stages when recurrence is clinically diagnosed, limiting the assessment's early recurrence value[13,14].

Table 2 The relationship between the expression of metastasis-associated factor-1, vacuolar ATP synthase and clinicopathological features of colon cancer

Clinicopathologcal features	Cases	MACC1 positive expression (%)	χ^2	*P* value	V-ATPase positive expression (%)	χ^2	*P* value
Age (years)							
≤ 55 years old	54	33 (61.11)	0.538	0.463	35 (64.81)	0.317	0.573
> 55 years old	50	34 (68.00)			35 (70.00)		
Gender							
Male	56	35 (62.50)	0.196	0.658	40 (71.43)	0.936	0.333
Female	48	32 (66.67)			30 (62.50)		
Tumor site							
Left colon	50	32 (64.00)	0.008	0.931	36 (72.00)	0.964	0.326
Right colon	54	35 (64.81)			34 (62.96)		
TNM staging							
Phase I-II	65	34 (52.31)	11.101	0.001	35 (53.85)	14.275	0.000
Phase III	39	33 (84.62)			35 (89.74)		
Degree of differentiation							
High differentiation	31	12 (38.71)	12.74	0.000	11 (35.48)	20.327	0.000
Medium and low differentiation	73	55 (75.34)			59 (80.82)		
Lymph node metastasis							
Yes	49	40 (81.63)	11.973	0.001	42 (85.71)	14.266	0.000
No	55	27 (49.09)			28 (50.91)		
Vascular infiltration							
Yes	41	24 (58.54)	1.023	0.312	26 (63.41)	0.466	0.496
No	63	43 (68.25)			44 (69.84)		
Nervous system infiltration							
Yes	32	22 (68.75)	0.378	0.539	21 (65.63)	0.059	0.807
No	72	45 (62.50)			49 (68.06)		
Tumor diameter							
> 5 cm	60	46 (76.67)	9.276	0.002	40 (66.67)	0.026	0.871
≤ 5 cm	44	21 (47.73)			30 (68.18)		

MACC1: Metastasis-associated factor-1; V-ATPase: Vacuolar ATP synthase.

Our study analyzed MACC1 and V-ATPase-two factors integral to tumor cell gene regulation and energy metabolism-providing a dependable recurrence risk prediction model for clinical use. We chose to examine MACC1 and V-ATPase expression due to their influence on the, regulation of colon cancer cell proliferation.

MACC1, a metastasis regulation-related factor, contains serine and sulfhydryl protein structures. These can impact the activity of tumor cell membrane-bound proteins *via* phosphorylation. MACC1's activation on G protein-coupled receptors in tumor cells can heighten the abnormal transcriptional activation of nuclear DNA in colon cancer cells. As an ATPase protein-binding factor, MACC1's; effect on adenosine triphosphate can boost ATP synthesis in tumor cells, the synthetic division of tumor cell spindles, and tumor cell proliferation[15]. Certain researchers have analyzed MACC1 expression in patients with colon cancer proposing that an elevated MACC1 positive expression rate may increase the risk of colon cancer[16,17]. On the other hand, studies on V-ATPase are sparse, with, most resorting to univariate analysis. To better understand these variables' relationships, we conducted a correlation study.

We discovered that the positive expression rates of MACC1 and V-ATPase proteins in colon cancer lesions significantly exceeded those in paracancerous tissues. This suggests that higher expression of these two proteins might impact the onset or progression of colon cancer. Such high expression is primarily driven by the activation of the transcriptional regulatory signaling pathway in colon cancer cells. This influences the synthesis rates of adenosine triphosphate and

Table 3 Correlation analysis

MACC1 expression	V-ATPase expression		r_s	*P* value
	Positive	Negative		
Positive	63	4	0.797	0.000
Negative	7	30		

MACC1: Metastasis-associated factor-1; V-ATPase: Vacuolar ATP synthase.

Table 4 Comparison of the expression of metastasis-associated factor-1 and vacuolar ATP synthase in colon cancer tissues between patients with postoperative recurrence and patients without postoperative recurrence

Group	Cases	MACC1 positive expression (%)	V-ATPase positive expression (%)
Recurrence	72	52 (72.22)	57 (79.17)
No recurrence	32	15 (46.88)	13 (40.63)

MACC1: Metastasis-associated factor-1; V-ATPase: Vacuolar ATP synthase.

Table 5 Results of logistic regression analysis

Factor	β	SE	Walds	*P* value	OR (95%CI)
TNM staging	1.844	0.411	20.130	0.000	6.322 (2.825-14.148)
Lymph node metastasis	1.234	0.315	15.346	0.000	3.435 (1.853-6.369)
MACC1 expression	0.987	0.264	13.977	0.000	2.683 (1.599-4.502)
V-ATPase expression	0.884	0.221	16.000	0.000	2.421 (1.570-3.733)

MACC1: Metastasis-associated factor-1; V-ATPase: Vacuolar ATP synthase.

guanosine triphosphate, enhances ATP supply, and ultimately impacts the tumor cells' metastasis and adhesion capabilities.

In patients with TNM stage III, medium and low differentiation, and lymph node metastasis, MACC1 and V-ATPase expression rates were significantly higher compared to patients with stage I-II, high differentiation, and no lymph node metastasis. This indicates that the expression of these two factors can markedly influence the prognosis of clinicopathological processes in patients with colon cancer. High expression of MACC1 primarily impacts clinical staging, lymph node metastasis, or tumor cell differentiation because it can affect the epithelial-mesenchymal transition process, intensify tumor cell infiltration and metastasis, and ultimately advance TNM staging. V-ATPase's influence on related pathological characteristics chiefly stems from its capacity to affect tumor cells' energy metabolism rate, leading to the compromised release of tumor cell differentiation and maturation-inducing factors, thereby promoting medium and low differentiation of tumor cells[18].

Further studies have also demonstrated that in colon cancer patients, the MACC1 expression level significantly rises with clinical staging progression. This increase is notably pronounced for patients in the advanced or terminal stages of colon cancer[19,20]. Our correlation analysis revealed a positive correlation between MACC1 and V-ATPase expression in colon cancer tissues, suggesting a collaborative role of MACC1 and V-ATPase in colon cancer progression. In patients who experienced recurrence, the positive expression rates of MACC1 and V-ATPase proteins markedly increased and surpassed those in non-recurrence patients. This statistically significant difference implies that high MACC1 and V-ATPase protein expression can influence colon cancer recurrence. However, the specific underlying mechanism remains unclear, but it could involve MACC1 and V-ATPase impacting the activity of residual tumor cells, leading to an enhanced self-proliferation capacity and ultimately promoting colon cancer recurrence. Risk factor analysis further identified TNM stage, lymph node metastasis, MACC1 expression, and V-ATPase expression as risk factors for postoperative recurrence, underscoring the influence of MACC1 and V-ATPase on colon cancer recurrence.

Colon cancer's development is governed by numerous cytokines. Clinical studies have largely focused on single-factor regulation, the functionality of which can be swayed by various environmental relationships. A multifactor correlation analysis could offer greater value for clinical diagnosis. In this study, we jointly examined MACC1 and V-ATPase's clinical value in this disease, using the patients' clinicopathological characteristics and MACC1 and V-ATPase expression as independent variables, and recurrence as the dependent variable for logistic regression analysis. The results suggested these two indicators might pose as risk factors for postoperative recurrence in colon cancer patients. High MACC1

expression could foster the metastasis of various tumor cells, although the specific mechanism of action remains unelucidated. MACC1 protein could not only augment tumor metastasis by regulating Met transcription but also modulate cell metastasis by activating the Akt/β-catenin signaling pathway or promoting the secretion of matrix metalloproteinases. Overexpression of V-ATPase in tumor cells plays a crucial role in maintaining the cytoplasm's alkaline environment, stimulating tumor cell growth, enhancing the extracellular acidic environment, promoting cell invasive growth and metastasis, and inducing the invasive phenotype of tumor cells. Thus, our study can serve as a reference for clinical prediction of the postoperative recurrence in colon cancer patients. However, there were some limitations of this study. The patients were selected from one single center, and the sample size was limited. The results of this study need to be confirmed by further studies.

CONCLUSION

In summary, the elevated expression of MACC1 and V-ATPase in colon cancer patients is associated with the clinicopathological features and post-radical surgery recurrence of colon cancer, and warrants further investigation.

ARTICLE HIGHLIGHTS

Research background

Clinical prognosis often worsens due to high recurrence rates following radical surgery for colon cancer. The examination of high-risk recurrence factors post-surgery provides critical insights for disease evaluation and treatment planning.

Research motivation

The factors influencing the recurrence of colon cancer after surgery remains unclear.

Research objectives

To explore the relationship between metastasis-associated factor-1 in colon cancer (MACC1) and vacuolar ATP synthase (V-ATPase) expression in colon cancer tissues, and recurrence rate in patients undergoing radical colon cancer surgery.

Research methods

We selected 104 patients treated with radical colon cancer surgery at our hospital from January 2018 to June 2021. Immunohistochemical staining was utilized to assess the expression levels of MACC1 and V-ATPase in these patients.

Research results

The positive rates of MACC1 and V-ATPase were significantly higher in patients with recurrence compared to those without. Logistic regression analysis revealed TNM stage, lymph node metastasis, MACC1 expression, and V-ATPase expression as risk factors for postoperative colon cancer recurrence.

Research conclusions

The upregulated expression of MACC1 and V-ATPase in colon cancer patients appears to correlate with clinicopathological features and post-radical surgery recurrence.

Research perspectives

This study can serve as a reference for clinical prediction of the postoperative recurrence in colon cancer patients.

FOOTNOTES

Author contributions: He M, Cao ZF, Huang L, Zhong WJ, and Wu XM designed the research study; Zeng XL, Wang J, He M and Cao ZF performed the research; Cao ZF, Huang L, Zhong WJ and Xu XM analyzed the data and wrote the manuscript; All authors have read and approve the final manuscript.

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Risk factors for anastomotic fistula development after radical colon cancer surgery and their impact on prognosis

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Abstract

BACKGROUND

Colon cancer is a common malignant tumor in the gastrointestinal tract that is typically treated surgically. However, postradical surgery is prone to complications such as anastomotic fistulas.

AIM

To investigate the risk factors for postoperative anastomotic fistulas and their impact on the prognosis of patients with colon cancer.

METHODS

We conducted a retrospective analysis of 488 patients with colon cancer who underwent radical surgery. This study was performed between April 2016 and April 2019 at a tertiary hospital in Wuxi, Jiangsu Province, China. A *t*-test was used to compare laboratory indicators between patients with and those without postoperative anastomotic fistulas. Multiple logistic regression analysis was performed to identify independent risk factors for postoperative anastomotic fistulas. The Functional Assessment of Cancer Therapy-Colorectal Cancer was also used to assess postoperative recovery.

RESULTS

Binary logistic regression analysis revealed that age [odds ratio (OR) = 1.043, P = 0.015], tumor, node, metastasis stage (OR = 2.337, P = 0.041), and surgical procedure were independent risk factors for postoperative anastomotic fistulas. Multiple linear regression analysis showed that the development of postoperative anastomotic fistula (P = 0.000), advanced age (P = 0.003), and the presence of diabetes mellitus (P = 0.015), among other factors, independently affected

prognosis.

CONCLUSION
Postoperative anastomotic fistulas significantly affect prognosis and survival rates. Therefore, focusing on the clinical characteristics and risk factors and immediately implementing individualized preventive measures are important to minimize their occurrence.

Key Words: Radical colon cancer surgery; Anastomotic fistula; Risk factors; Prognosis; Life expectancy; Survival rate

Core Tip: The incidence of anastomotic fistulas after radical colon cancer surgery is high and significantly affects patient prognosis. Additional targeted interventions should be supplemented to reduce the occurrence of anastomotic fistulas and improve the prognosis.

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INTRODUCTION

Colon cancer is a malignant tumor that originates from the colonic epithelium and often occurs at the sigmoid colorectal junction. While its etiology remains unclear, most colon cancers develop from adenomatous polyps and progress to carcinoma. As one of the most prevalent cancers worldwide, colon cancer is the second and third leading cause of cancer-related deaths globally[1] and in the United States, respectively[2]. In China, it is one of the most frequently diagnosed tumors, with an increasing incidence rate[3]. A recent report from the National Cancer Center in China published in the Journal of the National Cancer Center revealed that colon cancer is the third and fourth most commonly occurring cancer in women and men, respectively, in China[4]. An increase in the incidence of colon cancer has been reported among younger individuals, with approximately 11% of the cases occurring in those aged < 50 years. This incidence rate also increases by 1%-2% annually[5,6]. The statistics emphasize the current threat of colon cancer poses to human health. Additionally, a study indicated that the 5-year survival rates for patients with colon cancer aged 18-65 years with stages I, II, III, and IV are 91%, 82%, 66%, and 10%, respectively[7]. Furthermore, Dekker *et al*[8] reported that in 2017, approximately 140000 people were diagnosed with colon cancer, and approximately 50000 died from this disease.

Clinical symptoms of colon cancer primarily include abdominal distension, indigestion, and bloody stools. The initial mild symptoms, such as indigestion, bloody stools, and constipation, can progress to edema, jaundice, and ascites in advanced stages. Surgery remains the primary treatment option for patients with early-stage colon cancer, with approximately 20% of patients diagnosed with distant metastases ineligible for surgical resection[9]. Surgical resection is the mainstay of treatment for colon cancer[10]. In recent years, laparoscopic radical colon cancer surgery has become the preferred approach over open surgery because of its advantages including reduced trauma and postoperative pain[11]. However, regardless of the surgical method used, patients with colon cancer are prone to developing anastomotic fistulas following surgery[12]. Anastomotic fistulas are a common and severe postoperative complication following radical colon cancer surgery. If not promptly treated, they can result in permanent stomas, increase the risk of recurrence, and even lead to death[13]. The development of anastomotic fistulas can be attributed to various factors, including poor blood flow due to tight anastomotic sutures, inadequate preoperative intestinal preparation, poor postoperative nutritional status, and improper patient care during the postoperative period. These factors increase the risk of postoperative abdominal infection, further exacerbating the patient's condition[14,15]. Previous studies examined the risk factors associated with the development of anastomotic fistulas after radical colon cancer surgery, but their findings were inconsistent, and none of them investigated the prognostic implications of anastomotic fistulas on patients with colon cancer[12,16]. Therefore, this study aimed to identify independent risk factors for the development of anastomotic fistulas after radical colon cancer surgery and to investigate the effects of these fistulas on patient prognosis. The findings of this study may contribute to improving the postoperative well-being of patients, prolonging their life expectancy, and improving their prognosis.

MATERIALS AND METHODS

Research participants

A total of 488 patients who underwent radical colon cancer surgery at the Affiliated Hospital of Jiangnan University

between April 2016 and April 2019 were included in the study.

The inclusion criteria were as follows: (1) All patients underwent elective surgery; (2) pathological stage of tumor, node, metastasis (TNM) stages I-III; (3) postoperative pathology confirming colon cancer; (4) radical resection of colon cancer surgery; (5) preoperative imaging ruling out liver, lung, and other distant metastases; (6) availability of detailed medical records and complete postoperative pathological data; and (7) informed consent signed by patients and family members.

The exclusion criteria included: (1) Patients who died during hospitalization or were discharged automatically and terminated treatment; (2) patients with a planned stoma; (3) patients with severe coagulation abnormalities; (4) patients with confirmed unresectable tumor invasion of surrounding organs or advanced tumors with distant metastases, eligible only for palliative resection; (5) pregnant and lactating women; (6) patients who underwent emergency surgery for bleeding, perforation, and intestinal obstruction; and (7) patients with incomplete medical records during the treatment process that affected result evaluation (Figure 1).

The sample size was calculated using the following formula: $n = (Z1\text{-}\alpha/2/\delta)2P(1\text{-}P)$, with the postoperative development of an anastomotic fistula as the primary outcome index. Based on our clinical experience, the incidence of intestinal fistula (P) in patients after radical colon cancer surgery was approximately 7%. Taking α as 3% and δ as 0.05 (bilateral), and considering a 10% sample attrition rate, the sample size was determined to be $n = 306$ cases. Using a similar approach, the study population included 510 patients. After excluding 22 patients and accounting for loss to follow-up, 488 cases were finally included.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and informed consent was obtained from all patients.

General information questionnaire

The general information questionnaire collected demographic (*e.g.*, sex and age) and clinical data (*e.g.*, occurrence of anastomotic fistula, presence of hypertension and diabetes, site of lesion, type of tissue, type of pathology, TNM stage, surgical approach, presence of lymph node metastasis, presence of adjuvant chemotherapy, postoperative intensive care unit (ICU) stay, operative time, intraoperative bleeding, postoperative time to exhaustion, hospitalization time, preoperative and postoperative levels of carcinoembryonic antigen (CEA), carbohydrate antigen 125 (CA125), albumin (Alb), total protein (TP), hemoglobin (Hb), blood potassium (K), and platelet).

Diagnosis of anastomotic fistula

Anastomotic leak is defined as the drainage of colonic contents through a drain, wound, or abnormal orifice. It is typically diagnosed using computed tomography (CT) scan or surgery. The specific diagnostic methods used were as follows: Limited or diffuse abdominal pain, turbid purulent drainage fluid or presence of gas, liquid, or fecal discharge, abdominal incision with pus, or even fecal-like fluid overflowing from the abdominal cavity. For low rectal anastomotic fistula, it can be detected through rectal examination and presence of generalized fever; elevated C-reactive protein (CRP) levels in routine blood tests; computed tomography examination showing bubbles or inflammatory edema around the anastomosis, blurring of the surrounding fat planes, or suspected abdominal abscesses associated with the intestine; dilute barium enema imaging showing contrast agent leakage or injection of contrast agent through the drainage tube revealing the flow of contrast agent into the intestinal cavity; and endoscopy or re-operation assisting in confirming the diagnosis.

Prognostic assessment of Functional Assessment of Cancer Therapy-Colorectal

The Functional Assessment of Cancer Therapy-Colorectal (FACT-C) questionnaire is a validated and reliable measure of health-related quality of life in patients with colorectal cancer[17]. It consists of five subscales: physical well-being (seven items; score range 0-28), social well-being (seven items; score range 0-28), emotional well-being (six items; score range 0-24), functional well-being (seven items; score range 0-28), and a colorectal cancer subscale (seven items; score range 0-28). The FACT-C questionnaire comprises a total of 34 items with an overall score range of 0-136.

Statistical analysis

The scores obtained for each subscale were entered into a computer for conversion. All the statistical analyses were performed using SPSS version 26 (IBM Corp., Armonk, NY, United States). Measurement data are presented as means and standard deviations, and count data are expressed as frequencies and percentages. Intergroup comparisons were performed using the *t*-test and chi-square test, and binary logistic regression analysis was used to identify independent risk factors for postoperative anastomotic fistula. Multiple linear regression analysis was performed to determine independent risk factors for assessing patient prognosis. Statistical significance was defined as a two-sided P value of < 0.05.

RESULTS

Baseline data

Among the 488 patients included in this study, postoperative anastomotic fistulas developed in 38 patients (7.8%). The chi-square test and t-test revealed significant differences between patients with and those without postoperative anastomotic fistulas in terms of age, presence of diabetes, TNM stage, surgical method, preoperative radiotherapy, and

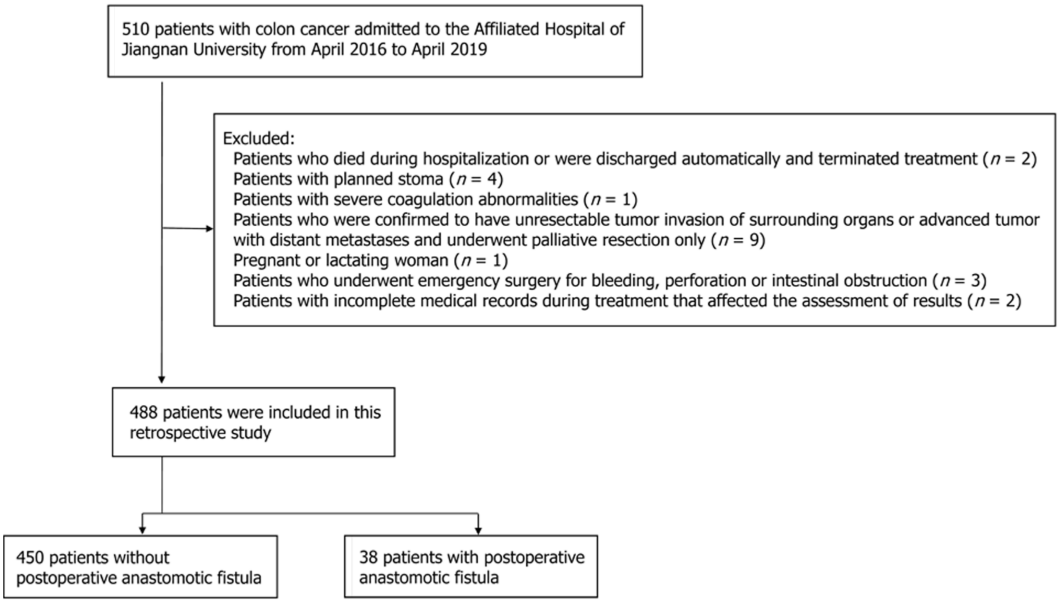

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Figure 1 Flow chart illustrating the patient selection process.

postoperative ICU stay ($P < 0.05$). The mean age of patients with postoperative anastomotic fistula was 58.95 ± 11.91 years, and that of patients without fistula was 52.90 ± 12.7 years. Among the patients with and without postoperative anastomotic fistula (38 and 450, respectively), 16 (42.1%) and 110 (24.4%) had diabetes mellitus, 20 (52.6%) and 323 (71.8%) had TNM stage I-II, 9 (23.7%) and 278 (61.8%) underwent laparoscopic radical surgery, and 29 (76.3%) and 172 (38.2%) underwent conventional radical surgery, 13 (34.2%) and 85 (18.9%) received preoperative radiotherapy, and 5 (13.2%) and 20 (4.4%) were transferred to the ICU postoperatively, respectively (Table 1).

Perioperative indicators of patients postoperatively

The *t*-test demonstrated significant differences between patients with and those without postoperative anastomotic fistulas in terms of operative time, intraoperative bleeding, and postoperative hospital stay ($P < 0.05$). The mean operative time, intraoperative bleeding, and postoperative hospital stay for patients with postoperative anastomotic fistula were 187.39 ± 16.31 min, 229.21 ± 60.81 mL, and 11.76 ± 2.57 d, respectively. Patients without fistula had a mean operative time of 179.96 ± 21.32 min, intraoperative bleeding of 187.51 ± 60.51 mL, and postoperative hospital stay of 10.76 ± 2.11 d (Table 2).

Laboratory indicators of patients preoperatively and postoperatively

The *t*-test revealed statistically significant differences between patients with and those without postoperative anastomotic fistulas in terms of preoperative and postoperative Alb, postoperative TP, postoperative Hb, and postoperative K levels ($P < 0.05$). In patients with and without postoperative anastomotic fistula, the preoperative Alb, postoperative Alb, postoperative TP, postoperative Hb, and postoperative K were 33.87 ± 4.74 g/L and 36.22 ± 4.72 g/L, 27.70 ± 3.24 g/L and 29.92 ± 3.56 g/L, 55.32 ± 8.83 g/L and 58.37 ± 8.67 g/L, 115.57 ± 14.00 g/L and 58.37 ± 8.67 g/L, and 4.89 ± 0.49 mmol/L and 4.71 ± 0.47 mmol/L, respectively (Table 3).

Postoperative FACT-C score of patients

The *t*-test demonstrated significant differences in all components of the FACT-C score between patients with and those without postoperative anastomotic fistulas ($P < 0.05$). The mean scores for physical well-being, social well-being, emotional well-being, functional well-being, colorectal cancer subscale, and total scores for patients with postoperative anastomotic fistula were 12.50 ± 3.80, 18.24 ± 3.77, 15.50 ± 3.45, 12.66 ± 3.78, 15.89 ± 4.59, and 74.79 ± 11.86, respectively, and those for patients without fistula were 15.62 ± 3.94, 20.06 ± 3.54, 18.32 ± 3.36, 15.53 ± 4.39, 19.52 ± 3.98, and 89.05 ± 13.32, respectively (Table 4).

Survival and recurrence rates of patients 1-3 years after surgery

The chi-square test revealed that the presence or absence of a postoperative anastomotic fistula significantly influenced the survival rate of patients 1 year after surgery (89.5% *vs* 96.7%, respectively; $P < 0.05$). However, no significant differences were observed in the 1- to 3-year recurrence and 2- to 3- survival rates between patients with and those without postoperative anastomotic fistulas ($P > 0.05$; Table 5).

Binary logistic regression of patients with postoperative anastomotic fistula

Binary logistic regression analysis identified patient age, TNM stage, surgical procedure, postoperative ICU stay after

Table 1 Comparison of clinical features of patients after radical colon cancer surgery

Item, *n* (%)	Anastomotic fistula group	Non-anastomotic fistula group	t/χ^2	*P* value
Gender				
Male	19 (50.0)	236 (52.4)	0.084	0.772
Female	19 (50.0)	214 (47.6)		
Age (yr)	58.95 ± 11.91	52.90 ± 12.7	-2.921	0.004
Hypertension or not				
Yes	17 (44.7)	171 (38.0)	0.672	0.413
No	21 (55.3)	279 (62.0)		
Diabetes or not				
Yes	16 (42.1)	110 (24.4)	5.706	0.017
No	22 (57.9)	340 (75.6)		
Site of lesion				
Left hemi-colon	17 (44.7)	227 (50.4)	0.892	0.640
Right hemi-colon	15 (39.5)	144 (25.3)		
Transverse colon	6 (15.8)	79 (17.6)		
Type of organization				
Low to moderately differentiated adenocarcinoma	27 (71.1)	325 (72.2)	0.024	0.877
Highly differentiated adenocarcinoma	11 (28.9)	125 (27.8)		
Type of TNM				
Type of I-II	20 (52.6)	323 (71.8)	6.151	0.013
Type of III	18 (47.4)	127 (28.2)		
Surgery method				
Laparoscopic radical surgery	9 (23.7)	278 (61.8)	20.991	0.000
Traditional radical surgery	29 (76.3)	172 (38.2)		
Lymph node metastasis or not				
Yes	11 (28.9)	122 (27.1)	0.060	0.807
No	27 (71.1)	328 (72.9)		
With preoperative adjuvant chemotherapy or not				
Yes	13 (34.2)	85 (18.9)	5.125	0.024
No	25 (65.8)	365 (81.1)		
Post-operative ICU stay				
Yes	5 (13.2)	20 (4.4)	5.474	0.019
No	33 (86.8)	430 (95.6)		
Type of pathology				
Ductal gland	30 (78.9)	332 (73.8)	0.489	0.484
Mucus gland	8 (21.1)	118 (26.2)		

TNM: Tumor node metastasis; ICU: Intensive care unit.

surgery, and postoperative Alb, Hb, and potassium levels as independent risk factors for postoperative anastomotic fistulas ($P < 0.05$; Table 6, Figure 2).

Linear regression of FACT-C of anastomotic fistula after radical colon cancer surgery

Multiple linear regression analysis revealed that postoperative anastomotic fistula, advanced age, presence of diabetes, lymph node metastasis, pathological mucinous glands, high postoperative CEA and CA125 Levels, and high preoperative

Table 2 Comparison of perioperative patients after radical colon cancer surgery

Item (mean ± SD)	Operating time (min)	Intraoperative bleeding (mL)	Post-operative time to exhaustion (d)	Postoperative hospitalization time (d)
Anastomotic fistula group	187.39 ± 16.31	229.21 ± 60.81	2.37 ± 0.91	11.76 ± 2.57
Non-anastomotic fistula group	179.96 ± 21.32	187.51 ± 60.51	2.21 ± 0.90	10.76 ± 2.11
t value	-2.098	-4.078	-1.053	-2.777
P value	0.036	0.000	0.293	0.006

Table 3 Comparison of preoperative and postoperative two groups

Item (mean ± SD)	CEA (ng/mL)	CA125 (U/mL)	Alb (g/L)	TP (g/L)	Hb (g/L)	K (mmol/L)
Preoperative group						
Anastomotic fistula group	7.71 ± 0.77	51.51 ± 10.78	33.87 ± 4.74	69.13 ± 9.31	135.18 ± 15.21	3.96 ± 0.18
Non-anastomotic fistula group	7.74 ± 0.81	52.53 ± 10.54	36.22 ± 4.72	69.77 ± 8.04	133.46 ± 13.64	3.94 ± 0.17
t value	0.240	0.574	2.951	0.465	-0.739	-0.549
P value	0.811	0.567	0.003	0.642	0.460	0.583
Postoperative group						
Anastomotic fistula group	5.12 ± 0.90	39.34 ± 10.00	27.70 ± 3.24	55.32 ± 8.83	115.57 ± 14.00	4.89 ± 0.49
Non-anastomotic fistula group	5.01 ± 0.87	39.93 ± 10.11	29.92 ± 3.56	58.37 ± 8.67	120.90 ± 14.06	4.71 ± 0.47
t value	-0.749	0.344	3.716	2.045	2.246	-2.266
P value	0.454	0.731	0.000	0.047	0.025	0.024

CEA: Carcinoembryonic antigen; CA125: Carbohydrate antigen; Alb: Albumin; TP: Total protein; Hb: Hemoglobin; K: Kalium.

Table 4 Functional Assessment of Cancer Therapy-Colorectal of patients after radical colon cancer surgery in two groups

Item (mean ± SD)	First group			Second group		
	PWB	SWB	EWB	FWB	CCS	Total
Anastomotic fistula group	12.50 ± 3.80	18.24 ± 3.77	15.50 ± 3.45	12.66 ± 3.78	15.89 ± 4.59	74.79 ± 11.86
Non-anastomotic fistula group	15.62 ± 3.94	20.06 ± 3.54	18.32 ± 3.36	15.53 ± 4.39	19.52 ± 3.98	89.05 ± 13.32
t value	4.705	3.024	4.962	3.909	4.724	6.389
P value	0	0.003	0	0	0	0

FACT-C: Functional Assessment of Cancer Therapy-Colorectal cancer; PWB: Physical well-being; SWB: Social well-being; EWB: Emotional well-being; FWB: Functional well-being; CCS: Colorectal cancer subscale.

CA125 Levels independently influenced the postoperative prognosis of the patients ($P < 0.05$; Table 7).

DISCUSSION

Colon cancer is a malignancy that is associated with high global incidence and mortality rates[1]. In 2014, colon cancer accounted for approximately one out of every 10 cancers in China[18]. In the United States, colon cancer is among the top three cancers in terms of incidence and mortality[1]. The treatment of colon cancer treatment involves the implementation of various modalities, which are carefully planned based on factors such as the patient's physical condition, tumor pathology, and invasion scope. Individualized and comprehensive treatment approaches are crucial in achieving efficient outcomes. Radical colon cancer surgery is a common clinical procedure that effectively removes diseased tissue. However, this procedure can lead to complications, such as anastomotic fistula, which significantly affects both the quality of life and survival rate of the patient[19]. Previous studies identified anastomotic fistulas as one of the most

Table 5 Survival and recurrence of patients in 1 year to 3 years after surgery in two groups

Item, *n* (%)	Recurrence 1 yr after surgery		Recurrence 2 yr after surgery		Recurrence 3 yr after surgery		Survival 1 yr after surgery		Survival 2 yr after surgery		Survival 3 yr after surgery	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Anastomotic fistula group	4 (10.5)	34 (89.5)	6 (15.8)	32 (84.2)	7 (18.4)	31 (81.6)	34 (89.5)	4 (10.5)	32 (84.2)	6 (15.8)	28 (73.7)	10 (26.3)
Non-anastomotic fistula group	22 (4.9)	428 (95.1)	40 (8.9)	410 (91.1)	50 (11.1)	400 (88.9)	435 (96.7)	15 (3.3)	412 (91.6)	38 (8.4)	382 (84.9)	68 (15.1)
t value	2.208		1.954		1.815		4.845		2.304		3.276	
P value	0.137		0.162		0.178		0.028		0.129		0.07	

serious complications of colon surgery, resulting in prolonged hospital stays and increased treatment costs. Consistent with these findings, our study also found that patients with postoperative anastomotic fistula had a significantly longer average hospital stay compared with those without postoperative anastomotic fistula[20]. The incidence of anastomotic fistula after colon cancer surgery varies from 2.7% to 15.9%[21], with reported postoperative fistula-related mortality rates ranging from 0.8% to 27%[22-24]. Early identification of anastomotic fistulas is, therefore, crucial to reduce subsequent adverse events.

In the present study, we observed an incidence of postoperative anastomotic fistula of 7.8%, which is consistent with previous research findings. The incidence rates of anastomotic fistulas after laparoscopic and open surgeries were 5.1% and 11.8%, respectively, with a statistically significant difference between the two approaches. Our binary logistic regression analysis further confirmed that the choice of surgical approach independently influenced the incidence of postoperative anastomotic fistula. This can be attributed to the advantages of laparoscopic surgery, including smaller incisions, reduced risk of postoperative infection, and faster wound healing, compared with open surgery. The use of carbon dioxide pneumoperitoneum and laparoscopic magnification provides a clearer intraoperative field of view, allowing for more precise tumor localization and avoidance of important structures, such as the blood vessels and nerves. These factors contribute to a lower risk of postoperative anastomotic fistula[25]. Additionally, our binary logistic regression analysis identified patient age, TNM stage, postoperative stay in the ICU, and postoperative Alb, Hb, and K levels as independent risk factors for postoperative anastomotic fistula. Increasing age has been recognized as an important risk factor for surgical patients, with a linear increase in the risk of postoperative complications among patients aged 18 to 69 years and a nearly 10-fold increase in those aged 70 years and older. A consensus exists among domestic and international scholars that surgical tolerance decreases as patients age, leading to increased procedural uncontrollability. The elderly body gradually experiences a decline in the ability to absorb nutrients and perform metabolic functions, resulting in difficulties absorbing the essential nutrients necessary for postsurgical recovery. This difficulty in healing wounds can contribute to the development of anastomotic fistulas. TNM stage serves as an important index for assessing the severity of colon cancer. Higher TNM stages indicate more severe tumor infiltration, invasion of surrounding organs, and a decline in overall body function, indicating a higher risk of postoperative complications[26]. Research has shown that, during the recovery process after radical colorectal surgery, cells require a significant amount of oxygen and nutrients for adequate energy production. Serum Alb, which is associated with protein synthesis and plasma osmolality, is widely used in clinical practice to assess the nutritional level of patients. A lower postoperative Alb level is indicative of poorer nutritional status[27]. Amino acids and proteins play an important role in wound scar stabilization during the remodeling phase[28]. In patients with colon cancer, who often experience chronic wasting, surgical trauma, perioperative fasting, and significant fluid dilution through intravenous rehydration, the postoperative serum Alb level is

Table 6 Binary Logistics regression of anastomotic after radical colon cancer surgery

Related factor	B	SE	Wald	*P* value	OR	95%CI	
						Upper	Lower
Surgery method	-2.304	0.878	6.890	0.009	0.100	0.558	0.018
Age (yr)	0.042	0.017	5.882	0.015	1.043	1.079	1.008
Diabetes	0.602	0.413	2.127	0.145	1.827	4.105	0.813
Type of TNM	0.849	0.415	4.187	0.041	2.337	5.268	1.036
Preoperative adjuvant chemotherapy	0.687	0.457	2.261	0.133	1.987	4.865	0.812
Post-operative ICU stay	1.348	0.664	4.124	0.042	3.850	14.144	1.048
Operating time (min)	-0.015	0.013	1.424	0.233	0.985	1.010	0.960
Intraoperative bleeding (mL)	-0.005	0.006	0.561	0.454	0.995	1.007	0.984
Postoperative hospitalization time (d)	0.160	0.093	2.993	0.084	1.174	1.408	0.979
Preoperative Alb (g/L)	-0.023	0.051	0.210	0.647	0.977	1.080	0.883
Postoperative Alb (g/L)	-0.203	0.078	6.693	0.010	0.817	0.952	0.701
Postoperative TP (g/L)	-0.038	0.025	2.406	0.121	0.963	1.010	0.917
Postoperative Hb (g/L)	-0.030	0.015	4.194	0.041	0.970	0.999	0.943
Postoperative K (mmol/L)	0.960	0.441	4.742	0.029	2.612	6.198	1.101

SE: Standard error; OR: Odds ratio; CI: Confidence interval; TNM: Tumor node metastasis; ICU: Intensive care unit; Alb: Albumin; Hb: Hemoglobin; K: Kalium.

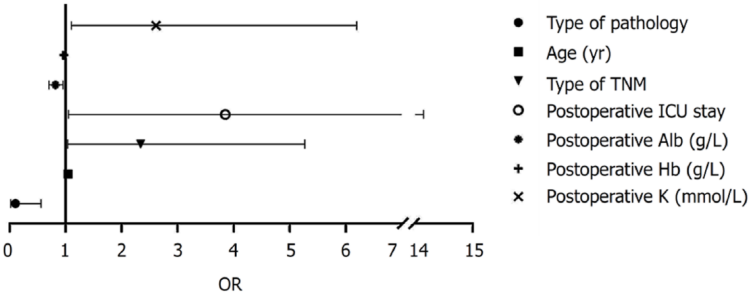

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Figure 2 Binary logistic regression analysis of anastomotic fistula following radical colon cancer surgery. TNM: Tumor, node, metastasis; ICU: Intensive care unit; Alb: Albumin; Hb: Hemoglobin; K: Potassium; OR: Odds ratio.

further reduced. In the state of low Alb level, surgical wound exudate is increased. Prolonged fluid accumulation, coupled with the postoperative inflammatory state, affects the healing of the surgical wound and anastomosis, consequently increasing the risk of anastomotic fistulas. Therefore, in clinical practice, medical staff needs to have a clear understanding of the indications for surgery and ensure timely supplementation of proteins and energy to reduce the risk of postoperative anastomotic fistulas.

Furthermore, the results of the multiple linear regression analysis in the present study revealed that several factors independently influenced the prognosis of patients postoperatively, including the occurrence of postoperative anastomotic fistula, advanced age, presence of diabetes mellitus, lymph node metastasis, pathological type of the mucinous gland, high postoperative CEA and CA125 Levels, and high preoperative CA125 Levels. The presence of postoperative anastomotic fistula significantly reduced the survival rate of patients at one year postoperatively. Diabetes mellitus, a metabolic disease, can lead to abnormal protein metabolism, water-electrolyte imbalance, acid-base disorders, and abnormal fat metabolism. Uncontrolled or unstable diabetes disrupts glucose metabolism, resulting in insufficient energy supply to tissue cells, weakened biological barrier function, and compromised bactericidal ability of the immune system[29]. Surgical procedures themselves, both mental and physical as well as the effects of anesthetic drugs, can increase blood glucose levels, exacerbating the negative impact on patient prognosis. Studies have demonstrated that patients with tubular adenocarcinoma show the highest cumulative survival rates at 1, 3, and 5 years postoperatively, whereas those with mucinous adenocarcinoma and papillary carcinoma have lower cumulative survival rates at 3 and 5 years postoperatively[30]. Lymph node metastasis and mucinous adenocarcinoma contribute to poorer prognosis due to

Table 7 Linear regression of Functional Assessment of Cancer Therapy–Colorectal anastomotic fistula after radical colon cancer surgery

Related factor	B	SE	*t* value	*P* value
Anastomotic fistula	-11.180	2.506	-4.461	0.000
Surgery method	0.060	3.204	0.019	0.985
Age (yr)	-0.148	0.049	-3.012	0.003
Gender	0.221	1.155	0.191	0.848
Hypertension	0.383	1.183	0.323	0.747
Diabetes	-3.292	1.348	-2.443	0.015
Site of lesion	-0.172	0.765	-0.224	0.823
Type of organization	-0.172	1.288	-0.134	0.894
Type of TNM	-2.414	1.322	-1.826	0.069
Lymph node metastasis	-2.694	1.286	-2.094	0.037
Preoperative adjuvant chemotherapy	-0.196	1.511	-0.130	0.897
Post-operative ICU stay	0.480	2.665	0.180	0.857
Type of pathology	-6.303	1.322	-4.768	0.000
Operating time (min)	0.040	0.036	1.116	0.265
Intraoperative bleeding (mL)	-0.014	0.024	-0.572	0.567
Post-operative time to exhaustion (d)	0.731	0.748	0.977	0.329
Postoperative hospitalization time (d)	-0.242	0.270	-0.894	0.372
Preoperative CEA (ng/mL)	0.912	0.709	1.287	0.199
Postoperative CEA (ng/mL)	-1.778	0.782	-2.274	0.023
Preoperative CA125 (U/mL)	0.488	0.170	2.865	0.004
Postoperative CA125 (U/mL)	-0.416	0.178	-2.333	0.020
Preoperative Alb (g/L)	0.077	0.158	0.490	0.624
Postoperative Alb (g/L)	0.381	0.209	1.818	0.070
Preoperative TP (g/L)	0.020	0.178	0.114	0.910
Postoperative TP (g/L)	0.018	0.168	0.108	0.914
Preoperative Hb (g/L)	0.060	0.132	0.455	0.649
Postoperative Hb (g/L)	-0.068	0.131	-0.523	0.601
Preoperative K (mmol/L)	0.244	3.504	0.070	0.945
Postoperative K (mmol/L)	0.437	1.239	0.353	0.724

SE: Standard error; TNM: Tumor node metastasis; ICU: Intensive care unit; CEA: Carcinoembryonic antigen; CA125: Carbohydrate antigen; Alb: Albumin; TP: Total protein; Hb: Hemoglobin; K: Kalium.

their higher malignancy, faster progression, and greater invasiveness.

In conclusion, numerous risk factors contribute to the development of anastomotic fistulas after radical colon cancer surgery. Therefore, healthcare professionals should carefully evaluate the patients' clinical data before surgery. If a high-risk postoperative anastomotic fistula is identified, prompt communication with patients and their families is essential to consider alternative surgical approaches and improve patient prognosis.

This study has two main limitations. First, it is a retrospective cohort study, which may be susceptible to selection bias. Second, it is a single-center clinical study with a relatively small sample size. Future multicenter clinical studies are warranted to validate these findings.

CONCLUSION

Postoperative anastomotic fistula has a significant impact on prognosis and survival rates. Careful consideration of the clinical characteristics and risk factors associated with anastomotic fistula and implementation of individualized preventive measures at an early stage are crucial to reduce its occurrence. In this manner, we can improve patients' prognosis and prolong their life expectancy.

ARTICLE HIGHLIGHTS

Research background

Patients are prone to complications such as anastomotic fistula after radical colon cancer surgery.

Research motivation

Postoperative complications such as anastomotic fistulas have a significant negative impact on patient prognosis.

Research objectives

This study aimed to investigate the risk factors for postoperative anastomotic fistulas and their impact on the prognosis of patients with colon cancer.

Research methods

This retrospective analysis of 488 patients with colon cancer who underwent radical surgery between April 2016 and April 2019 at our research center was summarized, and the risk factors for the development of anastomotic fistula and the impact of anastomotic fistula occurrence on patient prognosis were analyzed.

Research results

A total of 38 (7.8%) of 488 patients who underwent radical surgery for colon cancer had complications of postoperative anastomotic fistula with a mean Functional Assessment of Cancer Therapy-Colorectal score of 74.79 ± 11.86.

Research conclusions

Based on the results of our study, we present the independent risk factors affecting the development of anastomotic fistulas and the prognosis of patients with colon cancer after radical surgery. The main causes and preventive measures are also described.

Research perspectives

Based on the clinical data comparing patients who developed anastomotic fistulas with those who did not, the factors influencing the development of anastomotic fistulas in patients postoperatively were analyzed, and the prognoses of the two groups of patients were compared.

FOOTNOTES

Author contributions: Wang J designed the study; Li MH contributed to the analysis of the manuscript; all authors were involved in the data collection and writing of this article; and all authors have read and approved the final manuscript.

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Informed consent statement: The authors take full responsibility for the accuracy and integrity of the work. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and informed consent was obtained from all patients.

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ORIGINAL ARTICLE

Retrospective Study

Effects and mechanisms of nutritional interventions on extradigestive complications in obese patients

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Abstract

BACKGROUND

Obesity is associated with an increased risk of multiple extradigestive complications. Thus, understanding the global epidemiology of obesity and its relationship with extradigestive complications, such as cardiovascular disease, type 2 diabetes mellitus, and non-alcoholic fatty liver disease is important. However, nutritional intervention can positively manage issues associated with obesity. Hence, the identification of the current high prevalence of extradigestive complica-tions among patients with obesity and the potential role of nutritional interventions is also essential.

AIM

To determine the relationship between obesity and extradigestive complications and emphasize the importance of nutritional interventions in the management of patients with obesity.

METHODS

Overall, 110 patients with obesity admitted to our hospital from February 2020 to November 2022 and 100 healthy individuals were included in the present study. Information of the study population, including demographic characteristics, such as age, sex, body mass index, indicators of extradigestive complications, dietary intake, and biomarkers was collected. The study design, participant selection, interventions, and development of the nutritional intervention program were described. The collected data were analyzed to assess the effect of nutritional inter-ventions on extradigestive complications.

RESULTS

As a part of nutritional intervention, the dietary structure was modified to decrease the saturated fatty acid and cholesterol intake and increase the dietary fiber and polyunsaturated fatty acid intake to improve the blood lipid levels and cardiovascular health. Mechanistic studies showed that these nutritional inter-

ventions positively affected mechanisms that regulate lipid metabolism, improved inflammatory markers in the blood, and improved vascular functions.

CONCLUSION

The study discusses the consistency of the present results with previous findings to assess the clinical significance of the present findings. The study provides direction for future research on improving nutritional intervention strategies.

Key Words: Obesity; Nutritional interventions; Extradigestive complications; Cardiovascular disease; Type 2 diabetes; Non-alcoholic fatty liver disease

Core Tip: Nutritional interventions positively impact extradigestive complications in patients with obesity by modifying the dietary structure to improve lipid metabolism, inflammatory markers, and vascular functions. These findings emphasize the importance of nutritional interventions in managing obesity-related conditions, such as cardiovascular disease, type 2 diabetes, and non-alcoholic fatty liver disease, providing valuable insights for future research on optimizing intervention strategies.

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INTRODUCTION

Obesity is a metabolic disease correlated to an increased risk of multiple extradigestive complications. Nutritional intervention, a crucial management tool, can positively affect weight management, associated disease risk control, and the occurrence of extradigestive complications in patients with obesity by modifying the dietary structure and providing appropriate nutrients[1-5]. The global prevalence of obesity is increasing and is closely related to the development of extradigestive complications, such as cardiovascular disease (CVD), type 2 diabetes mellitus, and non-alcoholic fatty liver disease (NAFLD). Thus, nutritional intervention is clinically important as a nonpharmacological treatment strategy. By modifying the dietary structure and providing appropriate nutrients, nutritional interventions can help with weight management, control of the risk of associated diseases, and reduction in the occurrence of extradigestive complications[6-8].

Introduction to obesity and its worldwide epidemiological data and trends: The relationship between obesity and extradigestive complications has been discussed, highlighting their relevance and importance. Nutritional interventions are important tools for managing patients with obesity patients and preventing complications[9-11]. The association between CVD and obesity has been studied. Nutritional intervention strategies, such as limiting the energy intake, modifying fat and cholesterol intake, and increasing the dietary fiber and polyunsaturated fatty acid (PUFA) intake, are essential to reduce the risk of CVDs. The underlying mechanisms, such as improved lipid metabolism, reduced inflammatory responses, and improved vascular function may help achieve the desired effect of nutritional interventions. Furthermore, nutritional intervention strategies may play a role in improving the insulin sensitivity and glucose metabolism by controlling the glycemic response, weight management, and high-sugar food intake. The possible underlying mechanisms are improving insulin signaling, reduced insulin resistance, and fat accumulation. Additionally, nutritional intervention strategies may play a role in improving hepatic fat accumulation and reducing hepatic inflammation and fibrosis by reducing the fat and sugar intake and increasing the intake of dietary fiber and antioxidants. The possible underlying pathways may be the modulation of fatty acid synthesis and oxidation, amelioration of the hepatic inflammatory response, and reduction in oxidative stress. To summarize the important findings of studies on the effects and mechanisms of nutritional interventions on extradigestive complications in patients with obesity[12-15]. Thus, in the present study, we aimed to investigate the effect of nutritional interventions on extradigestive complications in patients with obesity and the mechanisms underlying this effect. Furthermore, we emphasized the potential and importance of nutritional interventions in preventing and managing obesity and obesity-related complications.

MATERIALS AND METHODS

Research design

The present study was conducted on 110 patients with obesity admitted to our hospital from February 2020 to November

2022 and 100 normal individuals. We selected the study design of "randomized controlled trial" to evaluate the effects and mechanisms of nutritional interventions on extradigestive complications in patients with obesity. The participants were randomized into the following two groups: An intervention group and a control group.

Research subjects

Patients with obesity meeting the following criteria were selected as study subjects: age range, 18-60 years, and diagnostic criterion, body mass index (BMI) ≥ 30 kg/m^2. The exclusion criteria were as follows: Patients with other important underlying diseases, including metabolic diseases and CVDs and patients undergoing other interventions, such as taking medications for other health conditions.

Nutritional intervention program

In the intervention group, a specific nutritional intervention program was implemented, which involved the following: Energy control: Individualized energy intake targets were set based on the participants' body composition, activity levels, and metabolic needs and dietary composition. The diets of the participants were modified to limit saturated fatty acid (SFA) and cholesterol intake and increase the dietary fiber and PUFA intake. Nutritional education and individualized dietary guidance were provided to help the patients understand and adopt healthy eating habits. The control group received routine standard care and non-interventional general advice such as general dietary guidance or lifestyle advice.

Observation indicators

(1) Pre and post-intervention data collection included, but was not limited to, the following demographic characteristics: age, sex, and BMI; (2) Indicators of extradigestive complications included information on the occurrence and severity of several extradigestive complications associated with obesity, such as the indicators of CVD risk, diabetes mellitus, and liver function; (3) Dietary intake data: Information on the patients' diets, including energy, fat, fiber, and other nutrients, was collected using the methods of recording food intake or dietary review, and (4) Biomarkers: Blood markers, such as lipid and blood glucose levels, liver function indicators, and urine markers.

Data analysis

Means and standard deviations were calculated to statistically analyze the demographic characteristics of the groups and baseline data. Changes in the indicators of extradigestive complications between the intervention and control groups were compared by statistical methods, such as the independent samples *t*-test and chi-square test. The relationship between the indicators of extradigestive complications and dietary intake data after the intervention was explored by calculating the pearson's correlation coefficient. Differences were considered statistically significant at $P < 0.05$.

RESULTS

General information

No statistically significant difference was observed between the intervention and control groups in terms of age (52.4 ± 1.0 years) *vs.* (51.2 ± 1.3 years), body weight, BMI, literacy level, and the monthly household income ($P > 0.05$). No difference was observed regarding the use of antihypertensive medications between the two groups at baseline. The dosage and frequency of drug consumption remained unchanged for the subjects throughout the trial, and no adverse effects or reactions were reported. None of the participants withdrew from the study for any reason. The baseline characteristics of the patients are summarized in Table 1.

Indicators of CVD risk

No difference in diastolic blood pressure was observed between the subjects in the two groups after the intervention, whereas the systolic blood pressure of the subjects in the intervention group was lower than that of the subjects in the control group ($P < 0.05$). After four weeks of dietary intervention, the systolic and diastolic blood pressures of the subjects in both groups decreased; however, the decrease observed in the intervention group was more pronounced, with a statistically significant difference (Table 2).

Nutrient intake of subjects in the control and intervention groups

The mean intake of protein, carbohydrates, dietary fiber, potassium, calcium, and magnesium in the intervention group was higher than that in the control group. Additionally, the mean intake of energy, fat, cholesterol, SFA, monounsaturated fatty acid, PUFA, and sodium in the intervention group was lower than that in the control group ($P < 0.05$ for both) (Table 3).

Comparison of liver function indices between the two groups before and after intervention

No statistically significant differences in the serum alanine transaminase (ALT) and aspartate aminotransferase (AST) levels were observed between the intervention and control groups before the intervention. After four weeks of dietary intervention, the ALT and AST levels in the intervention group were lower than those before the intervention, and the differences were statistically significant ($P < 0.05$) (Table 4).

Table 1 Baseline characteristics of the control and intervention groups (mean ± SE)

Variant	Control group (*n* = 110)	Intervention group (*n* = 110)	*P* value
Age (yr)	28-63 (51.2 ± 1.3)	36-68 (52.4 ± 1.0)	0.488
Sex [cases (%)]			
Males	25 (22.73)	27 (24.55)	0.605
Females	85 (77.27)	83 (75.45)	
Weight (kg)	67.7 ± 1.7	69.2 ± 1.6	0.526
Height (cm)	170.7 ± 1.4	172.4 ± 1.3	0.385
BMI (kg/m^2)	25.1 ± 0.4	25.1 ± 0.4	0.959
SBP (mmHg)	141.4 ± 1.4	141.9 ± 1.4	0.788
DBP (mmHg)	89.7 ± 1.5	89.5 ± 1.7	0.913
MDA (nmol/L)	4.24 ± 1.7	4.74 ± 1.5	0.196
GSH (μmol/L)	7.95 ± 3.2	6.93 ± 3.4	0.251
SOD (U/mL)	74.21 ± 12.3	67.66 ± 13.4	0.051
Heart rate (time/min)	78.1 ± 1.6	78.9 ± 1.3	0.693
[1]Educational level	3:16:16	4:18:14	0.827
[2]Monthly household income	8:14:13	6:15:15	0.799

[1]University/undergraduate and above: High school/junior high school: primary school and below.
[2]$20,000 and above: $10,000 to $20,000:$10,000 and below. BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; MDA: Mobile device assistant; GSH: Glutathione; SOD: Superoxide dismutase.

Table 2 Post-intervention changes in the blood pressure between the intervention and control groups (mean ± SE)

Norm	Control subjects		Intervention group	*P* value
DBP (mmHg)	Start of intervention	86.4 ± 1.4	83.9 ± 1.7	0.241
	End of intervention	82.8 ± 1.6	76.6 ± 1.6	0.007
	Amount of change before and after intervention	3.6 ± 1.1	7.3 ± 1.1	0.000
SBP (mmHg)	Start of intervention	137.3 ± 1.4	133.2 ± 1.1	0.021
	End of intervention	131.1 ± 1.6	116.3 ± 1.5	0.000
	Amount of change before and after intervention	6.2 ± 2.0	16.9 ± 1.4	0.022

SBP: Systolic blood pressure; DBP: Diastolic blood pressure.

Logistic multifactorial regression analysis of factors affecting the occurrence of extradigestive complications in patients with obesity

A logistic multifactorial regression analysis was performed on the dependent variables associated with extradigestive complications that occurred in patients with lacunar cerebral infarction. The indices with $P < 0.05$ in the above univariate analysis were used as independent variables. The results showed that a history of high blood pressure and high levels of low-density lipoprotein-C, platelet endothelial cell adhesion molecule (PECAM)-1, and fibroblast growth factor (FGF)21 were identified as risk factors for extradigestive complication occurrence in patients with lacunar cerebral infarction ($P < 0.01$), whereas high levels of low-density lipoprotein (HDL)-C and growth differentiation factor (GDF)11 were identified as protective factors ($P < 0.05$). High levels of HDL-C, PECAM-1, and FGF21 were identified as risk factors for extradigestive complication development in patients with lacunar cerebral infarction ($P < 0.01$), whereas high levels of serum HDL-C and GDF11 were identified as protective factors ($P < 0.05$) (Table 5).

Diagnostic value of serum PECAM-1, GDF11, and FGF21 levels for extradigestive complications in patients with obesity

The receiver operating characteristic (ROC) curve showed that the area under the curve (AUC) values of serum PECAM-1, GDF11, and FGF21 levels as well as the combination of these three diagnostic indicators for carotid atherosclerosis were

Table 3 Nutrient intake in the control and intervention groups (mean ± SE)

Original proposal	Control subjects	Intervention group	*P* value
Energy (kcal)	2033.74 ± 19.45	1953.01 ± 18.55	0.036
Fat (g)	94.21 ± 1.13	50.79 ± 0.75	0.001
Protein (g)	76.42 ± 0.97	97.72 ± 0.89	0.017
Carbohydrates (g)	226.79 ± 3.29	275.03 ± 4.21	0.029
Dietary fiber (g)	10.28 ± 0.11	25.22 ± 1.59	0.005
Cholesterol (mg)	554.96 ± 3.84	473.30 ± 7.33	0.012
SFA (g)	47.58 ± 1.21	27.83 ± 0.28	0.006
MUFA (g)	29.5 ± 0.37	12.44 ± 0.10	0.001
PUFA (g)	20.20 ± 0.21	12.34 ± 0.28	0.013
Sodium (mg)	4347.28 ± 46.34	2284.86 ± 12.43	0.001
Potassium (mg)	1663.15 ± 11.14	3088.78 ± 67.37	0.001
Calcium (mg)	483.84 ± 14.09	864.32 ± 21.60	0.001
Magnesium (mg)	259.97 ± 2.28	479.05 ± 14.12	0.014

SFA: Saturated fatty acid; MUFA: Modulation of fatty acid; PUFA: Polyunsaturated fatty acid.

Table 4 Comparison of the levels of oxidative stress indicators between the intervention and control groups (mean ± SE)

Norm	Control subjects		Intervention group	*P* value
ALT (nmol/L)	End of intervention	115.29 ± 1.2	63.94 ± 1.4	0.001
	Amount of change before and after intervention	21.25 ± 0.2	20.6 ± 0.1	0.015
AST (μmol/L)	End of intervention	157.15 ± 3.5	59.00 ± 2.8	0.017
	Amount of change before and after intervention	20.6 ± 0.2	22.17 ± 0.1	0.021

ALT: Alanine transaminas; AST: Aspartate aminotransferase.

Table 5 Logistic multifactorial regression analysis of factors affecting the occurrence of extradigestive complications in patients with obesity

Variables	β-value	SE value	Wald value	*P* value	OR value	95%CI
History of hypertension	1.296	0.421	9.470	0.002	3.654	1.601-8.343
TC high	0.226	0.138	2.685	0.101	1.254	0.957-1.643
TG high	0.305	0.211	2.091	0.148	1.356	0.897-2.051
HDL-C high	-0.247	0.123	4.002	0.045	0.781	0.613-0.995
LDL-C high	0.909	0.254	12.787	< 0.001	2.481	1.508-4.085
PECAM-1 high	0.070	0.019	12.930	< 0.001	1.073	1.032-1.114
GDF11 high	-0.008	0.003	9.199	0.002	0.992	0.987-0.997
FGF21 high	0.024	0.007	13.062	< 0.001	1.024	1.011-1.038

OR: Odds ratio; CI: Confidenceinterval; TC: Total cholesterol; TG: Triacylglycerol; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholestero; PECAM-1: Platelet endothelial cell adhesion molecule-1; GDF11: Growth differentiation factor 11; FGF21: Fibroblast growth factor 21.

Table 6 Receiver operating characteristic curve analysis of the serum levels of platelet endothelial cell adhesion molecule-1, growth differentiation factor 11, and fibroblast growth factor 21 in predicting the occurrence of extradigestive complications in patients with obesity

Indicators	Cut-of value	AUC (95%CI)	Sensitivity	Specificity	Jordon index
PECAM-1	40 μg/L	0.798 (0.595-0.974)	0.824	0.744	0.568
GDF11	650 μg/L	0.716 (0.509 -0.929)	0.716	0.733	0.449
FGF21	160 ng/L	0.813 (0.671-0.940)	0.811	0.791	0.602
Tripartite		0.909 (0.850-0.958)	0.919	0.884	0.803

AUC: Area under the curve; CI: Confidenceinterval; PECAM-1: Platelet endothelial cell adhesion molecule-1; GDF11: Growth differentiation factor 11; FGF21: Fibroblast growth factor 21.

0.798, 0.716, 0.813, and 0.909, respectively. Furthermore, the efficacy of the combination was higher than that of each indicator alone (Z/*P* = 2.097/0.036, 2.290/0.022, 2.005/0.045, 022, and 2.005/0.045) (Table 6).

DISCUSSION

Patients with obesity often show symptoms, such as high blood pressure, cholesterol, and blood glucose levels, which are considered CVD risk factors[16-18]. Nutritional interventions, such as limiting the energy intake and improving diet quality can reduce the risk of CVD. For instance, reducing the saturated fat and cholesterol intake, and increasing the dietary fiber and whole grain intake can help improve lipid and glycemic control.

Patients with obesity often suffer from disease. Nutritional interventions, such as limiting the energy intake can improve NAFLD by improving the lipid metabolism and reducing liver fat accumulation. A diet limiting the consumption of high-sugar and high-fat foods, increasing the antioxidant and anti-inflammatory food intake, and reducing alcohol consumption can positively affect liver health[19].

Obesity is an important risk factor of insulin resistance and type 2 diabetes. Nutritional interventions that reduce the energy intake, control the carbohydrate intake, and aid in the consumption of foods with a low glycemic index can reduce the risk of insulin resistance and diabetes by improving insulin sensitivity[20].

Finally, the ROC curve analysis showed that the serum levels of PECAM-1, GDF11, and FGF21 possessed high diagnostic values for extradigestive complications in patients with obesity, and the diagnostic value was further improved when the combination of the three indicators was considered (AUC = 0.909). The diagnostic sensitivity, specificity, and accuracy of the combination were 0.919, 0.884, and 0.900, respectively. Nutritional intervention is a clinically important non-pharmacological treatment strategy. By modifying the dietary structure and providing appropriate nutrients, nutritional interventions help control body weight, manage the risk of associated diseases, and reduce the incidence of extragastrointestinal complications. Despite the creativity of the study, it is not yet possible to list all the possibilities due to the limitations of the sample size and research model; future studies should expand the sample size and age structure to exclude these limitations.

CONCLUSION

In conclusion, the levels of PECAM-1, GDF11, and FGF21 are related to cerebral arterial hemodynamic parameters in extradigestive complications in patients with obesity; thus, they can be considered as factors affecting the extradigestive complications in patients with obesity. Moreover, the combination of the three has a better diagnostic value for extradigestive complications in patients with obesity.

ARTICLE HIGHLIGHTS

Research background

Obesity is associated with an increased risk of multiple extradigestive complications. Thus, understanding the global epidemiology of obesity and its relationship with extradigestive complications, such as cardiovascular disease, type 2 diabetes mellitus, and non-alcoholic fatty liver disease, is important. Nutritional interventions can also positively manage obesity-associated issues.

Research motivation

In the present study, we aimed to determine the relationship between obesity and extradigestive complications and

emphasize the importance of nutritional interventions in managing patients with obesity.

Research objectives

Hence, identification of the current high prevalence of extradigestive complications among patients with obesity and the potential role of nutritional interventions are essential.

Research methods

Overall, 110 patients with obesity admitted to our hospital from February 2020 to November 2022 and 100 healthy individuals were included in the present analysis. Information regarding demographic characteristics, such as age, sex, body mass index, indicators of extradigestive complications, dietary intake, and biomarkers, was collected. The study design, participant selection, interventions, and development of the nutritional intervention program were described. The collected data were analyzed to assess the effects of nutritional interventions on extradigestive complications.

Research results

As part of the nutritional intervention, the dietary structure was modified to decrease the saturated fatty acid and cholesterol intake and increase the dietary fiber and polyunsaturated fatty acid intake to improve the blood lipid levels and cardiovascular health. Mechanistic studies have shown that nutritional interventions positively affect mechanisms that regulate lipid metabolism, improve inflammatory markers in the blood, and improve vascular function.

Research conclusions

The present study explains the possible mechanisms by which nutritional interventions affect extradigestive complications in patients with obesity. Moreover, we discuss the consistency of the present results with previous findings to assess the clinical significance of the present findings.

Research perspectives

The study provides directions for future research on improving nutritional intervention strategies.

FOOTNOTES

Co-first authors: Li Jiang and Lu-Lian Xu.

Author contributions: Jiang L, Xu LL, Lu Y, Gu KF, Qian SY, Wang XP, and Xu X designed the research study; Jiang L, Xu LL, Lu Y, Gu KF, Qian SY, Wang XP, and Xu X performed the research; Jiang L, Xu LL, and Xu X contributed new reagents and analytic tools; Jiang L, Xu LL, and Xu X analyzed the data and wrote the manuscript; All authors have read and approved the final manuscript. Jiang L and Xu LL contributed equally to this work as co-first authors. The reasons for designating Jiang L and Xu LL as co-first authors are threefold. First, the research was performed as a collaborative effort, and the designation of co-first 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, the overall research team encompassed authors with a variety of expertise and skills from different fields, and the designation of co-first 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, Jiang L and Xu LL 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 Jiang L and Xu LL as co-first authors of is fitting for our manuscript as it accurately reflects our team's collaborative spirit, equal contributions, and diversity.

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ORIGINAL ARTICLE

Retrospective Study

Hepatic venous pressure gradient: Inaccurately estimates portal venous pressure gradient in alcoholic cirrhosis and portal hypertension

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Abstract

BACKGROUND

Portal hypertension (PHT) in patients with alcoholic cirrhosis causes a range of clinical symptoms, including gastroesophageal varices and ascites. The hepatic venous pressure gradient (HVPG), which is easier to measure, has replaced the portal venous pressure gradient (PPG) as the gold standard for diagnosing PHT in clinical practice. Therefore, attention should be paid to the correlation between HVPG and PPG.

AIM

To explore the correlation between HVPG and PPG in patients with alcoholic cirrhosis and PHT.

METHODS

Between January 2017 and June 2020, 134 patients with alcoholic cirrhosis and PHT who met the inclusion criteria underwent various pressure measurements during transjugular intrahepatic portosystemic shunt procedures. Correlations were assessed using Pearson's correlation coefficient to estimate the correlation coefficient (r) and determination coefficient (R^2). Bland-Altman plots were constructed to further analyze the agreement between the measurements. Disagreements were analyzed using paired *t* tests, and *P* values < 0.05 were considered statistically significant.

RESULTS

In this study, the correlation coefficient (r) and determination coefficient (R^2)

between HVPG and PPG were 0.201 and 0.040, respectively (P = 0.020). In the 108 patients with no collateral branch, the average wedged hepatic venous pressure was lower than the average portal venous pressure (30.65 ± 8.17 *vs*. 33.25 ± 6.60 mmHg, P = 0.002). Hepatic collaterals were identified in 26 cases with balloon occlusion hepatic venography (19.4%), while the average PPG was significantly higher than the average HVPG (25.94 ± 7.42 mmHg *vs* 9.86 ± 7.44 mmHg; P < 0.001). The differences between HVPG and PPG < 5 mmHg in the collateral *vs* no collateral branch groups were three cases (11.54%) and 44 cases (40.74%), respectively.

CONCLUSION

In most patients, HVPG cannot accurately represent PPG. The formation of hepatic collaterals is a vital reason for the strong underestimation of HVPG.

Key Words: Portal hypertension; Portal venous pressure gradient; Hepatic venous pressure gradient; Alcoholic cirrhosis; Hepatic collateral

Core Tip: Portal hypertension (PHT) in alcoholic cirrhosis causes a range of clinical symptoms, including gastroesophageal varices and ascites. Because it is easier to measure, the hepatic venous pressure gradient (HVPG) has replaced the portal venous pressure gradient (PPG) as the gold standard for diagnosing PHT in clinical practice. However, our study showed a poor correlation between HVPG and PPG in patients with PHT and alcoholic cirrhosis. The underestimation of HVPG may be related to the formation of hepatic collaterals.

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INTRODUCTION

Alcoholic cirrhosis is a vital factor in portal hypertension (PHT), with an increased prevalence in recent years[1]. The blood alcohol concentration in those with extended periods of heavy drinking tends to exceed the recommended consumption limits by far. With intrahepatic vasoconstriction, the blood flow is decreased, and hemodynamic disorder occurs, which can trigger hepatic microvascular disturbances and hypoxemia[2]. Hepatocellular necrosis can occur, leading to fibrosis. This gradual development causes the segmentation and destruction of the normal structure of the hepatic lobules, with the occurrence of pseudolobules and nodular regeneration of hepatocytes, development of alcoholic cirrhosis[3], and progression to PHT. The initial stage has no characteristic symptoms, while a series of clinical patterns may occur during decompensation in patients with alcoholic cirrhosis, including gastroesophageal varices, gastrointestinal bleeding, and ascites[4,5]. These symptoms are directly related to an increased portal venous pressure (PVP), which contributes to the accurate diagnosis and prognosis of patients with PHT[6]. The PVP gradient (PPG) is the gold standard for the diagnosis of PHT. PPG is calculated by subtracting the inferior vena cava (IVC) pressure (IVCP) from PVP. The portal vein is located in the abdominal cavity, and PVP measurements requires strong technical skills. PVP is measured by direct cannulation of the portal vein, which is more invasive and carries a higher risk than the wedged hepatic venous pressure (WHVP). Therefore, PVP cannot be applied in a broad range of clinical settings. Currently, WHVP is used to represent PVP. The hepatic venous pressure gradient (HVPG) is calculated by subtracting the free hepatic venous pressure (FHVP) from WHVP. Because the technique for measuring hepatic vein pressure is simple, HVPG has been the gold standard in PHT diagnosis, as it indirectly reflects PPG[7].

Few studies have deeply explored the relationship between HVPG and PPG in patients with alcoholic cirrhosis and PHT. Therefore, whether HVPG can represent PPG remains controversial.

The present study aimed to examine the correlation between HVPG and PPG in patients with alcoholic cirrhosis and complications of PHT as well as determine whether HVPG can represent PPG.

MATERIALS AND METHODS

Patients' basic information

We performed a retrospective study of patients with alcoholic cirrhosis and PHT complications who underwent transjugular intrahepatic portosystemic shunt (TIPS) placement and were admitted to our hospital between June 2017 and June 2020. Approval for the study was obtained from the ethics committee of our institution, and all patients provided informed consent to undergo TIPS creation and pressure measurements. The following inclusion criteria were applied: (1)

Table 1 Baseline characteristics of study patients

	Collateral branch (*n* = 26)	No collateral branch (*n* = 108)	*P* value
Sex (male/female)	24/2 (92.3/7.7%)	95/13 (88.0/12.0%)	0.776
Age (yr)[1]	52.3 ± 10.7	55.7 ± 10.6	0.143
Indications (*n*)			0.865
Gastrointestinal bleeding	17	60	
Refractory ascites	7	39	
Both	1	5	
Other conditions	1	4	
Child-Puph score[1]	7.2 ± 1.7	7.3 ± 1.7	0.878
Child-Pugh class			0.644
A	8 (30.8%)	44 (40.7%)	
B	15 (57.7%)	53 (49.1%)	
C	3 (11.5%)	11 (10.2%)	
Hepatocellular carcinoma	3 (11.5%)	12 (11.1%)	> 0.999

[1]Data are mean ± SD.

Indication for TIPS; (2) age of 18-75 years; (3) elective TIPS surgery; and (4) normal hepatic veins and IVC. The following exclusion criteria were applied: (1) Portal vein tumor thrombus; (2) arteriovenous fistula; (3) portal vein thrombosis affecting blood flow (*e.g.*, generally occurring over one-third of the main portal vein); (4) administration of drugs affecting PVP within 1 wk; and (5) intraoperative factors affecting the accuracy of manometry, such as gallbladder cardiac reflex and incomplete balloon closure.

A total of 134 patients with alcoholic cirrhosis and PHT complications undergoing TIPS were included in this study. Various venous pressures were measured during the TIPS procedure, and HVPG and PPG were calculated. Patient characteristics are summarized in Table 1. Patients were aged from 18–75 years old (average, 55.02 ± 10.65 years) and included 119 men (88.8%) and 15 women (11.2%). Of the 134 patients, 77 cases were complicated by gastrointestinal bleeding (57.5%), 46 had refractory ascites (34.3%), 6 had gastrointestinal bleeding associated with refractory ascites (4.5%), and 5 had other conditions (*e.g.*, shunt restenosis and abdominal pain). According to the Child-Pugh classification, 52 (38.8%) patients had class A, 68 (50.8%) had class B, and 14 (10.4%) had class C liver disease. Fifteen patients with alcoholic cirrhosis and PHT also had hepatocellular carcinoma.

Pressure measurement method

Preoperatively, all patients underwent various examinations, including a complete blood count, biochemical tests; quantitation of liver function; analysis of the indocyanine green retention rate at 15 min, blood ammonia level, blood type, coagulation status, and tumor markers; electrocardiogram; portal vein ultrasound; and enhanced abdominal CT and/or magnetic resonance examination. The coagulation status, platelet count, and bilirubin, albumin, and hemoglobin levels were adjusted to adapt to interventional surgery. The effects and risks of the surgery were explained to the patients and their families, and informed consent was obtained. The ethics committee of the hospital approved the protocol [2018(01)], and all patients provided written informed consent to participate in the study.

The method for measuring the hepatic pressure has been described previously[8]. Briefly, after routine disinfection and towel placement, the right internal jugular vein was punctured under local anesthesia and intubation was performed. The Rösch-Uchida Transjugular Liver Access Set (RUPS-100, specialized for TIPS; Cook Medical, United States) was placed in the right atrium and IVC, and the pressure was measured. A Fogarty balloon catheter (Edwards Lifesciences, United States) was inserted through the 10-French outer sheath. Under the guidance of the guidewire, the catheter was passed through the superior vena cava, right atrium, and IVC and was then advanced into the hepatic vein. The balloon-tipped catheter was placed 3–5 cm peripheral to the junction of the hepatic vein and the IVC. WHVP and FHVP measurements were obtained before and after occlusion of the hepatic vein using a balloon inflated with 5 mL of contrast medium. All measurements were performed three times. Pressure values were recorded when they were stable, and the mean WHVP and FHVP values were taken; HVPG was subsequently calculated. After measurements, the balloon was blocked to obtain occluded hepatic venography (15 mL of contrast agent, 5 mL/s, pressure 200–300 psi), and WHVP and FHVP were remeasured. After observing the balloon catheter occlusion after balloon expansion, the balloon catheter position was adjusted for retesting and angiography once occlusion occurred. The hepatic parenchyma and portal vein were punctured through the IVC or hepatic vein. After a successful puncture, a pigtail catheter was inserted into the splenic or superior mesenteric vein for venography. Before shunting, the pressure of the main trunk of the portal vein was measured three times for an average value, and PPG was calculated. Subsequently, the liver tissue from the preshunt

channel was obtained, and the shunt channel was established. The pressure of the main trunk of the portal vein was remeasured three times for an average value, and PPG was calculated. An indwelling catheter was placed in the portal vein for at least 24 h postoperatively, and PVP was measured three times daily. IVCP and right atrial pressure measurements were repeated three times during extubation to obtain average values.

Statistical methods

Statistical analyses were performed using SPSS (version 25.0; IBM SPSS Statistics, NC, United States) and GraphPad Prism 8 (GraphPad, Inc., La Jolla, CA, United States). The results are expressed as mean ± SD. Correlations were assessed using Pearson's correlation coefficient to estimate the correlation coefficient (r) and the determination coefficient (R^2). Bland-Altman plots were constructed to further analyze the agreement between measurements. Differences between PPG and HVPG, WHVP and PVP, and FHVP and IVCP were analyzed using paired t-test. Statistical significance was set at P values < 0.05.

RESULTS

Among the 134 patients with alcoholic cirrhosis with PHT complications, intraoperative venograms showed portal vein collateral formation in 26 (19.40%) patients and no portal vein collateralization in 108 (80.60%) patients (Figure 1). As shown in Figure 2, WHVP and HVPG were significantly lower than PVP and HVPG, respectively. The average FHVP was higher than the average IVCP.

In the 134 patients with alcoholic cirrhosis with PHT complications, the average WHVP was lower than the average PVP (28.70 ± 8.78 mmHg *vs* 33.58 ± 6.91 mmHg; $P < 0.001$) (Table 2). The r and R^2 values between WHVP and PVP were 0.270 and 0.073, respectively ($P = 0.002$), and the average difference between them was -4.82 ± 9.60 mmHg [95% limits of agreement (LoA) -23.64 to 13.99] (Table 3 and Figure 3). The average HVPG was lower than the average PPG (16.96 ± 9.41 mmHg *vs* 24.73 ± 6.92 mmHg; $P < 0.001$) (Table 2). The r and R^2 values between the HVPG and PPG were 0.201 and 0.040, respectively ($P = 0.020$), and the average difference between them was -7.77 ± 10.50 mmHg (95% LoA -28.35 to 12.80) (Table 3 and Figure 3).

In the 26 patients with collateral branches, the average WHVP was lower than the average PVP (20.89 ± 6.69 mmHg *vs* 34.96 ± 8.08 mmHg; $P < 0.001$) (Table 2). The r and R^2 values between WHVP and PVP were 0.303 and 0.092, respectively ($P = 0.133$), and the average difference between them was 14.07 ± 8.79 mmHg (95% LoA -3.16 to 31.31) (Table 3 and Figure 4). The average HVPG was lower than the average PPG (9.86 ± 7.44 mmHg *vs* 25.94 ± 7.42 mmHg; $P < 0.001$) (Table 2). The r and R^2 values between the HVPG and PPG were 0.208 and 0.043, respectively ($P = 0.309$), and the average difference between them was 16.08 ± 9.35 mmHg (95% LoA -2.25 to 34.40) (Table 3 and Figure 4).

In the 108 patients with no collateral branches, the average WHVP was lower than the average PVP (30.65 ± 8.17 mmHg *vs* 33.25 ± 6.60 mmHg; $P = 0.002$) (Table 2). The r and R^2 values between WHVP and PVP were 0.368 and 0.135, respectively ($P < 0.001$), and the average difference between them was 2.60 ± 8.41 mmHg (95% LoA -13.88 to 19.07) (Table 3 and Figure 5). The average HVPG was lower than the average PPG (18.67 ± 9.05 mmHg *vs* 24.44 ± 6.79 mmHg; $P < 0.001$) (Table 2). The r and R^2 values between the HVPG and PPG were 0.263 and 0.069, respectively ($P = 0.006$), and the average difference between them was 5.77 ± 9.79 mmHg (95% LoA -13.41 to 24.95 mmHg (mean) (Table 3 and Figure 5).

As shown in Figure 6, 3 (11.54%) patients in the collateral branches group and 59 (54.63%) patients in the no collateral branches groups had differences between WHVP and PVP of less than 5 mmHg. In addition, 3 (11.54%) patients in the collateral branches group and 44 (40.74%) patients in the no collateral branches groups had differences between HVPG and PPG of less than 5 mmHg.

DISCUSSION

Alcoholic cirrhosis associated with PHT is a common liver disease. Based on the pathological changes in the liver, significant changes in liver hemodynamics occur, and vascular resistance is increased, causing gradually elevated PVP. Clinically, the symptoms gradually become more conspicuous and their severity is directly associated with the degree of PVP[9]. In clinical practice, the degree of PHT in patients with liver cirrhosis is mainly evaluated based on clinical symptoms, signs, imaging examinations, and gastroscopy; however, these evaluation methods typically have a low sensitivity. Accurate assessments require direct PVP measurements[10]. Comparing the risks and benefits of the assessment, the technique is too complicated, and the trauma is too severe. In recent years, many researchers have measured the hepatic vein pressure instead of directly measuring PVP as the gold standard to reflect PVP in clinical applications[11,12]. Research on noninvasive portal vein manometry also considers the hepatic vein pressure as a standard. There are two principal ways to measure the hepatic vein pressure: Intubating the hepatic vein through the jugular or femoral vein to measure WHVP or FHVP, respectively. HVPG is calculated by subtracting FHVP from WHVP. WHVP can be measured using two methods: Measuring the pressure after the balloon blocks the hepatic vein or obtaining the pressure by inserting an end-hole catheter into the end of the branch of the hepatic vein. The former method is more accurate and is commonly used[13]. In normal liver hemodynamics, PVP is equal to or greater than the hepatic sinus pressure, WHVP is equal to the hepatic sinus pressure, and FHVP is 0.5–1.0 mmHg higher than IVCP[7]. Therefore, HVPG indirectly represents PPG and the portal vein perfusion pressure[8,14]. It is more meaningful to use PPG than PVP to predict the risk of various PHT complications[8,15]. Significant pathological changes occur in the hepatic tissue

Table 2 Differences between wedged hepatic venous pressure and portal venous pressure and between hepatic venous pressure gradient and portal venous pressure gradient in patients with and without collateral branches

	WHVP (mmHg)	PVP (mmHg)	*P* value	95%CI	HVPG (mmHg)	PPG (mmHg)	*P* value	95%CI
With collateral branches (*n* = 26)	20.89 ± 6.69	34.96 ± 8.08	< 0.001	10.52-17.63	9.86 ± 7.44	25.94 ± 7.42	< 0.001	12.30-19.86
No collateral branch (*n* = 108)	30.65 ± 8.17	33.25 ± 6.60	0.002	0.99-4.20	18.67 ± 9.05	24.44 ± 6.79	< 0.001	3.91-7.64
Total (*n* = 134)	28.70 ± 8.78	33.58 ± 6.91	< 0.001	3.18-6.46	16.96 ± 9.41	24.73 ± 6.92	< 0.001	5.98-9.57

95%CI: 95% confidence interval; WHVP: Wedged hepatic venous pressure; PVP: Portal venous pressure; HVPG: Hepatic venous pressure gradient; PPG: Portal venous pressure gradient.

Table 3 Relationships between wedged hepatic venous pressure and portal venous pressure and between hepatic venous pressure gradient and portal venous pressure gradient in patients with and without collateral branches

	WHVP and PVP				HVPG and PPG			
	r	R^2	*P* value	95% LoA (mmHg)	r	R^2	*P* value	95% LoA (mmHg)
With collateral branches (*n* = 26)	0.303	0.092	0.133	-3.16-31.31	0.208	0.043	0.309	-2.25-34.40
No collateral branch (*n* = 108)	0.368	0.135	< 0.001	-13.88-19.07	0.263	0.069	0.006	-13.41-24.95
Total (*n* = 134)	0.270	0.073	0.002	-23.64-13.99	0.201	0.040	0.020	-28.35-12.80

LoA: Limits of agreement; WHVP: Wedged hepatic venous pressure; PVP: Portal venous pressure; HVPG: Hepatic venous pressure gradient; PPG: Portal venous pressure gradient.

