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MINIREVIEWS

Surgical management of acute pancreatitis: Historical perspectives, challenges, and current management approaches

Nasser Alzerwi

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Nasser Alzerwi, Department of Surgery, Majmaah University, Riyadh 11952, Saudi Arabia

Corresponding author: Nasser Alzerwi, MBBS, SBGS, ABGS, FSMC(HPB), Associate Professor, Department of Surgery, Majmaah University, P. O. Box 66, Al-Majmaah City, Riyadh Region, Riyadh 11952, Saudi Arabia. n.alzerwi@mu.edu.sa

Abstract

Acute pancreatitis (AP) is a serious condition presenting catastrophic consequences. In severe AP, the mortality rate is high, and some patients initially diagnosed with mild-to-moderate AP can progress to a life-threatening severe state. Treatment of AP has evolved over the years. Drainage was the first surgical procedure performed for AP; however, later, surgical approaches were replaced by more conservative approaches due to the availability of advanced medical care and improved understanding of the course of AP. Currently, surgery is used to manage several complications of AP, such as pseudocysts, pancreatic fistulas, and biliary tract obstruction. Patients who are unresponsive to conservative treatment or have complications are typically considered for surgical intervention. This review focuses on the surgical approaches (endoscopic, percutaneous, and open) that have been established in recent studies to treat this acute condition and summarizes the common management guidelines for AP, discussing the relevant indications, significance, and complications. It is evident that despite their reduced involvement, surgeons lead the multidisciplinary care of patients with AP; however, given the gaps in existing knowledge, more research is required to standardize surgical protocols for AP.

Key Words: Acute pancreatitis; Surgery; Endoscopic management; Open surgery; Necrosectomy

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Core Tip: The surgical management of acute pancreatitis has evolved substantially during the last several decades. Conservative therapy is frequently more effective than surgery; nonetheless, surgical treatments are required in cases of non-responsive or complication-prone patients. Such cases may be treated using endoscopic, percutaneous, or open procedures, each with its own set of benefits and risks. Before settling on an acceptable surgical procedure, the AP severity, phase, and anatomical restrictions must be thoroughly reviewed for optimal clinical outcomes.

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INTRODUCTION

Acute pancreatitis (AP) is a prevalent gastrointestinal disorder resulting in localized damage, systemic inflammatory response syndrome, and organ failure (OF)[1,2]. With a worldwide incidence of 340 per million people overall and case fatality rates of up to 35% in severe instances, AP causes a great deal of distress, morbidity, and financial strain on the healthcare system[3-5].

In Western countries, the prevalence of AP has been steadily rising over the last half-century[6]. Gallstones and alcohol continue to be common causes of AP, contributing to 80% of AP cases, while the remaining occurrences are related to less common causes, such as drug interactions and solid and cystic pancreatic cancers. In particular, the global transition rate from the index AP to a recurring episode is in double digits. Given these concerns and the variety of long-term repercussions, it is prudent not to regard AP as a self-limiting condition[5].

The need for surgical intervention in AP has been under scrutiny for more than a century, with arguments ranging from conservative therapeutic strategies on the one hand to surgical approaches. However, in the last three decades, the discourse has changed significantly, with conservative management gaining favor due to the availability of advanced diagnostic modalities, improved noninvasive care, improved understanding of the underlying mechanisms, and improvements in interventional procedures. However, surgery still serves a critical function in managing AP, and there are specific situations in which minimally invasive or open surgical interventions are necessary.

This review offers a concise overview of the evolution of surgical management of AP, with an emphasis on contemporary surgical techniques. Recent ground-breaking studies have allowed the development of several sets of recommendations and guidelines for the management of AP. This review also summarizes some of these recommendations, focusing on surgical interventions for AP, including indications, staging, and techniques.

AP: ETIOLOGY, CLASSIFICATION, AND DIAGNOSIS

During the mid-twentieth century, researchers realized that AP could have various root causes, each of which required a unique diagnostic and therapeutic strategy. Approximately 40% of AP cases are now attributed to gallstones, and approximately 30% are considered to have alcohol as an etiological component[7] (Figure 1A). Researchers have also identified various other etiologies for AP, including metabolic, immunological, parasitic, genetic, anatomical, and endoscopic retrograde cholangiopancreatography (ERCP). Notably, the prevalence of hypertriglyceridemic AP has increased in recent years [8]. Idiopathic AP is AP with no identified explanation after primary laboratory and imaging studies[9, 10].

Early efforts to categorize pancreatitis focused mainly on describing its clinical and pathological aspects. Fitz distinguished between acute, hemorrhagic, and suppurative forms of pancreatitis[11]. Ranson *et al*[12] demarcated AP's key clinical and biochemical features, now known as the Ranson criteria. Another significant development was the Atlanta classification proposed in 1992[13], wherein objective criteria for severe, interstitial, and necrotizing AP, infected pancreatic necrosis (IPN), and pseudocysts were framed, with a stronger focus on the systemic effect of AP. Two new AP classification systems were released in 2012: Revised Atlanta classification and determinant-based classification[14, 15]. The revised Atlanta classification system is popular at the moment. The severity of AP may be classified as mild, moderately severe (MSAP), or severe (SAP), and there are also two distinct stages (early and late). In addition, it explains how AP is diagnosed, stresses the importance of pain as a benchmark, and singles out local complications, interstitial pancreatitis, and necrotizing pancreatitis (Table 1, Figure 2).

Table 1 Acute pancreatitis diagnosis, classification, and indications for surgery

	Criteria
Diagnosis of AP (any two)	Abdominal pain
	Serum lipase or amylase anomalies
	Characteristic radiological features
Mild AP[1]	No OF
	Absence of local or systemic complications
Moderately severe AP[1]	Transient OF (resolves in < 48 h)
	Local or systemic complications without persistent OF
Severe AP[1]	Persistent OF
Key indications for surgery	Infected necrosis
	Complications of pancreatitis
	Fistulas
	Pseudocyst
	Recurrent AP
	Abdominal compartment syndrome
	Systemic inflammatory response syndrome
	Acute necrotizing cholecystitis or intestinal ischemia
	Acute bleeding due to a failed endovascular approach

[1]Revised Atlanta Classification.
AP: Acute pancreatitis; OF: Organ failure.

The diagnosis of AP is based on the presence of characteristic abdominal pain, biochemical confirmation of pancreatitis, and radiographic proof (at least two out of the Diagnostic Triad and in that order)[2,16]. The early and late phases of AP last about two weeks and several weeks, respectively. Temporary local or systemic problems define MSAP or a transient OF, whereas SAP is defined by a lingering OF. Organized fluid collections within four weeks were denoted as acute peri/pancreatic fluid collections and pseudocysts after four weeks. The term "acute necrotic collections" (ANC) is used to describe necrosis-complicated collections that occur within four weeks, whereas "wall necrosis" (WON) is used to describe collections that occur later than four weeks (Figure 2)[14].

PATHOBIOLOGY OF PANCREATITIS

Various physical and genetic variables predispose individuals to AP[17]. Many studies have been conducted on acute pancreatic inflammation in the last century, but our understanding of its numerous pathophysiological implications remains limited[18]. Based on current research, collapse of the pancreatic acinar cell membrane and intracellular digesting enzymes that cause pancreatic damage are suspected to be significant contributors to AP[19]. In particular, in the early course of pancreatitis, enteropeptidase leads to premature activation of trypsinogen to trypsin in acinar cells (Figure 3). This activation sets off a chain reaction of digestive protease activation, which ultimately digests the acinar cells and causes pancreatitis. Although trypsinogen activation inside the acinar cells has a role in the first stages of acinar damage, the development of local and systemic inflammation in pancreatitis can occur independently. Indeed, in the early stages of pancreatitis, trypsin-mediated cell death causes pancreatic injury; however, multiple parallel mechanisms, including activation of inflammatory cascades, excess calcium (Ca^{2+})-induced endoplasmic reticulum stress, autophagy, and mitochondrial dysfunction in acinar cells, are now recognized as important in driving the profound systemic inflammatory response and extensive pancreatic injury in AP[18]. Notably, nuclear factor-kappaB activation occurs early, independent of trypsinogen activation, and leads to the release of inflammatory mediators and recruitment of inflammatory cells, causing acinar cell death at later stages of pancreatitis and driving the systemic inflammatory response observed in pancreatitis[20].

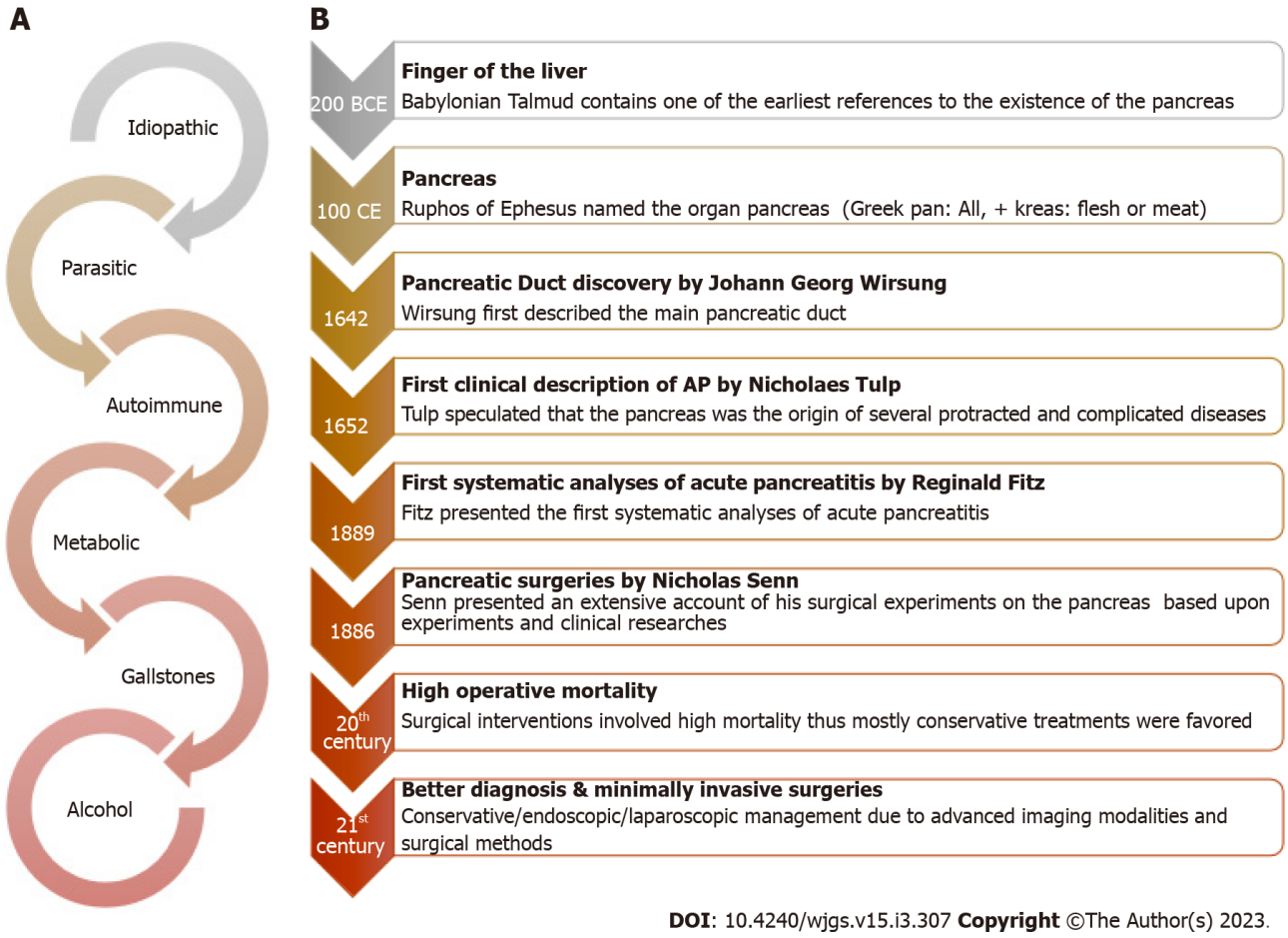

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Figure 1 Etiologies and evolution of surgical management of acute pancreatitis. A: Key acute pancreatitis etiologies; B: Evolution of surgical management.

HISTORICAL PERSPECTIVES ON THE PANCREAS AND EVOLUTION OF PANCREATIC SURGERY

One of the first allusions to the presence of the pancreas can be found in Babylonian Talmud and ancient Greek anatomists[21-23] (Figure 1B). Ruphos of Ephesus named the organ the "pancreas" after seeing that it lacked cartilage and bone in human cadavers (pan: All, kreas: Flesh). Galenus recognized the pancreas as a gland and named it kalikreas, a 'beautiful flesh'. It was not until the 17th century that scientists Johann Georg Wirsung and Giovanni Domenico Santorini discovered primary and secondary pancreatic ducts, respectively[24]. Abraham Vater (1684-1751) described the tubercle or diverticulum, later called the 'ampulla of Vater'[25]. Pannala *et al*[21] suggested that the pancreas plays a vital role in digestion. Subsequent researchers such as Willy Kuhne (trypsin identification), Alexander Marcet (lipase identification), Willy Kuhne (trypsin identification), Alexander Marcet (lipase discovery), and Ivan Pavlov (nerves of the pancreas) contributed greatly to the understanding of pancreatic physiology.