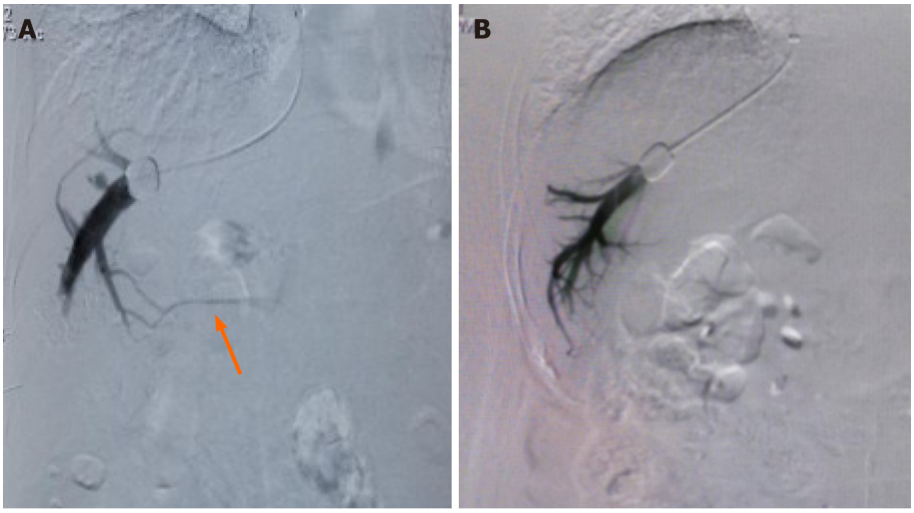

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Figure 1 Hepatic venography during transjugular intrahepatic portosystemic shunt. A: Hepatic vein collateral branches (orange arrow) as shown on venography imagery; B: Venography image demonstrating the absence of hepatic vein collateral branch.

structure of patients with alcoholic cirrhosis and PHT, resulting in significant changes in liver hemodynamics. Regarding whether WHVP is representative of PVP, some scholars believe that WHVP and PVP are correlated in patients with alcoholic cirrhosis[16,17]. However, this remains controversial, as the number of cases is limited. Difference in WHVP and PVP have been reported in patients with cirrhosis with the same etiology but different pathology types. In macronodular cirrhosis, WHVP and PVP are poorly correlated[18], possibly due to the existence of normal tissues between macronodules[16]. Few studies have reported whether HVPG can accurately reflect PPG. The results of this study showed that the correlation between WHVP and PVP is very poor, and the correlation between HVPG and PPG also poor. In 47 patients, PPG exceeded HVPG by less than 5 mmHg, accounting for 35.1% of patients. Therefore, most HVPG measurements cannot accurately represent PPG, partly because of the vascularization of the collateral branches of the

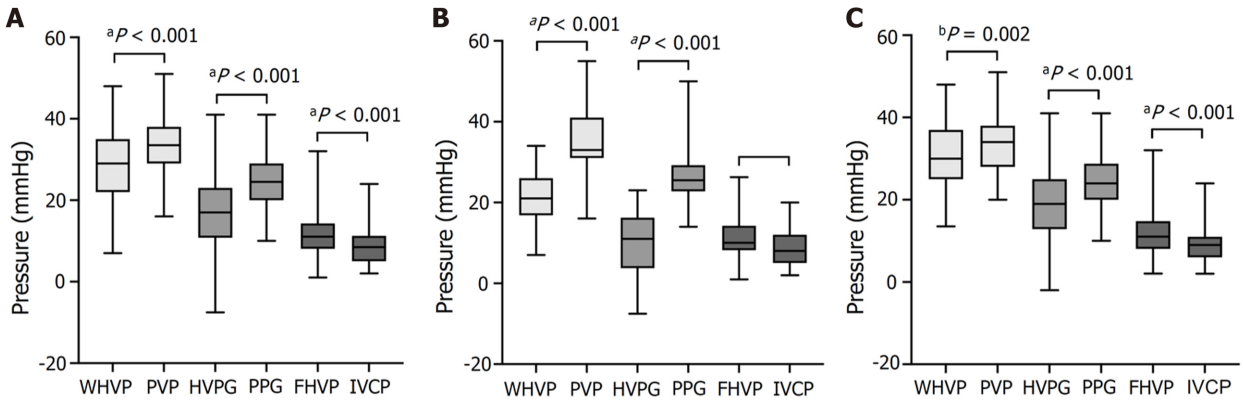

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Figure 2 Box plots of pressure differences during transjugular intrahepatic portosystemic shunt. A: All patients (*n* = 134); B: With hepatic vein collateral branches (*n* = 26); C: With no hepatic vein collateral branch (*n* = 108). *P* values were calculated by the paired *t*-test. WHVP: Wedged hepatic venous pressure; PVP: Portal venous pressure; HVPG: Hepatic venous pressure gradient; PPG: Portal venous pressure gradient; FHVP: Free hepatic venous pressure; IVCP: Inferior vena cava pressure.

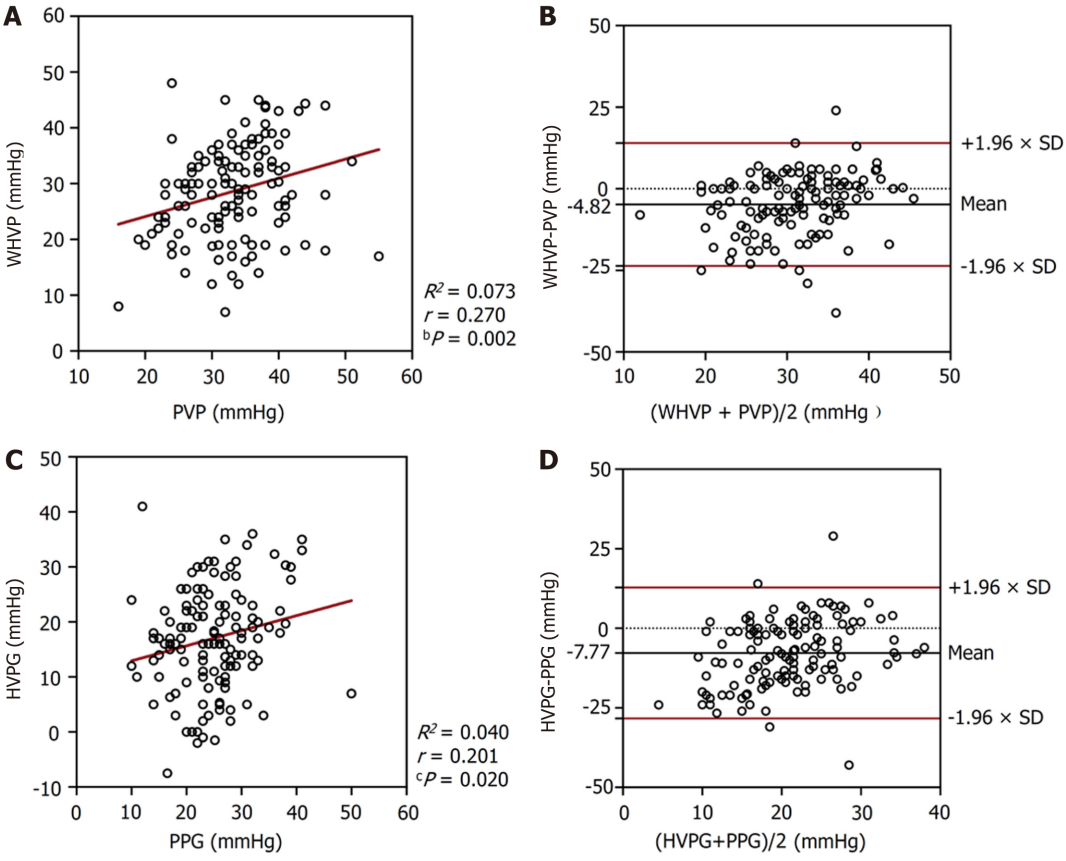

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Figure 3 Relationships between the pressures measured in all patients (*n* = 134). A: A scatterplot of wedged hepatic venous pressure (WHVP) against portal venous pressure (PVP); B: A Bland-Altman plot to assess agreement between WHVP and PVP; C: A scatterplot of hepatic venous pressure gradient (HVPG) against portal venous pressure gradient (PPG); D: A Bland-Altman plot to assess agreement between HVPG and PPG. WHVP: Wedged hepatic venous pressure; PVP: Portal venous pressure; HVPG: Hepatic venous pressure gradient; PPG: Portal venous pressure gradient.

hepatic vein. In our study, 26 patients (19.4%) had collateral branches of the hepatic vein, and WHVP and HVPG were both grossly underestimated. These results are consistent with those of other studies. Patients without collateral branches of the hepatic vein accounted for a large proportion (80.6%). The average WHVP was lower than the average PVP, and the average HVPG was significantly lower than the average PPG. For a small number of patients, the WHVP was greater than the PVP, and the HVPG was greater than the PPG. However, the underlying mechanism remains unclear. Reportedly, patients with a WHVP higher than the PVP are likely to have adverse hepatic blood flow, opening of the paraumbilical vein, anastomoses between the portal vein and IVC, and a gastrorenal shunt[16,19]. These scenarios were

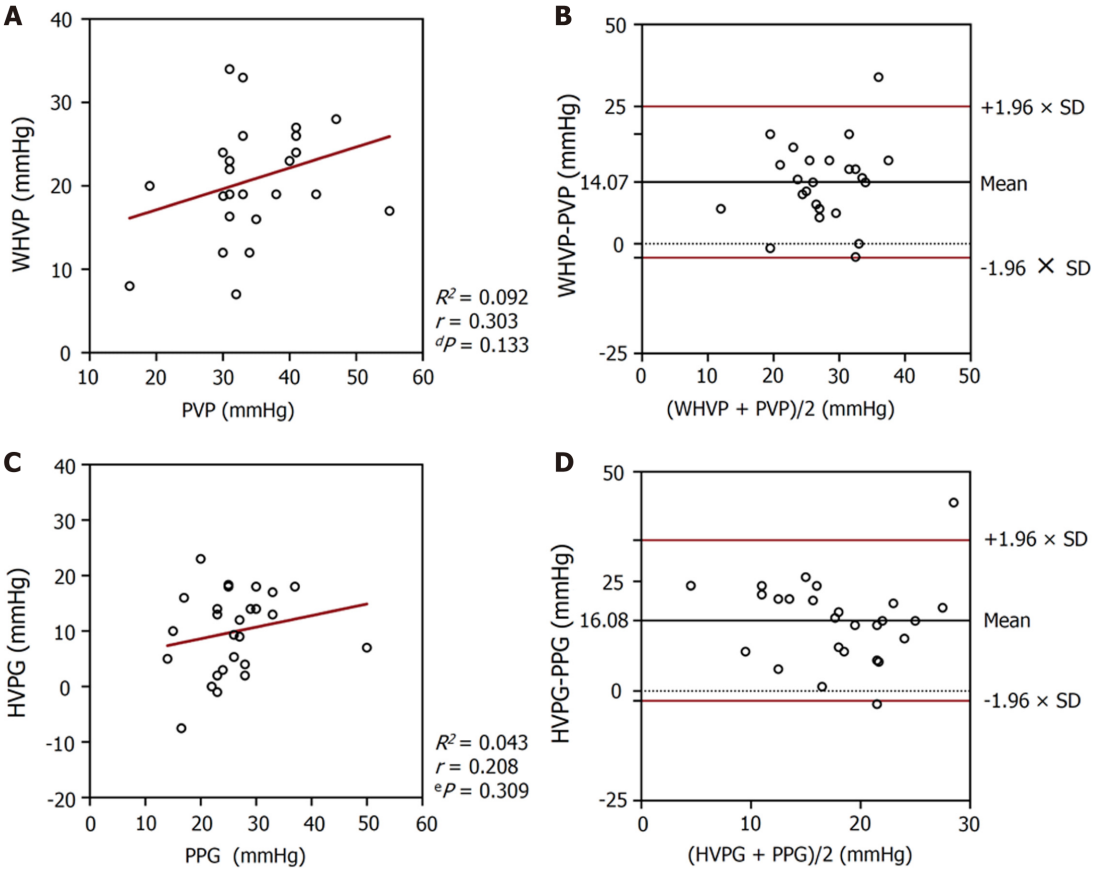

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Figure 4 Relationships between the pressures measured in patients with hepatic vein collateral branches (*n* = 26). A: A scatterplot of wedged hepatic venous pressure (WHVP) against portal venous pressure (PVP); B: A Bland-Altman plot to assess agreement between WHVP and PVP; C: A scatterplot of hepatic venous pressure gradient (HVPG) against portal venous pressure gradient (PPG); D: A Bland-Altman plot to assess agreement between HVPG and PPG. WHVP: Wedged hepatic venous pressure; PVP: Portal venous pressure; HVPG: Hepatic venous pressure gradient; PPG: Portal venous pressure gradient.

not present in the vast majority of patients in this study.

The factors influencing the pressure measurements were strictly controlled before the operation. Patients who received preoperative health education and those who underwent elective surgery were selected, and patients were given adequate psychological preparation to allow for active compliance with the procedure. Suitable paracentesis was performed for patients with large ascites, and the use of drugs that affect the venous pressure, such as non-selective β-receptor blockers that influence PVP[12,20-22], or propofol deep sedation, which can affect PPG[19,23], were avoided. During the TIPS procedure and pressure measurement, clinicians should perform local anesthesia, measure the pressure after the patient is stable, repeat the measurement several times, and ensure that the catheter is at the same location for each measurement. Gallbladder-heart reflections and incomplete balloon occlusion shoud be considered during the procedure. If these conditions are not corrected, patients should be excluded.

Our study was limited by the fact that this was a retrospective study with a small sample size. Although all study patients had alcoholic cirrhosis patients, the degree of progression of cirrhosis and the pathological type varied, with some cases progressing to hepatocellular carcinoma, resulting in different hepatic structural and hemodynamic changes, the potential impact of which is unclear. Considering these preliminary findings, prospective studies are necessary to validate our findings.

CONCLUSION

In conclusion, the correlation is very poor between WHVP and PVP as well as that between HVPG and PPG in patients with alcoholic cirrhosis and complications of PHT. HVPG cannot accurately represent PPG in most patients, and the former is lower than the latter. The formation of hepatic collaterals is a vital reason for the strong underestimation of HVPG. Except for the influencing factors of hepatic collateral branches in a few patients, the correlation in most cases remained poor. The cause remains unknown, and further investigations are required in this area to elucidate these mechanisms.

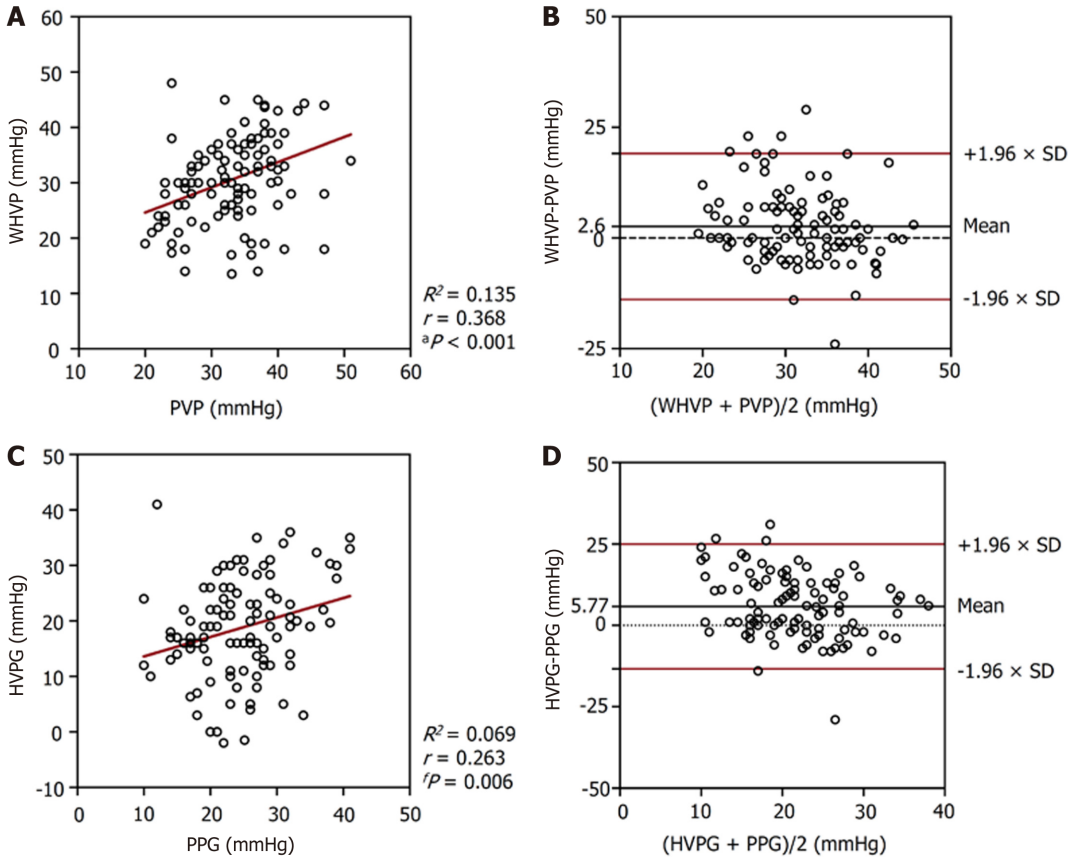

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Figure 5 Relationships between the pressures measured in patients with no hepatic vein collateral branch (*n* = 108). A: A scatterplot of wedged hepatic venous pressure (WHVP) against portal venous pressure (PVP); B: A Bland-Altman plot to assess agreement between WHVP and PVP; C: A scatterplot of hepatic venous pressure gradient (HVPG) against portal venous pressure gradient (PPG); D: A Bland-Altman plot to assess agreement between HVPG and PPG. WHVP: Wedged hepatic venous pressure; PVP: Portal venous pressure; HVPG: Hepatic venous pressure gradient; PPG: Portal venous pressure gradient.

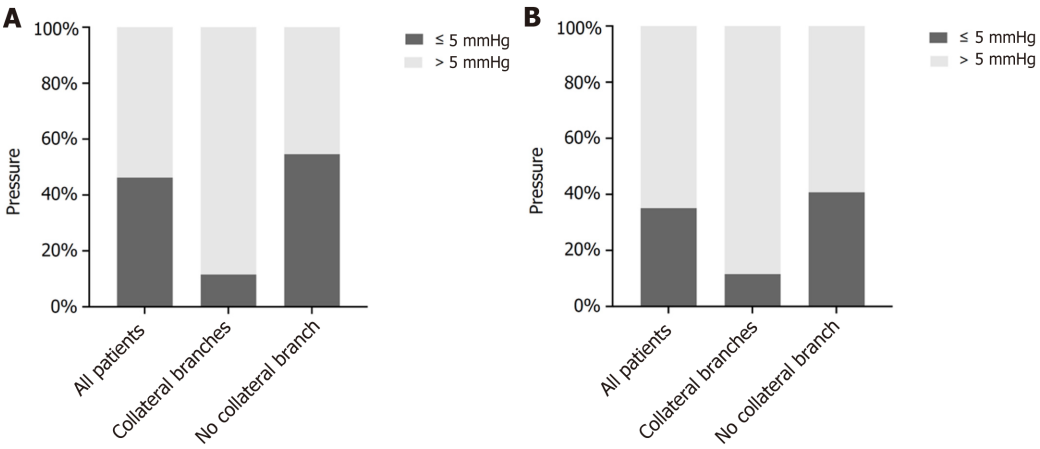

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Figure 6 Difference between the pressures measured in patients with alcoholic cirrhosis and portal hypertension. A: The difference between wedged hepatic venous pressure and portal venous pressure. B: The difference between hepatic venous pressure gradient and portal venous pressure gradient.

ARTICLE HIGHLIGHTS

Research background

The hepatic venous pressure gradient (HVPG), rather than the portal venous pressure gradient (PPG), is regarded as the gold standard for diagnosing portal hypertension (PHT).

Research motivation

The relationship between HVPG and PPG is controversial and lacks substantial research to prove it.

Research objectives

This study aimed to classify the correlation between HVPG and PPG in patients with alcoholic cirrhosis and PHT.

Research methods

This retrospective analysis of various pressures during transjugular intrahepatic portosystemic shunt (TIPS) procedures explored the relationship between HVPG and PPG in patients with alcoholic cirrhosis and PHT.

Research results

The correlation coefficient (r) and determination coefficient (R^2) between HVPG and PPG were 0.201 and 0.040, respectively (P = 0.020). Hepatic collaterals were identified in 26 patients with balloon occlusion hepatic venography (19.4%), while the average PPG was significantly higher than the average HVPG (25.94 ± 7.42 mmHg *vs* 9.86 ± 7.44 mmHg; P < 0.001). The collateral versus no collateral branches groups had 3 (11.54%) and 44 (40.74%) patients, respectively, with differences of < 5 mmHg between HVPG and PPG.

Research conclusions

HVPG cannot accurately represent PPG in most patients. The formation of hepatic collaterals is a vital reason for the strong underestimation of HVPG.

Research perspectives

Based on different pressures during TIPS procedures, the correlation and differences between HVPG and PPG of patients were explored.

FOOTNOTES

Author contributions: Liu FQ designed the research; Wang T, Yue ZD, Wang L, Fan ZH and Wu YF performed the research; Zhang D analyzed the data and wrote the paper; Liu FQ reviewed and revised the manuscript; All authors have read and approved the final manuscript.

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Institutional review board statement: The study was reviewed and approved by the Beijing Shijitan Hospital, Capital Medical University Institutional Review Board [2018(01)].

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: The authors declare that they have no conflict of interest.

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

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ORIGINAL ARTICLE

Retrospective Study

Nomogram for predicting early complications after distal gastrectomy

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Abstract

BACKGROUND

Reducing or preventing postoperative morbidity in patients with gastric cancer (GC) is particularly important in perioperative treatment plans.

AIM

To identify risk factors for early postoperative complications of GC post-distal gastrectomy and to establish a nomogram prediction model.

METHODS

This retrospective study included 131 patients with GC who underwent distal gastrectomy at the Second Hospital of Shandong University between January 2019 and February 2023. The factors influencing the development of complications after distal gastrectomy in these patients were evaluated using univariate and multivariate logistic regression analysis. Based on the results obtained, a predictive nomogram was established. The nomogram was validated using internal and external (n = 45) datasets. Its sensitivity and specificity were established by receiver operating characteristic curve analysis. Decision curve (DCA) analysis was used to determine its clinical benefit and ten-fold overfitting was used to establish its accuracy and stability.

RESULTS

Multivariate logistic regression analysis showed that hypertension, diabetes, history of abdominal surgery, and perioperative blood transfusion were independent predictors of postoperative complications of distal gastrectomy. The modeling and validation sets showed that the area under the curve was 0.843 [95% confidence interval (CI): 0.746-0.940] and 0.877 (95%CI: 0.719-1.000), the sensitivity was 0.762 and 0.778, respectively, and the specificity was 0.809 and 0.944, respectively, indicating that the model had good sensitivity and specificity. The C-indexes of the modeling and validation datasets were 0.843 (95%CI: 0.746-0.940) and 0.877 (95%CI: 0.719-1.000), respectively. The calibration curve (Hosmer

Lemeshow test: χ^2 = 7.33) showed that the model had good consistency. The results of the DCA analysis indicated that this model offered good clinical benefits. The accuracy of 10-fold cross-validation was 0.878, indicating that the model had good accuracy and stability.

CONCLUSION

The nomogram prediction model based on independent risk factors related to postoperative complications of distal gastrectomy can facilitate perioperative intervention for high-risk populations and reduce the incidence of postoperative complications.

Key Words: Blood transfusion; Gastroenterostomy; Nomograms; Postoperative complications; Stomach neoplasms; Risk factors

Core Tip: Using univariate and multivariate logistic regression analyses, we found that hypertension, diabetes, a history of abdominal surgery, and perioperative blood transfusion are predictors of complications after distal gastrectomy in patients with gastric cancer (GC). We then developed a novel nomogram for predicting early postoperative complications after distal gastrectomy. Using internal and external validations, we demonstrated that the model had good accuracy and stability. This model can facilitate identification of GC patients who are likely to develop complications, allowing early intervention and more appropriate management.

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INTRODUCTION

According to the Global Cancer Research Center, gastric cancer (GC) remains one of the most prevalent malignant tumors globally, contributing to the mortality due to malignant tumors[1]. In East Asia, particularly in China, GC is the third most common cancer and the second leading cause of cancer death[2]. Moreover, cancer affecting the lower one-third of the stomach is the most common type of GC[3].

At present, GC is treated comprehensively using surgery supplemented by chemotherapy, radiotherapy, immunotherapy, and targeted therapy. Radical surgical resection combined with local lymphadenectomy is currently the only curative treatment option[4]. Therefore, distal gastrectomy with D2 Lymph node dissection is recommended as a standard surgery for patients with distal GC[3]. It is suitable for clinical node positive (CN+) or T2-T4a tumors[5]. For early GC, laparoscopic distal gastrectomy was upgraded from research treatment to general practice in the 2014 version of the guidelines of the Japanese Society of Endoscopic Surgery[6]. Additionally, for advanced GC, large-scale randomized clinical trials were conducted in Japan, South Korea, and China. These studies confirmed the safety and long-term survival benefits of laparoscopic distal gastrectomy[7]. The postoperative morbidity and mortality of GC surgery ranges from 7.7%-57.9%, and 0%-13%, respectively. The most common postoperative complications include surgical site infection and anastomotic leakage[8]. Therefore, identifying methods to reduce or prevent postoperative morbidity in patients with GC has become a key focus point.

Although several studies have sought to predict postoperative complications in patients with GC, models for predicting the prognosis of patients with distal GC are lacking. Therefore, we aimed to evaluate the potential risk factors and build a nomogram model for predicting complications in individuals with distal GC.

MATERIALS AND METHODS

Patients

We retrospectively collected data from all patients who underwent distal gastrectomy with D2 Lymphadenectomy between January 2019 and February 2023 at the Second Hospital of Shandong University. Eventually, we included 131 patients who underwent surgery under standard general anesthesia, followed by distal gastrectomy with D2 lymph node dissection.

The study protocol was approved by the Ethics Committee of Second Hospital of Shandong University, China. This study complied with the principles of the Declaration of Helsinki. Due to the retrospective observational nature of the study, it involved minimal risks, did not threaten the patient's health did not require patient consent.

Inclusion and exclusion criteria

The inclusion criteria for this study were as follows: Distal gastrectomy with D2 lymphadenectomy, no neoadjuvant radiotherapy or chemotherapy before surgery, and complications occurring within 30-d postoperatively. The exclusion criteria were incomplete clinical data, failure to regain, distant metastasis or invasion, and conversion to open gastrectomy.

Data collection

The following patient baseline data were collected at admission: Age, sex (male or female), drinking history (yes or no), smoking history (yes or no), body mass index, history of abdominal surgery (yes or no), preoperative albumin level, preoperative hemoglobin level, American Society of Anesthesiologists stage (I–VI), presence of heart, liver, kidney, lung, and brain comorbidities (yes or no), diabetes, hypertension, and coronary heart disease (yes or no), operation time, laparoscopic surgery (yes or no), robotic surgery (yes or no), R0 resection (yes or no), blood transfusion (yes or no), postoperative intraperitoneal chemotherapy (yes or no), combined organ resection (yes or no). Simultaneously, the maximum tumor diameter, tumor-related markers, histological type, gross type, tumor-node-metastasis (TNM) stage, number of lymph node resections, number of positive lymph nodes, vascular invasion (yes or no), and nerve invasion (yes or no) were also measured. During the study period, albumin, prealbumin, and hemoglobin levels were recorded preoperatively at first admission. Blood transfusion refers to blood transfusion during the period from operation to discharge.

Definition of complications

Complications were defined as any deviation from the normal postoperative course[9]. We analyzed postoperative complications based on the Clavien-Dindo classification. Complications above level II were considered to be clinically significant. In this study, we observed early complications in patients undergoing distal gastrectomy, including abdominal bleeding, duodenal stump leakage, gastroparesis, abdominal infection, chylous leakage, pancreatic leakage, anastomotic leakage, and other related complications. The diagnosis of complications was primarily based on clinical symptoms and signs, computed tomography, endoscopy, drainage fluid, and individual laboratory examinations. The observed complications are listed in Table 1.

Statistical analyses

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS version 26.0; IBM SPSS Inc., Armonk, NY, United States) and R software (version 4.3.0; https://www.r-project.org/). For quantitative variables with a normal distribution, values are presented as mean ± SE of the mean, while for those with a non-normal distribution, values are expressed as the median and interquartile range. Groups were compared using two independent-sample *t*-tests and Wilcoxon rank-sum tests (nonparametric test, Mann-Whitney U test). Categorical variables were presented as frequencies and proportions, and the chi-square test, chi-square test with correction, and Fisher's exact test were used for comparisons between patient groups.

All variables were also categorized, and forward stepwise logistic regression models were constructed to determine involvement in postoperative morbidity. The presence or absence of postoperative complications after GC surgery were defined as the dependent variable. Univariate logistic regression analysis was used to study preoperative conditions, tumor-related factors, surgical procedures, and surgical complications after surgery. The variables that were significant ($P < 0.05$) in the univariate regression analysis were entered as independent variables in the multivariate logistic regression analysis, thereby establishing the regression model.

The R software (version 4.3.0) was used to construct the nomogram. The consistency between the predicted outcome probability of the model and the actual observation probability was evaluated by drawing a calibration curve represented by the consistency index (C-index). A receiver operating characteristic (ROC) curve was used to evaluate the predictive ability of the prediction model using the area under the curve (AUC). A decision curve (DCA) was drawn to evaluate the clinical benefits for patients. Finally, a ten-fold cross validation was performed to avoid overfitting and model bias. Statistical significance was set at $P < 0.05$.

RESULTS

Univariate analysis

A total of 131 patients with distal GC who underwent distal gastrectomy with D2 lymph node dissection were included in the study. Of them, 21 patients (16.03%) developed early postoperative complications. All patients were administered symptomatic treatment after a clear diagnosis, without death due to complications. The general characteristics and results of the univariate analysis of the patients are presented in Table 2. The univariate analysis between the two groups showed that prealbumin level, hypertension, diabetes, history of abdominal surgery, R0 resection, and blood transfusion were factors influencing early postoperative complications after distal gastrectomy (all $P < 0.05$).

Multivariate analysis

Inclusion of the above significant variables in the logistic regression analysis revealed that hypertension, diabetes, a history of abdominal surgery, and blood transfusion were independent predictors of early postoperative complications after distal gastrectomy ($P < 0.05$) (Table 3).

Table 1 Statistics on the proportion of complications

Complications	Number (%)
Abdominal bleeding	1 (4.8)
Abdominal infection	5 (42.9)
Incision infection	2 (9.5)
Chylous fistula	2 (9.5)
Duodenal stump leakage	4 (19.1)
Gastroparesis	1 (4.8)
Anastomotic stomatitis	2 (9.5)
Anastomotic fistula	3 (14.3)
Pancreatic leakage	1 (4.8)
Total	21

Establishment of the nomogram prediction model

A nomogram prediction model for early postoperative complications in patients with distal GC was constructed based on the independent risk factors identified by multivariate logistic regression analysis. As shown in Figure 1, if a patient had a history of hypertension, diabetes, and abdominal surgery before surgery and if blood transfusion was conducted during the perioperative period, the incidence of early complications after distal gastrectomy was 89.9%.

Validation of the nomogram prediction model

Internal validation was performed using calibration, ROC, and DCA curves, and 10-fold cross-validation. Simultaneously, data was collected from the patients at different time-points as validation sets (n = 45) for external validation.

The ROC curves for the modeling (Figure 2) and validation sets (Figure 3) yielded AUCs of 0.843 [95% confidence interval (CI): 0.746-0.940] and 0.877 (95%CI: 0.719-1.000); sensitivity of 0.762 and 0.778; and specificity of 0.809 and 0.944, respectively, indicating that the model had good sensitivity and specificity.

The calibration curve indicated good consistency (Hosmer-Lemeshow test: χ^2 = 7.33; P = 0.501) in the evaluation of the consistency between the predicted outcome probability of the model and the actual observed outcome, represented by the C-index. The C-indexes of the modeling set (Figure 4) and validation set (Figure 5) were 0.843 (95%CI: 0.746-0.940) and 0.877 (95%CI: 0.719-1.000).

The evaluation of the degree of clinical benefit to the patients by DCA showed that the model provided good clinical benefits in the modeling set (Figure 6) and validation set (Figure 7). Ten-fold cross-validation yielded an accuracy of 0.878, indicating good accuracy and stability of the model.

DISCUSSION

This study analyzed 42 variables potentially associated with early postoperative complications in 131 patients with distal GC who underwent distal gastrectomy. The univariate and multivariate logistic regression analyses identified hypertension, diabetes, history of abdominal surgery, and perioperative blood transfusion as predictors of complications after distal gastrectomy. Using multivariate analysis, we established a novel predictive nomogram for early postoperative complications after distal gastrectomy. Internal and external validations were performed and demonstrated accuracy and stability of the model.

This study showed that hypertension is an independent risk factor for early postoperative complications after distal GC, however, the relationship between hypertension and postoperative adverse outcomes remains unclear[10]. Some studies have shown that preoperative hypertension is an important predictor of postoperative incidence rate. For example, the prediction model created by Huang *et al* showed that a history of hypertension in patients > 70 years old is an independent predictor of a higher surgical incidence rate[11]. However, no conclusive data are currently available to support this concept[12]. Some studies have shown that only patients with chronic hypertension whose diastolic pressure ≥ 110 mmHg have an increased risk of perioperative complications. This may be because the increased blood pressure during surgery will generally expose patients to the risk of hemodynamic instability. Hypertension is also related to an increased risk of perioperative myocardial ischemia, leading to an increased incidence of cardiovascular complications and damaged cardiac output in these patients. This, in turn, may lead to insufficient perfusion and damage to the targeted terminal organs[13-15]. Another study suggested that perioperative cardiac complications are related to intraoperative hemodynamic instability, rather than to the occurrence of hypertension during surgery. Therefore, achieving hemodynamic stability may be more important than targeting any particular intraoperative blood pressure[16]. Taken together, these findings show that effective control of blood pressure and maintaining the stability of intraoperative hemodynamics may reduce the incidence of postoperative complications, although further prospective cohort studies are

Table 2 Clinicopathological data and univariate analysis of early postoperative complications in patients with distl gastric cancer

Factors		With early postoperative complications (%)	Without early postoperative complications (%)	χ^2/t	*P* value
Age (yr)		71 (60.5-74)	63 (5-70)	-2.14	0.032
Weight		66.15 ± 11.08	65.85 ± 10.01	0.118	0.906
Height		168.20 ± 6.869	165.52 ± 7.461	1.614	0.109
BMI		23.312 ± 3.22	24.00 ± 3.11	-0.905	0.367
Hemoglobin		129 (100.5-145)	128.5 (114.25-144.25)	-0.342	0.732
Albumin		39.9 (36.35-42.75)	41.35 (38.2-45)	-1.754	0.08
Prealbumin		18.9 (14.4-22.5)	21.45 (17.2-25.3)	-2.199	0.028
Alpha fetoprotein		3.02 (2.285-4.465)	2.495 (1.815-3.9225)	-1.383	0.167
Carcinoembryonic antigen		2.065 (1.4625-2.8625)	1.76 (1.265-3.38)	-0.511	0.609
CA199		7.3 (5-20.55)	9.04 (5.9925-16.05)	-0.326	0.744
CA125		9.66 (6.325-19.385)	8.685 (6.3-12.5)	-0.781	0.435
Number of positive lymph nodes		2 (0-8)	0.5 (0-6.25)	-0.643	0.526
Number of lymph node resections		29 (21-40)	28 (22-34)	-0.352	0.725
Tumor maximum diameter		4.5 (3-6)	4 (2.425-5.5)	-0.817	0.414
Surgical time		250 (205-265)	240 (210-282)	-0.141	0.888
Blood loss		50 (35-100)	50 (50-100)	-0.236	0.814
Organizational type				10.664	0.099
	Poorly differentiated adenocarcinoma	9 (27.3)	24 (72.7)		
	Moderate to poorly differentiated adenocarcinoma	7 (12.3)	5 (92.3)		
	Moderately differentiated adenocarcinoma	1 (7.7)	12 (85.7)		
	Medium to high differentiation adenocarcinoma	1 (12.5)	7 (87.5)		
	Highly differentiated adenocarcinoma	0 (0)	5 (100)		
	Diffuse large B-cell carcinoma	1 (100)	0 (0)		
	Signet ring cell carcinoma	2 (14.3)	12 (87.5)		
General type				3.202	0.921
	Concave type	2 (18.2)	9 (81.8)		
	Shallow concave type	1 (5.3)	18 (94.7)		
	Superficial uplift type	1 (14.3)	6 (86.7)		
	Shallow flat type	0 (0)	1 (100)		
	Nodular type	1 (33.3)	2 (66.7)		
	Infiltrating ulcer type	2 (15.4)	11 (84.6)		
	Ulcerative type	11 (19)	47 (81)		
	Protuberant type	2 (20)	8 (80)		
	Diffuse infiltrative type	1 (11.1)	8 (88.9)		
ASA				0.428	0.934
	I	0 (0)	1 (100)		

	II	10 (15.6)	54 (84.4)		
	III	11 (16.9)	54 (83.1)		
	IV	0 (0)	1 (100)		
Sex				0.21	0.647
	Male	17 (16.8)	84 (83.2)		
	Female	4 (13.3)	26 (86.7)		
Transfusion				11.342	0.001
	Yes	17 (27.4)	45 (72.6)		
	No	4 (5.8)	65 (94.2)		
P stage				3.143	0.37
	I	6 (11.5)	46 (88.5)		
	II	5 (22.7)	17 (77.3)		
	III	10 (19.6)	41 (80.4)		
	IV	0 (0)	6 (100)		
hypertension				1.581	0.001
	Yes	14 (31.1)	31 (68.9)		
	No	7 (8.1)	79 (91.9)		
Diabetes				9.27	0.002
	Yes	10 (37)	17 (63)		
	No	11 (10.6)	93 (89.4)		
Smoking history				3.262	0.071
	Yes	1 (3.4)	28 (96.6)		
	No	20 (19.6)	82 (80.4)		
History of drinking				0.017	0.896
	Yes	6 (15.4)	33 (84.6)		
	No	15 (16.3)	77 (83.7)		
History of abdominal surgery				7.199	0.007
	Yes	8 (38.1)	13 (61.9)		
	No	13 (11.8)	97 (88.2)		
Laparoscopy				0.002	0.962
	Yes	11 (16.2)	57 (83.8)		
	No	10 (15.9)	53 (84.1)		
Robot surgery				0.002	0.962
	Yes	10 (15.9)	53 (84.1)		
	No	11 (16.2)	57 (83.8)		
Intraperitoneal perfusion chemotherapy				0.001	0.971
	Yes	6 (16.2)	31 (83.8)		
	No	15 (16.0)	79 (84.0)		
R0				7.466	0.006
	Yes	18 (14.3)	108 (85.7)		
	No	2 (40)	3 (60)		
Vascular invasion				0.242	0.622

	Yes	11 (14.7)	64 (85.3)		
	No	10 (17.9)	46 (82.1)		
Lymphatic invasion				1.566	0.212
	Yes	4 (10)	36 (90)		
	No	17 (18.7)	74 (81.3)		
Combined organectomy				0.275	0.6
	Yes	19 (15.6)	103 (84.4)		
	No	2 (22.2)	7 (77.8)		
Liver				0.017	0.897
	Yes	1 (14.3)	6 (85.7)		
	No	20 (16.1)	104 (83.9)		
Lung				0.788	0.375
	Yes	0 (0)	4 (100)		
	No	21 (16.5)	106 (83.5)		
Kidney				0.788	0.375
	Yes	0 (0)	4 (100)		
	No	21 (16.5)	106 (83.5)		
Heart				2.193	0.144
	Yes	5 (27.8)	13 (72.2)		
	No	16 (14.2)	97 (85.8)		
Brain				2.329	0.127
	Yes	4 (30.8)	9 (69.2)		
	No	17 (14.4)	101 (85.6)		
T stage				0.47	0.493
	1	6 (13)	40 (87)		
	≥ 2	15 (17.6)	70 (82.4)		
N stage				0.639	0.888
	0	9 (14.3)	54 (85.7)		
	1	2 (13.3)	13 (86.7)		
	2	3 (16.7)	15 (83.3)		
	3	7 (20)	28 (80)		
M stage				1.2	0.273
	0	21 (16.8)	104 (83.2)		
	1	0 (0)	6 (100)		

BMI: Body mass index; ASA: American society of aneshesiologists.

required to verify this.

This study showed that diabetes is an independent risk factor for early postoperative complications in distal GC. Diabetes is a known risk factor for any postoperative complications[17]; however, the complications associated with diabetes remain controversial. Diabetes results in neutrophil dysfunction, which increases the risk of pathogen infection and reduces healing ability[18]. Additionally, it is related to tissue hypoxia and increased blood viscosity, which slows inflammatory reactions, thereby also affecting wound healing and increasing the risk of infection[18]. In addition, diabetes can also lead to lipid metabolism disorders, endothelial cell damage and dysfunction, abnormal platelet function, and vascular atherosclerosis, resulting in insufficient blood supply at the anastomoses and residual ends, thus increasing the risk of a fistula[19]. A meta-analysis revealed that the combined odds ratio of any complication for patients with as compared to patients without diabetes was 1.653 (1.487, 1.839), suggesting that diabetes is a risk factor for any postoperative complications. The two subtypes of diabetes insulin-dependent diabetes mellitus (IDDM) and non-IDDM

Table 3 Multivariate analysis of early postoperative complications in patients with distl gastric cancer

Factors	β	S.E.	Wald value	Freedom	*P* value	OR value (95%CI)
Age (yr)	-0.017	0.034	0.263	1	0.608	0.983 (0.92-1.05)
Prealbumin	-0.035	0.067	0.275	1	0.6	0.966 (0.847-1.1)
Transfusion	1.647	0.714	5.326	1	0.021	5.191 (1.282-21.02)
Hypertension	1.436	0.602	5.689	1	0.017	4.204 (1.292-13.683)
Diabetes	1.461	0.728	4.029	1	0.045	4.309 (1.035-17.936)
History of abdominal surgery	1.75	0.669	6.853	1	0.009	5.757 (1.553-21.348)
R0	-1.449	1.173	1.526	1	0.217	0.235 (0.024-2.339)
Constant	-1.019	3.136	0.106	1	0.745	0.361

OR: Odds ratio.

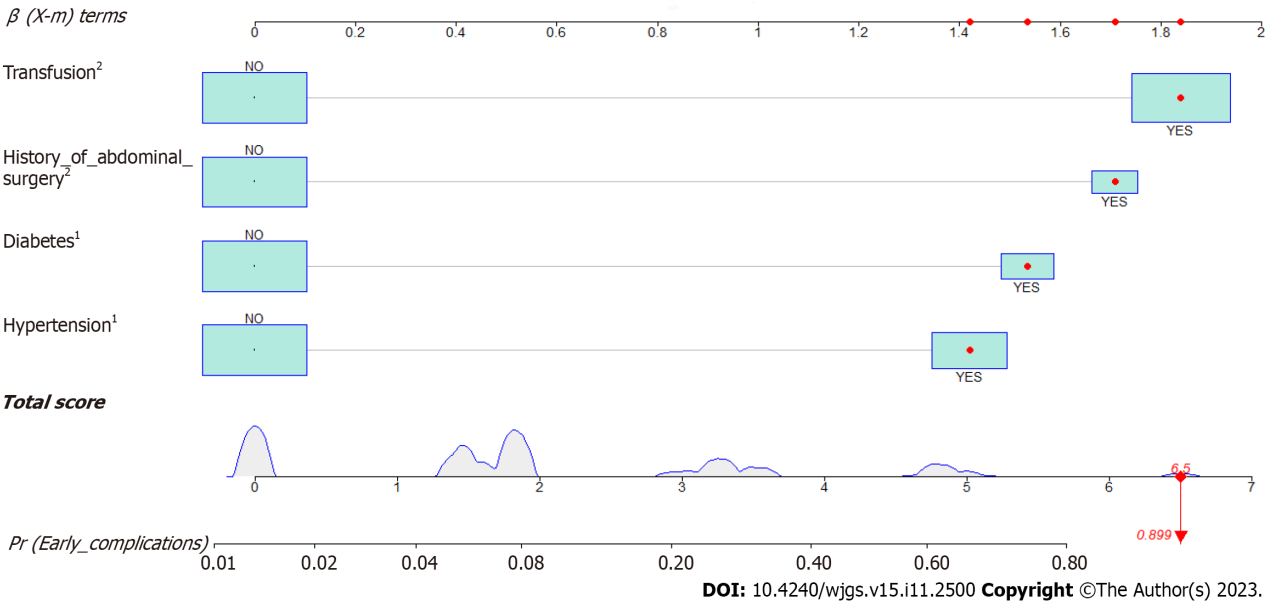

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Figure 1 Establishment of the nomogram prediction model. [1]Impact of this risk factor on complications. [2]Impact of this risk factor on complications. According to the size of the "OR value" in Table 3 (Multivariate analysis of early postoperative complications in patients with distl gas cancer), the larger the OR value, the greater the possibility of complications caused by the risk factor.

(NIDDM)) have different incidence rates, and the risk of IDDM is higher than that of NIDDM[20]. Golinvaux *et al* [21] stated that compared to individuals without diabetes, individuals with IDDM had an increased risk of postoperative complications, prolonged hospital stay, postoperative adverse events, and readmission risk than those with NIDDM. In addition, complications related to IDDM were more severe than those related to NIDDM. Therefore, evaluating whether a patient has IDDM or DM (type 1 or type 2) is important during preparation for surgery.

Traditionally, a history of abdominal surgery has been considered to be a relative contraindication for laparoscopic gastrectomy, and the rate of conversion to open gastrectomy is high[22,23]. However, with the improvement of surgical instruments and accumulation of experience, postoperative surgical outcomes between patients with and without a history of abdominal surgery have not been found to be different, which contradicts the results of the present study. However, according to autopsy research reports, 75%-90% of patients who have previously undergone abdominal surgery have adhesions[24]. Beck *et al*[25] reported that 83% and 7% of patients who had undergone and not undergone previous abdominal surgery had intra-abdominal adhesions, which can prolong surgical time. Moreover, recent research has confirmed that surgical time is an independent risk factor for postoperative complications of GC[26]. Zhou *et al*[27] conducted statistical analysis on clinical data of patients undergoing GC surgery and found that longer surgery time is an independent risk factor for postoperative complications; longer the surgery time, more the stimulation and trauma to the abdominal organs, leading to an increased risk of postoperative complications. Therefore, from this perspective, a history of abdominal surgery remains a noteworthy indicator of complications.

This study showed that perioperative blood transfusion is an independent risk factor for early postoperative complications after distal gastrectomy, which may be related to an increase in the activity of regulatory T lymphocytes and the

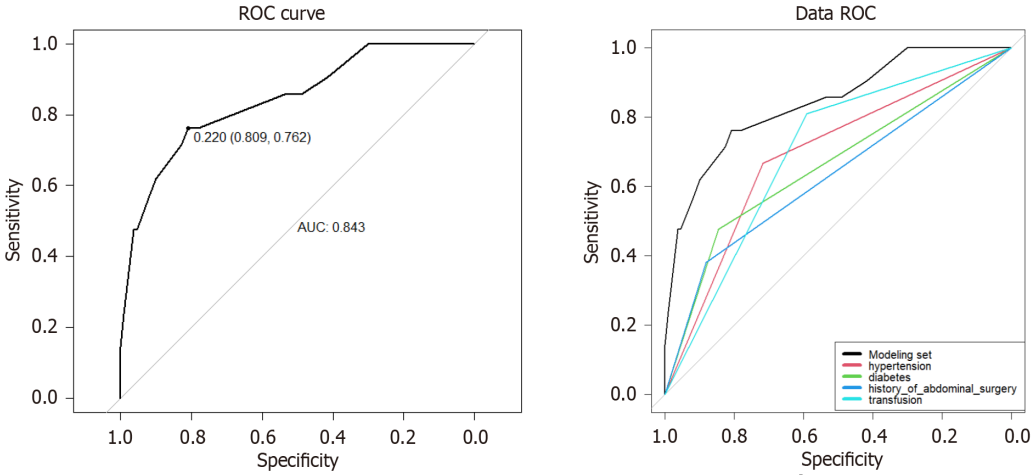

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Figure 2 The receiver operating characteristic curves for the modeling set. A: The receiver operating characteristic (ROC) for overall risk; B: The ROC for various risk factor. ROC: Receiver operating characteristic; AUC: Area under the curve.

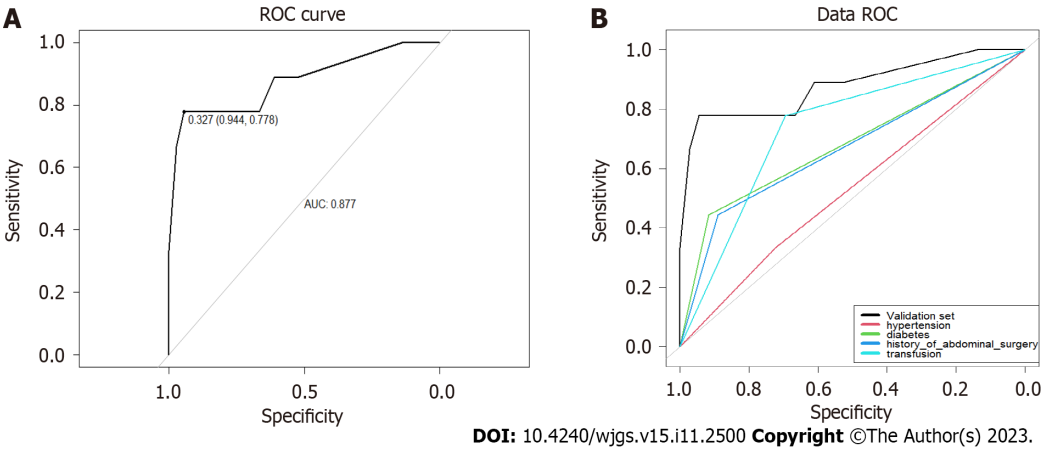

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Figure 3 The receiver operating characteristic curves for the validation set. A: The receiver operating characteristic (ROC) for overall risk; B: The ROC for various risk factor. ROC: Receiver operating characteristic; AUC: Area under the curve.

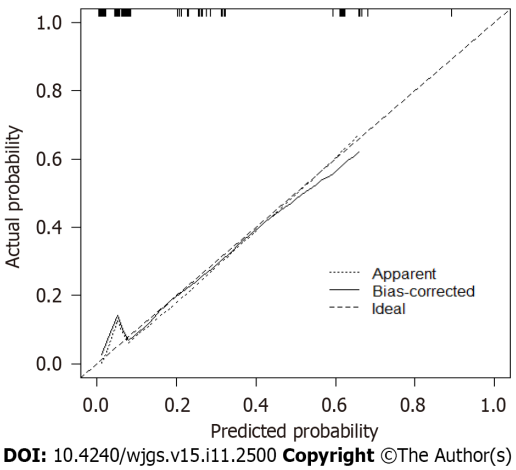

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Figure 4 The C-indexes of the modeling set.

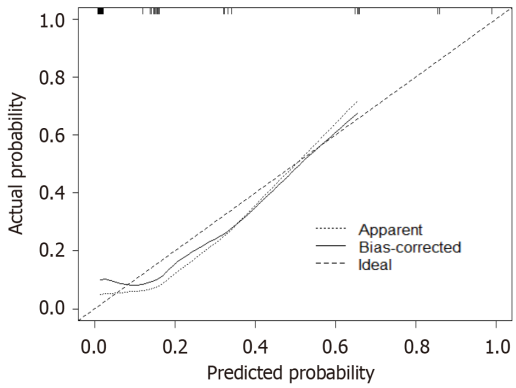

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Figure 5 The C-indexes of the validation set.

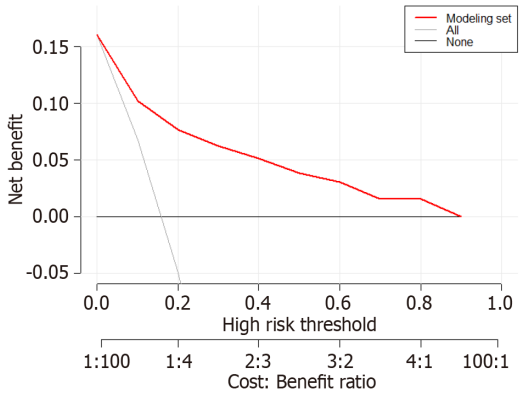

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Figure 6 The decision curve of the modeling set.

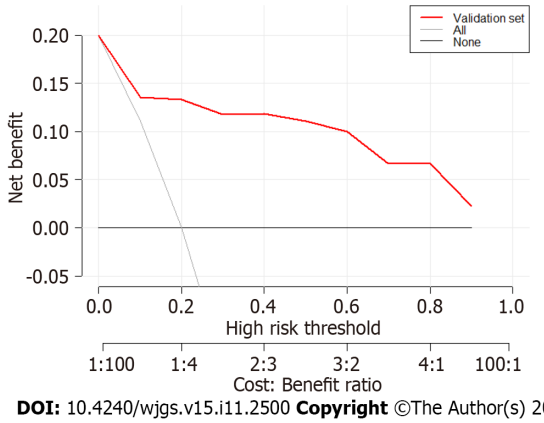

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Figure 7 The decision curve of the validation set.

inhibition of the functions of natural killer T cells, macrophages, and monocytes, which reduces the immune function of the body. Elmi *et al*[28] found that patients with GC who had undergone perioperative blood transfusion had a higher risk of postoperative complications, particularly in terms of the incidence of infection. Xue *et al*[29] also found that perioperative blood transfusion is associated with poor prognosis in patients with gastric adenocarcinoma, particularly those with TNM III, and that patients who had received transfusions had more postoperative complications than those who had not, which is consistent with the research results of Kawakami *et al*[30]. Therefore, understanding the relationship between blood transfusion and postoperative complications is of great clinical significance to reduce and prevent the occurrence of complications, reduce perioperative mortality, and improve the long-term survival rate of patients.

This study had some limitations. First, this was a retrospective study, and inevitably, some unknown factors could have led to bias. Additionally, this study did not consider information regarding the postoperative survival of patients, mainly because the included patients had a shorter postoperative time; however, follow-up studies on this cohort will

continue. In addition, to evaluate the performance of the model more accurately, external validation of big data from other centers is required. Nevertheless, the current results are encouraging.

CONCLUSION

In this study, preoperative and intraoperative factors were used to establish an early postoperative nomogram model. The results of this study suggest that hypertension, diabetes, a history of abdominal surgery, and perioperative blood transfusion are risk factors for early postoperative complications after distal gastrectomy. This prediction model can be used to guide the detection of early postoperative complications and has clinical reference value.

ARTICLE HIGHLIGHTS

Research background

Gastric cancer (GC) remains one of the most prevalent malignant tumors globally, contributing to the mortality due to malignant tumors.

Research motivation

Identifying methods to reduce or prevent postoperative morbidity in patients with GC has become a key focus point.

Research objectives

To establish a nomogram prediction model.

Research methods

We included 131 patients who underwent surgery under standard general anesthesia, followed by distal gastrectomy with D2 lymph node dissection.

Research results

The calibration curve (Hosmer Lemeshow test: $\chi^2 = 7.33$) showed that the model had good consistency. The results of the decision curve analysis indicated that this model offered good clinical benefits.

Research conclusions

This prediction model can be used to guide the detection of early postoperative complications and has clinical reference value.

Research perspectives

To evaluate the performance of the model more accurately, external validation of big data from other centers is required.

FOOTNOTES

Author contributions: Zhang B and Ji ZP designed the research study and performed the research; Zhang B and Zhu Q analyzed the data and wrote the manuscript; all authors have read and approve the final manuscript.

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Informed consent statement: All study participants or their legal guardian provided informed written consent about personal and medical data collection prior to study enrolment.

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ORIGINAL ARTICLE

Retrospective Study

Application of CD34 expression combined with three-phase dynamic contrast-enhanced computed tomography scanning in preoperative staging of gastric cancer

Hua Liu, Kang-Yan Zhao

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Abstract

BACKGROUND

Accurate preoperative staging of gastric cancer (GC), a common malignant tumor worldwide, is critical for appropriate treatment plans and prognosis. Dynamic three-phase enhanced computed tomography (CT) scanning for preoperative staging of GC has limitations in evaluating tumor angiogenesis. CD34, a marker on vascular endothelial cell surfaces, is promising in evaluating tumor angiogenesis. We explored the value of their combination for preoperative staging of GC to improve the efficacy and prognosis of patients with GC.

AIM

To explore the evaluation value of CD34 expression + dynamic three-phase enhanced CT scanning in preoperative staging of GC.

METHODS

Medical records of 106 patients with GC treated at the First People's Hospital of Lianyungang between February 2021 and January 2023 were retrospectively studied. All patients underwent three-phase dynamic contrast-enhanced CT scanning before surgery, and CD34 was detected in gastroscopic biopsy specimens. Using surgical and pathological results as the gold standard, the diagnostic results of three-phase dynamic contrast-enhanced CT scanning at different T and N stages were analyzed, and the expression of CD34-marked microvessel density (MVD) at different T and N stages was determined. The specificity and sensitivity of three-phase dynamic contrast-enhanced CT and CD34 in T and N staging were calculated; those of the combined diagnosis of the

two were evaluated in parallel. Independent factors affecting lymph node metastasis were analyzed using multiple logistic regression.

RESULTS

The accuracy of three-phase dynamic contrast-enhanced CT scanning in diagnosing stages T1, T2, T3 and T4 were 68.00%, 75.00%, 79.41%, and 73.68%, respectively, and for diagnosing stages N0, N1, N2, and N3 were 75.68%, 74.07%, 85.00%, and 77.27%, respectively. CD34-marked MVD expression increased with increasing T and N stages. Specificity and sensitivity of three-phase dynamic contrast-enhanced CT in T staging were 86.79% and 88.68%; for N staging, 89.06% and 92.86%; for CD34 in T staging, 64.15% and 88.68%; and for CD34 in N staging, 84.38% and 78.57%, respectively. Specificity and sensitivity of joint diagnosis in T staging were 55.68% and 98.72%, and N staging were 75.15% and 98.47%, respectively, with the area under the curve for diagnosis improving accordingly. According to multivariate analysis, a longer tumor diameter, higher pathological T stage, lower differentiation degree, and higher expression of CD34-marked MVD were independent risk factors for lymph node metastasis in patients with GC.

CONCLUSION

With high accuracy in preoperatively determining the invasion depth and lymph node metastasis of GC, CD34 expression and three-phase dynamic contrast-enhanced CT can provide a reliable basis for surgical resection.

Key Words: CD34; Three-phase dynamic contrast-enhanced computed tomography scanning; Gastric cancer; Preoperative staging; Invasion; Lymph node metastasis

Core Tip: We evaluated the value of CD34 expression combined with dynamic three-phase enhanced computed tomography (CT) scanning in the preoperative staging and invasion evaluation of gastric cancer (GC). This study demonstrated that the diagnostic accuracy of dynamic three-phase enhanced CT scanning for the T stage and the N stage was 68.00%-79.41% and 74.07%-85.00% respectively, and the addition of CD34-marked microvessel density improved the diagnostic efficiency. This combination can be used as a reliable basis to preoperatively assess the invasion depth and lymph node metastasis of GC and provide guidance for surgical treatment.

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INTRODUCTION

Gastric cancer (GC) is a commonly observed malignancy and a global health concern. Despite its gradually decreasing morbidity and mortality, the annual worldwide incidence of GC is greater than 1 million cases; thus, it is the fourth most frequently observed malignant tumor and the third leading cause of cancer-associated deaths[1,2]. Surgical treatment is required to control or cure GC. Even in the late stages of GC, the prognosis and symptoms of patients can be improved by surgery combined with other treatment schemes such as radiotherapy and chemotherapy[3].

Early and accurate preoperative evaluation can enable an ideal prognosis, which is essential for planning optimal treatment options, such as endoscopic mucosal resection, endoscopic submucosal dissection, and laparoscopic surgery [4]. Early diagnosis and accurate staging before surgery are critical for formulating reasonable treatment plans, selecting the optimal surgical method, and determining the prognosis[5]. Ordinary computed tomography (CT) has been adopted for the preoperative staging of GC, but its accuracy is controversial[6]. Three-phase dynamic contrast-enhanced CT scanning has improved the clarity of vascular images and helped effectively observe the degree of tumor invasion of the gastric wall with the injection of contrast media into patients[7].

CD34 is a transmembrane glycoprotein often expressed on the surface of hematopoietic stem cells and endothelial cells and is a marker of these cell types; it has been extensively used to evaluate the vascular system in tumors, that is, microvessel density (MVD)[8,9]. Similarly, the formation of new blood vessels influences the growth and progression of GC. One study has revealed higher MVD in diffuse GC than in intestinal-type GC and significantly lower MVD in highly/moderately differentiated GC than in poorly differentiated GC[10]. Compared to other microvascular markers, CD34 exhibits high specificity for endothelial cells, which indicates it is less likely to stain non-vascular cells, thus providing a more accurate MVD image[11]. Currently, CD34 has been adopted in the preoperative evaluation of colorectal cancer and the efficacy prediction of preoperative radiotherapy and chemotherapy[12,13]. In addition, several studies have indicated that a high MVD determined using CD34 staining is associated with poorer prognosis in patients with GC[14]. However, the application of CD34 expression combined with three-phase dynamic contrast-enhanced CT

scanning in the preoperative staging and evaluation of GC invasion has rarely been studied.

Thus, in this study, preoperative CD34 detection and three-phase dynamic contrast-enhanced CT scans were performed in 106 patients with GC and compared with postoperative histopathology to determine the applicability of this scheme.

MATERIALS AND METHODS

Patients' data

Medical records of 106 patients with GC treated at The First People's Hospital of Lianyungang between February 2021 and January 2023 were retrospectively studied. All patients underwent three-phase dynamic contrast-enhanced CT scanning before surgery, and CD34 was detected in gastroscopic biopsy specimens. Surgical and pathological results were used as gold standards. This study was conducted with permission from the Medical Ethics Committee of The First People's Hospital of Lianyungang.

The inclusion criteria were as follows: Patients who had received both CD34 detection and three-phase dynamic contrast-enhanced CT scanning, with a time difference between the two tests of less than 1 wk; patients whose lesions were obtained using surgical resection and sent for pathological diagnosis (the results were considered the gold standard); patients diagnosed with malignant GC; and patients with detailed medical data, namely medical records, past medical history, and laboratory and imaging examination results.

The exclusion criteria were as follows: Comorbidities with other malignant tumors, congenital malformations in the chest that would disrupt the imaging diagnosis, coagulation dysfunction, allergy to contrast media, pregnancy or lactation, and neoadjuvant therapy before testing.

Detection of CD34

CD34 is specifically expressed in microvascular endothelial cells, and its expression intensity is bound to the MVD; therefore, the MVD value can be adopted to represent CD34. The inclusion criterion was brownish-yellow microvascular endothelial cells. The procedure was as follows: A whole slice was browsed in a low-power field (× 100), three different fields of view in each slice were randomly selected and counted using a high-power lens (× 200), and the average value was obtained. The average value was the MVD in this case.

Three-phase dynamic contrast-enhanced CT scanning

A 128-row, 256-slice Philips spiral CT scanner was used, and the parameters were set as follows: Detector, 0.625 × 128 rows; pitch, 0.993; tube voltage, 120 KV; tube current, 250 mA; spiral scanning, 3.367 s; and acquisition matrix, 512 × 512. Nonionic contrast medium was injected through an intravenous bolus injection using a high-pressure syringe (concentration: 350 mg/mL) at a dose of 80-100 mL and an injection speed of 3 mL/s. Scanning was performed from the liver to the kidney at 25, 55, and 180 s after contrast injection to acquire the arterial, portal, and delayed phases. Part of the data was transmitted to the post-processing workstation for processing and reconstruction using multiplanar reconstruction and other techniques to show the relationship between the lesions and adjacent blood vessels. The corresponding parameters were recorded.

Diagnostic criteria of three-phase dynamic contrast-enhanced CT scanning for T staging

The diagnostic criteria of three-phase dynamic contrast-enhanced CT scanning for the T staging of patients with GC are as follows (Figure 1): T1, the tumor invades the lamina propria, muscularis mucosa, or submucosa; T2, the tumor invades the muscularis propria; T3, the tumor penetrates the subserous connective tissue but does not invade the visceral peritoneum or adjacent structures; and T4, the tumor invades the serosa (visceral peritoneum) or adjacent structures.

Diagnostic criteria of three-phase dynamic contrast-enhanced CT scanning for N staging

The following are the diagnostic criteria for three-phase dynamic contrast-enhanced CT scanning for the N staging of patients with GC (Figure 2). Positive criteria for lymph node metastasis: When the short axis diameter of abdominal lymph nodes was larger than 6 mm, and the size of gastric lymph nodes was larger than 8 mm, especially the nodes with a round shape and local necrosis in enhanced CT examination, the conclusion was a positive metastasis of lymph nodes. The N stage refers to the number of lymph nodes with metastases around the stomach. N0: No local lymph node metastasis; N1: 1-2 local lymph node metastases; N2: 3-6 local lymph node metastases; N3: 7 lymph node metastases or more.

Outcome measures

With the final pathological diagnosis results of patients as the gold standard, the diagnostic results of the two separate diagnostic methods and the joint diagnosis for the pathological staging of patients with GC were evaluated. Joint diagnosis was conducted in parallel, and the specificity and sensitivity of each diagnostic method were calculated and compared to evaluate diagnostic efficacy.

Statistical analyses

All data were processed using SPSS software (version 20.0; SPSS Inc., Chicago, IL, United States). The measurement data are presented as the mean ± SD. Normally distributed data were compared between groups using the independent-

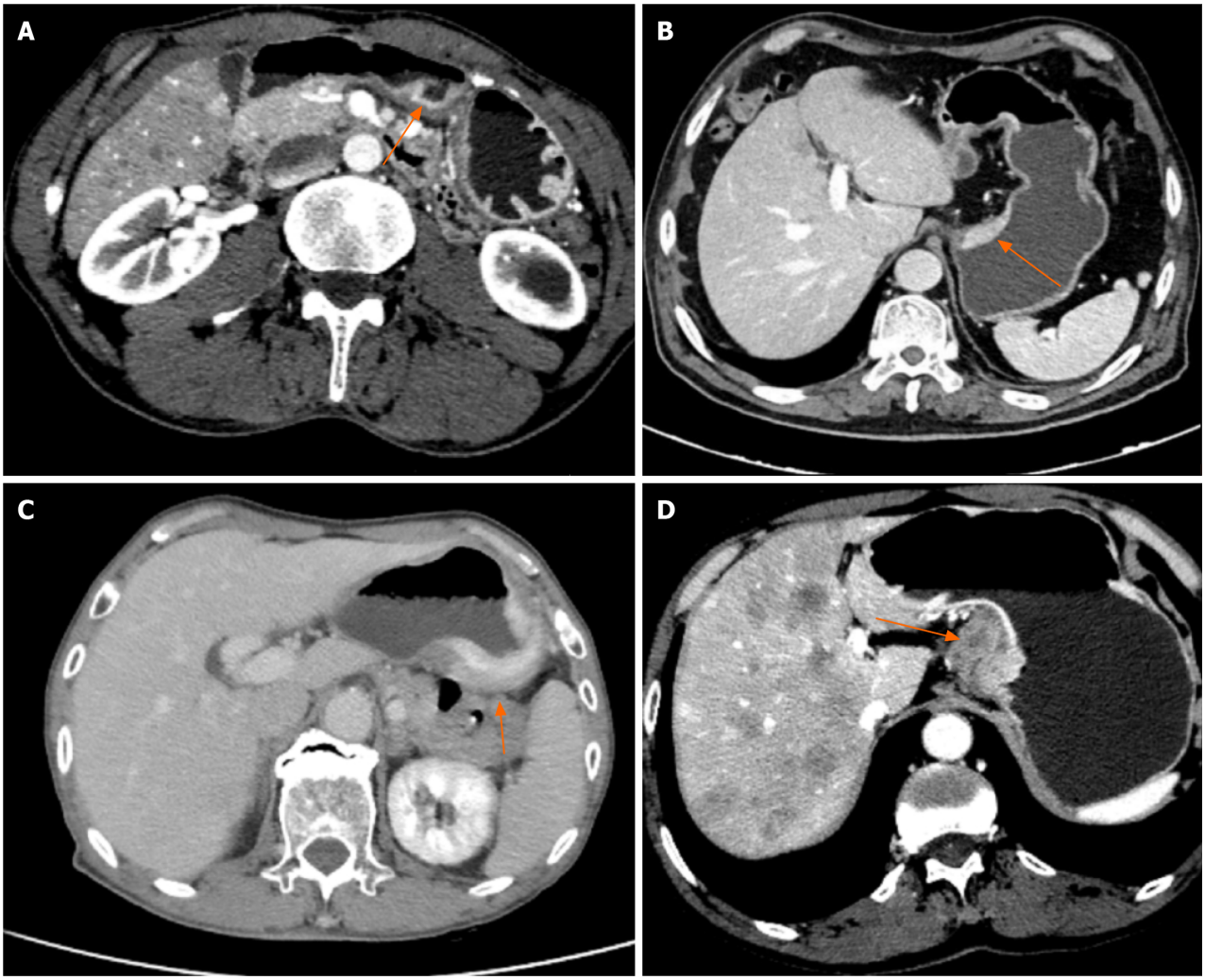

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Figure 1 T staging based on three-phase dynamic contrast-enhanced computed tomography scanning. A: In stage T1, the tumor invaded the muscularis mucosa of the stomach wall but did not invade the muscularis propria, and a clear fat layer can be seen (orange arrow); B: In stage T2, the local gastric wall of the lesser curvature of the stomach thickened uniformly and enhanced obviously, and the tumor invaded the muscularis propria. The low enhancement band of submucosal middle layer was interrupted and disappeared, and the residual part of the outer layer was slightly enhanced, with a smooth outer edge of the gastric wall (orange arrow); C: In stage T3, the highly enhanced tumor invaded the whole stomach wall, and a few short strips were observed on the serosa surface, with the surrounding fat space blurred (orange arrow); D: In stage T4, the soft tissue masses inside and outside the gastric wall of the lesser curvature side of the stomach were significantly enhanced, and the muscular interruption was clearly displayed, with the surrounding fat space banded with infiltration and accompanied by multiple liver metastases (orange arrow).

samples T test and presented as t. Counting data are expressed as percentages (%), analyzed using the chi-square test, and expressed as χ^2. Receiver operating characteristic curves were constructed to evaluate the diagnostic value of CD34 for T and N staging. Multivariate logistic regression analysis was conducted to analyze the independent factors for preoperative lymph node metastasis. Statistical significance was set at $P < 0.05$.

RESULTS

General data

The patients' general data are summarized in Table 1.

Diagnostic results of three-phase dynamic contrast-enhanced CT in T staging and expression of CD34 in different T stages

With pathological results as the gold standard, the diagnostic results of three-phase dynamic contrast-enhanced CT for stages T1-T4 are summarized in Table 2, and the expression of CD34-marked MVD in different T stages is summarized in Table 2.

Table 1 General data, *n* (%)

		n = 106
Age (yr)		57.5 ± 7.8
Gender		
	Male	81 (76.42)
	Female	25 (23.58)
Tumor length (cm)		5.02 ± 1.85
Pathological T staging		
	T1	25 (23.58)
	T2	28 (26.42)
	T3	34 (32.08)
	T4	19 (17.92)
Pathological N staging		
	N0	37 (34.91)
	N1	27 (25.47)
	N2	20 (18.87)
	N3	22 (20.75)
Tissue typing		
	Adenocarcinoma	83 (78.30)
	Signet-ring cell carcinoma	17 (16.04)
	Neuroendocrine carcinoma	6 (5.66)
Degree of differentiation		
	High differentiation	32 (30.19)
	Moderate differentiation	55 (51.89)
	Low differentiation	19 (17.92)

Table 2 Diagnostic results of three-phase dynamic contrast-enhanced computed tomography in T staging and the expression of CD34 in different T stages, *n* (%)

Pathological T staging	Three-phase dynamic contrast-enhanced CT in T staging					Expression of CD34-marked MVD
	T1	T2	T3	T4	Accuracy	
T1 (*n* = 25)	17	4	4	0	68.00	47.44 ± 10.22
T2 (*n* = 28)	4	21	3	0	75.00	63.41 ± 7.16
T3 (*n* = 34)	0	4	27	3	79.41	86.21 ± 8.36
T4 (*n* = 19)	0	2	3	14	73.68	103.71 ± 10.92

CT: Computed tomography; MVD: Microvessel density.

Diagnostic results of three-phase dynamic contrast-enhanced CT in N staging and expression of CD34 in different N stages

With pathological results as the gold standard, the diagnostic results of three-phase dynamic contrast-enhanced CT for N0-N3 are summarized in Table 3, and the expression of CD34-marked MVD in different N stages is summarized in Table 3.

Comparison of diagnostic efficacy between three-phase dynamic contrast-enhanced CT and CD34 in T staging

The sensitivity and specificity of three-phase dynamic contrast-enhanced CT in diagnosing stages T1-2 and T3-4 were calculated according to the results, and the sensitivity and specificity of CD34-marked MVD in diagnosing stages T1-2

Table 3 Diagnostic results of three-phase dynamic contrast-enhanced computed tomography in N staging and the expression of CD34 in different N stages, *n* (%)

Pathological N staging	N staging of three-phase dynamic contrast-enhanced CT					Expression of CD34-marked MVD
	N0	N1	N2	N3	Accuracy	
N0 (n = 37)	28	6	3	0	75.68	52.43 ± 12.77
N1 (n = 27)	3	20	4	0	74.07	71.89 ± 10.13
N2 (n = 20)	0	1	17	2	85.00	86.83 ± 9.74
N3 (n = 22)	0	2	3	17	77.27	102.07 ± 11.27

CT: Computed tomography; MVD: Microvessel density.

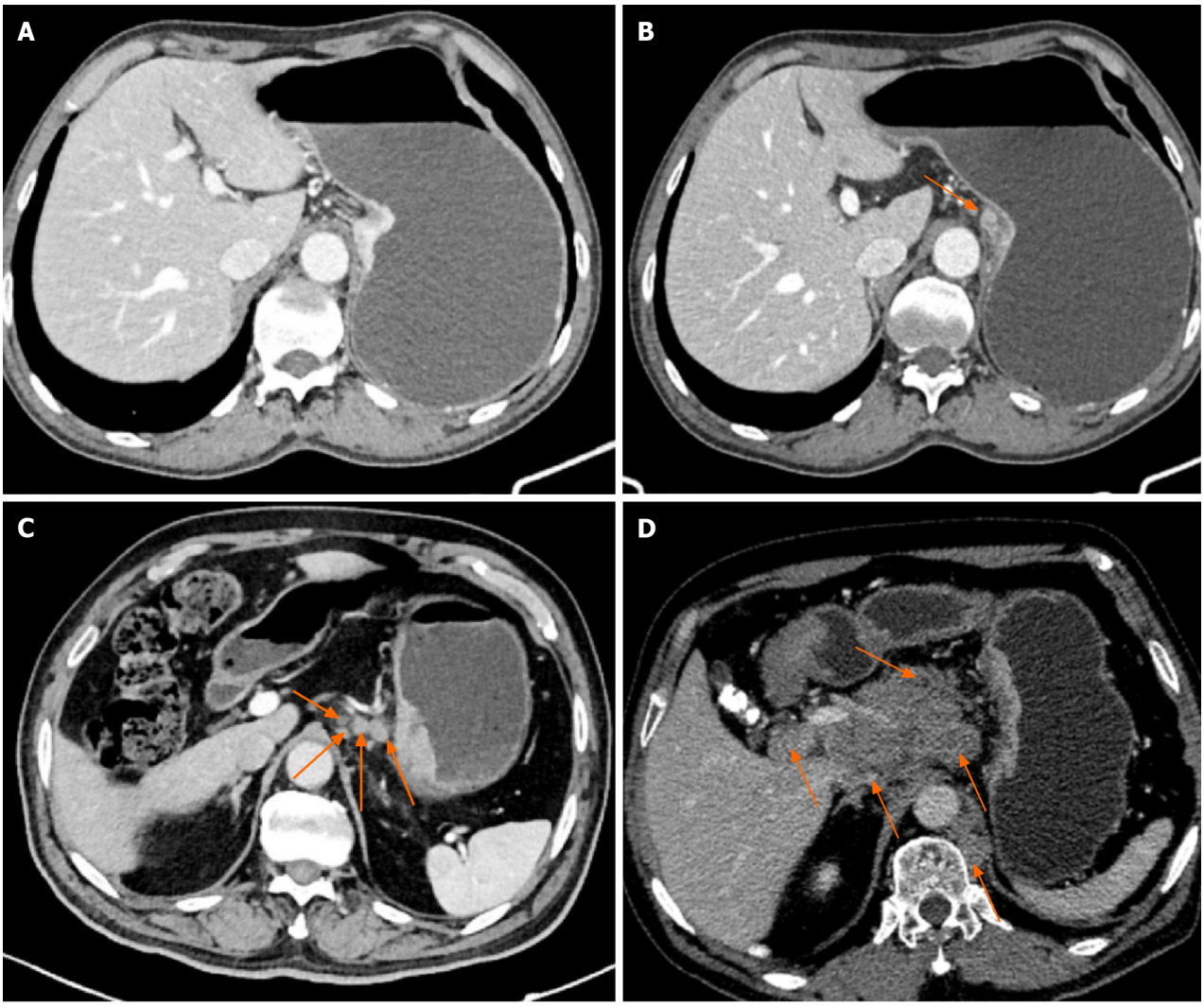

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Figure 2 N staging based on three-phase dynamic contrast-enhanced computed tomography scanning. A: N0: No local lymph node metastasis; B: N1: On the lesser curvature of the stomach, an enlarged lymph node with a diameter of approximately 10 mm is quasi-round, and slightly inhomogeneous enhancement can be observed (orange arrow); C: N2: More than 3 local lymph node metastases were in the left cardia, right cardia, and lesser curvature of the stomach, and the largest was located in the lesser curvature of the stomach, with a short diameter of approximately 12 mm (orange arrows); D: N3: There were more than 7 local lymph node metastases (*e.g.*, porta hepatic, common hepatic artery, left gastric artery, splenic artery, celiac trunk), the lymph nodes were fused into clusters, and the lymph nodes were necrotic and uneven enhancement (orange arrows).

and T3-4 were calculated according to the expression of CD34-marked MVD in T stages. The sensitivity and area under the curve (AUC) of the diagnosis improved through joint diagnosis (Figure 3, Table 4).

Comparison of diagnostic efficacy between three-phase dynamic contrast-enhanced CT and CD34 in N staging

The sensitivity and specificity of three-phase dynamic contrast-enhanced CT in N staging were calculated according to these results. The sensitivity and specificity of CD34-marked MVD in diagnosing stages N0-1 and stages N1-2 were also calculated according to the expression of CD34-marked MVD in N stages. The sensitivity and AUC of the diagnosis improved through joint diagnosis (Figure 4, Table 5).

Univariate analysis of lymph node metastasis in patients

Patients were divided into metastatic (n = 69) and non-metastatic (n = 37) groups based on the occurrence of lymph node metastasis. According to the univariate analysis, the two groups were not significantly different in age, tumor length, pathological T staging, histological classification, degree of differentiation, CD34, or expression of CD34-marked MVD (P < 0.05; Table 6).

Multivariate analysis of lymph node metastasis

Indexes with notable differences in the univariate analysis were subjected to multivariate logistic regression analysis. According to multivariate logistic regression analysis, a longer tumor diameter, higher pathological T staging, lower differentiation degree, and higher expression of CD34-marked MVD were independent risk factors for lymph node metastasis in patients with GC (Table 7).

DISCUSSION

The pathogenesis of GC remains under investigation. The causes of malignant gastric tumors are complicated, among which Helicobacter pylori infection is the most likely. However, personal living habits and family genetic factors are also causes and mechanisms that should be considered[15,16]. Early diagnosis and treatment are the most important aspects of early stage GC, and preoperative staging is necessary. Improving the accuracy of preoperative clinical staging can help increase the accuracy treatment plan for patients with GC, including the timing of chemotherapy drugs. Postoperative pathological classification and the number of lymph node metastases are crucial for the prognosis of patients with malignant tumors, and the depth of tumor invasion is a key factor affecting the prognosis of patients with GC[17,18]. In the literature, according to Cox regression analysis[19], the main factors affecting the prognosis of patients were tumor stage, invasion depth, lymph node metastasis, distant metastasis, and tumor size. Therefore, infiltration and metastasis of GC tumors are the main causes of clinical treatment failure and death. Accordingly, it is crucial to identify the tumor as early as possible and to correctly understand the tumor stage, infiltration depth, and existence of lymph node metastasis in the clinical treatment of patients with tumors.

T staging represents the depth of infiltration, a crucial reference for the selection of surgery for patients[20]. In this study, the accuracy of three-phase dynamic contrast-enhanced CT in diagnosing stage T1 was 68.00%, which was lower than that in diagnosing stages T2-T4 (75.00%, 79.41%, and 73.68%, respectively). A likely reason for this result is that three-phase dynamic contrast-enhanced CT cannot clearly display the low-density zone of the submucosa, resulting in a conclusion that the tumor has invaded it, resulting in excessive T staging. Wang *et al*[21] also explored the diagnostic results of dynamic contrast-enhanced CT for the T staging of GC and found that its accuracy in diagnosing stages T2-T4 was higher than that in diagnosing stage T1, which is similar to the results of this study. These results suggest that three-phase dynamic contrast-enhanced CT is suitable for determining the depth of invasion in advanced GC. GC mainly metastasizes *via* the lymphatic pathway. Three-phase enhanced scanning of the stomach before surgery and multi-CT angiography can help determine the variation in the perigastric blood vessels and the swollen lymph nodes along the blood vessels, which is beneficial for the clearance of lymph nodes during surgery[22,23]. In this study, the accuracies of three-phase dynamic contrast-enhanced CT for N staging were 75.68%, 74.07%, 85.00%, and 77.27%. Misdiagnosis may occur because the aggregation and fusion of lymph nodes reduce the number of lymph nodes, and when perigastric adipose tissue decreases, lymph nodes cannot be displayed because the contrast is insufficient, which reduces the number of lymph nodes. Chen *et al*[24] revealed that the diagnostic accuracy of dynamic contrast-enhanced CT in the N staging of GC is not high (the total accuracy is 78%), similar to the results of this study.

The growth of any solid tumor depends on the process of angiogenesis; that is, the endothelial cells of the host proliferate, sprout to form new blood vessels, grow toward the tumor, and construct tumor blood supply channels to provide nutrition and transport metabolites[25]. The greater the number of microvessels in a tumor, the greater the possibility of tumor cells entering the blood circulation. As the most specific marker of endothelial cells, CD34 is strongly associated with angiogenesis. An increasing number of studies have found a close relationship among an increase in MVD, the risk of tumor metastasis, and a decrease in survival rate[26]. In this study, CD34-marked MVD increased with an increase in T and N stages, indicating that CD34-marked MVD also increased with an increase in infiltration depth and lymph node metastasis. This result may be because with the development of GC, the primary tumor penetrates into the gastric parietal layer (corresponding to the T stage), or the invasion of local lymph nodes (corresponding to the N stage) requires increased angiogenesis to support its growth, increasing CD34 expression. Furthermore, advanced T stage, indicating larger tumor size or extensive local spread, is often associated with increased vascularization. Larger tumors require more blood supply, which can lead to higher MVD. Shi *et al*[27] explored the relationship among CD34 and clinicopathological features of gastric adenocarcinoma and found a positive correlation among high MVD values and

Table 4 Comparison of diagnostic efficacy between three-phase dynamic contrast-enhanced computed tomography and CD34 in T staging

Pathological T staging	Three-phase dynamic contrast-enhanced CT	CD34	Joint diagnosis
AUC	0.921	0.779	0.940
95%CI	0.870-0.972	0.690-0.869	0.897-0.984
Specificity (%)	86.79	64.15	55.6
Sensitivity (%)	88.68	88.68	98.72

CT: Computed tomography; AUC: Area under the curve; CI: Confidence interval.

Table 5 Comparison of diagnostic efficacy between three-phase dynamic contrast-enhanced computed tomography and CD34 in N staging

Pathological N staging	Three-phase dynamic contrast-enhanced CT	CD34	Joint diagnosis
AUC	0.952	0.839	0.989
95%CI	0.915-0.989	0.761-0.917	0.975-0.999
Specificity (%)	89.06	84.38	75.15
Sensitivity (%)	92.86	78.57	98.47

CT: Computed tomography; AUC: Area under the curve; CI: Confidence interval.

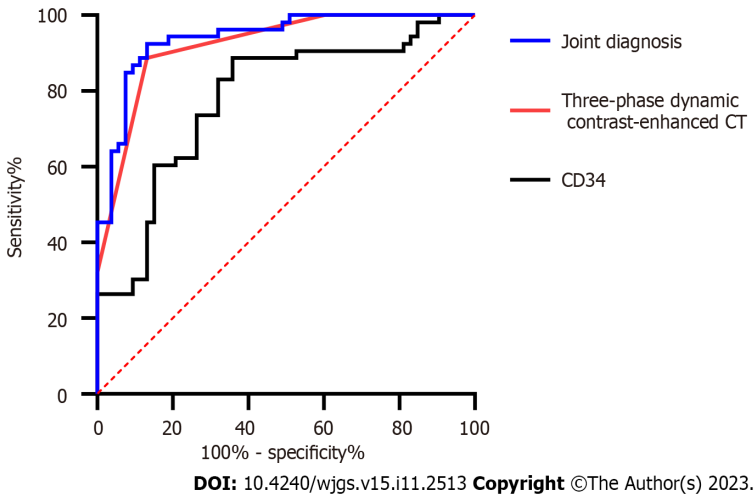

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Figure 3 Receiver operating characteristic curve of dynamic three-phase enhanced computed tomography and CD34 in the diagnosis of T stage. CT: Computed tomography.

lymph node metastasis and TNM staging, a negative correlation with high MVD values with pathological grade, and no correlation with tumor size or a patient's age or sex.

Finally, this study compared three-phase dynamic contrast-enhanced CT and CD34 in diagnosing stages T1-2 and T3-4 and stages N0-1 and N1-2. The specificity and sensitivity of the three-phase dynamic contrast-enhanced CT in T staging were 86.79% and 88.68%, respectively, and those for N staging were 89.06% and 92.86%, respectively. The specificity and sensitivity of CD34 in T staging were 64.15% and 88.68%, respectively, and those for N staging were 84.38% and 78.57%, respectively. Through parallel joint diagnosis, the sensitivity of T staging improved to 98.72%, and the sensitivity of N staging improved to 98.47%, with an improved AUC corresponding to the higher diagnostic value of joint diagnosis. According to multivariate analysis, a longer tumor diameter, higher pathological T stage, lower differentiation degree, and higher expression of CD34-marked MVD were independent risk factors for lymph node metastasis in patients with GC, suggesting an increase in attention to these risk factors before surgery.

Table 6 Univariate analysis

		Metastatic group (n = 69)	Non-metastatic group (n = 37)	χ^2/t	P value
Age (yr)		59.3 ± 7.6	54.2 ± 7.2	3.353	0.001
Gender				0.687	0.407
	Male	51 (73.91)	30 (81.08)		
	Female	18 (26.09)	7 (18.92)		
Tumor length (cm)		3.73 ± 1.25	5.72 ± 1.75	6.124	< 0.001
Pathological T staging				21.296	< 0.001
	T1	7 (10.14)	18 (48.65)		
	T2	19 (27.54)	9 (24.32)		
	T3	28 (40.58)	6 (16.22)		
	T4	15 (21.74)	4 (10.81)		
Tissue typing				6.226	0.046
	Adenocarcinoma	49 (71.01)	34 (91.89)		
	Signet-ring cell carcinoma	15 (21.74)	2 (5.41)		
	Neuroendocrine carcinoma	5 (7.25)	1 (2.70)		
Degree of differentiation				8.117	0.017
	High differentiation (n = 32)	15 (21.74)	17 (45.95)		
	Moderate differentiation (n = 55)	38 (55.07)	17 (45.95)		
	Low differentiation (n = 19)	16 (23.19)	3 (8.11)		
Expression of CD34-labelled MVD		84.57 ± 17.83	47.81 ± 14.93	10.686	< 0.001

MVD: Microvessel density.

Table 7 Multivariate analysis

	B	S.E.	Wals	Sig.	Exp(B)	95%CI for EXP (B)	
						Lower limit	Upper limit
Age (yr)	-0.071	0.097	0.526	0.468	0.932	0.770	1.128
Long diameter of tumor	1.367	0.527	6.728	0.009	3.923	1.397	11.019
T staging	2.544	0.714	12.697	0.001	12.73	3.141	51.586
Tissue typing	1.198	1.119	1.146	0.284	3.314	0.369	29.724
Degree of differentiation	2.417	0.921	6.882	0.009	11.209	1.842	68.194
Expression of CD34-labelled MVD	0.160	0.051	9.658	0.002	1.174	1.061	1.298

CI: Confidence interval; MVD: Microvessel density.

Limits of the study

Despite achieving our aim, this study still has limitations. First, there was an inevitable bias in this retrospective study. Second, the number of cases in this study was limited; therefore, further research should expand the sample size to support our results. Finally, three-phase dynamic contrast-enhanced CT is also affected by the experience of the doctor in analyzing the preoperative examination results, which may affect the accuracy of diagnosis.

CONCLUSION

In summary, CD34 expression combined with three-phase dynamic contrast-enhanced CT scanning has high accuracy in determining the invasion depth and lymph node metastasis of GC before surgery and can provide a reliable basis for

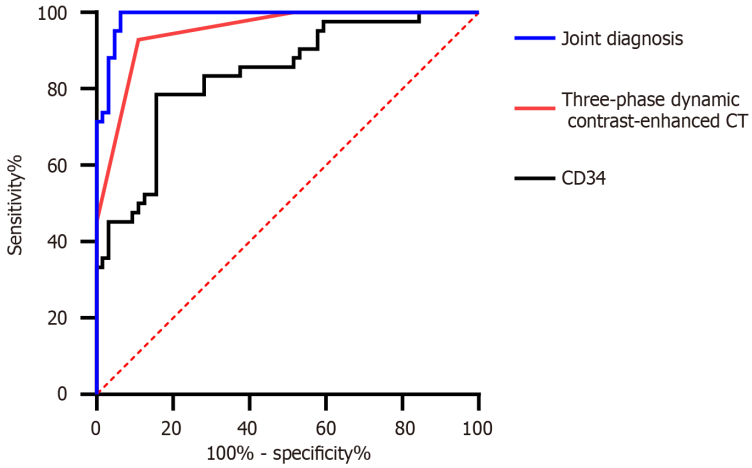

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Figure 4 Receiver operating characteristic curve of dynamic three-phase enhanced computed tomography and CD34 in the diagnosis of N stage. CT: Computed tomography.

surgical resection.

ARTICLE HIGHLIGHTS

Research background

Gastric cancer (GC) is a commonly observed malignancy and the main cause of cancer-related deaths worldwide. However, the accuracy of traditional computed tomography (CT) in preoperative staging remains controversial. CD34 is an endothelial cell marker that can help evaluate microvessel density (MVD) and angiogenesis in tumors. The combination of CD34 expression and dynamic three-phase enhanced CT can improve the accuracy of preoperative staging.

Research motivation

Early diagnosis, accurate staging, and detection of lymph node metastasis are crucial for the prognosis and development of treatment plans for patients with GC. This study aimed to evaluate the value of CD34 expression combined with dynamic three-phase enhanced CT in the preoperative staging and invasion evaluation of GC to explore new methods to improve the accuracy of preoperative evaluation and postoperative treatment.

Research objectives

The main goal of this study was to evaluate the value of CD34 expression combined with dynamic three-phase enhanced CT in the preoperative staging and invasion evaluation of GC. According to a study of 106 patients with GC, CD34-marked MVD positively correlated with the T and N stages, and CD34 expression combined with CT showed high sensitivity in GC staging. Tumor diameter, T stage, degree of differentiation, and CD34-marked MVD were independent risk factors for lymph node metastasis. The results of this study provide a new method for the preoperative staging and treatment planning of GC. The combination of CD34 expression and CT can improve staging accuracy and contribute to the evaluation of infiltration.

Research methods

In this study, the results of CD34 detection and dynamic three-phase enhanced CT scanning in 106 patients with GC were compared and analyzed with postoperative pathological results. The independent factors of preoperative lymph node metastasis were analyzed using multivariate logistic regression. The novelty of this study is that CD34 expression was combined with dynamic three-phase enhanced CT for diagnosis, and the accuracy of preoperative staging and invasion assessment of GC was improved through a comprehensive analysis of the two types of results. In addition, independent risk factors were determined using multivariate logistic regression analysis, which provided a scientific basis for clinical decision-making.

Research results

According to the results of this study, the combination of CD34 expression and dynamic three-phase enhanced CT showed a high sensitivity for preoperative staging of GC. Additionally, tumor diameter, T stage, degree of differentiation, and CD34-marked MVD were identified as independent risk factors for lymph node metastasis. Therefore, the combination of CD34 expression and dynamic three-phase-enhanced CT scanning can improve the accuracy of GC staging and help evaluate invasion. Although CD34 expression and dynamic three-phase enhanced CT scanning showed

high sensitivity in this study, their specificity and accuracy require further evaluation.

Research conclusions

This study highlights the critical role of angiogenesis in the development of GC and provides new theories and methods to improve preoperative staging and invasion evaluation of GC by combining CD34 expression with dynamic three-phase enhanced CT scanning. These new theories and methods will help deepen the understanding of the developmental mechanism of GC, guide clinical decision-making, and improve prognosis.

Research perspectives

Further research should verify and expand our research results by exploring new biomarkers and imaging technologies, studying the mechanisms of GC development, and developing individualized treatment strategies. These efforts will further improve the diagnosis and treatment of GC, improving the prognosis and quality of life of patients.

FOOTNOTES

Author contributions: Liu H designed the study and wrote the paper; Zhao KY designed the study and reviewed the manuscript; all authors annotated the manuscript.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of The First People's Hospital of Lianyungang.

Informed consent statement: This study is a retrospective study and used anonymous patients data from the past and did not pose any risks to patients, we have applied for exemption from informed consent.

Conflict-of-interest statement: We have no financial relationships to disclose.

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Country/Territory of origin: China

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ORIGINAL ARTICLE

Observational Study

Predictive value of frailty assessment tools in patients undergoing surgery for gastrointestinal cancer: An observational cohort study

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Abstract

BACKGROUND

Few studies have simultaneously compared the predictive value of various frailty assessment tools for outcome measures in patients undergoing gastrointestinal cancer surgery. Therefore, it is difficult to determine which assessment tool is most relevant to the prognosis of this population.

AIM

To investigate the predictive value of three frailty assessment tools for patient prognosis in patients undergoing gastrointestinal cancer surgery.

METHODS

This single-centre, observational, prospective cohort study was conducted at the Affiliated Lianyungang Hospital of Xuzhou Medical University from August 2021 to July 2022. A total of 229 patients aged ≥ 18 years who underwent surgery for gastrointestinal cancer were included in this study. We collected baseline data on the participants and administered three scales to assess frailty: The comprehensive geriatric assessment (CGA), Fried phenotype and FRAIL scale. The outcome measures were the postoperative severe complications and increased hospital

costs.

RESULTS

The prevalence of frailty when assessed with the CGA was 65.9%, 47.6% when assessed with the Fried phenotype, and 34.9% when assessed with the FRAIL scale. Using the CGA as a reference, kappa coefficients were 0.398 for the Fried phenotype and 0.291 for the FRAIL scale (both $P < 0.001$). Postoperative severe complications and increased hospital costs were observed in 29 (12.7%) and 57 (24.9%) patients, respectively. Multivariate logistic analysis confirmed that the CGA was independently associated with increased hospital costs (odds ratio = 2.298, 95% confidence interval: 1.044-5.057; $P = 0.039$). None of the frailty assessment tools were associated with postoperative severe complications.

CONCLUSION

The CGA was an independent predictor of increased hospital costs in patients undergoing surgery for gastrointestinal cancer.

Key Words: Gastrointestinal cancer; Frailty; Assessment tools; Prognostic; Complication; Hospital costs

Core Tip: Few studies have simultaneously compared the predictive value of various frailty assessment tools for the prognosis in patients undergoing gastrointestinal cancer surgery. Therefore, we investigated the predictive power of the comprehensive geriatric assessment (CGA), Fried phenotype and FRAIL scale for the prognosis of patients undergoing surgery for gastrointestinal cancer. There was a high prevalence of preoperative frailty. Scores on the CGA were positively related to patients' increased hospital costs.

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INTRODUCTION

Gastric and colorectal cancers have high morbidity and mortality rates in China and are a heavy burden on China's population health[1]. Surgery is the mainstay of treatment for patients with gastrointestinal cancer; however, surgical stress poses a challenge to patients[2,3]. It is important to identify the factors that affect postoperative adverse outcomes of patients, which can help us recognise the importance of frailty in evaluating patients before surgery. This can also provide a theoretical basis for formulating corresponding intervention measures. As such, frailty has gradually become a concern in recent years. It is considered a group of syndromes caused by a decreased physiological reserve or multisystem disorder resulting in increased vulnerability and weakened stress tolerance[4]. When frail patients attempt to cope with stressors (*e.g.*, surgery), it can easily lead to disability, falls, fractures and other adverse clinical outcomes. McGovern *et al*[5] and Ding *et al*[6] found that patients undergoing colorectal and gastric cancer surgery had a large range of difference in their prevalence of preoperative frailty, but it remained at a high level of 12.0% to 56.0% and 8.5% to 45.9%, respectively. Frailty was found to be an independent predictor of postoperative complications, mortality and overall survival in patients undergoing gastrointestinal cancer surgery[7-11]. It should be noted that frail patients may increase the incidence of severe complications due to their decreased ability to cope with stress, and frailty has the potential to compromise patient recovery following surgery, thereby increasing the cost of associated treatment, care and medications.

Currently, there is no consensus on the best frailty screening tool for surgical patients with gastrointestinal cancer[12]. Clegg *et al*[13] stated that the comprehensive geriatric assessment (CGA) is the gold standard for frailty assessment. The CGA includes multiple dimensions and is widely recommended for clinical use. However, the CGA is time consuming and requires a professionally trained healthcare provider. The Fried phenotype proposed by Fried was endorsed by the American College of Surgeons and the American Geriatrics Society for preoperative frailty assessment[14]. The Fried phenotype assessment is based on both self-assessment and objective measures and is a commonly used frailty assessment tool in clinical practice[15]. However, because the Fried phenotype assessment measures patients' physical activity, it can only be performed by medically stable and ambulatory patients. The FRAIL scale, proposed by the International Association for Nutrition, Health, and Aging, is recommended for frailty screening by the Australian and New Zealand Society for Sarcopenia and Frailty Research[16]. The FRAIL scale is based on patient self-report and is simple and quick to complete, facilitating clinical implementation. However, it does not distinguish between frailty and comorbidities. Interestingly, the FRAIL scale has, to date, not been used for patients undergoing gastrointestinal cancer surgery.

These three scales have their own advantages and disadvantages and differ in terms of items and dimensions. Few studies have simultaneously compared the predictive value of the three frailty assessment tools for patient prognosis. Therefore, it is difficult to determine which assessment tool is most relevant to the prognosis of patients undergoing gastrointestinal cancer surgery[17,18]. Thus, we prospectively analysed whether the three frailty scales were predictive of postoperative severe complications and increased hospital costs of patients undergoing gastrointestinal cancer surgery. We also determined which assessment tool was most associated with the measured outcomes by odds ratio.

MATERIALS AND METHODS

Patients

This single-centre, observational, prospective cohort study was conducted at the Lianyungang Hospital of Xuzhou Medical University from August 2021 to July 2022. The inclusion criteria were as follows: (1) Age ≥ 18 years; (2) Patients whose first pathological diagnosis was gastric, colon or rectal cancer; (3) Patients who underwent elective radical surgery; and (4) Patients who had complete clinical data that could be obtained. The exclusion criteria were as follows: (1) Patients who had cancer combined with other sites of malignant cancers; (2) Patients with a psychiatric history; and (3) Patients who were unable to cooperate with and complete data collection. The study was approved by the Ethics Committee of the Affiliated Lianyungang Hospital of Xuzhou Medical University, Jiangsu, China (ethics approval number: KY-20211029001-01) and was performed in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from all participants in this study.

Measures

CGA: A CGA typically assesses comorbidities, polypharmacy, functional status, cognition, psychological status and nutritional status[19-21]. In this study, the assessment tools and cut-off values included in the CGA were as follows: Charlson Comorbidity Index (CCI) ≥ 3 was considered multimorbidity[22]; ≥ 5 types of medication prescribed was classified as polypharmacy[22]; Barthel index (BI) < 100 or instrumental activities of daily living < 8 was considered impaired functional status[22,23]; cognition was assessed using the Mini-Mental State Examination, and cognitive impairment was defined according to the patient's education, in which illiteracy was ≤ 17, primary education was ≤ 20 and junior high school education or above was ≤ 24[24]; the Hospital Anxiety and Depression Scale was used to assess anxiety and depression, and anxiety scores or depression scores ≥ 8 were considered an impaired psychological status [25]; a Patient-Generated Subjective Global Assessment score ≤ 4 was considered malnutrition[26]. Based on previous studies, impairment in ≥ 2 domains within the CGA was defined as frailty[19,21].

Fried phenotype: The Fried phenotype includes five items: Weight loss, slowness, exhaustion, low physical activity and weakness. Handgrip strength was measured using an electronic handgrip dynamometer (EH101, Xiangshan, China); activity was assessed using the short form of the International Short Physical Activity Questionnaire[27]; and the criteria for other items were based on the Taiwanese version of the Fried phenotype cut-off[28]. Regarding scoring, there is one point per item according to the assessment criteria of said item. The total score can range from 0-5, with a score of 0 indicating robust, 1-2 indicating pre-frailty, and ≥ 3 indicating frailty[29]. Patients with Fried phenotype scores ≥ 3 were included in the frailty group and those with Fried phenotype scores of 0-2 were included in the non-frailty group[30].

FRAIL scale: The FRAIL scale includes five items: Fatigue, resistance, illness, ambulation and weight loss. The items are based on patients' self-assessment. There is one point for each item. The total score can range from 0-5, with 0 indicating robust, 1-2 indicating pre-frailty, and ≥ 3 indicating frailty[31]. Patients who scored ≥ 3 on the FRAIL scale were included in the frailty group and those who scored 0 to 2 were included in the non-frailty group[32].

Clinical data collection

Data collection was performed one day before surgery and included: (1) Baseline demographic data, including age, sex, body mass index (BMI), smoking history, drinking history, upper arm circumference, waist circumference, hip circumference and calf circumference; (2) Clinical data, including cancer type, CCI score, polypharmacy, neoadjuvant therapy, the American Society of Anesthesiologists (ASA) classification, Karnofsky Performance Scale (KPS) score, operative method, operation time, tumour node metastasis (TNM) stage, histological grade and postoperative length of stay; and (3) Laboratory data, including haemoglobin (HB), white blood cell count, platelets, lymphocyte count, lymphocyte ratio, creatinine, haematocrit, albumin and total protein. The scale can be filled out by the patient themselves, or the researcher can inform the patient of the items and help them fill it out. It was necessary to further confirm whether the patient met the inclusion and exclusion criteria after we collected patient data after surgery because the definite TNM stage of the patient and the possible suspension of surgery could not be determined before surgery.

Outcome measures

The outcome measures were severe complications and increased hospital costs. Only postoperative severe complications that developed during hospital were considered. Based on previous studies, severe complications were considered as Clavien-Dindo classification ≥ 3[33]. Increased hospital costs were defined as costs greater than the 75th percentile of the entire cohort[6]. All outcome measures were obtained using an electronic information system.

Sample size

We calculated the sample size for postoperative severe complications based on a previous study[34], the complication rate was 43% in frail patients and 17% in non-frail patients. We set an α-value of 0.05 and a power of 80% to calculate that 96 patients should be included in the study.

Statistical analysis

Taking the CGA as a reference, the kappa coefficient was used to analyse its agreement with the Fried phenotype and the FRAIL scale. The measurement data with a normal distribution were described using mean ± SD, and independent samples t tests were used for comparison between groups. The measurement data with a biased distribution were described by median and interquartile ranges, and the Mann-Whitney U test was used for comparison between groups. The enumeration data were described by frequency and percentage, and the χ^2 test, continuity correction χ^2 test and Mann-Whitney U test were used for comparison between groups. Risk factors for severe complications and increased hospital costs were analysed using the above statistical methods and univariate logistic regression. Factors with $P < 0.10$ in the univariate analysis combined with each of the three frailty assessment tools were included in a multivariate logistic regression model. All tests were two-sided, and $P < 0.05$ was considered statistically significant. SPSS version 25.0 (SPSS Inc., Chicago, IL, United States) was used for all statistical analyses.

RESULTS

Baseline patient characteristics

A total of 229 patients with gastrointestinal cancer who underwent surgery met our inclusion criteria and were enrolled in the study. Severe complications and increased hospital costs were observed in 29 (12.7%) and 57 (24.9%) patients, respectively. There were 13 (5.7%) patients with 3, and 16 (7.0%) patients with 4. The median for hospital costs was 65031 renminbi (RMB), with interquartile ranges of 58125 and 78973 RMB. Among them, 141 (61.6%) were men and 88 (38.4%) were women. Patients were aged 30-88 years, with a mean age of 66.31 years. Patients had a BMI (kg/m^2) ranging from 15.56-33.98 kg/m^2, with a mean of 23.71 kg/m^2. Regarding cancer type, 83 (36.2%) patients had gastric cancer, 81 (35.4%) had colon cancer, and 65 (28.4%) had rectal cancer. Based on the CGA, there were significant differences in age, BMI, CCI score, upper arm circumference, hip circumference, calf circumference, HB, lymphocyte ratio, haematocrit, albumin, ASA classification, KPS score, cancer type, operative method, histological grade, and hospital costs between frail and non-frail patients (all $P < 0.05$). The baseline characteristics of the frail and non-frail patients corresponding to each assessment tool are presented in Table 1.

Frailty assessment

The prevalence of preoperative frailty assessed using the CGA, Fried phenotype and FRAIL scale was 65.9%, 47.6% and 34.9%, respectively. Taking the CGA as a reference, kappa coefficients were 0.398 and 0.291 for the Fried phenotype and the FRAIL scale (both $P < 0.001$). Moreover, it showed poor agreement between scales for frailty assessment.

Univariate analysis of outcome measures

Our results showed that sex, age, smoking history, drinking history, lymphocyte count, albumin, total protein, ASA classification, and operation time were contributing factors of severe complications (Table 2). Smoking history, neoadjuvant therapy, waist circumference, ASA classification, KPS score, cancer type, histological grade, severe complications and postoperative length of stay were factors influencing increased hospital costs.

Association of frailty with outcome measures

The three frailty assessment tools were combined with factors with $P < 0.10$ from the univariate analysis of outcome measures (Table 3). The univariate and multivariate analyses showed that frailty assessed using all assessment tools was not associated with severe complications (all $P < 0.05$). Other independent factors included age, drinking history, albumin and operation time (all $P < 0.05$). Both univariate and multivariate analyses showed that the CGA was associated with increased hospital costs (odds ratio = 2.298, 95% confidence interval: 1.044-5.057; $P = 0.039$). Other independent factors included postoperative length of stay and neoadjuvant therapy (both $P < 0.05$).

DISCUSSION

We prospectively analysed whether the three frailty scales predicted severe complications and increased hospital costs in patients undergoing gastrointestinal cancer surgery. Our study revealed the CGA was an independent predictor of increased hospital costs in this population.

Our results showed a high prevalence of preoperative frailty in patients with gastrointestinal cancer undergoing surgery, ranging from 34.9% (FRAIL) to 65.9% (CGA). A study by Chen *et al*[21] found that the prevalence of frailty using the CGA, Geriatric 8 and the Flemish version of the Triage Risk Screening Tool ranged from 40.9% to 75.0% in newly diagnosed all types of cancer patients aged ≥ 20 years, similar to the results of this study. Zhang *et al*[35] showed that the prevalence of preoperative frailty in older adult patients with gastric and colorectal cancer was 43.8%, which is also

Table 1 Baseline patient characteristics

Variables	Comprehensive geriatric assessment			Fried phenotype			FRAIL scale		
	Non-frail (*n* = 78)	Frail (*n* = 151)	*P* value	Non-frail (*n* = 120)	Frail (*n* = 109)	*P* value	Non-frail (*n* = 149)	Frail (*n* = 80)	*P* value
Male, *n* (%)	53 (67.9)	88 (58.3)	0.154	78 (65.0)	63 (57.8)	0.263	96 (64.4)	45 (56.3)	0.225
Age, yr	66 (57-71)	68 (62-76)	0.020	65 (57-71)	70 (63-76)	< 0.001	66 (58-72)	69 (63-76)	0.012
BMI, kg/m^2	24.45 ± 3.47	23.33 ± 3.39	0.021	24.35 ± 3.12	23.0 ± 3.68	0.003	23.95 ± 3.27	23.27 ± 3.75	0.158
Smoking history, *n* (%)	35 (44.9)	71 (47.0)	0.757	62 (51.7)	44 (40.4)	0.087	76 (51.0)	30 (37.5)	0.051
Drinking history, *n* (%)	32 (41.0)	68 (45.0)	0.562	61 (50.8)	39 (35.8)	0.022	70 (47.0)	30 (37.5)	0.168
Neoadjuvant therapy, *n* (%)	2 (2.6)	10 (6.6)	0.321	4 (3.3)	8 (7.3)	0.174	5 (3.4)	7 (8.8)	0.151
CCI score, *n* (%)	78 (100)		0.001			0.091			0.003
0-2	0 (0)	133 (88.1)		114 (95.0)	97 (89.0)		143 (96.0)	68 (85.0)	
≥ 3	0 (0)	18 (11.9)		6 (5.0)	12 (11.0)		6 (4.0)	12 (15.0)	
Polypharmacy, *n* (%)		6 (4.0)	0.178	1 (0.8)	5 (4.6)	0.173	0 (0)	6 (7.5)	0.003
Upper arm circumference, cm	29.5 ± 2.5	28.2 ± 2.9	0.001	29.3 ± 2.4	27.8 ± 3.1	< 0.001	29.1 ± 2.6	27.8 ± 3.1	0.001
Waist circumference, cm	89.8 ± 9.8	87.5 ± 9.7	0.091	89 ± 39.4	87.1 ± 10.0	0.099	88.7 ± 9.8	87.3 ± 9.6	0.303
Hip circumference, cm	96.4 ± 6.3	93.6 ± 7.4	0.006	96.0 ± 6.0	92.9 ± 7.9	0.001	95.1 ± 6.7	93.7 ± 7.9	0.157
Calf circumference, cm	34.8 ± 3.2	33.0 ± 3.4	< 0.001	34.8 ± 3.0	32.3 ± 3.5	< 0.001	34.2 ± 3.2	32.5 ± 3.6	0.001
HB, g/L	130 (109-137)	116 (97-133)	0.003	130 (114-141)	108 (92-128)	< 0.001	127 (111-138)	106 (87-128)	< 0.001
WBC, 10^9/L	5.75 (4.50-6.84)	6.00 (4.70-7.22)	0.184	5.85 (4.52-6.97)	5.93 (4.72-6.90)	0.598	5.80 (4.53-6.81)	6.00 (4.76-7.54)	0.186
Platelet, 10^{12}/L	209 (178-244)	228 (186-270)	0.171	212 (181-249)	228 (186-274)	0.255	219 (179-254)	227 (190-278)	0.265
Lymphocyte count, 10^9/L	1.56 (1.17-1.97)	1.39 (1.07-1.77)	0.070	1.47 (1.17-1.96)	1.40 (1.04-1.74)	0.046	1.44 (1.16-1.94)	1.40 (0.92-1.74)	0.067
Lymphocyte ratio, %	28.6 (23.0-33.0)	23.5 (18.4-31.3)	0.002	28.2 (21.8-33.3)	23.4 (17.3-29.1)	0.003	27.6 ± 9.2	23.5 ± 9.7	0.013
Creatinine, μmmol/L	63.4 (53.8-71.0)	58.2 (48.5-72.3)	0.127	63.6 (54.4-73.2)	55.3 (47.0-67.5)	0.001	62.5 (52.6-72.5)	56.7 (47.3-69.5)	0.074
Haematocrit, %	39.3 (34.1-41.9)	35.4 (31.3-40.5)	0.003	39.3 (34.9-42.8)	33.5 (29.4-39.0)	< 0.001	38.8 (34.1-41.5)	32.7 (28.0-39.1)	< 0.001
Albumin, g/L	38. ± 13.7	36.4 ± 4.0	0.002	38.4 ± 3.5	35.4 ± 3.9	< 0.001	37.8 ± 3.7	35.4 ± 4.0	< 0.001
Total protein, g/L	62.7 ± 5.8	61.2 ± 5.9	0.059	62.8 ± 5.6	60.5 ± 6.0	0.003	62.4 ± 5.4	60.4 ± 6.6	0.011
ASA classification, *n* (%)			0.036			0.009			0.011
I-II	55 (70.5)	85 (56.3)		83 (69.2)	57 (52.3)		100 (67.1)	40 (50.0)	
III-IV	23 (29.5)	66 (43.7)		37 (30.8)	52 (47.7)		49 (32.9)	40 (50.0)	
KPS score, *n* (%)			< 0.001			< 0.001			< 0.001
≥ 70	76 (97.4)	118 (78.1)		119 (99.2)	75 (68.8)		144 (96.6)	50 (62.5)	
< 70	2 (2.6)	33 (21.9)		1 (0.8)	34 (31.2)		5 (3.4)	30 (37.5)	
Cancer type, *n* (%)			0.011			0.216			0.104
Stomach	18 (23.1)	65 (43.0)		40 (33.3)	43 (39.4)		49 (32.9)	34 (42.5)	
Colon	32 (41.0)	49 (32.5)		40 (33.3)	41 (37.6)		51 (34.2)	30 (37.5)	
Rectum	28 (35.9)	37 (24.5)		40 (33.3)	25 (22.9)		49 (32.9)	16 (20.0)	
Operative method, *n* (%)			0.005			0.008			0.187
Open surgery	13 (16.7)	52 (34.4)		25 (20.8)	40 (36.7)		38 (25.5)	27 (33.8)	

Laparoscopic surgery	65 (83.3)	99 (65.6)		95 (79.2)	69 (63.3)		111 (74.5)	53 (66.3)	
Operative time, min	156 (123-202)	169 (120-210)	0.578	165 (120-217)	163 (121-195)	0.486	165 (125-210)	160 (119-200)	0.412
TNM stage, *n* (%)			0.057			0.328			0.911
I-II	55 (70.5)	87 (57.6)		78 (65.0)	64 (58.7)		92 (61.7)	50 (62.5)	
III	23 (29.5)	64 (42.4)		42 (35.0)	45 (41.3)		57 (38.3)	30 (37.5)	
Histological grade, *n* (%)			0.012			0.545			0.374
Poorly differentiated	28 (35.9)	78 (51.7)		55 (45.8)	51 (46.8)		67 (45.0)	39 (48.8)	
Moderately differentiated	33 (42.3)	55 (36.4)		43 (35.8)	45 (41.3)		56 (37.6)	32 (40.0)	
Highly differentiated	17 (21.8)	18 (11.9)		22 (18.3)	13 (11.9)		26 (17.4)	9 (11.3)	
Postoperative length of stay, d	14 (12, 16)	14 (12, 19)	0.184	14 (12, 18)	15 (13, 18)	0.162	14 (12, 17)	15 (13, 19)	0.029
Hospital costs, RMB	62341 (58067, 71180)	67697 (59097, 81720)	0.006	63148 (57893, 74841)	67764 (59156, 82804)	0.047	63477 (57719, 76170)	69031 (59596, 82043)	0.023
Severe complications, *n* (%)	6 (7.7)	23 (15.2)	0.104	13 (10.8)	16 (14.7)	0.382	16 (10.7)	13 (16.3)	0.232

Data are presented as means ± SD, medians (interquartile ranges) or *n* (%).

CCI: Charlson Comorbidity Index; BMI: Body mass index; HB: Haemoglobin; WBC: White blood cell; ASA: American Society of Anesthesiologists; KPS: Karnofsky Performance Scale; TNM: Tumour node metastasis.

within the range of our findings. Conversely, Yin *et al*[36] assessed frailty using the 54-item Frailty Index, 9-item Clinical Frailty Scale and FRAIL scale and found that the prevalence of preoperative frailty in older adult patients undergoing elective abdominal surgery was 32.5%, 36.6%, and 43.8%, respectively, which is slightly lower than our findings. This may be related to the fact that our study population included only patients with gastrointestinal cancer. Due to the inherent and therapeutic factors of gastrointestinal cancer, their physiological and psychological reserve abilities are more susceptible to stress, leading to adverse outcomes[35], which likely contribute to the high prevalence of frailty in this population. The poor agreement between the CGA and the Fried phenotype and FRAIL scale showed that there were large differences between assessment tools for the diagnosis of frailty. In addition, the CGA was more sensitive at identifying frailty than the other two scales, possibly because the CGA includes more comprehensive dimensions, these being the physical and psychological dimensions. Psychological problems such as anxiety and depression are more common in cancer patients[37]; thus, the CGA is more sensitive at identifying frailty. The Fried phenotype and the FRAIL scale focus only on the physical dimensions and thus assess the prevalence of frailty as lower than what the CGA would assess[38].

Our study revealed that the CGA, Fried phenotype and FRAIL scale did not independently predict severe complications in patients with gastrointestinal cancer. Reisinger *et al*[39] and Richards *et al*[7] showed that frailty is not an independent influencing factor for severe complications in patients undergoing colorectal cancer surgery ($P = 0.19$ and $P = 0.62$), consistent with our study results. Conversely, the results of Lo *et al*[40] showed that frailty increases the risk of postoperative severe complications. This may be due to differences in the assessment tools used, study populations and geography. Additionally, none of the frailty assessment instruments in our study included a social dimension. Since the global coronavirus disease 2019 pandemic in 2020, social distancing has become an important public health initiative. Social frailty may also have an impact on adverse short-term outcomes in patients. Thus, social frailty items can be used as part of frailty assessment in the future to further explore the elements of frailty assessment tools that can predict postoperative complications in patients undergoing gastrointestinal cancer surgery. This will lead to the creation of more comprehensive assessment tools.

In addition, our study revealed that the CGA scores were positively related to patients' increased hospital costs. In a cohort study of 52012 adult patients undergoing surgery, Shaw *et al*[41] showed that patients' frailty led to an increase in healthcare costs by $6048. Lee *et al*[42] stated that hospital costs were higher in frail patients (adjusted odds ratio = 1.46, 95% confidence interval: 1.46-1.46, $P < 0.001$), possibly because of longer hospital stays and more expenditures for rescues and the intensive care unit. Considering that most of the patients in this study made a living through farming and had poor family financial situations, increased hospital costs may have aggravated their psychological and economic burden, thus affecting their attitude towards treatment. Therefore, it is of great significance for us to use the CGA to evaluate patients' frailty before surgery and provide psychological counselling for them.

Our study has certain strengths. First, this is the first study to use the FRAIL scale to assess frailty in patients with gastrointestinal cancer undergoing surgery. Second, most severe complications occur in hospitals and need to be highly valued, while there are few reports on our population. Third, we used prospective research methods to investigate the predictive value of various frailty assessment tools on patient outcomes, which has not been much reported in previous studies.

Table 2 Predictors of severe complications and increased hospital costs (univariate analysis)

Variables	Severe complications (-) (*n* = 200)	Severe complications (+) (*n* = 29)	*P* value	OR (95%CI)	*P* value	increased hospital costs (-) (*n* = 172)	increased hospital costs (+) (*n* = 57)	*P* value	OR (95%CI)	*P* value
Male, *n* (%)	119 (59.5)	22 (79.5)	0.090	0.467 (0.191, 1.145)	0.096	101 (58.7)	40 (70.2)	0.123	0.605 (0.318, 1.151)	0.125
Age, yr	66 (58-73)	70 (65-77)	0.004	1.070 (1.022, 1.120)	0.004	67 (58, 73)	68 (64, 74)	0.212	1.024 (0.993, 1.056)	0.124
BMI, kg/m^2	23.52 (21.22-25.72)	23.73 (21.22-26.64)	0.588	1.024 (0.916, 1.146)	0.671	23.52 (21.28, 25.53)	23.59 (20.83, 26.30)	0.876	0.993 (0.911, 1.084)	0.883
Smoking history, *n* (%)	87 (43.5)	19 (65.5)	0.026	2.468 (1.092, 5.576)	0.030	73 (42.4)	33 (57.9)	0.043	1.865 (1.017, 3.420)	0.044
Drinking history, *n* (%)	81 (40.5)	19 (65.5)	0.011	2.791 (1.234, 6.313)	0.014	70 (40.7)	30 (52.6)	0.115	1.619 (0.886, 2.957)	0.117
Neoadjuvant therapy, *n* (%)	12 (6.0)	0 (0)	0.363	NA[1]		5 (2.9)	7 (12.3)	0.016	4.676 (1.422, 15.376)	0.011
CCI score, *n* (%)										
0-2	184 (92.0)	27 (93.1)	1.000	0.852 (0.185, 3.912)	0.837	158 (91.9)	53 (93.0)	1.000	0.852 (0.269, 2.701)	0.785
≥ 3	16 (8.0)	2 (6.9)	1.000	1.393 (0.157, 12.362)	0.766	14 (8.1)	4 (7.0)	0.336	3.130 (0.614, 15.963)	0.170
Polypharmacy, *n* (%)	5 (2.5)	1 (3.4)				3 (1.7)	3 (5.3)			
Upper arm circumference, cm	28.7 ± 2.8	28.3 ± 3.3	0.453	0.949 (0.827, 1.088)	0.452	28.6 ± 2.8	28.8 ± 2.9	0.633	1.026 (0.923, 1.140)	0.632
Waist circumference, cm	87.9 ± 9.4	90.3 ± 11.9	0.318	1.025 (0.985, 1.067)	0.226	87.6 ± 9.7	90.1 ± 9.7	0.094	1.027 (0.995, 1.059)	0.095
Hip circumference, cm	94.0 (90.7-98.8)	96.0 (89.5-101.3)	0.454	0.998 (0.945, 1.054)	0.938	94.5 ± 7.0	94.9 ± 7.6	0.663	1.009 (0.968, 1.053)	0.661
Calf circumference, cm	33.8 (31.5-35.9)	34.6 (31.8-37.5)	0.719	0.989 (0.883, 1.107)	0.843	33.6 ± 3.4	33.7 ± 3.5	0.768	1.013 (0.928, 1.106)	0.766
HB, g/L	121 (103-135)	119 (100-135)	0.872	0.998 (0.982, 1.015)	0.836	124 (104, 135)	112 (97, 134)	0.208	0.992 (0.979, 1.005)	0.206
WBC, 10^9/L	5.91 (4.71-6.99)	5.93 (4.20-6.68)	0.441	0.952 (0.782, 1.158)	0.621	5.85 (4.52, 7.03)	5.96 (5.14, 6.85)	0.557	1.008 (0.874, 1.162)	0.917
Platelet, 10^{12}/L	221 (182-263)	204 (168-247)	0.279	0.996 (0.990, 1.001)	0.147	220 (183, 260)	227 (168, 270)	0.809	0.999 (0.995, 1.003)	0.652
Lymphocyte count, 10^9/L	1.47 (1.16-1.88)	1.22 (1.03-1.77)	0.057	0.483 (0.218, 1.067)	0.072	1.42 (1.10, 1.84)	1.46 (1.20, 1.87)	0.509	1.043 (0.620, 1.756)	0.873
Lymphocyte ratio, %	26.4 ± 9.5	24.0 ± 9.8	0.198	0.972 (0.931, 1.015)	0.198	25.3 (20.4, 32.5)	23.6 (18.6, 31.3)	0.581	0.999 (0.968, 1.031)	0.962
Creatinine, μmmol/L	59.8 (49.8-71.4)	65.7 (55.1-71.3)	0.244	1.008 (0.992,	0.342	59.8 (50.5, 71.4)	61.1 (49.9, 71.0)	0.896	0.993 (0.977,	0.408

				1.023)					1.010)	
Haematocrit, %	37.2 (32.1-41.0)	35.9 (30.3-41.5)	0.981	0.994 (0.935, 1.058)	0.859	37.8 (32.5, 41.1)	35.0 (31.2, 41.1)	0.294	0.973 (0.928, 1.021)	0.262
Albumin, g/L	37.3 ± 3.9	34.9 ± 4.1	0.002	0.856 (0.772, 0.948)	0.003	37.2 ± 3.8	36.4 ± 4.3	0.236	0.955 (0.885, 1.030)	0.236
Total protein, g/L	61.8 (58.3-65.8)	58.9 (56.6-62.4)	0.012	0.921 (0.857, 0.989)	0.023	61.6 (58.0, 65.3)	60.5 (57.6, 64.7)	0.977	1.015 (0.965, 1.068)	0.567
ASA classification, *n* (%)										
I-II	127 (63.5)	13 (44.8)	0.054	2.141 (0.975, 4.701)	0.058	112 (65.1)	28 (49.1)	0.032	1.933 (1.054, 3.546)	0.033
III-IV	73 (36.5)	16 (55.2)				60 (34.9)	29 (50.9)			
KPS score, *n* (%)										
≥ 70	170 (85.0)	24 (82.8)	0.970	1.181 (0.418, 3.336)	0.754	150 (87.2)	44 (77.2)	0.069	2.014 (0.939, 4.323)	0.072
< 70	30 (15.0)	5 (17.2)				22 (12.8)	13 (22.8)			
Cancer type, *n* (%)										
Stomach	74 (37.0)	9 (31.0)	0.743	Reference		56 (32.6)	27 (47.4)	0.114	Reference	
Colon	69 (34.5)	12 (41.4)		1.430 (0.567, 3.604)	0.448	63 (36.6)	18 (31.6)		0.593 (0.295, 1.189)	0.141
Rectum	57 (28.5)	8 (27.6)		1.154 (0.419, 3.178)	0.782	53 (30.8)	12 (21.1)		0.470 (0.216, 1.021)	0.057
Operative method, *n* (%)										
Open surgery	58 (29.0)	7 (24.1)	0.587	1.284 (0.520, 3.169)	0.588	52 (30.2)	13 (22.8)	0.281	1.467 (0.729, 2.951)	0.283
Laparoscopic surgery	142 (71.0)	22 (75.9)				120 (69.8)	44 (77.2)			
Operative time, min	159 (120-202)	180 (135-225)	0.097	1.006 (1.000, 1.012)	0.053	157 (120, 196)	170 (131, 220)	0.157	1.004 (0.999, 1.009)	0.112
TNM stage, *n* (%)										
I-II	124 (62.0)	18 (62.1)	0.994	0.997 (0.447, 2.225)	0.994	111 (64.5)	31 (54.4)	0.171	1.526 (0.831, 2.802)	0.173
III	76 (38.0)	11 (37.9)				61 (35.5)	26 (45.6)			
Histological grade, *n* (%)										
Poorly differentiated	91 (45.5)	15 (51.7)	0.322	0.725 (0.408, 1.287)	0.272	74 (43.0)	32 (56.1)	0.073	0.674 (0.434, 1.048)	0.080
Moderately differentiated	76 (38.0)	12 (41.4)				69 (40.1)	19 (33.3)			
Highly differentiated	33 (16.5)	2 (6.9)				29 (16.9)	6 (10.5)			
Severe complications, *n* (%)	-	-	-	-	-	14 (8.1)	15 (26.3)	< 0.001	4.031 (1.804, 9.005)	0.001
Postoperative	-	-	-	-	-	14 (12, 16)	17 (14, 24)	<	1.160	<

length of stay, d	0.001	(1.094, 1.229)	0.001

[1]NA: Low number of observations.

Data are presented as means ± SD, medians (interquartile ranges) or *n* (%). CCI: Charlson Comorbidity Index; BMI: Body mass index; HB: Haemoglobin; WBC: White blood cell; ASA: American Society of Anesthesiologists; KPS: Karnofsky Performance Scale; TNM: Tumour node metastasis; OR: Odds ratio; CI: Confidence interval.

Table 3 Impact of frailty on severe complications and increased hospital costs by the multivariate logistic regression

	Frail group	Non-frail group	Univariate		Multivariate		
			Frailty: OR (95%CI)	*P* value	Frailty: OR (95%CI)	*P* value	Other significant predictors, OR (95%CI), *P* value
Severe complications							
Comprehensive geriatric assessment, *N* = 151, *n* = 78	23 (15.2)	6 (7.7)	2.156 (0.839, 5.541)	0.111	-	-	Age: 1.064 (1.010, 1.122); *P* = 0.019. Drinking history: 3.649 (1.504, 8.855); *P* = 0.004. Albumin: 0.880 (0.783, 0.989); *P* = 0.032. Operative time: 1.008 (1.001, 1.015); *P* = 0.022
Fried phenotype, *N* = 109, *n* = 120	16 (14.7)	13 (10.8)	1.416 (0.647, 3.098)	0.384	-	-	Age: 1.064 (1.010, 1.122); *P* = 0.019. Drinking history: 3.649 (1.504, 8.855); *P* = 0.004. Albumin: 0.880 (0.783, 0.989); *P* = 0.032. Operative time: 1.008 (1.001, 1.015); *P* = 0.022
FRAIL scale, *N* = 80, *n* = 149	13 (16.3)	16 (10.7)	1.112 (0.866, 1.428)	0.406	-	-	Age: 1.064 (1.010, 1.122); *P* = 0.019. Drinking history: 3.649 (1.504, 8.855); *P* = 0.004. Albumin: 0.880 (0.783, 0.989); *P* = 0.032. Operative time: 1.008 (1.001, 1.015); *P* = 0.022
Increased hospital costs							
Comprehensive geriatric assessment, *N* = 151, *n* = 78	46 (30.5)	11 (14.1)	2.668 (1.291, 5.513)	0.008	2.298 (1.044, 5.057)	0.039	Postoperative length of stay: 1.167 (1.098, 1.241); *P* < 0.001. Neoadjuvant therapy: 5.778 (1.601, 20.860); *P* = 0.007
Fried phenotype, *N* = 109, *n* = 120	33 (30.3)	24 (20.0)	1.737 (0.948, 3.183)	0.074	-	-	Postoperative length of stay: 1.168 (1.100, 1.241); *P* < 0.001. Neoadjuvant therapy: 6.348 (1.792, 22.484); *P* = 0.004
FRAIL scale, *N* = 80, *n* = 149	25 (31.3)	32 (21.5)	1.662 (0.900, 3.069)	0.105	-	-	Postoperative length of stay: 1.168 (1.100, 1.241); *P* < 0.001. Neoadjuvant therapy: 6.348 (1.792, 22.484); *P* = 0.004

N: Number in frailty group; n: Number in non-frailty group; OR: Odds ratio; CI: Confidence interval.

Our study had several limitations that need to be noted. First, this was a small, single-centre study, and the conclusions obtained need to be validated in patients from other regions and hospitals. Second, our study population included only patients with gastrointestinal cancer who underwent elective radical surgery. Patients who underwent emergency admission and palliative surgery were not included. Third, we did not analyse the different diseases in gastrointestinal cancer separately.

Finally, based on our study, more long-term outcome measures (including relapse-free survival time and overall survival) should be of interest. In addition, we hope to form a multidisciplinary team including nutritionists, psychologists, rehabilitation therapists, gastrointestinal surgeons, and nurses to help patients develop personalized pre-rehabilitation measures, which can be implemented at home, in the hospital or a combination of both. We should improve the frail state of patients before operation with as little expenditure as possible to reduce the hospitalization expenses of patients. A pre-rehabilitation program suitable for China's national conditions is urgently needed.

CONCLUSION

The prevalence of preoperative frailty was high in patients undergoing gastrointestinal cancer surgery, as assessed by different frailty scales. The CGA is an independent predictor of increased hospital costs in patients undergoing gastrointestinal cancer surgery. It is hoped that our study will arouse the attention of health care providers and the CGA should be included as part of routine preoperative risk assessment in patients undergoing surgery for gastrointestinal cancer.

ARTICLE HIGHLIGHTS

Research background

Few studies have simultaneously compared the predictive value of various frailty assessment tools for the prognosis in patients undergoing gastrointestinal cancer surgery. Therefore, it is difficult to determine which assessment tool is most relevant to the prognosis of this population.

Research motivation

We used three commonly used frailty assessment tools to investigate the status of preoperative frailty and to analyse their predictive value for prognosis in patients undergoing surgery for gastrointestinal cancer.

Research objectives

To investigate the predictive value of different frailty assessment tools for postoperative severe complications and increased hospital costs in patients undergoing surgery for gastrointestinal cancer.

Research methods

A single-centre, observational, prospective cohort study was conducted at the Affiliated Lianyungang Hospital of Xuzhou Medical University from August 2021 to July 2022. A total of 229 patients aged ≥ 18 years who underwent surgery for gastrointestinal cancer were included in this study. We collected baseline data on the participants and administered three scales to assess frailty: The comprehensive geriatric assessment (CGA), Fried phenotype and FRAIL scale. The outcome measures were postoperative severe complications and increased hospital costs.

Research results

The prevalence of frailty when assessed with the CGA was 65.9%, 47.6% when assessed with the Fried phenotype and 34.9% when assessed with the FRAIL scale. Using the CGA as a reference, kappa coefficients were 0.398 for the Fried phenotype and 0.291 for the FRAIL scale (both $P < 0.001$). Postoperative severe complications and increased hospital costs were observed in 29 (12.7%) and 57 (24.9%) patients, respectively. Multivariate logistic analysis confirmed that the CGA was independently associated with increased hospital costs (odds ratio = 2.298, 95% confidence interval: 1.044-5.057; $P = 0.039$). None of the frailty assessment tools were associated with postoperative severe complications.

Research conclusions

The CGA has a significant effect on increased hospital costs for patients undergoing gastrointestinal cancer surgery, and should be included as part of routine preoperative risk assessment in this population.

Research perspectives

More long-term outcome measures (including relapse-free survival time and overall survival) should be of interest. In addition, there is an urgent need for a pre-rehabilitation program which is suitable for China's national conditions to improve preoperative frailty in patients undergoing gastrointestinal cancer surgery.

FOOTNOTES

Author contributions: Zhang HP, Zhang HL, and Chen GJ designed the study; Zhang HP and Zhou XM collected data; Zhang HP wrote the manuscript; Zhang HL, Chen GJ, Zhou QF, and Wang W revised the manuscript; Tang J and Zhu ZY analysed the data; and all authors read and approved the final manuscript.

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ORIGINAL ARTICLE

Observational Study

Multi-national observational study to assess quality of life and treatment preferences in patients with Crohn's perianal fistulas

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Abstract

BACKGROUND

Patients with Crohn's disease (CD) are at risk of developing complications such as perianal fistulas. Patients with Crohn's perianal fistulas (CPF) are affected by fecal incontinence (FI), bleeding, pain, swelling, and purulent perianal discharge, and

generally face a higher treatment burden than patients with CD without CPF.

AIM

To gain insights into the burden of illness/quality of life in patients with CPF and their treatment preferences and satisfaction.

METHODS

This cross-sectional observational study was conducted in patients with CD aged 21-90 years *via* a web-enabled questionnaire in seven countries (April-August 2021). Patients were recruited into three cohorts: Cohort 1 included patients without perianal fistulas; cohort 2 included patients with perianal fistulas without fistula-related surgery; and cohort 3 included patients with perianal fistulas and fistula-related surgery. Validated patient-reported outcome measures were used to assess quality of life. Drivers of treatment preferences were measured using a discrete choice experiment (DCE).

RESULTS

In total, 929 patients were recruited (cohort 1, n = 620; cohort 2, n = 174; cohort 3, n = 135). Short Inflammatory Bowel Disease Questionnaire scores were worse for patients with CPF (cohorts 2 and 3) than for those with CD without CPF (cohort 1): Mean score 3.8 and 3.7 *vs* 4.1, respectively, (P < 0.001). Similarly, mean Revised FI and FI Quality of Life scores were worse for patients with CPF than for those with CD without CPF. Quality of Life with Anal Fistula scores were similar in patients with CPF with or without CPF-related surgery (cohorts 2 and 3): Mean score 41 and 42, respectively. In the DCE, postoperative discomfort and fistula healing rate were the most important treatment attributes influencing treatment choice: Mean relative importance 35.7 and 24.7, respectively.

CONCLUSION

The burden of illness in CD is significantly higher for patients with CPF and patients rate lower postoperative discomfort and higher healing rates as the most desirable treatment attributes.

Key Words: Burden of illness; Crohn's disease; Discrete choice experiment; Perianal fistulas; Patient-reported outcomes; Treatment preferences

Core Tip: This is the largest known observational study to quantify the burden of illness associated with Crohn's perianal fistulas (CPF) across multiple countries, utilizing a comprehensive set of outcomes including symptom burden and impacts, and treatment experience, satisfaction, and preferences. This study confirmed that the burden of illness for patients with Crohn's disease is significantly higher for those with CPF than those without. Patients with CPF rated lower postoperative discomfort and higher healing rates as the most desirable treatment attributes. Assessing patient treatment preferences is key to helping healthcare professionals with clinical management and treatment decisions associated with CPF.

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INTRODUCTION

Crohn's disease (CD) is a chronic progressive inflammatory disease of the gastrointestinal tract, with an annual global incidence of up to 20.2 cases per 100000 persons[1,2]. Patients with CD are at risk of developing complications such as perianal fistulas (PF), which are estimated to develop in up to 50% of patients[3,4]. It has been estimated that up to 73% of patients with Crohn's perianal fistulas (CPF) are affected by fecal incontinence (FI)[5-7]. Symptoms specifically related to fistulas often include bleeding, pain, swelling, and purulent perianal discharge, and patients with CPF generally face a higher treatment burden than patients with CD without PF[3,8-10].

There are many treatments utilized for the care of patients with CPF that are aimed at initial disease control, symptom reduction, or fistula healing, depending on the nature of the fistulas and surrounding perianal disease, overall luminal disease, and the personal treatment goals. Treatment options for the management of CPF include seton placement for drainage, pharmacological therapies (*e.g.*, antibiotics, immunomodulators, and anti-tumor necrosis factor agents), and surgical procedures (*e.g.*, ligation of the intersphincteric fistula tract, advancement flaps, and newer procedures including fistula plugs, fibrin glue, and fistula tract laser closure)[8,11]; however, with limited evidence to support the use of these treatments, there is a lack of consensus on the standard of care for patients with CPF[3,12-15]. Most treatments for CPF

are associated with low rates of remission and high rates of relapse or treatment failure, leading to patients undergoing repeated cycles of treatments and surgeries[4,16-18].

Published studies on the burden of illness and quality of life for patients with CPF are limited[4]. This cross-sectional multi-country observational study was conducted to gain a more in-depth understanding of the burden of illness of CPF through a comparison of the disease burden, treatment experiences, preferences and satisfaction, and health-related quality of life (HRQoL) for patients with CPF and patients with CD without PF. Furthermore, this study compared these outcomes for patients with and without PF-related surgery to assess the impact of PF-related surgery on the burden on CPF.

Assessing patient treatment preferences is key to helping healthcare professionals with clinical management and treatment decisions associated with CPF. Given the heterogeneous treatment options available to patients with CPF (pharmacological therapies, seton placement/palliative treatment, surgical options, and stem cell therapies), this study assessed patients' treatment preferences and satisfaction using a discrete choice experiment (DCE) methodology. DCEs are designed to elicit preferences in the healthcare setting and have been utilized increasingly over the past decade[19-23]. In a DCE, patients are asked to select their preferred choice from a set of hypothetical treatment profiles that describe attributes such as treatment efficacy, treatment side effects, or health states to identify the relative importance of these treatment attributes and an underlying utility function[24]. To our knowledge, this study includes the first DCE conducted in a population of patients with CPF.

MATERIALS AND METHODS

Study design

This cross-sectional observational study was conducted *via* a 45-min web-enabled patient questionnaire in seven countries (France, Germany, Spain, United Kingdom, Canada, Australia, and Japan) from April 2021 to August 2021. Patient recruitment was undertaken by a third-party recruitment company, Dynata LLC (New York, United States). Patients in Dynata's online panel of patients were invited to participate based on profile data including self-reported physician-diagnosed CD. The questionnaire was pre-tested by conducting patient interviews (n = 7, 60 min each) across key countries to assess whether the comprehension of the questions was as intended and to identify potential sources of response error. Patients aged 21-90 years at the time of consent were eligible if they had a self-reported physician diagnosis of CD and had either been treated for CPF in the past 12 mo (CPF cohorts) or never experienced PF (non-PF CD cohort). Patients with a diagnosis of ulcerative colitis were excluded.

Based on maximum feasibility, research questions, and the objectives of the study, the global target study size was N = 855 (n = 150 Canada, France, Germany, and United Kingdom; n = 120 Spain; n = 90 Australia; n = 45 Japan). Patients were recruited into one of three cohorts based on their responses to carefully tailored screening questions prior to entering the web-enabled questionnaire: Cohort 1 included patients with CD who had never experienced perianal fistulas (non-PF CD), cohort 2 included patients with CPF who had no PF-related surgery in the past 12 mo but may have received pharmacotherapy and/or seton placement, and cohort 3 included patients with CPF who had PF-related surgery in the past 12 mo (with or without pharmacotherapy and/or seton placement). For the purposes of this study, only reparative/interventional PF-related procedures were considered as surgery (seton placement was not included in this description because almost all patients with CPF will undergo seton placement); hence patients in cohort 2 (without PF-related surgery) as well as patients in cohort 3 may have received seton placement.

Study objectives

The co-primary objectives of the study were to compare the HRQoL and treatment experiences, preferences, and satisfaction of patients with CD with and without CPF in an international study across seven countries, using standard validated general and disease-specific patient-reported outcomes measures and a DCE.

The secondary objective of the study was to compare HRQoL and treatment experiences, preferences, and satisfaction among patients with CPF who had PF-related surgery (with or without pharmacotherapy) with those patients with CPF who had no PF-related surgery in the past 12 mo.

Study measures

Patient-reported outcome measures were used to assess the HRQoL (disease specific), FI, and its impact on HRQoL, and general health status of participating patients.

HRQoL

The HRQoL measures administered in this study included the Short Inflammatory Bowel Disease Questionnaire (SIBDQ)[25] and the Quality of Life in patients with Anal Fistula (QoLAF) questionnaire[26]. SIBDQ is a 10-item questionnaire designed to assess the impact of inflammatory bowel diseases in general on HRQoL, with each item scored on a 7-point scale (1 = poor health-related quality of life, 7 = optimum health-related quality of life). The recall period was 2 wk, and a difference of 9 points was considered a clinically significant difference based on total score (prior to dividing the total score by 10)[26]. The QoLAF questionnaire, designed to specifically assess the impact of anal fistulas on HRQoL, is composed of physical impact and biopsychosocial impact domains and summed scores range from 14 to 70 (14 points = zero impact, 15-28 points = limited impact, 29-42 points = moderate impact, 43-56 points = high impact, and 57-70 points = very high impact)[26,27].

Fecal incontinence

FI and its impact on daily life was measured using the Revised Faecal Incontinence Score (RFIS)[28] and the Fecal Incontinence Quality of Life (FIQL) questionnaire[29]. The RFIS is a questionnaire with five items related to FI and leakage altering a person's lifestyle and two additional items related to FI associated with urge and undergarment soiling. Scores range from 0 to 20 (≤ 3 = none or very mild FI, 4-6 mild FI, 7-12 moderate FI, ≥ 13 severe FI). Scores for each item were summed and the mean was taken. The recall period for the RFIS was 4 wk. The FIQL is a 29-item questionnaire composed of four domains: Lifestyle, coping/behavior, depression/self-perception, and embarrassment. Scores range from 1 to 5 for each domain (no overall score), with a lower score indicating a worse HRQoL in that domain. The minimally important difference is 1.1-1.2 points per subscale[29,30]. The recall period for the FIQL was "the last month".

Health status (EQ-5D)

The EuroQol EQ-5D-5L questionnaire was utilized to assess the overall health status of the participating patients at the time of survey completion[31]. The questionnaire measures five dimensions of health including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression and also includes a visual analog scale (VAS) to rate overall health. Each dimension has 5 levels: No problems, slight problems, moderate problems, severe problems, and extreme problems. The total score ranges from 0 to 1, with a higher score indicating a better HRQoL. In countries where descriptions for only 3 levels of each dimension were published (EQ-5D-3L), a crosswalk score that maps EQ-5D-3L to EQ-5D-5L (3 *vs* 5 response options) was utilized.

Drivers of treatment preferences: DCE

Patient preferences for CPF treatment attributes were assessed through a DCE in patients with CPF. The DCE for this study included six treatment attributes across 2-4 levels (Table 1). It was estimated that a sample size of 260 patients would be sufficient to analyze each attribute, based on guidance by Yang *et al*[32]. Levels for each treatment attribute were derived from evidence in currently available literature[33-46] and used to develop hypothetical treatment profiles. The attributes included type of treatment, treatment success rate (overall success rate, potentially including radiologic healing rate), postoperative pain (pain following the treatment), rehabilitation time (time to resuming normal daily activities), recurrence rate (proportion of patients with a recurrence of CPF following treatment), and FI rate (proportion of patients with FI following treatment). In total, 10 choice sets were presented to each patient with two hypothetical treatments available for each choice. Patients had the option of selecting one hypothetical treatment profile as their most preferred treatment in each choice set, or to select neither.

Table 1 Discrete choice experiment attributes and levels

Attribute	Level			
	1	2	3	4
Postoperative discomfort	Low	Medium	High	-
Fistula healing: Proportion of patients who have fistula closure/fistula healing and minimal fluid collection in the fistula after treatment	48%	55%	60%	95%
Fecal incontinence: Proportion of patients who experienced fecal incontinence after treatment	0%	16%	20%	34%
Recurrence: Proportion of patients with a return of symptoms related to anal fistula (discharge, pain, odor) after treatment	15%	25%	35%	60%
Rehabilitation time: Time taken to resume normal daily activities	Up to 1 wk	More than 1 wk, up to 4 wk	-	-
Invasiveness: Does the treatment involve cutting or puncturing of the skin?	Yes, involves cutting or puncturing and insertion of surgical instruments into the anal area	Yes, involves minimal cutting or puncturing and an injection of the treatment into the anal area	-	-

Disease insights and experience

Patients were asked to complete a list of questions to assess their treatment experience and CD experience. Questions included a wide range of demographic and clinical characteristics including diagnosis, treatment, and disease severity and complications, with medication and surgical experience being of particular interest. Interference with patients' lives due to CD/CPF and specific disease attributes was assessed over the past 12 mo using a score ranging from 1 to 9 (a higher number indicating more significant interference with life). The impact of CPF on activities of daily living (ADL) over the past 12 mo was assessed using a score ranging from 1 to 7 (a higher number indicating more significant interference with ADL).

Patient satisfaction with currently available treatments for CPF was measured by assessing patient satisfaction with current PF treatments and PF treatment attributes, both scored 1-9 (low score indicating low satisfaction).

Patients were asked to rate their level of involvement in CD/PF treatment decision making as "not at all", "slightly", "moderately", "very much", or "I don't feel the need to be involved".

Statistical analysis

For all endpoints, data were analyzed using descriptive statistics, *P* values were calculated using *t*-tests and statistical significance was assessed at the 5% level. Bivariate comparisons were made between CPF cohorts (cohorts 2 and 3) and the non-PF cohort (cohort 1). Generalized linear models were used to statistically control for the effects of potential confounders in the data between patients with and without CPF.

The DCE data were analyzed using a hierarchical Bayesian model using the attribute levels as predictor variables and choice as the outcome variable. This model generated a mean relative attribute importance score for each attribute and a mean relative preference weight (RPW) for each level within the attributes tested.

Ethics

This study was conducted in accordance with the World Medical Association Declaration of Helsinki and Guidelines for Good Pharmacoepidemiology Practices and submitted to all applicable local Institutional Review Boards and Ethics Committees to ensure compliance with all ethical standards in each country.

RESULTS

Study population

In total, 929 patients were recruited; 620 patients had CD without PF (non-PF CD, cohort 1) and 309 patients had CPF (cohorts 2 and 3 combined; Figure 1). From each country, except Australia and Japan, 100 and 50 patients were recruited to cohort 1 and cohorts 2 and 3 combined, respectively. Australia and Japan both recruited 60 patients to cohort 1, and 29 and 30 patients to cohorts 2 and 3 combined, respectively.

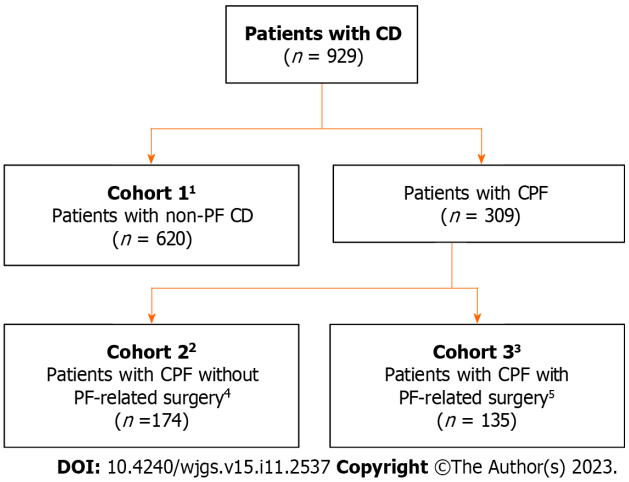

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Figure 1 Patient disposition. [1]Cohort 1: France, Germany, Spain, United Kingdom, and Canada: n = 100; Australia and Japan: n = 60; [2]Cohort 2: France, n = 32; Germany, n = 17; Spain, n = 36; United Kingdom, n = 33; Canada, n = 24; Australia, n = 12; Japan, n = 20; [3]Cohort 3: France, n = 18; Germany, n = 33; Spain, n = 14; United Kingdom, n = 17; Canada, n = 26; Australia, n = 17; Japan, n = 10; [4]Patients received pharmacotherapy and/or seton placement but no PF-related surgery in the past 12 mo; [5]With or without pharmacotherapy. CD: Crohn's disease; CPF: Crohn's perianal fistulas; PF: Perianal fistulas.

The age distribution of patients was similar across the cohorts, with the exception that the non-PF CD cohort (cohort 1) had a greater proportion of patients aged 61-80 years than cohorts 2 and 3 (Table 2). A greater proportion of patients in the CPF cohorts were male compared with the non-PF CD cohort. Further patient demographics and characteristics used in the multivariable analyses to control for potential confounders in the patient-reported outcomes (comorbidities, CD flare-up status, employment status, and marital status) are provided in Table 2 and Supplementary Table 1.

The questionnaire was generally well understood by respondents in the pre-test cognitive interviews and no major changes were required; however, in response to respondent feedback, minor modifications were made to the sentence structure and wording for further clarification.

Disease-specific patient-reported outcome measures

HRQoL: Overall SIBDQ scores were lower (worse) for patients with CPF (cohorts 2 and 3) than those with non-PF CD (cohort 1) with significantly lower scores across all four domains of the SIBDQ (Figure 2A). Multivariable analyses to control for potential confounders (patient demographics and characteristics, identified *via* a model building approach) showed that SIBDQ scores after adjustment were still significantly lower for patients with CPF compared with those

Table 2 Baseline demographics and patient characteristics

	Cohort 1	Cohort 2	Cohort 3	Cohorts 2 + 3
	All non-PF CD (*n* = 620)	CPF no surgery (*n* = 174)	CPF with surgery (*n* = 135)	All CPF (*n* = 309)
Sex, *n* (%)				
Male	360 (58)[a]	116 (67)[b]	93 (69)[b]	209 (68)[c]
Age, yr, *n* (%)[1]				
21-40	340 (55)[a,d,e]	112 (64)[c]	90 (67)[c]	202 (65)[c]
41-60	208 (34)[b]	59 (34)[b]	44 (33)[b]	103 (33)[b]
61-80	72 (12)[a,d,e]	3 (2)[c]	1 (1)[c]	4 (1)[c]
CD flare-up status, *n* (%)				
Recent flare-up	270 (44)[a,e]	85 (49)[e]	87 (64)[c,d]	172 (56)[c]
Comorbidities, *n* (%)				
Asthma	88 (14)[b]	27 (16)[b]	30 (22)[b]	57 (18)[b]
Obesity	87 (14)[b]	31 (18)[b]	22 (16)[b]	53 (17)[b]
Cardiovascular disease	33 (5)[a,e]	13 (7)[b]	17 (13)[c]	30 (10)[c]
COPD	17 (3)[e]	4 (2)[d]	11 (8)[c,d]	15 (5)[b]
Cancer	22 (4)[b]	7 (4)[b]	7 (5)[b]	14 (5)[b]
Renal disease	14 (2)[b]	6 (3)[b]	6 (4)[b]	12 (4)[b]

[a]$P < 0.05$ *vs* cohort 2 and 3 combined.
[b]No statistically significant difference versus any other cohort.
[c]$P < 0.05$ *vs* cohort 1.
[d]$P < 0.05$ *vs* cohort 2.
[e]$P < 0.05$ *vs* cohort 3.
[1]None of the patients were aged < 21 or > 80 yr.
P values are shown where there is a statistically significant difference between specified cohorts. Bonferroni adjustment was applied when comparing more than 2 groups at $P < 0.05$. CD: Crohn's disease; COPD: Chronic obstructive pulmonary disease; CPF: Crohn's perianal fistulas; PF: Perianal fistulas.

without CPF (other variables that were statistically significant are shown in Supplementary Table 2).

In patients with CPF, total (overall) QoLAF scores were comparable between cohorts 2 and 3. Biopsychosocial impact scores were similar, but for the physical impact domain, patients in cohort 3 (who had PF-related surgery) had a significantly higher (worse) score than those in cohort 2 (patients with no surgery, Figure 2B).

Fecal incontinence

Overall, 47% of patients reported FI and completed the RFIS and FIQL questionnaires. A significantly lower proportion of patients with non-PF CD reported FI than those with CPF (40% in cohort 1 *vs* 59% and 59% in cohorts 2 and 3, respectively). Furthermore, mean RFIS scores were significantly higher (worse) in patients with CPF than in those without (Figure 3A). After using multivariable analyses to control for patient demographics (identified *via* a model building approach), RFIS scores were still significantly higher for patients with CPF compared with those without CPF (other variables that were statistically significant are shown in Supplementary Table 3).

Significantly lower (worse) FIQL scores were noted for patients with CPF and no PF-related surgery experience than for those with non-PF CD (cohort 2 *vs* cohort 1) across all domains except coping/behavior, whereas patients with PF-related surgery experience (cohort 3) reported significantly lower RFIS scores than cohort 1 only for the embarrassment domain (Figure 3B).

Health status (EQ-5D)

EQ-5D scores were not significantly different between cohorts, except in France where scores were significantly higher (better) for patients with non-PF CD (cohort 1) than those with CPF without PF-related surgery (cohort 2), and in Japan where scores were significantly higher for patients with non-PF CD than those with CPF, irrespective of PF-related surgery experience (Figure 4). After adjusting for confounding variables (identified *via* a model building approach), CPF was found to have a significantly negative impact on EQ-5D-5L scores in France, Germany, and Japan, but not in the other countries. EQ-5D VAS scores for overall health were not significantly different between cohorts across all countries (Supplementary Figure 1).

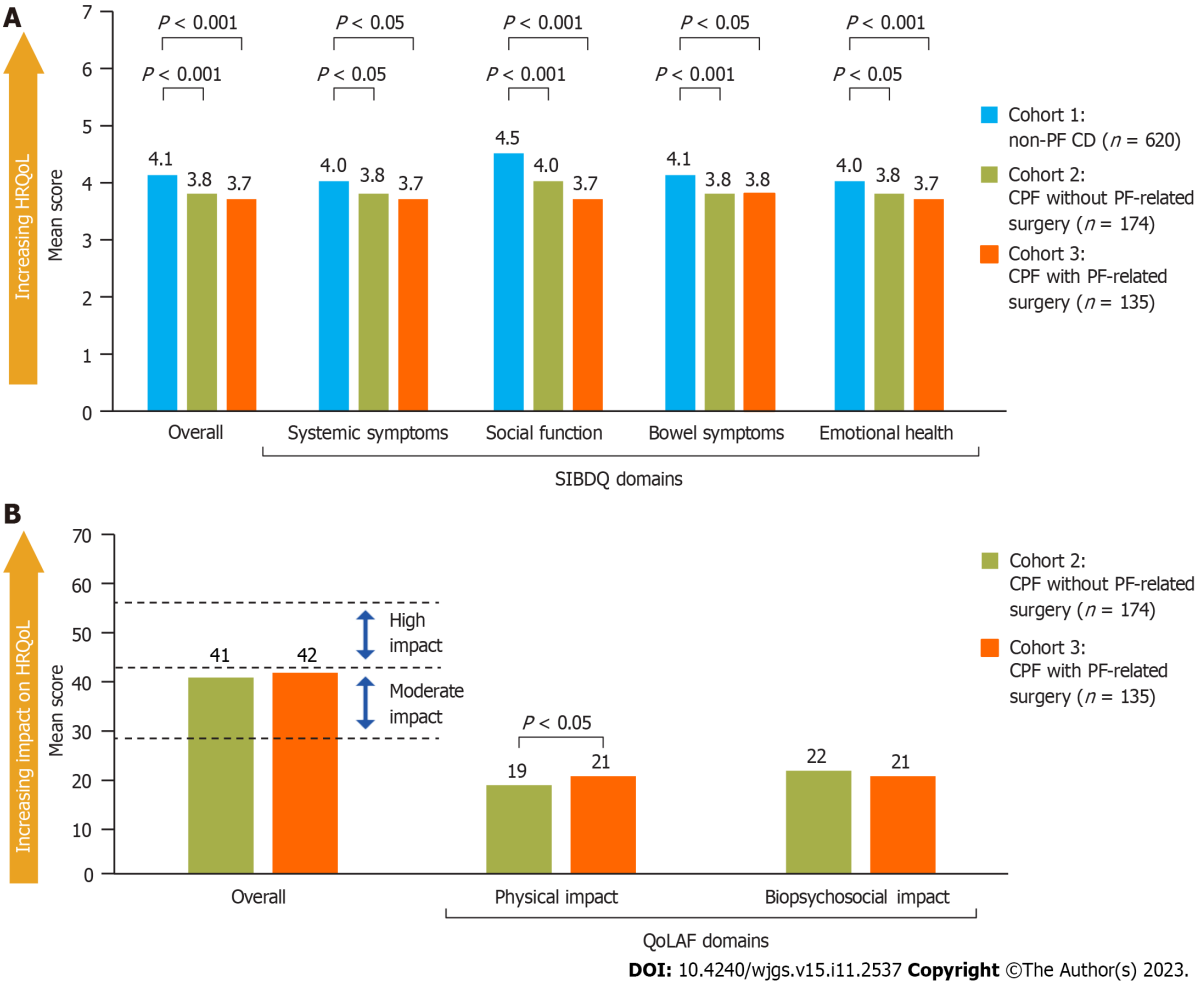

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Figure 2 Comparison of Short Inflammatory Bowel Disease Questionnaire scores and Quality of Life in patients with Anal Fistula scores in patients with Crohn's disease, with and without perianal fistula. A: Short Inflammatory Bowel Disease Questionnaire (SIBDQ) scores; B: Quality of Life in patients with Anal Fistula scores. Scoring key for SIBDQ (range 1-7): Poor health-related quality of life (HRQoL) = 1 point and optimum HRQoL = 7 points. Scoring key for QoLAF (range 14-70): Zero impact = 14 points, limited impact = 15-28 points, moderate impact = 29-42 points, high impact = 43-56 points, very high impact = 57-70 points. CD: Crohn's disease; CPF: Crohn's perianal fistulas; HRQoL: Health-related quality of life; PF: Perianal fistulas; QoLAF: Quality of Life in patients with Anal Fistula; SE: Standard error; SIBDQ: Short Inflammatory Bowel Disease Questionnaire.

Treatment experience

A higher proportion of patients with CPF had moderate or severe disease, CD-related complications, and had experienced reported FI, compared with patients with non-PF CD (Table 3). CD-related complications included fatigue, abdominal pain/cramping, gastrointestinal pain, pain/difficulty with bowel movements, and pain when sitting (Supplementary Table 4). At the time of enrollment, a higher proportion of patients with CPF were currently taking or had previously taken CD-related medication than those with non-PF CD (98% *vs* 94%, respectively, $P < 0.05$; Table 4). Also, a higher proportion of patients with CPF had CD-related surgeries than those without CPF (cohort 1) and the proportion was greatest in those who had PF-related surgery (cohort 3). This likely accounts for the higher proportion of patients in cohort 3 with surgical failures compared with cohorts 1 and 2.

In patients with CPF and PF-related surgery experience (cohort 3), 78% had three or more such procedures or surgeries related to their PF and 87% of patients experienced ≥ 1 complication after surgery or seton placement. The most frequent complications after PF-related surgery or seton placement included fever/infection, worsening of pain/swelling around the anus, and worsening of bloody or foul-smelling discharge from an opening around the anus (Supplementary Table 5).

Drivers of treatment preferences: DCE

The mean RPW provided an estimation of the strength of preference for each level within the attributes tested (higher RPWs indicated a higher preference and lower RPWs indicated a lower preference). Patient preferences were driven by levels of postoperative discomfort [mean RPW (standard error, SE) of 0.20 (0.03) for low levels of discomfort *vs* -0.28 (0.03) for high levels of discomfort]. Patients also preferred treatments that result in high rates of fistula healing with minimal fluid collection [mean RPW (SE) of 0.24 (0.04) for treatments with approximately 95% fistula healing rate *vs* -0.09 (0.04) for treatments with approximately 48% or approximately 55% fistula healing rate]. Levels of FI after treatment were also a driving factor in patient treatment preferences [mean RPW (SE) of 0.13 (0.04) for no FI *vs* -0.10 (0.04) for approximately 34% rate of FI after treatment]. Overall, of the tested attributes, postoperative discomfort and fistula healing rate were the

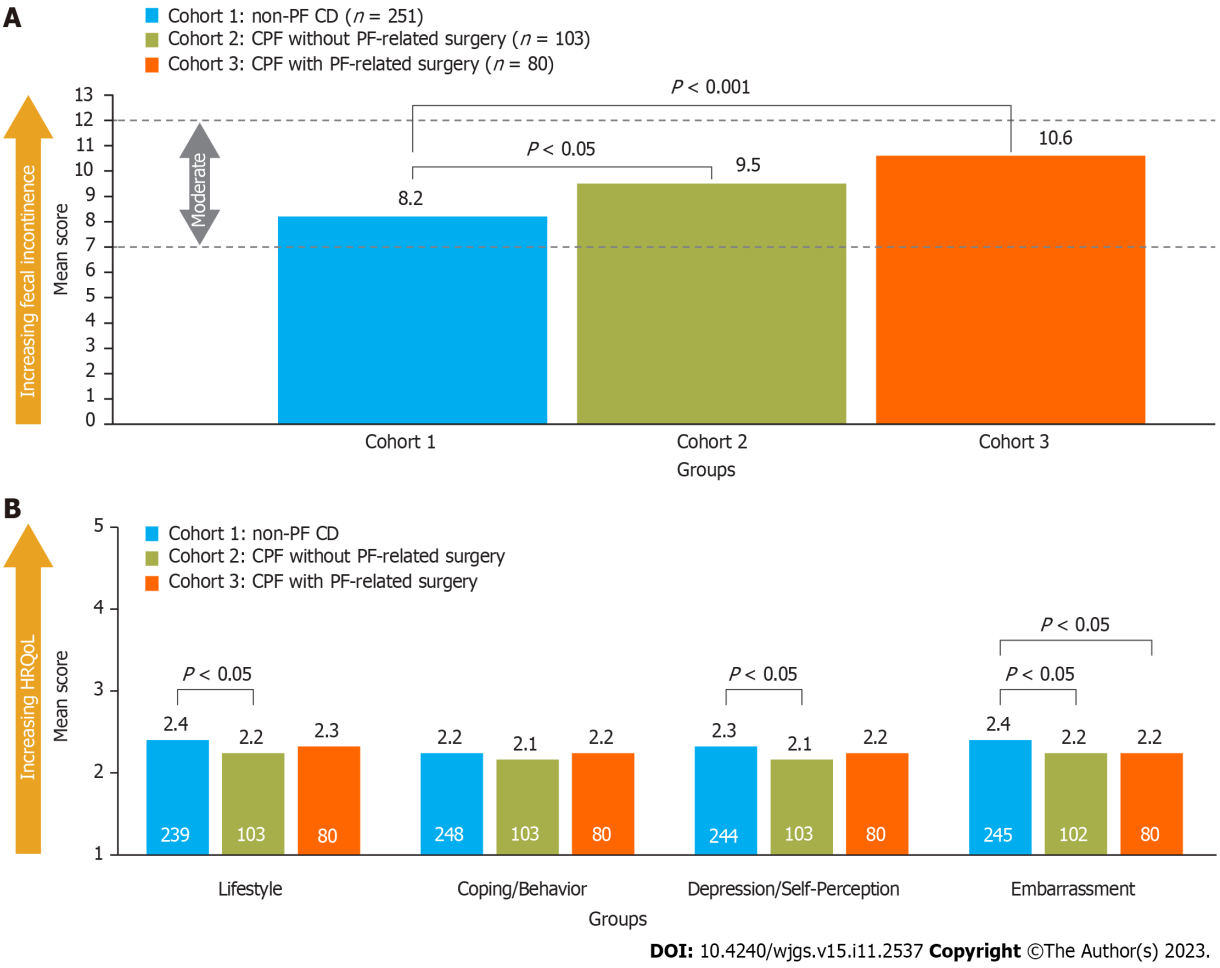

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Figure 3 Comparison of Revised Faecal Incontinence Scale and Fecal Incontinence Quality of Life scores in patients with Crohn's disease, with and without perianal fistula. A: Revised Faecal Incontinence Scale scores; B: Fecal Incontinence Quality of Life scores. Scoring key for RFIS (range 0-20): No fecal incontinence = 0 points, very mild ≤ 3 points, mild = 4-6 points, moderate = 7-12 points, severe ≥ 13 points; scores for each item were summed and the mean taken, with lower scores indicating less fecal incontinence. Scoring key for FIQL (range 1-5): Lower scores indicating lower health-related quality of life; the minimally important difference is 1.1-1.2 points per subscale. Numbers inside the bars present the number of patients. CD: Crohn's disease; CPF: Crohn's perianal fistulas; FIQL: Fecal Incontinence Quality of life; HRQoL: Health-related quality of life; PF: Perianal fistulas; RFIS: Revised Faecal Incontinence Scale.

most important attributes influencing patient choice in the treatment of CPF (Figure 5).