The Dutch anatomist Nicholaes Tulp is accredited with the first publication on the clinical description of AP in 1652. In 1889, Reginald Fitz of Boston offered the first comprehensive analysis of AP in a landmark study. In 1886, Nicholas Senn provided a detailed report of his surgical trials on pancreatic disorders, describing the excision and drainage of retention cysts[26]. In the late nineteenth century, exploratory laparotomy became popular for diagnosing AP and drainage of pancreatic abscesses, and necrotic tissue debridement was performed in some cases. However, despite growing knowledge of pancreatitis, the distinction between chronic pancreatitis and AP was recognized only in the mid-20th century. Surgeons such as Mickulicz, Mayo Robson, and Moynihan were encouraged to employ laparotomy to treat the complications of severe AP as anesthetics developed in the early twentieth century. In the first few decades of the twentieth century, various procedures were performed, such as drainage, resection, and cholecystostomy, but the operative mortality rate remained close to 60%[21].

Later, as the understanding of pancreatic physiology improved and diagnostic modalities advanced, conservative management of patients gained preference. If there is no secondary infection, surgical treatment is not required. With the identification of WON or organized pancreatic necrosis and the advent of advanced antibiotics to curb systemic toxicity and OF, the treatment of pancreatic necrosis has

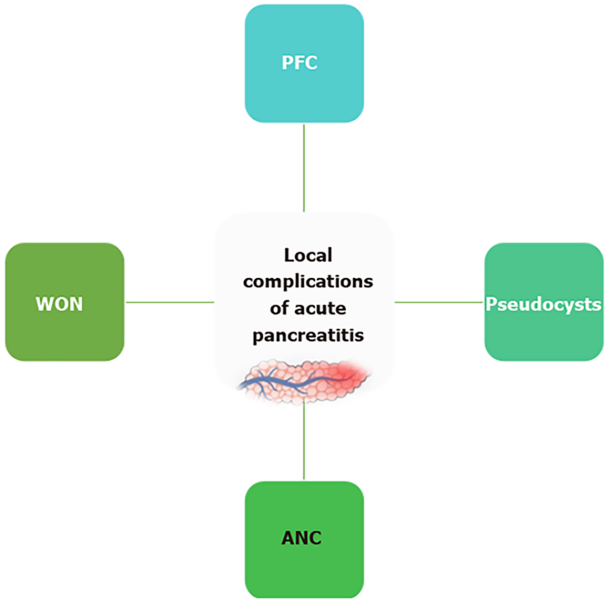

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Figure 2 Local complications in acute pancreatitis. ANC: Acute necrotic collections; PFC: Peripancreatic fluid collections; WON: Walled-off necrosis.

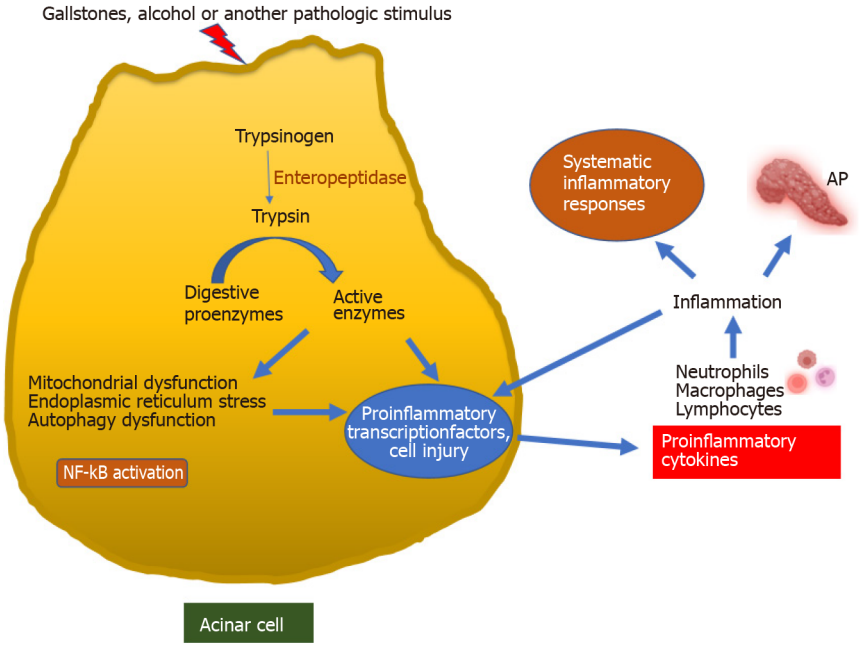

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Figure 3 Pathogenesis of acute pancreatitis. Early activation of trypsinogen to trypsin in acinar cells triggers a cascade of pathogenic events, resulting in acute pancreatitis. AP: Acute pancreatitis; NF-kB: Nuclear factor kB.

evolved further, and delayed necrosectomy is commonly performed for sterile pancreatic necrosis[27,28]. Minimally invasive laparoscopic, endoscopic, and percutaneous techniques have been established in recent decades to treat pancreatic necrosis; however, surgery remains an essential treatment for people with severe pathology. Endoscopic ultrasound (US)-guided therapy for pancreatic necrosis and other AP sequelae is also increasingly gaining popularity[10,27,29,30].

SURGICAL MANAGEMENT

Summary of major guidelines

For the treatment of AP, the guidelines of the International Association of Pancreatology (IAP)/American Pancreatic Association (2013)[31], the World Society of Emergency Surgery (2019)[4], and the American Gastroenterological Association (AGA) published in 2018[32] and 2020[33] are particularly notable. The recommendations of these guidelines for diagnosing and treating AP coincide significantly. The next section briefly summarizes the rationale for surgical interventions and the methods laid forth in the pivotal guidelines.

IAP guidelines: Due to the self-limiting nature and minimal mortality risk, the IAP guidelines explicitly indicate that mild AP is not a justification for surgery. Surgery and drainage are primarily necessary for the clinical indications of sepsis, and early surgery (14 d from the start) should be avoided, especially if patients respond well to conservative therapy. Timing is particularly critical, as cardiac and respiratory failures are common in the early phases of the disease. Furthermore, delaying surgery to a time that provides an improved delineation of the necrotic zone will allow optimal surgical circumstances.

The best surgical approach is removing necrotic tissues while minimizing the risk of subsequent infections, bleeding, necrosis, and inflammation. Most retroperitoneal (RP) debris and exudates are removed postoperatively. Because the pancreas is the main organ responsible for numerous endocrine and exocrine activities, pancreatectomy, whether entire or partial, may cause endocrine inefficiency. Organ preservation techniques such as debridement or necrosectomy are also favored. Although there is no consensus on the ideal strategy for necrosectomy, postoperative mortality has been reported to be less than 15% in various combinations of open necrosectomy with planned relaparotomy. In addition to the open approach, less invasive procedures for necrosectomy are being developed. However, the IAP advises that such treatments should be used in a subset of patients with confined or well-defined necrosis.

Gallstone-associated AP (GSAP) has its own set of management problems, as well as additional co-occurring comorbidities. GSAP requires early management, irrespective of the appearance of obstructive jaundice or severe cholangitis. Because there is no explicit agreement on this topic, the IAP did not recommend the use of endoscopic sphincterotomy (ES) and ERCP for severe GSAP. However, these are needed in the presence of obstructive jaundice or severe cholangitis. In patients with severe GSAP, open cholecystectomy with supraduodenal bile duct exploration and T-tube insertion is often considered an unsatisfactory emergency surgery. If a patient has undergone ES for acute gallstone-associated pancreatitis, the gallbladder should be removed because of the possible risk of gallbladder complications.

Cholecystectomy and clearance of the major bile ducts (when clinical, biochemical, and radiological indicators of persistent biliary obstruction are present) can be performed to prevent the recurrence of biliary pancreatitis. In cases of mild AP associated with gallstones, it should be performed immediately after the patient recovers from the attack. However, in acute GSAP, cholecystectomy should be performed after the inflammatory process has stopped and the patient has recovered clinically to make treatment easier and safer. ES can be used in patients who cannot undergo cholecystectomy; however, the possibility of intervention-induced infections should not be ignored.

Japanese guidelines: The Japanese guidelines[34] for the management of AP were first published in 2006 and have since been amended in 2012 and 2015, respectively. To avoid GSAP recurrence, cholecystectomy is indicated when such an operation is feasible. Because abdominal compartment syndrome (ACS) increases the mortality risk in such situations, sequential IAP monitoring is suggested in patients with abnormal fluid infusion and respiratory or kidney problems.

When an IAP of 12 mmHg persists or recurs, conservative therapy is recommended to maintain it at 15 mmHg. Surgical decompression can be explored when the IAP is greater than 20 mmHg, conservative therapy is ineffective, and OF is a significant concern. Conservative treatment for necrotizing pancreatitis should be attempted first. Suspected or confirmed infections and worsening state are the best justifications for intervention.

IPN is considered when clinical symptoms worsen, along with blood test results that support infection. Four weeks after onset, therapeutic intervention should be initiated when the necrosis is adequately walled off or during the WON phase. Drainage (percutaneous or endoscopic) should be explored, and if no improvement is observed, necrosectomy is a viable approach to treat IPN.

AGA (2018), American College of Gastroenterology (2013), and AGA (2020) guidelines: The 2018 AGA [32] guidelines focused on the initial management of AP. The AGA recommends that AP management during the first 48-72 h after admission should focus on outcome-specific fluid resuscitation. Hydroxyethyl starch fluids are discouraged, and prophylactic antibiotics are not recommended for SAP and necrotizing pancreatitis. AGA advocates early oral feeding and enteral nutrition rather than parenteral nutrition.

Immediate ERCP may be conducted in patients with cholangitis; however, this is not indicated in the context of acute biliary pancreatitis. Cholecystectomy is recommended for patients with acute biliary

pancreatitis, ideally before discharge from the hospital. AGA also recommends same-admission cholecystectomy and short alcohol intercession for biliary and alcohol-induced pancreatitis. AGA does not recommend the regular use of preventive antibiotics in SAP or routine ERCP in patients with AP in the absence of cholangitis.

The 2013 ACG guidelines also indicate that cholecystectomy should be performed before discharge in patients with mild AP with gallstones to avoid recurrent AP[35]. However, cholecystectomy must be postponed in necrotizing biliary AP until active inflammation and fluid collection are managed or stabilized. Asymptomatic pseudocysts and necrosis did not require intervention. In cases of infected necrosis, if the patient's condition is stable, drainage interventions should be postponed for at least four weeks. This period allows the contents to liquefy and forms a fibrous wall surrounding the necrosis. Minimally invasive necrosectomy is preferable to open necrosectomy in symptomatic individuals with infected necrosis. ERCP must be performed within 24 h after admission in patients with AP complicated by acute cholangitis, and pancreatic duct stents and non-steroidal anti-inflammatory drug suppositories should be used in high-risk patients to limit the risk of post-ERCP pancreatitis. Asymptomatic pancreatic and/or extrapancreatic necrosis and/or pseudocysts, regardless of their size, location, or extension, do not require intervention. In infected necrosis, if the condition of the patient is stable, surgical drainage must be postponed for at least four weeks.

The 2020 AGA guidelines focus on pancreatic necrosis[33] and align with the IAP and World Society of Emergency Surgery (WSES) guidelines on most accounts. AGA recognized the importance of surgery and recommended that in cases where clinical experience may be inadequate, patients with substantial pancreatic necrosis should be transferred to a suitable tertiary care hospital. According to the AGA 2020, direct endoscopic necrosectomy (DEN) is an option in cases of extensive necrosis and can also be used in cases of limited necrosis if the patient does not respond well to endoscopic transmural drainage. For debridement of acute necrotizing pancreatitis, minimally invasive surgical approaches should be used instead of open necrosectomy due to the lower risk of morbidity. Multiple debridement techniques should be explored, including videoscopic RP, laparoscopic transgastric, and open transgastric techniques. Distal pancreatectomy can be performed in patients with the detachment of the left pancreatic remnant after acute necrotizing necrosis of the middle body. A step-up approach involving percutaneous drainage or endoscopic transmural drainage followed by DEN and surgical debridement is practical. However, the optimal intervention may differ depending on the accessible clinical expertise.

WSES guidelines: The WSES[4] guidelines aim to provide evidence-based worldwide consensus statements on the treatment of SAP. These guidelines resulted from a special meeting of specialists at the World Congress of Emergency Surgery. According to the IAP guidelines, the WSES does not recommend regular ERCP for GSAP, although it has been suggested for cases of GSAP + cholangitis and GSAP + bile duct obstruction. Infected necrotizing pancreatitis should be treated by percutaneous endoscopic drainage (ED). Surgical approaches may be performed when conservative treatments such as percutaneous or endoscopic approaches do not improve the patient's condition. Surgical intervention is indicated for ACS, hemorrhage, and intestinal ischemia. Regarding surgery, the WSES recommends deferring the operation until four weeks after the initial stage due to better differentiation of necrosis from other vital tissues.

In terms of surgical technique, drainage is the first-line therapy; however, currently, there is not enough information to indicate the best surgical procedure (open or laparoscopic). In the presence of WON and a severed pancreatic duct, a single-stage surgical transgastric necrosectomy may be considered. Laparoscopic cholecystectomy (LCC) is recommended during index hospitalization in patients with moderate GSAP. The risk of recurrent pancreatitis is reduced when sphincterotomy and ERCP are performed during the index hospitalization, although same-admission cholecystectomy is still recommended due to the increased risk of additional biliary problems. Cholecystectomy should be avoided in acute GSAP until fluid collection is clear or stable and acute inflammation subsides.

Surgical decompression and an open abdomen (OA) can be considered for intra-abdominal hypertension/ACS if conservative and noninvasive treatments fail. Negative pressure peritoneal treatment is indicated for the OA because of its shorter duration, fewer dressing changes, and lower reexploration rates.

SUMMARY OF GUIDELINES: MEDICAL TREATMENT OPTIONS

Based on available guidelines, it is evident that the treatment of AP depends significantly on its etiology (Figure 4). The cornerstone of therapy for MSAP patients is supportive care, including resuscitation, pain management, and mobilization. Active rehydration, post-pyloric feeding, and pancreatin inhibitors are first-line therapies for AP. In the event of MSAP, a regular diet should be initiated as soon as possible after admission, and in the case of SAP, enteral nutrition should be initiated as soon as possible after admission. The most common reason for intervention is an infection, and surgery is often necessary to remove necrotic tissue once ACS and/or intestinal ischemia develop[36]. Antibiotics are not required to treat sterile necrosis, and non-operative treatment is preferred. However, antibiotics and image-guided drainage should be used as step-up treatments for patients with infections. As first-line

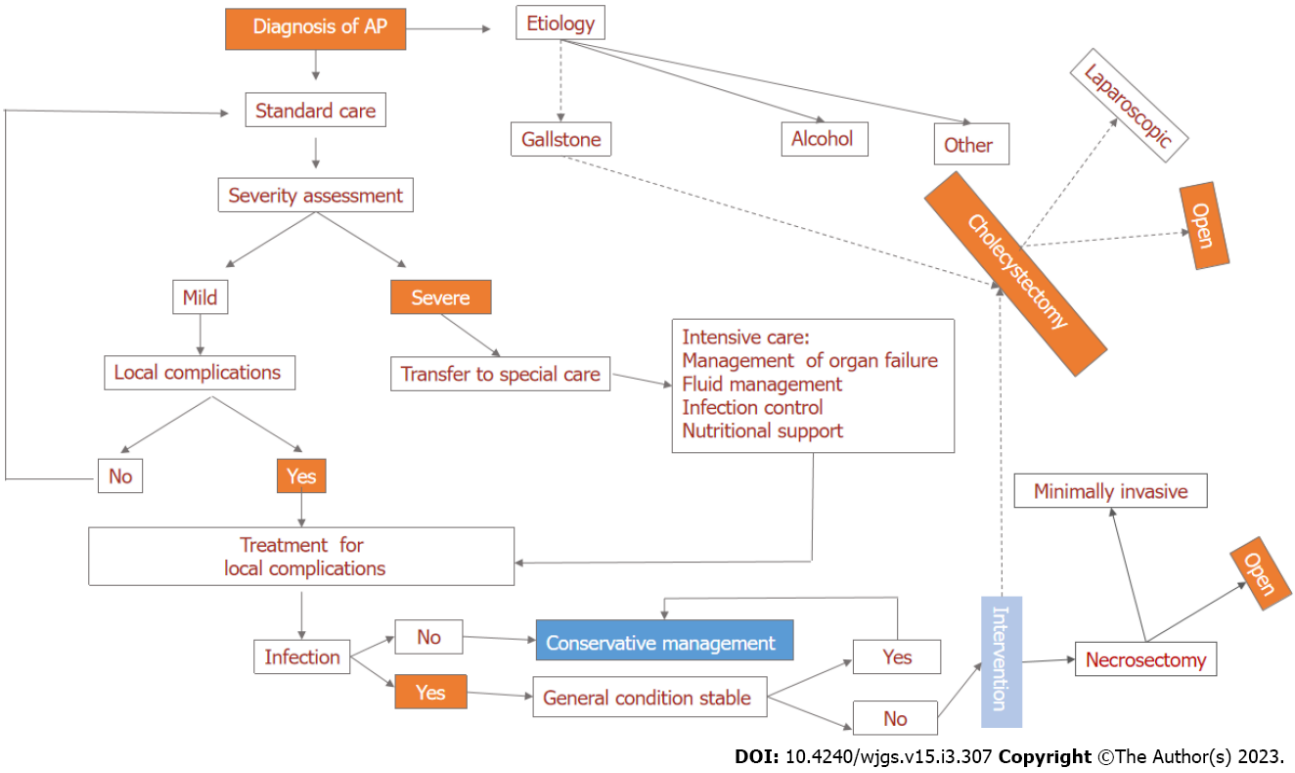

Figure 4 Flow chart of surgical management of acute pancreatitis. AP: Acute pancreatitis.

treatment, minimally invasive image-guided or ED is advised; repeated drains could be required.

Surgery should be considered when less invasive treatments fail but should be postponed until the delineation of necrotic pancreatic tissue (Table 2). Asymptomatic pseudocysts in the pancreas must be treated nonoperatively; in contrast, symptomatic, infectious, or expanding pseudocysts require surgical intervention. Unless there is a strong clinical suspicion of sepsis, fine-needle aspiration (FNA) should be avoided because of the risk of contamination of an otherwise sterile sample; however, in the case of suspected infected necrosis, an image-guided FNA with culture should be performed to distinguish it from sterile necrosis. Pancreatic necrosis may cause OF, and its treatment includes debridement or necrosectomy, peritoneal lavage, drainage, or a "step-up" technique. This step-up strategy is used primarily to treat WON. It consists of prior draining (either endoscopic or percutaneous), followed by a waiting period to allow the wall to mature and debridement using endoscopic or minimally invasive surgical approaches[37]. Due to high mortality, infectious complications, and prolonged hospitalization [38], open surgery is recommended only when the step-up approach fails. Furthermore, in the event of IPN, surgical interventions should be performed after a few weeks (preferably four) of onset to allow the collection to be 'walled off'. Percutaneous drainage can provide adequate source control of necrosis in most individuals (23%-47 %). Open debridement with external drainage is still used in cases where less invasive treatments have failed or are not an option.

ERCP should be performed within 48 h in patients with persistent or progressive bile duct obstruction (as suspected clinically, biochemically, and/or radiologically) or cholangitis. Percutaneous transhepatic gallbladder drainage should be considered if ERCP is impractical. Cholecystectomy should be performed in patients with mild AP during their first hospital stay (same-admission cholecystectomy approach) but not in patients with severe AP until their clinical state has improved. If cholecystectomy is contraindicated due to medical comorbidities, patients with GSAP should undergo ERCP and sphincterotomy before discharge to prevent recurrence until the interval for which cholecystectomy is deemed feasible and safe. Cholecystectomy is considered safe and feasible in most cases of biliary pancreatitis; however, the risks of biliary damage and postoperative leakage of bile must be considered. It is essential to realize that each intervention for the management of AP has specific indications with benefits and downsides that must be considered in a case-specific manner[10,29,30,39].

SURGICAL DECISION TARGETS (DECISION-MAKING MAP)

The first step after confirming the diagnosis of AP (by at least two out of the diagnostic triad) should be the differential diagnosis of AP by ruling out other major conditions that have overlapping clinical (epigastric abdominal pain radiating to the back) and biochemical (hyperamylasemia) diagnostic criteria

Table 2 Summary of key surgical recommendations in different guidelines for acute pancreatitis management

IAP[1] (grade A and B)[31]	WSES[2] (grade 1A, 1B, or 1C)[4]	AGA (pancreatic necrosis)[33]
Mild AP is not an indication for pancreatic surgery (grade B recommendation)	Routine ERCP is not indicated (1A)	Drainage and/or debridement of pancreatic necrosis is indicated in patients with IPN
IPN in patients with clinical signs and symptoms of sepsis is an indication for intervention (recommendation grade B)	ERCP is indicated in patients with GSAP and cholangitis (1B)	Pancreatic debridement should be avoided in the early, acute period (first two weeks)
Early surgery is not recommended within 14 d after the onset of the disease in patients with necrotic pancreatitis (recommendation grade B)	Clinical deterioration with signs of INP is an indication of intervention (1C)	Percutaneous and transmural ED are both appropriate first-line nonsurgical approaches to the management of patients with WON
Interventional management should favor an organ-preserving approach (grade B recommendation)	As a continuum in a step-up approach after percutaneous/endoscopic procedure (1C)	Percutaneous drainage of pancreatic necrosis should be considered in patients with infected or symptomatic necrotic collections in the early acute period (< 2 wk)
ES is an alternative to cholecystectomy in those who are not fit to undergo surgery (grade B recommendation)	In IPN, percutaneous drainage as the first-line of treatment (1A)	SEMS in the form of LAMS appears superior to plastic stents for endoscopic transmural drainage of necrosis
	Minimally invasive surgical strategies result in fewer postoperative new-onset OF (1B)	The use of DEN should be reserved for those patients with limited necrosis and not responding to endoscopic transmural drainage
	Laparoscopic cholecystectomy is recommended during index admission in mild GSAP (1A)	Minimally invasive operative approaches to the debridement of IPN are preferred to open approaches
	The risk of recurrent pancreatitis is reduced when ERCP and sphincterotomy are performed during index admission (1B)	
	Over-resuscitation of patients with early SAP should be avoided; intra-abdominal pressure monitoring is necessary (1C)	A step-up approach consisting of percutaneous drainage or endoscopic transmural drainage, followed by DEN, and then surgical debridement is reasonable
	OA should be avoided if other strategies can be used to manage IAH (1C)	
	Not to use OA after necrosectomy (1C)	
	Not to debride or perform an early necrosectomy if forced to perform an early OA due to ACS (1A)	
		For patients with disconnected left pancreatic remnants after acute necrotizing mid-body necrosis, definitive surgical management with distal pancreatectomy can be performed

[1]Grade A: Strong evidence that requires a meta-analysis of randomized controlled trials or at least one randomized controlled trial (evidence categories Ia and Ib); Grade B: Intermediate evidence, requires nonrandomized clinical studies (evidence categories IIa, IIb, and III).
[2]Grading of recommendations assessment 1A: Strong recommendation, high-quality evidence; 1B: Strong recommendation, moderate-quality evidence; 1C: Strong recommendation, low-quality or very low-quality evidence.
ACS: Abdominal compartment syndrome; AP: Acute pancreatitis; DEN: Direct endoscopic necrosectomy; ES: Endoscopic sphincterotomy; LAMS: Lumen-apposing metal stents; OA: Open abdomen; SAP: Severe acute pancreatitis; SEMS: Self-expanding metal stents; VARD: Video-assisted retroperitoneal debridement; WON: Walled-off necrosis; ERCP: Endoscopic retrograde cholangiopancreatography; IPN: Infected pancreatic necrosis; IAP: International Association of Pancreatology; WSES: World Society of Emergency Surgery; AGA: American Gastroenterological Association; GSAP: Gallstone-associated acute pancreatitis; INP: Infected necrotizing pancreatitis; ED: Endoscopic drainage.

of AP, such as mesenteric ischemia, perforated viscus, inferior wall myocardial infarction, and lower lobar pneumonia, confirming that the diagnosis of AP is not enough. It is still necessary and essential to rule out these serious differentials, as AP itself can be a contributing trigger factor of these differentials (AP can cause aspiration leading to lower lobar pneumonia and affect the portal vein/superior mesenteric vein junction in its inflammatory process, which causes portal vein thrombosis and venous mesenteric ischemia, or unstable angina can lead to a full-blown inferior wall myocardial infarction due to sheer physiological stress and increased demand for cardiac output and oxygen delivery) (Figure 5). Grading the systemic severity of AP, with careful monitoring of hemodynamic stability and OF, and staging of local severity by differentiating between edematous/interstitial and necrotizing types of AP are also crucial at this stage. Once these problems are resolved, the focus should shift to the etiology of AP, the cautious management of systemic and local consequences, and the prioritization of symptomatic support. When the etiology is established, definitive or temporizing management of the underlying distal etiology, for example, by performing preoperative common bile duct exploration and clearance for persistent choledocholithiasis (clinical, biochemical, and/or radiological indicators of persistent