Disease insights and experiences

Overall impact of CD/CPF on life: Disease impact (in terms of interference with a patient's life) was significantly greater in patients with CPF than those without, with worse impact scores for all cohorts during flare-up (Supplementary Table 6).

Impact of CD/CPF disease attributes on HRQoL: Patients with CPF experienced a significantly higher impact of disease attributes on their HRQoL than patients with non-PF CD (Supplementary Table 7). The most impactful disease attributes were diarrhea (cohorts 1 and 2) and anorectal stricture (patients with PF-related surgery, cohort 3).

Impact of CD/CPF disease attributes on activities of daily living: Overall, significantly higher scores (higher impact) across all activities were recorded for patients with CPF *vs* those without. For patients without CPF, the most affected activities were exercising [mean ± SD 4.0 (1.6)], being satisfied with life [4.0 (1.7)], and ability to go to school [including any level of education; 4.0 (1.6)]. For patients with CPF, the most affected activities were exercising [4.6 (1.5)], being satisfied with life [4.6 (1.5)], and ability to work outside home [4.6 (1.5)].

Treatment satisfaction: Mean satisfaction scores were moderate (6.2-6.9) for all PF treatment options and similar in both cohorts of patients with CPF; however, patients with PF-related surgery (cohort 3) had significantly less satisfaction with long-term seton placement than those without PF-related surgery (cohort 2): 6.2 *vs* 6.7, respectively; $P < 0.05$ (Table 5).

Involvement in CD/PF treatment decision making: The majority of patients across all cohorts in all countries were either moderately or very much involved in their CD/CPF treatment decision making (78%-81%); 1%-3% indicated no involvement and 1%-2% indicated they did not feel the need to be involved.

Table 3 Disease presentation and symptom severity

	Cohort 1	Cohort 2	Cohort 3	Cohorts 2 + 3
	All non-PF CD (*n* = 620)	CPF no surgery (*n* = 174)	CPF with surgery (*n* = 135)	All CPF (*n* = 309)
Ever experienced fecal incontinence, *n* (%)	251 (40)[a,b,c]	103 (59)[d]	80 (59)[d]	183 (59)[d]
More than 5 CD complications, *n* (%)	266 (43)[a,b,c]	135 (78)[d]	111 (82)[d]	246 (80)[d]
PF experience				
Number of unique PFs (mean ± SD)	NA	2.3 (1.4)[b]	3.0 (3.0)[a]	NA
Experience with PF recurrence/persistence, *n* (%)	NA	84 (48)[e]	80 (59)[e]	NA
CD severity (physician classified) at diagnosis, *n* (%)				
Mild	187 (30)[a,b,c]	24 (14)[d]	23 (17)[d]	47 (15)[d]
Moderate	298 (48)[a,b,c]	123 (71)[b,d]	78 (58)[a,d]	201 (65)[d]
Severe	86 (14)[b]	22 (13)[b]	31 (23)[a,d]	53 (17)[e]
Not sure	49 (8)[a,b,c]	5 (3)[d]	3 (2)[d]	8 (3)[d]

[a]$P < 0.05$ *vs* cohort 2.
[b]$P < 0.05$ *vs* cohort 3.
[c]$P < 0.05$ *vs* cohort 2 and 3 combined.
[d]$P < 0.05$ *vs* cohort 1.
[e]No statistically significant difference versus any other cohort.
P values are shown where there is a statistically significant difference between specified cohorts. Bonferroni adjustment was applied when comparing more than 2 groups at $P < 0.05$. CD complications include reported frequency of intestinal obstructions, perianal abscesses, fissures, malabsorption and malnutrition, diarrhea, small intestinal bacterial overgrowth, megacolon, perforation of the intestine, colovesical fistulas, coloenteric fistulas, rectovaginal fistulas, multiple fistulas, anorectal strictures, fistulas in the upper part of the sphincter complex, enterocutaneous fistulas, ulcer, severe bleeding, intestinal strictures neoplasm, and "other". CD: Crohn's disease; CPF: Crohn's perianal fistulas; NA: Not applicable; PF: Perianal fistulas.

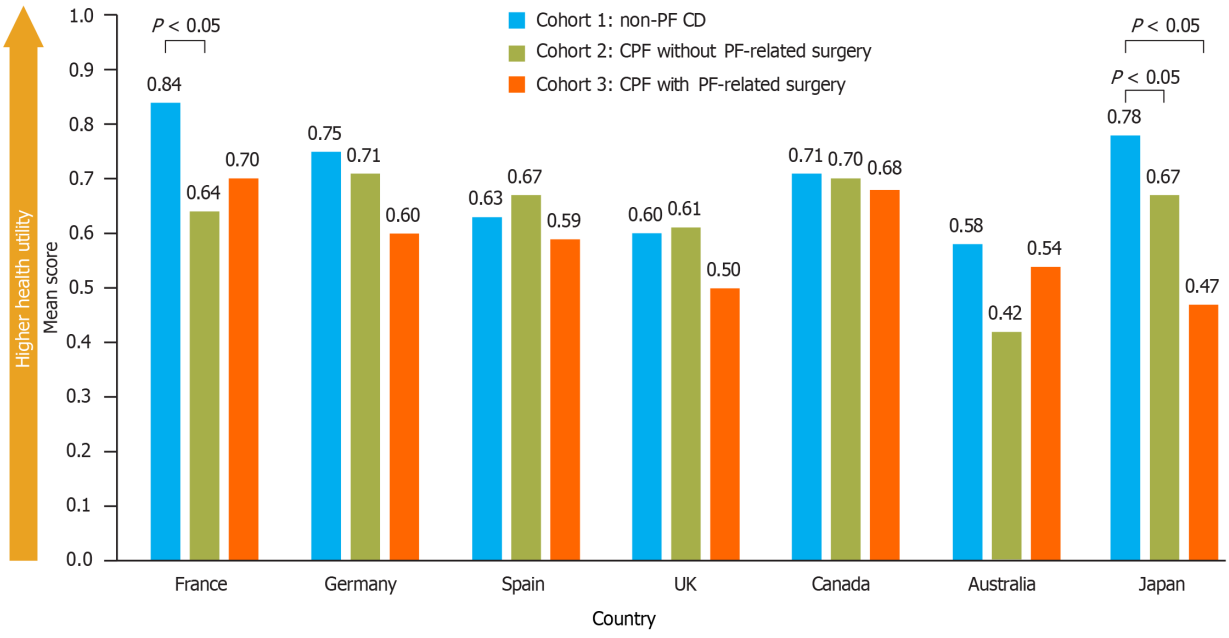

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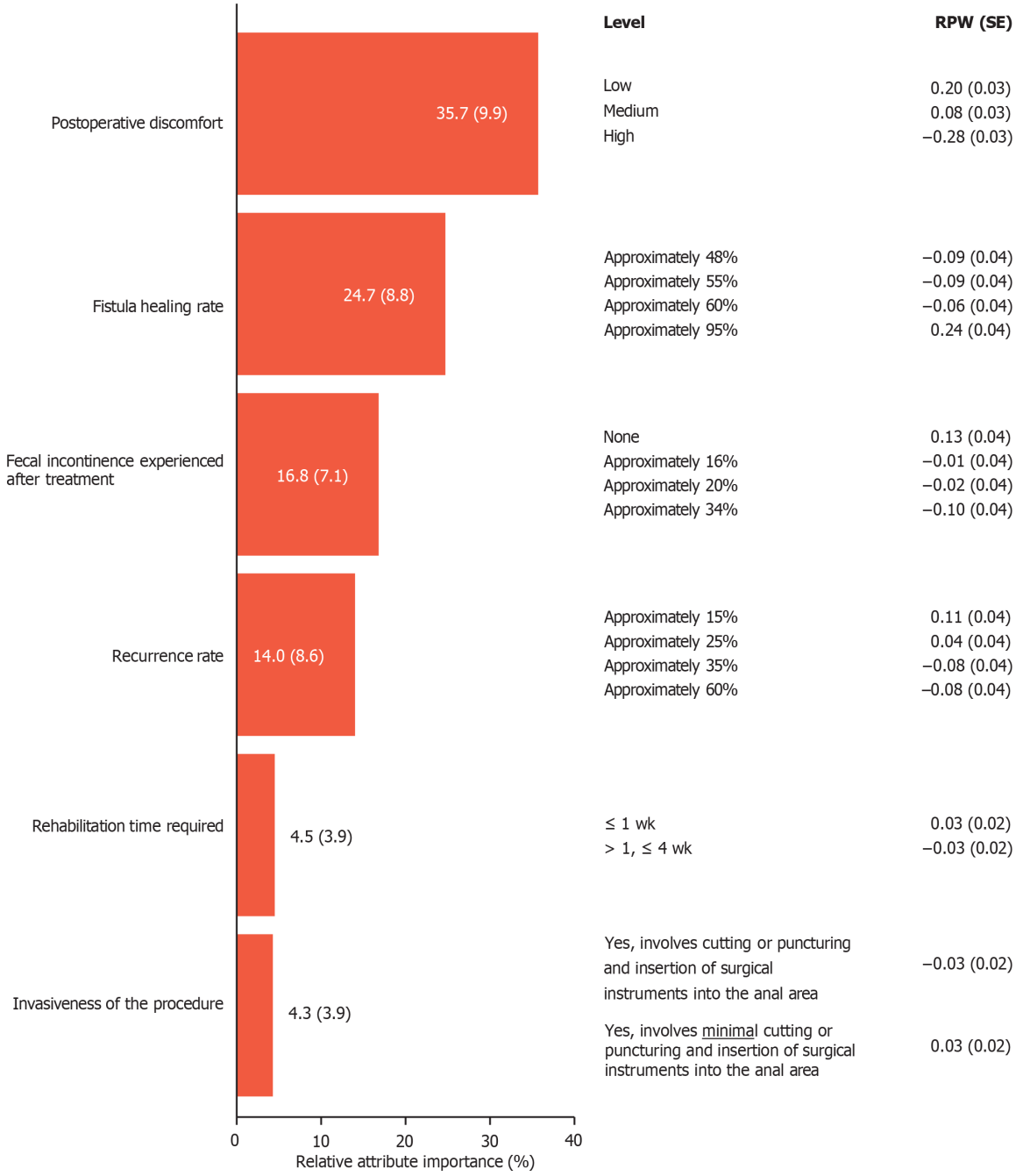
Figure 4 Comparison of EQ-5D health status scores in patients with Crohn's disease, with and without perianal fistula. Scoring key for EQ-5D (range 0-1): Higher scores indicate better health-related quality of life. United Kingdom, Spain, and Australia used a shortened form of the EQ-5D-5L (i.e., the EQ-5D-3L). Populations for each country for cohorts 1, 2, and 3, respectively: France, n = 100, n = 32, and n = 18; Germany, n = 100, n = 17, and n = 33; Spain, n = 100, n = 36, and n = 14; United Kingdom, n = 100, n = 33, and n = 17; Canada, n = 100, n = 24, and n = 26; Australia, n = 60, n = 13, and n = 17; Japan, n = 60, n = 20, and n = 10. CD: Crohn's disease; CPF: Crohn's perianal fistulas; PF: Perianal fistulas.



DOI: 10.4240/wjgs.v15.i11.2537

Figure 5 Patient-rated importance of Crohn's perianal fistula treatment attribute options in a discrete choice experiment. Data inside/beside bars represent relative attribute importance ± SD. Cohorts 2 + 3: n = 309. RPW: Relative preference weight; SE: Standard error.

DISCUSSION

Patients with CPF are a subset of patients with CD that experience a more complex clinical disease course and may require unique treatment considerations. This large multi-country study used validated patient-reported outcome measures and general questionnaires to assess the burden of illness for patients with CPF compared with patients with non-PF CD. For patients with CPF, these outcomes were also compared between those who had PF-related surgery and those who did not. A DCE was also conducted to assess the treatment preferences of patients with CPF.

As shown in this study, patients with CPF have an incrementally higher symptom burden due to both CD and PF than patients with non-PF CD. Severity of CD is higher in patients with CPF than in those with non-PF CD, with the greatest severity observed in those with PF-related surgery: A higher proportion of patients with CPF experience FI and CD-related complications such as fatigue, abdominal and gastrointestinal pain, and difficulty with bowel movements. In addition, patients with CPF can experience symptoms directly related to their fistulas such as purulent discharge, perianal pain, and FI. The greater CD severity in patients with CPF is reflected in the higher proportion of patients with CPF who received CD-related medications and surgery than in patients with non-PF CD. Furthermore, patients with CPF

Table 4 Medication and surgical experience

	Cohort 1	Cohort 2	Cohort 3	Cohorts 2 + 3
	All non-PF CD (*n* = 620)	CPF no surgery (*n* = 174)	CPF with surgery (*n* = 135)	All CPF (*n* = 309)
CD-related medication experience, *n* (%)				
Currently taking	429 (69)[a,b,c]	147 (84)[d]	108 (80)[d]	255 (83)[d]
Previously taken	155 (25)[a,b,c]	27 (16)[d]	22 (16)[d]	49 (16)[d]
Never taken	36 (6)[a,c]	0[b,d]	5 (4)[a]	5 (2)[d]
CD-related surgical experience				
Frequency of surgical experience ever, *n* (%)	190 (31)[a,b,c]	78 (45)[b,d]	119 (88)[a,d]	197 (64)[d]
Number of surgeries in the past 12 mo (mean ± SD)	1.5 (0.9)[b,c]	1.8 (1.1)[b]	2.2 (1.3)[a,d]	2.0 (1.3)[d]
Number of surgeries in the past 12 mo (median)	1[e]	1[e]	2[e]	2[e]
Frequency of surgical failure ever, *n* (%)	52 (27)[b,c]	22 (28)[b]	55 (46)[a,d]	77 (39)[d]
Number of failed surgeries ever (mean ± SD)	1.7 (2.1)[e]	2.2 (1.6)[e]	1.9 (1.8)[e]	2.0 (1.7)[e]
Number of failed surgeries ever (median)	1[e]	2[e]	1[e]	1[e]
PF-related surgical care				
PF-related procedure or surgery frequency (mean ± SD)	NA	NA	5.6 (3.5)[e]	NA
One PF-related procedure or surgery	NA	NA	9 (7)[e]	NA
Two PF-related procedures or surgeries	NA	NA	21 (16)[e]	NA
Three or more PF-related procedures or surgeries	NA	NA	105 (78)[e]	NA
Failure of PF-related procedure or surgical care (at any time) ever, *n* (%)				
One failed PF-related procedure or surgery	NA	NA	35 (26)[e]	NA
Two or more failed PF-related procedure or surgery	NA	NA	19 (14)[e]	NA

[a]$P < 0.05$ *vs* cohort 2.
[b]$P < 0.05$ *vs* cohort 3.
[c]$P < 0.05$ *vs* cohort 2 + 3 combined.
[d]$P < 0.05$ *vs* cohort 1.
[e]No statistically significant difference versus any other cohort.
P values are shown where there is a statistically significant difference between specified cohorts. Bonferroni adjustment was applied when comparing more than 2 groups at $P < 0.05$. CD: Crohn's disease; CPF: Crohn's perianal fistulas; NA: Not applicable; PF: Perianal fistulas.

were shown to have a significant impact on their overall HRQoL. This finding is in line with a 2023 study by Spinelli *et al* [47], where patients with CPF reported a greater impact on overall quality of life, well-being, relationships, social life, and work life than those with CD without CPF[47]. In the current study, there was no significant difference in reported HRQoL between patients who had PF-related surgery and those who had not. Patients with CPF reported a greater impact of CD/CPF disease attributes on HRQoL, irrespective of PF-related surgery, than patients with non-PF CD.

A high proportion of patients in this study reported being actively involved in their treatment decision making, and for patients with CPF, satisfaction with PF treatment options was only moderate, regardless of whether they had experienced surgical intervention or not. The DCE performed in this study showed that patients with CPF prioritize postoperative discomfort and healing rate as the primary attributes when selecting a hypothetical treatment choice. To the best of the authors' knowledge, this is the first time a DCE has been performed in this patient population, offering a unique perspective on patient preferences for CPF treatments.

The key findings from this study are in keeping with the core outcomes identified by Sahnan *et al*[48] and are comparable with the findings of a recent study in a similar patient population conducted in the United States[48,49]. Further research on the potential impact of age, sex, and disease severity on patients' treatment preferences could support healthcare professionals in the clinical management and treatment decisions for CPF.

There are some limitations that should be acknowledged with studies of this type. Patient responses to questionnaires can be subject to recall, selection, and/or social desirability bias, and inaccuracies owing to self-reported diagnosis and the use of complex medical terminology. The risks of such effects were partly mitigated by limiting the recall period to 12 mo or less and using pre-test telephone interviews and a web-enabled questionnaire. There was no validation sample of patients in relation to self-reported diagnosis (for cohort categorization) because it was assumed that patients would know whether or not they have CPF. Finally, the sample population may not have been representative of the wider

Table 5 Satisfaction with perianal fistula treatments

	Cohort 2	Cohort 3
	CPF no surgery (*n* = 174)	CPF with surgery (*n* = 135)
Satisfaction with PF treatments (on a scale of 1-9), mean ± SD, % rated ≥ 7		
Medication	6.5 (1.4), 57[a]	6.4 (1.5), 50[a]
Long-term seton placement	6.7 (1.5), 57[b]	6.2 (1.7), 47[c]
Endorectal/anal advancement flap	6.2 (1.7), 52[a]	6.3 (1.7), 52[a]
Fibrin glue	6.4 (1.9), 61[a]	6.2 (1.6), 45[a]
Anal fistula plug	6.6 (1.8), 66[a]	6.5 (1.6), 56[a]
Fistulectomy/fistulotomy	6.9 (1.6), 68[a]	6.3 (1.9), 50[a]
LIFT (ligation of intersphincteric fistula tract)	6.7 (1.5), 65[a]	6.2 (1.7), 46[a]
Satisfaction with PF treatment attributes (on a scale of 1-9), mean ± SD, % rated ≥ 7		
Aids in closure of external opening of the fistulas	6.4 (1.5), 48[a]	6.5 (1.6), 55[a]
Reduction or no drainage	6.4 (1.6), 54[a]	6.4 (1.6), 51[a]
Time required for symptom improvement	6.3 (1.6), 54[a]	6.3 (1.7), 50[a]
Time required for rehabilitation	6.2 (1.7), 51[a]	6.2 (1.8), 52[a]
Length of duration before symptom(s) recur	6.3 (1.7), 52[a]	6.3 (1.8), 52[a]
Has minimal side effects (local pain, redness, itchiness)	6.2 (1.9), 54[a]	6.3 (1.8), 53[a]
Minimal risk of fecal incontinence	6.3 (1.7), 51[a]	6.4 (1.7), 53[a]
Not requiring a long-term seton placement	6.4 (1.7), 52[a]	6.6 (1.7), 59[a]
Less invasive nature of treatment (not requiring incision)	6.4 (1.7), 56[a]	6.3 (1.8), 48[a]

[a]No statistically significant difference versus the other cohort.
[b]$P < 0.05$ *vs* cohort 3.
[c]$P < 0.05$ *vs* cohort 2.
On a scale of 1-9, a higher number indicates a greater satisfaction. *P* values are shown where there is a statistically significant difference between specified cohorts. Bonferroni adjustment was applied when comparing more than 2 groups at $P < 0.05$. CPF: Crohn's perianal fistulas; PF: Perianal fistulas.

population of patients with CD, and any country/regional differences need to be further evaluated.

CONCLUSION

This is the largest known observational study to quantify the burden of illness associated with CPF across multiple countries utilizing a comprehensive set of outcomes including symptom burden and impacts, and treatment experience, satisfaction, and preferences. This study confirmed that the burden of illness for patients with CD is significantly higher for those with CPF than those without. CPF management should aim to reduce the overall disease burden, including treatment-related burden or complications, such as FI, to improve HRQoL for these patients.

ARTICLE HIGHLIGHTS

Research background

The burden of illness in patients with Crohn's disease (CD) is perceived to be greater in those with perianal fistulas *vs* those without. However, there is limited literature directly comparing the symptom burden, impact on quality of life and the treatment experiences, and preferences in patients with CD with and without perianal fistula.

Research motivation

A more in-depth understanding of disease burden and treatment preferences of patients with Crohn's perianal fistula will be key in raising disease awareness and helping healthcare professionals with the clinical management of these patients.

Research objectives

To examine the symptom burden, health-related quality of life, and treatment experiences, satisfaction, and preferences for patients with CD with and without perianal fistula, and to further assess the incremental burden of these measures for patients who have and have not received perianal fistula-related surgery.

Research methods

A large cross-sectional, multi-country observational study was conducted *via* a pre-tested web-enabled questionnaire in seven countries. Data on disease insights and experiences were collected, and validated patient-reported outcome measures were used to assess the disease-specific health-related quality of life, fecal incontinence, and general health status of participating patients. All participating patients had CD and comparisons were made between patients without perianal fistula and those with perianal fistula (with further comparisons between those with and without perianal fistula-related surgery). Patient preferences for perianal fistula treatments were also assessed using a discrete choice experiment.

Research results

This study demonstrated that symptom burden, severity of disease, CD-related medication/surgical interventions, and impact on health-related quality of life in patients with CD are significantly higher for those with perianal fistula than those without. Patients with Crohn's perianal fistula were found to prioritize postoperative discomfort and healing rate as the primary attributes when selecting a hypothetical surgical treatment choice.

Research conclusions

For patients with CD, the symptom and treatment burden and impact on health-related quality of life are significantly higher for those with perianal fistula than those without. Future Crohn's perianal fistula management should aim to reduce the treatment-related burden or complications, in order to improve health-related quality of life for these patients.

Research perspectives

The patient satisfaction rates and surgical treatment preferences highlighted in this study should be considered by healthcare professionals when making decisions regarding the clinical management of patients with Crohn's perianal fistula.

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FOOTNOTES

Author contributions: Karki C, Athavale A, Abilash V, Hantsbarger G, Geransar P, Lee K, Milicevic S, Perovic M, Raven L, Sajak-Szczerba M, Silber A, Yoon A, and Tozer P contributed to the conceptualization of the study; Athavale A, Abilash V, and Silber A contributed to the data curation; Athavale A, Abilash V, and Silber A contributed to the formal analysis; Karki C contributed to the funding acquisition; Karki C, Athavale A, Abilash V, and Silber A contributed to the investigation; Karki C, Athavale A, Abilash V, Hantsbarger G, and Tozer P performed the methodology; Athavale A, Abilash V, and Silber A contributed to the project administration; Karki C and Athavale A contributed to the resourcing; Athavale A provided software expertise; Karki C and Athavale A contributed to the supervision of the study; Athavale A, Abilash V, Hantsbarger G, Geransar P, Lee K, Milicevic S, Perovic M, Raven L, Sajak-Szczerba M, Silber A, Yoon A, and Tozer P contributed to the validation; Athavale A, Abilash V, and Silber A contributed to the visualization; Karki C, Athavale A, Abilash V, Hantsbarger G, Geransar P, Lee K, Milicevic S, Perovic M, Raven L, Sajak-Szczerba M, Silber A, Yoon A, and Tozer P contributed to the writing, review, and editing of the manuscript.

Institutional review board statement: This study was conducted in accordance with the World Medical Association Declaration of Helsinki and Guidelines for Good Pharmacoepidemiology Practices (GPP) and submitted to all applicable local Institutional Review Boards and Ethics Committees to ensure compliance with all ethical standards in each country.

Informed consent statement: Personally identifiable data were not collected in this study. As this was an observational study, consent to any interventional procedure or treatment was not applicable. Consent for participation in the study was solicited by requesting participants to agree to a statement indicating the purpose of the study and a brief summary of the information to be collected. This was carried out prior to entry into the web-enabled questionnaire with a description of the study and its purpose, and responses.

Conflict-of-interest statement: CK is an employee and shareholder of Takeda Pharmaceuticals. AA is an employee of Trinity Life Sciences, commissioned by Takeda Pharmaceuticals to conduct this study. VA is an employee of Trinity Life Sciences, commissioned by Takeda Pharmaceuticals to conduct this study. GH is an employee and shareholder of Takeda Pharmaceuticals. PG is an employee and shareholder of Takeda Pharmaceuticals. KL has served on advisory boards for Takeda Pharmaceuticals. SM is an employee and shareholder of Takeda Pharmaceuticals. MP has no conflicts of interest to disclose. LR has served on advisory boards for Roche and Takeda Pharmaceuticals. MSS has nothing to disclose. AS is an employee of Trinity Life Sciences, commissioned by Takeda

Pharmaceuticals to conduct this study. AY is an employee of Takeda Pharmaceuticals. PT has received speaker's fees from Ferring and Takeda Pharmaceuticals and served on advisory boards for Takeda Pharmaceuticals.

Data sharing statement: Data sets supporting the results from this study are available from the corresponding author upon reasonable request. The data sets will be provided after deidentification, in compliance with applicable privacy laws, data protection, and requirements for consent and anonymization.

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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ORIGINAL ARTICLE

Observational Study

Does gastric stump cancer really differ from primary proximal gastric cancer? A multicentre, propensity score matching-used, retrospective cohort study

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Abstract

BACKGROUND

Although the location of proximal cancer of the remnant stomach is the same as that of primary proximal cancer of the stomach, its clinical characteristics and prognosis are still controversial.

AIM

To evaluate the clinicopathological features and prognosis factors of gastric stump cancer (GSC) and primary proximal gastric cancer (PGC).

METHODS

From January, 2005 to December, 2016, 178 patients with GSC and 957 cases with PGC who received surgical treatment were enrolled. Patients in both groups underwent 1:1 propensity score matching analysis, and both clinical and pathological data were systematically collected for statistical purposes. Quality of

life was evaluated by the C30 and STO22 scale between GSC-malignant (GSC following gastric cancer) and GSC-benign (GSC following benign lesions of the stomach).

RESULTS

One hundred and fifty-two pairs were successfully matched after propensity score matching analysis. Of the 15 demographic and pathological variables collected, the analysis further revealed that the number of lymph nodes and positive lymph nodes were different prognostic and clinicopathological factors between PGC and GSC. Univariate and multivariate analyses showed that gender, differentiation degree and tumor-node-metastasis stage were independent risk factors for patients with GSC. Gender, vascular invasion, differentiation degree, depth of infiltration, positive lymph nodes, and tumor-node-metastasis stage were independent risk factors for patients with PGC. The 5-year overall survival and cancer-specific survival of patients with GSC were significantly lower than those in the PGC group, the scores for overall quality of life in the GSC-malignant group were lower than the GSC-benign, and the differences were statistically significant.

CONCLUSION

The differences in clinicopathological characteristics between GSC and PGC were clarified, and PGC had a better prognosis than GSC.

Key Words: Gastric stump cancer; Primary gastric cancer; Clinicopathological risk factors; Quality of life; Propensity score matching

Core Tip: Although the location of gastric stump cancer (GSC) is the same as that of primary proximal gastric cancer (PGC) , its clinical characteristics and prognosis are still controversial. In our research, 152 pairs of patients were successfully matched after propensity score matching analysis. The differences in clinicopathological characteristics between GSC and PGC were clarified, and PGC had a better prognosis than GSC. The scores for overall quality of life in the GSC-malignant group were lower than the GSC-benign group, and the differences were statistically significant.

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INTRODUCTION

Gastric cancer is one of the most common malignant tumours of the digestive tract worldwide. According to the latest statistics, there were approximately 1.034 million new cases of gastric cancer worldwide in 2018, resulting in a total of approximately 783000 deaths[1-3]. The 5-year survival rate of early gastric cancer patients exceeds 90%. However, the diagnostic rate of early gastric cancer is < 10%[4], and the 5-year survival rate of advanced gastric cancer is still < 50%[5, 6]. In recent years, gastric stump cancer (GSC), which accounts for only approximately 1%-7% of gastric cancers, has attracted more attention from scholars[7-10].

The concept of GSC was first proposed as the occurrence of residual cancer after surgery for benign lesions in 1922 by Balfour[11]. The current definition of GSC is, regardless of the method of first surgical resection or type of reconstruction, cancer found in the stump stomach 5 years after primary surgery for benign diseases or 10 years after primary surgery for malignant diseases. Although the detection rate of early gastric cancer continues to increase, due to the lack of typical symptoms and longer postoperative time leading to a decrease in patients' willingness to undergo gastroscopy, GSC is often still in the late stage when detected, which seriously reduces the survival time of patients. Although radical surgery is still the only treatment method for GSC, this complex surgery still has a high incidence of postoperative complications and mortality. Anatomical changes, intra-abdominal adhesions, and frequent combined resection of other organs make the surgery of GSC difficult. Currently, most studies on this surgical treatment have only registered a few patients and provided a brief descriptive analysis of their complications.

It is worth noting that although GSC originates from the same region after distal gastrectomy for gastric cancer and proximal gastric cancer (PGC), the lymphatic drainage direction of GSC patients and PGC patients is different due to the influence of first-time surgical lymph node dissection. Moreover, intra-abdominal adhesions in GSC patients may affect the quality of lymph node dissection. Although the clinical and pathological characteristics of GSC and PGC have been compared in the past, clinical studies on GSC are very rare, especially high-quality, large-scale randomised controlled studies. In recent years, there has been continuous literature exploring the prognosis of GSC and PGC, there is still controversy in this regard, partly due to the limited number of GSC patients. In addition, the scope of lymph node dissection and how these patients should be staged are still unresolved issues. It is necessary to understand the character-

istics of GSC to determine its prognosis and appropriate treatment strategies.

This study aims to evaluate the differences in clinical pathological characteristics and prognosis between PGC and GSC. Moreover, for patients with GSC caused by benign or malignant lesions, we evaluated their postoperative quality of life (QoL) to explore the impact of disease duration and psychological factors.

MATERIALS AND METHODS

This article is in line with the STROCSS criteria[12].

Patients and Follow-up

One hundred and seventy-eight patients with GSC and 957 patients with PGC were enrolled as the control group from January, 2005 to December, 2016. None of the patients received neoadjuvant therapy. The clinical and pathological data of the patients were collected, including age, gender, tumor-node-metastasis (TNM) stage (T and N stages were classified according to the criteria described in the American Joint Committee on Cancer Staging Manual, 8th edition), number of lymph nodes obtained, nerve invasion, vascular invasion, surgical methods, blood transfusion, length of hospital stay, American Society of Anaesthesiologists (ASA) grade, and bypass type. Variables that were initially recorded as continuous variables were also included in the current analysis.

In this study, the survival time ranged from the day of surgery to the day of death *via* telephone and outpatient visits, which included enhanced computed tomography every 6 mo, routine blood tests, and biochemical and tumour indicators, and terminated when the patients died. In the first year after surgery, all GSC patients who were still alive during the follow-up period were followed up to assess QoL, and the scoring scale was used to record the patient's general living conditions.

QoL

QoL was evaluated using the Chinese version of the EORTC QLQ-C30 and QLQ-STO22[13,14]. After the patients were introduced, they completed the questionnaire. Based on the EORTC QLQ-C30 and QLQ-STO22 scoring manuals, the original data of each scale were converted into 0-100. Statistical processing was performed using the EORTC QLQ-C30 questionnaire survey. For the QLQ-STO22 questionnaire survey, the higher the score, the worse the QoL. The *t*-test was used to compare the QoL.

Propensity score matching

In this propensity score matching (PSM) analysis, the following variables were considered potential confounders between the groups and were adjusted: Gender (female *vs* male), age (> 55 *vs* ≤ 55 years), and ASA score (ASA I/II *vs* III/IV). Propensity scores were calculated by bivariate logistic regression, using a 1:1 case-control match with a caliper value of 0.1 (one-to-one nearest-neighbor matching). The standardized difference (10% or 0.1) was used to compare the distribution of all paired.

Statistical analysis

The Cox proportional hazards regression model with backward variable selection was used to determine the factors independently related to survival time. It has also been reported that the 95% confidence interval (CI) of the hazard ratio (HR) has a significant effect. In this study, a P value of < 0.05 was used to define statistical significance, and all analyses were performed using SPSS 19.0.

RESULTS

Results of the PSM analysis

In this cohort, a total of 178 patients with GSC underwent surgical treatment in the general surgery department of the three hospitals (Figure 1). The mean age was 63 years. According to the American Joint Committee on Cancer Staging Manual, there were 15, 43 and 94 cases of stage I, II and III GSC, respectively. Nine hundred and fifty-seven patients with PGC underwent surgical treatment in the three hospitals. There were 736 male patients and 221 female patients. The mean age was 67 years. According to the American Joint Committee on Cancer Staging Manual, there were 132, 168, and 657 cases of stage I, II and III PGC, respectively.

Before PSM, there were significant differences in the number of lymph nodes, blood transfusion, TNM stage and differentiation degree between the PGC and GSC group. After PSM, there were 152 cases in these two groups, the statistical results showed that there were significant differences in the number of lymph nodes, positive lymph nodes, and differentiation degree between two groups (Table 1).

Risk factors

Table 2 shows that gender, degree of differentiation, and TNM stage were found to be risk factors for GSC. The prognostic factors in PGC determined by the univariate analysis were as follows: Gender, vascular invasion, degree of differentiation, depth of infiltration, number of positive lymph nodes, and TNM stage were found to be risk factors for

Table 1 Clinicopathologic characteristics of included patients before and after propensity score matching

Variables	Before PSM				After PSM			
	GSC (*n* = 178)	PGC (*n* = 957)	χ^2/Z	*P* value	GSC (*n* = 152)	PGC (*n* = 152)	χ^2/Z	*P* value
Gender			0.222	0.638			0.017	0.895
Female	44	221			38	39		
Male	134	736			114	113		
Age (yr)			0.452	0.502			0.020	0.0889
> 55	127	706			120	119		
≤ 55	51	251			32	33		
Tumor size			2.300	0.129			2.608	0.106
> 3.5 cm	103	611			91	77		
≤ 3.5 cm	75	346			61	75		
ASA grade			2.590	0.108			0.058	0.809
I/II	112	540			99	101		
III/IV	66	417			53	51		
Hospital stay after surgery (d)	12.65 ± 5.13	12.77 ± 4.42	1.023	0.133	11.13 ± 4.71	11.45 ± 5.90	1.156	0.232
Blood transfusion			10.705	0.001			2.114	0.156
Yes	42	127			34	57		
No	126	780			108	85		
Vascular invasion			0.405	0.525			0.920	0.337
Positive	36	339			32	70		
Negative	51	415			49	82		
Missing	91	203			71	-		
Nerve invasion			0.475	0.491			0.280	0.596
Positive	49	389			40	63		
Negative	55	378			49	89		
Missing	74	190			63	-		
Differentiation degree			18.537	0.000			1.452	0.028
High/median	38	100			27	21		
Low	128	824			115	131		
Missing	12	33			10	-		
Depth of infiltration			0.310	0.578			0.838	0.360
T1/T2	40	198			36	43		
T3/T4	138	762			116	109		
Number of lymph nodes			3.859	0.049			6.752	0.009
≥ 7	101	617			94	115		
< 7	77	340			58	37		
Positive lymph nodes			0.570	0.450			19.667	0.000
≥ 3	86	433			71	109		
< 3	92	524			81	43		
TNM stage			10.367	0.006			0.062	0.969
I	15	132			17	18		
II	43	168			38	39		

III	94	657	97	95

PSM: Propensity score matching; GSC: Gastric stump cancer; PGC: Proximal gastric cancer; TNM: Tumor-node-metastasis; ASA: American Society of Anaesthesiologists.

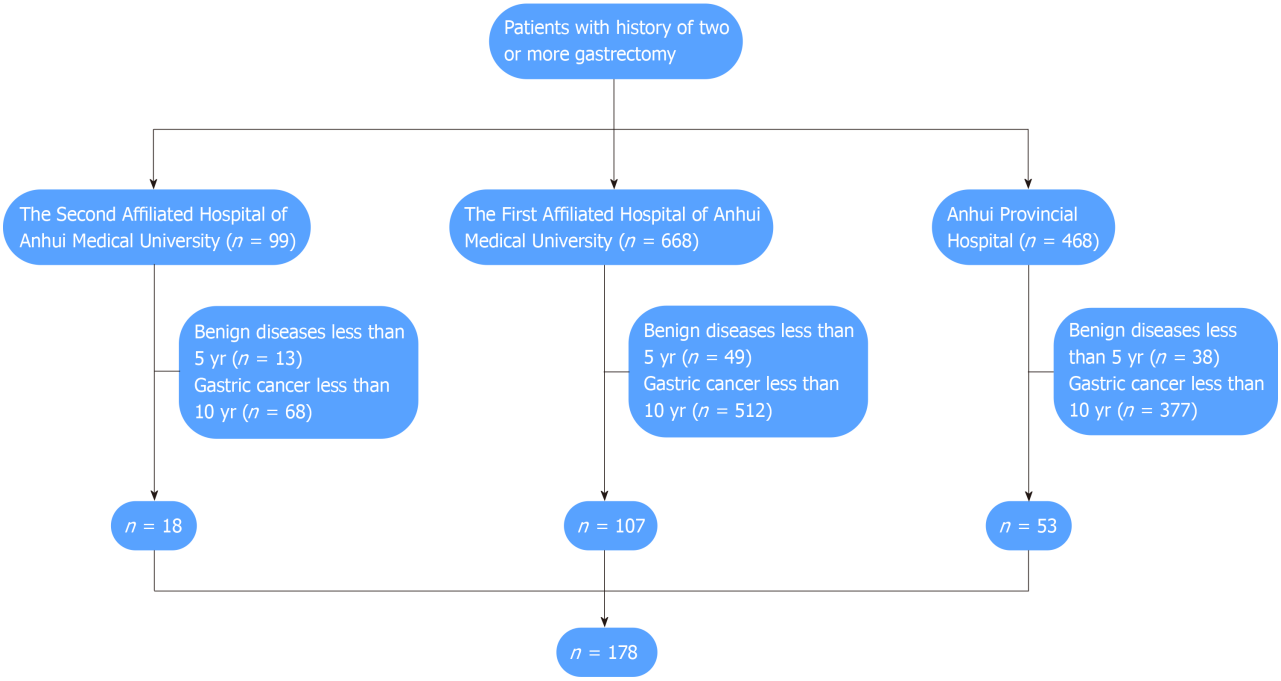

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Figure 1 Flow chart of gastric stump cancer patient selection.

PGC. Multivariate analyses were conducted to identify the independent prognostic factors, and the results are shown in Table 3. The degree of differentiation, and TNM stage were independent prognostic factors for patients with GSC and differentiation degree, depth of infiltration, positive lymph nodes and TNM stage were independent prognostic factors for PGC patients.

Actual survival

The median follow-up time in the PGC group was 83 mo. At the last follow-up in June 2022, 72.2% of patients had died. The median follow-up time in the GSC group was 80 mo, and 82.1% of patients had died. The overall median survival in the PGC group was 34 mo and was 24 mo in the GSC group. The risk of death after GSC radical surgery was not constant. Most patients with GSC experienced overall-cause death or cancer-specific death in the first 3 years after surgery. After a period of evaluation, the probability of all-cause death and cancer-specific death peaked at 12 mo after surgery and then gradually decreased. We also evaluated the probability of survival for patients with GSC over a period and showed that the probability of cancer-specific survival increased with prolongation of postoperative survival. Correspondingly, with the prolongation of survival time, the recurrence rate in patients with GSC decreased. In the GSC control group, the overall survival during the follow-up period was significantly lower than that in the PGC group (HR = 0.7290, 95%CI: 0.5578-0.9529, P = 0.0207, Figure 2A), the cancer specific survival in the PGC group was also significantly higher than that in the GSC group (HR = 0.7504; 95%CI: 0.5686-0.9902, P = 0.0424, Figure 2B).

QoL

According to the QLQ-C30 questionnaire, the overall health status scores of patients with GSC-benign (GSC-B) and those with GSC-malignant (GSC-M) were 67.15 ± 20.1 and 56.2 ± 18.5, respectively. There was a significant difference between the two groups by statistical analysis, which showed that the overall health status of the GSC-M group was worse than that of the GSC-B group. In terms of function scale, the scores for physical, emotional and cognitive function in patients on the symptom scale, and the scores for fatigue, pain, diarrhea, economic difficulties, and reflux in the two groups were not different.

Table 2 Univariate analysis of cancer-specific survival in gastric stump cancer and proximal gastric cancer

Variables	GSC				PGC			
	n = 152	HR	95%CI	*P* value	*n* = 152	HR	95%CI	*P* value
Gender		1.991	0.937-3.422	0.038[a]		1.991	0.937-3.422	0.038[a]
Female	38				38			
Male	114				114			
Age (yr)		1.117	0.681-1.833	0.900		1.111	0.690-1.804	0.893
> 55	120				119			
≤ 55	32				33			
Tumor size		1.012	0.622-1.646	0.961		1.405	0.598-1.837	0.902
> 3.5 cm	91				77			
≤ 3.5 cm	61				75			
ASA grade		1.338	0.792-2.260	0.276		1.257	0.777-2.900	0.331
I/II	99				101			
III/IV	53				51			
Hospital stay after surgery (d)	11.13 ± 4.71	0.635	0.308-1.307	0.218	12.45 ± 5.90	0.873	0.299-1.780	0.412
Blood transfusion		1.114	0.655-1.896	0.690		1.296	0.588-2.001	0.255
Yes	44				67			
No	108				85			
Vascular invasion		1.662	0.210-2.138	0.630		1.603	1.000-9.568	0.049[a]
Positive	32				70			
Negative	49				82			
Missing	71				-			
Nerve invasion		1.710	0.971-3.012	0.063		4.660	0.981-22.134	0.053
Positive	40				63			
Negative	49				89			
Missing	63				-			
Differentiation degree		2.714	1.603-4.596	0.000[a]		3.503	1.734-11.385	0.000[a]
High/median	27				21			
Low	115				131			
Missing	10				-			
Depth of infiltration		3.614	2.290-4.289	0.080		2.332	0.074-4.498	0.041[a]
T1/T2	36				43			
T3/T4	116				109			
Number of lymph nodes		0.792	0.336-1.869	0.595		3.432	0.874-12.441	0.077
≥ 7	94				115			
< 7	58				37			
Positive lymph nodes		0.223	0.110-0.881	0.124		0.485	0.260-0.906	0.023[a]
≥ 3	71				109			
< 3	81				43			
TNM stage		5.727	2.579- 12.715	0.000[a]		5.446	2.555-11.992	0.000[a]
I	17				18			
II	38				39			

III	97	95

[a]*P* < 0.05.

HR: Hazard ratio; CI: Confidence interval; GSC: Gastric stump cancer; PGC: Proximal gastric cancer; TNM: Tumor-node-metastasis; ASA: American Society of Anaesthesiologists.

Table 3 Multivariate analysis of factors affecting cancer-specific survival

	GSC			PGC		
	HR	95%CI	*P* value	HR	95%CI	*P* value
Gender	1.552	0.129-3.428	0.058	1.847	0.135-2.990	0.043
Differentiation degree	1.430	1.055-1.938	0.021[a]	1.999	0.636-3.004	0.027[a]
Depth of infiltration				2.929	1.383-4.691	0.000[a]
Positive lymph nodes				2.452	1.085-3.942	0.012[a]
TNM stage	1.426	1.040-1.955	0.027[a]	2.771	1.448-4.662	0.000[a]
Vascular invasion				1.269	0.680-3.998	0.070

[a]*P* < 0.05.

HR: Hazard ratio; CI: Confidence interval; GSC: Gastric stump cancer; PGC: Proximal gastric cancer.

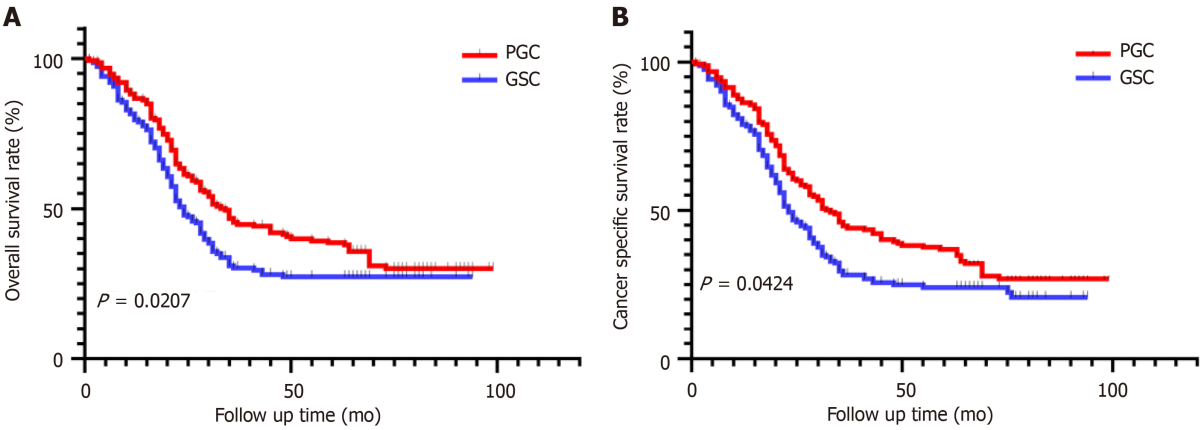

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Figure 2 Differences in survival between proximal gastric cancer patients and gastric stump cancer patients. A: Overall survival in proximal gastric cancer (PGC) and gastric stump cancer (GSC) patients; B: Cancer-specific survival in PGC and GSC patients. PGC: Proximal gastric cancer; GSC: Gastric stump cancer.

DISCUSSION

There has been no large-scale high-quality study in the field of GSC. Previous studies on GSC are few, especially clinical trials with more than 100 cases. A study by Japanese scholars included 156 GSC patients and 755 PGC patients and the authors believed that the prognosis of GSC patients was worse than that of PGC patients, moreover, GSC secondary to malignant lesions occurred earlier than that of benign lesions after surgery[15]. Wang *et al*[16] focused on cardiac cancer, and included 48 GSC patients and 96 primary cardiac cancer patients. The results confirmed that the survival rate of patients with residual gastric cardia cancer after radical resection was lower than that of primary cardiac cancer patients, but the survival rate of patients without serous infiltration or lymph node metastasis was similar to that of primary cardiac cancer patients. Ramos *et al*[17] also obtained similar results, indicating that there is still a lot of controversy regarding the prognosis of GSC and PGC patients, and further clarification is needed in large-scale clinical trials, especially high-quality randomised controlled trials.

At present, the definition of GSC is still controversial. These disputes easily make researchers focus on the time interval and the nature of the primary disease, and often ignore the nature of GSC, its cause. The incidence of GSC has been increasing in recent years, and the reason for this is unclear. However, some scholars believe that damage to the epithelial cells of the gastric mucosa and weakening of the gastric mucosal barrier by alkaline reflux after the previous surgery are important factors in the occurrence of GSC. Healed anastomoses or suture ulcers are important factors in stress

stimulation; the occurrence and development of some GSCs may be related to Epstein-Barr virus infection; the occurrence of GSCs is also related to the previous surgical method[18,19]. After partial resection, Billroth II (B-II) surgery is associated with a higher incidence of GSC due to its higher reflux rate. In this study, more than half of patients in the GSC group underwent B-II anastomosis during their first surgery, while the proportion of Roux-en-Y (R-Y) anastomosis was less than 11%. It can be seen that the proportion of GSC in patients with B-II anastomosis was higher. Undeniably, R-Y anastomosis performs better in resisting digestive reflux.

R-Y anastomosis can reduce reflux, the occurrence of residual gastritis, and the incidence of GSC[20-22]. Cutting the vagus nerve during distal gastrectomy also causes cancer. After cutting, the gastric defence factors are reduced, and the blood circulation, secretion, and regeneration of the gastric mucosa are affected, resulting in cell DNA mutations during the proliferation process. This is carcinogenic[23], and its occurrence is related to factors such as age, heredity, and sex. Research shows that in patients diagnosed with GSC, the median age is between 67 and 71 years and male patients are at greater (4-9 times) risk of developing GSC than female patients[24]. In this study, the number of male patients with GSC was more than three times that of female patients, with a mean age of 63 (range, 39-76) years.

It is worth noting that in this study, only 36.2% of patients who underwent surgical treatment for benign diseases developed GSC, while the proportion of patients with GSC-M was 63.8%. Due to the fact that the biological behavior of tumor cells, especially their metastatic ability, may vary depending on the location of the tumor, in order to avoid this bias, we only selected one-third of primary PGC patients as the control group. Overall, the GSC group exhibited similar characteristics to PGC patients. In addition, survival data processed by statistical methods showed a difference in survival time between the GSC group and the PGC group, which is contrary to the previous research results of Ramos *et al*[17]. As expected, among the patients we included, the number of lymph nodes after GSC surgery was significantly lower than that in the PGC group. Some studies have shown that the characteristics of lymph node metastasis in GSC are different due to the interruption of lymphatic pathways during the first operation, which may lead to more involvement of the splenic artery, splenic hilum, lower mediastinum and jejunum mesentery lymph nodes[25-27]. However, the standard extension for lymph node resection has not yet been determined. It is well known that an enlarged lymph node resection in this area can seriously affect the QoL after surgery. Therefore, the scope of mesentery lymph node resection should be determined according to the extent of lymph node involvement, taking into account the risks and benefits[28].

In recent years, the application of neoadjuvant therapy in the perioperative period of gastric cancer has become a consensus. However, the application of this conclusion in GSC still needs more evidence. Patients with neoadjuvant therapy were not included in this study as the number of patients with GSC receiving neoadjuvant therapy was small, and the inclusion of too many patients with neoadjuvant therapy in the PGC group may have a significant impact on the results. There is no denying that neoadjuvant therapy has several potential advantages, including improving R0 removal rates, testing tumour response to a specific treatment regimen, and not only that, it provides a time window to evaluate tumour biology. Despite local control, an important risk of neoadjuvant therapy is that it may introduce a greater probability of distant metastasis if treatment fails to control tumour progression. The best approach, however, is unclear. In conclusion, selective addition of neoadjuvant chemotherapy and/or radiotherapy is beneficial in specific anatomical and histopathological subtypes.

The clinical symptoms of GSC lack specificity, the resection rate is low after diagnosis, and the prognosis is poor. It causes damage to the patients' physical, psychological, and social functions and affects their health-related QoL (HRQOL). However, few studies have evaluated the postoperative QoL in patients with GSC. In this study, the HRQOL in two groups of GSC patients caused by benign (GSC-B) and malignant (GSC-M) lesions was comprehensively evaluated using the QLQ-C30 and gastric cancer-specific scale QLQ-STO22. The results of this study show that the scores for overall QoL in the GSC-B group were higher than those in the GSC-M group and there was no significant statistical difference in other aspects. We speculate that this may be related to the postoperative chemotherapy received by patients in the GSC-M group, as the proportion of postoperative chemotherapy in the GSC-M group was significantly higher. On the other hand, we found that the differentiation level of patients in the GSC-M group was worse than that in the GSC-B group, and the proportion of poorly differentiated patients was higher, which may also be a reason for the decline in their QoL. Early clinical diagnosis, appropriate treatment, timely control of disease progression, and reduction of physical symptoms are conducive to improving patients' HRQOL. While improving their physiological function, patients should recognise the positive role of psychological and spiritual factors in the course of cancer, carry out necessary psychological treatment and intervention, alleviate psychological obstacles, and eliminate the negative impact of bad emotions on HRQOL as far as possible.

CONCLUSION

The differences in clinicopathological characteristics between GSC and PGC were clarified, and PGC had a better prognosis than GSC.

ARTICLE HIGHLIGHTS

Research background

The clinicopathological characteristics of gastric stump cancer (GSC) and proximal gastric cancer (PGC) have not yet been confirmed. There has always been controversy regarding the differences in treatment and prognosis prediction.

Research motivation
Evaluation of the differences between GSC and primary PGC using a larger sample size.

Research objectives
The object of this study was to evaluate the clinicopathological features, and prognostic factors of GSC and primary PGC.

Research methods
After detailed data statistics and data collection, 178 GSC patients and 957 PGC patients underwent surgical treatment at multiple centers. A 1:1 propensity score matching analysis was conducted on the two groups of patients, with 152 patients in each group entering the final analysis. Single factor and multivariate analysis were used to study the risk factors in gastric cancer patients. The survival curve was plotted to compare the differences in survival time between the two groups. The quality of life (QoL) of GSC-malignant (GSC-M) (post cancer GSC) and GSC-benign (GSC-B) (post benign gastric lesion GSC) patients was evaluated using the C30 and STO22 scales.

Research results
The number of lymph nodes and positive lymph nodes were different prognostic and clinicopathological factors between PGC and GSC. The 5-year overall survival and cancer-specific survival of patients with GSC were significantly lower than the PGC group, the scores for overall QoL in the GSC-M group were lower than the GSC-B group, and the differences were statistically significant.

Research conclusions
The differences in clinicopathological characteristics between GSC and PGC were significant, and compared to GSC patients, PGC patients had a better prognosis, and the overall health status of the GSC-M group was worse than that of the GSC-B group.

Research perspectives
More large-scale randomised controlled trial studies are needed to provide higher-level evidence regarding the comparison between PGC and GSC.

FOOTNOTES

Co-corresponding authors: He Li and Kong-Wang Hu.

Author contributions: Wang SH and Zhang JC contributed to the data statistics and writing; Wang SH, Zhang JC, and Zhu L collected the data; Li H and Hu KW were involved in the design of ideas and quality control; Wang SH and Zhang JC contributed equally to this work. KW Hu and Li H contributed equally to this work as co-corresponding authors. There are several reasons for this decision. First of all, although the two authors have slight differences in their contributions to the research, they have maintained close communication and effective discussion throughout the whole process of the project, which has made the project move forward in the right direction and finally improved the quality of the paper. In terms of project design, our original plan was not the research idea presented now, but with deepening of the research, the two authors timely revised the direction of the article, and finally achieved successful publication of the manuscript. We believe that the designation of co-authors accurately reflects the degree of contribution to the research and reflects the collaborative spirit of the team.

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SYSTEMATIC REVIEWS

Global, regional, and national burden of gallbladder and biliary diseases from 1990 to 2019

Zhong-Zhuan Li, Lin-Jing Guan, Rong Ouyang, Zhi-Xin Chen, Guo-Qing Ouyang, Hai-Xing Jiang

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Abstract

BACKGROUND

Gallbladder and biliary diseases (GABDs) are a major public health issue.

AIM

To analysis the cause-specific incidence, prevalence, and years lived with disability (YLDs) and its temporal trends of GABDs at the global, regional, and national level. Data on GABD were available from the Global Burden of Disease study 2019.

METHODS

The estimated annual percentage change (EAPC) was used to quantify temporal trend in GABD age-standardized incidence rates (ASIRs), age-standardized prevalence rate (ASPR), and age-standardized YLD rate (ASYR) by region, sex. We analyzed the relationship between the GABD burden and country development level using the human development index (HDI).

RESULTS

In 2019, the incident cases of GABD were 52003772, with an ASIR of 63432/100000 population. Globally, the number of incident cases and ASIR of GABD increased 97% and 58.9% between 1990 and 2019. Although, the ASPR and ASYR decreased from 1990 to 2019, the number of prevalent and YLDs cases increased. The highest

ASIR was observed in Italy, and the highest ASPR and ASYR was observed in United Kingdom. The highest burden of GABD was found in low-SDI region, and the burden in female was significantly higher than males. A generally negative correlation (ρ = -0.24, $P < 0.05$) of GABD with the EAPC and human development index (HDI) (in 2021) were observed for ASIR. What's more, no correlation in ASPR (ρ = -0.06, $P = 0.39$) and ASYR (ρ = -0.07, $P = 0.36$) of GABD with the EAPC and HDI (in 2021) were observed, respectively.

CONCLUSION

GABD remain a major global public health challenge; however, the burden of GABD varies geographically. Globally, the number of incident cases and ASIR of GABD increased between 1990 and 2019. The results of our study provide insight into the global disease burden of GABD and may assist policymakers in formulating effective policies to mitigate modifiable risk factors.

Key Words: Gallbladder and biliary diseases, incidence, prevalence, years lived with disability; The Global Burden of Diseases study; Estimated annual percentage changes

Core Tip: Gallbladder and biliary disease (GABD) remains a major global public health challenge, and the disease burden varies geographically. From 1990 to 2019, the number of cases and age-standardized incidence rate of GABD increased globally. What's more, although GABD age-standardized prevalence rate and age-standardized years lived with disability rate decreased, the number of prevalent and years lived with disability cases increased. The highest burden of GABD was observed in low-sociodemographic index regions, and the burden was significantly higher among females than males. We believe that the findings of this study will provide insight into the global disease burden of GABD and assist policymakers in formulating effective policies to mitigate modifiable risk factors.

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INTRODUCTION

Gallbladder and biliary diseases (GABDs) are common digestive system disorders comprising cholelithiasis, cholecystitis, other diseases of gallbladder and other diseases of biliary tract, such as cholangitis and bile duct obstruction)[1-3]. According to the National Health and Nutrition Examination Survey III, gallbladder disease affects more than 20 million adults in the United States, including 14.2 million women and 6.3 million men[4], with an estimated cost of $6.2 billion [5]. In the general population, the overall prevalence of gallstones is estimated to be between 10% and 15%; however, there is some variation between countries[6]. Biliary colic symptoms are present in up to 20% of gallstone patients[7]. If left undiagnosed and untreated, gallstones have a yearly risk of 1%-2% of developing into more complicated diseases. Moreover, severe conditions can quickly progress to systemic inflammatory response syndrome, sepsis, and even death [8-10].

GABDs not only have long-term detrimental effects on quality of life and productivity, but also frequently require hospitalization and surgical interventions, resulting in substantial healthcare costs and a significant financial burden on society[11]. According to the data set of the United States Medical Survey, the total cost of cholelithiasis and cholecystitis in the United States alone was over $2.2 billion in 2009, rising to $4 billion in 2014[12]. Therefore, a proper understanding of epidemiologic data and identification of groups at high risk of GABD is important to make sound health policy decisions and for effective resource allocations.

A study based on the Global Burden of Diseases Study (GBD) 2019 data reported an increase in the prevalence, death, and disability-adjusted life years (DALYs) rates of GABD from 1990 to 2019. however, the age-standardized rates (ASRs) decreased over the 30-year period[13]. In addition to presenting global prevalence, death, and DALY rates, this study did not include an analysis of the incidence and years lived with disability (YLD) rates. Furthermore, it did not provide information on the regional and national burden. Moreover, the study only assessed the correlations between ASR and the sociodemographic index (SDI)[13] and not between the number of events and the human development index (HDI) and baseline ASR. Therefore, a comprehensive analysis of the incidence, prevalence, and YLDs of GABD is needed to enable informed policy making and for further research to reduce its burden.

In this study, using data from the GBD 2019 study, we presented the incidence, prevalence, and YLDs of GABD and their temporal trends from 1990 to 2019 in 204 countries and territories at the global, regional, and national levels. The association between estimated annual percentage changes (EAPCs), age-standardized incidence rates (ASIRs), age-standardized prevalence rates (ASPRs), and age-standardized YLDs rates (ASYRs) (1990), and HDI (2021) were also assessed at the national level.

MATERIALS AND METHODS

Study data

The GBD 2019 study conducted by the Institute for Health Metrics and Evaluation provided a comprehensive epidemiological assessment of 369 diseases and injuries, 286 causes of death, and 87 risk factors across regions, countries, gender, and etiology[14]. The study reported burden levels and trends of major diseases, injuries, and risk factors by region, sex, country, and age in 204 countries and territories, 7 super regions, and 21 regions from 1990 to 2019. In our study, we utilized data obtained from the Global Health Data Exchange query tool (http://ghdx.healthdata.org/gbd-results-tool), which included the number of incidences and ASIR, as well as their percentages, from 1990 to 2019 based on global, regional, and national cause.

GBD 2019 categorized 204 countries and territories into 5 regions according to SDI quintiles-low-, low-middle-, middle-, high-middle-, and high-SDI regions-and into 21 GBD geographic regions[14-19]. The present study was conducted in accordance with the Guidelines for Accurate and Transparent Health Estimates Reporting statement[19]. DisMod-MR 2.1 model, an epidemiological state transition disease modeling software, and MR-BRT, a Bayesian meta-regression software, were used to produce consistent disease estimates[14,18]. The 2019 HDI for 187 countries and territories was provided by the United Nations Development Program. The HDI is a combined measure of health, education, and income in a given country: a long and healthy life, a knowledgeable, and a decent standard of living[20].

The 10th revision of the International Classification of Diseases coded GABDs as K80, K81, K82, and K83[14,18]. In the present study, the data were extracted from the GBD 2019 and were estimated from the literature, clinical administrative, Poland claims, hospital discharges, the United States MarketScan claims, and southern sub-Saharan Africa data[14,18].

Statistical analysis

To analyze GABD trends from 1990 to 2019, the EAPCs in ASR were calculated[21]. EAPC is a comprehensive statistical and widely used measure for assessing the ASR trends within a specific interval[22]. The ASR and EAPC calculations have been proposed in previous studies[23]. In brief, we fit the natural logarithm of ASR to calendar years to calculate the EAPC, which describes the long-term trend of the GABD burden. If the EAPC value and its lower boundary of 95% confidence interval (CI) were both greater than 0, we considered the ASR of GABD to increase, and if the EAPC value and its upper boundary of 95%CI were lower than 0, we considered the ASR to decrease. In addition, if the 95%CI of EAPC contained 0, we considered ASR to be stable over time[23]. In addition, we also analyzed the correlations between EAPC and ASR in 1990 and between EAPC and HDI in 2019 at the national level to explore the factors influencing EAPC. All statistics were analyzed using the R statistical software program (version 3.4.2; R Foundation for Statistical Computing, Vienna, Austria). *P*-values ≤ 0.05 were considered statistically significant.

Patient involvement

In this study, secondary data analysis was performed and no patients were recruited as study participants. Patients did not participate in the formulation of the research question, study design, or overall conduct of the study. The dissemination of study findings does not involve patient involvement. All data analyzed in this study were previously published or existing data sources.

RESULTS

Global and national levels

In 2019, the incident cases of GABD were 52003772 [95% uncertainty interval (UI): 44202143-61211622), with an ASIR of 634.32 per 100000 population (540.21-742.93) (Table 1). From 1990 to 2019, the global number of incident cases of GABD increased by 97% (90% to 105%), and the global ASIR increased by EAPC = 0.59 (0.42-0.76). Globally, the number of prevalent cases due to GABD was 193493378 (166626338-229375433) in 2019, and the ASPR was 2350.78 per 100000 population (2029.59-2778.69). The global number of prevalent cases of GABD increased by 52% (45% to 59%), and the global ASPR decreased by EAPC = -0.60 (-0.68 to -0.52) from 1990 to 2019. In 2019, GABD accounted for 4061843 (2595493-5953096) YLDs, with an ASR of 49.33 per 100000 population (31.51-71.96). The number of LYDs increased by 51% (44%-58%), and the ASR decreased by EAPC = -0.59 (-1.16 to -0.03) from 1990 to 2019 (Table 1).

In 2019, Italy [1718.36 per 100000 population (1441.49-2039.23] had the highest ASIR, followed by Japan [1614.18 per 100000 population (1366.14-1898.78)] and the United Kingdom [1593.45 per 100000 population (1339.08-1878.10), whereas Somalia (38.06 per 100000 population (33.42-43.73)], Guinea [38.40 per 100000 population (33.08-45.33)], and Guinea-Bissau [38.78 per 100000 population (33.57-44.46)] had the lowest ASIRs (Figure 1A, Supplementary Table 1). From 1990 to 2019, Qatar (775%, 689% to 856%) and Latvia (-14%, -21% to -6%) had the most pronounced increased and decreased and decreased changes, respectively (Figure 1B). From 1990 to 2019, the largest ASIR increase was observed in India (EAPC = 3.18, 2.92-3.45) and Brazil (EAPC = 1.68, 1.55-1.82). During this period, a total of 32 countries or territories had a decrease in the GABD ASIR, with the largest ASIR decrease occurring in Argentina (EAPC = -1.43, -1.72 to -1.14) (Figure 1C, Supplementary Table 1).

In 2019□the United Kingdom [6508.08 per 100000 population (5545.0 to 7764.50)] observed the highest ASPR, followed by Honduras [6070.86 per 100000 population (5273.68-7142.56)] and Italy [5448.65 per 100000 population (4619.27-6558.62)], whereas Cabo Verde [241.78 per 100000 population (196.60-290.47)], Sao Tome and Principe [277.51 per 100000 population (233.02-326.76)], and Nigeria [288.85 per 100000 population (235.57-356.61)] had the lowest ASPRs. From 1990

Table 1 Prevalent cases, incident cases, and years lived with disability for gallbladder and biliary diseases in 2019 for both sexes and estimated annual percentage change of age-standardized rates per 100000 populations from 1990 to 2019 by global burden of disease regions

	Incidence (95%UI)			Prevalence (95%UI)			YLDs (95%UI)		
	Counts	ASR per 100000 population (95%UI)	EAPC, No. (95%UI)	Counts	ASR per 100000 population (95%UI)	EAPC, No. (95%UI)	Counts	ASR per 100000 population (95%UI)	EAPC, No. (95%UI)
Global	52003772 (44202142 to 61211622)	634.3 (540.2 to 742.9)	0.59 (0.42 to 0.76)	193493378 (166626338 to 229375433)	2350.8 (2029.6 to 2778.7)	-0.6 (-0.68 to -0.52)	4061842 (2595493 to 5953095)	49.3 (31.5 to 72)	-0.59 (-1.16 to -0.03)
High SDI	12860583 (11042248 to 15000364)	903.1 (775.9 to 1051.1)	0.34 (0.2 to 0.48)	38543062 (34374485 to 44512280)	2697.1 (2368.1 to 3139.5)	-0.39 (-0.47 to -0.32)	797414 (519404 to 1163424)	56.5 (36.4 to 81.8)	-0.39 (-0.93 to 0.15)
High-middle SDI	14445160 (12091786 to 17193072)	779.3 (656.4 to 919.7)	0.58 (0.43 to 0.74)	49687139 (42506863 to 59548790)	2648.5 (2270.6 to 3164.9)	-0.89 (-0.97 to -0.82)	1044155 (667259 to 1533326)	55.9 (35.6 to 82.2)	-0.87 (-1.4 to -0.34)
Low SDI	1253652 (1062794 to 1455528)	159.3 (135.8 to 184.5)	1.93 (1.55 to 2.3)	6977018 (5870056 to 8390276)	931.6 (797.2 to 1100.5)	0.44 (0.3 to 0.58)	147359 (93751 to 214884)	19.3 (12.3 to 27.9)	0.44 (-0.52 to 1.41)
Low-middle SDI	6865087 (5883526 to 8041685)	428.2 (368.6 to 498.2)	1.54 (1.32 to 1.76)	33838143 (28644490 to 40159266)	2139.3 (1828.8 to 2532.3)	0 (-0.09 to 0.09)	711283 (454776 to 1033739)	44.6 (28.6 to 64.7)	0 (-0.62 to 0.62)
Middle SDI	16564482 (13930955 to 19595424)	634.3 (538.9 to 741.3)	1.07 (0.89 to 1.24)	64380264 (54532616 to 77437635)	2444.2 (2087.2 to 2916.3)	-0.63 (-0.71 to -0.55)	1360202 (858233 to 2012102)	51.5 (32.6 to 75.8)	-0.62 (-1.17 to -0.07)
Andean Latin America	154442 (134082 to 182018)	250.5 (218.7 to 293.5)	-0.49 (-0.75 to -0.23)	752040 (648059 to 886084)	1229.9 (1064.1 to 1449.3)	-2.06 (-2.17 to -1.96)	15980 (10166 to 23987)	26.1 (16.6 to 39)	-2.05 (-2.77 to -1.33)
Australasia	164233 (138271 to 195727)	522.8 (435.9 to 625.1)	0.43 (0.25 to 0.6)	530968 (446679 to 635872)	1658.9 (1374 to 1998.3)	-0.02 (-0.11 to 0.08)	11021 (6917 to 16707)	34.8 (21.9 to 52.4)	-0.01 (-0.66 to 0.64)
Caribbean	156296 (136832 to 182179)	313.1 (274.3 to 364.6)	0.03 (-0.2 to 0.27)	825072 (715970 to 974166)	1643.7 (1426.3 to 1934.8)	-0.53 (-0.63 to -0.43)	17420 (11138 to 25766)	34.8 (22.2 to 51.5)	-0.53 (-1.21 to 0.16)
Central Asia	387014 (334541 to 458388)	425.3 (371 to 499.6)	0.2 (0 to 0.4)	1871025 (1603526 to 2211405)	2095 (1818.5 to 2462.2)	-0.59 (-0.68 to -0.51)	39825 (25171 to 59685)	44.3 (28.1 to 66)	-0.59 (-1.18 to 0)
Central Europe	1640445 (1422211 to 1907708)	1009.9 (881.2 to 1171.3)	-0.12 (-0.25 to 0.01)	6029758 (5329152 to 7049974)	3597.1 (3168.9 to 4175.4)	-0.91 (-0.98 to -0.85)	125330 (81455 to 184592)	75.7 (48.7 to 111.5)	-0.9 (-1.34 to -0.46)
Central Latin America	2823891 (2424360 to 3299583)	1112.7 (958.4 to 1295.3)	0.86 (0.74 to 0.99)	12055660 (10362891 to 14277940)	4759.3 (4118.6 to 5625.1)	-0.15 (-0.21 to -0.09)	255373 (162045 to 378776)	100.6 (64 to 149.3)	-0.14 (-0.53 to 0.24)
Central Sub-Saharan Africa	45585 (38869 to 53755)	47.6 (42.3 to 55.6)	0.76 (0.13 to 1.39)	354446 (297953 to 420852)	392.3 (340.3 to 465.3)	-0.43 (-0.63 to -0.23)	7621 (4750 to 11506)	8.3 (5.3 to 12.4)	-0.41 (-1.78 to 0.98)
East Asia	18820462 (15683952 to 22743373)	958.8 (807.5 to 1136.8)	1.24 (1.09 to 1.39)	67192926 (56174716 to 81311137)	3359.2 (2836 to 4046.1)	-1.01 (-1.08 to -0.94)	1421896 (901930 to 2106987)	71.2 (45.3 to 105.1)	-0.99 (-1.45 to -0.52)
Eastern Europe	2197594 (1834757 to 2592937)	786.1 (662.1 to 925.4)	-0.04 (-0.19 to 0.11)	6878984 (5840942 to 8299739)	2418.7 (2034.8 to 2922.3)	-0.93 (-1.01 to -0.85)	143158 (90605 to 211511)	50.8 (32 to 75.3)	-0.9 (-1.45 to -0.36)
Eastern Sub-Saharan Africa	153056 (129067 to 181593)	51.7 (45.5 to 59.8)	0.94 (0.32 to 1.56)	1006771 (840990 to 1196816)	356.5 (308.4 to 425.6)	-0.6 (-0.81 to -0.39)	21824 (13715 to 32318)	7.6 (4.9 to 11.1)	-0.57 (-2.02 to 0.9)
High-income Asia Pacific	4261261 (3621403 to 5024854)	1426.2 (1211.6 to 1670.2)	0.73 (0.62 to 0.85)	10575603 (9303195 to 12379585)	3496.8 (3033.3 to 4141.8)	-0.52 (-0.59 to -0.46)	220728 (143767 to 327523)	74.5 (47.9 to 110)	-0.51 (-0.98 to -0.04)
High-income North	3976462 (3402556 to	833.9 (713.7 to 978.7)	0.39 (0.24 to 0.53)	11080847 (9984794 to	2324.7 (2069.7 to 2645.6)	0.41 (0.32 to 0.49)	225645 (148721 to	48 (31.5 to 69.6)	0.4 (-0.2 to 1)

America	4629606)			12425862)			327151)		
North Africa and Middle East	1609636 (1383286 to 1897397)	291 (252 to 340.5)	0.72 (0.48 to 0.97)	6763347 (5788935 to 8068118)	1247.5 (1085.6 to 1473.5)	-0.53 (-0.64 to -0.42)	142529 (91198 to 212150)	26.1 (16.8 to 38.5)	-0.54 (-1.28 to 0.22)
Oceania	15179 (13016 to 17782)	142.3 (124.1 to 166.2)	0.26 (-0.09 to 0.62)	103798 (87862 to 122071)	1030 (890 to 1209.7)	-0.15 (-0.27 to -0.02)	2197 (1378 to 3314)	21.5 (13.6 to 31.9)	-0.15 (-1.03 to 0.74)
South Asia	5531859 (4673821 to 6539869)	330.3 (281 to 388.4)	2.92 (2.64 to 3.2)	29094356 (23807912 to 35617848)	1770 (1466.9 to 2132)	1.4 (1.29 to 1.5)	605844 (385259 to 891933)	36.5 (23.2 to 53.8)	1.41 (0.65 to 2.17)
Southeast Asia	1847177 (1576905 to 2179276)	264.5 (227.7 to 309.9)	0.59 (0.32 to 0.86)	8621326 (7282497 to 10377424)	1234.4 (1053.7 to 1468.8)	-0.63 (-0.75 to -0.52)	183587 (115690 to 270067)	26.2 (16.6 to 38.3)	-0.6 (-1.38 to 0.18)
Southern Latin America	136733 (119283 to 163208)	180.1 (156.7 to 214.9)	-1.08 (-1.37 to -0.79)	575576 (498407 to 689250)	750.5 (647.3 to 892.9)	-1.8 (-1.94 to -1.67)	12072 (7685 to 18082)	15.8 (10 to 23.8)	-1.79 (-2.72 to -0.85)
Southern Sub-Saharan Africa	79802 (67747 to 95538)	110 (94 to 129.4)	0.37 (-0.04 to 0.77)	407700 (341430 to 497514)	570.7 (484.9 to 685.7)	-0.29 (-0.46 to -0.13)	8595 (5415 to 12848)	11.9 (7.6 to 17.7)	-0.32 (-1.45 to 0.82)
Tropical Latin America	2540250 (2130623 to 3009490)	1041 (872.8 to 1229.3)	1.66 (1.53 to 1.79)	9474074 (8114339 to 11187862)	3805.6 (3278 to 4483.6)	0.22 (0.15 to 0.29)	200063 (126946 to 299227)	80.4 (51.1 to 119.7)	0.26 (-0.2 to 0.72)
Western Europe	5213990 (4455521 to 6122601)	825.8 (703.3 to 973.7)	0.26 (0.11 to 0.41)	18016694 (15824985 to 21165825)	2844.3 (2454.3 to 3387.2)	-0.75 (-0.83 to -0.68)	373349 (243198 to 543429)	59.7 (37.9 to 86.7)	-0.73 (-1.26 to -0.19)
Western Sub-Saharan Africa	190886 (158890 to 228070)	52.3 (45.1 to 60.9)	0.69 (0.09 to 1.3)	1102747 (904235 to 1358653)	317.9 (268.7 to 379.2)	-0.27 (-0.5 to -0.04)	24038 (15081 to 36021)	6.8 (4.3 to 10)	-0.25 (-1.82 to 1.33)

95%UI: Uncertainty interval; YLD: Years lived with disability; ASR: Age-standardized rate; EAPC: Estimated annual percentage change; SDI: Sociodemographic index.

to 2019, the most pronounced increased and decreased changes in the number of prevalent cases were observed in the United Arab Emirates (581%, 496% to 669%) and Latvia (-27%, -34% to -21%), respectively (Supplementary Table 2). The largest ASPR increases were observed in India (EAPC = 1.64, 1.54-1.74) and New Zealand (EAPC = 0.90, 0.82-0.97) from 1990 to 2019. During this period, a total of 185 countries or territories experienced decreases in the GABD ASPR, with the largest ASPR decrease occurring in Peru (EAPC = -2.88, -2.98 to -2.78) (Supplementary Table 2).

At the national level, the highest GABD ASYR was observed in the United Kingdom [136.51 per 100000 population (86.400199.28)] in 2019, followed by Honduras [128.37 per 100000 population (82.34-192.13)] and Italy [115.01 per 100000 population (72.88-168.92)], whereas Cabo Verde [5.23 per 100000 population (3.28-7.82)], Sao Tome and Principe [5.97 per 100000 population (3.72-9.08)], and Nigeria [6.19 per 100000 population (3.89-9.17)] had the lowest. From 1990 to 2019, the most pronounced increased and decreased changes in the number of YLDs were observed in the United Arab Emirates (571.7%, 447.4% to 723.5%) and Latvia (-27.4%, -34.3% to -20.0%), respectively (Supplementary Figure 1 and Supplementary Table 3). The largest ASYR increases were observed in India (EAPC = 1.66, 0.94-2.38) and New Zealand (EPC = 0.93, 0.42-1.44) between 1990 and 2019. A total of 185 countries or territories experienced an ASYR decrease during this period, with the largest decrease occurring in Peru (EAPC =-2.86, -3.56 to -2.14) (Supplementary Table 3).

SDI regions levels

From 1990 to 2019, the number of incident cases showed an increasing trend in both sexes, and since 2018, it began to decrease in the high- and middle-SDI quintiles. The numbers of incident cases increased in males and females across high-middle-SDI, low-, and low-middle-SDI quintiles from 1990 to 2019. In 2019, the highest increases in incident cases were observed in the middle-SDI regions [16564482.19 (95%UI: 13930955.39-19595424.22)], whereas the greatest decreases were observed in the low-SDI regions [1253652.02 (95%UI: 1062794.93-1455528.77)] (Figure 2A). From 1990 to 2019, the numbers of prevalent and YLD cases showed an increasing trend in both sexes in all SDI quintiles. The highest numbers of prevalent cases were observed in the middle-SDI regions [64380264.74 (95%UI: 54532616.95-77437635.83)], and the lowest prevalence cases were observed in low-SDI regions [6977018.13 (95%UI: 5870056.77-8390276.97)] in 2019. The highest YLD cases were observed in the middle-SDI regions [1360202.73 (95%UI: 858233.94-2012102.01)], and the lowest YLD cases were observed in the low-SDI regions [147359.90 (95%UI: 93751.28-214884.56)] in 2019. From 1990 to 2019, low-SDI regions showed a more prominent increase in incident cases (4.6-fold) than high-SDI regions (Figure 2A). Low-SDI regions showed a more prominent increase in prevalent (4.2-fold) and YLD cases (4.2-fold) than high-middle-SDI regions.