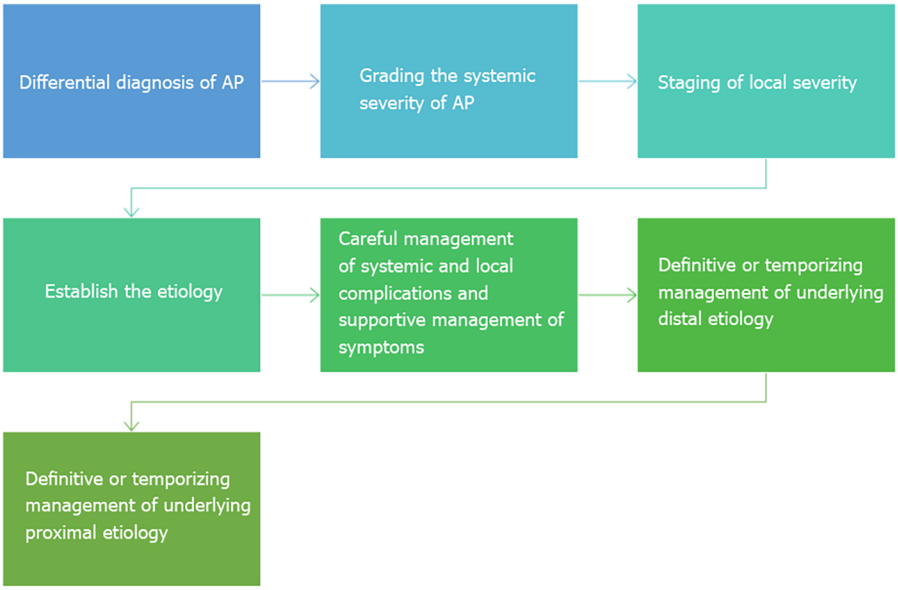

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Figure 5 Decision-making targets in the surgical management of acute pancreatitis (decision-making map). AP: Acute pancreatitis.

biliary/ampullary obstruction) by ERCP, should be attempted, followed by definitive or temporizing management of the underlying proximal etiology, such as cholecystectomy to prevent recurrence of biliary/ampullary obstruction. Finally, malignant obstruction (biliary, ampullary, or pancreatodochal) can be the most proximal etiology and should always be ruled out.

COMMENTARY ON KEY SURGICAL PROCEDURES FOR AP

MSAP and SAP are related to local or systemic sequelae such as peripancreatic fluid accumulation, which presents a risk of compressive or pressure symptoms, organ damage, and mortality[29]. The publication of clinical trials and case reports has increased consistently over the last few decades (Figure 6). The subsequent section reviews some of the most contemporary results of lavage and drainage, necrosectomy, ERCP, and biliary surgery, focusing on open, endoscopic, and percutaneous techniques.

Lavage and drainage

Endoscopic, percutaneous, and open surgical drainage are among the different methods of drainage, each with its own set of benefits and drawbacks[40]. For the first time, Freeny *et al*[41] presented a unique method known as the step-up technique aimed at gradually controlling infections rather than rapidly removing necrosis. It is based on percutaneous catheter drainage (PCD), which is considered the least invasive procedure for managing necrosis of infected AP, with reduced length of stay [intensive care unit (ICU) and hospital], hemorrhage, mortality, fistulas, and OF, compared to open surgery[42,43].

PCD is not optimal as an early invasive intervention or treatment and is recommended at least four weeks later when necrosis is expected to form a wrap. A retrospective cohort study addressed this issue and described a novel insert catheter approach known as abdominal paracentesis drainage (APD)[44]. APD can lower intestinal barrier damage and SAP severity[45]. Early treatment by APD reduces the release of inflammatory factors and improves the prognosis. Furthermore, in MSAP or SAP, APD does not increase infection or mortality complications compared to a strategy without APD[46].

A recent meta-analysis found that APD significantly reduced all-cause mortality, length of hospital stay, and procedure cost compared to conventional follow-up treatment, with no discernible differences in the risk of infection or OF[29]. Another study examined the function of APD before PCD as a variation of the step-up strategy. The use of APD before PCD is also effective in managing AP with abdominal fluid accumulation; however, the conditions under which APD should be used have not been thoroughly explained[47].

According to most international guidelines, catheter drainage should be delayed until the "WON stage" is achieved, which usually takes four weeks after the onset of AP. Interestingly, the practicality of surgical necrosectomy is the primary basis for this advice. van Grinsven *et al*[48] argued that deferring drainage may not be necessary and that early drainage of infected necrosis may improve the results. However, a multicenter randomized superiority trial did not indicate that early drainage was preferable to delayed drainage in terms of complications in cases of IPN[49]. Another recent study compared

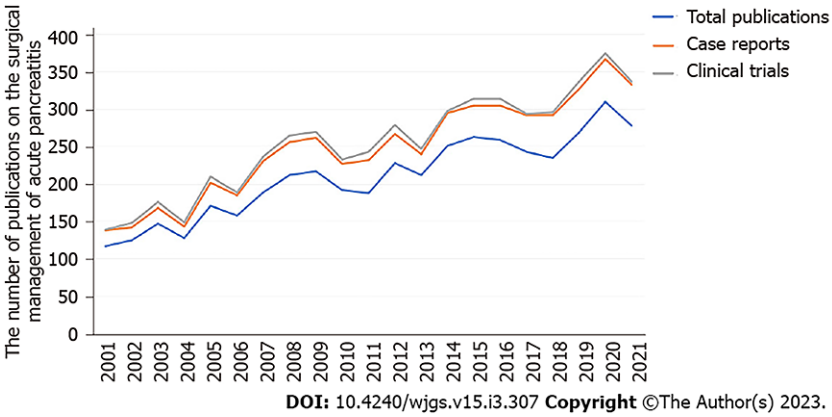

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Figure 6 Year-wise growth in the number of publications on the surgical management of acute pancreatitis.

combined endoscopic and percutaneous drainage for necrotic fluid collection (NFC) in the "early" and "late" drainage groups. The study found that early draining of NFC is feasible and safe when performed in a tertiary care facility with therapeutic endoscopic US proficiency[50]. These findings underscore the importance of clinical competence in treating complicated AP.

PCD is usually performed under US or computed tomography (CT) guidance. A study examined the effectiveness of the US/CT image fusion guide, reporting that the US/CT-PCD group showed significantly fewer puncture-related problems, shorter hospital stays and intubation time, and lower treatment costs than the US-PCD group. The authors concluded that for PCD, the US/CT image fusion guide is a reliable approach for SAP with infected WON[51].

EUS-TD has progressed from the involvement of multiple plastic stents to fully covered self-expanding metal stents and lumen-apposing metal stents (LAMS), resulting in a number of procedural and therapeutic advantages without increasing total treatment costs[52]. In early AP, transluminal ED is associated with a shorter resolution period and lower requirement for salvage surgery than PCD[53]. Furthermore, regardless of infection, EUS-guided drainage (EUS-D) has been shown to offer advantages over PCD in terms of clinical success and faster resolution of WON[54]. Prolonged OF is more frequently an indication of PCD in ANC than in WON, although suspected infection is more commonly an indication in WON than in ANC[55]. A study comparing RP and transperitoneal (TP) found that both are safe and effective, although TP has a higher clinical success rate[56].

Another study examined the efficacy of minimally invasive endoscopic procedures in treating IPN. The mortality rate did not differ significantly; however, the incidence of enteral or pancreaticutaneous fistulas was much lower in the endoscopic group. Furthermore, in the endoscopic approach group, physical health scores for quality of life (QoL) were higher, and the mean total cost of treatment was lower[57]. A systematic review compared the effects of ED with various surgical drainage procedures in necrotizing pancreatitis, indicating that ED had a lower incidence of fistula development than other surgical drainage methods[58]. Another study found that the use of a minimally invasive draining technique in patients with IPN was associated with shorter stays in the ICU and hospital[59].

A systematic review compared endoscopic and surgical treatments in patients with infected walled necrosis. There were no differences in mortality; however, the endoscopic group had fewer new-onset OF and perforations or fistulas[60]. Another study revealed that the endoscopic method could provide superior QoL to surgical necrosectomy[61].

Necrosectomy

The standard therapy for infected pancreatitis necrosis is open necrosectomy, which helps remove necrotic tissue and drain contaminated compartments. The upfront approach has recently gained popularity because of its low mortality and morbidity risks. A prospective multicenter randomized trial found that open necrosectomy was associated with a higher incidence of new-onset multiple OF and mortality equivalent to the step-up approach[37]. In response to further improvements, a one-step laparoscopic pancreatic necrosectomy was developed, with a shorter hospital stay than the surgical step-up group but no equivalent mortality or morbidity burden[62]. Infracolic necrosectomy and selective Roux-en-Y cystjejunostomy have also been reported as safe operational alternatives for difficult SAP that are not susceptible to drainage/debridement using standard procedures[63].

Endoscopic, minimally invasive, and video-assisted retroperitoneal techniques for debridement have gained increasing attention in recent decades, with an emphasis on reducing mortality and morbidity. A meta-analysis found that endoscopic therapy, as opposed to minimally invasive surgery, substantially reduced complications in patients with infected necrotizing pancreatitis[64]. Recently, Xiao *et al*[65] examined the efficacy of open necrosectomy, minimally invasive surgery, and the endoscopic step-up technique, indicating that the endoscopic step-up group had fewer complications and shorter hospital

stay.

Step-up procedures have become the standard therapy for WON based on extensive evidence from randomized controlled trials[66-69]; however, it is crucial to be wary of pancreatic fistulas and stent-related problems during the endoscopic step-up approach[70]. It should also be noted that there is currently no harmonized strategy for the endoscopic treatment of pancreatic necrosis that considers local knowledge, anatomical characteristics of necrosis, and concomitant disorders[30].

According to Minami *et al*[71], in cases of infected ANC/WON, the open necrosectomy may be performed if clinically necessary. Recently, Jagielski *et al*[72] showed that percutaneous endoscopic necrosectomy (PEN) using self-expanding esophageal metal stents (SEMS) is potentially efficacious and has an acceptable incidence of complications. Ke *et al*[73] verified that the use of SEMS during PEN techniques reduced hospital stay, new-onset sepsis, and duration of the procedure. It should be noted that ED and direct endoscopic necrosectomy (DEN) have been the preferred treatment techniques since the discovery of LAMS, especially when there is considerable solid debris or infection[74]. However, because long-term problems after DEN are comparable to those observed after pancreatectomy, Kim *et al*[75] cautioned that DEN should be performed methodically while avoiding injury to viable pancreatic tissues with appropriate antibiotic escalation. Although the postoperative QoL of patients after minimally invasive pancreatic interventions has not yet been identified, it is widely accepted that customized interventional surgical therapy should be attempted in SAP management to obtain the best clinical and QoL outcomes[76-78].

ERCP and biliary surgery

If gallstones are confirmed to be the source of the problem, cholecystectomy is recommended to avoid repeated episodes and, perhaps, biliary sepsis. It is important to note that GSAP improves when the stone is removed. Novikov *et al*[79] examined all patients admitted to a nationwide inpatient sample for GSAP between 2004 and 2014. These findings support early ERCP in patients with GSAP but without cholangitis. A systematic review evaluated the clinical utility of early ERCP *vs* early conservative therapy in conjunction with ERCP in selected cases, reporting the absence of significant advantages of early routine ERCP in terms of mortality or local or systemic pancreatitis[80]. A randomized controlled study compared the composite outcomes of immediate ERCP with sphincterotomy and conservative treatment in patients with severe GSAP. Compared to conservative therapy, immediate ERCP with sphincterotomy did not reduce the composite outcome[81]. Other studies have also not demonstrated the benefits of early ERCP with biliary sphincterotomy in improving the prognosis of patients with GSAP who do not have associated cholangitis[39,82].

A study examined whether LCC can prevent recurring acute IAP. During surgery, biliary stones or sludge was found in 23/39 (59%) patients, and the authors concluded that when all other plausible causes of pancreatitis were ruled out, LCC could successfully prevent the recurrence of IAP[83]. Faur *et al*[84] investigated the effects of early biliary decompression using a minimally invasive method in patients with acute biliary pancreatitis.

CONCLUSION

Most patients with AP have a moderate, self-limiting, and straightforward clinical course. Mild and life-threatening sequelae, local and systemic, include pancreatic and/or peripancreatic fluid collections, walled necrosis, and IPN. Surgical complication management has undergone a dramatic transformation in recent decades. Patients with sterile necrosis who experience symptoms need intervention less often than those with infected necrosis. Pancreatic necrosis has traditionally been treated by open necrosectomy; however, in recent decades, less invasive methods, including endoscopic treatments, have become the norm. Technological advancements have improved the safety and effectiveness of endoscopic operations. However, certain problems still require further correction. Unfortunately, there is no standardized endoscopic approach or protocol for the treatment of various types and complications of SAP, considering parameters such as clinical competence, infection management, anatomical characteristics of necrosis, and comorbidity profiles. The lack of knowledge of the biology of the disease has also resulted in a scarcity of pharmacological and surgical treatment options for AP. Furthermore, controlled studies are required to determine the efficacy of etiology-specific intervention therapy on outcomes such as recurrent AP, treatment costs, progression to chronic pancreatitis and cancer, QoL, and mortality.

FOOTNOTES

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Country/Territory of origin: Saudi Arabia

ORCID number: Nasser Alzerwi 0000-0002-4877-2152.

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MINIREVIEWS

Current trends in perioperative treatment of resectable gastric cancer

İbrahim Yıldız, Leyla Özer, Elif Şenocak Taşçı, İbrahim Vedat Bayoglu, Erman Aytac

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İbrahim Yıldız, Leyla Özer, Department of Medical Oncology, Acıbadem MAA University, İstanbul 34567, Turkey

Elif Şenocak Taşçı, Department of Medical Oncology, Acıbadem University, İstanbul 34567, Turkey

İbrahim Vedat Bayoglu, Department of Medical Oncology, Marmara University, İstanbul 12345, Turkey

Erman Aytac, Department of Surgery, Acibadem University School of Medicine, Istanbul 34567, Turkey

Corresponding author: Leyla Özer, MD, Associate Professor, Department of Medical Oncology, Acıbadem MAA University, Halkalı Merkez, Turgut Özal Bulvarı No:16, Küçükçekmece/İstanbul, İstanbul 34567, Turkey. leyla.ozer@acibadem.com

Abstract

In the last few decades, the treatment strategy for locally advanced resectable gastric cancer (GC) has shifted to a multimodal approach, which potentially decreases recurrence risk and improves survival rates. Perioperative therapy leads to downstaging, increased curative resection rates, and prolonged disease-free and overall survival, by preventing micrometastases in patients with resectable GC. Application of neoadjuvant therapy provides information about tumor biology and *in vivo* sensitivity. A consensus regarding the therapeutic approach for non-metastatic GC does not exist, and many clinical trials aim to clarify this aspect. Advances in precision medicine and the role of immunotherapy have been the focus of research in GC treatment. Herein, the current status and possible future developments of perioperative therapy for locally advanced resectable GC are reviewed, based on the most recent randomized clinical trials.

Key Words: Perioperative treatment; Immunotherapy; Neoadjuvant; Chemotherapy; Gastric cancer; Adjuvant

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Core Tip: The results of the most recent randomized studies have led to a shift from traditional care concepts towards evidence-based multimodal treatment strategies for gastric cancer (GC). Perioperative chemotherapy has become the standard of care for resectable GC. Molecular-based modifications of the backbone treatment increase the efficacy of therapy.

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INTRODUCTION

Gastric cancer (GC) includes histologically heterogeneous and microscopically distinct cell types and can be classified using various systems such as the Lauren and the World Health Organization (WHO) classifications[1,2]. According to the Lauren classification, GC is categorized into two subtypes: Intestinal and diffuse. The WHO classification defines five different subtypes, *i.e.*, papillary, tubular, mucinous, poorly cohesive, and mixed adenocarcinoma.

Recently, molecular classification systems were published by the Cancer Genome Atlas (TCGA) and Asian Cancer Research Group, providing a molecular subtyping structure, as well as a guide to targeted agents[3,4]. TCGA identifies a comprehensive set of genetic changes associated with GC and further classifies GC into four subtypes: Chromosomal instability (CIN) (50%), microsatellite instability (MSI) (22%), genomically stable (GS) (20%), and Epstein-Barr virus-positive (EBV) tumors (9%). The EBV subtype has an excellent prognosis, whereas patients with the CIN subtype achieve the greatest benefit following adjuvant chemotherapy [hazard ratio (HR) = 0.39; 95% confidence interval (CI): 0.16-0.94; P = 0.03][5]. However, patients with the GS subtype are characterized by poor chemotherapy benefit and worse prognosis. MSI-high (MSI-H) GC is considered a distinct subtype and has higher mutation rates with unique DNA methylation patterns. Both EBV and MSI-H GC patients are highly responsive to immune checkpoint inhibitors (ICIs)[6].

Despite the significant progress in the therapeutic strategies and surgical techniques for GC in the last decade, the number of patients experiencing relapse and dying after being diagnosed with localized GC remains rather high, even in the early stages. Adjuvant chemotherapy, chemoradiotherapy, and perioperative chemotherapy are different approaches that are proven to improve survival compared with surgery alone. The administration modality and chemotherapy protocols differ between Eastern and Western countries. In Asia, Europe and Northern America adjuvant chemotherapy is administered after surgery; after preoperative chemotherapy and surgery (perioperative chemotherapy) an in combination with radiotherapy (chemoradiotherapy), respectively. Since the onset of the fluorouracil, leucovorin, oxaliplatin, docetaxel (FLOT)4-AIO trial[7], perioperative FLOT administration has become the new standard of care for locally advanced gastric and gastroesophageal junction [GC/esophagogastric junction (EGJ)] cancers. Advances in precision medicine and the role of immunotherapy have been the focus of GC treatment research. In this review, the current status and possible future developments of perioperative chemotherapy or resectable GC are summarized.

MANAGEMENT OF RESECTABLE GC

Upper endoscopy, endoscopic ultrasound, contrast-enhanced computed tomography (CT) and positron emission tomography are the main tools for staging. Peritoneal carcinomatosis can be identified in approximately 20% of patients without radiological evidence[8]. It is more frequently encountered in diffuse-type GC[9]. Thus, staging laparoscopy with peritoneal washing should be utilized to screen for peritoneal disease in these patients who are candidates for perioperative CT (Figure 1). Endoscopic resection is recommended in early GC with intestinal histotype, according to Lauren's classification, T1a, < 2 cm, well-differentiated, non-ulcerated, and without clinically suspected lymph node involvement[10]. Standard surgery is defined as total or subtotal gastrectomy with D2 lymph node dissection and recommended in cases with ≥ cT1b or cN+ and M0 GC. According to the National Comprehensive Cancer Network (NCCN) guidelines, perioperative chemotherapy (category 1) or preoperative chemoradiation (category 2B) followed by surgery should be offered to resectable ≥ T2 disease in appropriate candidates[10].

Adjuvant treatment

Adjuvant CT alone is the standard of care in Eastern Asia, due to its improved survival benefits reported in the CLASSIC[11] and ACTS-GC[12] trials (Table 1). A large meta-analysis of randomized

Table 1 Landmark trials of perioperative treatment in gastric cancer

Treatment	Study	Arms	*n*	R0	pCR	PFS	HR (*P* value)	OS	HR (*P* value)	Ref.
NAC	EORTC 40954	PF-S	72	82%			NA	2-yr: 73%	0.84 (0.47)	[18]
		S alone	72	67%				2-yr: 70%		
	OEO2	PFx2-S	400	60%			NA	5-yr: 23%	0.84 (0.03)	[17]
		S alone	402	54%				5-yr: 17%		
	OE05	PFx2-S	451	59%	3%			3-yr: 39%	0.90 (0.19)	[19]
		ECXx4-S	446	66%	11%			3-yr: 42%		
NACRT	CROSS	RT + pacli-carbo, w-S	180	92%	29%	5-yr: 44%	0.61 (0.006)	5-yr: 47%	0.68 (0.003)	[21]
		S alone	188	69%		5-yr: 27%		5-yr: 33%		
Perioperative CT (+/-targeted)	MAGIC Trial	ECFx3-S-ECFx3	250	74%	8%	NR	0.66 (< 0.001)	5-yr: 36%	0.75 (0.009)	[22]
		S alone	253	68%		NR		5-yr: 23%		
	FNLCC/FCCD	PFx2-S-PFx4	113	84%	3%	5-yr: 34%	0.65 (0.003)	5-yr: 38%	0.69 (0.02)	[23]
		S alone	111	73%		5-yr: 19%		5-yr: 24%		
	The FLOT-4	FLOTx4-S-FLOTx4	356	84.0%	15.6%			5-yr: 45%	0.77 (0.012)	[7]
		ECX/ECFx3-S-ECX/ECFx3	360	77%	5.8%			5-yr: 36%		
	ST03	ECXx3-S-ECXx3	533	64%	8%			3-yr: 50.3%	1.08 (0.36)	[35]
		ECXx3 + BV-S-ECXx3 + BV	530	61%	11%			3-yr: 48.1%		
	PETRARCA (abstract only, ESMO 2020)	FLOTx4-S-FLOTx4	41	90%	12%	26 mo	0.57 (0.114)			[32]
		FLOT + T + Px4-S-FLOT + T + Px4 + 9 (T + P)	40	93%	35%	NR				
	RAMSES[36] (abstract only, ESMO 2020)	FLOTx4-S-FLOTx4	90	83%	30%					
		FLOT + RAM x4-S-FLOT + RAM x4 + 16 RAM	90	97%	27%					
NAC, adjuvant CT -/+ RT	CRITICS	ECXx3-S-ECXx3	393			5-yr: 39%	0.99 (0.9)	5-yr: 42%	1.01 (0.9)	[24]
		ECXx3-S-CRT	395			5-yr: 38%		5-yr: 40%		
Perioperative CT *vs* adjuvant CT	RESOLVE	S-XELOXx8	345	NR		3-yr: 51.1%	0.86 (0.17) (SOX *vs* XELOX)			[28]
		S-SOXx8	337	NR		3-yr: 56.5%				
		3SOX-S-3SOX	365	NR		3-yr: 59.4%	0.77 (0.03) (SOX *vs* XELOX)			
NAC *vs* CRT	PRODIGY	DOSX3-S-S1x8	266	95%	10%	3-yr: 66.3%	0.70 (0.023)			[29]
		S-S-1x8	264	84%		3-yr: 60.3%				
	POET	PFLX3-RT (30 Gy)/C-S	62	71%	15.6%	3-yr: 47.4%	0.67 (0.07)	5-yr: 39.5%	0.65 (0.055)	[66]
		PFL2-S	64	69%	2%	3-yr: 22.7%		5-yr: 24.4%		
	NEORES	CF-RT (40 Gy)-S	91	87%	28%			3-yr: 47%	(0.77)	[64]

		CF-S	90	74%	9%			3-yr: 49%		
Adjuvant CRT	INT-0116 trial	5FU/LVx1-CRT-5FU/LVx2	281			3-yr: 48%	0.66 (0.001)	3-yr: 50%	0.74 (0.005)	[14]
		S alone	275			3-yr: 31%		3-yr: 41%		
	CALGB 80101 Trial	5FU/LVx1-CRT-5FU/LVx2	280			3-yr: 46%	1.00 (0.99)	3-yr: 50%	1.03 (0.80)	[71]
		ECFx1-CRT-ECFx2	266			3-yr: 47%		3-yr: 52%		
	ARTIST trial	XPx2-XRT-XP2	230			3-yr: 78%	0.74 (0.09)	5-yr: 75%	1.13 (0.53)	[15]
		XPx6	228			3-yr: 74%		5-yr: 73%		
	ARTIST trial-2	S-1 (x12 mo)	182			3-yr: 65%	0.69 (0.04) (S-1 *vs* SOX)	NR	NR	[16]
		SOX (x6 mo)	181			3-yr: 74%	0.72 (0.07) (S-1 *vs* SOXRT)	NR	NR	
		SOXRT	183			3-yr: 73%	0.97 (0.88) (SOX *vs* SOXRT)	NR	NR	
Adjuvant CT	ACTS-GC trial	S1 (12 mo)	529			5-yr: 65%	0.65	5-yr: 72%	0.67	[14]
		S alone	530			5-yr: 53%		5-yr: 61%		
	CLASSIC trial	XELOXx8 (6 mo)	520			5-yr: 68%	0.58 (< 0.0001)	5-yr: 78%	0.66 (0.53)	[11]
		S alone	515			5-yr: 53%		5-yr: 69%		

5FU: 5-fluorouracil; BV: Bevacizumab; CF: Cisplatin and 5-fluorouracil; CRT: Chemoradiotherapy; CT: Chemotherapy; DOS: Docetaxel, oxaliplatin, S-1; ECF: Epirubicin, cisplatin, fluorouracil; ECX: Cisplatin, epirubicin, and capecitabine; ESMO: European Society for Medical Oncology; FLOT: Fluorouracil, leucovorin, oxaliplatin, docetaxel; HR: Hazard ratio; LV: Leucovorin; NA: Not available; NAC: Neoadjuvant chemotherapy; NACRT: Neoadjuvant chemoradiation; NR: No response; OS: Overall survival; pacli-carbo: Paclitaxel and carboplatin; pCR: Pathological complete response; PF: Cisplatin and fluorouracil; PFL: Cisplatin, fluorouracil, leucovorin; PFS: Progression-free survival; RAM: Ramucirumab; RT: Radiotherapy; S: S-1; SOX: S-1 and Oxaliplatin; T + P: Trastuzumab + pertuzumab; w-S: Followed by surgery; XELOX: Capecitabine and oxaliplatin; XP: Capecitabine and cisplatin.

controlled trials investigating the impact of postoperative CT *vs* surgery alone in GC reinforced the survival impact of adjuvant CT[13]. The United States Intergroup-0116 trial (SWOG 9008/INT-0116) indicated improved disease-free survival (DFS) and overall survival (OS) with adjuvant chemoradiotherapy compared to those with surgery alone[14]. The drawbacks of this trial were substantial rates of acute toxicity (33% had ≥ grade 3 gastrointestinal toxicity) associated with CRT, low rates and extent of nodal dissection (D2 dissection in 10%), relatively simple (and currently outdated) radiotherapy techniques and choice of CT regimen. It has been concluded that adjuvant CRT was only effective in patients who underwent limited (D1 or less) lymph node dissection and were compensated for poor surgery. Additionally, the high toxicity rates have limited the use of postoperative CRT in Europe, and a particular CT regimen is no longer preferred in the United States either.