From 1990 to 2019, GABD ASIR in females decreased from 1990 in the high-SDI and high-middle-SDI regions and increased after 1995. This was then followed by a decline in 2010, an increase after 2015, and a decrease again after reaching its peak in 2018. ASIR in males decreased from 1990, began to increase after 1995, and decreased after reaching its peak in 2018. In the high-middle-SDI regions, ASIR in males decreased in 1990, began to increase after 1994, and

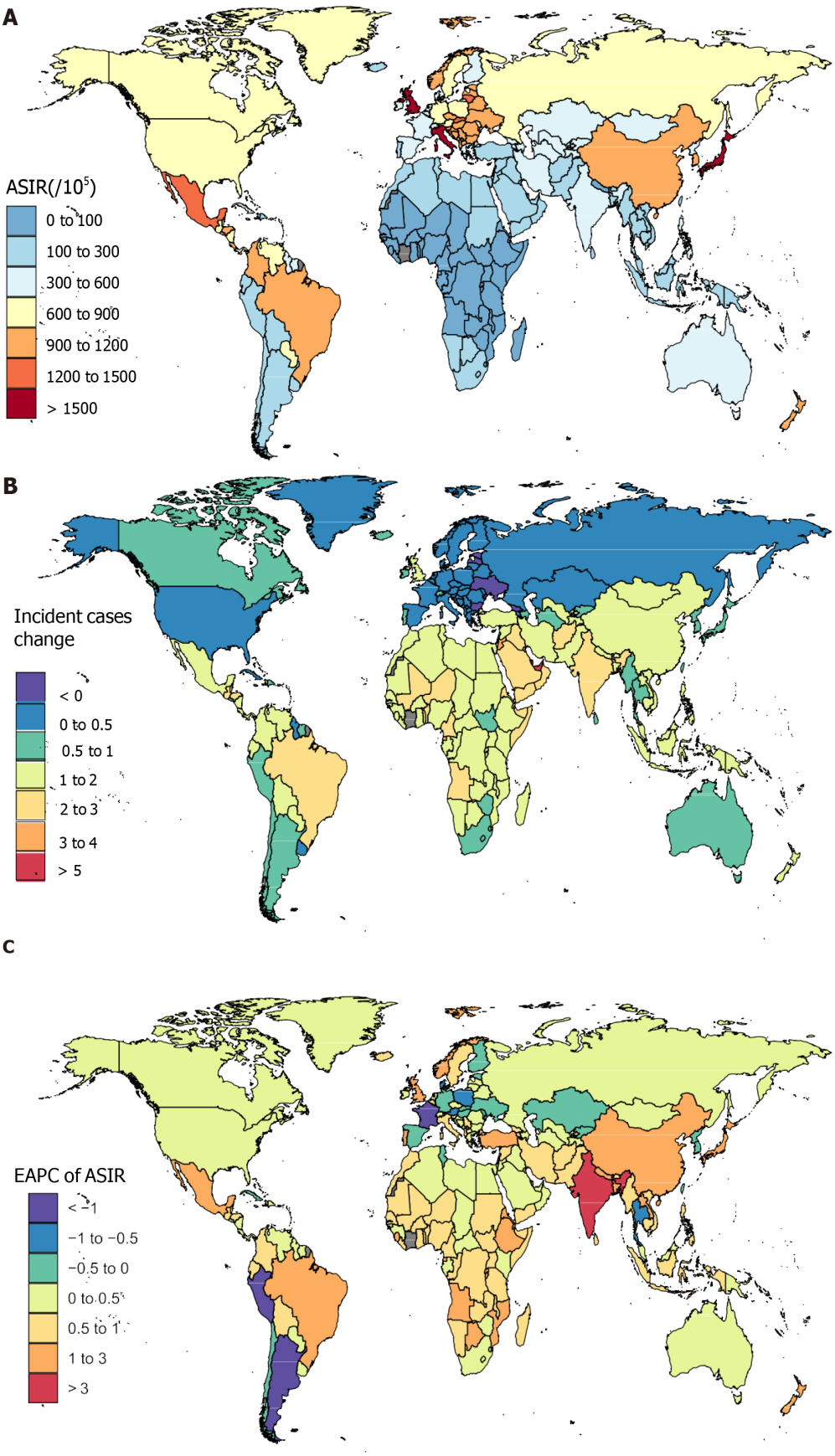

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Figure 1 The global disease burden of gallbladder and biliary diseases for both sexes in 204 countries and territories. A: The age-standardized incidence rate (ASIR) of gallbladder and biliary disease (GABD) in 2019; B: The relative change in incident cases of GABD between 1990 and 2019; C: The estimated annual percentage change of GABD ASIR from 1990 to 2019. ASIR: Age-standardized incidence rate; EAPC: Estimated annual percentage change.

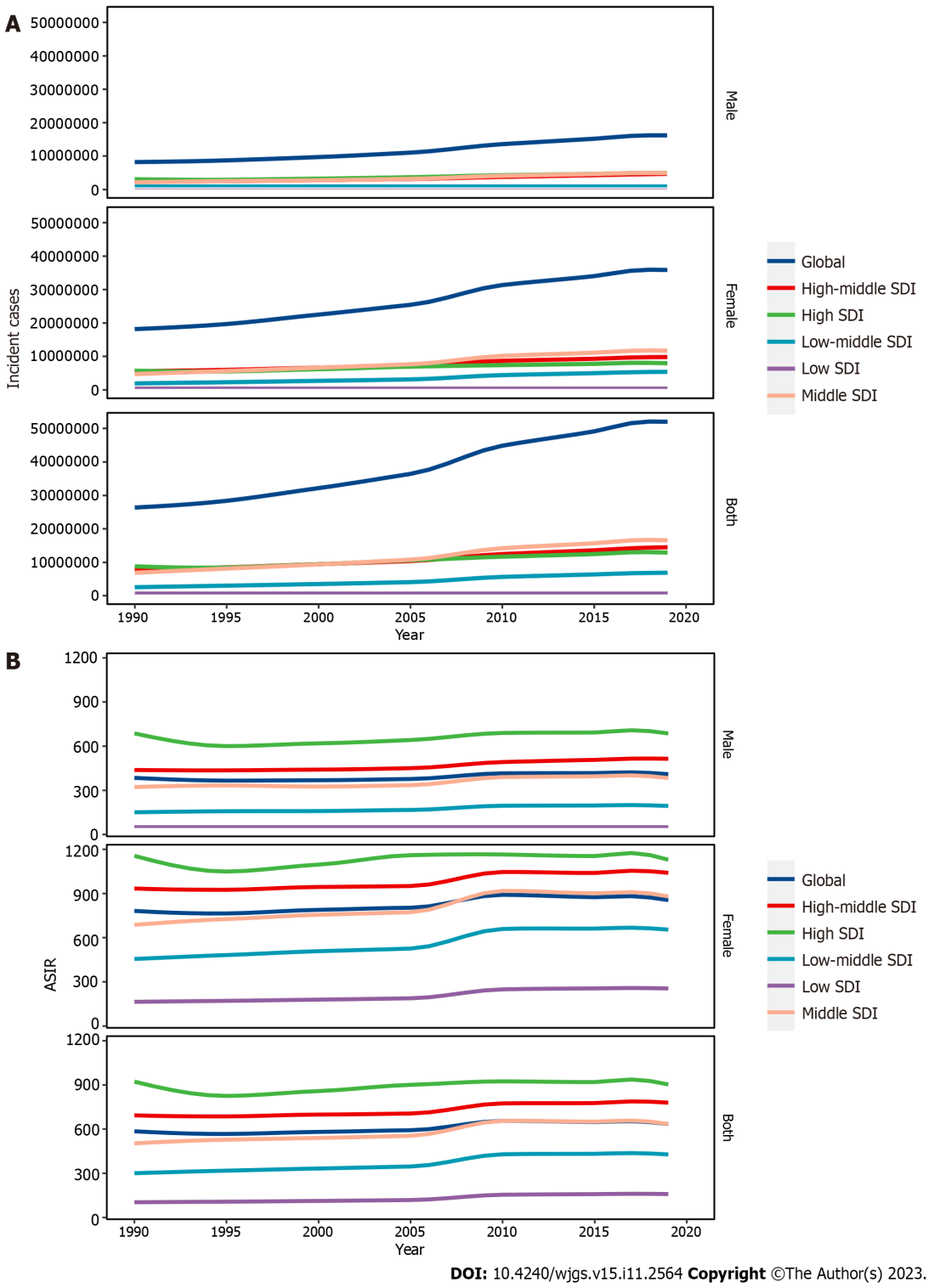

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Figure 2 Incident cases, age-standardized incidence rate of gallbladder and biliary diseases at global and regional level from 1990 to 2019. A: Incident cases; B: Age-standardized incidence rate. ASIR: Age-standardized incidence rate; SDI: Sociodemographic index.

decreased after reaching its peak in 2018. However, the ASIR in low-SDI and low-middle-SDI regions showed an increasing trend in both sexes. In the middle-SDI regions, ASIR in females increased in 1990, and decreased after reaching its peak in 2010. Furthermore, ASIR in males increased in 1990 and decreased after reaching its peak in 2017. The highest ASIR was observed in high-SDI regions [903 (95%UI: 776-1051)], and the lowest ASIR was observed in low-SDI regions [159 (95%UI: 136-184)] in 2019 (Figure 2B).

In the high-SDI regions, GABD ASPR in females decreased in 1990, increased after 1996, declined in 2000, increased again after 2011, declined again in 2015, and increased again in 2017. ASPR in males decreased in 1990 and began to increase after 2011. In the high-middle-SDI quintile, the ASPR in both sexes gradually declined. In the low-SDI, low-middle-SDI, and middle-SDI regions, ASPR in females and males decreased in 1990, began to increase after 2005, and then decline after 2010. The highest ASPRs were observed in high-SDI regions [2697 (95%UI: 2368-3139)], and the lowest

ASPRs were observed in low-SDI regions [932 (95%UI: 797-1100)] in 2019.

The ASYR in females and males showed a decreasing trend in the high-SDI and high-middle-SDI regions. In the low SDI and low-middle-SDI regions, the ASYR in both sexes gradually decreased until 2005 and declined after reaching a maximum in 2010. The ASYR in males gradually decreased until 2006 and declined after reaching a maximum in 2011 in the middle-SDI regions. The ASYR in females gradually decreased until 2005 and declined after reaching a maximum in 2010 in the middle-SDI regions. The highest ASYR cases were observed in high-SDI regions [57 (95%UI: 36-82)], and the lowest ASYR cases were observed in low-SDI regions [19 (95%UI: 12-28)] in 2019. Compared to high-SDI regions, low-SDI regions showed a more prominent increase in ASIR (5.6-fold). The highest decrease in the absolute ASPR (2.0-fold) and ASYR (2.0-fold) was observed in the high-middle-SDI quintile. The greatest increasing changes in the absolute ASIR were observed in low-SDI regions [EAPC = 1.93 (1.55 to 2.30)] from 1990 to 2019. The greatest increasing ASPR and ASYR changes were observed in low-SDI regions [EAPC = 0.44 (0.30-0.58), and EAPC = 0.44 (-0.52 to 1.41), respectively], whereas the greatest decreasing ASPR and ASYR changes were observed in high-middle-SDI regions [EAPC = -0.89 (-0.97 to -0.82), and EAPC = -0.87 (-1.40 to -0.34), respectively] (Table 1).

21 GBD regions levels

In 2019, among the 21 GBD regions, the highest numbers of incident, prevalent, and YLD cases was observed in East Asia [18820462 (15683952-22743374), 67192927 (56174716-81311138), and 1421897 (901930-2106987), respectively] and South Asia [5531860 (4673821-6539869), 29094357 (23807912-35617849), and 605844 (385259-891933), respectively], and the lowest number of cases was Oceania [15180 (13016-17782), 103799 (87862-122072), and 2197 (1379-3315), respectively] and Central sub-Saharan Africa [45585 (38870-53756), 354446 (297954-420852), and 7621 (4751-11507), respectively] (Figure 3A, Supplementary Figures 2A and 3A). From 1990 to 2019, the changes in the numbers of incident, prevalent, and YLD cases differed between the 21 GBD regions, with the largest increases and decrease in all metrics observed in South Asia [2.62 (2.43-2.83), 1.58 (1.41-1.73), and 1.56 (1.39-1.72), respectively]. and Eastern Europe [0.06 (0.01-0.13), -0.14 (-0.19 to -0.08), and -0.14 (-0.19 to -0.08), respectively] (Figure 3B, Supplementary Figures 2B and 3B).

The highest ASIRs, ASPRs and ASYRs were observed in high-income Asia Pacific [1426.23 per 100000 population (1211.62-1670.16)], Central Latin America [4759.26 per 100000 population (4118.61-5625.11)], and Central Latin America [100.62 per 100000 population (64.01-149.28), respectively] (Figure 3C, Supplementary Figures 4A and 5A). From 1990 to 2019, the changes in the ASIR were also different between the 21 GBD regions, with most countries showing an increasing trend. The largest decrease was observed in the Southern Latin America [-107.9% (-137.0% to -78.7%)], whereas the largest increases were observed in South Asia [292.0% (264.0%-320.1%)] and Tropical Latin America [166.0% (152.6%-179.5%)] (Figure 3D). Furthermore, during this period, the changes in the ASPR and ASYR were also different between the 21 GBD regions, with most countries showing a decreasing trend. Andean Latin America [-206.4% (-216.9% to -196.0%) and -205.0% (-276.7% to -132.7%), respectively] had the largest decrease in ASPR and ASYR (Supplementary Figures 4B and 5B).

Age and sex patterns

Incident cases, prevalent cases, and YLDs varied by age and sex. In addition, these metrics increased with age, reaching their highest levels in the 50-54 age groups for both females and males. This was then followed by a decreasing tend with increasing age. The number of incident, prevalent, and YLD cases was higher in females than in males across all age groups. The ASIR, ASPR, and ASYR of GABD increased nonlinearly with increasing age and were higher in females than in males for all age groups in 2019 (Figure 4, Supplementary Figures 6 and 7).

Factors influencing EAPC

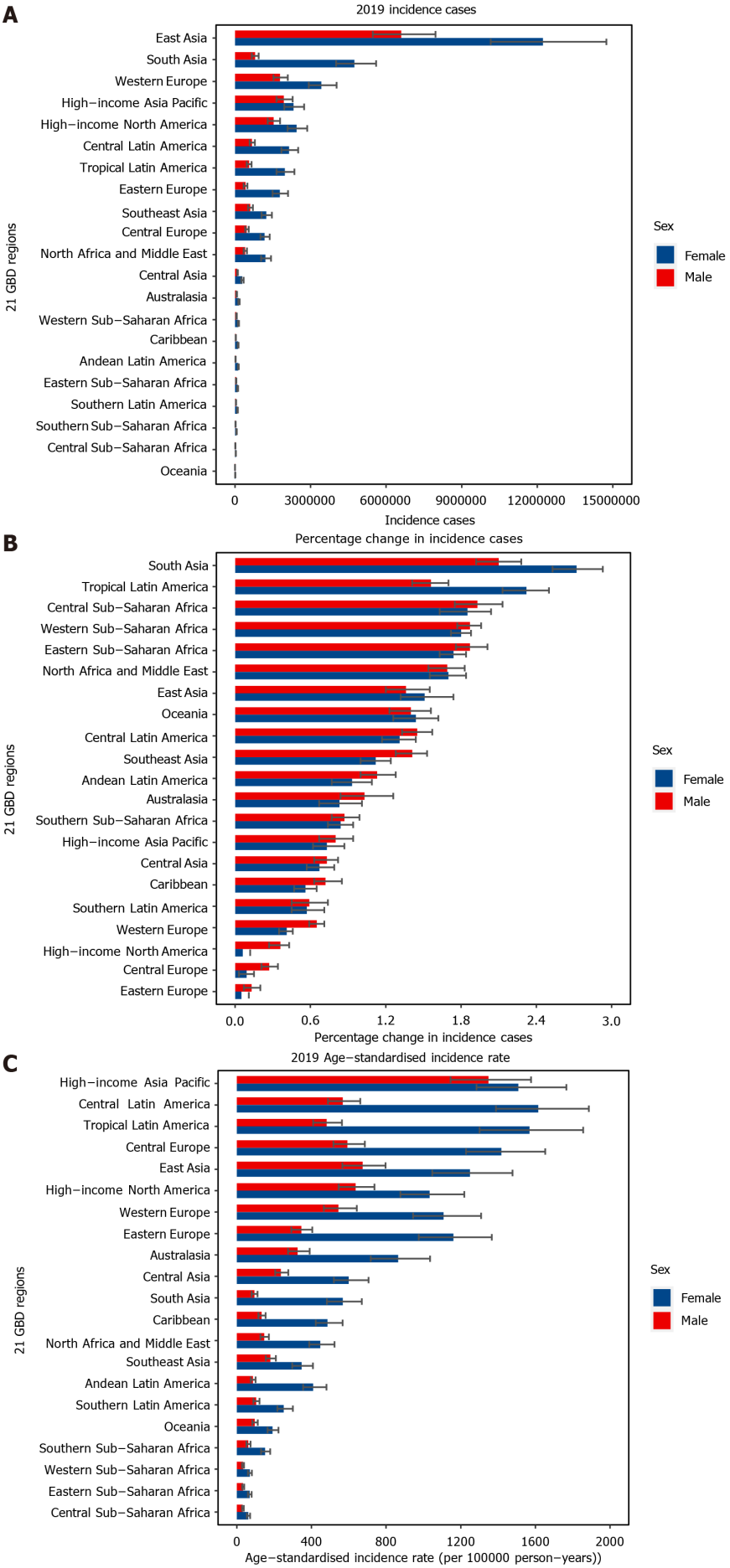
As shown in Figures 5A and B, EAPC was significantly associated with the ASIR (in 1990) and HDI (in 2021). A significant negative correlation (ρ = -0.46, P < 0.05) between the EAPC and ASIR (in 1990) was found when the baseline ASIR was ≤ 380 per 100000 population. However, no correlation was found when the ASIR was ≥ 380 per 100000 population (ρ = 0.08, P = 0.54). In addition, GABD negatively correlated (ρ = -0.24, P < 0.05) of GABD with the EAPC and HDI (in 2021).

Supplementary Figures 8A and B show that EAPC significantly associated with ASPR (in 1990) but not with HDI (in 2021). A significant negative correlation (ρ = -0.18, P < 0.05) between EAPC and ASPR (in 1990) was found when the baseline ASPR was ≥ 600 per 100000 population. Similarly, a significant negative correlation was found when ASPR was ≤ 600 per 100000 population (ρ = 0.32, P < 0.05). However, no correlation (ρ = -0.06, P = 0.39) between EAPC and HDI (in 2021) was observed.

Supplementary Figures 9A and B show that the EAPC significantly correlated with ASYR (in 1990) but not with HDI (in 2021). A significant negative correlation (ρ = -0.15, P < 0.05) between EAPC and ASYR (in 1990) was found when the baseline ASYR was ≥ 30 per 100000 population. In contrast, no correlation was found when the ASYR was ≤ 10 per 100000 population (ρ = -0.20, P = 0.24). However, no negative correlation (ρ = -0.07, P = 0.36) of GABD between EAPC and HDI (in 2021) were found.

DISCUSSION

In this study, we analyzed the temporal trends of GABD incidence, prevalence and YLDs at the global, regional, and national levels from 1990 to 2019. During this period, while the global GABD ASIR showed an increasing trend, ASPR and ASYR experienced an overall decreasing trend. By contrast, the number of incidents, prevalence, and YLD cases


A
2019 incidence cases
East Asia
South Asia
Western Europe
High−income Asia Pacific
High−income North America
Central Latin America
Tropical Latin America
Eastern Europe
Southeast Asia
Central Europe
North Africa and Middle East
Central Asia
Australasia
Western Sub−Saharan Africa
Caribbean
Andean Latin America
Eastern Sub−Saharan Africa
Southern Latin America
Southern Sub−Saharan Africa
Central Sub−Saharan Africa
Oceania
21 GBD regions
0
3000000
6000000
9000000
12000000
15000000
Incidence cases
Sex
Female
Male
B
Percentage change in incidence cases
South Asia
Tropical Latin America
Central Sub−Saharan Africa
Western Sub−Saharan Africa
Eastern Sub−Saharan Africa
North Africa and Middle East
East Asia
Oceania
Central Latin America
Southeast Asia
Andean Latin America
Australasia
Southern Sub−Saharan Africa
High−income Asia Pacific
Central Asia
Caribbean
Southern Latin America
Western Europe
High−income North America
Central Europe
Eastern Europe
21 GBD regions
0.0
0.6
1.2
1.8
2.4
3.0
Percentage change in incidence cases
Sex
Female
Male
C
2019 Age−standardised incidence rate
High−income Asia Pacific
Central Latin America
Tropical Latin America
Central Europe
East Asia
High−income North America
Western Europe
Eastern Europe
Australasia
Central Asia
South Asia
Caribbean
North Africa and Middle East
Southeast Asia
Andean Latin America
Southern Latin America
Oceania
Southern Sub−Saharan Africa
Western Sub−Saharan Africa
Eastern Sub−Saharan Africa
Central Sub−Saharan Africa
21 GBD regions
0
400
800
1200
1600
2000
Age−standardised incidence rate (per 100000 person−years))
Sex
Female
Male

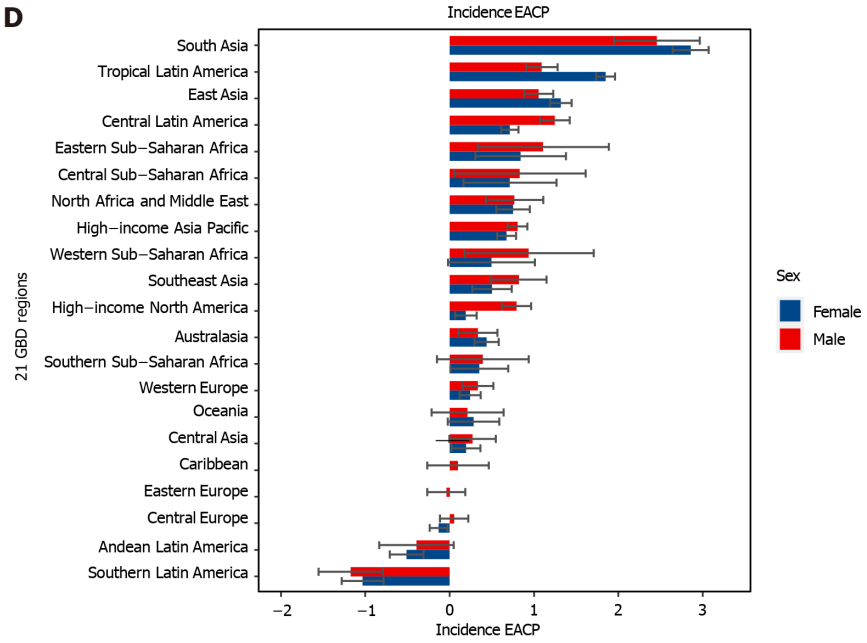


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Figure 3 Levels and trends in all ages incidence cases of gallbladder and biliary diseases across 21 global burden of diseases regions by sex. A: The incidence cases of gallbladder and biliary disease (GABD) in 2019; B: The percentage change in incidence cases of GABD from 1990 to 2019; C: The age-standardized incidence rate (ASIR) of GABD in 2019; D: The percentage change in ASIR of GABD from 1990 to 2019. GBD: Global Burden of Diseases Study; EAPC: Estimated annual percentage change.

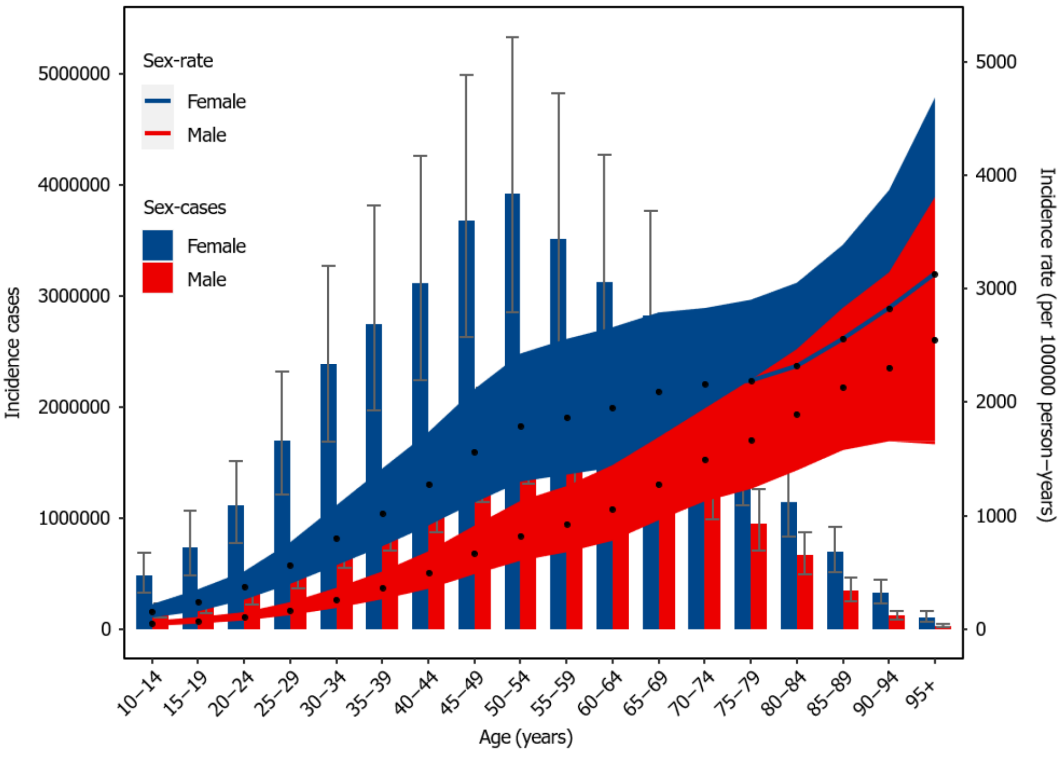

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Figure 4 Age-specific numbers and rates of incident cases of gallbladder and biliary diseases by sex, 2019.

increased from 1990 to 2019. Consistent with previous research[13], this study suggested that GABD is one of the major causes of burden globally. In contrast to prior research[13], our study specifically analyzed the number, ASIR rate, and YLD rate of GABD globally and in 5 SDI regions, 21 GBD regions, and 204 countries. In addition, we employed the EAPC method to quantify GABD trends over the last 30 years.

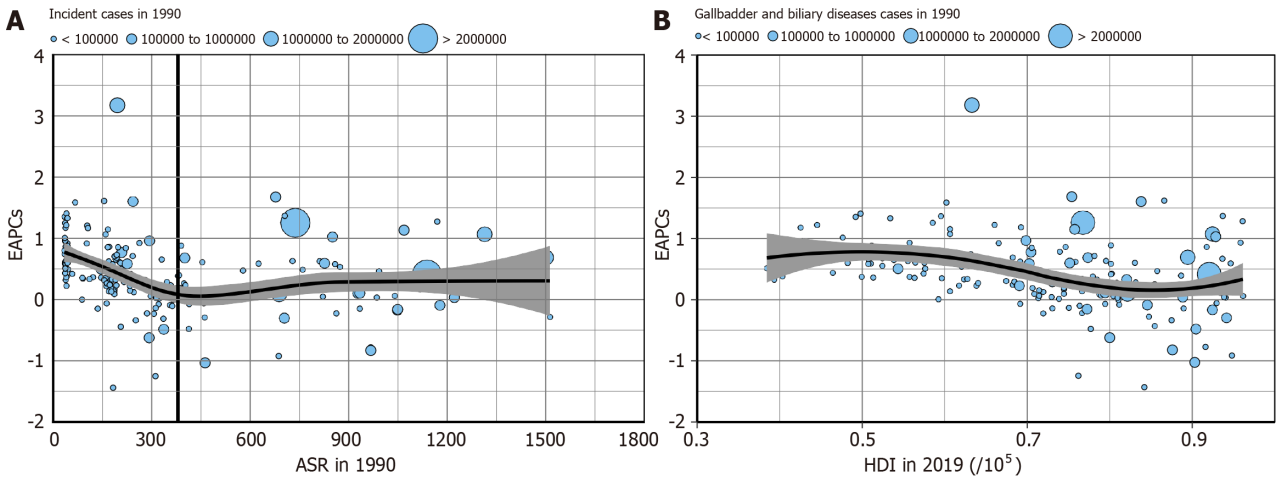

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Figure 5 The correlation between estimated annual percentage change and gallbladder and biliary diseases age-standardized incidence rate in 1990 and human development index in 2021. A: The correlation between estimated annual percentage change (EAPC) and gallbladder and biliary diseases age-standardized incidence rate in 1990; B: The correlation between EAPC and human development index (HDI) in 2021. The circles represent countries that were available on HDI data. The size of the circle is increased with the cases of gallbladder and biliary diseases. The ρ indices and *P*-values presented in (A) and (B) were derived from Pearson correlation analysis. EAPC: Estimated annual percentage change; HDI: Human development index; ASR: Age-standardized rate.

From 1990 to 2019, both the number of incident cases and ASIR experienced an increasing trend globally, which may be attributed to the growing global population and increased life expectancy in recent years. We found that high-SDI regions had the highest ASIR, ASPR, and ASYR in 2019. However, low-SDI regions experienced the greatest increased in ASIR and an increasing trend in ASPR and ASYR. In addition, high-SDI regions had the lowest increased in ASIR. These finding indicated that the GABD burden may be related to factors such as obesity, dietary patterns, and physical exercise. The prevalence of obesity was higher in high-SDI regions than in low-SDI regions, which could be attributed to food shortages in the latter[24,25]. However, healthy dietary patterns in high-SDI regions, such as decreased consumption of preserved and salted foods and increased consumption of fresh fruits and vegetables, and physical exercise, may have contributed to a lower increase in ASIR from 1990 to 2019. On the contrary, improved diets, such as increased consumption of fat and high-calorie foods, in low-SDI regions may have led to an increasing trend of ASIR in GABD[26]. Laparoscopic cholecystectomy (LC) is the gold standard procedure for the treatment of acute gallbladder diseases. However, nonsurgical management includes endoscopic ultrasound-guided gallbladder drainage (EUS-GBD) and percutaneous transhepatic gallbladder drainage (PT-GBD) was also a choice for the treatment of acute cholecystitis. However, in some low-SDI regions, they can only conduct open cholecystectomy and cannot performed less invasive LC, EUS-GBD, and PT-GBD due to limited medical resources, which may lead to higher prevalence and YLDs[27,28]. Furthermore, we found that high-income Asia Pacific countries, including Japan, have a high ASIR of GABD, whereas the least developed regions such as the sub-Saharan Africa region (*e.g.*, Somalia and Guinea) had lower ASIR in 2019. From 1990 to 2019, developing countries, such as India and Brazil, showed a high increasing trend[29]. Our study was consistent with this finding that developed countries or regions have a higher GABD burden. Taken together, these results suggested that developed countries had higher ASIR, whereas developing and underdeveloped regions and countries showed a higher increasing trend.

Previous studies have identified age, gender, obesity, and diabetes mellitus, among other, as the risk factors for GABD [4]. In this study, we observed an increased incidence rate of GABD in females compared to males across all age groups, with the highest rates observed in the 50-54 age group. These findings indicated that the GABD burden is greater in females than in males and that new cases are more common in the middle-aged population. A previous study reported a cumulative incidence of 0.81% in females and 0.66% in males in Italy, in line with our study[30]. The standardized incidence rate of GABD was higher in female (≥ 15 per 100000 person-years) than in male (≤ 6 per 100000 person-years) children from 1993 to 2012[31]. This could be attributed to the following factors. First, estrogen increases the secretion of biliary cholesterol and reduces gallbladder contraction, leading to an increased cholesterol saturation in bile, which can promote gallstone formation and the development of biliary diseases. Females have higher levels of estrogen than males, particularly during their reproductive years, which may explain their increased susceptibility to GABD[32,33]. Moreover, previous animal studies have shown that female reproductive hormones stimulate the formation of gallstones by increasing bile cholesterol excretion and endogenous synthesis[33]. Second, females are more likely to be obese, have a sedentary lifestyle, and consume a high-fat diet, all of which are risk factors for GABD[25,30]. A high-fat diet may result in reduced fecal excretion of bile acids, thus decreasing the bile acid pool and promoting bile supersaturation, leading to lithogenicity[34]. Third, pregnancy increases the risk of developing gallstones due to changes in progesterone and estrogen levels and increased pressure on the gallbladder from the growing uterus[4,35,36]. Finally, genetic factors may make females more susceptible to GABD than males[37]. Given the higher burden of GABD in females, we recommend that greater attention be paid to the prevention and treatment of GABD in this population by implementing interventions to reduce this disparity. Ascorbic acid supplementation, treating iron deficiency, and increasing vegetable consumption are potential interventions that may reduce the GABD burden in females[38].

A study indicated that the incidence of stone formation is almost twice as high in females compared to males, and this disparity decreases after menopause[39]. In the 20-24 age group, the GABD incidence rate in females is 3.5 times higher than in males; however, this ratio decreases to 1.2 times in the 85-89 age group, which represents the smallest gender gap. This finding confirms the reduction in the incidence gap between males and females after menopause The highest incidence rates of GABD in both males and females were observed in the 95-plus age group, highlighting the higher risk of gallstone disease in older individuals[40,41]. Therefore, more attention and resources, such as regular health check-ups, encouraging physical activity, improving their dietary habits, and managing chronic conditions such as diabetes and metabolic syndrome, should be allocated to elderly individuals to prevent GABD.

Although Li *et al*[13] evaluated the relationship with SDI, to our knowledge, our study was the first to assess the correlation between ASIRs and EAPCs and HDI in each country. Compared with SDI, HDI is more widely used for comparing levels of human development between countries and over time. From 1990 to 2019, the amplitudes of ASIR variations were significantly negatively associated with the baseline ASIRs. This finding indicated that countries with lower ASIRs in 1990 may have experienced an increase in ASIRs. This may be attributed to limited public health resources, which prevented these countries from prioritizing GABD prevention over other public health disease prevention initiatives. Furthermore, our analysis found a significant negative association between EAPC and HDI in 2019 for GABD, suggesting that countries with higher HDI in 2019 experienced a lower burden of GABD. For instance, developed nations such as France and Denmark exhibited a decrease in GABD.

The present study has several limitations. First, the robustness and reliability of GBD estimates for GABDs could be influenced by the quality and quantity of the modeling data. Due to the absence or sparsity of data from some countries and territories, the burden estimates relied heavily on the modeling data. Therefore, large-scale population-based health surveys should be conducted to obtain more representative and comprehensive data for better estimation. Second, variations in prevention strategies, diagnostic criteria, and management policies in different countries and territories were not evaluated, which may cause substantial discrepancies even among countries with similar HDI. Third, stratification by anatomic location of GABD was not provided in the GBD 209 estimates. Therefore, to improve the accuracy of the estimates, data including information on anatomic subtypes should be obtained, if feasible. Fourth, the potential variations in the effects of prevention and management strategies between low- to middle-SDI and high-SDI countries were not considered in this study. Therefore, future studies exploring these variations to better understand their impacts on the disease burden are warranted.

CONCLUSION

GABD remains a major global public health challenge, and the disease burden varies geographically. Between 1990 and 2019, the number of cases and ASIR of GABD increased globally. In addition, although GABD ASPR and ASYR decreased, the number of prevalent and YLD cases increased. The highest burden of GABD was observed in low-SDI regions, and the burden was significantly higher among females than males. We believe that the findings of this study will provide insight into the global disease burden of GABD and assist policymakers in formulating effective policies to mitigate modifiable risk factors.

ARTICLE HIGHLIGHTS

Research background

Gallbladder and biliary disease (GABD) remains a major global public health challenge, and the disease burden varies geographically.

Research motivation

From 1990 to 2019, the number of cases and age-standardized incidence rate (ASIR) of GABD increased globally. What's more, although GABD age-standardized prevalence rate (ASPR) and age-standardized lived with disability (YLD) rate (ASYR) decreased, the number of prevalent and YLD cases increased.

Research objectives

We aim to research the incidence, prevalence, and YLDs of GABD and their temporal trends from 1990 to 2019 in 204 countries and territories at the global, regional, and national levels. The association between estimated annual percentage changes (EAPCs), ASIRs, ASPRs, and ASYRs (1990), and human development index (HDI) (2021) were also assessed at the national level.

Research methods

The study used EAPC to quantify the age-standardized incidence of GABD by region, sex, and cause. ASIRs, ASPR and ASYR. Socio-demographic index (SDI) was used to analyze the relationship between GABD burden and national development level.

Research results

In 2019, the incident cases of GABD were 52003772, with an ASIR of 634.32 per 100000 population. Globally, the number of incident cases and ASIR of GABD increased 97% and 58.9% between 1990 and 2019. Although, the ASPR and ASYR decreased from 1990 to 2019, the number of prevalent and YLDs cases increased. The highest ASIR was observed in Italy, and the highest ASPR and ASYR was observed in United Kingdom. The highest burden of GABD was found in low-SDI region, and the burden in female was significantly higher than males. A generally negative correlation (ρ = -0.24, P < 0.05) of GABD with the EAPC and HDI (in 2021) were observed for ASIR. What's more, no correlation in ASPR (ρ = -0.06, P = 0.39) and ASYR (ρ = -0.07, P = 0.36) of GABD with the EAPC and HDI (in 2021) were observed, respectively.

Research conclusions

From 1990 to 2019, the number of cases and ASIR of GABD increased globally. What's more, although GABD ASPR and ASYR decreased, the number of prevalent and YLD cases increased. The highest burden of GABD was observed in low-SDI regions, and the burden was significantly higher among females than males.

Research perspectives

We believe that the findings of this study will provide insight into the global disease burden of GABD and assist policy-makers in formulating effective policies to mitigate modifiable risk factors.

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FOOTNOTES

Co-first authors: Zhong-Zhuan Li and Lin-Jing Guan.

Co-corresponding authors: Guo-Qing Ouyang and Hai-Xing Jiang.

Author contributions: Li ZZ, Guan LJ, Jiang HX, and Ouyang GQ conceived, designed and refined the study protocol; Li ZZ, Guan LJ, Ouyang R, and Chen ZX were involved in the data collection; Li ZZ, Guan LJ, and Ouyang GQ analyzed the data; Li ZZ, Guan LJ, and Jiang HX drafted the manuscript; All authors were involved in the critical review of the results and have contributed to, read, and approved the final manuscript. Li ZZ and Guan LJ contributed equally to this work as co-first authors; Ouyang GQ and Jiang HX contributed equally to this work as co-corresponding authors. The reasons for designating Ouyang GQ and Jiang HX as co-corresponding authors are threefold. First, the research was performed as a collaborative effort, and the designation of 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-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, Ouyang GQ and Jiang HX contributed efforts of equal substance throughout the research process. The choice of these researchers as 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 Ouyang GQ and Jiang HX as co-corresponding authors of is fitting for our manuscript as it accurately reflects our team's collaborative spirit, equal contributions, and diversity.

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SYSTEMATIC REVIEWS

Risk and management of post-operative infectious complications in inflammatory bowel disease: A systematic review

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Abstract

BACKGROUND

Indications for surgery in inflammatory bowel disease (IBD) include treatment-refractory disease or severe complications such as obstruction, severe colitis, dysplasia, or neoplasia. Infectious complications following colorectal surgery in IBD are significant, particularly in high-risk patients.

AIM

To gather evidence on risk factors associated with increased post-operative infectious complications in IBD and explore management strategies to reduce morbidity and mortality.

METHODS

A systematic review adhering to PRISMA-P guidelines was conducted. MEDLINE (PubMed) and Cochrane Library databases were searched using specific keywords. Inclusion criteria encompassed studies involving patients with IBD undergoing abdominal surgery with infectious complications within 30 d postoperatively. Exclusion criteria included patients under 18 years and non-infectious complications. Selected papers were analyzed to identify factors contributing to post-operative infections. A narrative analysis was performed to provide evidence-based recommendations for management. The data were then extracted and assessed based on the *Reference Citation Analysis* (https://www.referencecitation-analysis.com/).

RESULTS

The initial database search yielded 1800 articles, with 330 articles undergoing full-text review. After excluding duplicates and irrelevant papers, 35 articles were included for analysis. Risk factors for post-operative complications in patients with IBD included hypoalbuminemia, malnutrition, preoperative abscess, and obesity. Perioperative blood transfusion was associated with increased infectious complications. Medications such as 5-aminosalicylates and immunomodulators did not increase post-operative complications. Corticosteroids were associated

with an increased risk of complications. Ustekinumab and vedolizumab showed similar rates of infectious complications compared to other treatments. The impact of minimally invasive surgery on post-operative complications varied across studies.

CONCLUSION
In order to reduce post-operative infectious complications in patients with IBD, a comprehensive approach involving multiple disciplines is necessary.

Key Words: Inflammatory bowel disease; Ulcerative colitis; Crohn's disease; Peri-operative infections; Infliximab.

Core Tip: This paper highlights the risk factors associated with post-operative infectious complications in patients with inflammatory bowel disease (IBD) undergoing abdominal surgery and explores management strategies to reduce morbidity and mortality. Key findings include the association of hypoalbuminemia, malnutrition, preoperative abscess, obesity, and perioperative blood transfusion with increased infectious complications. Corticosteroids were found to be a risk factor, while medications such as 5-aminosalicylates and immunomodulators did not increase complications. Ustekinumab and vedolizumab showed comparable rates of infectious complications to other treatments. The impact of minimally invasive surgery on complications varied. This paper emphasizes the importance of a comprehensive approach involving multiple disciplines to mitigate post-operative infections in IBD patients. Understanding these risk factors and implementing appropriate management strategies can improve outcomes in this patient population.

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INTRODUCTION

Inflammatory bowel disease (IBD) comprises ulcerative colitis (UC) and Crohn's disease (CD), which are chronic autoinflammatory conditions characterized by periods of relapses and remissions. UC affects the colon and rectum mucosa, while CD involves transmural inflammation in any part of the gastrointestinal tract. Both diseases can have extraintestinal manifestations affecting the skin, joints, and eyes. The prevalence of IBD has been increasing in newly industrialized countries due to dietary changes, such as the consumption of processed food and reduced intake of plant-based fibers[1,2].

IBD can cause debilitating physical and psychosocial symptoms, resulting in a significant economic burden associated with diagnosis, follow-up, and treatment[3]. Medical therapies, including 5-aminosalicylates (5-ASA), steroids, immunomodulators, small molecules, and biologics, aim to alleviate symptoms and achieve mucosal healing based on disease severity. Current treatment approaches focus on achieving endoscopic and clinical remission. However, despite the availability of various medical treatments, approximately 50% of CD patients and 16% of UC patients require surgery within 10 years of diagnosis[1,2].

Indications for surgery in IBD include treatment-refractory disease or severe complications such as obstruction, severe colitis, dysplasia, or neoplasia[4]. Infectious complications following colorectal surgery in IBD are significant, particularly in high-risk patients[5]. Early post-operative complications within 30 d of surgery include abdominal wound infection, anastomotic leakage, and pelvic sepsis. Late complications involve anastomotic leakage with pelvic sepsis, anastomotic stricture, and pouchitis following ileal pouch anal anastomosis (IPAA). These post-operative infectious complications contribute to increased morbidity, mortality, length of hospital stay, and healthcare costs. Several factors, including a patient's general status and medications, are associated with these infectious complications.

Surgical treatment in the emergency setting presents challenges due to limited time for multidisciplinary interventions and the typically unstable condition of patients. Indications for emergent surgery include lack of improvement with medical therapy within 48 to 96 h, hemodynamic instability with multi-organ failure, bleeding, toxic megacolon, bowel obstruction, perforation, and intra-abdominal abscess (IAA) in CD. In these cases, an open approach is recommended for faster procedures, as laparoscopy may pose difficulties in handling the bowels. Damage control surgery is typically performed, involving bowel resection, stapling off both ends, laparotomy, and subsequent return to the intensive care unit for continuous care. A second-look laparotomy is performed within 24-48 h for bowel inspection and consideration of a stoma or anastomosis.

Laparoscopic surgery is indicated for hemodynamically stable patients with local expertise available. It is known to reduce the length of hospital stay and infectious complications[6]. An open port insertion technique should be employed to prevent perforation of distended bowel loops, with a multi-port approach being preferable to a single-port approach. In the acute setting, subtotal colectomy with ileostomy is recommended. The decision on anastomosis after intestinal

resection depends on the patient's clinical status and the indication for surgery. In patients with a compromised general health status in the emergency setting, resection with a stoma is preferred. In elective scenarios, side-to-side anastomosis is preferred.

Elective surgery is indicated for cases of chronic active or steroid-dependent colitis that is refractory to conventional or biological maintenance therapies. Subtotal colectomy with subsequent IPAA is the treatment of choice for UC. For CD, the surgical treatment options depend on the affected intestinal segment and presence of complications, including subtotal colectomy with ileorectal anastomosis, total proctocolectomy, segmental bowel resection, and strictureplasty[7]. In elective settings, these procedures can be performed laparoscopically as one- or two-stage procedures, with a single-stage procedure being an option for selected patients.

Post-operative infectious complications in IBD include surgical site infections (SSI) and extra-abdominal infections. SSI encompasses superficial wound infections, deep wound infections affecting the fascia, and organ space infections such as abdominal and pelvic abscesses and anastomotic leakage. Diagnosis of SSI is based on the presence of purulent tissue discharge from the incision site or drain, isolation of organisms from culture of fluids or tissue obtained from the incision site, and the presence of an open wound with signs and symptoms of infection. Extra-abdominal infections include pneumonia and urinary tract infections. These infections can lead to life-threatening complications such as sepsis and septic shock[5].

One risk factor associated with patient general status is serum albumin[5,8]. Serum albumin plays a crucial role in wound healing and collagen synthesis at the anastomotic site. Hypoalbuminemia adversely affects the immune system, increasing the risk of post-operative morbidity. Preoperative correction of hypoalbuminemia is necessary, and in some cases, a diverting colostomy or ileostomy may be warranted. Early assessment and optimization of nutritional status are also essential[9,10].

The presence of preoperative abscess is another risk factor indicating advanced disease[5]. It independently increases the risk of intra-abdominal septic complications (IASC). In such cases, surgery should be avoided, and medical treatment, including percutaneous drainage with antibiotics, is preferred.

Additionally, obesity has been associated with an increased risk of post-operative complications in patients with IBD, possibly due to enhanced inflammatory processes[11].

Perioperative blood transfusion is an independent risk factor associated with adverse outcomes, suggesting the need for a restricted transfusion policy[12,13].

Certain medications used in the preoperative setting, such as steroids and biologics such as anti-tumor necrosis factor (TNF)-α, have been linked to increased post-operative infectious complications. A Cochrane systematic review by Law *et al*[14] reported higher rates of infectious complications in patients using steroids, likely due to impaired anastomotic healing and altered patient condition resulting from prolonged use[14]. The use of anti-TNF-α remains controversial. The Patients Undergoing Surgery to Identify Risk Factors for Postoperative Infection (PUCCINI) trial, a multicenter prospective cohort study, found no independent association between anti-TNF-α and increased infectious complications when used within 3 mo preoperatively or with detectable serum levels at the time of surgery[15]. However, the Cochrane review by Law *et al*[14] showed an overall increase in post-operative complications when anti-TNF-α was used in CD patients within 8 wk of surgery. Due to conflicting results, delaying surgery for patients who have taken their last dose of anti-TNF-α more than 4 wk before surgery is not justified.

For patients with risk factors, minimally invasive surgery offers advantages such as faster gastrointestinal function recovery, shorter hospital stays, and reduced scarring. Side-to-side stapled anastomosis following ileocolic resection is preferred, as it is associated with lower post-operative complications and a decreased need for reoperation due to restenosis[16,17].

This literature review aims to gather evidence on risk factors associated with increased post-operative infectious complications in IBD and explore management strategies to reduce morbidity and mortality.

MATERIALS AND METHODS

This systematic review was performed adhering to the PRISMA-P guidelines[18]. The research aimed to identify, select, and critically appraise the existing literature to explore similarities and differences related to the research question.

Search strategy

Searches were conducted in the MEDLINE (PubMed) and Cochrane Library databases using the following command: ("inflammatory bowel disease" OR "Crohn's disease" OR "Ulcerative Colitis") AND ("Surgery" OR "Postoperative" OR "operation") AND ("infection" OR "sepsis" OR "septic shock"). The retrieved data were categorized into different headings, including complications, medications, and risk factors. Papers unrelated to the topic were excluded, and a summary of the remaining papers was conducted, noting useful information and reviewing the selected articles. *Reference Citation Analysis* (https://www.referencecitationanalysis.com/) was used to supplement the search.

Study selection

Systematic reviews, meta-analyses, retrospective cohort studies, prospective cohort studies, and case-control studies were included in the selection process. The search was expanded to include "related articles" from PubMed. Papers were restricted to English and French languages, with no date of publication restriction. All selected papers were manually searched.

Inclusion criteria

The study included patients diagnosed with IBD (UC or CD) based on clinical, endoscopic, radiological, or histopathological evidence. These patients underwent elective or emergent abdominal surgery related to the disease in primary, secondary, or tertiary healthcare settings. Participants were aged over 18 years and experienced infectious complications within 30 d of surgery. Infectious complications encompassed organ space infections (IAA), pneumonia, SSI, deep SSI, anastomosis leakage, sepsis, fistula, or urinary tract infections.

Exclusion criteria

Patients under 18 years of age and pregnant women were excluded. Complications other than infectious ones were also excluded. Additionally, infectious complications occurring after 30 d of surgery were not included.

Analysis

The selected papers were analyzed to address key questions regarding post-operative infectious complications, the impact of medications used to relieve inflammation on their occurrence, and other patient and surgery-related factors contributing to these complications. The results were combined in a narrative analysis to provide evidence-based factors responsible for an increase in post-operative infectious complications and recommendations for their management to reduce morbidity and mortality.

RESULTS

The PUBMED database and its related searches yielded an initial pool of 1800 articles. After screening the titles and abstracts, 1470 articles were deemed irrelevant and excluded. The remaining 330 articles underwent full-text review, resulting in the exclusion of 150 articles. Further removal of duplicates was conducted, leaving 70 articles for eligibility assessment. Among these, 35 articles were excluded either due to duplication or unavailability of full text. Figure 1 summarizes the search strategy. The results will be categorized into three main areas: Risk factors for post-operative complications, medications used to treat IBD and their association with post-operative complications, and the impact of the choice of surgical procedure on the occurrence of surgical complications.

Risk factors for post-operative complications in patients with IBD

Hypoalbuminemia: Retrospective studies conducted by Nguyen *et al*[8], Liu *et al*[19], Ghoneima *et al*[4], and Yang *et al*[20] have consistently shown that hypoalbuminemia is associated with an increased risk of post-operative infectious complications. This finding was further supported by a meta-analysis of eight studies conducted by Huang *et al*[5]. Specifically, hypoalbuminemia can serve as a valuable predictive factor for post-operative infectious complications, including SSI (Table 1).

Malnutrition: This is a well-established risk factor for unfavorable post-operative outcomes[19]. It is defined by criteria such as weight loss exceeding 10%-15% within 6 mo, a body mass index (BMI) below 18.5 kg/m^2, or a serum albumin level below 30 g/L. In a study conducted by Yamamoto *et al*[10], two groups of patients with IBD were compared to identify risk factors for infectious complications following surgery. One group received biological therapy, while the control group did not. Both groups included malnourished patients based on the aforementioned criteria. The results showed that poor nutritional status significantly increased the incidence of infectious complications in the group receiving biological therapy. In the control group, although the rate of infectious complications was also higher among those with poor nutrition, it did not reach statistical significance. However, a multivariate analysis involving 140 patients revealed that poor nutrition remained an independent risk factor for post-operative infectious complications[10]. In a separate retrospective study conducted by Maeda *et al*[9], Onodera's Prognostic Nutritional Index (OPNI) was utilized to assess the nutritional status of patients with CD. The OPNI is calculated using two parameters: Serum albumin concentration and total lymphocyte count [OPNI: (10 × serum albumin g/dL) + (0.005 × Total lymphocyte count)]. The findings of this study also supported the notion that malnutrition is an independent risk factor for SSI[9]. These studies collectively underscore the importance of addressing and managing malnutrition as a critical factor in reducing post-operative infectious complications in patients with IBD (Table 2).

Preoperative abscess: One retrospective study and a meta-analysis were conducted to investigate the impact of preoperative abscess on post-operative outcomes. Morar *et al*[21] conducted a retrospective study spanning 6 years, involving 163 patients who underwent ileocolonic surgeries for CD. The primary objective of the study was to determine the incidence of IASC within 30 d following surgery. The presence of an IAA or intraoperative sepsis was identified as an independent risk factor for developing IASC[21]. These findings align with the results of a meta-analysis conducted by Huang *et al*[5], which included a comprehensive analysis of 12 studies[5]. The meta-analysis further supported the association between the presence of preoperative abscess and an increased risk of adverse post-operative outcomes (Table 3).

Obesity: Obese patients with IBD face a higher risk of experiencing post-operative infectious complications, including wound infections and SSIs, when compared to overweight or non-obese patients. This finding has been substantiated by a systematic review and meta-analysis conducted by Jiang. The analysis encompassed 15 retrospective observational studies, which involved a total of 2294 obese patients with IBD and 1119 overweight patients with IBD. Obesity was

Table 1 Hypoalbuminemia

Ref.	Year	Studies	Cohort	Results
Nguyen *et al*[8]	2019	Retrospective (2005-2012)	CD and UC	Moderate to severe hypoalbuminemia is associated with increased post-operative infection: CD 20% *vs* 13%, $P < 0.01$; UC 28% *vs* 15%, $P < 0.01$. In the case of severe hypoalbuminemia, increased risk of intra-abdominal infection, sepsis, shock and pneumonia; additional risk for urinary tract infection in UC
Huang *et al* [5]	2015	Meta-analysis: 8 studies for hypoalbuminemia: Cohort; case control; case control; case control; case control; case control; cohort; case control	CD	Hypoalbuminemia is a risk factor for infectious complications
Liu *et al*[19]	2017	Retrospective 2014-2016	CD	Increased surgical site infection with hypoalbuminemia
Ghoneima *et al*[4]	2019	Retrospective 2012-2017	CD	Hypoalbuminemia is a predictive risk for septic complications especially if associated with anemia and high CRP
Yang *et al* [20]	2012	Retrospective 1991-2010	CD	Preoperative albumin < 30 g/L increased the risk of post-operative complication by 2.6 fold

CD: Crohn's disease; UC: Ulcerative colitis; CRP: C-reactive protein.

Table 2 Malnutrition

Ref.	Year	Cohort	Studies	Results
Maeda *et al*[9]	2014	CD	Retrospective 2005-2013	Increased surgical site infections
Liu *et al*[19]	2017	CD	Retrospective 2014-2016	Increased surgical site infection
Yamamoto *et al* [10]	2019	UC and CD	Case control	Increased infectious complications postoperatively; this becomes significant when associated with biologics

CD: Crohn's disease; UC: Ulcerative colitis.

Table 3 Preoperative abscess

Ref.	Year	Cohort	Studies	Results
Morar *et al*[21]	2015	CD	Retrospective; single center	Increased risk of IASC
Huang *et al*[5]	2015	CD	Meta-analysis 12 studies	Preoperative abscess increases risk of IASCs

CD: Crohn's disease; IASC: Intra-abdominal septic complications.

defined as having a BMI greater than 30 kg/m^2, while overweight was defined as having a BMI between 25 and 30 kg/m^2. Patients with a BMI below 25 kg/m^2 were classified as normal weight. When comparing overweight patients to normal weight patients, the overweight group exhibited an increased risk of wound complications, such as incisional hernia and fasciothesis, as well as sepsis. However, the overall complications did not demonstrate a statistically significant difference between the two groups. Conversely, when comparing obese patients (including overweight individuals) to non-obese patients, there was a notable increase in overall post-operative complications, with a particular emphasis on wound infections and SSIs[11]. These findings emphasize the importance of considering obesity as a significant risk factor for post-operative infectious complications in patients with IBD (Table 4).

Perioperative blood transfusion: Perioperative allogenic blood transfusion has been identified as an independent risk factor for increasing infectious complications in patients undergoing surgery for IBD. Madbouly conducted a study involving 1202 patients with UC who underwent IPAA. Among the participants, 240 received allogenic blood transfusion within 2 wk prior to surgery or 48 h postoperatively (TRAN group), while 962 did not receive any transfusion (NON group). The study found that the overall incidence of infectious complications was significantly higher in the TRAN group compared to the NON group[12]. Similarly, Lan *et al*[13] conducted a cohort study involving 10100 patients with CD between 2005 and 2013. Of these patients, 611 received perioperative blood transfusion. The study evaluated the presence of various post-operative infections, including superficial, deep, organ or space SSIs, wound dehiscence, pneumonia, urinary tract infection, sepsis, or septic shock within 30 d of surgery. The findings revealed an increased rate of post-operative infections among patients who received intraoperative or post-operative blood transfusion. The

Table 4 Obesity

Ref.	Year	Cohort	Studies	Results
Jiang *et al* [11]	2022	IBD	Systematic review and meta-analysis of 15 retrospective observational studies	Obesity increases post-operative infection, wound infection and surgical site infection

IBD: Inflammatory bowel disease.

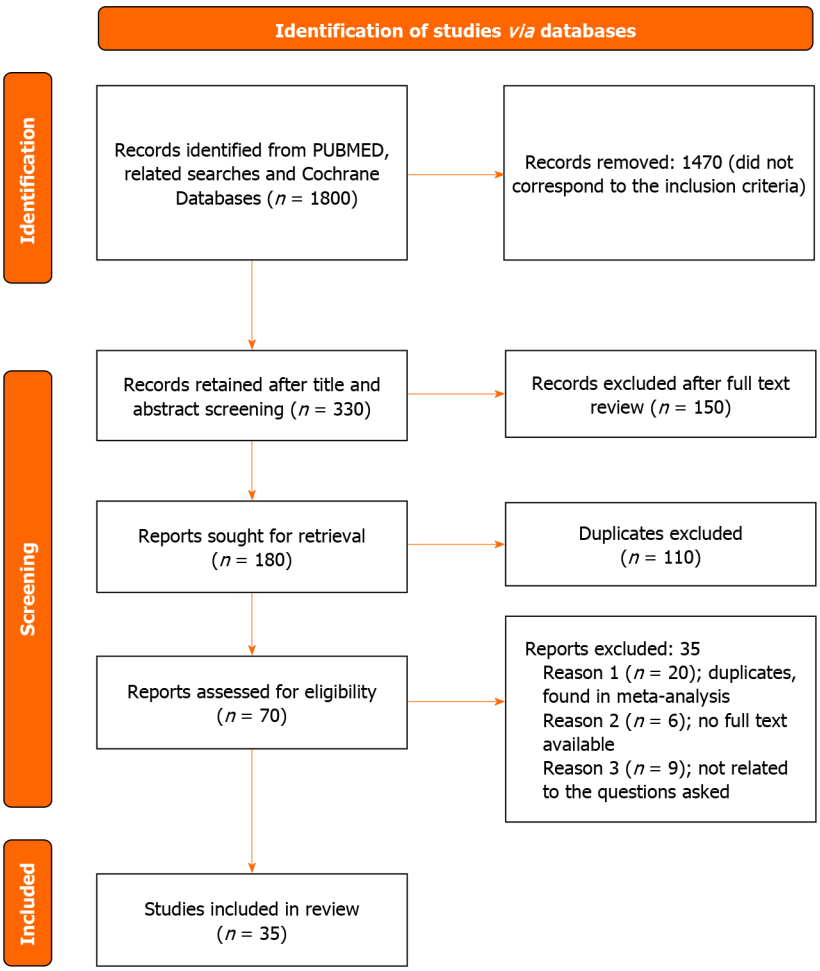

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Figure 1 PRISMA-P flowchart.

multivariate analysis, incorporating other statistically significant factors identified in the univariate analysis, showed an odds ratio (OR) of 2.1 [95% confidence interval (CI): 1.7-2.6] for post-operative infections associated with blood transfusion. Furthermore, the overall OR for infection was 1.3 (95%CI: 1.2-1.5) for each unit of blood transfused intraoperatively, indicating a dose-dependent relationship[13]. These studies highlight the potential detrimental effects of perioperative allogenic blood transfusion on infectious complications in patients with IBD undergoing surgery. The findings underscore the importance of considering alternative strategies to minimize the need for blood transfusion and mitigate the associated risks in this patient population (Table 5).

Medications used to treat IBD and post-operative complications

5-ASA: A comprehensive analysis conducted by Law *et al*[14] combined data from six studies to compare the use of 5-ASA *vs* controls in a cohort comprising patients with both UC and CD[14]. The findings of the study indicated that the use of 5-ASA did not result in an overall increase in infectious complications.

Immunomodulators: The study conducted by Aberra *et al*[22] did not observe an increase in post-operative infectious complications when using immunomodulators, specifically mercaptopurine/azathioprine (MCP/AZP), compared to placebo[22]. Similarly, a meta-analysis conducted by Law *et al*[14], which included 31 studies, found no statistically significant difference between the group receiving immunomodulators and the group receiving no immunomodulators

Table 5 Perioperative blood transfusion

Ref.	Year	Cohort	Study	Results
Madbouly *et al* [12]	2006	UC	Retrospective study	Increased overall infection
Lan *et al*[13]	2018	CD	Retrospective study: 10100 patients, 611 underwent blood transfusion	Increases rate of infection and this was dose-dependent

CD: Crohn's disease; UC: Ulcerative colitis.

[14]. The OR was 1.11, with a 95%CI ranging from 0.97 to 1.26.

Corticosteroids: The retrospective studies conducted by Aberra *et al*[22] and Nguyen *et al*[23], as well as the prospective study by the REMIND group and the meta-analysis by Subramanian *et al*[24] and Law *et al*[14], have consistently demonstrated an association between the preoperative use of corticosteroids and increased post-operative infectious complications[14,22-25]. Aberra *et al*[22] retrospectively investigated the risk of post-operative infection in 159 UC and CD patients undergoing elective bowel surgery. They compared patients who received corticosteroids and/or MCP/AZP prior to surgery with those who did not. The study concluded that preoperative corticosteroid use was associated with an increase in overall infectious complications, but this was not observed when MCP/AZP alone was used[22]. Nguyen *et al* [23] conducted a retrospective study using the ACS NSQIP database from 2005 to 2012, including 8260 CD patients and 7235 UC patients. This study provided a robust analysis due to its large sample size and inclusion of both UC and CD patients. The results showed an increase in post-operative infectious complications, such as sepsis, septic shock, intra-abdominal infection, and wound dehiscence, with the use of steroids prior to surgery[23]. The REMIND group, led by Fumery *et al*[25], performed a prospective study involving 209 CD patients who underwent ileocecal resections in nine nationwide French IBD centers from 2010 to 2014. They found that exposure to corticosteroids four weeks before surgery was associated with an overall increase in complications, including IASC and extra-abdominal septic complications[25]. Subramanian *et al*[24] conducted a meta-analysis of seven observational studies involving 1532 patients with IBD. The analysis revealed an increased rate of post-operative infectious complications when corticosteroids were used preoperatively, particularly when the dosage exceeded 40 mg/day[25]. Law *et al*[14] conducted a comprehensive analysis of 35 studies comparing the preoperative use of corticosteroids with no corticosteroid treatment in patients with IBD. The findings consistently showed an increase in overall infectious complications. Subgroup analyses focusing on UC and CD patients yielded similar results[14]. Overall, these studies provide strong evidence supporting the association between preoperative corticosteroid use and increased risk of post-operative infectious complications in patients with IBD (Table 6).

Anti-interleukin antibodies 12/23 (Ustekinumab): A meta-analysis was conducted to assess the use of Ustekinumab (UST) administered 12 to 16 wk prior to surgery in CD patients. The analysis included five retrospective studies in CD patients, comparing UST to different treatment modalities: UST *vs* anti-TNF in two studies; UST *vs* Vedolizumab (VDZ); UST *vs* a combination of anti-TNF, VDZ, or no biologics; UST *vs* no biologics. The meta-analysis found that the post-operative infectious complication rate in the UST group was comparable to that of the VDZ or anti-TNF groups. However, in the study comparing UST to no biologics, an increased incidence of intra-abdominal sepsis was observed in the UST group. This finding could potentially be attributed to the higher use of preoperative immunomodulators in that group and a larger number of patients in the no biologics group undergoing laparoscopic procedures. It is important to note that this meta-analysis had some limitations, including the inclusion of retrospective studies from small tertiary care referral centers and inconsistencies in the time period of preoperative UST administration across the studies. Nevertheless, the overall conclusion of the meta-analysis was that the preoperative use of UST appears to be safe when compared to VDZ or anti-TNF therapies[26] (Table 7).

Anti-integrin antibodies (VDZ and Natalizumab): Law *et al*[14] conducted a comprehensive meta-analysis involving 5 studies, which included a total of 307 patients receiving VDZ, 490 patients receiving anti-TNF drugs, and 535 patients who did not receive any biologic agents. The findings of this analysis indicated that there were no significant differences in the rates of overall infectious complications among individuals treated with VDZ compared to those receiving anti-TNF agents or those without biologic exposure[27]. Another meta-analysis conducted by Yung *et al*[28] included 4 studies encompassing a total of 1080 patients with either CD or UC. These patients were exposed to VDZ, anti-TNF agents, or no biologics. The results of the analysis showed that UC patients who were exposed to VDZ had a significantly lower overall post-operative complication rate compared to those exposed to anti-TNF agents. However, no significant differences were observed in terms of infectious complications or SSIs between VDZ and anti-TNF treatments in both UC and CD patients. Furthermore, no significant differences were found between VDZ and no biologic treatment in terms of infectious or SSIs [28]. Guo *et al*[29] conducted a larger-scale meta-analysis involving 12 studies and a total of 1925 patients with IBD. Among these patients, 709 received VDZ, while the remaining patients received either anti-TNF therapy, no biologics, other biological therapies, UST, or placebo. The analysis revealed an overall decrease in infectious complications; however, there was an increase in specific site infections[29]. These meta-analyses provide valuable insights into the comparative effectiveness of VDZ and other treatments in terms of infectious complications in patients with IBD (Table 8).

Table 6 Corticosteroids

Ref.	Year	Cohort	Study	Results
Aberra *et al*[22]	2003	UC and CD; 159 patients	Retrospective 1999-2000	Increased post-operative infection; No increase observed when 6 MCP/AZP were used
Nguyen *et al*[23]	2014	UC and CD; 15945 patients	Retrospective 2005-2012	Increased post-operative infection
Fumery *et al*[25] (REMIND group)	2017	CD; 209 patients	Prospective study 2010-2014	Increased overall post-operative complications, intra- and extra-abdominal septic complications
Subramanian *et al*[24]	2008	UC and CD	Meta-analysis; 7 studies	Increased infectious complications postoperatively and these increase with a dose of > 40 mg/day of corticosteroids
Law *et al*[14]	2020	UC and CD	Meta-analysis; 35 studies	Increased infectious complications and intra-abdominal infections

CD: Crohn's disease; UC: Ulcerative colitis; MCP/AZP: Mercaptopurine/azathioprine.

Table 7 Ustekinumab

Ref.	Year	Study	Patient cohort	Last dose taken	Overall results
Garg *et al*[26]	2021	Meta-analysis 5 retrospective studies; comparison of UST to either VDZ, anti-TNF or no biologics	Crohn disease	16 wk	Relative safety of UST use preoperatively

UST: Ustekinumab; VDZ: Vedolizumab; TNF: Tumor Necrosis Factor.

Table 8 Anti-integrin antibodies

Ref.	Year	Patient cohort	Studies comparing VDZ to either anti-TNF or no biologics	Last dose of VDZ	Overall results
Law *et al*[27]	2018	IBD: UC and CD	5 studies: UC only, retrospective; Retrospective; Retrospective; Post hoc analysis; Retrospective	Within 16 wk; Within 12 wk; Within 12 wk; N/A; Within 4 wk	No significant increase in post-operative infectious complications when compared to anti-TNF treatment or no biologics
Yung *et al*[28]	2018	IBD: UC and CD	4 studies: UC only, retrospective; CD only, retrospective; Retrospective; Retrospective	16 wk; 12 wk; 12 wk; 4 wk	No significant differences in infectious complications and SSI were noted in the group VDZ *vs* anti-TNF or no biologics; the results were similar in UC and CD patients
Guo *et al*[29]	2021	IBD: UC and CD	12 studies	4-16 wk	Decreased risk of overall post-operative infection complications; however, risk of infection at specific sites-SSI, deep SSI increased

CD: Crohn's disease; UC: Ulcerative colitis; IBD: Inflammatory bowel disease; SSI: surgical site infection; VDZ: Vedolizumab; TNF: Tumor Necrosis Factor.

Anti-TNF Therapy (infliximab, adalimumab, certolizumab): The findings regarding the use of anti-TNF therapy, specifically infliximab (IFX), in the perioperative period of patients with IBD are conflicting and have been subject to extensive research. In a meta-analysis conducted by Billioud *et al*[30] in 2013, it was concluded that preoperative use of anti-TNF agents slightly increased overall post-operative complications in patients with IBD, particularly infectious complications in patients with CD[30]. Similarly, Ahmed Ali *et al*[31], in a meta-analysis, also found a higher risk of complications in CD patients receiving preoperative anti-TNF agents[31]. Narula *et al*[32] (15 studies) and Yang *et al*[33] (10 studies) performed separate meta-analyses, both reporting higher rates of post-operative infectious complications in CD patients who received IFX within 30 d prior to surgery[32,33]. However, a Cochrane systematic review conducted by Law *et al*[14] in 2020 found that there was an increase in infectious complications in CD patients when anti-TNF therapy was used within 8 wk of surgery, but no such increase was observed when the therapy was initiated earlier than 8 wk before surgery[14]. On the other hand, Xu *et al*'s meta-analysis in 2019, which included 1407 patients with CD treated with IFX preoperatively, found no significant difference in the rates of infectious complications compared to 4589 patients who did not receive the treatment[34]. Yang *et al*[35] analyzed 13 studies involving 2933 UC patients receiving IFX and similarly found no correlation between IFX therapy and post-operative morbidity[35]. Rosenfeld *et al*[36] also reported similar results in patients with CD[36]. Most of these studies had limitations, such as being retrospective, conducted at single centers, having significant heterogeneity, and small sample sizes. There were also confounding variables that were not adequately controlled, such as concomitant medical therapy, with steroid use known to increase the risk of infectious

complications in patients with IBD in the perioperative period. To address the conflicting results and provide more definitive answers, the Postoperative Cohort of UC and CD PUCCINI trial was conducted. This prospective, observational, multicenter study aimed to determine whether anti-TNF therapy is an independent risk factor for post-operative infectious complications within 30 d of surgery in patients with IBD. The trial enrolled 947 patients from September 2014 to June 2017 who underwent abdominal surgery, with 382 patients receiving preoperative anti-TNF therapy (within 12 wk of surgery) and 573 patients who did not. Preoperative serum anti-TNF levels were measured and reported as either detectable or undetectable. The investigators found no significant increase in the risk of any infection or SSIs in the anti-TNF patients compared to those not receiving anti-TNF therapy. Secondary analyses also did not find any association between detectable serum anti-TNF levels and post-operative infections. The large prospective nature of the PUCCINI trial makes it a valuable source of information on the preoperative management of anti-TNF therapy in patients with IBD undergoing abdominal surgery[15] (Table 9).

Small molecules (Tofacitinib): Limited data are available regarding the perioperative use of tofacitinib, a new addition in the treatment of moderate to severe UC. Law *et al*[14], in their Cochrane systematic review, did not identify any eligible studies specifically assessing the perioperative use of tofacitinib[14]. Therefore, further research is needed to evaluate its efficacy and safety in the perioperative setting.

Minimally invasive surgery (laparoscopic surgery and robotic surgery) vs open surgery

Several studies have compared minimally invasive surgery to open surgery in the context of IBD, and the results have been conflicting.

Dasari *et al*[37] conducted a Cochrane systematic review that included 120 patients from 2 randomized controlled trials (RCTs). They found no significant differences in perioperative complications, such as wound infection, IAA, or anastomotic leak, when comparing minimally invasive surgery to open surgery. However, the study was limited by its small sample size[37].

In contrast, other studies have reported different findings. Lee performed a retrospective analysis from 2005 to 2009, including 1917 cases, of which 644 underwent laparoscopic procedures. The laparoscopic group had a significantly lower rate of post-operative sepsis compared to the open surgery group[38].

Patel *et al*[39] conducted a meta-analysis of 33 studies (including observational studies and RCTs) involving patients with CD undergoing surgery. The laparoscopic group (1079 patients) had a decreased risk of perioperative complications compared to the open surgery group (1221 patients). Subgroup analysis of 2 RCTs yielded similar results[39].

Wu *et al*[40] conducted a meta-analysis specifically focusing on patients with UC undergoing laparoscopic surgery. The overall complication rate was lower in the laparoscopic group compared to the open surgery group[40].

Lo *et al*[41] conducted a large retrospective cohort study involving 8644 patients with UC who underwent total abdominal colectomy without ileoanal anastomosis. They concluded that there was a decreased rate of post-operative sepsis/septic shock in both elective and emergent procedures in the laparoscopic group. Similar results were observed in patients on steroids who underwent laparoscopic surgery[41].

Another retrospective study by Hota *et al*[42] compared outcomes in open, laparoscopic, and robotic surgery for patients with CD. The rates of anastomotic leaks were higher in the open surgery group (5%) compared to the minimally invasive groups (laparoscopic: 3%, robotic: 7%), and post-operative wound infections were higher in open ileocecectomy (16%) compared to laparoscopic (9%) or robotic (7%) surgery[42].

Overall, the literature provides mixed evidence regarding the comparison of minimally invasive surgery to open surgery in IBD. Further research is needed to better understand the potential benefits and risks associated with each approach (Table 10).

DISCUSSION

Management of IBD requires a multidisciplinary approach, and post-operative infection is a significant concern that can impact patient outcomes. Hypoalbuminemia, characterized by serum albumin levels below 30 g/L, is a key factor associated with poor surgical outcomes in patients with IBD. It leads to tissue edema, collagen synthesis disorders, and impaired immune function, increasing the risk of complications[8]. Meta-analyses by Vincent *et al*[43] and Huang *et al*[5] have demonstrated the independent association between severe hypoalbuminemia and post-operative infectious complications in patients with IBD undergoing surgery[5,43].

Malnutrition is prevalent in the IBD population, particularly in patients with CD. Various factors contribute to malnutrition, including increased nutritional requirements, nutrient losses, reduced dietary intake, and intestinal inflammation[44]. The European Society for Clinical Nutrition and Metabolism (ESPEN) recommends regular screening for malnutrition and the use of tools like the OPNI to assess nutritional status[9]. Malnutrition has been identified as an independent risk factor for adverse post-operative outcomes, specifically SSIs[9,10,19].

Optimizing nutritional status is crucial to reduce these complications. ESPEN guidelines recommend delaying surgery for malnourished patients and initiating intensive artificial feeding. Enteral feeding is preferred over parenteral nutrition, with parenteral nutrition considered after seven days of enteral feeding if protein requirements are not met or if the enteral route is contraindicated[45].

Assessing and correcting preoperative nutritional needs can lead to improved surgical outcomes. However, the optimal timing for preoperative optimization with enteral or parenteral nutrition remains uncertain.

Table 9 Anti-tumor necrosis factor therapy

Ref.	Year	Cohort	Studies	Results
Billioud *et al* [30]	2013	UC an-d CD	Meta-analysis	Slight increase in overall post-operative complications, infectious complications in CD patients in particular
Ahmed Ali *et al* [31]	2014	CD	Meta-analysis	Increased wound infection and sepsis
Yang *et al*[33]	2014	CD	Meta-analysis; 10 studies	Modest increase in post-operative infectious complications
Narula *et al*[32]	2013	UC and CD	Meta-analysis; 15 studies	Modest increase in post-operative infectious complications
Law *et al*[14]	2020	UC and CD	Systematic review; Cochrane	Increased infectious complications in CD patients when treatment started within 8 wk of surgery
Yang *et al*[35]	2012	UC	Meta-analysis; 13 studies	No increase in post-operative early complications
Rosenfeld *et al* [36]	2013	CD	Systematic review and meta-analysis: 6 studies; 1159 patients	No significant difference in major complications noted between infliximab and control groups
Xu *et al*[34]	2019	CD	Meta-analysis: 14 studies for infectious complications	No increased risk of post-operative infection with preoperative infliximab
Cohen *et al*[15]	2019	UC and CD	Prospective	No increase in infection or SSI

CD: Crohn's disease; UC: Ulcerative colitis; SSI: Surgical site infection.

Table 10 Minimally invasive surgery (laparoscopic surgery and robotic surgery) versus open surgery

Ref.	Year	Cohort	Study	Results
Dasari *et al*[37]	2011	CD	Meta-analysis of 2 RCTs	No differences found in post-operative infectious complications
Lee *et al*[38]	2012	CD	Retrospective	Decreased sepsis in laparoscopic group
Patel *et al*[39]	2013	CD	Meta-analysis	Decreased infectious complications in laparoscopic group
Wu *et al*[40]	2010	UC	Meta-analysis and systematic review	Decreased total complication rate
Lo *et al*[41]	2021	UC	Retrospective	Decreased sepsis, even in patients on steroids
Hota *et al*[42]	2021	CD	Retrospective	Decreased anastomotic leaks and wound infections in minimally invasive group

CD: Crohn's disease; UC: Ulcerative colitis; RCT: Randomized controlled trials.

One of the complications of CD is spontaneous IAA with an incidence ranging from 10%-30%[46]. It remains an independent risk factor for post-operative IASC in patients undergoing intestinal resection. IASC is a term that collectively describes anastomotic leaks, pus collection, and intra-abdominal abscesses[47].

The pathophysiology of spontaneous IAA in CD patients is related to the transmural inflammatory nature of the disease, leading to deep fissuring, ulceration, and eventually perforation or fistulae in the bowel wall. The presence of exudates on the surface of the inflamed bowel attracts adjacent bowel loops, resulting in the formation of a localized walled-off abscess within an inflammatory mass[48].

IAA can arise from different regions such as the ileocecal region, presenting as a right iliac fossa mass, or from sigmoid disease or ileosigmoid fistula, presenting on the left side. Pelvic abscesses are also common and primarily originate from the terminal ileum or sigmoid disease.

The conventional treatment approach for IAA involves initial surgical incision and drainage of the abscess, followed by definitive resection of the diseased bowel or fistula. However, surgery performed in the presence of an abscess increases the risk of septic complications. Therefore, managing an IAA with active CD requires a multidisciplinary approach.

Percutaneous drainage of the abscess, guided by ultrasound or computed tomography, serves as a bridge to elective surgery and allows time for supportive treatment. It is indicated for technically accessible, well-defined abscesses where interventional radiology is available. Müller-Wille *et al*[46], in a prospective study of 25 patients, found a statistically significant difference in post-operative IASC between the group that underwent percutaneous abscess drainage and the group that had no preoperative drainage[46]. Similar results were reported by El-Hussuna *et al*[48] and Xie *et al*[49] in their retrospective studies[48,49].

Based on the evidence, preoperative percutaneous drainage combined with antibiotics should be the first-line treatment for preoperatively detected IAA in order to avoid emergency surgery. Elective surgery can be planned after an interval of 2-4 wk to allow for complete resolution of the abscess and preoperative optimization[48].

Obesity, defined by the World Health Organization as a BMI ≥ 30 kg/m², is prevalent among patients with IBD, ranging from 15%-40%[11]. Obesity has long been associated with poor post-operative outcomes in general surgical procedures. Jiang *et al*[11], in their meta-analysis of 15 studies on patients with IBD, found that compared to non-obese patients (including overweight), obese patients had an increased rate of post-operative infectious complications[11].

This can be attributed to the fact that obese patients are at an increased risk of other comorbidities such as diabetes, hypertension, renal impairment, and atherosclerotic vascular disease, which contribute to overall post-operative outcomes. Additionally, obesity affects the immune system and homeostasis.

Obesity is characterized by a state of low-grade inflammation with elevated C-reactive protein (CRP) levels, even in the absence of inflammation or infection. Cytokines, neuropeptides, and adipocytokines produced in adipocytes, macrophages, and lymphocytes infiltrating mesenteric fat play a role in this inflammatory state. The overexpression of these inflammatory mediators in mesenteric fat of CD patients may contribute to the pathogenesis of CD and the increased risk of infection[50,51].

Furthermore, the pharmacokinetics of drugs used in IBD management, such as 5-ASA, corticosteroids, anti-TNF agents, and anti-integrin drugs, may be altered in obese patients, resulting in reduced efficacy and lower drug concentrations[52]. These factors collectively contribute to the increased risk of post-operative infectious complications observed in obese patients.

Allogenic perioperative blood transfusion is commonly used in patients with IBD to correct anemia and manage intraoperative bleeding. However, the adverse effects of blood transfusion on post-operative outcomes, particularly infectious complications, are often overlooked. Studies by Madbouly *et al*[12] and Lan *et al*[13] demonstrated that perioperative blood transfusion is an independent risk factor for post-operative septic complications. Preoperative transfusion aimed at correcting anemia may improve overall health status and reduce complications. Restricting transfusion to patients with hemoglobin levels below 8 g/dL and addressing preoperative anemia with erythropoietin and iron can help minimize adverse outcomes[12,13].

Aminosalicylates, which inhibit macrophage chemotaxis and promote proliferation of intestinal epithelial cells, have shown no significant difference in overall post-operative infectious complications[14]. Therefore, the use of aminosalicylates in the preoperative period is considered safe.

Immunomodulators do not increase post-operative infection rates, as indicated by studies conducted by Law *et al*[14]. However, earlier studies showed an increase in infectious complications, which may be confounded by the severity of the disease. As a result, immunomodulators do not need to be stopped prior to surgery[14].

Corticosteroids, despite their immunosuppressive effects, are a matter of concern in the preoperative period due to their impact on wound healing and increased risk of post-operative infectious complications. Multiple studies, including the TREAT Registry, the REMIND Group, and meta-analyses by Subramanian *et al*[24] and Law *et al*[14], have demonstrated corticosteroids as a risk factor for adverse post-operative outcomes. It is advisable to either stop or taper the dose of corticosteroids to less than 40 mg/day[14,25,53].

UST, approved for CD treatment, has shown comparable rates of infectious complications to VDZ and anti-TNF agents in a meta-analysis by Garg *et al*[26] The role of UST in the treatment algorithm for IBD is still being determined[26,54,55].

VDZ, which targets leukocyte migration, has not shown a significant difference in post-operative infection rates compared to anti-TNF agents or other biologics in meta-analyses. Pharmacokinetic studies suggest that a longer withdrawal period is not necessary for patients on VDZ, and surgery can be safely performed even when the drug was administered every 8 or 4 wk after induction[29,56,57].

The perioperative use of anti-TNF agents in patients with IBD has yielded mixed results in retrospective, prospective, and meta-analyses studies. The prospective PUCCINI trial, along with other meta-analyses, indicates the safety of anti-TNF agents in the preoperative setting. Delaying surgery is unnecessary if the last infusion dose was received more than 4 wk prior to surgery, considering the drug's clearance time (half-life: 7-14 d). Measuring serum anti-TNF levels preoperatively does not provide additional benefit[15].

Limited data exist on the perioperative use of Tofacitinib in patients with IBD. Guidelines from the 2017 ACR/AAHKS recommend stopping Tofacitinib 7 d prior to surgery and resuming it 14 d after surgery. However, in urgent or emergent cases, surgery should not be delayed to avoid increased post-operative complications[58].