The Adjuvant chemoRadioTherapy In Stomach Tumors (ARTIST-1) trial investigated the role of adjuvant CRT in GC patients after D2 gastrectomy[15]. Although radiotherapy did not demonstrate significant survival benefit, it reduced the rate of local recurrence by 6%. Subgroup analysis suggested that lymph node positivity and intestinal subtype were the independent factors for survival benefit with adjuvant radiotherapy. In the ARTIST-2 trial[16], adjuvant oxaliplatin combined with S-1 (SOX) and SOXRT were associated with a reduced hazard of recurrence risk compared to S-1 monotherapy in patients with D2-resected stage II or III lymph node-positive GC with no survival benefits. The addition of radiotherapy to SOX did not significantly reduce the rate of recurrence after D2 gastrectomy compared to SOX alone. DFS between patients treated with adjuvant CT and CRT was similar across all subgroups.

Neoadjuvant CT

A significant number of patients are diagnosed at advanced stages owing to the asymptomatic nature of GC. Neoadjuvant CT (NAC) helps to achieve better control of tumor progression with improved therapeutic response and treatment tolerance in patients with GC. NAC potentially improves OS by downstaging, increasing pathological response rates and reducing the risk of relapses by eradicating the micrometastatis. The trials on NAC for GC have revealed conflicting results. First, the United Kingdom Medical Research Council Esophageal Cancer Trial (OEO2) randomly assigned both patients with adenocarcinoma (67%) and squamous cell carcinoma (SCC) (33%) into two treatment groups: Surgery

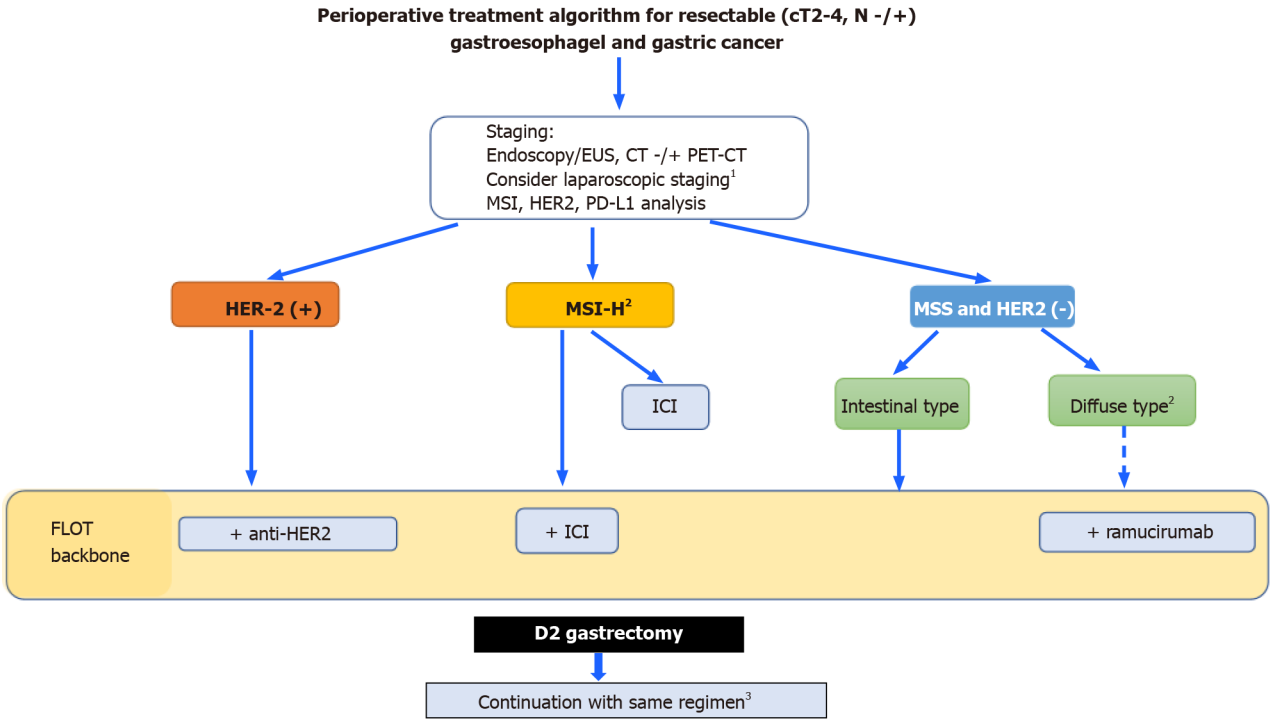

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Figure 1 Perioperative algorithm for resectable gastric cancer. [1]Strongly recommended for diffuse type gastric cancer. [2]Upfront surgery may be recommended. [3]Radiotherapy for R1/2 resection. CT: Computed tomography; PET-CT: Positron emission tomography computed tomography; EUS: Endoscopic ultrasound; FLOT: Fluorouracil, leucovorin, oxaliplatin, docetaxel; MSI: Microsatellite instability; HER2: Human epidermal growth factor 2; ICI: Immune checkpoint inhibitor; MSI-H: High microsatellite instability; MSS: Microsatellite stability; PD-L1: Programmed death-ligand 1.

plus preoperative CT [two cycles of cisplatin and fluorouracil (CF)] and surgery alone[17]. In this study, the R0 resection rates (60% *vs* 54%) and 5-year OS (23% *vs* 17%) data favored the NAC arm. In the European Organization for Research and Treatment of Cancer (EORTC-40954) trial, patients with locally advanced adenocarcinoma of the stomach or EGJ[18] were randomized to the preoperative CF and upfront surgery arms. Although neoadjuvant therapy improved the radical resection rates (82% *vs* 67%, $P = 0.036$), it did not improve survival.

The United Kingdom Medical Research Council OE05 trial compared the triplet cisplatin, epirubicin, and capecitabine or 5-fluorouracil (ECX/ECF) regimen with the CF regimen and reported that the intensified triplet regimen did not increase survival in EGJ cancers[19]. Despite the increased rates of toxicity, the ECX group had a higher R0 resection rate and pathological complete response (pCR); however, the addition of epirubicin to cisplatin and fluoropyrimidine backbone did not provide any survival benefit.

Neoadjuvant CRT

Several trials evaluated whether neoadjuvant chemoradiation (NACRT) followed by surgery would improve survival compared to surgery alone; however, most of the early studies were small case series that were underpowered[20]. The pivotal Chemoradiotherapy for Oesophageal Cancer Followed by Surgery (CROSS) trial established the benefit of neoadjuvant taxane-based chemoradiation for patients with ≥ T2 esophageal or EGJ cancer patients (75% adenocarcinoma)[21]. Complete resection (R0) was achieved in 92% of the CRT-surgery group *vs* 69% of the surgery group ($P < 0.001$). The median OS (mOS) was 49 and 24 mo in CRT and surgery alone groups, respectively [HR = 0.66; $P = 0.003$ and 5-year OS: 47% *vs* 34%]. Postoperative complications were similar in both groups. The survival benefit was highest in the SCC subgroup, with mOS of 81.6 mo in the NACRT plus surgery group and 21.1 mo in the surgery alone group (HR = 0.48; $P = 0.008$). Patients with SCC also had a higher rate of pathologic complete response (49%) compared to patients with adenocarcinoma (23%, $P = 0.008$).

Perioperative CT

The MAGIC trial is unquestionably a milestone in the development of perioperative GC treatment[22]. In this trial, ECF therapy was evaluated as a perioperative treatment compared with surgery alone in patients with resectable stages II and III adenocarcinoma of the stomach (74%), EGJ (11%-12%), and lower esophagus (14%-15%). The results showed that preoperative NAC significantly increased the R0 resection rate (79% *vs* 70%) and increased pathological response compared to surgery alone. The OS rate (5-year OS: 36% *vs* 23%; $P = 0.009$) and PFS rate after the perioperative regimen were improved

compared to those after surgery alone. Postoperative morbidity and mortality were similar in both arms.

In contrast, the FNCLCC/FFCD ACCORD (French) trial evaluated the role of perioperative treatment compared to surgery alone in 224 patients with operable adenocarcinoma of the stomach (25%), EGJ (64%), and lower esophagus (11%)[23]. A significant increase in the R0 resection rates (84% *vs* 73%, P = 0.04) were achieved in the neoadjuvant group compared to the surgery alone group, in addition to improved OS (38% *vs* 24%, P = 0.02) and 5-year DFS (34% *vs* 19%, P = 0.01).

The MAGIC trial predominantly recruited patients with GC, whereas the French study primarily included patients with proximal tumor. Therefore, the perioperative treatment approach may be considered as evidence-based for both tumor sites. The limitation in both trials was the lack of standard D2 lymph node dissection in the majority of cases, causing a heterogeneous patient population. The German cancer research group recently showed the efficacy of NAC in patients undergoing D2 lymph node dissection in the FLOT4 trial[7].

The FLOT4 trial included patients with locally advanced gastric and EGJ adenocarcinoma. The perioperative FLOT regimen increased the R0 resection rate and prolonged the median PFS and mOS compared to the ECF/ECX regimen. The pCR in the FLOT perioperative group was significantly improved compared to that in the perioperative ECF/ECX group (16% *vs* 6%). Notably, patients in the FLOT arm showed higher 5-year OS rates (45% *vs* 36%). The success of this trial was attributed to the use of docetaxel in the FLOT regimen instead of epirubicin used in the ECF/ECX regimen.In the FLOT trial, D2 resection was performed in most patients with GC. The FLOT regimen caused lower grade 3 or 4 non-hematological toxicities. Conversely, grade 3 or 4 neutropenia, diarrhea, and neuropathy were more often observed with FLOT than with ECF/ECX.

In the MAGIC, FCCD/FNCLCC, and FLOT trials, approximately 10% of the patients could not complete preoperative CT, and approximately 50% were unfit for postoperative CT. Perioperative treatment should be considered beforehand for resectable GC because of the reduced patient compliance with adjuvant treatment. Perioperative CT is recommended by both the NCCN and European Society for Medical Oncology guidelines to treat ≥ T2 GC, regardless of lymphatic involvement[10,24].

Role of adjuvant chemoradiation in the perioperative approach

The CRITICS study was designed to compare the OS between the perioperative CT (ECX/epirubicin, oxaliplatin, capecitabine) with preoperative CT and postoperative CRT[25]. Postoperative CRT did not improve OS compared to postoperative CT. However, recent long-term follow-up results of the trial, including per-protocol analysis of patients who started the allocated postoperative treatment, showed better 5-year OS rates with postoperative CT (57.9% *vs* 45.5%, P = 0.0004)[26].

Perioperative vs adjuvant treatment alone

A meta-analysis of 2093 patients with GC randomized in 14 clinical trials reported remarkable results favoring perioperative treatment[27]. The global analysis showed a significant benefit of OS (HR = 0.48, P < 0.001), PFS, and R0 resection rates for the perioperative arm compared to those of the adjuvant-only arm. In the RESOLVE trial[28], 1094 patients who underwent D2 gastrectomy for locally advanced GC were randomly assigned to either the perioperative SOX arm or the postoperative adjuvant CT with SOX or capecitabine and oxaliplatin arm. Perioperative SOX was superior to postoperative capecitabine and oxaliplatin in terms of the 3-year DFS. In addition, postoperative SOX showed equivocal results compared with postoperative capecitabine and oxaliplatin. The PRODIGY study[29], a phase III randomized clinical trial from South Korea, investigated the outcomes of perioperative CT with docetaxel, oxaliplatin and S-1 against adjuvant S-1 for resectable GC. Significant tumor downstaging and improved PFS (HR = 0.70; P = 0.023) were observed in the perioperative arm, whereas OS was similar regardless of the treatment modality (HR = 0.84; P = 0.338).

Perioperative CT plus targeted therapy/immunotherapy

Experimental research is focused on biomarkers that may be valid for the selection of patients who may benefit from further treatment (*i.e.*, conventional chemotherapeutic agents, immunotherapies and targeted therapies) besides surgery. The identification of different molecular subtypes of GC has greatly accelerated this process.

Several regimens including cytotoxic agents plus targeted molecules or ICIs have been tested as neoadjuvant and adjuvant approaches. Due to their established efficacy in metastatic disease, human epidermal growth factor 2 (HER2) and vascular endothelial growth factor-targeted agents were explored in perioperative regimens with the FLOT backbone.

Anti-HER2

HER2 overexpression or amplification is recorded in approximately 15%-20% of gastric and EGJ adenocarcinomas. It is more common in intestinal type and EGJ cancers than in diffuse/mixed-type cancers and cancers of the gastric body. HER2-positivity is defined by the presence of 3+ immunohistochemical score or 2+ score with positive fluorescence *in situ* hybridization test.

In patients with metastatic HER2-positive GC, the addition of trastuzumab to platinum-based chemotherapy as a first-line treatment has been proven to increase the mOS compared to chemotherapy alone in the landmark ToGA study[30]. Trastuzumab plus chemotherapy is now the standard first-line therapy for patients with HER2+ advanced-stage G/EGJ cancers. New HER2- targeted agents and combinations have been developed to overcome intrinsic and acquired resistance. In a randomized phase II trial (DESTINY-Gastric01)[31], medically compromised patients with HER2+ advanced-stage G/EGJ cancers who had received at least two previous lines of therapy, trastuzumab deructexan, demonstrated a significantly higher response rate and longer OS than those who had received chemotherapy.

Limited data exist on the efficacy of anti-HER2 targeted therapy in the perioperative setting. In the phase II PETRARCA trial (presented at the European Society for Medical Oncology 2020), the addition of trastuzumab and pertuzumab to perioperative FLOT regimen increased the pCR rates (35% *vs* 12%) and nodal response (68% *vs* 39%) in HER2- positive resectable EGJ cancer[32]. The R0 resection (90% *vs* 93%) and surgical morbidity (43% *vs* 44%) and mortality (2.5% *vs* 2.5%) rates were comparable. More adverse events of grades > 3 were reported with trastuzumab and pertuzumab, especially diarrhea (5% *vs* 41%) and leukopenia (13% *vs* 23%). However, large-scale phase III randomized controlled studies are warranted to confirm the efficacy.

HER2-targeted agents may upregulate the expression of programmed death cell 1 (PD-1) or programmed death cell ligand 1 (PD-L1), increase the extent of tumor immune cell infiltration and promote antigen presentation *via* dendritic cells, all of which could enhance the efficacy of anti-PD-1/anti-PD-L1 antibodies[33]. A randomized phase III trial evaluating the efficacy of pembrolizumab plus trastuzumab and chemotherapy is currently ongoing (KEYNOTE-811)[34]. The first interim analysis of KEYNOTE-811 showed that adding pembrolizumab to standard therapy with trastuzumab and chemotherapy results in a meaningful improvement in objective response rate as first-line treatment of HER2-positive GC.

Anti-vascular endothelial growth factor

The United Kingdom Medical Research Council ST03 trial compared perioperative ECX with ECX plus bevacizumab in patients with locally advanced resectable gastric, esophageal, and EGJ adenocarcinoma [35]. The 3-year OS and DFS rates were comparable between the combined bevacizumab and control groups. The incidence of impaired wound healing and anastomotic leakage was higher in the bevacizumab group.

The randomized phase II/III RAMSES/FLOT7 trial (presented at the European Society for Medical Oncology 2020) evaluated the addition of the vascular endothelial growth factor-R2 inhibitor, ramucirumab, to the FLOT regimen for resectable GC patients in the perioperative setting[36]. In the phase II of this trial, the addition of ramucirumab to perioperative FLOT significantly improved R0 resection rates (97% *vs* 83%, $P = 0.0049$) with similar complete/near-complete pathologic response (30% *vs* 27%) and operative morbidity. In the subgroup analysis, the relative benefit of FLOT-ramucirumab on the R0 resection rate was more pronounced in the cT4 (25% *vs* 100%) and diffuse-/mixed-type histology groups (77% *vs* 95%). Even though the anti-angiogenic therapy seems favorable and was successfully used for clinical purposes, further prospective randomized studies are needed to evaluate the use of the drugs included as part of this therapy for localized disease. Additionally, some of these agents have been associated with serious safety issues. Because angiogenesis is an important step in the healing process, agents targeting the angiogenesis pathway may interfere with wound healing, thus increasing the risk of surgical complications, bleeding, and infection.

Immunotherapy

The inhibition of PD-1/PD-L1 interactions, through the use of ICI, is able to reactivate immune response against cancer and has changed the treatment landscape of GC, especially in the metastatic phase. Higher PD-L1 expression, assessed according to the combined positivity score (CPS), is associated with better response to ICI in advanced GC, as observed for other tumors[37].

In advanced GC adenocarcinoma, the combination of nivolumab and chemotherapy improved OS in tumors with PD-L1 CPS ≥ 5 in CheckMate-649 trial[38] and pembrolizumab plus chemotherapy (with PDL-1 CPS ≥ 10) in KEYNOTE-590 trial[39], as first-line treatment. Nivolumab demonstrated superior OS regardless of PD-L1 expression as third-line therapy in Attraction-02[40] trial and pembrolizumab prolonged the duration of response in PD-L1 positive patients with CPS ≥ 1 (KEYNOTE-059)[41].

ICI therapies have been the standard of care for the treatment of advanced MSI-H tumors. MSI is characterized by high mutation rates and the generation of frameshift-peptide neoantigens, which foster a highly immunogenic environment with increased peritumoral and tumor-infiltrating lymphocytes [42]. The incidence of MSI in G/EGJ cancers varies between 5% and 20%[43]. MSI-H GC has unique clinical characteristics, including a distal location, high frequency of intestinal-type histology, lower stage and a good prognosis[44].

MSI-H status has been confirmed as a biomarker for pembrolizumab therapy in patients with advanced G/EGJ cancers regardless of the previous lines of therapies. In a *post hoc* cohort analysis of three trials (KEYNOTE-059, KEYNOTE-061, and KEYNOTE-062) including 84 of 1614 patients with confirmed MSI-H advanced G/EGJ cancers, treatment with pembrolizumab therapy alone or in

combination with CT was associated with improved OS, PFS, and durable response[45]. The effect of ICI treatment in the perioperative setting is under investigation in several clinical trials (Table 2). Durvalumab (NCT04592913), pembrolizumab (NCT03221426), atezolizumab (NCT03421288), and avelumab (NCT03399071) studies evaluated the efficacy and safety of ICI plus CT (FLOT) compared to CT alone as a perioperative treatment for localized G/EGJ adenocarcinoma regardless of the PD-L1 status. Although MSI is a strong predictor of response to ICI treatment, the clinical value of PD-L1 expression is still under investigation[46].

Recent studies have shown that tumor mutational burden is a predictive factor of survival in GC patients receiving ICIs[47,48]. In June 2020, the Food and Drug Administration granted accelerated approval for the treatment of patients with unresectable or metastatic tumor mutational burden-high (≥ 10 mutations per megabase) solid tumors who progressed after prior treatment. The efficacy of immunotherapy was also shown in MSI-H metastatic GC, however currently, no phase III data are present for patients with resectable GC. Promising results have been observed in two latest phase II studies, GERCOR NEONIPIGA and DANTE trials[49,50].

Neoadjuvant nivolumab plus ipilimumab plus adjuvant nivolumab were evaluated in the phase II GERCOR NEONIPIGA study in patients with localized dMMR esophagogastric adenocarcinoma[49]. Neoadjuvant therapy with nivolumab and ipilimumab was feasible and associated with a high pCR rate in patients with MSI/dMMR resectable esogastric adenocarcinoma. Among 29 patients with localized MSI/dMMR disease, a pCR rate of 59% was reached, whereas, normally, a pCR rate of about 10% would be expected with platinum- and fluoropyrimidine-based NAC in this particular molecular subtype. DANTE trial evaluated atezolizumab in the perioperative treatment of resectable G/EGJ cancers in combination with FLOT[50]. Higher pCR rates were observed in the ICI arm (50% *vs* 27%).

The benefit of perioperative CT is unclear in MSI-H GC. In a large study, 5-fluorouracil-based adjuvant CT improved DFS (P = 0.002) in microsatellite stable/MSI-low group but showed no benefit in the MSI-H group[51]. In the CLASSIC trial[52], patients with MSI-H GC had no survival benefit from adjuvant CT. In the MAGIC trial[53], which evaluated the role of perioperative CT in resectable GC, MSI-H status was associated with worse survival in the CT-plus-surgery arm compared to microsatellite stable/MSI-low GC. A meta-analysis of pooled data from the CLASSIC, MAGIC, ARTIST, and ITACA-S trials, which compared different curative multimodal treatments for GC, revealed that MSI-H status was associated with longer OS but reported no benefit from perioperative or adjuvant CT[54]. Thus, some centers currently recommend upfront surgery for patients with MSI-H tumors and consider perioperative immunotherapy for advanced locoregional disease.

The CheckMate 577 study[55] investigated the role of adjuvant immunotherapy in residual disease after NACRT in esophageal cancers. Patients with esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma or EGJ cancer received NACRT followed by adjuvant nivolumab for up to 1 year in case of residual pathologic disease (ypT+ and/or ypN+; R0 resection). Adjuvant nivolumab provided superior DFS with a 31% reduction in recurrence risk or death and doubled the median DFS.

CHALLENGING ASPECTS AND FUTURE PERSPECTIVES

Impact of histology

The impact of histological subtypes on decision-making of perioperative treatment is neglected in international guidelines. However, tumor histology is an essential denominator for treatment response and its subsequent outcomes. A multicenter phase II study of perioperative CT for GC reported a significantly longer OS and an improved PFS for patients with intestinal-type tumors compared to non-intestinal-type tumors[56]. Homann *et al*[57] reported that the pCR rate was the highest with intestinal-type tumors (30.8%) and the lowest with diffuse/mixed-type tumors (0%). Al-Batran *et al*[58] also found that the tumor regression grade was significantly better in intestinal GC than diffuse GC after NAC with FLOT or ECF.

A previous study showed that NAC conferred better outcomes, although the therapeutic response was relatively weak for gastric signet ring cell carcinoma (SRCC)[59]. Conversely, other studies suggested that NAC provided no survival benefit in this population[60,61]. Another recent analysis confirmed the poor outcomes associated with signet ring cell histology in terms of R0 resection and histopathological response in GC and EGJ cancer patients undergoing NAC[62]. Despite the lack of validated approaches for GC treatment according to histotype, CT seems to be a feasible approach for diffuse GC with SRCC. Nevertheless, these results imply the need for dedicated clinical trials focusing on operable diffuse and/or SRCCs. In the PRODIGE19 trial, presented in the American Society of Clinical Oncology (ASCO) 2019, a perioperative approach with ECF *vs* an upfront surgery followed by adjuvant treatment for resectable gastric SRCC was assessed[63]. Resection and median survival rates were higher with perioperative chemotherapy [R0, 88% *vs* 78%; 2-year OS, 60% *vs* 53%; median survival, 39 *vs* 28 mo (HR = 0.71; 95%CI: 0.40-2.64)]. Consequently, a diagnosis of SRCC does not change the indication of perioperative treatment in patients with locally advanced GC.

Table 2 Overview of ongoing trials of biological and immunological agents in the perioperative treatment for gastric cancer

NCT	Agent	Target structure	Trial	Phase	Study design	Primary endpoint	Ref.
NCT04592913	Durvalumab	PD-L1	Matterhorn	III	FLOT + durvalumab	EFS	[72]
					FLOT + placebo		
NCT03221426	Pembrolizumab	PD-1	Keynote-585	III	CF/FLOT + pembrolizumab	pCR, OS, EFS	[73]
					FLOT + placebo		
NCT03421288	Atezolizumab	PD-L1	Dante	II	FLOT + atezolizumab	DFS	[50]
					FLOT + placebo		
NCT03399071	Avelumab	PD-L1	Iconic	II	FLOT + avelumab	pCR	[74]
NCT05504720	Pembrolizumab + trastuzumab	PD-1/HER2	PherFlot	II	FLOT + pembrolizumab + trastuzumab	DFS, pCR	[75]
NCT02205047	Trastuzumab +/- pertuzumab	HER2	Innovation	II	CT	pCR	[76]
					CT + trastuzumab		
					CT + trastuzumab + pertzumab		

CF: Cisplatin and 5-fluorouracil; CT: Chemotherapy; DFS: Disease free survival, EFS: Event free survival; FLOT: Fluorouracil, leucovorin, oxaliplatin, docetaxel; HER: Human epidermal growth factor; OS: Overall survival; pCR: Pathological complete response; PD: Programmed cell death; PDL: Programmed cell death ligand.