In the pre-biological era, a significant proportion of patients with IBD required intestinal surgery within 10 years of diagnosis, with high rates of recurrence[3,58]. However, the introduction of biological therapies has led to a decline in the surgery rate[3,58]. Nonetheless, a considerable number of CD and UC patients still require surgery within 1 year[2,3,58]. The choice of surgical approach depends on the patient's condition and disease severity[3,58]. Emergency settings often result in extended intestinal resection and a higher stoma rate, which are associated with increased post-operative infections[3,58]. Laparoscopic surgery is the preferred option but should be limited to specialized tertiary centers with expertise in this field[3,58]. Minimally invasive surgery offers advantages such as shorter hospital stays, improved cosmetic outcomes, reduced morbidity, and faster recovery[3,58]. Side-to-side anastomosis has shown superior outcomes compared to end-to-end anastomosis in terms of reducing post-operative anastomotic leaks[16,17,37,59]. Furthermore, it is crucial to consider the potential presence of differential diagnosis and extra-intestinal manifestations and its impact on the overall management of these patients[3,58-64]. Additionally, post-operative CD recurrence typically presents on a continuum from histologic findings to endoscopic findings to clinical presentation, underscoring the need for early monitoring and tailored pharmacologic therapy[3]. The advancement of effective medical treatments for CD has led to a tendency to consider surgical treatment as a last resort, but the choice between surgery and medical treatment is a patient's personal preference under the guidance of the treating physician[2,3,58-60,65].

To guide the care of patients with IBD, an algorithm proposed by Zangenberg *et al*[65] can be followed. This involves assessing the patient's hemodynamic status, diagnosing disease severity using flexible sigmoidoscopy, considering medical therapy with IV corticosteroids and subsequent anti-TNF agents in cases of systemic toxicity, withdrawing

corticosteroids if surgery is required, and reserving routine antibiotic administration for cases involving percutaneous drainage of an intra-abdominal abscess[65].

There are some recently added medications in the therapeutic arsenal for the treatment of patients with IBD, and their role in post-operative complications is yet to be determined. Ozanimod, a selective sphingosine-1-phosphate receptor modulator, has shown effectiveness in inducing and maintaining remission in patients with UC[66,67]. Risankizumab, an interleukin (IL)-23 p19 inhibitor, has demonstrated efficacy as induction and maintenance therapy for CD and is also being investigated as a therapy for UC[68-70]. Upadacitinib, an oral selective Janus kinase inhibitor, has shown promise in both induction and maintenance therapy for CD and UC[71,72]. These recent clinical trials highlight the expanding treatment options for patients with IBD, potentially improving their quality of life and disease management.

CONCLUSION

In conclusion, in order to reduce post-operative infectious complications in patients with IBD, a comprehensive approach involving multiple disciplines is necessary. The analysis of the literature highlights several key strategies: Firstly, preoperative optimization should include nutritional risk screening to identify and address any malnutrition. Additionally, addressing preoperative anemia is important to minimize the need for blood transfusion during or after surgery. Steroids should be gradually withdrawn and tapered to reach physiological levels prior to the surgical procedure. Regarding medication management, thiopurines can be safely used in patients with IBD. While biological agents appear to be relatively safe, it is advisable to plan the timing of surgery in relation to the last dose of the drug.

ARTICLE HIGHLIGHTS

Research background

Inflammatory bowel disease (IBD), including ulcerative colitis and Crohn's disease, are chronic auto-inflammatory conditions marked by relapses and remissions, with increasing prevalence due to dietary changes. These diseases bring substantial physical, psychosocial, and economic burdens. Despite various available treatments, a significant proportion of patients require surgery within a decade of diagnosis. Surgical intervention poses challenges, particularly in emergency cases, with infectious complications being a major concern. Surgical approaches range from open procedures for emergencies to laparoscopic techniques for stable patients, aiming to minimize complications and hospital stays.

Research motivation

The study's focus stems from the escalating IBD prevalence, the inadequacies of current treatments leading to surgeries, and the associated risk of post-operative infections. Addressing these issues is vital to enhance patient outcomes and reduce healthcare costs. Identifying risk factors linked to infections post-surgery, such as patient general status, preoperative abscess presence, obesity, and perioperative blood transfusions, is pivotal for preemptive measures. Understanding the impact of medications, such as steroids and anti-tumor necrosis factor (TNF), on post-operative complications is essential for informed treatment decisions. The significance lies in improving surgical practices and patient management, subsequently curbing infection-related morbidity and mortality.

Research objectives

This study primarily aims to investigate risk factors contributing to heightened post-operative infectious complications in IBD patients undergoing surgery. By systematically analyzing patient factors such as serum albumin levels, preoperative abscess presence, obesity, and perioperative blood transfusion requirements, the study aims to elucidate their role in infection susceptibility. Furthermore, the research delves into the impact of medications, specifically steroids and anti-TNF-α, on post-operative infection rates. Achieving these objectives will furnish insights into preoperative assessment and optimization strategies, influencing surgical decisions and post-operative care. Ultimately, the study's significance lies in refining surgical practices and patient care to ameliorate post-operative morbidity, mortality, and overall quality of life in IBD patients undergoing surgery.

Research methods

The systematic review adhered to PRISMA-P guidelines and aimed to explore existing literature related to post-operative infectious complications in IBD surgery. Searches were conducted in MEDLINE (PubMed) and Cochrane Library using keywords related to IBD, surgery, and infection. The retrieved data were categorized into complications, medications, and risk factors. Inclusion criteria encompassed patients aged over 18, diagnosed with IBD, undergoing abdominal surgery, and experiencing infectious complications within 30 d post-surgery. Exclusions included patients under 18, pregnant women, and complications occurring after 30 d. Selected studies included systematic reviews, retrospective/prospective cohort studies, and case-control studies in English and French. The chosen papers were analyzed to address questions about infectious complications, medication impact, and contributing factors. The results underwent narrative analysis to derive evidence-based factors leading to increased complications and offer management recommendations.

Research results

The research outcomes contribute significant insights into post-operative complications in patients with IBD. The study encompassed a rigorous selection process, yielding 70 articles for analysis. Categorizing results into distinct domains highlighted the critical aspects of risk factors and medication effects on post-operative outcomes. The investigation identified several noteworthy risk factors, including hypoalbuminemia, malnutrition, preoperative abscess, obesity, and perioperative blood transfusion. Hypoalbuminemia consistently emerged as a predictor of infectious complications, emphasizing its clinical relevance. Malnutrition, determined by weight loss and serum albumin, consistently heightened the risk of complications, highlighting its importance in patient management. Further analysis revealed the impact of medications. 5-aminosalicylates demonstrated no overall increase in infectious complications. Immunomodulators, corticosteroids, and anti-interleukin antibodies displayed varying associations with post-operative outcomes. While some studies suggested increased infectious risks, others contradicted these findings. Additionally, anti-TNF therapy's impact showed conflicting results, possibly influenced by timing and patient population. The inclusion of large prospective trials such as Patients Undergoing Surgery to Identify Risk Factors for Postoperative Infection contributed valuable evidence regarding the safety of anti-TNF therapy. Comparing minimally invasive (laparoscopic and robotic) open surgery yielded mixed findings. While some studies reported reduced complications with minimally invasive approaches, others showed no significant differences. The field benefits from these insights, although further research is needed to clarify the optimal surgical approach. Overall, this research advances the understanding of post-operative complications in IBD patients. By comprehensively addressing risk factors and medication effects, the study guides clinical decision-making and highlights areas for future investigation.

Research conclusions

This study contributes significant insights into the management of post-operative complications in patients with IBD. The findings underscore the importance of addressing risk factors such as hypoalbuminemia and malnutrition, which have been consistently associated with increased infectious complications following surgery. The study highlights the critical role of optimizing nutritional status, utilizing tools like Onodera's Prognostic Nutritional Index, and considering interventions such as percutaneous drainage for managing intra-abdominal abscesses. Obesity's impact on immune function and altered pharmacokinetics of IBD medications emphasize its association with post-operative infectious complications. The research also provides clarity regarding the use of various medications, including corticosteroids, immunomodulators, and biologics, in the preoperative period, offering valuable guidance for clinical practice.

Research perspectives

Future research should delve deeper into the dynamics of nutritional interventions to mitigate infectious complications in IBD patients undergoing surgery. Longitudinal studies exploring the influence of personalized nutritional strategies on surgical outcomes are warranted. Additionally, further investigation into the role of emerging therapies such as ustekinumab, vedolizumab, and tofacitinib in the perioperative setting is essential. Prospective studies with larger cohorts are needed to definitively determine the impact of anti-TNF agents on post-operative infections in IBD patients. The ongoing evolution of IBD management, including the emergence of new medications like ozanimod, risankizumab, and upadacitinib, necessitates comprehensive studies to ascertain their effects on surgical outcomes. Future research directions should aim to refine treatment algorithms, considering individual patient characteristics and disease severity, ultimately enhancing patient care and minimizing post-operative complications.

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FOOTNOTES

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SYSTEMATIC REVIEWS

Effect of perioperative branched chain amino acids supplementation in liver cancer patients undergoing surgical intervention: A systematic review

Kwan Yi Yap, HongHui Chi, Sherryl Ng, Doris HL Ng, Vishal G Shelat

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Abstract

BACKGROUND

Branched chain amino acid (BCAA) supplementation has been associated with favourable outcomes in liver malignancies requiring definitive resection or liver transplantation. Currently, there are no updated systematic reviews evaluating the efficacy of perioperative BCAA supplementation in patients undergoing surgery for liver cancer.

AIM

To evaluate the efficacy of perioperative BCAA supplementation in patients undergoing surgery for liver cancer.

METHODS

A systematic review of randomized control trials and observational studies was conducted on PubMed, Embase, Cochrane Library, Scopus, and Web of Science to evaluate the effect of perioperative BCAA supplementation compared to standard in-hospital diet, in liver cancer patients undergoing surgery. Clinical outcomes were extracted, and a meta-analysis was performed on relevant outcomes.

RESULTS

16 studies including 1389 patients were included. Perioperative BCAA administration was associated with reduced postoperative infection [risk ratio (RR) = 0.58 95% confidence intervals (CI): 0.39 to 0.84, *P* = 0.005] and ascites [RR = 0.57 (95%CI: 0.38 to 0.85), *P* = 0.005]. There was also a reduction in length of hospital stay (LOS) [weighted mean difference (WMD) = -3.03 d (95%CI: -5.49 to -0.57), *P* = 0.02] and increase in body weight [WMD = 1.98 kg (95%CI: 0.35 to 3.61, *P* = 0.02]. No significant differences were found in mortality, cancer recurrence and overall survival. No significant safety concerns were identified.

CONCLUSION

Perioperative BCAA administration is efficacious in reducing postoperative infection, ascites, LOS, and increases body weight in liver cancer patients undergoing surgical resection.

Key Words: Branched-chain amino acid; Liver cancer; Liver surgery; Nutritional supplement; Perioperative supplementation

Core Tip: Liver surgery has been associated with anthropometric disturbances and systemic catabolism, which can be improved with perioperative branched chain amino acid (BCAA) supplementation. However, it remains undetermined if the reported advantages of BCAA supplementation warrant routine perioperative use. This systematic review compares sixteen studies including 1389 patients. We found that perioperative BCAA supplementation was efficacious in reducing postoperative infection, ascites, length of hospital stay and increases body weight in liver cancer patients undergoing surgical resection.

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INTRODUCTION

Liver cancer is a global health issue with an estimated incidence of over 1 million cases by 2025[1]. Secondary liver cancer is more prevalent than primary liver cancer[2-4]. Lung and colorectal primaries account for half of the cases[5]. Hepatocellular carcinoma (HCC) accounts for approximately 90 percent of all primary liver cancers[1], and is the third most common cause of cancer mortality in the world[6]. Hepatectomy and liver transplant are the predominant curative treatments for liver cancers[7,8].

Although technological innovation and adoption of prehabilitation strategies have made hepatic surgery safe, there are still substantial morbidity risks, especially in cirrhotic patients[9]. Emerging evidence suggests that levels of branched chain amino acids (BCAAs), namely valine (Val), leucine (Leu) and isoleucine (Ile), are decreased in various forms of hepatic injury[10]. As important substrates for protein synthesis and regulators of protein turnover, BCAAs are involved in the pathophysiology of HCC by affecting gene expression, apoptosis, and regeneration of hepatocytes[10]. Additionally, advanced liver diseases are usually associated with systemic catabolism and depletion of muscle mass[11].

In rat model studies, BCAAs have been reported to promote hepatocyte proliferation and suppress growth of HCC. Kim *et al*[12] reported that after major hepatectomy, supplementation with BCAAs helps not only to maintain a stable plasma BCAA/aromatic amino acids ratio, but also promotes liver regeneration in rats. BCAAs delay progression of carbon tetrachloride(CCl_4)-induced chronic liver injury by attenuating hepatic apoptosis and stimulating the production of hepatocyte growth factors[13,14]. Miuma *et al*[15] reported that all three BCAAs down-regulate vascular endothelial growth factor (VEGF) expression during HCC development. Through these mechanisms, supplementation with BCAA may potentially suppress HCC development and accelerate post-surgical recovery. Furthermore, many studies have reported that preoperative malnutrition increases the risks of postoperative morbidity and mortality[16-19]. The benefits of administering BCAA to patients with HCC undergoing surgical treatment appear clear and promising.

Despite studies favouring BCAA supplementation, evidence of actual and measurable benefit is lacking. A 2012 Cochrane review showed that nutritional interventions for patients undergoing liver transplant did not offer benefits[20]. Another review demonstrated that oral BCAA supplementation improved 3-year mortality in HCC patients, but without impact on cancer recurrence[21]. In a meta-analysis on the use of supplemental BCAAs during the perioperative period in gastrointestinal cancer patients, Cogo *et al*[22] reported an improvement in morbidity from postoperative infection but no reduction in cancer recurrence.

Therefore, from current literature, it is unclear if the reported advantages of BCAA supplementation during surgical interventions in liver cancer warrant routine perioperative administration. Given these knowledge gaps, it is necessary to appraise the current evidence to determine if BCAA supplementation has beneficial impact on patients undergoing liver resection for various oncological indications. Thus, the aim of this systematic review and meta-analysis is to evaluate the role of perioperative BCAA supplementation in patients undergoing liver resection.

MATERIALS AND METHODS

Literature search

This systematic review was performed in accordance with the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) guidelines[23]. This review is part of a systematic review protocol registered on PROSPERO (CRD42022341658). Search of five databases (PubMed, Embase, Cochrane Library, Scopus, and Web of Science) was conducted on July 6, 2022 for articles published since inception up to 6 July 2022. Keywords related to the terms ("BCAA" or "Branched-chain amino acid" or "Leu" or "Val" or "Ile" or "amino acid"), [("liver" or "hepatic" or "hepatocellular") and ("carcinoma" or "cancer" or "malignancy" or "tumour" or "neoplasm")], ("resection" or "surgery" or "preoperative" or "perioperative" or "postoperative" or "hepatectomy" or "liver transplantation") were used in literature search. The full search strategy is available in Supplementary Table 1.

Study selection

Studies comparing outcomes of BCAA *vs* no supplementation in the perioperative period among liver cancer patients were considered for inclusion. Clinical trials and observational studies fulfilling the following criteria were included in the review: (1) Patients with a diagnosis of primary or secondary cancer in the liver; (2) patients underwent either hepatectomy or liver transplant; and (3) study has a control arm (placebo or normal usual diet). We excluded studies with patients undergoing liver surgery for other indications, or undergoing treatment procedures for liver cancer, such as radiofrequency ablation or transarterial chemoembolisation, without surgical intervention. All other studies were included, and details of source databases used in each included study were collected. The details of inclusion and exclusion criteria of this review according to the Population, Intervention, Comparison, Outcomes and Study framework are documented in Supplementary Table 2.

Data extraction

Three reviewers (Yap KY, Chi H, Ng S) independently performed the literature search and data extraction and all disagreements were resolved by mutual consensus. Data extracted include information on patient demographics (number of patients, age, sex, comorbid liver disease), cancer type and histopathology (HCC or metastatic or other cancers, tumour size and number, stage of cancer), surgical details (extent of hepatectomy, type of liver transplant) and mean duration of follow-up.

Risk of bias

Risk of bias and quality of studies were assessed. For randomised control trials (RCTs), quality control was performed by two co-authors (Yap KY and Chi H) using the Cochrane Risk of Bias tool 2[24], which assesses five domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. For observational studies, quality control was performed using the ROBINS-1 tool[25], which assesses seven domains in total: for pre-intervention (confounding and participation selection), during intervention (classification of intervention) and post-intervention (deviations from intended interventions, missing data, measurement of outcomes and selection of reported results) stages.

Outcomes of review

Primary outcomes of interest in this review were perioperative and oncological outcomes. Perioperative outcomes include postoperative morbidity, mortality, and length of stay (LOS). Oncological outcomes include recurrence and overall survival (OS). Secondary outcomes were changes in serum albumin, anthropometrics, and overall quality of life (QOL) in patients.

Postoperative infections were defined as any infectious complication arising in the postoperative period, including surgical site infections, septic complications, urinary tract infections, chest infections, liver abscesses and infected ascites. Ascites was defined as either new onset postoperative ascites or refractory ascites requiring diuretic agent for control. All-cause mortality was derived from OS in most studies, with a minimal follow-up time of 3 years (Supplementary Table 3). Recurrence was defined as reappearance of tumour with typical findings on imaging modalities. Changes in serum albumin were determined by comparing preoperative to postoperative measurements reported at 6- and 12-mo intervals. Anthropometrics reported by studies include body weight change, triceps skin-fold thickness and mid-arm circumference, but only body weight changes were included in this analysis.

Statistical analysis

Review Manager version 5.4 was used to pool and analyse results with reference to approaches from the Cochrane Handbook[26]. In studies without SD, *P*-values or confidence intervals (CI) were converted to SD. For studies without SD, *P*-values, and CI, we used the square-root of weighted mean variance of all other studies to estimate the SD[27]. Pre-intervention baseline imbalances were corrected using the simple analysis of change scores method for panel data and longitudinal outcomes. In studies reporting the outcome in different scales, a simple unit conversion was performed. Inverse variance was used to derive the pooled outcomes. The random-effects model was used in accounting for between-study variance. I^2 and τ^2 statistics were used to present between-study heterogeneity: Low heterogeneity (I^2 < 30%), moderate heterogeneity (I^2 30%-60%), and substantial heterogeneity (I^2 > 60%). Two-sided *P* value of < 0.05 was regarded as significant[26,28,29]. The statistical methods of this study were reviewed by Vishal G Shelat from National University of Singapore.

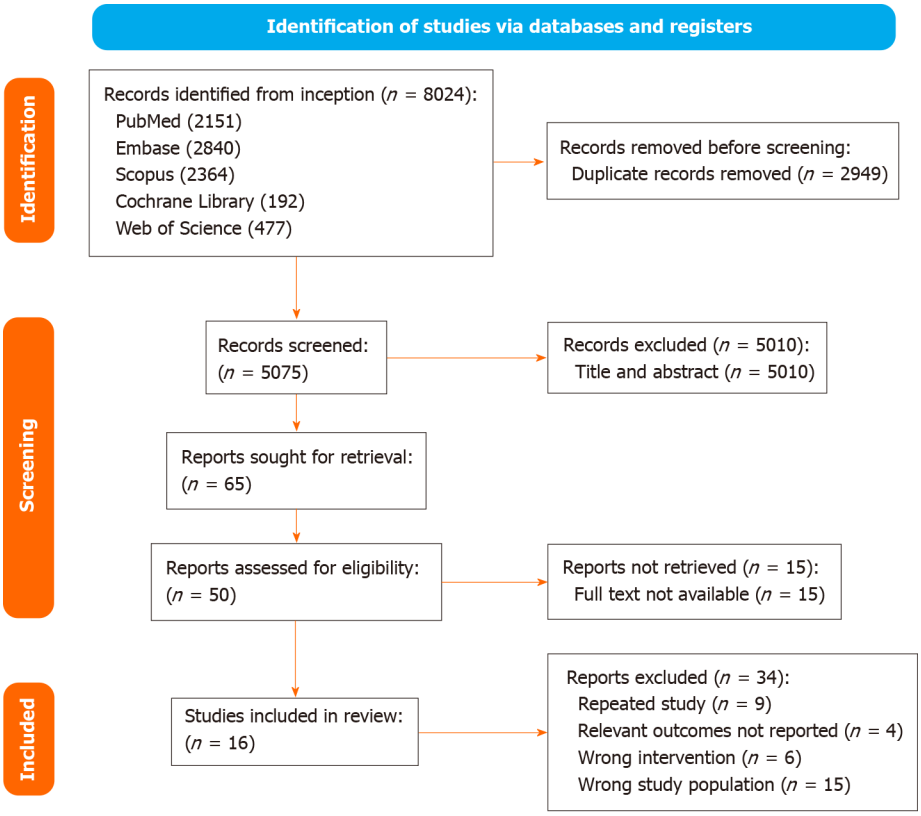

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Figure 1 Preferred reporting items of systematic reviews and meta-analyses flow diagram of study selection.

RESULTS

Study selection

A systematic search identified 8024 studies, of which 2949 duplicate studies were excluded. Subsequent screening of title and abstract performed independently by authors (Yap KY, Chi H, Ng S) identified 50 studies for full-text evaluation. Finally, 12 prospective RCTs and 4 non-randomised studies (1 non-randomised trial and 3 observational studies) were included. A detailed PRISMA diagram is shown in Figure 1. The studies included were assessed for risk of bias, with a summary of the assessment shown in Figure 2 and Table 1 for trials and non-interventional studies, respectively. The PRISMA checklist is appended in Supplementary Figure 1.

Table 1 Risk of bias assessment of non-randomised studies, using Cochrane ROBINS-1 tool

Ref.	Confounding factor bias	Selection bias	Bias in classification of interventions	Bias due to deviations from intended intervention	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall bias
Ardito *et al* [45]	Low	Low	Low	Low	Low	Low	Low	Low
Kobayashi *et al*[36]	Low	Moderate	Low	Low	Low	Low	Moderate	Moderate
Okabayashi *et al*[33]	Low	Low	Low	Low	Low	Low	Low	Low
Shirabe *et al* [37]	Low	Low	Low	Low	Low	Low	Low	Low

Baseline characteristics

The sixteen studies comprised a total cohort of 1389 patients. 645 patients were randomized into the intervention group, consisting of various perioperative regimens of BCAA supplementation, and 744 patients into the control group. The total sample mean age is 60.5 years, intervention mean age is 62.3 years, control mean age is 58.9 years, and the total sample

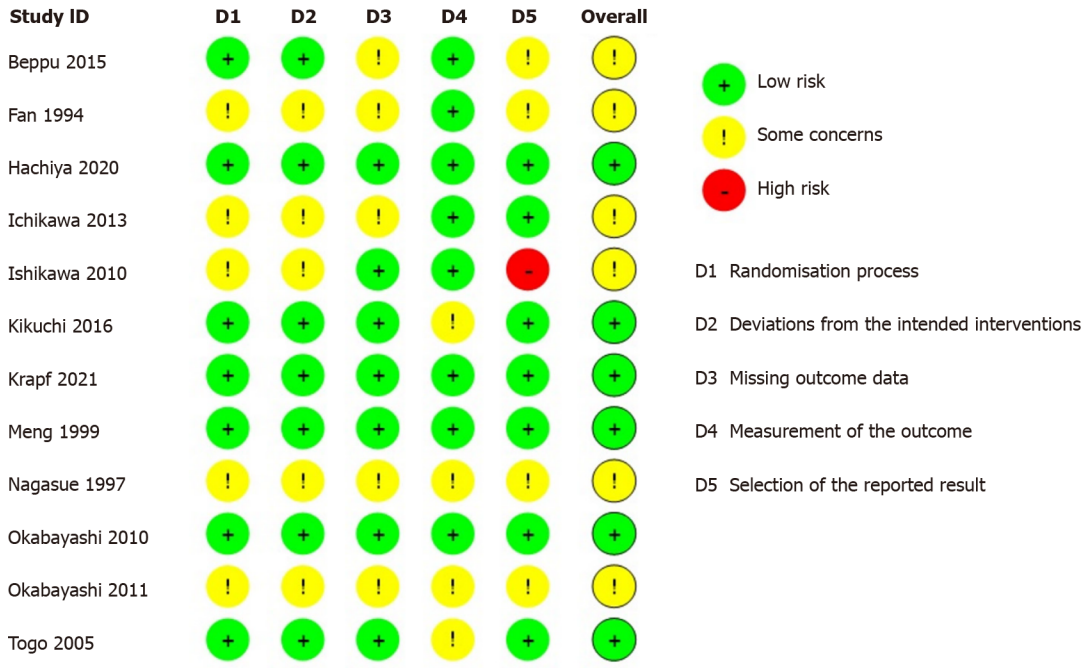

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Figure 2 Risk of bias assessment of included randomised control trials, using version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2).

male is 78.7%. Table 2 summarises the baseline data of included studies. The subsequent tables outline surgical details (Table 3) and the presence and severity of comorbid liver diseases (Table 4).

Use of BCAA supplementation

The BCAA supplementation used were mainly Aminoleban EN (Ajinomoto Pharma, Tokyo, Japan)[30-37] and Livact (Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan)[37-42]. The compositions of Aminoleban EN and Livact are compared in Supplementary Table 4. Three studies used generic BCAA supplements[43-45]. The BCAA supplements were administered perioperatively in varying dose and duration, while patients in the control groups did not receive BCAA supplements for the same specified duration. Table 5 summarises the intervention and control protocol of all included studies. Patients were not blinded due to the lack of suitable placebos that share similar taste to the BCAA supplements.

Postoperative infections

Seven out of sixteen studies[30,31,35,36,40,41,43] including 473 patients (227 in the BCAA group and 246 in the control group) reported data on postoperative infections. There was low statistical heterogeneity between studies (I^2 = 0%). Postoperative infections were found to be significantly lower in the BCAA group [risk ratio (RR) = 0.58 (95%CI: 0.39 to 0.84), P = 0.005] (Figure 3).

In a study involving BCAA supplementation in liver transplant patients, Shirabe *et al*[37] discovered that normal usual diet without BCAA supplementation significantly increased the risk of postoperative bacteraemia [OR = 4.32 (95%CI: 1.137 to 16.483), P = 0.031]. Although more than half of the study population had liver cancer, the study was not included in the meta-analysis as it was unclear if the effect of BCAA supplementation was generalisable to liver cancer patients.

Postoperative ascites

Five out of sixteen studies[35,40-43] including 412 patients (190 in the BCAA group and 222 in the control group) reported data on postoperative ascites. There was low statistical heterogeneity between studies (I^2 = 0%). Postoperative ascites was found to be significantly lower in the BCAA group [RR = 0.57 (95%CI: 0.38 to 0.85), P = 0.005] (Figure 4). Additionally, Kikuchi *et al*[41] reported that the incidence of refractory ascites and/or pleural effusion in the BCAA group was significantly lower than in the non-BCAA group (P = 0.047).

All-cause mortality (> 3 years follow-up)

Six out of sixteen studies[31,32,35,36,39,40] including 534 patients (254 in the BCAA group and 280 in the control group) reported data on mortality due to all causes (> 3 years follow-up). Follow-up periods were between 3-4 years for most included studies, and 3.5-6 years for one study. There was low statistical heterogeneity between included studies (I^2 = 14%). There was no evidence of significant difference between the BCAA and control groups for all-cause mortality [RR = 1.05 (95%CI: 0.79 to 1.40), P = 0.72] (Figure 5). A separate analysis did not find any significant difference in 90-day mortality between the BCAA and control group [RR = 1.69 (95%CI: 0.23 to 12.24), P = 0.60] (Supplementary Figure 2).

Table 2 Baseline participant information of included randomised control trials, observational studies and non-randomised trials

Ref.	Country/year	Study design	Sample size			Gender (M/F)		Male (%)		Age (yr)		Pathology		
			Intervention	Control	Total	Intervention	Control	Intervention	Control	Intervention	Control		Intervention	Control
Beppu *et al*[38]	Japan, 2015	RCT	13	15	28	9/4	10/5	69.2	66.7	64.7 (30.0)	68.4 (18.0)	Metastasis	1	2
												HCC	11	10
												Cholangiocarcinoma	1	3
												Others	0	0
Fan *et al*[43]	Hong Kong, 1994	RCT	64	60	124	56/9	53/7	87.5	88.3	51 (33.4)	53 (35)	Metastasis	0	0
												HCC	64	60
												Cholangiocarcinoma	0	0
												Others	0	0
Hachiya *et al*[39]	Japan, 2020	RCT	74	80	154	59/15	66/14	79.7	82.5	NR	NR	Metastasis	0	0
												HCC	74	80
												Cholangiocarcinoma	0	0
												Others	0	0
Ichikawa *et al*[40]	Japan, 2013	RCT	26	30	56	20/6	18/12	76.9	60	64.5 (11.4)	64.7 (9.8)	Metastasis	0	0
												HCC	26	30
												Cholangiocarcinoma	0	0
												Others	0	0
Ishikawa *et al*[30]	Japan, 2010	RCT	10	10	20	NR	NR	NR	NR	NR	NR	Metastasis	2	1
												HCC	7	7
												Cholangiocarcinoma	1	2
												Others[1]	1	3
Kikuchi *et al*[41]	Japan, 2016	RCT	39	38	77	31/8	29/9	79.5	76.3	69.4 (7.5)	71.9 (7.4)	Metastasis	0	0
												HCC	39	38
												Cholangiocarcinoma	0	0
												Others	0	0
Krapf *et al*[44]	Austria, 2021	RCT	12	9	21	NR	NR	NR	NR	NR	NR	Metastasis	NR	NR

											HCC	NR	NR
											Cholangiocarcinoma	NR	NR
											Others	NR	NR
Meng *et al*[31]	Hong Kong, 1999	RCT	21	23	44	19/2	18/5	90.5	78.3	51.5 (10.8)	53.3 (12.8)	Metastasis	0	0
												HCC	21	23
												Cholangiocarcinoma	0	0
												Others	0	0
Nagasue *et al*[32]	Japan, 1997	RCT	67	65	132	54/13	55/10	80.6	84.6	NR	NR	Metastasis	NR	NR
												HCC	NR	NR
												Cholangiocarcinoma	NR	NR
												Others	NR	NR
Okabayashi *et al*[33]	Japan, 2010	RCT	13	13	26	9/4	8/5	69.2	61.5	68.2 (11.0)	63.5 (5.7)	Metastasis	0	0
												HCC	8	7
												Adenocarcinoma	5	6
												Cholangiocarcinoma	0	0
												Others	0	0
Okabayashi *et al*[34]	Japan, 2011	RCT	40	36	76	29/11	24/12	72.5	66.7	68.7 (7.6)	65.1 (11.3)	Metastasis	0	0
												HCC	32	26
												Cholangiocarcinoma	8	10
												Others	0	0
Togo *et al*[42]	Japan, 2005	RCT	21	22	43	17/5	17/6	81	77.3	66.5 (4.5)	64.3 (9.1)	Metastasis	NR	NR
												HCC	NR	NR
												Cholangiocarcinoma	NR	NR
												Others	NR	NR
Ardito *et al*[45]	Japan, 2020	Retrospective Cohort	107	205	312	NR	NR	NA	NA	NR	NR	Metastasis	83	163
												HCC	18	36
												Cholangiocarcinoma	6	6
												Others[2]	6	48

Okabayashi *et al*[35]	Japan, 2008	Retrospective Cohort	40	72	112	29/11	55/17	72.5	76.4	65.7 (8.6)	68.3 (8.1)	Metastasis	0	0
												HCC	40	72
												Cholangiocarcinoma	0	0
												Others	0	0
Shirabe *et al*[37]	Japan, 2011	Retrospective Cohort	72	56	128	NR	NR	NR	NR	NR	NR	Metastasis	NR	NR
												HCC	72	56
												Cholangiocarcinoma	NR	NR
												Others	NR	NR
Kobayashi *et al*[36]	Japan, 2019	Non- randomised trial	26	10	36	21/5	5/5	80.8	50	69.2 (29.0)	64.8 (26.7)	Metastasis	4	2
												HCC	22	8
												Cholangiocarcinoma	0	0
												Others	0	0

[1]Benign.
[2]Benign, intra-hepatic stones, others.
RCT: Randomised controlled trial; HCC: Hepatocellular carcinoma; NR: Not reported.

LOS

Six out of sixteen studies[31,35,40,41,43,45] including 787 patients (303 in the BCAA group and 484 in the control group) reported LOS data. There was considerable statistical heterogeneity between studies (I^2 = 69%), and a random effects model was employed. LOS was reduced by 3.03 d in the BCAA group compared to controls [weighted mean difference (WMD) = -3.03 d (95%CI: -5.49 to -0.57), P = 0.02] (Figure 6).

Recurrence

Five out of sixteen studies [31,32,39,40,42] including 429 patients (209 in the BCAA group and 220 in the control group) reported data on cancer recurrence. Median follow-up period varied from 12 to 30 mo. One author reported recurrence but was not included in analysis as recurrence was not an end point in the original study[34]. A subgroup analysis in Hachiya *et al*[39] of patients under 72 years of age with haemoglobin A1C levels below 6.4% revealed that recurrence-free survival was higher in the BCAA group compared to the control group (P = 0.015). There was low statistical heterogeneity between included studies (I^2 = 0%). There was no statistically significant difference between the BCAA and control groups for recurrence [RR = 0.88 (95%CI: 0.71 to 1.08), P = 0.22] (Figure 7).

OS

Four out of sixteen studies[35,36,39,40] reported OS data. There was low statistical heterogeneity (I^2 = 0%). OS did not differ significantly between the BCAA and control groups [hazard ratio = 1.26 (95%CI: 0.72 to 2.21), P = 0.41] (Figure 8).

Table 3 Relevant surgical details of included studies

Ref.	Surgical method		Intervention	Control	Blood loss/mL[1]	
					Intervention	Control
Ardito *et al*[45], 2020	Hepatectomy	Minimally invasive liver surgery	33	74	NR	NR
		Major hepatic resection	16	62		
		Multiple resections	43	44		
		Total	92	180		
Beppu *et al*[38], 2015	Hepatectomy	Right hemihepatectomy	8	7	NR	NR
		Left hemihepatectomy	0	1		
		Sectionectomy	1	3		
		Left hemihepatectomy + sectionectomy	0	1		
		Total	9	12		
Fan *et al*[43], 1994	Hepatectomy	Major hepatic resection	47	42	2600 (300-20000)	1900 (400-10500)
		Minor hepatic resection	17	18		
		Total	64	60		
Hachiya *et al*[39], 2020	Hepatectomy	Non-anatomical resections	19	25	348 (5-3400)	359 (5-3741)
		Anatomical resections	55	55		
		Total	74	80		
Ichikawa *et al*[40], 2013	Hepatectomy	Major hepatic resection	10	14	716 +/- 704	492 +/- 329
		Limited resection of the liver	16	16		
		Total	26	30		
Ishikawa *et al*[30], 2010	Hepatectomy	Major hepatic resection	7	5	802.7 +/- 350.6	838.8 +/- 597.6
		Minor hepatic resection	6	8		
		Total	13	13		
Kikuchi *et al*[41], 2016	Hepatectomy	Partial hepatectomy	13	12	665.7 +/- 528.9	578.5 +/- 492.1
		Segmentectomy	0	6		
		Bisgmentectomy/sectionectomy	13	10		
		Bisectionectomy or more	13	10		
		Total	39	38		
Kobayashi *et al*[36], 2019	Hepatectomy	Major hepatic resection	4	0	454 (140-5103)	365 (35-3650)
		Minor hepatic resection	22	10		
		Total	26	10		
Krapf *et al*[44], 2021	Liver transplant-Hepatectomy	Major hepatic resection	24	12	NR	NR
		Hepatic resection	9	12		
		Total	33	24		
Meng *et al*[31], 1999	Hepatectomy	Major hepatic resection	13	18	NR	NR
		Minor hepatic resection	8	5		
		Total	21	23		
Nagasue *et al*[32], 1997	Hepatectomy	Major hepatic resection	19	26	NR	NR
		Minor hepatic resection	48	39		
		Total	67	65		
Okabayashi *et al*[35], 2008	Hepatectomy	Major hepatic resection	10	19	516 +/- 354	821 +/- 552
		Minor hepatic resection	30	53		

		Total	40	72		
Okabayashi *et al*[33], 2010	Hepatectomy	Major hepatic resection	5	7	1252 +/- 1205	669 +/- 575
		Minor hepatic resection	8	6		
		Total	13	13		
Okabayashi *et al*[34], 2011	Hepatectomy	Hemihepatectomy	4	4	945 +/- 827	676 +/- 695
		Segmentectomy	12	10		
		Limited hepatic resection	24	22		
		Total	40	36		
Shirabe *et al*[37], 2011	Liver transplant	Total	129	107	7388 +/- 9031	6448 +/- 6547
Togo *et al*[42], 2005	Hepatectomy	Partial hepatectomy	8	8	1163 +/- 853	1209 +/- 872
		Segmentectomy	7	8		
		Sectionectomy	4	3		
		Hemihepatectomy	2	3		
		Total	21	22		

[1]Data is expressed as *n* or mean +/- SD (median, range).
NR: Not reported.

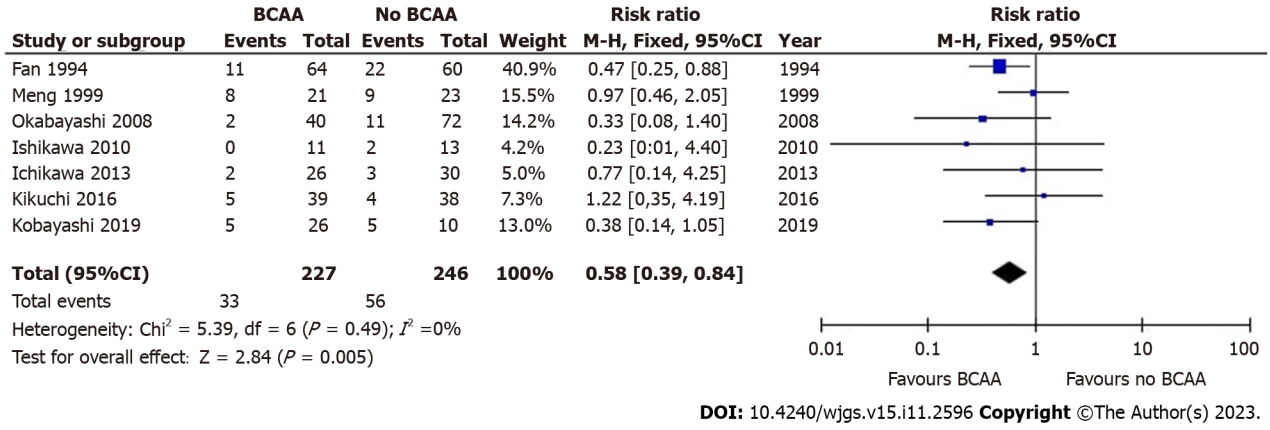

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Figure 3 Forest plot of meta-analysis on postoperative infection. BCAA: Branched chain amino acid; CI: Confidence interval.

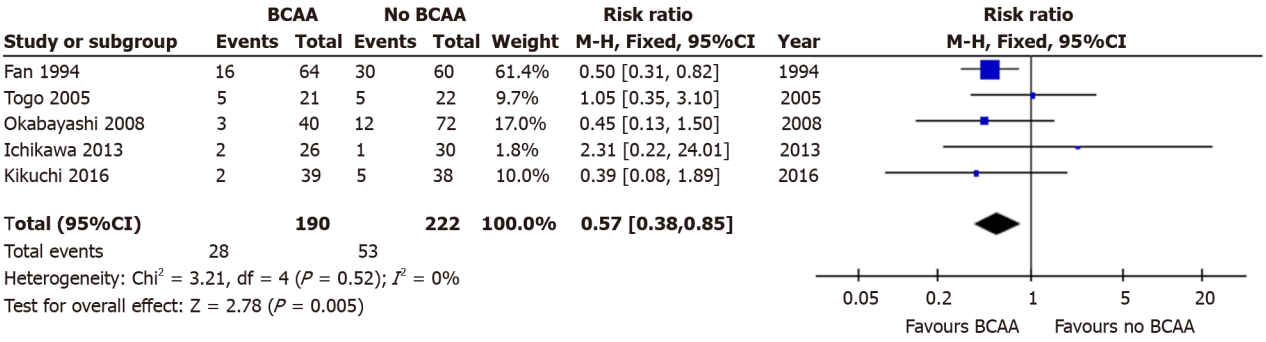

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Figure 4 Forest plot of meta-analysis on all-cause postoperative ascites. BCAA: Branched chain amino acid; CI: Confidence interval.

Postoperative change in serum albumin

Five out of sixteen studies[31,32,34,35,42] including 427 patients (197 in the BCAA group and 230 in the control group) reported data on change in serum albumin. There was low statistical heterogeneity (I^2 = 0%). While individual studies reported faster albumin increase in the intervention group compared to the control group[22], change in serum albumin was not significant at 6 mo [WMD = 0.10 (95%CI: -0.08 to 0.29), P = 0.28] and 12 mo [WMD = -0.05 (95%CI: -0.24 to 0.15), P = 0.63] (Figures 9 and 10).

Anthropometrics

Four out of sixteen studies[34,36,40,43] including 292 patients (156 in the BCAA group and 136 in the control group) reported data on postoperative body weight change. There was considerable heterogeneity between studies (I^2 = 74%), and a random effects model was employed. Postoperative body weight increased significantly by 1.98 kg in the BCAA group [WMD = 1.98 kg (95%CI: 0.35 to 3.61), P = 0.02] (Figure 11).

QOL

Three out of sixteen studies[32,34,44] reported data on QOL measures. Krapf *et al*[44] used the European Organisation for Research and Treatment of Cancer QOL Questionnaire Core 30 (EORTC QLQ-C30) to look at physical, psychological, and social functions across 30 questions, and found that there was no significant difference between study groups. However, the study authors noted that patients in the BCAA group had a greater amount of food intake and significantly better subjective rating of the meals.

Okabayashi *et al*[34] using the short-form 36 (SF-36) health sheet reported significant improvement in all 8 parameters (physical functioning, role physical, bodily pain, general health perceptions, vitality, social functioning, role emotional and mental health) in the BCAA group at the 12-month follow-up while the control group shown no significant differences in postoperative QOL.

Nagasue *et al*[32] used the Kanovsky scale to evaluate performance status and reported that the percentage change from baseline to the 12 mo follow-up was significantly higher in the BCAA group.

Other outcomes

It is worth nothing that two of the sixteen studies included in this review described unique outcomes of BCAA supplementation. Beppu *et al*[38] found that patients undergoing portal vein embolisation (PVE) and subsequent major hepatectomy had significantly greater functional liver regeneration after PVE (P = 0.079) and better postoperative outcomes in the BCAA group compared to controls. A 2010 study by Okabayashi *et al*[33] concluded that BCAA supplementation resulted in significantly reduced immediate postoperative insulin resistance (P = 0.039), improved blood glucose levels and decreased need for insulin therapy in liver cancer patients.

DISCUSSION

This study shows perioperative BCAAs supplementation increases body weight, reduces infection, LOS and ascites in cancer patients undergoing liver surgery.

BCAAs are essential amino acids and contribute to protein synthesis, act as precursors of the tricarboxylic acid cycle intermediates and are involved in key signalling pathways[46-48]. Figure 12A summarises the molecular effects of BCAA on skeletal muscle and liver. Figure 12B summarises the cellular signalling pathways involving BCAA with downstream effects. Leu, the most abundant amino acid, plays a major role in protein synthesis and cellular growth. It promotes mammalian target of rapamycin (mTOR) pathway activation by binding to Sestrin2, preventing the latter from inhibiting mTOR complex 1 activity[49]. This contributes to downstream phosphorylation of ribosomal proteins and upregulates mRNA translation[50]. Val catabolites also serve signalling functions, particularly 3-hydroxyisobutyrate (3-HIB) and beta-amino-isobutyric acid (BAIBA). 3-HIB promotes the endothelial uptake of fatty acids into muscle, acting as an intermediary between protein and lipid metabolism[51]. BAIBA promotes hepatic beta-oxidation and reduce hepatic endoplasmic reticulum stress[52]. Ile is less well-studied. Some authors have postulated its immune modulating role in inducing the expression of host defence peptides and improving innate immunity by maintaining skin mucus barrier[53,54].

BCAAs in liver disease

Over 85% of liver cancer patients are cachectic[55], resulting from malignancy and protein energy malnutrition on a background of cirrhosis[56]. Liver surgeries are often associated with ischemia-reperfusion periods. Poor nutritional status further exacerbates ischemic injury by accelerating glycolysis and rapidly depleting adenosine triphosphate, leading to irreversible cellular necrosis[57-59]. BCAA supplementation is well-established in liver disease. The European Society for Clinical Nutrition and Metabolism[60] recommend long-term oral BCAA supplements (0.25 g × kg^{-1} × d^{-1}) in patients with advanced cirrhosis to improve event-free survival or QOL. The American Association for the Study of Liver [61] recommend BCAA administration as an alternative or additional agent to treat hepatic encephalopathy in patients who are unresponsive to conventional therapy. However, the evidence of benefit for BCAAs in liver cancer patients managed by surgical approaches is less clear.

Table 4 Presence and severity of liver diseases in patients of included studies

Ref.	Hepatitis		Cirrhosis		Child-Pugh Score		
	Intervention	Control	Intervention	Control		Intervention	Control
Ardito *et al*[45], 2020	NR	NR	NR	NR	A	NR	NR
					B	NR	NR
					C	NR	NR
Beppu *et al*[38], 2015[1]	9	8	NR	NR	A	NR	NR
					B	NR	NR
					C	NR	NR
Fan *et al*[43], 1994	18	12	39	33	A	NR	NR
					B	NR	NR
					C	NR	NR
Hachiya *et al*[39], 2020	74	80	NR	NR	A	61	64
					B	13	16
					C	0	0
Ichikawa *et al*[40], 2013	10	7	16	23	A	21	25
					B	5	5
					C	0	0
Ishikawa *et al*[30], 2010[1]	4	2	5	5	A	10	12
					B	1	1
					C	0	0
Kikuchi *et al*[41], 2016	39	38	NR	NR	A	39	38
					B	0	0
					C	0	0
Kobayashi *et al*[36], 2019[1]	20	6	12	8	A	NR	NR
					B	NR	NR
					C	NR	NR
Krapf *et al*[44], 2021	NR	NR	NR	NR	A	NR	NR
					B	NR	NR
					C	NR	NR
Meng *et al*[31], 1999	18	19	15	15	A	17	20
					B	4	3
					C	0	0
Nagasue *et al*[32], 1997	21	10	46	53	A	53	50
					B	13	14
					C	1	1
Okabayashi *et al*[35], 2008	33	54	NR	NR	A	33	62
					B	7	10
					C	0	0
Okabayashi *et al*[33], 2010	8	7	NR	NR	A	10	11
					B	3	2
					C	0	0
Okabayashi *et al*[34],	22	16	NR	NR	A	28	25

2011[1]					B	12	10
					C	0	0
Shirabe *et al*[37], 2011	NR	NR	26	18	A	3	18
					B	36	39
					C	90	50
Togo *et al*[42], 2005	21	22	21	22	A	15	17
					B	7	5
					C	0	0

[1]All participants, including non-hepatocellular carcinoma patients were included.
NR: Not reported.

Importance of optimising nutrition in perioperative patients

Despite many studies reporting a strong association between malnutrition and poor surgical outcomes, oncological patients often lack opportune time to delay treatment for nutritional optimisation. In a study of nutrition and HCC, Huang *et al*[62] noted that patients assessed by dietitians to be malnourished had a significantly higher rate of major complications[63]. With an increasing focus on optimisation of postoperative surgical recovery, enhanced recovery after surgery protocols and prehabilitation initiatives have also emphasised the importance of perioperative nutrition[64].

Relevance of BCAAs to outcomes

This review investigated perioperative and oncological outcomes of BCAA supplementation in patients undergoing surgery for liver cancers unlike the previous review that included diverse oncological diagnoses[22]. We demonstrated that BCAA supplementation significantly reduced postoperative complications, with over 40% relative risk reduction of postoperative infection and ascites. The BCAA group also had slightly higher body weight and performed better on both perceived and actual QOL metrics, suggesting that BCAA intake can optimise recovery and function after surgery.

Effect of BCAA on oncological outcomes

BCAA supplementation had no impact on cancer recurrence and OS. This is consistent with the conclusions of recent meta-analyses[22,65]. The relationship between BCAA and liver cancer at the molecular level has been explored[66-68]. BCAAs suppress the development of liver cancers in rodent models[69,70], presumably improving insulin resistance in obesity or diabetes mellitus. Insulin resistance is involved in the pathogenesis of HCC, as insulin has oncogenic properties on HCC cells, stimulating cell growth and inducing anti-apoptotic activity[71,72]. Another study postulated suppression of VEGF expression in tumour cells as an alternative mechanism[73]. The catabolism of BCAAs has also been extensively implicated in carcinogenesis[67] through various molecular pathways, including accumulation of branched-chain α-ketoacids and activation of the mTORC1 pathway[74,75]. Ericksen *et al*[76] validated oncogenic pathways and linked high dietary BCAA intake to tumour burden and mortality specifically in HCC patients.

Given the apparent contradictory effects of BCAA on liver cancer development and prognosis, it may be challenging to interpret our findings. BCAAs may potentially improve liver function and body weight postoperatively but also contribute to tumour recurrence *via* the above-mentioned pathways. The beneficial oncological effects of BCAA supplementation remain inconclusive.

Effect of BCAA on postoperative complications

While oncological outcomes do not support routine use of BCAA supplementation in the perioperative period, our review found that the risk of postoperative infection and ascites were significantly lowered in BCAA groups.

Postoperative infection is a frequent complication of hepatic resection, with reported rates of up to 25%[77,78]. It can be associated with significant morbidity in the absence of early recognition and treatment[79]. After major liver surgery, impairment of innate immune function increases host susceptibility to infection[80]. Furthermore, surgery in HCC patients results in higher risk of infectious sequelae, presumably due to underlying cirrhosis and chronic liver dysfunction, bile leak with risk of abdominal sepsis, and postoperative pneumonia due to upper abdominal incision[81]. Another major risk factor for infection is malnutrition[82-85]. BCAA supplementation directly improves patients' preoperative nutritional status[86]. BCAAs also play an essential role in immune cell function relating to protein synthesis [87], and in immune regulation in patients with advanced cirrhosis[88-90].

Postoperative ascites is reported in 5% to 56% patients undergoing hepatectomy[91], and is associated with liver failure [92,93]. Chan *et al*[94] described higher 1-year mortality and lower recurrence-free survival rates attributed to postoperative ascites.

BCAAs increase the synthesis and secretion of albumin by hepatocytes[95], and improve impaired metabolic turnover of albumin in cirrhotic patients[96]. Fukushima *et al*[97] reported that BCAAs effectively improved the oxidisation/reduction imbalance of albumin in cirrhosis. In our study, BCAA supplementation did not significantly increase postoperative serum albumin levels. The underlying mechanisms behind the demonstrated efficacy of BCAA supplementation in reducing postoperative ascites remain uncertain.

Table 5 Intervention and control protocol for all included studies

Ref.	Intervention type	Intervention protocol[1]						Control protocol	Follow up period[2]			
		Pre-operative regime	Total BCAA received (g)/d	Duration	Post-operative regime	Total BCAA received (g)/d	Duration		Intervention		Control	
									Mean	Range	Mean	Range
Ardito *et al*[45], 2020	Preoperative, postoperative	BCAA 500 mg 2 tablets TDS with personalised diet (ERAS)	3	2/52	BCAA 500 mg 2 tablets TDS (ERAS)	3	1/12	Normal usual diet (ERAS)	NR	NR	NR	NR
Beppu *et al*[38], 2015	Preoperative, postoperative	Livact 4.15 g BD	8	6/12	NIL	NIL	NIL	Normal usual diet	NR	NR	NR	NR
Fan *et al*[43], 1994	Preoperative, postoperative	BCAA 1.5 g/kg	Weight dependent	1/52	BCAA 1.5 g/kg	Weight dependent	1/52	Normal usual diet	NR	NR	NR	NR
Hachiya *et al* [39], 2020	Postoperative	NIL	NIL	NIL	Livact 4 g TDS	12	4 yr	Normal usual diet	21.8	1.2-48	NR	NR
Ichikawa *et al* [40], 2013	Preoperative, postoperative	Livact 4.74 g TDS	12	2/52	Livact 4.74 g TDS	12	≥ 6/12	Normal usual diet	39.5 mo	7-48 mo	36.0 mo	6-50 mo
Ishikawa *et al* [30], 2010	Preoperative, postoperative	Aminoleban EN 50 g BD	11.123	2/52	Aminoleban EN 50 g BD	11.123	1/52	Normal usual diet	NR	NR	NR	NR
Kikuchi *et al* [41], 2016	Preoperative, postoperative	Livact 4.74 g TDS	12	1/12	Livact 4.74 g TDS	12	1 yr	Normal usual diet (35-40 kcal/kg/d) + 4.74 g Livact TDS × 1 yr post-operatively	NR	NR	NR	NR
Kobayashi *et al* [36], 2019	Preoperative, postoperative	Aminoleban EN 50 g ON	5.5615	2/52	Aminoleban EN ON	5.5615	12/52	Normal usual diet	NR	NR	NR	NR
Krapf *et al*[44], 2021	Postoperative	NIL	NIL	NIL	High BCAA diet	NA	2/52	Normal usual diet (standard isocaloric meal plan)	NR	NR	NR	NR
Meng *et al*[31], 1999	Postoperative	NIL	NIL	NIL	Aminoleban EN TDS with 40 g protein/d + 6300 kJ/d	NA	12/52	Normal usual diet (80 g protein/d + 6300 kJ/d)	511.6d	6-982 d	512.7d	48-983 d
Nagasue *et al* [32], 1997	Postoperative	NIL	NIL	2/52	Aminoleban EN 50 g BD	11.123	≥ 1 yr	Normal usual diet	35.8 mo (17.9)	NR	36.0 mo (17.7)	NR
Okabayashi *et al*[35], 2008	Preoperative	Aminoleban EN 50 g BD	11.123	2/52	NIL	NIL	NIL	Normal usual diet	16.3 mo	2-47 mo	23.3 mo	2-84 mo
Okabayashi *et al*[33], 2010	Preoperative	Aminoleban EN 50 g BD	11.123	2/52	NIL	NIL	NIL	Normal usual diet	NR	NR	NR	NR
Okabayashi *et al*[34], 2011	Preoperative, postoperative	Aminoleban EN 50 g BD	11.123	2/52	Aminoleban EN 50 g BD	11.123	≥ 6/12	Normal usual diet	NR	NR	NR	NR
Shirabe *et al* [37], 2011	Preoperative	Regime 1: Livact 3 packets OD Regime 2: Aminoleban EN 50 g	Regime 1: 12Regime 2:	> 1/12	NIL	NIL	NIL	Normal usual diet	NR	NR	NR	NR

		1 to 3 packets	5.5615-16.6845									
Togo *et al*[42], 2005	Post-operative	NIL	NIL	NIL	Livact 4.74 g TDS	12	1 yr	Normal usual diet	NR	NR	NR	NR

[1]Composition of livact and Aminoleban described in supplementary table 4.

[2]Data is expressed as n or mean +/- SD (median, range).

Participants on branched chain amino acid supplementation were also taking normal usual diet. BCAA: Branched chain amino acid; ERAS: Enhanced recovery after surgery; TDS: Ter die sumendum ; NR: Not reported; NIL: Nothing.

Effect of BCAA on QOL

2 out of 3 included studies[34,44] demonstrated significant improvement in QOL with BCAAs, but differing methodologies and domains for assessment were employed. Krapf *et al*[44] noted a significantly higher subjective rating of high BCAA content diet compared to normal usual diet, despite similar preparation methods and staff. If such an outcome is indeed replicated in future QOL studies, it may represent a potential benefit of BCAA supplementation in improving oral intake and avoiding malnutrition in post-surgical patients. These results are consistent with QOL improvements seen in RCTs on BCAA supplementation in cirrhosis[98,99].

Overall, more robust, large-scale clinical studies of surgical patients with liver cancer would need to be conducted with standardisation of total calorie and protein intake in intervention and control groups to conclude on the risk-benefit calculation of BCAA supplementation. Future studies should report BCAA to total protein intake ratio, protein to calorie ratio and type of BCAA to understand cause effect relation on perioperative outcomes of BCAA supplementation.

Side effects of BCAA

We reviewed side effects reported from routine BCAA ingestion in the included studies. Most studies did not report side effects with the exception that one RCT[43] reported 2 events (3%) relating to intravenous administration, while another [32] reported that 3 patients were unable to continue with BCAA administration due to adverse reactions. Overall, BCAAs have an extremely low incidence of side effects in the included studies.

Strengths and limitations

The strengths of this study include data pooling from newer RCTs and multiple real-world observational studies. While RCTs are considered the gold standard for ascertaining the efficacy and safety of a treatment, their methodologies may limit generalizability. The inclusion of observational studies provides more generalizable results applicable in the real-world situation. Since both types of study design have their strengths and limitations, they provide insight into the efficacy of BCAA supplementation.

Though many Japanese studies were included, exclusion of non-English articles may have led to language biases as a potential confounding factor in our conclusions. The included studies had varying doses of BCAA supplementation and a lack of data on composition of normal usual diet in the participating institutions. Most of the patients in this review had Child-Pugh score A cirrhosis and thus might not be malnourished. Further, there is no population data to suggest that HCC patients have deficiency of BCAA. A lack of long-term follow-up data in the included studies makes it difficult to study the impact of BCAA supplementation on oncological outcomes.

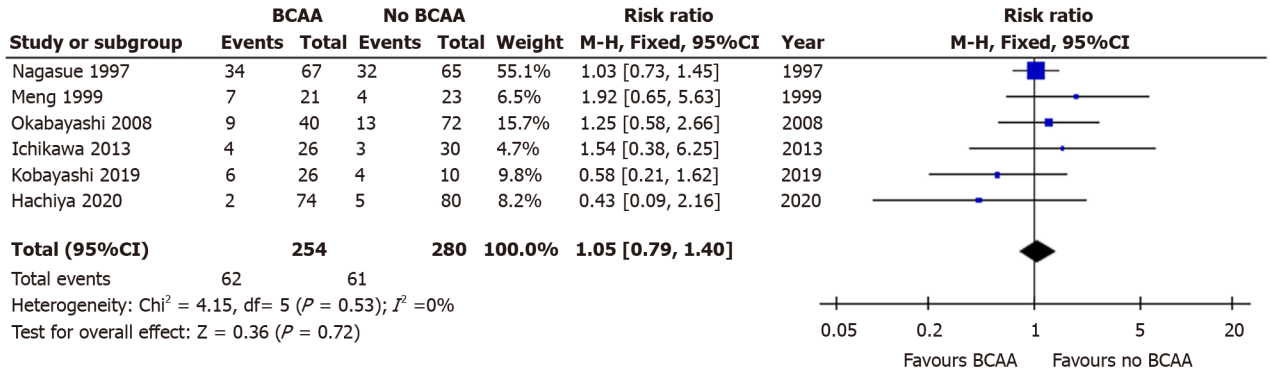

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Figure 5 Forest plot of meta-analysis on all-cause mortality. BCAA: Branched chain amino acid; CI: Confidence interval.

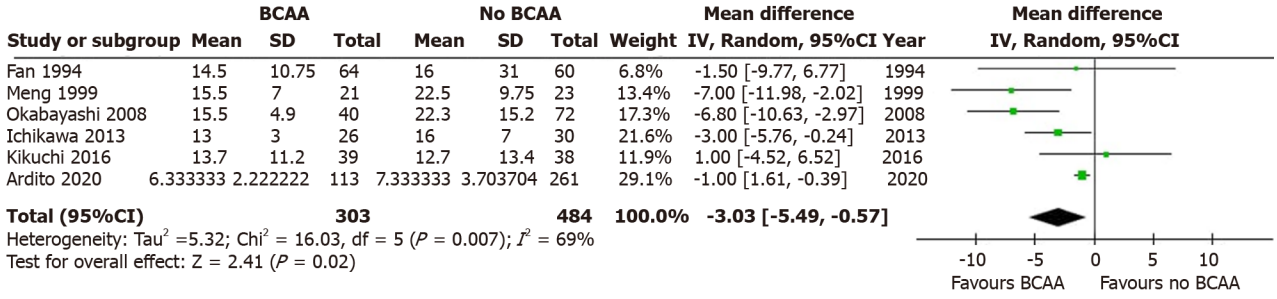

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Figure 6 Forest plot of meta-analysis on length of hospital stay. BCAA: Branched chain amino acid; CI: Confidence interval.

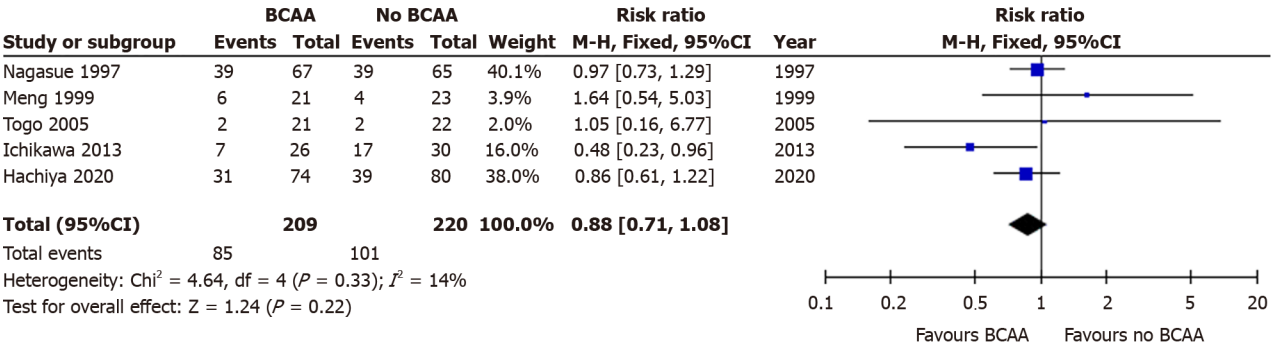

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Figure 7 Forest plot of meta-analysis on recurrence. BCAA: Branched chain amino acid; CI: Confidence interval.

CONCLUSION

Perioperative BCAA administration increases body weight and reduces postoperative infection, ascites, and LOS in liver cancer patients undergoing surgery.

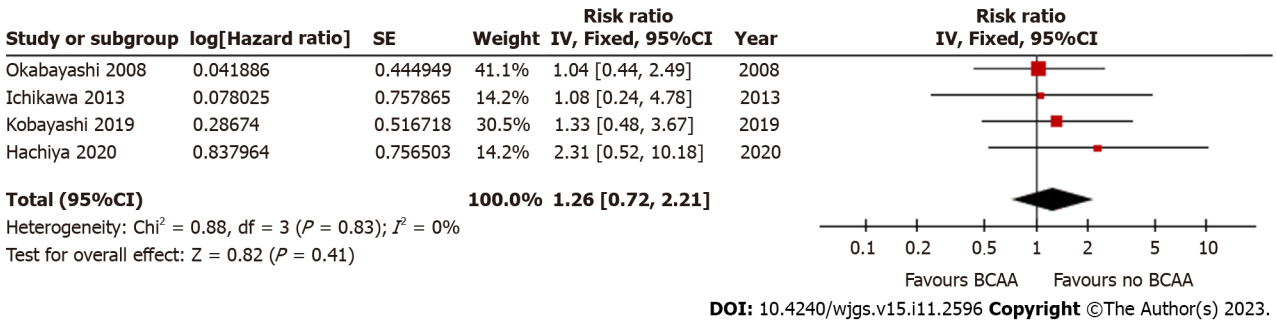

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Figure 8 Forest plot of meta-analysis on overall survival. BCAA: Branched chain amino acid; CI: Confidence interval.

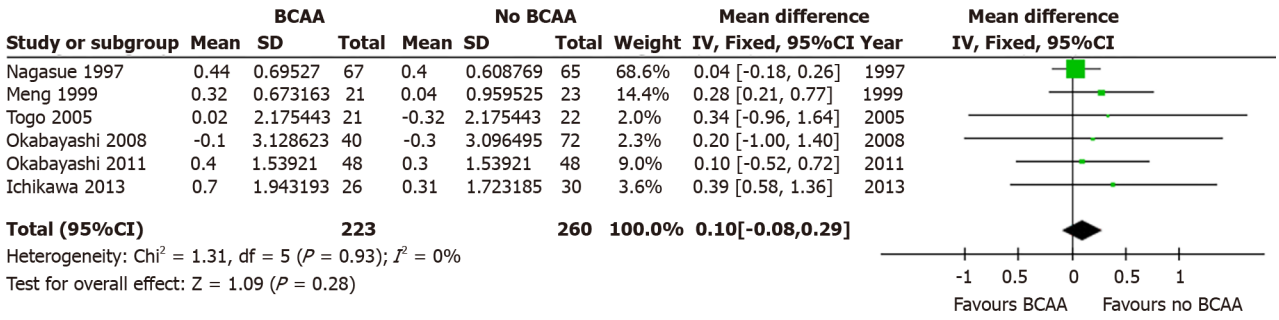

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Figure 9 Forest plot of meta-analysis on change in serum albumin at 6 mo postoperatively. BCAA: Branched chain amino acid; CI: Confidence interval.

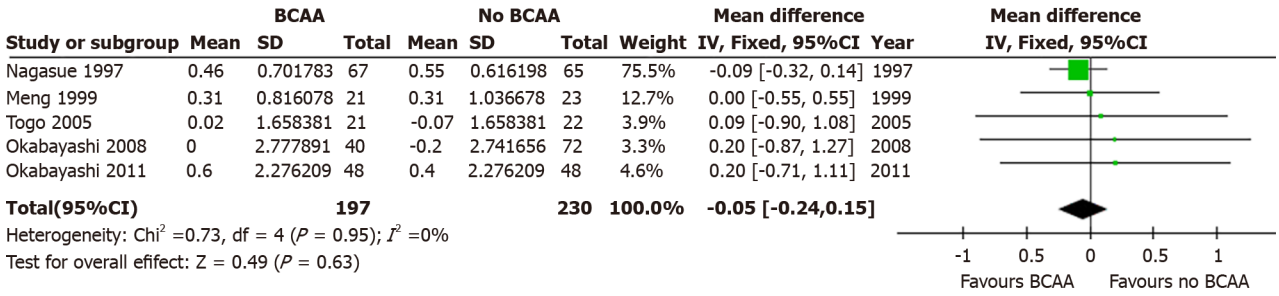

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Figure 10 Forest plot of meta-analysis on change in serum albumin at 12 mo postoperatively. BCAA: Branched chain amino acid; CI: Confidence interval.

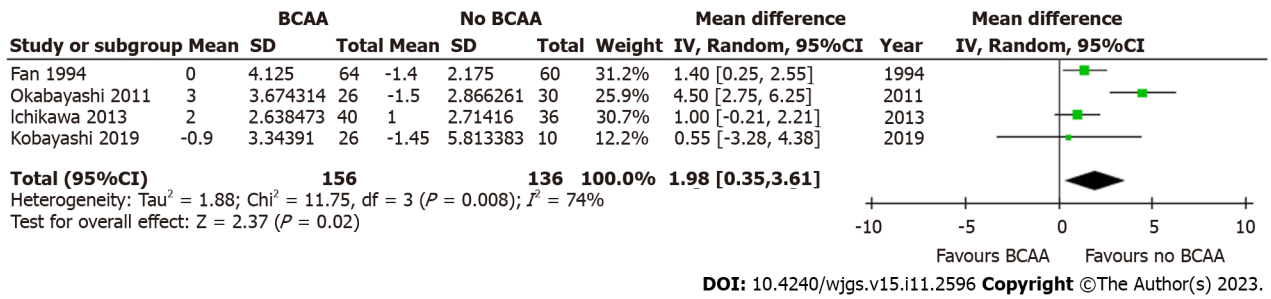

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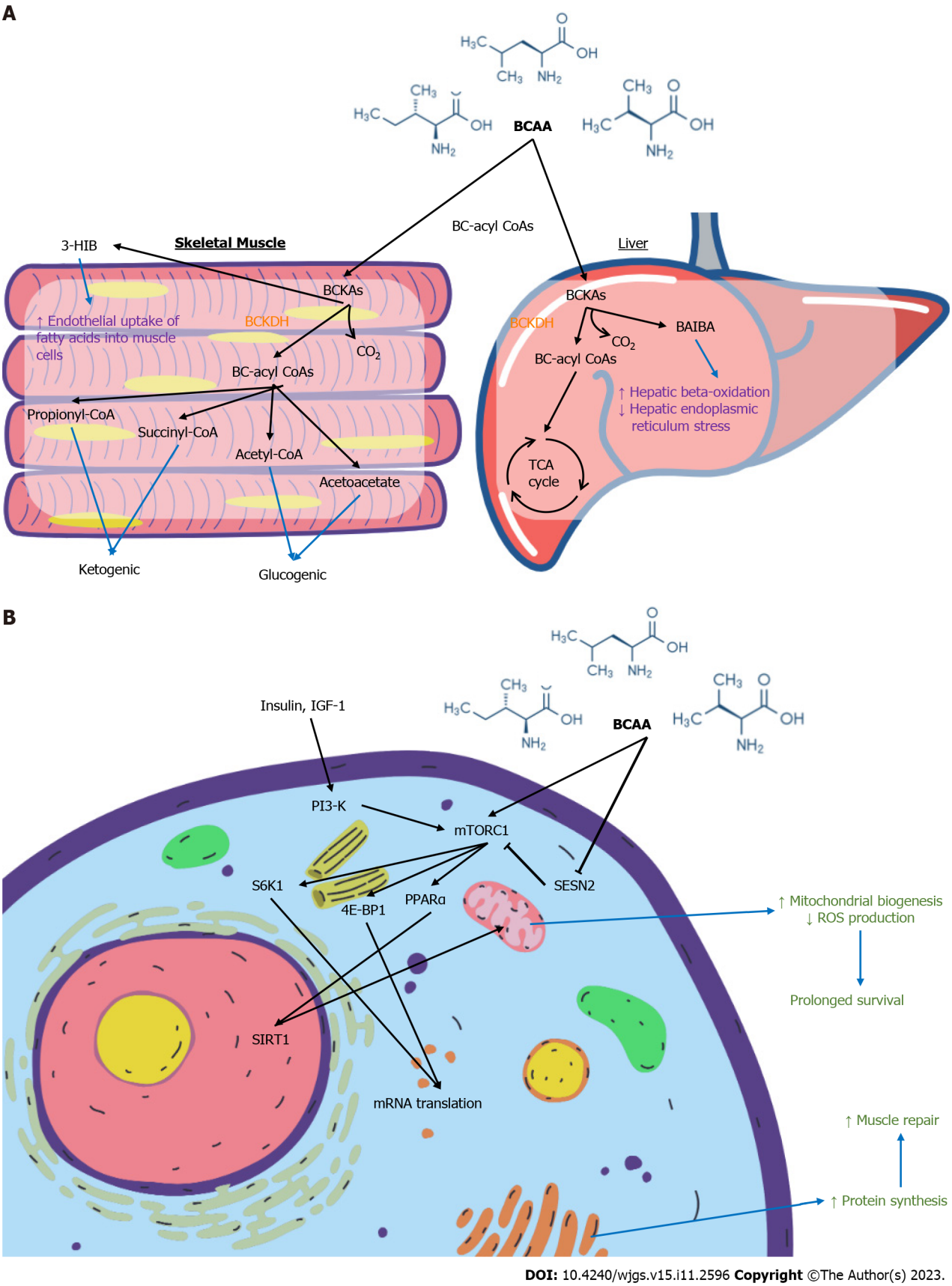
Figure 11 Forest plot of meta-analysis on postoperative body weight change for branched chain amino acid group relative to control. BCAA: Branched chain amino acid; CI: Confidence interval.



DOI: 10.4240/wjgs.v15.i11.2596

Figure 12 Branched chain amino acid. A: Biochemical effect of Branched chain amino acid (BCAA) on skeletal muscles and the liver; B: Signalling pathways involving BCAA.

ARTICLE HIGHLIGHTS

Research background

Branched chain amino acids (BCAA) show promising results in improving surgical outcomes in liver cancer patients and potential for routine use.

Research motivation

Current studies on BCAA supplementation show varying results but with no clear conclusion and no updated reviews on the matter.

Research objectives

To provide the most updated review on whether BCAA supplementation provides measurable benefits in liver cancer patients for surgical intervention.

Research methods

Current trials and studies on BCAA supplementation in liver cancer patients undergoing surgery were appraised by three independent authors. Studies were identified and data extracted for meta-analysis of the relevant outcomes.

Research results

Perioperative BCAA supplementation reduced postoperative infections, length of stay and increased body weight in the studied patient groups but did not improve mortality, oncological recurrence, and long-term survival.

Research conclusions

This review has shown that BCAA supplementation improves postoperative outcomes with no significant side effects. However, benefits on oncological outcomes remain inconclusive.

Research perspectives

This review highlights the possible routine use of BCAA for liver cancer patients for surgical intervention. Further clinical research can be directed at assessing optimal BCAA supplementation regime for such patients.

FOOTNOTES

Co-first authors: Kwan Yi Yap and HongHui Chi.

Author contributions: Yap KY acquisition of data, analysis and interpretation of data, drafting the article, revising the article, final approval; Chi H acquisition of data, analysis and interpretation of data, drafting the article, revising the article, final approval; Ng S acquisition of data, interpretation of data, final approval; Ng DH revising the article; Shelat VG supervision, critical revision, final approval. Yap KY and Chi H contributed equally to this work as co-first authors. This research is the product of the collaborative effort of the team, and the designation of co-first authors authorship is reflective of the time and effort invested by the co-first authors into the completion of the research. Furthermore, the decision of co-first authors authorship acknowledges and respects the equal contribution made by both co-first authors throughout the process of writing the paper. As a whole, the team believes that designating Yap KY and Chi H as co-first authors is appropriate and reflective of the team's collective spirit and wishes.

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L-Editor: A
P-Editor: Wu RR

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CASE REPORT

Organ sparing to cure stage IV rectal cancer: A case report and review of literature

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Abstract

BACKGROUND

Rectal sparing is an option for some rectal cancers with complete or good response after chemoradiotherapy (CRT); however, it has never been evaluated in patients with metastases. We assessed long-term outcomes of a rectal-sparing approach in a liver-first strategy for patients with rectal cancer with resectable liver metastases.

CASE SUMMARY

We examined patients who underwent an organ-sparing approach for rectal cancer with synchronous liver metastases using a liver-first strategy during 2010-2015 (n = 8). Patients received primary chemotherapy and pelvic CRT. Liver surgery was performed during the interval between CRT completion and rectal tumor re-evaluation. Clinical and oncological characteristics and long-term outcomes were assessed.

CASE SUMMARY

All patients underwent liver metastatic resection with curative intent. The R0 rate was 100%. Six and two patients underwent local excision and a watch-and-wait (WW) approach, respectively. All patients had T3N1 tumors at diagnosis and had good clinical response after CRT. The median survival time was 60 (range, 14-127) mo. Three patients were disease free for 5, 8, and 10 years after the procedure. Five patients developed metastatic recurrence in the liver (n = 5) and/or lungs (n = 2). Only one patient developed local recurrence concurrent with metastatic recurrence 24 mo after the WW approach. Two patients died during follow-up.

CONCLUSION

The results suggest good local control in patients undergoing organ-sparing strategies for rectal cancer with synchronous liver metastasis. Prospective trials are required to validate these data and identify good candidates for these strategies.

Key Words: Colorectal cancer; Liver metastasis; Rectal sparing; Pver-first strategy

Core Tip: Our liver first strategy allows long course randomized controlled trial achievement without compromising systemic treatment. In case of good response after chemoradiotherapy, rectal sparing has never been evaluated in patients with metastases. Rectal sparing strategy results in low morbidity and improved patient's long-term quality of life. With a follow-up more than 5 years, we described a good local control in 8 patients with metastases. Prospective trials are required to validate these data and identify good candidates for these strategies.

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INTRODUCTION

Rectal cancer affects nearly 10000 new patients every year in France, among whom 20%-25% present with synchronous liver metastases. Despite oncological advances, the only potentially curative therapy remains surgical resection or destruction of lesions at both sites[1]. Rectal and liver resections can achieve 5-year survival rates of > 50%[1,2] compared with only approximately 5% for patients treated with palliative intent[3].

Because the prognosis of these patients is directly related to the presence of liver metastases and because complications of rectal surgery are common after chemoradiotherapy (CRT) and may therefore delay the start of appropriate metastatic treatments, the liver-first approach has been proposed for patients with locally advanced rectal cancer and synchronous liver metastases[4-7]. Thus, patients receive computed tomography (CT) first, followed by liver surgery, before and/or after CRT depending on the team. Triplet CT and newer targeted therapies such as cetuximab and bevacizumab have led to improved response rates at both sites[8] and conversion rates to hepatic resectability[9,10].

Rectal pathological complete response has been observed in 15%-20% of patients after standard CRT[11] and in up to one-third of cases after adding triplet CT, following the same pattern as that for patients with metastases[12].

In these conditions, the question of whether to maintain the indication for radical surgery or total mesorectal excision (TME) has been raised by several therapeutic trials evaluating rectal-sparing strategies in patients without metastasis[13,14]. In France, the most widely evaluated strategy is local excision (LE) *via* the transanal approach. This strategy is reserved for patients with an initially favorable lesion (T2 or low T3 of less than 40 mm). The rationale of this strategy compared to radical surgery is based on the preservation of quality of life (QoL) and digestive and urogenital functions with identical oncological efficacy owing to rectal preservation and the absence of surgical nerve damage[15,16]. Recent studies have shown that LE is a safe alternative for TME for patients who are good responders after CRT for T2T3N0-1 mid-to-low rectal cancer[13,17] with a 5-year local recurrence rate of 7%. Although this strategy has not been evaluated in patients with metastases, the rationale remains similar, i.e., to improve the QoL of patients whose prognosis is related to a higher risk of hepatic recurrence than the risk of local recurrence. Thus, this study aimed to assess long-term outcomes of a rectal-sparing approach in a liver-first strategy for selected patients with rectal cancer with resectable liver metastases.

CASE PRESENTATION

Chief complaints

Between 2010 and 2015, 65 patients were treated for rectal cancer (≤ 8 cm from the anal verge) with synchronous resectable liver metastases at the Institut Paoli-Calmettes, Marseille (France). Eight (12.3%) underwent a rectal-sparing strategy.

Data were prospectively collected from a clinical database labeled by the National Institute for Data Protection (NCT 02869503). The study was approved by institutional review board and consent was waived owing to the retrospective nature of the study.

History of present illness

Seven patients were men, and the mean age of the patients was 65 years. Patient characteristics are summarized in Table 1. All patients had poor long-term prognoses with elevated carcinoembryonic antigen (CEA) levels (n = 2) and

Table 1 Demographic data

Patient No.	Age (yr)	Sex	BMI	Comorbid conditions	ASA score	CEA level	Rectal tumor		Liver metastasis			
							Size (mm)	Distance to anal verge (mm)	staging	Nb of lesions	bilobar	Size of the largest metastasis
1	65	M	31	HTN, DM, Smocking	2	14000	40	30	T3N1	15	1	73
2	78	M	29	HTN	2	55	25	40	T3N1	1	0	46
3	58	M	23	DM, Smocking	3	18	18	25	T3N1	3	1	25
4	77	M	24	HTN	2	134	30	50	T3N1	2	0	42
5	68	M	26	Myasthenia	2	7	30	38	T3N0	5	1	70
6	58	M	25	Smocking	2	1	40	25	T3N1	13	1	20
7	59	M	27	COPD	2	27	40	20	T3N1	6	1	26
8	64	F	23	HTN	2	281	25	35	T3N1	2	0	52

BMI: Body mass index; ASA: American society of anesthesiologists; CEA: Carcinoembryonic antigen; HTN: Hypertension; DM: Diabetes mellitus; COPD: Chronic obstructive pulmonary disease.

more than two lesions (n = 5).

Laboratory examinations

Tumors were classified using the 8th Union for International Cancer Control/tumour-node-metastasis staging system[18]. R0 resection included a surgical margin of at least 1 mm for both LE and TME specimens. Tumor regression grade (TRG) was scored according to the Dworak classification[19].

Based on histopathological findings, LE was considered adequate, and patients were observed without further surgery when the following favorable features were present: YpT0, ypT1, in-depth and lateral R0 resection, and on a case-by-case basis, ypT2 with favorable TRG 1 or 2. LE was considered inadequate and TME was recommended in other cases (ypT3 or higher, positive margins, TRG of at least 3, or lymphovascular invasion). An R0 Liver resection was defined as microscopically tumor-free resection margin.

Imaging examinations

Initial evaluation included thoracoabdominopelvic CT, rectal and liver magnetic resonance imaging (MRI), endorectal ultrasound (EUS) and CEA test before and after 4-6 cycles of CT. All patients suitable for neoadjuvant treatment and surgery (performance status < 3) first received CT. Complete reassessment was systematically performed after 4-6 cycles of CT according to the same modalities. In patients with stable liver disease or those with expected clinical response after margin negative resection (R0), pelvic CRT was performed followed by liver surgery in the interval between pelvic CRT completion and planned rectal surgery, as an optimized liver-first strategy (Figure 1).

MULTIDISCIPLINARY EXPERT CONSULTATION

The oncological strategy was chosen as a function of the overall condition of the patient and the resectability of the liver metastasis and rectal tumor in our multidisciplinary meetings (including liver surgeons, rectal surgeons, oncologists, radiotherapists, radiologists, and pathologists).

FINAL DIAGNOSIS

Rectal sparing within a liver-first strategy for rectal cancer with resectable liver metastases.

TREATMENT

Medical treatment: Liver-first strategy

All patients received neoadjuvant CT in line with current recommendations[2,9] and concomitant normofractionated chemoradiation (45-50 Gy in 25 fractions combined with capecitabine).

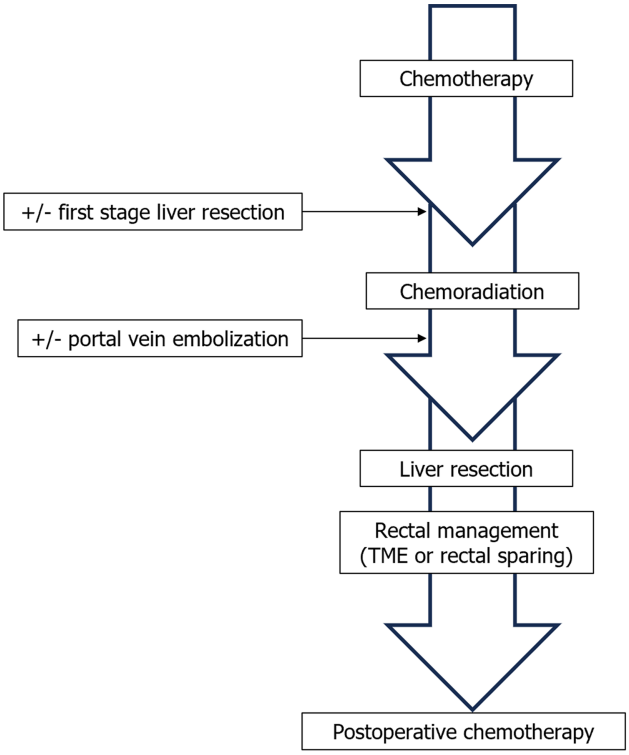

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Figure 1 Flow chart representing the scheme of the liver-first strategy for rectal cancer with resectable liver metastases. TME: Total mesorectal excision.

Liver surgery

Liver surgery was scheduled according to response to CT. When the expected future liver remnant was < 30% of the initial volume, portal venous embolization was performed to prevent postoperative liver failure. Liver surgery was performed in one or two stages and consisted of anatomical or non-anatomical resections, and/or thermoablations.

Rectal surgery

Rectal surgery was performed 8-12 wk after CRT completion. A rectal-sparing strategy was proposed for patients with initially favorable lesions (low T3 or < 40 mm with extramural vascular invasion < 3) and a good or complete clinical response after CT and CRT. A good clinical response was defined by the absence of a mass on digital rectal examination and a residual scar of 2 cm or less with no vegetative component, significant hollow, or deep infiltration into the muscular layer[13].

A watch-and-wait (WW) strategy was proposed in the absence of residual lesions. In other cases, an LE was performed with conventional full-thickness excision of the tumor or scar and the rectal wall *via* direct or transanal endoscopic microsurgery, including 1-cm lateral tissue margins. The deep margin corresponding to mesorectal fat was inked by the surgeon before being sent for histopathological analysis.

Follow-up in all patients consisted of physical examination and thoracoabdominal CT 1 mo after the last surgery and then every 3 mo. In addition, EUS and pelvic MRI were performed every 3 mo. Local recurrence was defined as a radiologically and biopsy-proven pelvic tumor. Distant recurrence was defined as radiological evidence of a tumor in any distant organ. Disease recurrence was defined as a suspicious lesion on imaging in the setting of an elevated CEA level and pathological confirmation. Overall survival and disease-free survival were determined based on the diagnosis. Patients considered disease free were censored at the time of the latest follow-up clinical assessment.

OUTCOME AND FOLLOW-UP

Liver surgery

All patients had unfavorable long-term prognoses with multiple (n = 6), often bilobar (n = 5), or bulky (n = 4) lesions (Table 2). An increased CEA level was observed in seven patients. Liver surgery was performed in one (n = 6) or two stages (n = 2). Portal vein embolization was necessary in three patients. The postoperative mortality rate was nil. Only one patient had severe complications and required radiological drainage of the bilioma. The R0 resection rate was 100%.

Table 2 Oncologic and surgical treatment

Patient No.	Preoperative treatment	Liver surgery			Rectal strategy				Postoperative treatment
		Type	PVE	Two stage	Restaging	Type	Delay[1]	Histologic analysis	
1	Folfox × 12 then CRT	Major hepatectomy	1	0	T0N0	LE	9	T0R0	0
2	Folfiri × 6 then CRT	Segmentectomy	0	0	T0N0	LE	11	T0R0	Patient's refusal
3	Folfox × 10 then CRT	Major hepatectomy	0	0	T1N0	LE	9	T0R0	0
4	Folfox × 4 then CRT	Major hepatectomy	0	0	T0N0	LE	12	T2R0 (TRG1)	Folfiri-cetux × 8
5	Folfirinox × 8 then CRT	Major hepatectomy + Tum + RF	1	1	T2N0	LE	11	T0R0	
6	Folfirinox × 6 then CRT	Major hepatectomy + Tum + RF	1	1	T1N0	LE	10	T2R0 (TRG1)	Folfox × 6
7	Folfirinox × 4 then CRT	Tum + RF	0	0	T0N0	WW	-	-	Folfox × 8
8	Folfiri cetux × 6 then CRT	Tum + segmentectomy	0	0	T0N0	WW	-	-	Folfox × 6

[1]Delay between the end of chemoradiation and rectal surgery. CRT: Chemoradiation; PVE: Portal vein embolization; RF: Radiofrequence; LE: Local excision; WW: Watch and wait; TRG: Tumor regression grade.

Rectal primary management

All patients had locally advanced rectal tumors at diagnosis and were good (n = 6) or complete (n = 2) clinical responders to CRT (Table 2). The median interval between CRT completion and rectal examination was 10 (range, 9-12) mo. In the absence of a visible scar, the WW strategy was performed in two patients. In other cases, patients underwent LE and histopathological analysis confirmed a good tumor response in all patients. No TME completion was necessary. Four patients had tumors defined as ypT0 and two patients had tumors defined as ypT2 with a favorable TRG score; the R0 resection rate was 100%. Postoperative mortality and severe morbidity rates were nil.

Long-term outcomes

The median follow-up duration was 82 mo (range, 48-142). Two patients developed metastatic recurrence of the disease in the liver at 8 and 11 mo and underwent curative treatment for the recurrence. Currently, the patients are in remission. Local rectal recurrence concomitant with liver recurrence occurred in one patient after the WW strategy at 24 mo after rectal examination. The patient underwent second-line CT followed by curative surgery for liver recurrence but refused TME. Only one patient died owing to laryngeal cancer, which was diagnosed 3 years after completing treatment for rectal cancer.

DISCUSSION

Currently, the treatment of colorectal liver metastases (CRLM) remains a major clinical challenge without a consensus [20]. The case-by-case treatment strategy is determined according to: (1) Tumor and disease-related characteristics, patient-related factors, and treatment-related factors such as toxicity and main oncological problems; (2) presence or absence of predictive factors for rectal and liver resection morbidity; and (3) response to initial CT. New regional and systemic chemotherapies associated with biological agents combined with technical advances in liver surgery have made it possible to broaden indications for CRLM resection by offering personalized treatment.

For rectal tumors, TME remains the only available treatment option with curative intent in patients with metastatic rectal cancer, regardless of the response to neoadjuvant therapy. However, a complete clinical response or a very good response is observed in 15%-20% of patients after standard CRT and in up to one-third of cases after addicting CT, as suggested by a recent randomized controlled trial (RCT) in patients without metastasis[12,21].

Rare cases of rectal-sparing strategies in patients with metastases have been described: WW[22,23] and LE[4] in the liver-first strategy. A WW strategy was used in nine cases as a result of primary tumor disappearance after RCT[22-24]. Unfortunately, no study has specified the characteristics of rectal lesions or oncological outcomes of these patients. Mentha *et al*[4] and Buchs *et al*[25] reported two cases of LE with complete clinical response after RCT. One case in 2006[4] did not have any long-term data. Another case in 2015[25] had a confirmed pathological response after RCT but had recurrence 11 mo later and underwent abdominoperineal resection with a final staging of pT3Nx.

In a Dutch study[7], a rectal-sparing strategy could have been proposed in ten patients who had a complete response of their primary tumor after complete treatment according to a liver-first strategy, as introduced by Mentha *et al*[4]. This strategy involves systematic preoperative CT and resection of CRLM, followed by pelvic RCT and rectal resection. In our optimised liver-first strategy, liver surgery is performed at the interval between radiotherapy completion and rectal surgery. This strategy allows rectal re-evaluation without increasing the time without CT. Prolonging the interval between CRT completion and rectal staging increases the complete clinical response rate[26]. Thus, it allows for a better selection of patients who can benefit from a rectal-sparing strategy without increasing surgical morbidity[26,27].

Short-course radiotherapy followed by CT and delayed rectal surgery[21] is an option in the neoadjuvant setting of resectable rectal cancer that could potentially be adapted for patients with metastases[24]. This would make it possible to limit the time without CT while maintaining a delayed rectal reassessment and possibly proposing a rectal-sparing strategy in cases of good clinical response. Nevertheless, the oncological safety of this strategy has not been evaluated in specific studies.

It is important to note that we have a highly selected population after applying the two-stage selection criteria in the organ preservation for rectal cancer (GRECCAR 2) trial; we considered the initial rectal tumor characteristics and the clinical response to CRT. Seven of the eight patients studied had an initial N + tumor according to routine EUS and MRI. The initial lymph node involvement, especially the lymph node response after CT and RCT, is difficult to specify formally [28].

In addition to oncological multidisciplinary meetings, weekly meetings are organized with specialized radiologists and colorectal surgeons to review all examinations, including surveillance MRI, to improve our patient selection. Our results are consistent with those of GRECCAR 2 study[13], as we observed no lymph node recurrence among patients undergoing LE. Four patients had no residual tumor (ypT0), but two patients had residual ypT2 tumors equivalent to a risk of residual lymph node involvement evaluated at 8%. This risk is probably lower given the low TRG (TRG 1: few residual cells). Given the discordant results and the absence of validated criteria, the WW strategy seems to be reserved only for patients without residual scarring and is subject to very strict surveillance.

In patients without metastasis, the GRECCAR 2 trial's 5-year results provide no evidence of differences in long-term survival (84% *vs*. 82%; $P = 0.85$) or cancer-specific mortality (7% *vs*. 10%; $P = 0.53$) between LE and TME[17].

In all cases, a favorable pathological response is associated with good prognosis and survival benefit[29]. Under these conditions, whether to maintain the indication for radical surgery in good responders or even in complete clinical responders is an issue that has never been raised in patients with metastases.

The oncological safety of rectal-sparing strategy has never been evaluated in patients with metastases but needs to be balanced with morbidity or functional benefits. Minimizing operative morbidity is a major issue for strategy treatment choice as it is an independent factor for overall survival and disease-free survival after CRLM resection[30]. The rectal-sparing strategy induces a more favorable global health status and bowel function than TME after CRT[16,31]. The effect of rectal cancer treatment on functional outcomes and patients' QoL must now be considered in the decision-making process whenever possible.

To the best of our knowledge, this is the first study to provide detailed characteristics and long-term results of patients undergoing a rectal-sparing strategy for rectal cancer with synchronous liver metastasis. Our results are encouraging compared to the prognoses of patients with metastases in the literature because only one patient had a local rectal recurrence with concurrent hepatic recurrence using the WW strategy 3 years after liver surgery.

The present study has some limitations and caution must be exercised in interpreting its results given the small sample size. The rectal-sparing strategy requires coordinated action by a multidisciplinary team and depends on many criteria, including treatment times and tumor response to therapy. Moreover, patients are not always referred to our center at the time of diagnosis and have already started CRT, which does not allow for a first liver strategy and limits potential inclusions.

Second, this was a retrospective single-center study. In the absence of clear recommendations, practices vary widely from one center to another in the surgical and oncological management of CRLM, which hinders the realization of a multicenter study. Imposing the same protocol on several teams and institutions, with selection criteria often different from their usual practice, is an obstacle to its large-scale implementation.

CONCLUSION

In conclusion, although our findings should be interpreted with caution given the small sample size and high patient selection, we suggest that rectal-sparing strategies must become an option in expert centers to improve the QoL of patients with CRLM.

FOOTNOTES

Author contributions: Meillat H, Lelong B, Ewald J, Mitry E study conception and design; Palen A, Garnier J, Tyran M acquisition of data; Meillat H, Garnier J analysis an interpretation of data; Meillat H, Palen A, Mitry E drafting of manuscript; de Chaisemartin C, Lelong B, Tyran M, Ewald J critical revision of manuscript; All authors have reviewed and approved the final manuscript.

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CASE REPORT

Metachronous primary esophageal squamous cell carcinoma and duodenal adenocarcinoma: A case report and review of literature

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Abstract

BACKGROUND

The prevalence of multiple primary malignant neoplasms (MPMNs) is increasing in parallel with the incidence of malignancies, the continual improvement of diagnostic models, and the extended life of patients with tumors, especially those of the digestive system. However, the co-existence of MPMNs and duodenal adenocarcinoma (DA) is rarely reported. In addition, there is a lack of comprehensive analysis of MPMNs regarding multi-omics and the tumor microenvironment (TME).

CASE SUMMARY

In this article, we report the case of a 56-year-old man who presented with a complaint of chest discomfort and abdominal distension. The patient was diagnosed with metachronous esophageal squamous cell carcinoma and DA in the Department of Oncology. He underwent radical resection and chemotherapy for the esophageal tumor, as well as chemotherapy combined with a programmed death-1 inhibitor for the duodenal tumor. The overall survival was 16.6 mo. Extensive evaluation of the multi-omics and microenvironment features of primary and metastatic tumors was conducted to: (1) Identify the reasons responsible for the poor prognosis and treatment resistance in this case; and (2) Offer novel diagnostic and therapeutic approaches for MPMNs. This case demonstrated that the development of a second malignancy may be independent of the location of the first tumor. Thus, tumor recurrence (including metastases) should be distinguished from the second primary for an accurate diagnosis of MPMNs.

CONCLUSION

Multi-omics characteristics and the TME may facilitate treatment selection, improve efficacy, and assist in the prediction of prognosis.

Key Words: Multiple primary malignancies; Esophageal tumor; Duodenal adenocarcinoma; Multi-omics; Tumor microenvironment; Case report

Core Tip: Multiple primary malignant neoplasms (MPMNs) are increasingly prevalent in clinical practice, most frequently in the digestive system. We report a rare case of MPMN with a combination of esophageal squamous cell carcinoma and duodenal adenocarcinoma. According to PubMed-indexed literature, there are no standard guidelines or expert consensus on the etiology and comprehensive treatment. We also conducted a detailed study of the features of primary and metastatic tumors. The aim of this report was to identify the reasons responsible for the poor prognosis and treatment resistance in this case through histological data and provide new diagnostic and treatment directions for MPMNs.

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INTRODUCTION

Multiple primary malignant neoplasms (MPMNs), also termed multiple primary cancers, refer to two or more primary tumors that occur simultaneously or sequentially in a single or multiple organs[1]. According to the time interval from the diagnosis of the first tumor, MPMNs are divided into synchronous cancer (SC) (< 6 mo) and metachronous cancer (MC) (≥ 6 mo)[2]. The detection rate of the second or multiple primary tumors is also on the rise due to newer diagnostic methods and treatments, as well as the longer survival times of patients with cancer. MPMNs are most commonly reported in the digestive system; however, their occurrence in combination with duodenal adenocarcinoma (DA) is extremely rare. In this article, we describe the case of a patient who had metachronous esophageal squamous cell carcinoma (ESCC) and DA with multiple metastases. In this analysis, we thoroughly examined the multi-omics features and tumor-related immune microenvironment.

CASE PRESENTATION

Chief complaints

A 56-year-old Chinese man presented to a local hospital with a complaint of chest discomfort and abdominal distension.

History of present illness

The symptoms developed 2 mo before presentation to hospital.

History of past illness

Endoscopic examination, performed on February 1, 2021, revealed the presence of ulcerative lesions in the left wall of the esophagus. These lesions were brittle and prone to bleeding when touched. Frosty ulcers were also detected in the duodenal bulb. Histopathological analysis of the esophagus indicated moderately differentiated squamous cell carcinoma. The patient visited the Thoracic Surgery Department of the General Hospital for further treatment. The preoperative levels of alpha-fetoprotein were 16.6 ng/mL (0-7 ng/mL), whereas those of other gastrointestinal tumor indicators were within the normal range. The upper gastrointestinal tract barium meal revealed a localization in the lower and middle esophagus (Figure 1A). Further evaluation through enhanced computed tomography (CT) of the chest and upper abdomen showed thickening and enhancement of the lower esophagus wall (Figure 1B). A thoracoscopic laparoscopy combined with radical resection of esophageal tumors was carried out on February 24, 2021. Postoperative pathological analysis revealed that the tumor was completely located in the esophagus and did not involve the gastroesophageal junction; the tumor dimensions were 3 cm × 2 cm × 1 cm. The examination confirmed the presence of a highly differentiated squamous cell carcinoma (Figure 1C), staged according to pTNM, American Joint Committee on Cancer 8th Edition: Phase IIIA (T2N1M0). As shown in Table 1, a pathological investigation demonstrated nerve invasion, while immunohistochemistry indicated proficient mismatch repair (pMMR). Subsequently, an adjuvant DP chemotherapy regimen (cisplatin 20 mg through intravenous infusion on days 1-5 combined with doxorubicin 60 mg on days 1 and 8) was initiated (one cycle per 3 wk) from postoperative day 37 to July 29, 2021. The administration of treatment was delayed due to the development of anemia. Consequently, a total of three cycles were carried out during this period. According to the RECIST 1.1 guideline, the condition was evaluated as a stable disease.

Table 1 Genetic testing and immunohistochemical data

Gene	Mutant/variation	Plasma	Esophagus	Duodenum	Liver
CDKN2A	c.322G>T (p.D108Y)	-	22.0%	-	-
NF1	c.6173 7127-1115del	9.1%	-	3.2%	0.9%
TP53	c.560-2A>T	0.1%	15.4%	-	-
TP53	c.557 558delinsG	-	13.1%	-	-
APC	Deletion mutation	7.8%	-	8.2%	1.5%
CCND1	Amplification	-	CN:5.1	-	-
FGF19	Amplification	-	CN:4.4	-	-
MDM2	Amplification	-	-	CN:4.4	-
SMAD4	c.456 478dup	23.4%	-	17.1%	5.9%
SMARCA4	c.2506G>T (p.G836*)	-	-	6.9%	-
CREBBP	c.6666 6677del	0.1%	-	-	3.4%
EP300	c.4751 4752delinsAT	-	12.2%	-	-
GATA3	c.527 528delinsAG	-	-	2.1%	-
RPTOR	c.2000T>C (p.L667P)	-	2.3%	-	-
TMBs		5.1/Mb (50.4%)	8.2/Mb (29%)	4.1/Mb (59.3%)	3.1/Mb (68.9%)
Microsatellite analysis		MSS/MSI-L	MSS/MSI-L	MSS/MSI-L	MSS/MSI-L
MMR-related mutations		None	None	None	None
Immunohistochemistry					
CR			-		
D2-40			-		
Ki67			About 67%+		About 70%+
P40			+	-	-
S-100			+		
SMA			+		
CAM5.2				+	
CD56				-	
CgA				-	
P63				-	
Syn				-	
CDH17				-	
CDX2					Weak +
CK19					+
CK20					-
CK7					+
SATB2					-
TTF					-
Villin					+
Her2			+	+	
MLH1			Complete expression	Complete expression	
MSH2			Complete expression	Complete expression	
MSH6			Complete expression	Complete expression	

MSH6	Complete expression	Complete expression	
PD-L1	< 1%+	CPS < 1	
EBER	-		-
EGFR	3+	2+	
VEGF	-	-	
CD15	Part+	-	Part-
CD163	+	+	+
CD4	About 5%+	About 8%+	About 10%+
CD68	+	+	+
CD8	About 10%+	About 5%+	About 15%+

CDKN2A: Cyclin-dependent kinase inhibitor 2A; NF1: Neurofibromin 1; TP53: Tumor protein p53; APC: Adenomatosis polyposis coli; CCND1: Cyclin D1; FGF19: Fibroblast growth factor 19; MDM2: Mouse double minute 2; SMAD4: SMAD family member 4; SMARCA4: SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily A, member 4; CREBBP: Recombinant CREB binding protein; EP300: E1A binding protein p300; GATA3: Recombinant GATA blinding protein 3; RPTOR: Regulatory-associated protein of mTOR; TMBs: Tumor mutational burdens; MSS: Microsatellite stability; MSI-L: Microsatellite instability-low; MMR: Mismatch repair; CR: Calretinin; P40: Protein 40; SMA: Smooth muscle actin; CAM5.2: Cell adhesion molecule 5.2; CD56: Cluster of differentiation 56; CgA: Chromogranin A; CDH17: Cadherin 17; CDX2: Caudal type homeobox 2; CK7: Cytokeratin 7; SATB2: Special AT-rich sequence-binding protein 2; TTF: Thyroid transcription factor; MLH1: MutL homolog 1; MSH2: MutS homolog 2; MSH6: Muts homolog 6; PD-L1: Programmed death-ligand 1; EBER: Epstein barr encoded RNA; EGFR: Epidermal growth factor receptor; VEGF: Vascular endothelial growth factor.

Personal and family history

The patient had a history of hypertension and syphilis with symptomatic treatment, and a 30-year history of smoking. However, he denied alcohol consumption, and did not report any family history of malignant tumors.

Physical examination

On physical examination, the vital signs were as follows: Body temperature, 36.5 °C; blood pressure, 137/88 mmHg; heart rate, 83 beats per min; respiratory rate, 18 breaths per min. Furthermore, the patient exhibited an anemic appearance without iris and skin jaundice. There was no abdominal pressure or percussion pain.

Laboratory examinations

The levels of serum tumor markers were mostly normal (carcinoembryonic antigen, 2.79 ng/mL; carbohydrate antigen 19-9, < 2 U/mL), except for alpha-fetoprotein (17.2 ng/mL; normal range: 0-7 ng/mL) without clinical significance. The concentration of hemoglobin in blood was 68 g/L. There were no abnormalities found in other routine blood, urine, and fecal analyses.

Imaging examinations

During the postoperative checkup, CT enhancement of the upper abdomen (September 28, 2021) revealed multiple liver metastases (diameter of the largest lesion: 1.5 cm) (Figure 1D). After consultation, the patient was referred to the Department of Oncology for treatment. On October 19, 2021, a needle biopsy of liver mass was performed under ultrasound guidance. The postoperative pathological findings suggested that the liver lesion was compatible with invasive intermediate differentiated adenocarcinoma (Figure 1E). According to the immunohistochemistry findings, the biliopancreatic duct, gastric, and small intestinal sources were considered, as detailed in Table 1. Before the biopsy, a gastroscopy and magnetic resonance enhancement of the abdomen were performed additionally. The former revealed the presence of an ulcerative neoplasm in the descending portion of the duodenum (Figure 1F). The latter indicated multiple metastases in the liver, occupancy of segments 2-3 of the duodenum, and the need for the identification of spinal metastases (Figure 1G). Consequently, a further bone scan was carried out, which detected an abnormal radio concentration lesion in the right iliac bone. Ultimately, pathological examination of the biopsied specimen confirmed a moderately to poorly differentiated DA (Figure 1H), with immunohistochemistry indicating a combined positive score < 1 and pMMR (Table 1). Additionally, the esophagus, duodenum, hepatic lesions, and peripheral blood of the patient were analyzed for 473 genetic loci (Table 1).

FINAL DIAGNOSIS

Based on the examination results and medical history, the patient was eventually diagnosed with esophageal squamous carcinoma postoperative stage IIIA (pT2N1M0) and DA stage IV (cTxNxM1) (liver metastasis, bone metastasis) after multi-disciplinary evaluation.

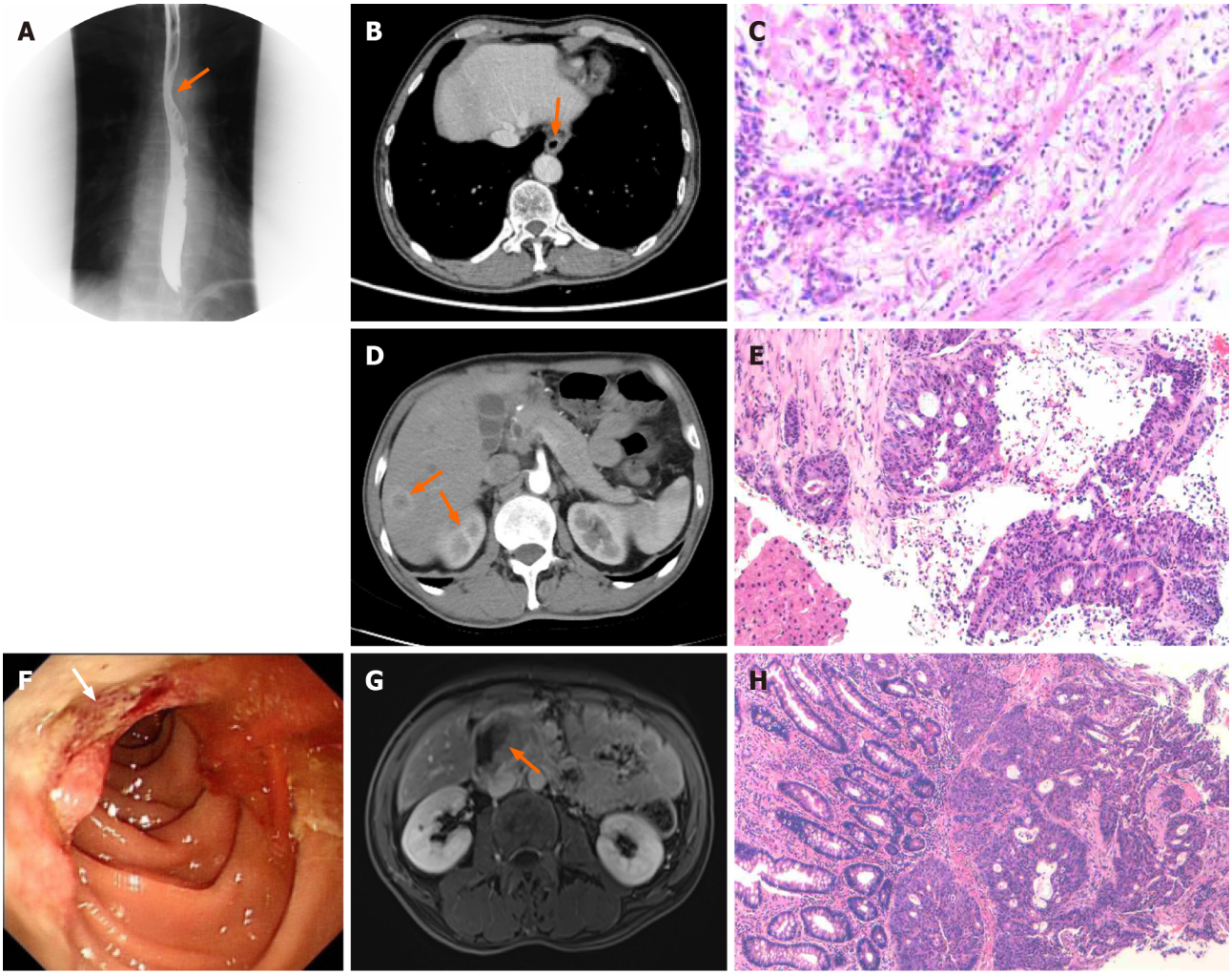

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Figure 1 Diagnostic information of primary carcinomas and metastases. A: The upper gastrointestinal tract barium meal revealed a localization in the lower-middle esophagus on February 20, 2021; B: The enhanced computed tomography (CT) scan of the chest and upper abdomen showed thickness and enhancement of the lower esophagus wall on February 19, 2021; C: Postoperative pathology revealed that the tumor was completely located in the esophagus on February 24, 2021. It was a highly differentiated squamous cell carcinoma (original magnification × 200); D: Abdominal CT enhancement showed multiple metastatic nodules in the liver on September 18, 2021; E: "A needle biopsy of liver mass" was done under ultrasound guidance, and the pathology suggested that the liver lesion was compatible with invasive intermediate differentiated adenocarcinoma on October 19, 2021 (original magnification × 200); F: The gastroscopy revealed an ulcerated neoplasm in the descending portion of the duodenum on October 13, 2021; G: Abdominal magnetic resonance imaging showed an occupancy in the descending and horizontal parts of the duodenum on October 10, 2021; H: Pathology of needle biopsy revealed a medium-low differentiated adenocarcinoma (original magnification × 100).

TREATMENT

The patient received two cycles of XELOX (oxaliplatin 160 mg through intravenous infusion on day 1, combined with capecitabine 1.5 g orally twice daily on days 1-14 every 21 d). This was followed by CT enhancement performed on October 22, 2021, to evaluate progressive disease (PD). Therefore, from December 9, 2021, the treatment plan was changed to GS (gemcitabine 1.2 g through intravenous infusion on days 1 and 8, combined with tegafur 40 mg orally twice daily on days 1-14 every 21 d) along with a programmed death-1 (PD-1) inhibitor (sintilimab 200 mg through intravenous infusion on day 1). However, despite the two cycles of chemotherapy, the condition continued to be rated as PD (January 28, 2022) by CT. Due to the high cost of sintilimab, the regimen was changed to one cycle of monotherapy with irinotecan (200 mg through intravenous infusion on day 1) on January 29, 2022. The patient later declined to continue a second cycle of irinotecan chemotherapy due to a low nutritional state and prolonged grade IV myelosuppression. The tumor continued to grow rapidly after two cycles of immunotherapy with sintilimab again, and all anticancer therapy was discontinued.

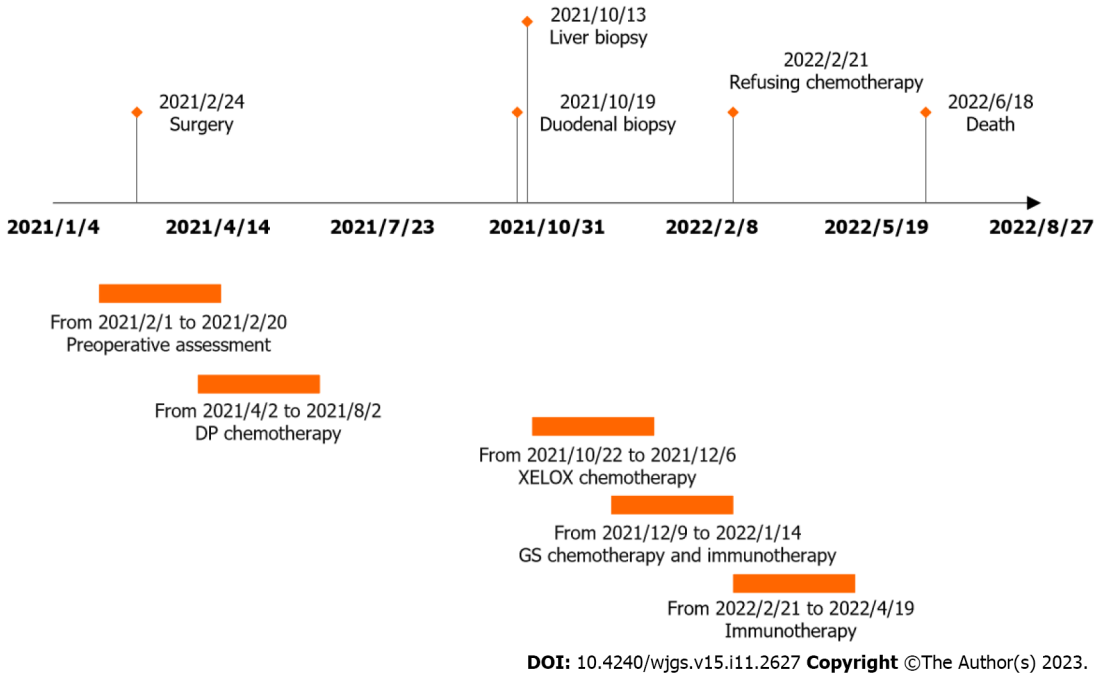

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Figure 2 Time points correspond to the diagnostic and therapeutic process. DP: Doxorubicin and platinum; GS: Gemcitabine and s-1.

OUTCOME AND FOLLOW-UP

The patient was eventually followed up until clinical death on June 18, 2022 (Figure 2), with an overall survival (OS) of 16.6 mo.

DISCUSSION

The prevalence of MPMNs is increasing in parallel with the incidence of malignancies, the continual improvement of diagnostic models, and the extended life of patients with tumors. MPMNs represent 0.7%-11.7% of all cancer cases worldwide[3]. In China, this rate is only 0.99%[4]. A multicenter investigation demonstrated that MPMNs are more commonly detected in individuals aged > 65 years. Men are associated with a higher incidence rate than women, and MC is significantly more common than SC[5]. MPMNs are prevalent in the digestive system[6]. The morbidity rate of MPMNs linked to esophageal cancer ranges from 9.5% to 21.9%[7], with gastric (4.7%), head and neck (2.7%), colorectal (1.2%), and lung (0.7%) cancer being the most common types of combined malignancies. It has also been discovered that approximately one in five patients with ESCC who survive > 6 mo in Western societies develop a second primary cancer within 15 years[8]. Notably, due to the rarity of small bowel tumors and their nonspecific symptoms[9], primary DA and associated MPMNs are rarely reported. Even fewer studies that examine the genomics and immunomics of MPMNs in depth have been published. In this article, we provide a thorough assessment based on the current diagnostic and therapeutic options for MPMNs, taking into account the case of MC. We also conducted an extensive evaluation of the immune microenvironment features of primary and metastatic tumors. Through the analysis of histology data, we sought to: (1) Identify the reasons responsible for the poor prognosis and treatment resistance observed in this case; and (2) Offer novel diagnostic and therapeutic approaches for MPMNs.

The etiology of MPMNs has not been identified; potential causes include abnormal activation of oncogenes, silencing of oncogenes, epigenetic alterations, chromosomal instability, immunodeficiency, environmental exposure, and unhealthy lifestyle habits[10]. The patient in this case had a long history of smoking, which is a risk factor for MPMNs. Of note, the esophagus and duodenum originate in the foregut, and mutation of the lining cells during intrauterine life cannot be excluded in this case.

Tumor recurrence (including metastases) should be distinguished from the second primary for an accurate diagnosis of MPMNs. Firstly, the initial gastroscopic examination at another regional center hospital without pathological biopsies revealed the presence of ulcerative lesions in the duodenal bulb. This finding emphasized the need for a comprehensive assessment at the time of diagnosis of the first tumor. Moreover, a thorough histological analysis of each abnormal lesion is crucial. Secondly, rather than automatically assuming that newly discovered lesions are tumor metastases, clinicians ought to be alert to any new lesions that arise while a patient is receiving therapy. There is a rare possibility of primary or metastatic lesion involvement in the duodenum. Of note, lung cancer, renal cell carcinoma, breast cancer, and malignant melanoma are the most common types of primary tumors that metastasize to the pancreaticoduodenal region[11]. Thirdly, though rare, the incidental detection of one or more additional primary tumors during CT staging of a patient with a known malignancy is possible. Following the detection of masses in the liver by radiologists, an intensive search

and identification of the primary site should be performed. The selection between CT, magnetic resonance imaging, positron emission tomography, and ultrasound depends on the tumor type or body region[12]. However, CT (especially contrast-enhanced CT) remains the preferred modality for the staging of tumors and evaluation of treatment efficacy in patients diagnosed with cancer[13]. In addition, the appearance and progression of liver metastases on CT were accompanied by an increase in the levels of carbohydrate antigen 72-4 and carcinoembryonic antigen (Table 2). A dramatic increase in the levels of carcinoembryonic antigen when liver metastases continue to spread and the burden of systemic tumors continues to rise, which may indicate rapid progression of disease.

Factors that affect the prognosis of patients with MPMNs include age at initial cancer diagnosis (≥ 60 years) and tumor stage[14]. The 2- and 5-year survival rates of patients with MPMNs are 40.8% and 4.6%, respectively[4]. The median OS for patients with MC-MPMNs and SC-MPMNs is 91 mo and 30 mo, respectively[15]. The presence of MC-MPMNs and patient age < 60 years at the time of initial diagnosis of the primary tumor indicate a good prognosis. Nevertheless, the OS of the present patient was only 16.6 mo. Therefore, it is necessary to further analyze the reasons responsible for the poor prognosis. Although studies on the tumor microenvironment (TME) have yielded some promising results, there is a lack of investigations focusing on MPMNs. In this case, we examined several areas (*i.e.*, genomics, immunomics, inflammatory markers, and lipid metabolism) to accurately explain the histological features of the three malignancies identified in this patient.

Firstly, the development of second malignancies is largely caused by genetic susceptibility, with approximately 100 mutated genes causing one or more cancers[16]. The "multicentric origin" theory[17,18] suggests that different primary cancers in the same patient may have different mutation profiles and be driven by different genes. Patients with two or more characteristic cancers (synchronous or asynchronous) should undergo genetic testing. Therefore, in this case, the patient underwent prompt genetic testing after the discovery of DA. Table 1 demonstrates the results of gene high-throughput sequencing. Interestingly, cyclin-dependent kinase inhibitor 2A (*CDKN2A*), tumor protein p53 (*TP53*), cyclin D1 (*CCND1*), and E1A binding protein p300 (*EP300*) showed mutations only in ESCC tissue, while neurofibromin 1, adenomatosis polyposis coli (*APC*), and SMAD family member 4 (*SMAD4*) showed mutations in peripheral blood, the duodenal tumor, and liver metastatic carcinoma. Similarly, genes involved in the cell cycle and apoptosis regulation (*e.g.*, *CDKN2A*, *TP53*, and *CCND1*) are mutated in 99% of ESCC cases[19]. In particular, increased *CDKN2A* gene deletion in somatic cells, which is mainly reported in lung and upper gastrointestinal tumors, may provide an early warning sign of esophageal cancer. In this case, the rate of *CDKN2A* gene mutation in the esophageal tumor tissue was 22%, suggesting a poor prognosis. In addition, the *EP300* gene is involved in the epigenetic process of histone modification in ESCC, and is associated with poor prognosis[20,21]. We found few genetic studies on primary duodenal cancer. The detection of duodenal lesions revealed in this case was based on the findings of Schrock *et al*[22] in genomic studies of small bowel cancer. The investigators of that study concluded that *APC* and *SMAD4* are commonly altered genes, and the rate of *APC* mutations is relatively low.

Secondly, some immunohistological features have been identified as susceptibility factors for second primary carcinogenesis. It has been suggested that microsatellite instability (MSI) and defective DNA damage repair are associated with the occurrence of MPMNs[23]. The probable mechanism underlying this relationship is the existence of Lynch syndrome, a genetic disorder caused by mutations in mismatch repair genes. MSI appears to be more prevalent in MPMNs than sporadic cancers. Cancer of the small intestine belongs to the Lynch syndrome spectrum of tumors. The lifetime risk in carriers is 4%, independent of the development of colon cancer[24]. Immunohistochemical typing of both primary tumor tissues in this case revealed pMMR. In addition, gene sequencing suggested that the MSI status was microsatellite stability, indicating that this patient was less likely to have Lynch syndrome and suggesting possible low responsiveness to immunotherapy.

Thirdly, the TME is a complex system consisting of multiple cell types. Previous studies showed that CD68 and CD163 are phenotypic markers of M1- and M2-type tumor-associated macrophages (TAMs), respectively[25]. It has been shown that increased numbers of CD163 + M2 macrophages contribute to angiogenesis, tumor aggressiveness, and ESCC progression[26]. These processes can deplete CD8+ T cells that exert specific anti-tumor effects *via* the PD-1/programmed death-ligand 1 (PD-1/PD-L1) pathway, thereby increasing the risk of immune escape of tumor cells[27]. However, there is controversy regarding the relationship between CD68 + M1 macrophages and the prognosis of gastrointestinal malignancies. Wang *et al*[28] concluded that the extent of CD68+ macrophage infiltration was negatively associated with survival time and prognosis. In contrast, Tang *et al*[29] argued that the abundance of CD68+ TAMs is not associated with ESCC progression, while that of CD163+ M2 TAMs is a potential risk factor. Based on data reported by previous studies and the validation of the clinical prognosis prediction of this patient, we performed immunohistochemical staining for CD68 and CD163 molecules in three cancerous tissues. The results showed consistently positive expression; high expression of CD68 and CD163 was associated with a poorer prognosis in this patient[30]. In addition to TAMs, tumor-associated neutrophils may promote T cell-mediated immunity through costimulatory molecules that enhance the proliferation of CD4+ and CD8+ T cells and increase the anti-tumor activity in early-stage disease[31]. As a cell surface glycoprotein regulated by neutrophil function, CD15 is thought to be associated with adverse OS[32]. In this case, the esophageal cancer tissue exhibited positivity for CD15, and the patient had a poor prognosis. These findings are consistent with those of previous studies. Therefore, genomics and immunomics play an important role in determining the degree of tumor malignancy, and can further guide the assessment of the prognosis of MPMNs.

Fourthly, immune-inflammatory cells in peripheral blood play an important role in tumors and can be used to predict prognosis and assess outcomes. It has been reported that the neutrophil-lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMR), and platelet-lymphocyte ratio (PLR) are useful in predicting the prognosis of ESCC. For instance, preoperative high NLR (> 3.29) and low LMR (< 2.95) in patients with ESCC are associated with worse OS[33,34]. Such evidence reflects an imbalance between the pro-cancer inflammatory response and the anti-cancer immune response. Moreover, LMR has been previously proposed as a poor prognostic factor for DA[35]. Furthermore, high PLR is

Table 2 Laboratory date

Date	Reference range	February 19, 2021[1]	March 31, 2021[2]	October 8, 2021[3]	December 7, 2021[4]	January28, 2022[5]	May 14, 2022[6]
CA72-4 (u/mL)	0-6.9	1.64	19.1	6.48	8.61	74.6	227
CEA (ng/mL)	0-5	2.54	2.29	2.79	14.6	47.1	742
AFP (ng/mL)	0-5	16.6	18.8	17.2	18.3	16.2	10.8
NLR	-	7.25	1.47	1.76	2.21	2.21	15.89
LMR	-	1.29	4.07	3.34	2.37	2.37	1.3
PLR	-	376.72	220.86	305.44	278.89	278.89	258.46
IL-6 (pg/mL)	0-5.3	-	-	7.18	7.12	27.82	918.02
IL-8 (pg/mL)	0-20.6	-	-	9.55	10.21	17.73	230.94
ω-3-C22:5 (μmol/L)	0.74-3.11	-	-	0.448	0.529	0.348	0.295
ω-6-C22:5 (μmol/L)	0.37-1.86	-	-	0.293	0.193	0.138	0.136
ω-6/ω-3	< 10	-	-	13.68	18.75	27.01	8.04
UDCA (nmol/L)	40-758	-	-	4.6	4.7	11.3	13.9

[1]Preoperative.
[2]After surgery.
[3]After three cycles of "DP" chemotherapy.
[4]After two cycles of "XELOX" chemotherapy.
[5]After two cycles of immunotherapy.
[6]2 mo after giving up treatment.
CA72-4: Carbohydrate antigen 72-4; CEA: Carcinoembryonic antigen; AFP: Alpha-fetoprotein; NLR: Neutrophil-lymphocyte ratio; LMR: Lymphocyte-monocyte ratio; PLR: Platelet-lymphocyte ratio; IL-6: Interleukin-6; IL-8: Interleukin-8; UDCA: Ursodeoxycholic acid.

associated with poor OS/cancer-specific survival, event-free survival, and malignant phenotype in tumors such as ESCC [36]. In this case, although the preoperative NLR was only 2.09, the LMR was at a low level during radical treatment of esophageal cancer (Table 2), and the PLR was at a high level. These findings are consistent with the poor prognosis of this patient. The overall surveillance trend showed a progressive increase in NLR accompanied by the development of DA and the development of metastases; the opposite was true for LMR. These observations suggest that lower lymphocyte counts and relatively weak anti-tumor immunity may contribute to increased tumor size and poor prognosis. Additionally, the circulating blood inflammation-associated cytokine interleukin-6 (IL-6) is considered a typical pro-tumor cytokine in the IL-6 cytokine family. It is involved in the formation of the local TME and is considered a hallmark feature of tumor growth initiation and progression[37,38]. IL-8 is a pro-inflammatory chemokine, and/or its receptors are expressed in cancer cells, endothelial cells, and TAMs. Increased expression of IL-8 is associated with tumor angiogenesis, tumorigenicity, and metastasis[39]. The present patient had high IL-6 levels (7.18 pg/mL; normal range: 0-5.3 pg/mL) at the time of diagnosis of DA, showing a progressive increase with tumor progression. Following the discontinuation of chemotherapy, the levels of IL-6 and IL-8 rose rapidly at 918.02 pg/mL and 230.94 pg/mL, respectively. These data were highly suggestive of rapid disease progression.

Finally, reprogramming of lipid metabolism is one of the most prominent metabolic alterations in cancer, including fatty acid and bile acid (BA). It has been suggested that ω-3 polyunsaturated fatty acids (PUFA) may exert an anti-angiogenesis effect in tumors, inhibit cancer cell invasion and metastasis, and reverse chemotherapy multi-drug resistance in tumor cells. In contrast, ω-6 PUFA and total PUFA may exacerbate the risk of cancer[40]. According to the fatty acid metabolism indices of this patient (Table 2), the levels of ω-3 PUFA were low, while those of ω-6/ω-3 were higher than the maximum normal value of 10. The high levels of eicosatetraenoic acid, which belongs to the ω-6 group, led to the analysis of the predominance of cancer-promoting factors in this case. Predominance of pro-carcinogenic factors was suggested. In addition, the high-BA environment could promote apoptosis and inhibit the migration of cancer cells, particularly in colon cancer cells[41,42]. However, BA is metabolized by the intestinal microbiota; disruption of the balance between the two systems can lead to abnormal BA concentrations and pools, triggering the abnormal proliferation of intestinal stem cells[41]. In particular, it is thought that ursodeoxycholic acid enhances anti-tumor immunity by degrading transforming growth factor-β, thereby inhibiting the differentiation and activation of regulatory T cells. Moreover, it synergizes with PD-L1 to enhance tumor-specific immune memory[43]. Consequently, the levels of ursodeoxycholic acid in this patient were low throughout the evaluation. This observation is associated, to some extent, with the continuous progression of DA and poor efficacy of immunotherapy.

Currently, there are no standard guidelines or expert consensus for the comprehensive treatment of MPMNs. Therapy is generally based on a combination of several factors, such as patient age, clinicopathological features of the different

tumors, biological and genomic expression profiles, life expectancy, and comorbid diseases. For MC-MPMNs, the treatment approach invariably involves sequential treatment of all tumors; however, for SC-MPMNs, individualized and unique treatment plans are generally developed after multidisciplinary discussions[44]. In this case, the patient presented with two successive asynchronous tumors of different histological origins, namely esophageal squamous epithelial carcinoma and DA. Therefore, radical surgery combined with adjuvant chemotherapy was performed for the esophageal tumor, and complete remission was achieved. For the DA and liver metastases, oxaliplatin-based regimens appear to be the most commonly used and effective options in first-line treatment[45]. In this case, the preferred XELOX regimen did not prevent PD after two cycles of chemotherapy. This unsatisfactory outcome may be attributed to the development of adverse effects linked to chemotherapy for ESCC, such as malnutrition, and bone marrow suppression. These effects are poorly tolerated by patients with a poor physical status. The combination of metastases suggests that the tumor has progressed to an advanced stage and the general treatment is less effective. Mouse double minute 2 (*MDM2*) in genomics may reduce the efficacy of chemotherapeutic agents, such as platinum, by inhibiting the action of *TP53*. It has also been suggested that 5-fluorouracil and capecitabine exhibit poorer efficacy in patients with *TP53* mutation *vs* wild-type *TP53* [46].

The role and efficacy of emerging immunotherapies in DA are currently under investigation. The investigators of the phase II KEYNOTE-158 study concluded that pembrolizumab is an effective option for previously treated patients with MSI-high small bowel adenocarcinoma[47]. Given the possible benefit of immunosuppression with negative PD-L1 expression, this patient was treated with sintilimab in combination with second-line therapy.

However, the effectiveness of immunotherapy is limited, probably due to the following reasons. Firstly, the patient was in an immunosuppressed state before immunotherapy: The CD4+ and CD8+ T cells in three tumor tissues were poorly infiltrated, and immune cells (*e.g.*, lymphocytes, B cells, and natural killer cells) in peripheral blood were below the normal range, particularly neutrophils, CD4+ T and CD8+ T cells. Therefore, overcoming the immunosuppressed state is a major challenge for immunotherapy. Secondly, the PD-L1 expression in the second primary cancer was negative. As an immune checkpoint inhibitor (ICI), sintilimab cannot block the immune checkpoint pathway or reactivate T cell-mediated anti-tumor immunity. Thirdly, the low tumor mutational burden in all three pathological tissues indicates that neoantigens are not exposed to the immune system, thus affecting ICI therapy. Fourthly, both primary carcinomas and metastases are in a microsatellite stable state/pMMR. The immune escape mechanisms in these tumors include the expression of relatively low levels of immunosuppressive ligands, low tumor mutational load, and lack of immune cell infiltration, compromising the effectiveness of immunotherapy. Fifthly, the mutational status of *TP53* (an important oncogene in humans) correlated with the efficacy of ICIs. Sixthly, *MDM2* gene amplification in liver metastatic tumor tissues and immunohistochemical analysis of the duodenal pathology suggested the involvement of epidermal growth factor receptor (2+), which is associated with hyper-progression during immunotherapy[48]. Finally, peripheral blood findings indicated the presence of Epstein-Barr virus, which is thought to transform tumor precursor cells into Epstein-Barr virus-associated malignancies, and can shape the immunosuppressive microenvironment to induce oncogenesis[49, 50]. It is proposed that the poor efficacy and poor prognosis observed in this patient are the results of multiple factors and omics-coordinated regulation.

CONCLUSION

In this article, we report the case of a middle-aged male with MC-MPMNs, diagnosed with ESCC and DA with liver and bone metastases after an 8.4-mo interval. Based on clinical and pathological features, chemotherapy and immunotherapy were administered against the second primary tumor after multidisciplinary treatment. The patient had an OS of 16.6 mo. Such cases raise awareness among clinicians regarding MPMNs. Although the incidence of MPMNs is low, regular follow-up, vigilance, and comprehensive analysis are crucial for the diagnosis of second primary malignancies. Moreover, in addition to tumor markers, endoscopy, and imaging techniques, emerging inflammatory immunomarkers, genomics, immunomics, and metabolomics can reveal the high heterogeneity of tumors. This approach may facilitate the selection of treatment, improve efficacy, and predict prognosis. Due to the rarity of MPMNs, enhanced collaboration among multiple clinical centers is warranted to conduct prospective clinical studies. Such studies would require expanded sample sizes for TME and multi-omics studies concerning MPMNs.

FOOTNOTES

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CASE REPORT

Isolated traumatic gallbladder injury: A case report

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Abstract

BACKGROUND

Isolated gallbladder injury (GI) (IGI) directly induced by abdominal trauma is rare. Symptoms, indications, and imaging examinations of IGI are frequently non-specific, posing tremendous diagnostic challenges, which are simple to overlook and may have severe implications. Improving doctors' understanding of gallbladder injury (GI) facilitates early detection and decreases the likelihood of severe consequences, including death.

CASE SUMMARY

We report a case of IGI caused by blunt violence (after falling from three meters with the umbilicus as the stress point) and performed laparoscopic repair of the gallbladder rupture, which helps clinicians understand IGI and reduce the severe consequences of delayed diagnosis. Through extensive medical history and dynamic abdominal ultrasound evaluation, doctors can identify GI early and begin surgery, thereby decreasing the devastating repercussions of delayed diagnosis.

CONCLUSION

This article aims to improve clinicians' understanding of IGI and propose a method for the diagnosis and treatment of GI.

Key Words: Isolated gallbladder injury; Blunt abdominal trauma; Gall bladder trauma; Case report

Core Tip: Blunt-force closed abdominal injury is a prevalent clinical condition. Gallbladder injury directly caused by blunt violence in the abdomen is rare, and isolated traumatic gallbladder injury is even rarer. No literature study has determined the likelihood of solitary traumatic gallbladder injury in closed abdominal injury. Therefore, in the diagnosis and treatment of closed abdominal trauma, gallbladder injury is easy to be ignored by clinicians because gallbladder injury is rare. If undiagnosed and untreated, it can cause significant consequences, including death.

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INTRODUCTION

Here, we reported a gallbladder wall rupture due to blunt violence on the abdomen. After surgery, the patient had isolated gallbladder injury (GI) (IGI) but no other organ damage. Finally, the patient underwent gallbladder repair and was discharged on the 7th day after the operation. This research aims to improve doctors' awareness of GI in diagnosing and treating closed abdominal trauma and present diagnostic thinking to improve the early detection rate and lower the risk of serious consequences, including death.

CASE PRESENTATION

Chief complaints

Abdominal pain for 1 h due to trauma.

History of present illness

A 48-year-old man fell from a 3-meter building, initially falling with his umbilicus towards the floor. The umbilicus was bluntly hit, which caused significant abdominal pain. The patient was admitted to our hospital for emergency treatment. The patient reported severe abdominal pain radiating to the right shoulder, along with dysuria, nausea, vomiting, abdominal distension, diarrhea, dizziness, headache, palpitations, chest tightness, and shortness of breath, among other symptoms.

History of past illness

History of appendectomies.

Personal and family history

No special personal history, and family history.

Physical examination

A clear mind was observed, and vital signs were (body temperature: 36.6 °C; heart rate: 51 beats/min; respiration: 22 beats/min; blood pressure: 141/71 mmHg). No abnormalities were observed in the heart or the lungs. The abdominal muscles were slightly tense, the abdomen was tender, and rebound pain was absent. There were no discernible distinctions in the rest.

Laboratory examinations

No evident abnormality was found in the routine blood test, biochemistry, coagulation function, amylase and creatinine of ascites.

Imaging examinations

During the initial treatment, the team conducted an abdominal color ultrasound examination of the patient, suggesting a lamellar middle and low echo in the gallbladder cavity cholestasis? or silty stone (Figure 1)? For postprandial gallbladder status, the gallbladder wall thickens, sound transmission is good, and there is a low and medium echo in the cavity. The boundary was unclear, and the shape was uneven. No obvious abnormality was observed in the rest. Over an hour after the injury, the patient's abdomen pain worsened. An abdominal color ultrasound examination was performed again, indicating ascites. Simultaneously, a computed tomography (CT) examination showed a small, high-density area in the gallbladder and cholestasis. The examination indicates a possible stone, alongside observed rectal dilatation and fecal accumulation. There is also evidence of abdominal and pelvic effusion. It is recommended that further examination be conducted (Figure 2). An abdominal anteroposterior radiograph displays that a part of the intestine in the middle abdomen is dilated (Figure 3). A diagnostic abdominal puncture was performed two hours after the injury to clarify

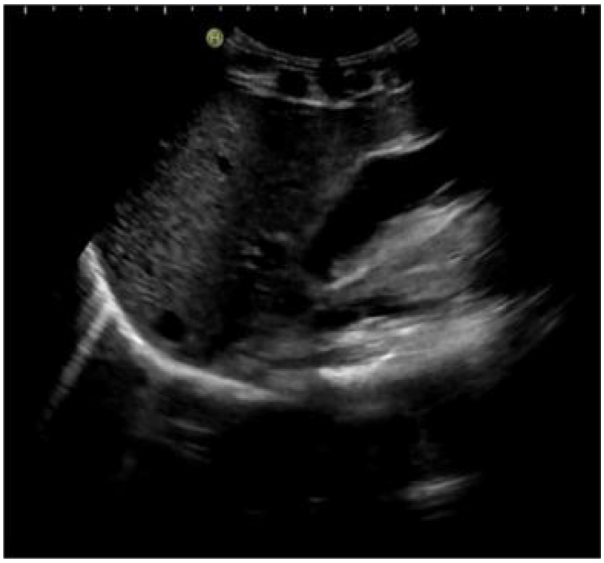

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Figure 1 Itrasound examination suggested the lamellar middle and low echo in the gallbladder cavity.

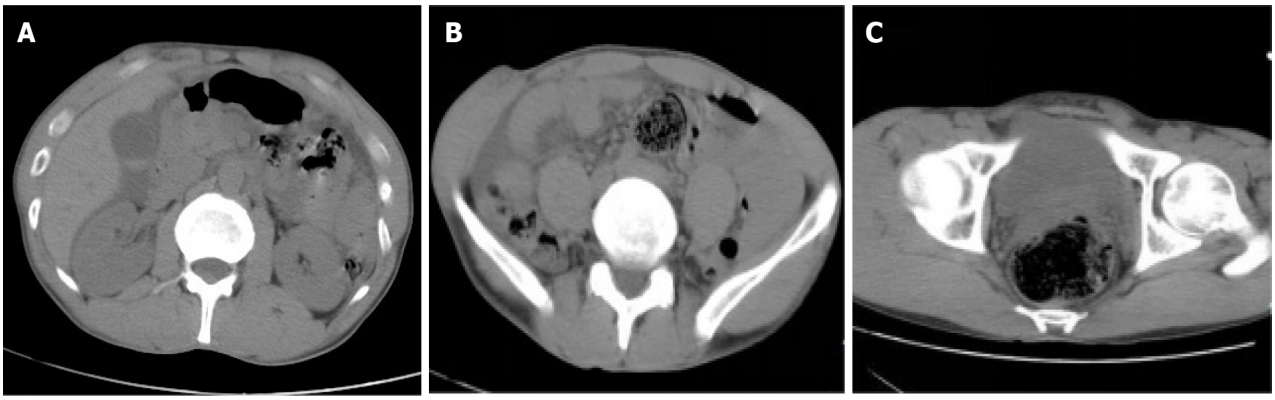

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Figure 2 Abdominal computed tomography examination results. A: This computed tomography (CT) image showed a little high-density area in the gallbladder and cholestasis; B: This CT image indicated abdominal dropsy; C: This CT image showed pelvic effusion, rectal dilatation and fecal accumulation.

ascites. Reddish abdominal ascites were extracted through abdominal paracentesis (Figure 4). Five hours after the injury, the abdominal CT showed cholestasis and a slightly high-density gallbladder stone. Again, the abdominal and pelvic effusions increased (Figure 5A and B).

FINAL DIAGNOSIS

Through laparoscopic examination, we ultimately determined that the patient had isolated traumatic gallbladder injury.

TREATMENT

Although clinical symptoms, signs, and imaging investigations have not yet revealed the site of an abdominal injury, changes in abdominal symptoms and signs and the increase in ascites suggested by CT strongly indicate abdominal organ injury. The disease progressed rapidly; thus, performing an enhanced CT examination was impossible. Finally, the patients and their families agreed to undergo emergency surgical exploration. Laparoscopic exploration was preferred. We made an arc incision on the umbilicus and placed a 10 mm trocar as the observation hole. Through laparoscopic exploration, we can observe extensive fluid accumulation in the abdominal cavity, presenting about 1000 mL of bile-like fluid, no bruises on the liver and spleen, the gallbladder was approximately 8 cm × 6 cm × 3 cm in size, and there was a rupture on the anterior wall of the gallbladder, approximately 4 cm × 1 cm (Figure 5C).

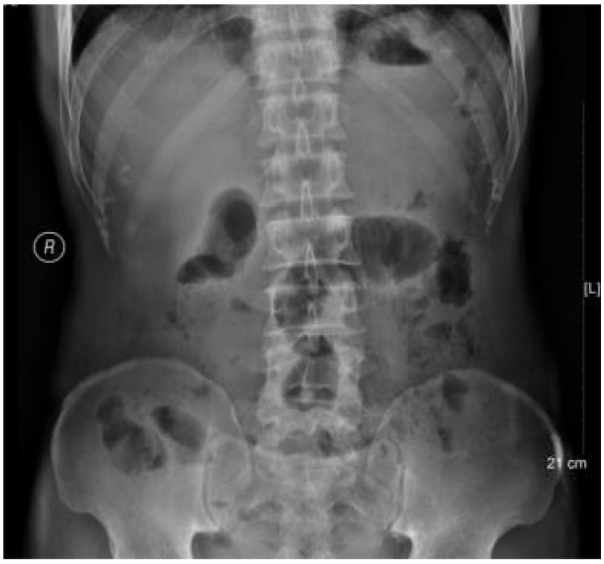

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Figure 3 Abdominal anteroposterior radiograph showed that part of the intestine in the middle abdomen is dilated.

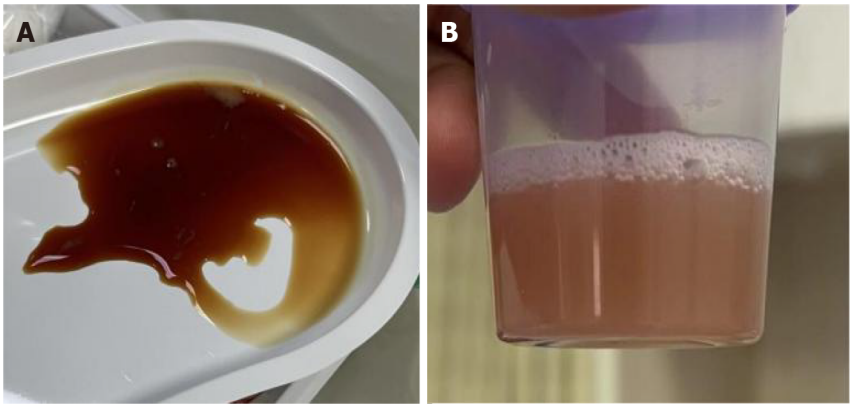

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Figure 4 Results of diagnostic abdominal puncture. A: Light red liquid through the abdominal hole was extracted; B: The puncture drainage fluid was sent to the laboratory for Amylase determination.

There were no apparent active bleeding symptoms; however, blood clots and bile were visible, and no evident bruises were observed on the first hepatic hilus. In the right lower abdomen, parts of the omentum and intestines were linked to the anterior abdominal wall. Accordingly, we performed laparoscopic repair of the gallbladder perforation and continuously sutured the gallbladder contusion with the absorbable barbed suture lines. The suture was strengthened using a seromuscular layer to prevent postoperative bile leakage. Although the gallbladder was repaired laparoscopically, superficial GI caused by clinical trauma is infrequent. It was necessary to further explore the damage to the viscera around the gallbladder, specifically the injury of the retroperitoneal intestinal duct, and the patient was transferred for open exploration. By taking the median abdominal incision, the transverse colon mesentery edema is prominent, and hematoma formation can be seen locally, but the blood supply and peristalsis of the intestine are regular. The peritoneum was opened around the liver curvature of the colon and the lateral part of the descending duodenum to observe substantial tissue edema, discoloration, and hematoma development. The visible descending duodenum, stomach, pancreas, duodenal bulb, small intestine, large intestine, and mesentery were not obvious contusions or lacerations. After the surgical investigation, three drainage tubes were inserted into the right lower liver, appropriate peritoneal space, and pelvic cavity to drain the ascites and prevent serious consequences. After the procedure, the patient was transferred to the hepatobiliary surgery department.

OUTCOME AND FOLLOW-UP

After the operation, the patient was in good condition, and the symptoms improved significantly. The patient reported little incision site pain on the first day after the procedure, but no further noticeable discomfort was noted. On the second

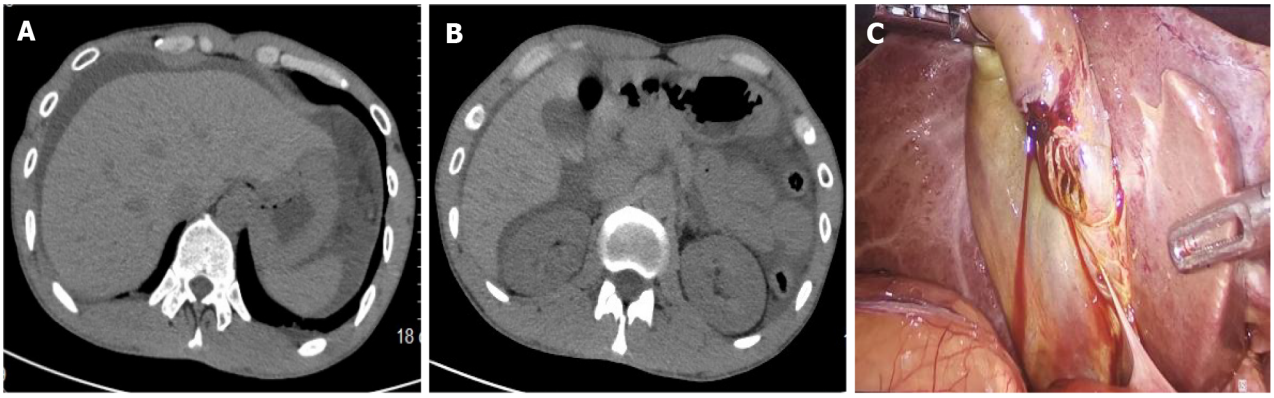

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Figure 5 The second computed tomography examination results and intraoperative images. A: The computed tomography (CT) image indicated that abdominal and pelvic effusion increased; B: The abdominal CT showed cholestasis and a slightly high-density gallbladder; C: This image showed that a lacerated wound on the anterior wall of the gallbladder, about 4 cm × 1 cm.

postoperative day, the patient consumed a small amount of liquid diet after anal exhaust. One week after the process, the abdominal CT was rechecked. CT results did not reveal any problems. The ascites in the abdominal cavity were absorbed. The patient recovered well postoperatively. The symptoms, signs, and infections were controlled. There were no postoperative complications, like "postoperative biliary leakage and intestinal obstruction", thus he was discharged. During the regular follow-up process of six months after surgery, the patient showed no abnormalities.

DISCUSSION

Closed abdominal injury caused by blunt violence is among the common clinical diseases. Most closed abdominal injuries are caused by blunt violence, which directly affects the abdomen. Injuries to the liver, spleen, and small intestine are the most common types of closed abdominal injuries[1]. Clinicians focus on the liver, spleen, small intestine, and other injuries when diagnosing and treating blunt closed abdominal injuries. GI is often neglected because it is rare and can easily cause serious complications, including death[2,3]. No literature study has determined the likelihood of solitary traumatic gallbladder injury in closed abdominal injury[4].

Thin-walled and dilated gallbladders, long-term alcohol consumption, and liver cirrhosis are major research causes[5-8].

This case was caused by blunt violence in the abdomen during fasting, resulting in gallbladder rupture. The impact point is at the umbilicus, and non-blunt violence immediately affects the right upper abdomen, which has not been documented in earlier reports. Under fasting conditions, a large amount of bile secreted by the liver is stored in the gallbladder, which is relatively complete. When the abdomen is subjected to blunt violence, the pressure in the bile duct rises sharply, causing gallbladder rupture, which is among the critical factors causing GI in this patient, consistent with the common inducing factors of GI mentioned by Abouelazayem *et al*[5]. By exploring the abdomen, we also found that the tissues adjacent to the gallbladder, mesentery of the colon, lateral peritoneum, and posterior peritoneum also had contusion manifestations such as tissue edema and hematoma formation. Therefore, the gallbladder and adjacent tissues at this time should be hedged injuries formed after the impact. In conclusion, external forces on the larger gallbladder during fasting and the sudden increase in biliary tract pressure may have caused the patient's gallbladder to rupture.

Reviewing previous literature reports, the early symptoms and signs in isolated patients with GI are non-specific, as in this patient. Due to the non-specific symptoms and signs of the disease and the absence of obvious abnormalities on the patient's abdominal CT plain scan, we decided to continue observing the changes in the patient's symptoms and signs and did not directly perform enhanced CT in the early stages of diagnosis, which is one of the reasons why enhanced CT examination was not performed. If the patient's symptoms and signs worsened, we rechecked color ultrasound and CT scans, carefully read the examination images and reports, and still did not observe any obvious organ damage. Compared with the results of the two examinations, no significant abnormal changes were observed. Meanwhile, considering the high cost of enhanced CT and the absence of obvious organ damage in the two examination results, we did not choose to perform enhanced CT examination during the relatively stable period of the condition, which is also one of the reasons why patients did not undergo enhanced CT examination. However, in this case, the injured part of the patient was not in the right upper abdomen. Abdominal X-ray, CT, and ultrasound did not show gallbladder rupture, which has rarely been reported[9,10]. Therefore, in diagnosing and treating these diseases, we did not consider the possibility of GI. During disease progression, considering the specific impact site of the patient's abdomen, abdominal pain, difficulty in urinating, and the increase in ascites volume indicated by imaging examinations, we not only considered the damage to organs such as the liver, spleen, and small intestine but also the possibility of bladder rupture. To clarify the nature and source of ascites, we chose CT-guided abdominal puncture, and the ascites obtained from the puncture were sent for amylase and creatinine examination. No obvious abnormalities were found, so the possibility of rupture of the liver, spleen, small intestine, and bladder was preliminarily ruled out. Although we have actively conducted diagnostic puncture of ascites,

the bile-like fluid was not extracted, which may be related to the short time of injury and the formation of a package around the omentum after GI, resulting in the bile not spreading to the whole abdominal cavity. Therefore, this poses a significant challenge for diagnosis.

Color Doppler ultrasound, CT, and magnetic resonance imaging (MRI) are important examinations for diagnosing abdominal injuries, including GI.

Abdominal ultrasonography showed thickening of the gallbladder and gallbladder wall after a meal. Combined with the patient's history of fasting, it can highly suspect the possibility of GI[8,11,12]. Due to its convenience and fast, continuous dynamic observation of gallbladder size, wall thickness, and cavity contents, ultrasonography has become the preferred choice for identification of gallbladder illness despite its low sensitivity, specificity, and difficulty in locating the injury. In patients with negative CT findings, repeated ultrasound re-examinations often have unintended discoveries [11]. Therefore, dynamic ultrasound examination is critical.

CT has been proven to be another essential examination method for detecting GI[13]. Regular CT plain scans can determine whether the abdominal organs are damaged promptly. According to relevant literature reports, enhanced CT is one of the most effective tools for identifying GI[14]. Enhanced CT can help determine the diseases of abdominal organs, especially gallbladder stones and intracavitary bleeding, which are difficult to identify on plain scans. This is an essential examination for diagnosing GI. MRI can effectively identify soft tissue injuries[15] but is unsuitable for patients with acute abdomen because of its long examination time[16].

According to Reitz *et al*[17], there are methods for using retrograde cholangiography to determine the specific location of GI. However, this method is based on the premise that no obvious damage site is detected under laparoscopy, which is not consistent with our medical records.

Accordingly, we believe that to diagnose GI, we must first understand the medical history (the origin of the injury, the process of occurrence—if it directly affects the right upper abdomen, whether it is empty is vital for closed abdominal injury). Second, ultrasound examination and conventional abdominal CT are necessary, and even enhanced CT examination is required if conditions permit. In this case, CT cannot indicate the source of ascites, but it still had a unique diagnostic value. Comparing new and old images shows that ascites increase, which helps clinicians choose the best treatment regimen.

The patient's symptoms and signs are supposed to continue progressing, as in this case report. In this case, the patient moves from non-specific single abdominal pain symptoms to obvious peritoneal irritation signs, and we recommend that a diagnostic laparoscopy be performed as soon as possible. Laparoscopy can reduce organ damage, serious consequences, and even death by rapidly locating the injury site. It is also one of the methods of less damage in invasive examinations. Many recent studies have reported that laparoscopic cholecystectomy is the first-line treatment for gallbladder trauma[1, 18]. However, considering that the patient had no history of gallstones, and the previous routine physical examination did not indicate gallbladder lesions, the chief surgeon team finally decided to perform laparoscopic gallbladder rupture repair with the absorbable barbed suture lines and reinforcement suture of the seromuscular layer. We recommend this surgical suture approach to prevent postoperative biliary leakage.

Moreover, in this case, although the gallbladder was repaired under laparoscopy, considering the need for further exploration of other abdominal organs, mesentery, and retroperitoneal injuries and determining whether further intervention is needed, we chose to open the investigation. According to our hospital's experience in treating closed abdominal injuries, laparoscopic exploration can miss tiny intestinal and retroperitoneal injuries. This has also been mentioned in previous literature[19], and in this case, blunt violence acts on the umbilicus, resulting in IGI, which is extremely rare. We suspected damage to other abdominal organs; thus, we chose to perform open exploration. The patient recovered well postoperatively during the regular return visit, and no related complications were found.

CONCLUSION

GI caused by blunt violence is rare, and IGI is even rarer. Symptoms, indications, and imaging examinations of solitary GI are frequently non-specific, pose tremendous diagnostic challenges, are simple to overlook, and may have severe implications. This article aims to improve clinicians' understanding of IGI and propose a method for the diagnosis and treatment of GI. Through extensive medical history and dynamic abdominal ultrasound evaluation, doctors can immediately identify GI and begin surgery, thereby decreasing the devastating repercussions of delayed diagnosis.

FOOTNOTES

Author contributions: Liu DL contributed to manuscript writing and editing, and data collection; Pan JY, Huang TC, Li CZ, Feng WD contributed to conceptualization and supervision; Wang GX provided clinical advice, reviewed the manuscript, and gave final approval; all authors have read and approved the final manuscript.

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CASE REPORT

Comprehensive treatment and a rare presentation of Cronkhite–Canada syndrome: Two case reports and review of literature

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Abstract

BACKGROUND

Cronkhite–Canada syndrome (CCS) is a rare sporadic polyposis syndrome that presents with gastrointestinal and ectodermal symptoms in addition to nutritional deficiencies. CCS combined with hypothyroidism is an even rarer condition, with no standard treatment guidelines.

CASE SUMMARY

The present study described 2 patients with CCS: A 67-year-old woman with concomitant hypothyroidism and 68-year-old man treated with endoscopic mucosal resection (EMR). Both patients had multiple gastrointestinal symptoms and ectodermal changes, along with multiple gastrointestinal polyps. Microscopic examination showed that the mucosa in both patients was hyperemic and edematous, with pathologic examination showing distorted, atrophic, and dilated glands. Patient 1 had concomitant hypothyroidism and was treated with levothyroxine. Due to her self-reduction of hormone dose, her disease relapsed. Patient 2 underwent EMR, but refused further hormonal or biological treatments. Subsequently, he was treated with an oral Chinese medical preparation.

CONCLUSION

Pharmacotherapy can induce and maintain remission in CCS patients, with adjuvant EMR, long-term follow-up, and endoscopic surveillance being necessary.

Key Words: Cronkhite–Canada syndrome; Clinical features; Gastrointestinal polyps; Hypothyroidism; Case report

Core Tip: Cronkhite–Canada syndrome (CCS) is a rare, non-genetic syndrome characterized by ectodermal abnormalities and diffuse gastrointestinal polyps with protein loss. To date, 7 patients with CCS combined with hypothyroidism have been identified. We report two cases, one of which is combined with hypothyroidism. Through indexing and analyzing PubMed, Web of Science, and Embase databases, we summarized the clinical characteristics of CCS combined with hypothyroidism. Additionally, we concluded that pharmacotherapy can induce and maintain remission in CCS patients, with adjuvant endoscopic mucosal resection, long-term follow-up, and endoscopic surveillance being necessary.

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INTRODUCTION

Cronkhite–Canada syndrome (CCS), or polyposis hyperpigmentation alopecia nail dystrophy syndrome, is a rare, non-genetic syndrome characterized by ectodermal changes and gastrointestinal symptoms. Patients with CCS have a poor prognosis, with a 5-year mortality rate of 55%[1]. There are no standardized treatments, as the etiology and pathogenesis of CCS are unknown. At present, glucocorticoid is the primary treatment, either alone or combined with immunosuppressive or biological agents. Other treatments include nutritional support, anti-Helicobacter pylori treatment, tumor necrosis factor- (TNF-) inhibitors, and traditional Chinese medicines. This report describes the clinical characteristics of 2 patients diagnosed with CCS at the First Bethune Hospital of Jilin University and presents a review of the literature. Patient 1 was a 67-year-old woman diagnosed with CCS, with concomitant hypothyroidism, whereas Patient 2 was a 68-year-old man diagnosed with CCS, who underwent endoscopic mucosal resection (EMR). The aim of this study was to provide the basis for basic and clinical research on CCS.

CASE PRESENTATION

Chief complaints

Case 1: A 67-year-old woman was admitted to our hospital in August 2016, due to intermittent diarrhea for 2 mo, aggravated with bloody stool for 1 mo.

Case 2: A 68-year-old man was admitted to our hospital in May 2023, due to hypogeusia and diarrhea for 1 mo.

History of present illness

Case 1: Two months prior to admission, the patient had developed yellowish watery diarrhea (3–5 times per day). One month later, the frequency of defecation had increased to 5–8 times per day, accompanied by a small amount of dark red bloody stool, abdominal pain, and tenesmus. The patient experienced nausea and vomited her gastric contents occasionally. She also experienced fatigue, apathy, loss of appetite, hypogeusia, and alopecia, with a weight loss of 5 kg.

Case 2: One month prior to admission, the patient had developed hypogeusia, loss of appetite, abdominal pain, and yellowish watery diarrhea at a frequency of 4–10 times per day, after eating and without obvious inducement. One week prior to admission, colonoscopy at a local hospital showed colonic mucosal lesions and multiple polypoid mucosal bulges throughout the rectum. He also experienced alopecia, exfoliation of the skin on the hands and face, poor diet and sleep, and a weight loss of 15.5 kg during the previous month.

History of past illness

Case 1: The patient denied a specific previous medical history.

Case 2: The patient denied a specific previous medical history.

Personal and family history

Case 1: The patient denied any personal history or family history related to the disease.

Case 2: The patient denied any personal history or family history related to the disease.

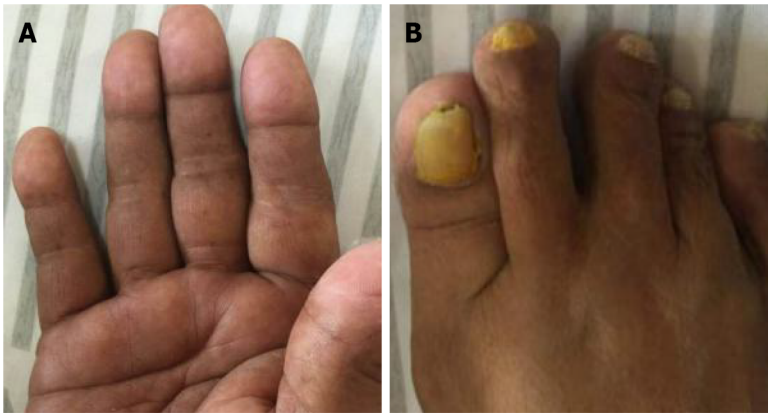

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Figure 1 Cutaneous hyperpigmentation of Patient 1. A: Hands; B: Feet (with nail dystrophy).

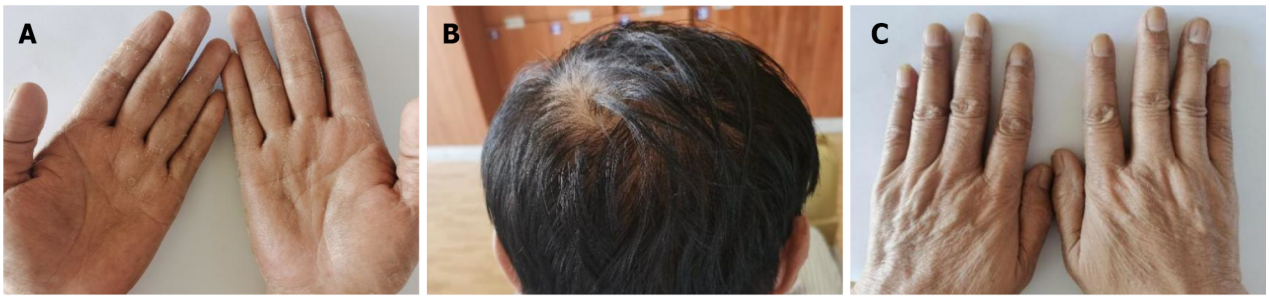

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Figure 2 Physical examination findings of Patient 2. A and C: Hyperpigmentation on the (A) palms and (C) back of the hands; B: Alopecia.

Physical examination

Case 1: On physical examination, the vital signs were as follows: Body temperature, 36.5 °C; blood pressure, 107/63 mmHg; heart rate, 78 beats per min; respiratory rate, 16 breaths per min. Furthermore, examination showed malnutrition, hyperpigmentation of the skin on the hands and feet, alopecia, and nail dystrophy (Figure 1).

Case 2: The vital signs were as follows: Body temperature, 36.6 °C; blood pressure, 96/61 mmHg; heart rate, 90 beats per min; respiratory rate, 18 breaths per min. Physical examination showed malnutrition, exfoliated skin on the face and hands, hyperpigmentation on the palms and backs of the hands (Figure 2A), alopecia (Figure 2B), and thickened and fragile nails on both hands and feet (Figure 2C). No edema was noted in either lower limb.

Laboratory examinations

Case 1: Laboratory examination showed that the C-reactive protein level in this patient was 8.34 mg/L. Evaluation of thyroid function showed that her thyroid stimulating hormone (TSH) concentration was 26.080 μIU/mL (normal range: 0.27–4.2 μIU/mL) and her free thyroxine (FT4) concentration was 10.63 pmol/L (normal range: 12.0–22.0 pmol/L). Rheumatic and immune-related results were normal. Other laboratory results are summarized in Table 1.

Case 2: Laboratory examinations showed that the patient had a cytokeratin 19 concentration of 8.63 ng/mL, a carcinoembryonic antigen of 9.26 ng/mL, a carbohydrate antigen 242 concentration of 40.05 U/mL, and a carbohydrate antigen 199 concentration of 55.83 U/mL. Routine blood tests, liver and kidney function tests, and blood lipids showed no significant abnormalities, and he was negative for IgG4, IgG9, and anti-mitochondrial antibody M2. Other laboratory results are summarized in Table 1.

Imaging examinations

Case 1: The second phase of contrast-enhanced computed tomography (CT) colonography in this patient showed that the gastric wall of the antrum and angle was thickened, with nodular protrusions and partial enhancement. The partial small intestinal wall was also thickened and heterogeneously enhanced. Diffuse wall thickening and polypoid masses with heterogeneous enhancements were observed throughout the colon, especially in the left colon.

The patient also underwent endoscopic examinations. Gastroscopy showed a thickened edematous mucosa with extensive congestion. The gastric antrum showed scattered nodular-like mucosal uplift. The duodenal bulb and descending segment showed multiple mucosal protrusions of different shapes and sizes (Figure 3). Colonoscopy showed that the mucosa of the large intestine was rough, with nodular and polypoid protuberances of different shapes and sizes.

Table 1 Results of laboratory examinations of Patients 1 and 2

Parameter	Patient 1	Patient 2	Normal range
RBC as × 10^{12}/L	5.15	3.43	3.8-5.1/4.3–5.8
Hb in g/L	152	124	115–150/130–175
K^+ in mmol/L	2.73	3.87	3.5–5.5
Na^+ in mmol/L	135.6	136.3	137–147
Ca^{2+} in mmol/L	1.99	2.04	2.11–2.52
TP in g/L	45.9	63.5	65.0–85.0
Albumin in g/L	26.5	37.6	40.0–55.0
Routine urine	Normal	Normal	
Fecal occult blood test	Positive	Positive	Negative
Fecal fat globule test	Negative	0-1	
Fecal culture	Negative	Negative	
ANA	Negative	Negative	
T-SPOT.TB	Negative	Negative	

ANA: Anti-nuclear antibody; Hb: Hemoglobin; RBC: Red blood cells; TP: Total protein; T-SPOT.TB: T-cell spot of tuberculosis test.

While the mucosa at the protuberances was hyperemic and edematous, the vascular texture of the intervening intestinal wall disappeared and turned white (Figure 4). On pathological examination, multiple biopsies of the stomach and large intestine showed that the mucosal glands were atrophic and dilated. Proliferation of interstitial granulation tissue was observed, accompanied by the infiltration of lymphocytes and eosinophils, suggesting hamartomatous polyposis. A tubular adenoma was observed in the transverse colon, with moderate to severe epithelial dysplasia (Figure 5).

Case 2: Both plain and three-stage enhanced CT of the abdomen showed gastric wall thickening in the lesser curvature and antrum.

Gastroscopy showed hyperemic and edematous mucosa (with a hyperplastic and nodular appearance) in the fundus, angle, antrum, duodenal bulb, and descending segment; this was prominent between the lesions (Figure 6). Colonoscopy showed similar results in colonic mucosa. However, the nodules were of different sizes. A mucosal intumescent lesion measuring 2.5 cm × 2.5 cm was observed 10 cm from the anal verge (Figure 7). EMR was performed, with biopsy samples obtained at multiple sites.

Gastroscopic pathology suggested that the lesions of the gastric body were consistent with hyperplastic polyps, acute and chronic mucosal inflammation. In the duodenum, distorted, branched, and hyperplastic glands were observed, indicating active chronic inflammation (Figure 8). Colonoscopy pathology showed active chronic enteritis and cryptitis in the terminal ileum, with round and blunt villi, and distorted glands, with infiltration of about 50 eosinophils per high-power field. Additionally, the pathology reports showed evidence of active chronic colitis, cryptitis, and crypt abscesses, with hyperplastic or atrophic, dilated, and distorted glands. This was accompanied by interstitial edema and eosinophil infiltration. The mucosal glands of the sigmoid colon and rectosigmoid junction were hyperplastic, with interstitial edema and crypt abscesses. CCS-related polyps could not be excluded (Figure 8). Examination of the rectal mass removed by EMR (Figure 7F) showed a villous tubular adenoma, consistent with high-grade intraepithelial neoplasia, with no apparent involvement of blood vessels or surgical margins. Immunohistochemical examination showed that about 60% of the cells were positive for Ki67, with high expression of MLH1 (+++), MSH2 (+++), MSH6 (+++), and PMS2 (+++), slight expression of P53 (+), and CK (+), and negative for CD31 and CD34 (Figure 8).

FINAL DIAGNOSIS

Case 1: Based on the aforementioned findings, Patient 1 was diagnosed with CCS and hypothyroidism.

Case 2: Based on the aforementioned findings, Patient 2 was diagnosed with CCS.

TREATMENT

Case 1: Treatment of Patient 1 included nutritional support, thyroid hormone supplementation (12.5 ug/d for the 1st 3 d, 25 ug/d thereafter), administration of prednisone tablets (30 mg/d), and symptomatic treatment during hospitalization.

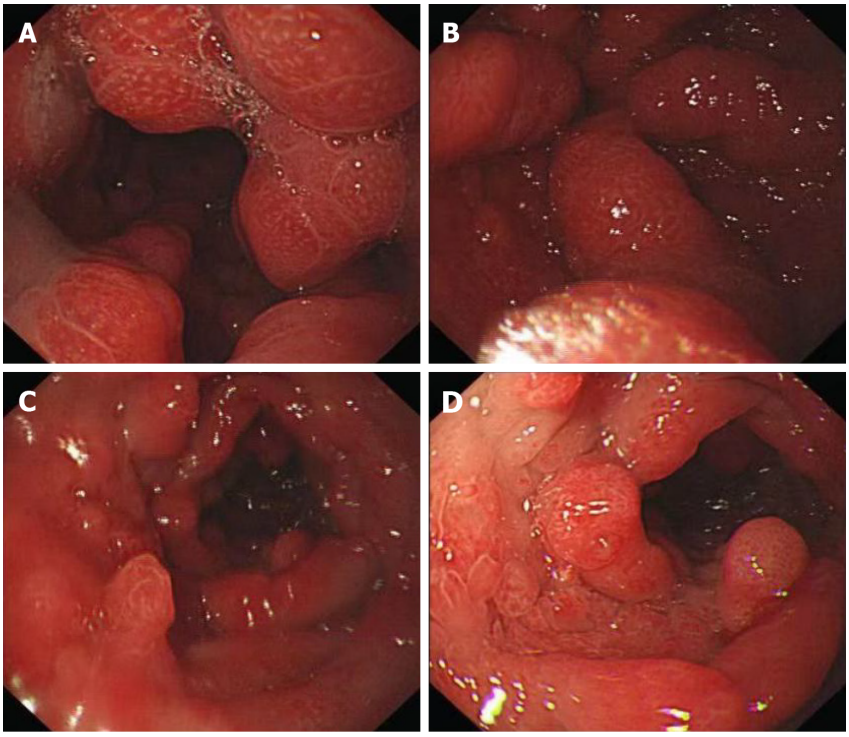

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Figure 3 Gastroscopy of Patient 1. A and B: Thickened edematous mucosa with extensive congestion in the gastric body and antrum, with scattered, nodular-like mucosal uplift in the latter; C and D: Multiple mucosal protrusions of different shapes and sizes in the duodenal bulb and descending segment.

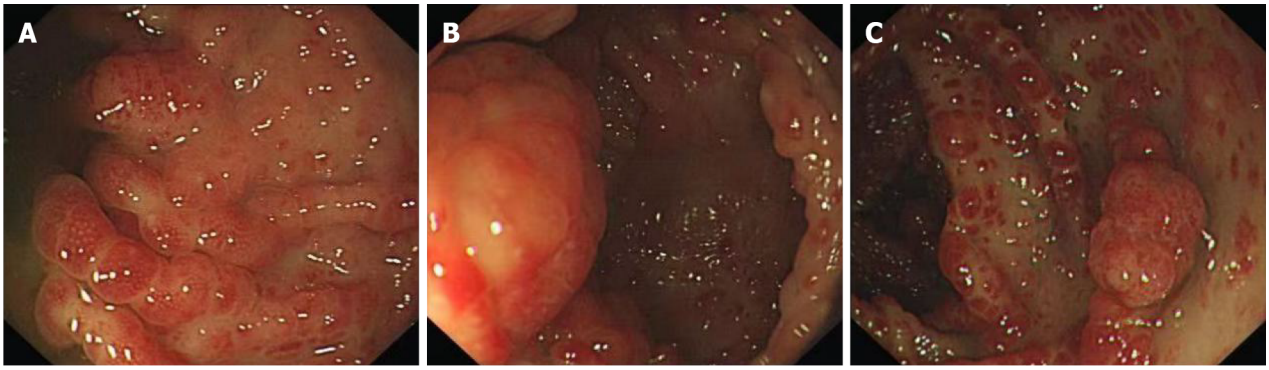

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Figure 4 Colonoscopy of Patient 1. A-C: The mucosa of the large intestine was rough, with nodular and polypoid protuberances of different shapes and sizes. The mucosa at the protuberances was hyperemic and edematous, and the vascular texture of the intestinal wall between the protuberances disappeared and turned white.

After discharge, she was continued on prednisone tablets (30 mg/d).

Case 2: The patient was initially treated with acid suppression (proton pump inhibitors) and nutritional support, followed by EMR for the removal of colonic polypoid lesions and the rectal mass. After endoscopic surgery, however, the patient and his family refused further hormonal or biological treatments and asked to be discharged.

OUTCOME AND FOLLOW-UP

Case 1: After 9 d of comprehensive treatment, her symptoms, including diarrhea and bloody stool, significantly improved. Hair and nail loss, however, did not significantly improve. Two months after discharge, this patient elected to reduce her dose of prednisone to 10 mg/d, and 3 mo later to 5 mg/d. Four months after the diagnosis of CCS, the patient suddenly developed nausea, vomiting, abdominal distension, and other manifestations of intestinal obstruction. Unfortunately, we did not obtain the results of thyroid function reevaluation for this patient after discharge. Because histopathologic examination of her colon showed tubular adenoma and moderate to severe epithelial dysplasia, the possibility of

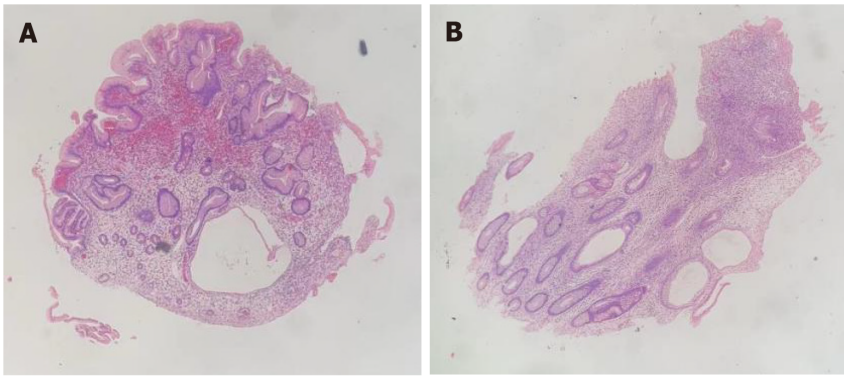

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Figure 5 Biopsy from Patient 1 shows atrophic and dilated mucosal glands with infiltration of lymphocytes and eosinophils. A: Stomach; B: Intestine. Magnification: 4 ×.

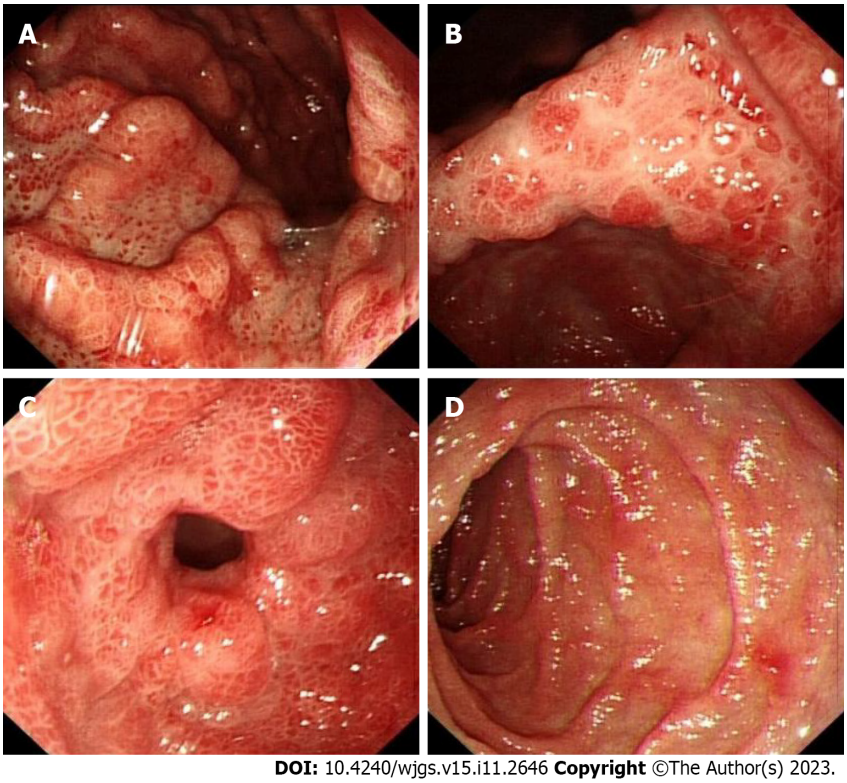

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Figure 6 Endoscopic examination of Patient 2. A-D: Mucosae of the body (A), angle (B), antrum (C), and duodenal (D) descending segment were hyperemic and edematous, with a hyperplastic and nodular appearance.

malignant transformation was considered. The patient died of multiple organ failure after 1 wk of treatment in a local hospital.

Case 2: One month later, the patient was followed up by telephone. At present, the patient is receiving symptomatic and supportive treatment and has been treated with an oral Chinese medicine for more than 20 d. His hypogeusia and appetite have improved, his new nails are soft, and his skin pigmentation has improved. However, his alopecia has not changed, and he continues to have yellow watery diarrhea, 2–8 times per day. His body weight is 4.5 kg lower than his pre-discharge weight.

DISCUSSION

CCS is a rare, non-genetic syndrome characterized by ectodermal abnormalities and diffuse gastrointestinal polyps with protein loss. Since first described in 1955[2], more than 500 patients with CCS have been reported worldwide; most of these patients were Asian, with Japan accounting for more than 75%[3]. The average age at onset is 59 years, with more

Table 2 Description of patients with Cronkhite–Canada syndrome combined with hypothyroidism

Ref.	Age/sex	Country	Thyroid function	Ectodermal changes	Gastrointestinal symptoms	Treatment	Outcome
Størset *et al*[29], 1979	66/F	Sweden	T4 36 nmol/L, TSH 45.0 μU/mL, no thyroid antibodies detected	Alopecia, onychodystrophy	Diarrhea, gastrointestinal polyposis	Thyroxine-sodium	Improved symptoms, but no changes in neurological and electromyographic findings
Jones *et al* [30], 1984	82/F	United States	TT4 1.0 μg/dL, TSH 31.5 mIU/ml	Alopecia, onychodystrophy, hyperpigmentation	Diarrhea, gastrointestinal polyposis	Prednisone therapy was initiated at 20 mg/d orally, tapered to 10 mg/d within 2 wk, accompanied by nutritional support	Improved
Qiao *et al* [9], 2005	60/F	China	T3, TSH ↑, FT4 ↓	Alopecia, nail dystrophy, hyperpigmentation	Diarrhea, intermittent abdominal pain, generalized gastrointestinal polyposis	Symptomatic treatments	Improved
Berzin *et al* [8], 2012	72/M	United States	TSH 1.72 mIU/L (after supplementing with levothyroxine)	Alopecia, onycholysis, and yellow nail discoloration	Diarrhea, hypogeusia, early satiety, generalized gastrointestinal polyposis	Prednisone 30 mg/d, symptomatic treatments	Died
No author [31], 2016	55/F	Korea	ND	Alopecia, onychodystrophy	Diarrhea with intermittent blood, nausea, abdominal pain, generalized gastrointestinal polyposis	Steroids and nutritional support	Improved
No author [32], 2018	56/M	United Kingdom	TSH 160 mIU/L, FT4 < 5 pmol/L	Alopecia, onychodystrophy, hyperpigmentation	Diarrhea, generalized gastrointestinal polyposis	Prednisolone	Improved
Dawra *et al*[33], 2018	60/M	India	TSH 94.65 μg/dL	Alopecia, onychodystrophy, hyperpigmentation	Diarrhea, anorexia, dysgeusia, multiple polyps	Cefixime, rifaximin, mesalamine, thyroid replacement, zinc supplementation (100 mg/d), along with micronutrient supplementation	Improved

F: Female; FT4: Free thyroxine 4; M: Male; ND: Not Described; T3: Thyroxine 3; T4: Thyroxine 4; TSH: Thyroid stimulating hormone.

than 80% of these patients aged over 50 years at diagnosis[4]. The male to female ratio ranges from 1.5 to 2:1[5]. Patient prognosis is poor, with a 5-year mortality rate as high as 55%[1]. The 2 patients described in this study included one woman and one man, both aged over 50 years.

At present, the etiology of the disease is unclear. Autoimmune factors have been reported to be involved in its possible etiology and pathogenesis. Many patients with CCS show positive plasma antinuclear antibody (ANA) series, elevated IgG4 levels, or IgG4 (+) plasma cells infiltrating into the polyps. Elevated levels of plasma IgE have also been reported in 1 patient with CCS[5]. CCS was also found to be associated with hypothyroidism and other autoimmune diseases[6], such as membranous nephropathy[7], systemic lupus erythematosus, rheumatoid arthritis, and scleroderma. The involvement of autoimmune factors is supported by the overall good clinical response of CCS patients to immunosuppressive therapy. Both patients in the present study had normal ANA and plasma IgG4 levels, although Patient 1, who had CCS and hypothyroidism, had a significantly increased TSH level, accompanied by apathy and loss of appetite. To date, 7 patients with CCS have been diagnosed with associated hypothyroidism, making this condition extremely rare (Table 2). Furthermore, prior to this article, there was only one reported case of CCS with concomitant hypothyroidism in China. All patients were aged over 59 years at diagnosis, with the oldest patient being 82 years. All 7 patients had alopecia, nail dystrophy, diarrhea, and multiple polyps. After clinical treatments, the symptoms of 6 patients were relieved to varying degrees, whereas the 7th patient died of respiratory failure 1 year after treatment. This patient had hypothyroidism

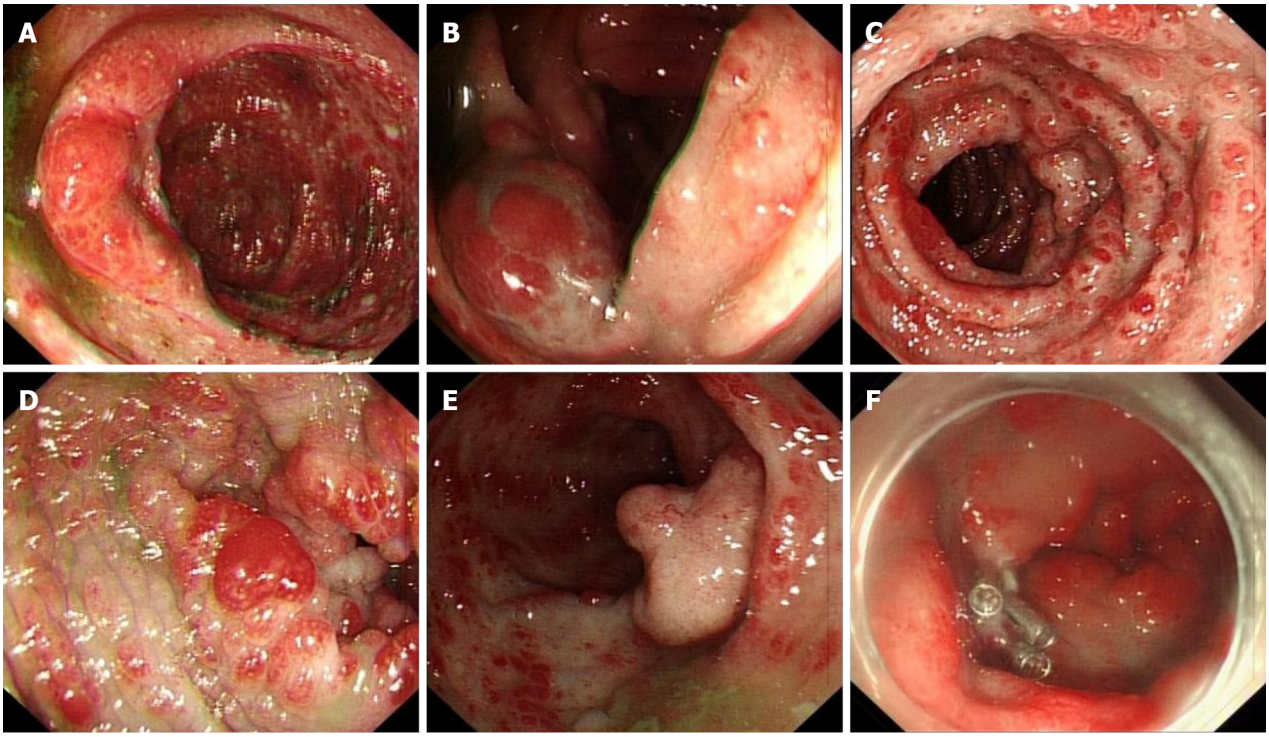

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Figure 7 Colonoscopic examination of Patient 2. A-F: Mucosa of the entire colon was diffusely hyperemic and edematous, with nodules of different sizes. A mucosal intumescent lesion measuring 2.5 cm × 2.5 cm was observed 10 cm from the anal verge.

following surgery for Graves' disease. The original text did not mention whether auto-antibodies were positive. However, because Graves' disease is associated with autoimmune antibodies, we can be certain that the patient had autoimmune abnormalities. This further confirms the association of CCS with autoimmune factors[8]. Qiao *et al*[9] reported a CCS case in which the patient, however, had normal serum levels of antithyroglobulin and anti-thyroid peroxidase antibodies. Taken together, these findings indicate that the etiology of CCS and its relationship to autoimmunity are unclear, necessitating further research.

Infectious factors have also been associated with CCS. For example, *Helicobacter pylori (H. pylori)* infection has been associated with CCS, with symptoms being relieved after anti-*H. pylori* treatment[10]. Antibodies to Saccharomyces cerevisiae have also been detected in the plasma of CCS patients[11-13], and Clostridium difficile has been identified in the feces of patients with CCS[14]. These findings suggest that infection with several types of pathogenic bacteria is associated with CCS.

Although CCS is regarded as a non-genetic disease, genetic factors may be associated with its development. Although both patients in the present study denied that anyone in their families had a similar history, genome-wide association study revealed that mutations in the *PRKDC* gene, normally encoding the catalytic subunit of DNA-dependent protein kinase, may play a role in the pathogenesis of CCS[15]. Genetic analysis of a Chinese mother and child who were diagnosed with CCS revealed C.3921-3925delAAAAG (p.Ile1307fsX6) mutation in the *APC* gene[5].

Other factors associated with CCS included mental and physical stress[6], allergy[12], and gut microbiota[16]. Discontinuation of allergy-inducing agents, such as hair dyes and certain drugs, was found to reduce IgE concentrations and eosinophil infiltration, as well as to improve clinical symptoms in patients with CCS[12]. Moreover, the remission and regression of polyps after prednisolone (PSL) treatment of patients with CCS was accompanied by changes in the abundance and diversity of gut microbiota[16]. PSL can not only inhibit proinflammatory cytokines but can also mediate polyp regression by altering the composition of gut microbiota. Additional studies are needed to better understand the associations between proinflammatory cytokines and microecological dysbiosis, which might be involved in the pathogenesis of CCS.

CCS is characterized by ectodermal abnormalities, gastrointestinal symptoms, and protein loss. Ectodermal changes include alopecia, skin pigmentation, and nail dystrophy, including nail yellowing, atrophy, and loss. The main gastrointestinal symptoms are abdominal pain and diarrhea, frequently accompanied by nausea, acid regurgitation, anorexia, and abnormal taste. The occurrence of fractures has also been reported[17]. Based on the initial symptom, CCS can be divided into five types: Diarrhea (type 1), hypogeusia (type 2), dry or strange sensation in the mouth (type 3), abdominal pain (type 4), and alopecia (type 5)[18]. Patients 1 and 2 in the present study had types 1 and 2 CCS, respectively. Both patients had three main ectodermal changes, abdominal pain and nausea, with Patient 1 also having vomiting. Due to oral mucosal lesions, including inflammation and infection, and zinc and copper deficiency, patients may lose their taste[19]. Alopecia can be caused by malnutrition[20], whereas nail dystrophy has been associated with the bad nutritional status and inflammatory response[19]. Polyps in patients with CCS are distributed throughout the digestive tract, being common in the stomach and colon, less common in the small intestine and rectum, and almost

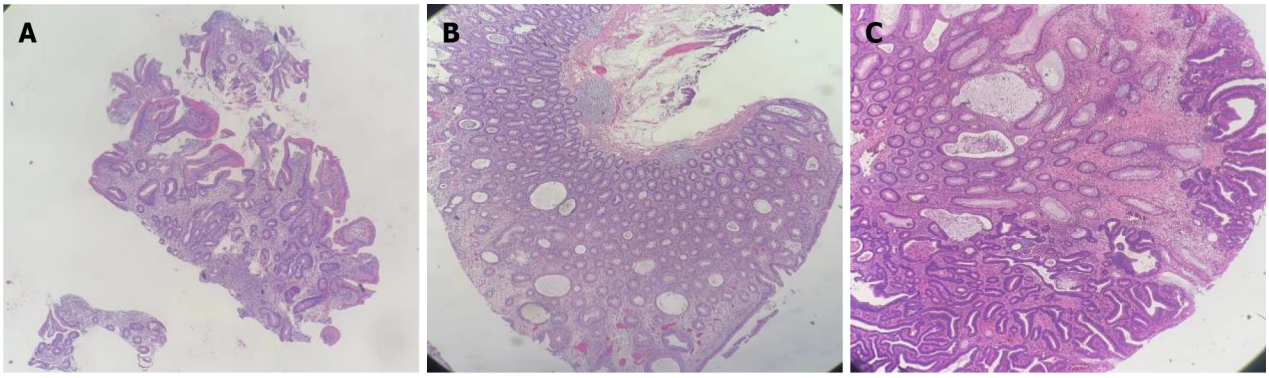

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Figure 8 Histologic examination of biopsy samples from Patient 2. A: Gastroscopic pathology, suggesting active chronic inflammation with distorted, branched, and hyperplastic glands; B: Presence of active chronic colitis, cryptitis and crypt abscesses, with hyperplastic or atrophic, dilated, and distorted glands. Interstitial edema and eosinophil infiltration were also observed; C: The rectal mass was a villous tubular adenoma, indicative of high-grade intraepithelial neoplasia, with no apparent involvement of blood vessels or surgical margins. Magnification: 4 ×.

nonexistent in the esophagus[10,21]. Polyps are usually diffusely distributed and nodular, with different shapes and sizes. Histologically observed glandular hyperplasia and cystic dilatation are accompanied by the infiltration of inflammatory cells, especially eosinophils. Both patients in the present study had both gastric and intestinal polyps, with findings on gastrointestinal endoscopy being consistent with CCS.

The pathology of CCS is not specific, with four histological types: hyperplastic, adenomatous, juvenile, and inflammatory polyps. The evolution of polyps may follow the mucosal hyperplasia (C-C polyps)-adenoma-carcinoma pathway [22]. About 12.5% of polyps are estimated to become cancerous, with this being a significant cause of death. Pathologic analysis of the polyps in Patient 1 showed tubular adenoma and moderate to severe epithelial dysplasia, complicated with an intestinal obstruction 4 mo after the diagnosis of CCS, suggesting malignant transformation of the adenoma. The rectal mass in Patient 2 was pathologically diagnosed as a high-grade intraepithelial neoplasia, necessitating immediate EMR. These findings emphasize the importance of close surveillance and prompt removal of polyps.

The average recovery times for diarrhea, taste abnormality, and ectodermal changes in patients with CCS are 51, 84, and 9 d, respectively, and the mean times to resolution of gastric and colonic polyps are 248 and 238 d, respectively[23]. Currently, there are no standard treatment guidelines, including duration of treatment, with most CCS patients receiving comprehensive empirical treatment based on glucocorticoids. Several studies have recommended treatment for 6–12 mo [24], suggesting that the steroid dose should be slowly tapered only after endoscopic confirmation of the regression of polyposis[25]. Although 30–49 mg/d oral prednisone was reported to have the optimal effect during the active stage of CCS[26], patients may relapse when glucocorticoid dose is gradually reduced. Additional studies in larger patient cohorts are needed to determine whether to use glucocorticoids, their duration and dose, regimens for reduction, and the need for maintenance therapy with other medications. Nutritional support is often combined with other treatments, making it difficult to accurately determine the effectiveness of nutritional support in patients with CCS[10]. Other treatments can include immunosuppressive agents, acid suppression, traditional Chinese medicines, salicylic acid preparations, TNF-inhibitors[27], and endoscopic or surgical treatment. Achieving a sustained endoscopic response is the therapeutic goal and associated with a reduced risk of cancer[4,25]. Kim *et al*[28] reported a successful case of fecal microbiota transplantation in the treatment of steroid-refractory CCS. The etiology and pathogenesis of this disease are not yet fully understood, and various other methods are still being explored.

CONCLUSION

In summary, CCS is a rare syndrome primarily affecting male patients with a relatively poor prognosis. Its etiology remains unclear, but current research suggests a strong association with autoimmunity. Based on the results of literature review in this article, it can be inferred that a clear diagnosis and treatment of hypothyroidism contribute to improving the prognosis. Clinical manifestations are diverse, including diarrhea, gastrointestinal polyps, skin hyperpigmentation, alopecia, and nail atrophy. Comprehensive treatment based on hormone therapy can lead to partial or complete remission of clinical symptoms. Polyps meeting the indications for endoscopic surgery should be actively treated surgically, which can prevent polyp malignancy and the occurrence of complications, such as intestinal obstruction and intussusception. Early diagnosis and treatment are crucial for inducing remission and improving disease prognosis. Long-term follow-up is necessary for subsequent treatment of this disease. In the future, this disease will still require further basic and clinical research, especially regarding its etiology and treatment approaches.

FOOTNOTES

Author contributions: Lv YQ collected and sorted out the cases, reviewed the literature, and wrote the manuscript; Wang ML reviewed the literature; Tang TY contributed to the content and editing of the manuscript; Li YQ reviewed and revised the manuscript; All authors have read and approved the final manuscript.

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CASE REPORT

Gastric inflammatory myofibroblastic tumor, a rare mesenchymal neoplasm: A case report

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Abstract

BACKGROUND

The inflammatory myofibroblastic tumor (IMT) is a rare mesenquimal tumor of doubtful biological behaviour. It's characterised for affecting mainly children and young adults, although it can appear at any age, being the lungs the primary affected organ (in children it represents 20% of all primary pulmonary tumors).

CASE SUMMARY

We present the case of a 45 year old woman, with a computed tomography (CT) finding of injury on the anterior surface of the fundus/gastric body and a solid perigastric injury of 12 mm in the ecoendoscopy. The case is presented in the tumor committee deciding to perform a laparoscopic wedge resection. The histological diagnosis was a IMT. The diagnosis is based on imaging tests like the abdominal CT, abdominal ecography and the ecoendoscopy but to confirm the diagnosis a pathological study is necessary.

CONCLUSION

Due to the unpredictable nature of this tumor, surgical resection is the best therapeutic option.

Key Words: Inflammatory myofibroblastic tumor; Gastric; Wedge resection; *ALK*-mutation; Case report

Core Tip: The inflammatory myofibroblastic tumor is a rare mesenquimal tumor of doubtful biological behaviour. It's characterised for affecting mainly children and young adults, although it can appear at any age, being the lungs the primary affected organ. The unusual thing about the case is the gastric location of the tumor (the majority are pulmonary) and the unpredictable nature of this tumor. That is why the surgical resection is the best therapeutic option.

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INTRODUCTION

The inflammatory myofibroblastic tumor (IMT) is a rare mesenquimal tumor of doubtful biological behaviour[1]. Previously known as inflammatory pseudotumor, plasmatic cell granulome, inflammatory miofibroblastoma and inflammatory miofibrohistiocityc proliferation, it's characterised for affecting mainly children and young adults, although it can appear at any age, being the lungs the primary affected organ (in children it represents 20% of all primary pulmonary tumors)[2].

CASE PRESENTATION

Chief complaints

We present the case of a 45 year old woman who requested a follow-up in our center for a second opinión after discovery of injuries that could relate to a peritoneal carcinomatosis in other center.

History of present illness

She was examined in another center given her clinic of difuse abdominal pain of long evolution without association with any other clinical manifestation, identifying in a computed tomography (CT) a "nodular isodense image, at omental level, adyacent to the anterior right abdominal wall, without discarding infiltration of the anterior right abdominal rectum. Increase in density and trabeculation of the mesenteric fat and inespecific micronodular images, findings which could relate to a peritoneal carcinomatosis".

Personal and family history

She has a history of venous insuficiency and cronic gastritis, cesarean and adenoidectomy. She denied family history of malignant tumours.

Physical examination

On physical examination, the vital signs were as follows: Body temperature, 36.8°C; blood pressure, 121/70 mmHg; heart rate, 89 beats per min; respiratory rate: 17 breaths per min. Furthermore, the patient did not have abdominal pain, but minimal ascitites in flanks was found.

Laboratory examinations

Levels of serum tumour markers were normal [carcinoembryonic antigen < 0.5 ng/mL (0.0-3.0), carbohydrate antigen (CA) 125 14.0 U/mL (0.0-35.0), CA 19-9 5.0 U/mL (0.0-40.0), CA 15-3 14.9 U/mL (0.0-28.0)]. No abnormality was found in routine blood analyses.

Imaging examinations

A gastroscopy is requested evidencing a gastric submucous injury of 1 cm in lesser curvature and a biopsy is performed. The anatomopatological diagnosis was superficial cronic gastritis not observing an intestinal metaplasia.

Subsequently, a positron emission tomography CT is performed with the following results: "Decrease in the size of the nodular image in greater omentum, with a mild affinity for FDG. Improvement of the ascitis and the trabeculation of the omental and mesenteric fat. Hepatic injury without metabolic translation".

Further diagnostic work-up

A core needle biopsy is performed of the omental injury observing fibrous tissue with no tumoral infiltration and tumor

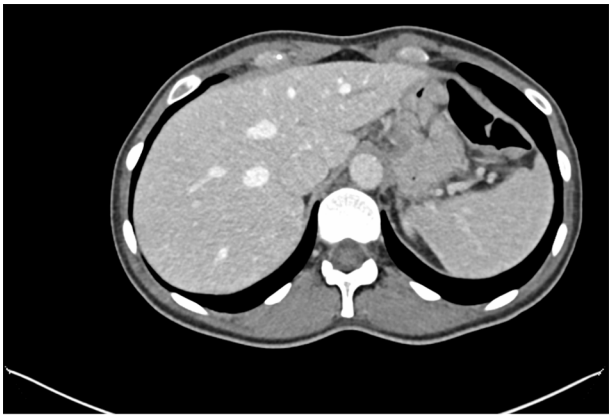

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Figure 1 Nodulary injury on the anterior surface of the fundus/gastric body.

markers are requested, which come out negative.

The control CT evidences "resolution of previous peritoneal affectation with persistence and stability of a left subdiafragmatic nodulary injury on the anterior surface of the fundus /gastric body" (Figure 1). A gastric Ecoendoscopy is requested identifying a solid perigastric injury of 12 mm with indeterminate endosonographic appearance. A biopsy is performed on 3 occasions, without obtaining a representative sample.

MULTIDISCIPLINARY EXPERT CONSULTATION

The case is presented in the tumor committee deciding to perform an exploratory laparoscopy.

FINAL DIAGNOSIS

The pathology study reported a "mesenquimal injury of 1.3 cm growing in the muscular layer of the gastric wall, which is in contact with the resection margin. It's sparsely celular, mainly constituted by fibrous tissue predominantly colagenised, with presence of spindle-shaped cells without significant atypia. Presence of psammomatous calcifications is also observed. The inmunophenotype of the tumor is: CK AE1-AE3+, Actina 1A4+ muy focal, ALK1-, Actina HHF35-, desmina-, caldesmon-, calponina-, CD34-, CKIT-, S100-" (Figure 2). Being the final diagnosis a IMT.

TREATMENT

We perform an exploratory laparoscopy. During the intervention, an injury of aproximately 2 cm is identified on the anterior gastric face, and a wedge resection of the injury is performed. The patient evolves favourably and is discharged to the second postoperative day.

OUTCOME AND FOLLOW-UP

At 1 mo postoperatively, the patient was still alive. Given these findings, the case is presented again to the multidisciplinar committee, which decides to carry out an annual Ecoendoscopy and toracic CT to examine the pulmonar nodule.

DISCUSSION

The IMT is rare tumor, predominantly located in the lungs but can also be found in the retroperitoneum, mesentery, head, neck and stomach. The latter case, presented by our patient, is extremely rare, with very few described in literature (Table 1).

It is characterized by local recurrence but rarely incurs in distant metastasis[3]. Risk factors for the development of IMT have not been established, but cases have been described which suggest association with Virus Epstein bar, genetic alterations like the reorganisation of the anaplastic lymphoma kinase (*ALK)* gene in the 2p23 cromosome or alterations of the inmune system[3,4]. They are usually asymptomatic or present inespecific symptoms like abdominal pain, toracic

Table 1 Clinicopathological characteristics of inflammatory myofibroblastic tumors in adults, described in the literature

Ref.	Sex/age	Presenting symptoms	Tumor localization in the stomach	Tumor size (cm)	Mitosis	Histologic pattern	Treatment	Follow-up
París-Sans *et al*[1]	M/88	AP, vomiting, jaundice	GDJ	4	/	Proliferation of spindle-shaped mesenchymal cells mixed with lymphocytes	PG	/
Cheng *et al* [3]	W/52	AP	Antrum (exophytic)	4.3	0-1	Proliferation of fusiform cells	DG	6 mo
Bjelovic *et al* [4]	W/43	AP, nausea	Distal Stomach	6	44928	Hypercellular spindle cell proliferation with vague fascicular areas	DG	2 yr
Shi *et al*[5]	M/36	AP, AM	Antrum, LC	4.5	44928	Myxoid hypocellular with some fascicular areas	PG	5 yr (NED)
Shi *et al*[5]	M/42	AP, UGH, AM,	Upper body, GC	8	44928	Fascicular with some myxoid areas	PG	Recurrence at 12 mo
Shi *et al*[5]	M/40	AM	Upper body, AW	6.3	44928	Myxoid hypocellular with some fascicular areas	PG	3 yr (NED)
Shi *et al*[5]	M/45	AP, AM	Angle	5.5	44928	Myxoid hypocellular with some fascicular areas	PG	2.6 yr (NED)
Shi *et al*[5]	W/45	AP, AM	Lower body, PW	5.8	44928	Fascicular with some myxoid and sclerotic areas	PG	4 yr (NED)
Katakwar *et al*[6]	M/45	AP	AW	5	44928	Hypocellular, collagenized, myofibroblatic cells	DG	Recurrence at 1 mo
Leon *et al*[7]	W/50	Vomiting, weight loss	PW	7	44928	Patternless round and spindle cell proliferation	PG	2 yr (NED)
Park *et al*[8]	W/55	AP, hematoperitoneum	Upper body, GC	8	44928	Vague fascicular proliferation	Gastric wedge resection	/
Jadhav *et al* [9]	M/18	AM, weight loss	LC	9	44928	Pleomorphic cells, spindle-shaped to stellate cells arranged in a background of myxoid	Excision	5 yr
Qiu *et al*[10]	W/61	Fever	LC	3	/	Spindle cells with inflammatory infiltrate of neutrophils, eosinophils, lymphocytes, and plasma cells.	DG	3 mo (NED)
Kim *et al* [11]	M/25	AM	GEJ	8	/	/	/	/
Albayrak *et al*[12]	W/56	Nausea, vomiting, UGH	Cardia	11	44928	Granulation-type and storiform spindle cell proliferation	PG	8 mo (NED)
Our Study	W/ 45	AP	AW (exophytic)	1.3	/	Spindle/stellate cells with inflammatory cells	Gastric wedge resection	1 mo

AP: Abdominal pain; AM: Abdominal mass; UGH: Upper gastrointestinal hemorrhage; LC: Lesser curvature of the stomach; GC: Greater curvature of the stomach; AW: Anterior wall of the stomach; PW: Posterior wall of the stomach; C: Cardia; PG: Partial gastrectomy; DG: Distal gastrectomy; NED: No evidence of disease; GDJ: Gastroduodenal junction; GEJ: Gastroesophagus junction; M: Male; F: Female.

pain, and up to 30% develop a constitutional syndrome[1,2].

The diagnosis is based on imaging tests like the abdominal TC, abdominal ecography and the ecoendoscopy[5].

The differential diagnosis includes gastrointestinal stroma tumor, fibroid inflammatory polyp, single fibrous tumor or peripheral nerve tumors, amongst others[6].

Confirmation diagnosis is obtained with histological examination, which evidences proliferations of myofibroblasts, lymphoplasmacytic infiltrate, and a myxoid stroma[5].

Fifty-six percent of IMT present reorganisation of gene ALK. These patients present a higher risk of local recurrence but not distant metastasis (negative ALK), which suggests that reactivity to the ALK could be a protective factor[3].

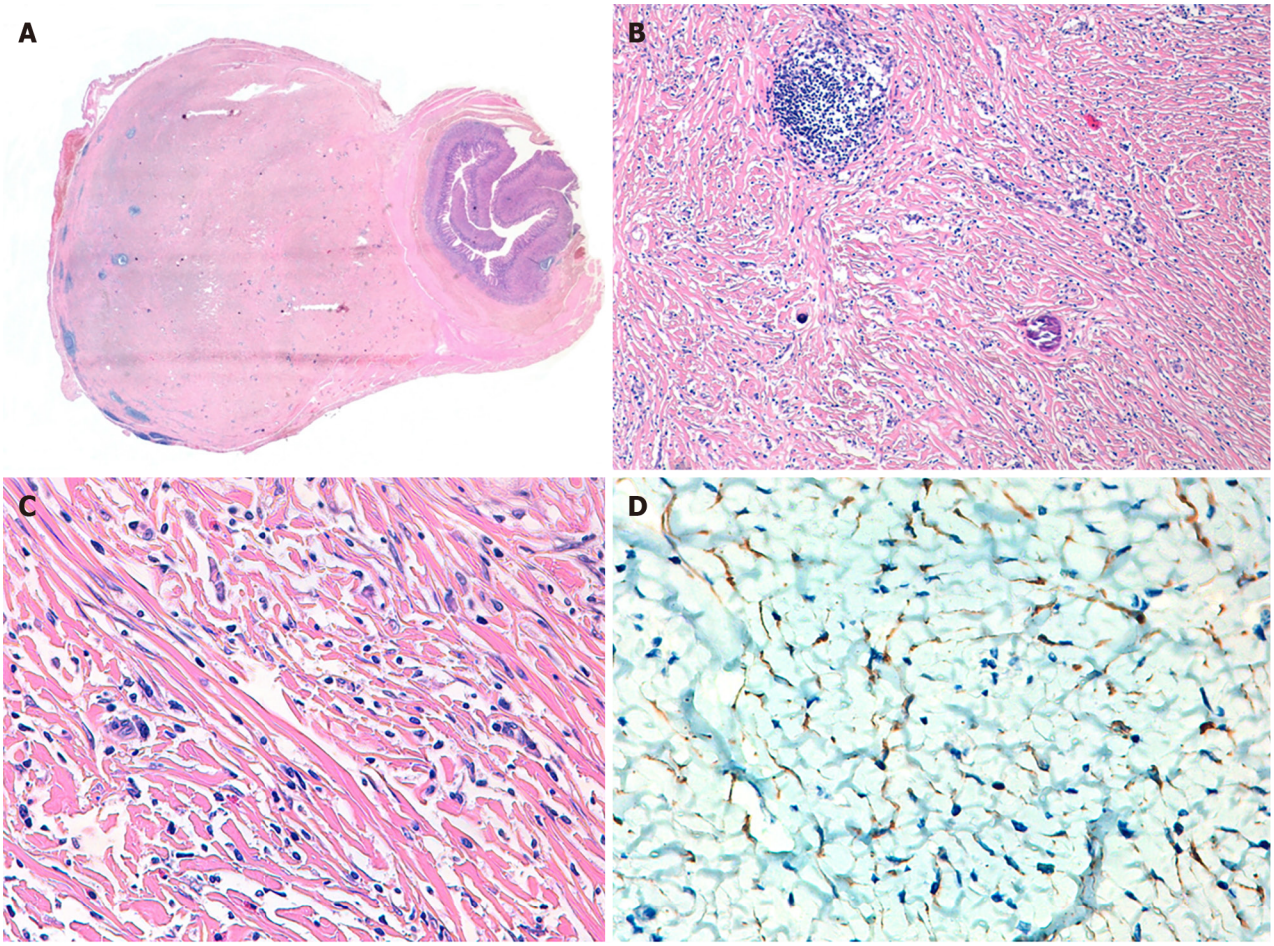

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Figure 2 Histopathological analysis and immunohistochemical examination of the resected specimen. A: Panoramic image of the lesion; B: Mesenquimal injury and psamomatous calcifications; C: Mesenquimal lesion with infiltrate of eosinophils, plasma cells and masts cells; D: Positive expression of Cytokeratins AE1-AE3.

CONCLUSION

Due to the unpredictable nature of this tumor, surgical resection is the best therapeutic option. Regarding gastric IMTs, depending on the tumor's location, options go from a wedge resection to a partial gastrectomy[1-3]. Patients which cannot undergo surgical interventions, can be treated with a combination of radiotherapy and chemotherapy. Patients with metastatic tumors or local advanced tumors resistent to conventional chemotherapy can be treated with Crizotinib if they present a mutation of ALK or Larotrectinib o Entrectinib, if they present mutations in the gene TRK[2].

The recurrence rate in the first year after surgery is of 15%-37%, therefore clinical and radiological follow-ups are indicated, without finding in the literature a defined periodicity for them[3,4].

FOOTNOTES

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CASE REPORT

Systematic sequential therapy for *ex vivo* liver resection and autotransplantation: A case report and review of literature

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Abstract

BACKGROUND

Perihilar cholangiocarcinoma (pCCA) is a highly malignant tumor arising from the biliary tree. Radical surgery is the only treatment offering a chance of long-term survival. However, limited by the tumor's anatomic location and peri-vascular invasion, most patients lose the chance for curative treatment. Therefore, more methods to increase the resectability of tumors as well as to improve outcomes are needed.

CASE SUMMARY

A 68-year-old female patient had a hepatic hilar mass without obvious symptoms. Laboratory results showed hepatitis B positivity. Magnetic resonance imaging indicated that the mass (maximum diameter: 41 mm) invaded the left and right branches of the main portal vein, as well as the middle, left and right hepatic veins; enlarged lymph nodes were also detected in the hilum. The patient was diagnosed with pCCA, and the clinical stage was determined to be T4N1M0 (stage IIIC). Considering the tumor's anatomic location and vascular invasion, systematic conversion therapy followed by *ex vivo* liver resection and autotransplantation (ELRA) was determined as personalized treatment for this patient. Our original systemic sequential therapeutic strategy (lenvatinib and tislelizumab in

combination with gemcitabine and cisplatin) was successfully adopted as conversion therapy because she achieved partial response after three cycles of treatment, without severe toxicity. ELRA, anastomotic reconstruction of the middle hepatic vein, right hepatic vein, root of portal vein, inferior vena cava and right hepatic artery, and lymph node dissection were performed at one month after systemic therapy. Pathological and immunohistochemical examination confirmed the diagnosis of pCCA with lymph node metastasis. Although the middle hepatic vein was partially obstructed four months later, hepatic vein stent implantation successfully addressed this problem. The patient has survived for 22 mo after the diagnosis, with no evidence of recurrence or metastasis.

CONCLUSION

An effective therapeutic strategy for conversion therapy greatly increases the feasibility and efficiency of ELRA.

Key Words: Perihilar cholangiocarcinoma; *Ex vivo* liver resection and autotransplantation; Systemic sequential therapy; Conversion therapy; Case report

Core Tip: Limited by tumor's anatomic location and peri-vascular invasion, most perihilar cholangiocarcinoma patients lose the chance for curative treatment. In this case, we originally put forward systematic conversion therapy followed by *ex vivo* liver resection and autotransplantation (ELRA). The patient achieved partial response after three cycles of systemic sequential treatment without severe toxicities. Soon afterwards, ELRA, anastomotic reconstruction of the middle hepatic vein, the right hepatic vein, the root of portal vein, inferior vena cava and right hepatic artery, and lymph node dissection were performed with success. The patient achieved long time survival and has survived 22 mo following diagnosis with no evidence of recurrence or metastasis.

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INTRODUCTION

Originating from the biliary tree and/or within the hepatic parenchyma, cholangiocarcinoma (CCA) is a highly lethal epithelial cell malignancy. CCA predominantly arises from bile duct epithelial cells and displays features of cholangiocyte differentiation[1]. These heterogeneous cancers can be classified according to anatomic subtype as intrahepatic CCA (iCCA), perihilar CCA (pCCA) or distal CCA (dCCA). pCCA is localized between the second-order bile ducts and the junction of the cystic duct into the common bile duct, dCCA is confined to the common bile duct below the cystic duct insertion, and iCCA is located within the liver parenchyma[2,3]. Each of the anatomic subtypes is characterized by unique genetic aberrations, clinical presentations and management options.

As the most common subtype of CCA, pCCA accounts for more than 50% of cases, and radical surgical resection is the only treatment offering a chance of long-term survival for patients with pCCA[4]. Unfortunately, due to its highly invasive biological characteristics and lack of specific symptoms, most pCCA patients are diagnosed with advanced disease, which decreases the opportunity of radical surgery[5]. In addition, extensive hilar invasion, liver involvement and vascular encasement often preclude curative resection. Therefore, the traditional surgical effect is far from satisfactory; liver transplantation may be a more promising option for pCCA patients[6].

In 1988, *ex vivo* liver resection and autotransplantation (ELRA) was first introduced by Professor Pichlmayr *et al*[7] as an alternative to liver transplantation for unresectable hepatic tumors, and ELRA has been constantly developed to improve the resectability of hepatobiliary malignancies. In 2003, Chui *et al*[8] first reported a type IV pCCA patient who underwent ELRA and survived for two years without any sign of tumor recurrence. Currently, the rapid development of autologous liver transplantation surgical techniques and vascular reconstruction techniques as well as the application of novel immunosuppressive agents are greatly contributing to expanding the limits of resectability and reducing the incidence of chronic allograft rejection, which may greatly benefit select patients[9,10]. However, because of the rigorous admission criteria for liver transplantation, more methods to increase the feasibility of ELRA are needed[11].

Recently, conversion therapy using systematic therapy and/or nonsurgical local therapy to inhibit tumor progression, reduce the tumor burden, and even decrease TNM staging has provided patients with the opportunity for radical surgery and significantly improved prognosis[1,12,13]. In 2021, we first reported that an original systemic sequential therapeutic strategy (gemcitabine 1000 mg/m^2 and cisplatin 25 mg/m^2 on days 1 and 8; lenvatinib 8 mg/d from days 1 to 21; tislelizumab 200 mg on day 15) showed reliable treatment effects on conversion surgery for advanced iCCA patients[14]. Here, we present our new single-center experience with this conversion therapy strategy for treatment of pCCA before ELRA. The prognosis of our 68-year-old female patient was favorable, and no evidence of tumor recurrence was found until July

15, 2023.

CASE PRESENTATION

Chief complaints

A 68-year-old female patient was incidentally found to have a mass in the second hepatic portal region to the caudate lobe at a local hospital and was admitted to our hospital for treatment on August 30, 2021.

History of present illness

No special discomfort was reported by the patient.

History of past illness

None.

Personal and family history

None.

Physical examination

No signs were detected by physical examination.

Laboratory examinations

No abnormal laboratory results were recorded, except for alanine aminotransferase (ALT) 43 U/L and aspartate aminotransferase (AST) 46 U/L; anti-HBs (+), anti-HBe (+) and anti-HBc (+) were also obtained. We performed liver biopsy, and the results revealed moderately poorly differentiated adenocarcinoma (Figure 1A and B). Immunohistochemical staining results were as follows: CK7 (+), CK19 (+), HepPar-1 (-), arginase-1 (-) and Ki-67 labeling index 40%.

Imaging examinations

B-scan ultrasound showed a hilar mass that led to expansion of the intrahepatic bile duct in the left lobe of the liver. Contrast-enhanced magnetic resonance imaging (MRI) scanning found that the mass (maximum diameter: 41 mm) invaded the left and right branches of the main portal vein as well as the middle, left and right hepatic veins (Figure 2A-D). Enlarged hilar lymph nodes were also detected by MRI (Figure 2E). However, there was no invasion of the abdominal aorta or its branches and no filling defect in the inferior vena cava according to computed tomography (CT) imaging of abdominal vessels.

FINAL DIAGNOSIS

We made a diagnosis of pCCA with lymph node metastasis. The Child-Pugh score was A with 5 points. The TNM clinical stage was determined as T4N1M0 (stage IIIC) according to the American Joint Committee on Cancer staging system, 8th edition.

TREATMENT

After full consideration, we determined that the patient had lost the chance for surgery and was scheduled for a personalized therapeutic scheme (intravenous gemcitabine 1000 mg/m^2 and cisplatin 25 mg/m^2 on day 1, day 8; oral lenvatinib 8 mg/d from day 1 to day 21; intravenous tislelizumab 200 mg on day 15). No grade 3/4 treatment-related adverse effects were detected after three cycles of systemic treatment. Further MRI indicated that the mass in the hilar was significantly smaller than that previously (Figure 2F-I). The diameter of the largest lesion had decreased from 41 mm to 21 mm. According to the standard RECIST 1.1 criteria, the patient successfully achieved partial response (PR), and the lymph nodes in the hilar region were also smaller than before (Figure 2J). Consequently, the preoperative multidisciplinary team carefully reviewed all preoperative results and proposed a surgical strategy for autologous liver segment autotransplantation.

The surgery was performed on December 1, 2021, and lasted for 740 min. Three-dimensional reconstruction (Figure 3A) and intraoperative exploration revealed that the tumor invaded the root of the left and right hepatic ducts, left and right portal veins, and middle and right hepatic veins. First, the left hemiliver was completely removed *in vivo*, and the middle hepatic vein was retained in the right lobe (Figure 3B). When the right lobe including the tumor was resected (Figure 3C), the right lobe was immediately placed in an ice basin and perfused with 4°C histidine-tryptophan-ketoglutarate solution. *In vitro*, the tumor was completely resected, and we further used the allogeneic iliac vein to lengthen the middle and right hepatic veins. In addition, the allogeneic iliac vein was used as the bypass between the portal vein and inferior vena cava during the anhepatic phase. Finally, anastomotic reconstruction of the middle hepatic vein, the right hepatic vein, the root of portal vein, inferior vena cava, and right hepatic artery were performed sequen-

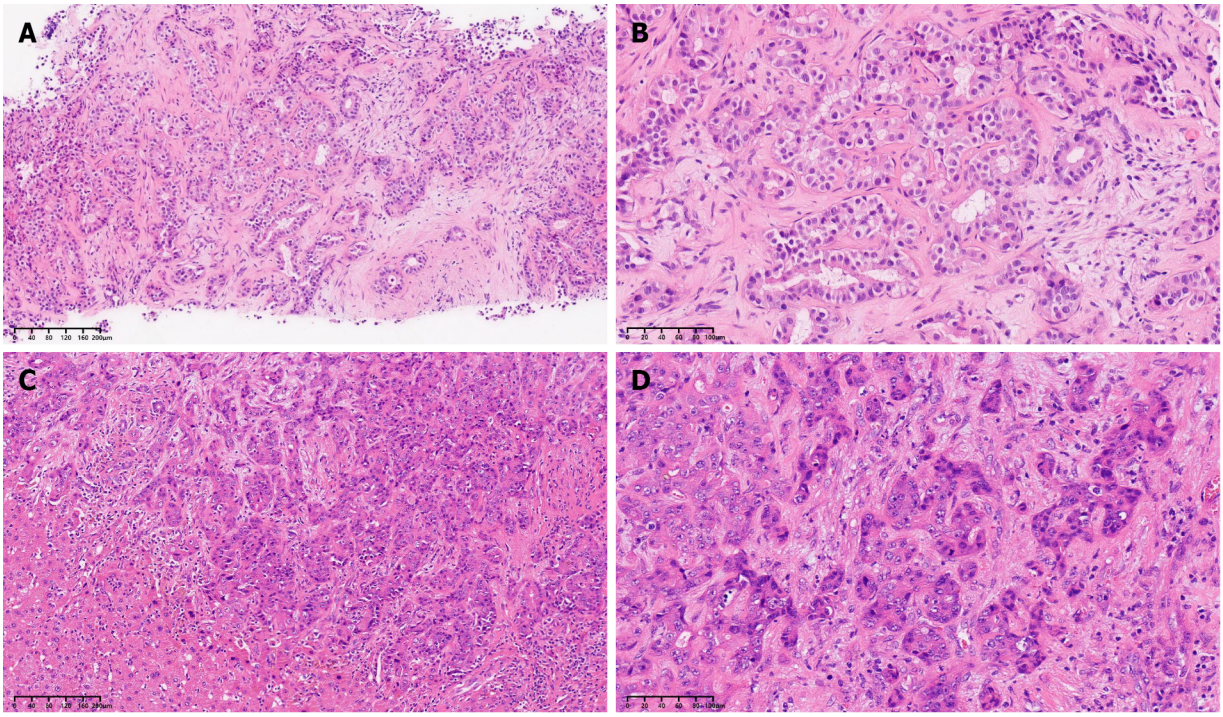

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Figure 1 Pathological examination of the tumor before and after systematic sequential therapy. A and C: Hematoxylin and eosin (H&E), original magnification × 100; B and D: H&E, original magnification × 200.

tially (Figure 3D). Moreover, the hepatic portal lymph nodes and para-esophageal lymph nodes were dissected.

OUTCOME AND FOLLOW-UP

Postoperative pathological examination (Figure 1C and D) showed the following: The tumor bed with a large necrotic area, interstitial fibrosis and tumor residue was 4.0 cm × 3.0 cm in size as well as a negative surgical margin; the hepatic portal lymph nodes were 0/3 positive, but the para-esophageal lymph nodes were 2/2 positive; no microvascular or Glisson's capsule invasion was found. Results of immunohistochemical analysis were as follows: CK7 (+), CK19 (+), HepPar-1 (-), Arginase-1(-) and Ki-67 labeling index 80% (Figure 4). The patient was sent to the intensive care unit and extubated on postoperative day 2. Tacrolimus (0.5 mg, QD7; 1 mg, QD19) was administered to prevent immune rejection, and the value of FK506 was closely monitored. According to postoperative ultrasound, the maximum blood flow velocities of the portal vein, hepatic artery, right hepatic vein and middle hepatic vein were 40.64 cm/s, 70.96 cm/s, 69.02 cm/s and 23.22 cm/s, respectively. No severe complications occurred during hospitalization. The patient was successfully discharged on postoperative day 22 with normal liver and heart function.

At 2 mo after the surgery, the patient continued to take oral capecitabine (1750 mg, twice daily) and lenvatinib (8 mg, once daily) as maintenance treatments. At a 3 mo follow-up, the patient felt subjectively well, and no obvious abnormity was found by contrast-enhanced MRI re-examination (Figure 5A and B). Unfortunately, abdominal enhanced CT indicated the existence of hepatic congestion and hepatomegaly on April 19, 2022 (Figure 5C). Her liver function and coagulation function were abnormal, showing the following: ALT 52 U/L, AST 92 U/L, total bilirubin 40.3 μmol/L, direct bilirubin 17.5 μmol/L, indirect bilirubin 22.8 μmol/L, albumin 32.1 g/L, and serum D-dimer 1040 μg/L. Furthermore, the middle hepatic vein was partially obstructed, and the maximum blood flow velocities of the portal vein, hepatic artery, right hepatic vein and middle hepatic vein were significantly slower than before. Considering that a thrombus may further impair liver function, the patient underwent hepatic vein stent implantation on May 5, 2022. After treatment, her liver function returned to normal levels. Postoperative ultrasonography indicated that blood flow in the stent was clear, and the maximum blood flow velocity of the stenting area was 118.8 cm/s.

One month later, the patient received six cycles of targeted therapy and immunotherapy (lenvatinib 8 mg/d from day 1 to day 21; tislelizumab 200 mg on day 15). Further follow-ups showed no evidence of local recurrence or distant metastasis, and the hepatic vein stent was good (Figure 5D). To date, the patient has survived well without any severe discomfort for more than 22 mo. Figure 6 shows this patient's timeline of initial diagnosis, systemic therapy, surgery, adjuvant therapy and follow-up.

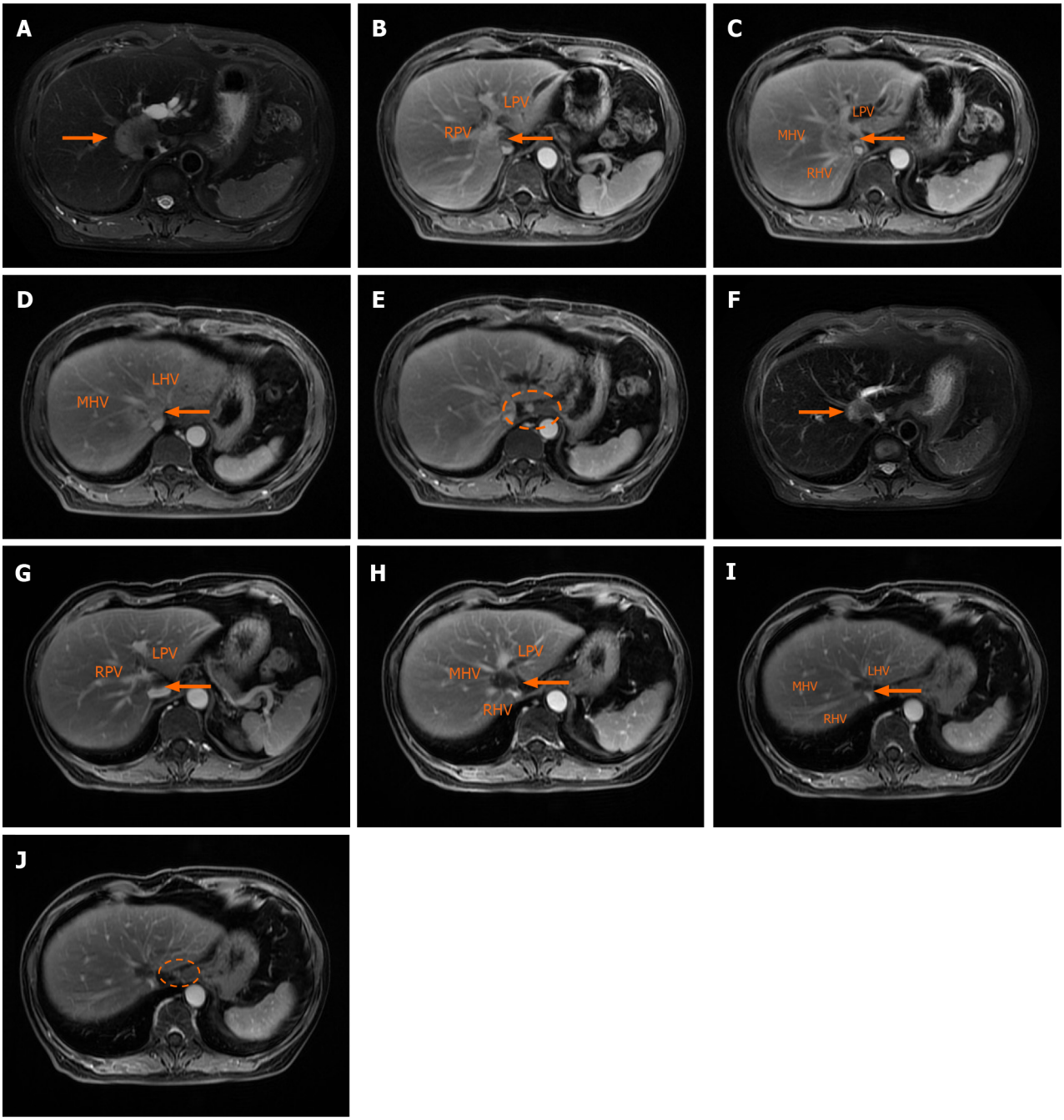

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Figure 2 Contrast-enhanced magnetic resonance images of the irregular tumor or enlarged hilar lymph node before and after systematic sequential therapy. The white arrow indicates the tumor, and the white circle contains an enlarged lymph node. A: T2 phase image before therapy showing a hilar mass with a maximum diameter of 41 mm; B-D: Portal venous phase image before therapy showing that the tumor invaded the main portal vein with left and right branches, as well as the middle, left and right hepatic veins; E: Portal venous phase image before therapy showing the enlarged hilar lymph node; F: T2 phase image after therapy showing that a hilar mass shrunk to a maximum diameter of 21 mm; G-I: Portal venous phase image after therapy; J: Portal venous phase image after therapy showing that the enlarged hilar lymph nodes were smaller. RPV: Right portal vein; LPV: Left portal vein; MHV: Middle hepatic vein; RHV: Right hepatic vein; LHV: Left hepatic vein.

DISCUSSION

Currently, pCCA is a malignancy with the most dismal prognoses, and the gold standard curative therapy is radical resection. Unfortunately, less than 50% of pCCA patients are eligible for resection[15], and the incidence of R0 resection reported in patients undergoing surgery is only 45%[16]. A need for improvement in tumor resectability and resection safety therefore seems obvious. Of note, in contrast to liver resection, liver transplantation is logically an attractive alternative to address most problems, such as the high potential of residual tumor as well as unresectable disease with vascular involvement[6]. ELRA, a unique type of liver transplantation, provides several benefits. It may improve tumor accessibility to achieve complete tumor resection with clear margins, achieve complex vascular reconstruction, reduce

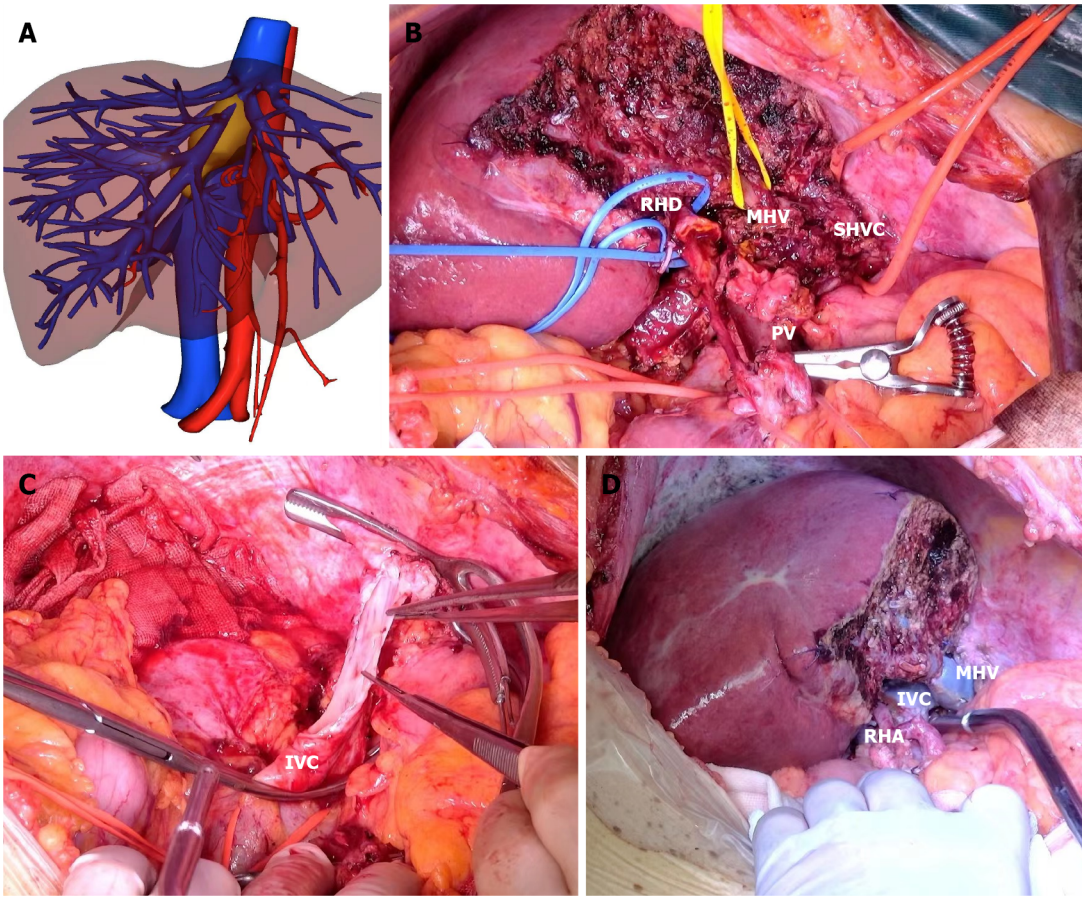

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Figure 3 The key intraoperative process. A: Three-dimensional reconstruction of the relationship between the hepatic vein and tumor after systematic sequential therapy; B: The right hemiliver retaining the middle hepatic vein; C: Removal of the right hemiliver and resection of the tumor invading the inferior vena cava; D: Reconstruction of the middle hepatic vein, inferior vena cava and right hepatic artery. IVC: Inferior vena cava; MHV: Middle hepatic vein; PV: Portal vein; RHA: Right hepatic artery; RHD: Right hepatic duct; SHVC: Superior hepatic vena cava.

ischemic damage to the organ through use of cold preservation solution, decrease demand for organ donors and reduce immunosuppression compared with allotransplantation[17]. In recent years, there have been numerous reports related to successful treatment with ELRA[9,18-21]. Based on their large collective experience, Weiner *et al*[9] reported relatively favorable outcomes after ELRA in select patients. A systematic review and meta-analysis revealed an R0 resection rate of 93.4% and a 1-year survival of 78.4% with ELRA[22]. In addition, one study demonstrated that liver transplantation for pCCA led to similar or even better outcomes than with hepatocellular carcinoma or cirrhosis due to various causes[23]. Therefore, ELRA may become a more widely accepted and practical treatment option for conventionally unresectable hepatobiliary tumors.

However, not all patients are eligible for ELRA. Ideal candidates are those with good functional reserve, can tolerate the procedures, and have a less aggressive malignant tumor[17]. According to data from the Mayo Clinic, a mass not larger than 3 cm in diameter is the selection criterion for pCCA[24]. In our case, the malignancy was 4.1 cm in diameter, and the tumor was located in the porta hepatis with involvement of the middle hepatic vein, portal vein and inferior vena cava. Although ELRA and vascular reconstruction may offer R0 resection and excellent survival, the patient did not have sufficient indications. Hence, it was crucial to reduce the tumor burden by some effective means before ELRA to allow the patient to obtain more benefits.

Based on our center's experience, conversion therapy[25] involving multidisciplinary systematic treatment preoperatively and aiming to render the tumor more amenable to surgical removal can be regarded as a more suitable pre-ELRA treatment for this patient. At present, there are various systematic treatment strategies. Over the last decade, doublet chemotherapy with gemcitabine and cisplatin has been considered the most effective first-line treatment for pCCA, as based on the results of the ABC-02 trial (NCT00262769) reported in 2010[26]. In the new era of targeted therapy and immunotherapy, systemic therapy with molecular and immune therapies has dramatically changed management of pCCA at advanced stages. Notably, the randomized, double-blind, phase 3 TOPAZ-1 trial (NCT03875235) showed that adding the PD-L1 inhibitor durvalumab to gemcitabine and cisplatin significantly improved overall survival (OS) for advanced biliary tract cancer (BTC) compared with gemcitabine and cisplatin alone: Median OS: 12.8 mo [95% confidence interval (95%CI): 11.1-14.0] *vs*. 11.5 mo (95%CI: 10.1-12.5); hazard ratio (HR) 0.80; two-sided $P = 0.021$[27]. Another recent phase 3 clinical trial (KEYNOTE-966; NCT04003636) found that adding pembrolizumab to gemcitabine and cisplatin remarkably ameliorated OS for advanced BTC [median OS: 12.7 mo (95%CI: 11.5-13.6) in the pembrolizumab group *vs*.

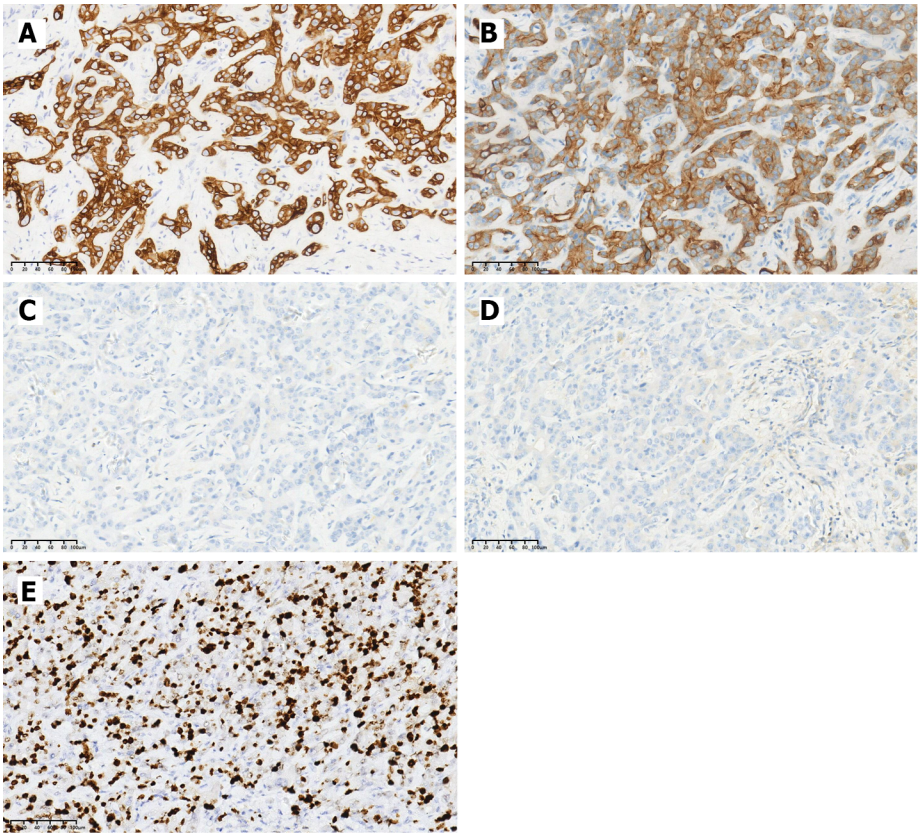

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Figure 4 Immunohistochemical staining results for the tumor. A: CK7 (+); B: CK19 (+); C: HepPar-1 (-); D: Arginase-1 (-); E: Ki-67.

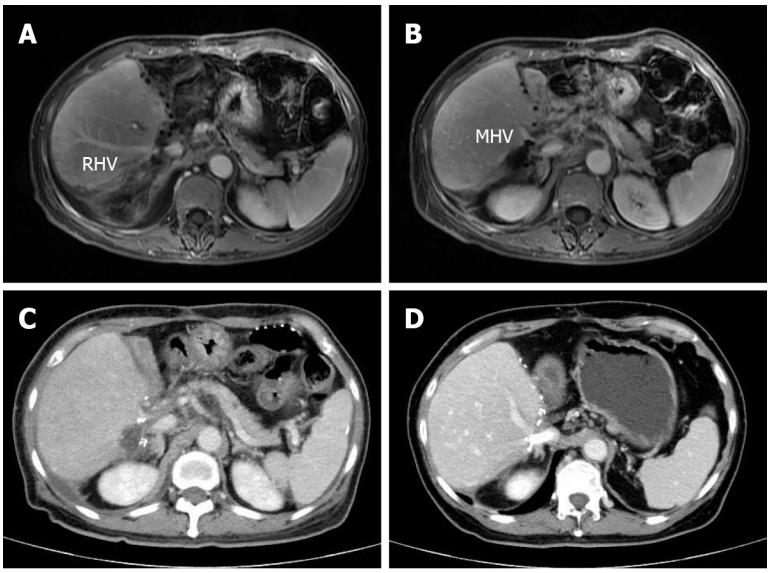

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Figure 5 Contrast-enhanced magnetic resonance images and computed tomography images after surgery. A and B: Portal venous phase image after surgery clearly showing the middle hepatic vein and right portal vein, respectively; C: Portal venous phase image showing the existence of hepatic congestion and hepatomegaly; D: Portal venous phase image showing the hepatic vein stent. MHV: Middle hepatic vein; RHV: Right hepatic vein.

10.9 mo (95%CI: 9.9-11.6) in the placebo group; HR 0.83; one-sided P = 0.0034][28]. Thus, combination chemotherapy and immunotherapy are safe and effective for patients with pCCA.

Lenvatinib, a multikinase inhibitor that targets vascular endothelial growth factor (VEGF) receptor 1-3, fibroblast growth factor receptor 1-4, platelet-derived growth factor receptor-α, RET, and KIT, is widely used for many solid tumors, especially hepatobiliary malignancies[29-33]. More than 50% VEGF overexpression is detected in CCA[34]. Based on this evidence, we deeply considered whether systematic therapy, including chemotherapy, targeted therapy and

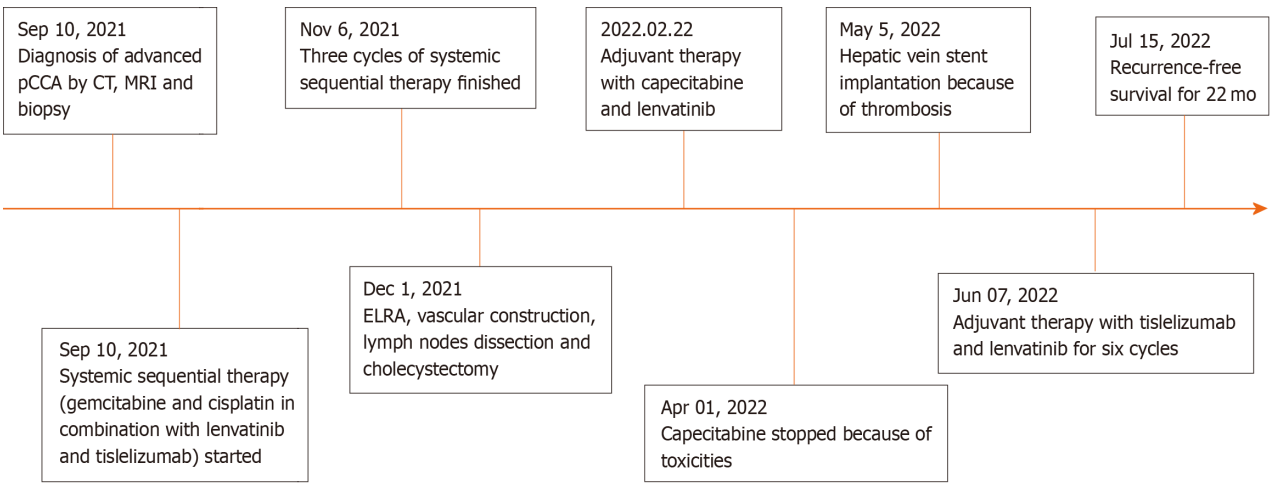

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Figure 6 Timeline of the initial diagnosis, systemic therapy, surgery, adjuvant therapy and follow-up. ELRA: *Ex vivo* liver resection and autotransplantation; Pcca: Perihilar cholangiocarcinoma; CT: Computed tomography; MRI: Magnetic resonance imaging.

immunotherapy, is sensible for CCA patients. We first reported based on our previous clinical practice that systemic sequential therapy with gemcitabine, cisplatin, lenvatinib and tislelizumab offers great therapeutic effects for preoperative advanced iCCA conversion therapy[14]. Zhang *et al*[35] reported a patient with iCCA who first received six cycles of conversion therapy (gemcitabine 1000 mg/m^2 and cisplatin 25 mg/m^2 on day 1 and day 8; pembrolizumab, 200 mg every 3 wk; lenvatinib 8 mg from day 1 to day 21) and achieved pathologic PR without severe toxicity, followed by radical liver resection, cholecystectomy and hilar lymph node dissection. A single-arm phase 2 study (NCT03951597) to explore the efficacy and safety of a similar systemic sequential therapy for iCCA was completed in 2022[36]. The objective response rate was 80% and the median OS 22.5 mo (95%CI: 15.6-29.3) after combination therapy of toripalimab, lenvatinib, and gemcitabine plus oxaliplatin for advanced iCCA when the median follow-up time was 23.5 mo. In our case, our previous systemic sequential therapy (gemcitabine 1000 mg/m^2 and cisplatin 25 mg/m^2 on day 1 and day 8; lenvatinib 8 mg from day 1 to day 21; tislelizumab 200 mg on day 15) was successfully administered to a pCCA patient as conversion therapy, without any grade 3/4 adverse effects, before ELRA and allogeneic vascular reconstruction. The old patients ultimately achieved excellent outcomes.

CONCLUSION

In conclusion, this is the first case report of a novel systemic sequential therapeutic strategy followed by ELRA and vascular reconstruction for pCCA. The female patient achieved PR after the scheduled therapy, and no obvious overlapping toxicities occurred during that period. Considering the tumor's anatomic location and vascular invasion, ELRA and vascular reconstruction was considered to be a better treatment option. The tumor was successfully resected *ex vivo* with a negative surgical margin; the hepatic vein and inferior vena cava were smoothly reconstructed with the allogeneic iliac vein. This case indicates that an effective therapeutic strategy for conversion therapy can greatly increase the feasibility and efficiency of ELRA and vascular reconstruction. Currently, our phase 2 clinical trial (NCT05532059), designed to explore the efficacy and safety of this systemic therapy for CCA patients, is ongoing, and we hope to provide more beneficial treatment options for advanced CCA.

FOOTNOTES

Co-first authors: Chen-Lu Hu and Xin Han.

Co-corresponding authors: Sheng Yan and Yuan Ding.

Author contributions: Yan S and Ding Y conceived of, designed and refined the study protocol; Hu CL, Han X, Gao ZZ, Zhou B, Tang JL, Fei XR, Lu JN, Xu Q, and Shen XP were involved in the data collection and analysis; Hu CL and Han X drafted the manuscript; all authors were involved in the critical review of the results and contributed to, read, and approved the final manuscript. Hu CL and Han X equally contributed to this work as co-first authors; Yan S and Ding Y contributed equally to this work as co-corresponding authors. There are two reasons for this designation. First, the research was performed as a collaborative effort, and the designation of co-corresponding authorship accurately reflects the distribution of responsibilities and burdens associated with the time and effort required to complete the study and the resulting paper. This also ensures effective communication and management of postsubmission matters, ultimately enhancing the paper's quality and reliability. Second, Hu CL and Han X contributed equally to 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 Hu CL and Han X as co-first authors/Yan S and

Ding Y as co-corresponding authors is appropriate for our manuscript, as it accurately reflects our team's collaborative spirit, equal contributions, and diversity.

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 they have no competing interests.

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