EGJ tumors

The treatment options for resectable adenocarcinoma of EGJ include perioperative CT and NACRT. FLOT has been the standard perioperative CT protocol for resectable EGJ and GC. The preference between NACRT and CT alone in EGJ cancer is challenging. Head-to-head comparisons are lacking, and cross-trial comparisons are limited because of the heterogeneities in patient characteristics and surgical management. Although radiosensitivity of SCC and adenocarcinoma are different, previous studies usually analyze these two histological subtypes in a single group[21,64]. Certainly, patients with SCC achieved more benefit from CRT in the CROSS trial. While the FLOT trial included no SCC patients, an exploratory network meta-analysis revealed no significant difference between the CROSS and FLOT trials in terms of OS[64]. In a current meta-analysis, NACRT provided a higher R0 resection and pCR rates and lower local recurrence and distant metastasis rates compared to NAC[65]. NACRT may be particularly preferred for SCC histology because of its increased radiosensitivity, and for bulky adenocarcinomas, where achieving an R0 margin is a prior concern.

Likewise, other studies revealed that NACRT and NAC are comparable in terms of OS[64,66]. The NeoRes trial randomized 181 patients with esophageal cancer to receive preoperative CF with or without concurrent radiotherapy[64]. Although pCRs (the primary endpoint) and R0 resection rates were higher with NACRT, there were no significant differences in PFS or OS. Moreover, subgroup analysis showed no relation in terms of tumor histology (adenocarcinoma *vs* SCC). The POET trial compared NAC to NACRT followed by surgery and included only locally advanced adenocarcinomas of the EGJ (Siewert types I and II)[66]. Although the study was terminated early due to relatively higher in-hospital mortality in the NACRT group (10.2% *vs* 3.8%), the mOS and median PFS were similar in both arms.

Both the NeoRes and POET trials have used regimens that are no longer standard of care for EGJ tumors and were underpowered to detect differences in OS. Recent trials have aimed to compare current NAC (FLOT) and CRT (CROSS) regimens in phase III studies (Neo-AEGIS[67], ESOPEC[68], TOPGEAR[69]). In the Neo-AEGIS trial in which the preliminary results were presented at the ASCO 2021, 377 patients with adenocarcinoma of the esophagus or EGJ were randomized to perioperative CT (ECF/ECX or FLOT) regimen *vs* NACRT based on the CROSS regimen[67]. At a median follow-up of 24.5 mo, there were 143 deaths at the second futility analysis (60% of planned events), with a 3-year estimated survival probability of 56% and 57%, respectively. The R0 resection rates (95% *vs* 82%) and pCR (16% *vs* 5%) data favored the NACRT arm. Anastomotic leak and postoperative in-hospital mortality were comparable.

The use of trastuzumab in combination with NACRT for HER2-overexpressing EAC was evaluated in the NRG Oncology/RTOG 1010 study[70]. The addition of CRT failed to meet the primary endpoint of DFS. The median DFS was 19.6 mo with CRT and trastuzumab *vs* 14.2 mo with CRT alone (HR = 0.99; 95%CI: 0.71-1.39).

The CRITICS study showed no benefit of the addition of postoperative radiotherapy, which may be partially attributed to poor patient compliance with the adjuvant treatment[25]. Therefore, subsequent studies have focused on the optimization of preoperative treatment strategies. Determining the clinical value of adding further systemic perioperative CT to NACRT was addressed in the TOPGEAR study [69], which studied the responses in patients with operable GC and gastroesophageal cancer randomized to either perioperative CT or preoperative CT and CRT, followed by adjuvant CT.

Future directions

G/EGJ cancers have high levels of both genomic and phenotypic variability even within individual tumors, and this underlying heterogeneity is considered to be the major reason for the failure of biomarker-based clinical trials. Currently, only the following three biomarkers are routinely used in GC: HER2, PD-L1, and MSI. Other potential targetable genetic alterations, including fibroblast growth factor receptor 2 amplification, epidermal growth factor receptor amplification, MET amplification, Claudin 18.2 expression and NTRK fusion are being tested in ongoing trials in advanced GC. Despite a lack of clinically relevant biomarkers, many clinical trials are underway to study the expression of biomarkers that could provide insight to intratumoral heterogeneity conditioning of the response to treatment. This could lead to an improvement in selection of patients candidates for targeted therapies.

There is little data to support the routine use of molecular therapies or immunotherapy in resectable GC. Nevertheless, the results of early studies on anti-HER2 targeted therapies and ICIs are promising. However, anti-HER2 therapies may improve the response rate, but no survival benefit has been demonstrated yet. In the GERCOR NEONIPIGA trial, the high pCR rates with neoadjuvant ICI are promising, on the perioperative use of immunotherapies in resectable MSI-H GC. The preliminary results of the DANTE study also showed that adding ICI to FLOT therapy in the perioperative setting, regardless of PD-L1 status, may be a very rational approach. The results of these studies can help optimize the selection of patients to receive targeted therapies, thereby facilitating precision medicine approaches for patients with G/EGJ cancers.

In determining patients who are most likely to benefit from immune therapies, a more accurate definition of potential patients who will benefit from chemotherapy, might improve outcomes in the near future, when used along with novel biomarkers, such as MSI and EBV.

CONCLUSION

Appropriate treatment modalities should be planned by a multidisciplinary team specialized in the management of GC because of the complex nature of the disease. Perioperative treatment has become the major denominator of multimodal treatment, as the current standard of care for resectable GC. Biomarkers, MSI, PD-L1, tumor mutational burden, HER2, and genomic subtypes help determine the immunotherapy and targeted therapy options to consolidate the efficacy of the backbone treatment.

FOOTNOTES

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Country/Territory of origin: Turkey

ORCID number: İbrahim Yıldız 0000-0001-9094-7289; Leyla Özer 0000-0003-4092-5051; Elif Şenocak Taşçı 0000-0002-1686-1628; İbrahim Vedat Bayoglu 0000-0002-0481-1084; Erman Aytac 0000-0002-8803-0874.

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MINIREVIEWS

Vascular injury during laparoscopic cholecystectomy: An often-overlooked complication

Antonio Pesce, Nicolò Fabbri, Carlo Vittorio Feo

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Antonio Pesce, Nicolò Fabbri, Carlo Vittorio Feo, Department of Surgery, University of Ferrara, Azienda USL of Ferrara, Azienda USL of Ferrara, Lagosanto 44023, Ferrara, Italy

Corresponding author: Antonio Pesce, FACS, MD, PhD, Research Fellow, Surgeon, Department of Surgery, University of Ferrara, Azienda USL of Ferrara, Azienda USL of Ferrara, 2 Via Valle Oppio, Lagosanto 44023, Ferrara, Italy. antonio.pesce@ausl.fe.it

Abstract

Laparoscopic cholecystectomy is one of the most frequently performed procedures in gastrointestinal surgery worldwide. Bleeding complications due to vascular injuries represent an important cause of morbidity and mortality, especially when facing major bleeding during laparoscopy, where bleeding control can be technically challenging in inexperienced hands. Interestingly, the reported incidence rate of conversion to open surgery due to vascular lesions is approximately 0%-1.9%, with a mortality rate of approximately 0.02%. The primary aim of this article was to perform an up-to-date overview regarding the incidence and surgical management of vascular injuries during laparoscopic cholecystectomy according to the available scientific evidence.

Key Words: Laparoscopic cholecystectomy; Vascular injury; Vascular anomalies; Surgical management; Specialized hepatobiliary centers

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Core Tip: The theme of biliary injuries in laparoscopic cholecystectomy and the prevention and management of bile duct lesions have been extensively exanimated. However, little attention has been given to vascular injuries. Bleeding complications due to vascular injuries represent an important cause of morbidity and mortality, as well as the negative outcomes of biliary reconstruction when associated with biliary injuries. The vascular lesions should be correctly identified, and surgeons must choose the best therapeutic option to quickly repair the vascular lesion, depending on their own surgical experience and medical center resources. Currently, the management of referrals to specialized hepatobiliary centers for multidisciplinary approaches is mandatory.

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INTRODUCTION

Laparoscopic cholecystectomy (LC) is one of the most frequently performed procedures in general surgery worldwide[1]. Iatrogenic vascular and bile duct injuries still represent a major public health problem related to both medico-legal implications and health care costs[1,2]. The theme of biliary injuries in laparoscopic cholecystectomy and the prevention and management of bile duct lesions have been extensively exanimated. However, little attention has been given to vascular lesions[3]. Bleeding complications due to vascular injuries are an important cause of morbidity and mortality, especially during laparoscopy, where bleeding control can be technically challenging in inexperienced hands. Vascular injuries during laparoscopic cholecystectomy may mainly occur during trocar or Veress needle insertion or during dissection of the hepato-cystic triangle. Interestingly, the reported incidence rate of conversion to open surgery due to intra-operative vascular lesions is approximately 0%-1.9%, with a mortality rate of approximately 0.02%[3-5]. The aim of this article was to analyze and explore the incidence, diagnosis and surgical management of vascular injuries in laparoscopic cholecystectomy according to the available scientific evidence. MEDLINE and PubMed searches were performed using the MeSH terms "vascular injury", "vascular lesion", "vasculo-biliary injury", and "laparoscopic cholecystectomy" to identify relevant articles (cohort studies, systematic reviews, case reports, multicenter studies) published in English, French, Spanish, and Italian over the last twenty years.

INCIDENCE AND RISK FACTORS

Several risk factors may contribute to vascular injuries during laparoscopic cholecystectomy: Anatomical factors, including vascular anomalies, patient-related factors, the gallbladder pathology and surgeon's experience, as summarized in Table 1. Concerning the anatomical factors, the different variants of vascular anatomy may represent a possible cause of bile duct injuries, particularly anomalies of the cystic artery and right hepatic artery (RHA). If surgeons are not aware of possible variations of the RHA, such as in the case of acute and chronic cholecystitis with unclear anatomy of Calot's triangle, the RHA may be accidentally injured or mistaken for the cystic artery and actively cut off. In a study assessing the frequency of anatomical variations of biliary and vascular systems from Singh *et al*[6], the operative findings revealed 197 (26.62%) vascular anomalies, mostly related to cystic artery and RHA anatomy. Arterial anomalies are more common, occurring in at least 50% of individuals, and can be recognized only by careful dissection[7]. Based on the classification proposed by Smadja and Blumgart [8], the cystic artery is considered normally positioned when located in the center of the hepato-cystic triangle. In a recent Spanish study performed on a sample of 2000 Laparoscopic cholecystectomy procedures, Noguera *et al*[9] found an origin of the cystic artery from the RHA in 91.5% of cases. These data are similar to those of Bergamaschi *et al*[10], where, in a study of 90 consecutive human cadavers, a single artery was found in 59 of 70 specimens (84.3% of all cases).The incidence of third structures within the hepato-cystic triangle was found to be arteries in 36.2% of cases, with a reported incidence of caterpillar hump of the RHA in 12.9% of all cases and double cystic arteries in 5.7%. The most common variations of cystic artery are shown in Figure 1, according to the literature data[7-10]. Among the patient-related factors, overweight and pathological obesity, a history of biliary surgery or endoscopic procedures, and hepatic cirrhosis or chronic liver disease appear to be factors correlated with the development of perioperative complications, both for biliary and vascular structures. However, emergent cholecystectomy for acute cholecystitis increases the risk of iatrogenic lesions, as gallbladder inflammation causes a series of anatomical changes that are associated with an increased risk of iatrogenic injury. Ultimately, the surgeon's experience plays an important role, and for this reason the importance of a correct "learning curve" for young surgeons should be stressed.

HEPATIC ARTERY INJURIES

Intra-operative bleeding is certainly the most common and feared complication of arterial injury during laparoscopic procedures, followed by ligation. Among hepatic artery injuries, lesions of the RHA are the most described complication that may occur during laparoscopic cholecystectomy. Hepatic artery closure is usually well tolerated without any particular consequences due to the portal flow and a dense series of collateral arterial branches coming from the hepatic hilum. However, in such cases, hepatic

Table 1 Summary of risk factors associated to vascular injuries

Anatomical factors	Description
Common vascular variants of cystic artery and right hepatic artery	Single cystic artery[6]
	Two arteries (superficial and deep)[6]
	Single short cystic artery originated from caterpillar right hepatic artery[4,5,10]
	Long single cystic artery not from right hepatic artery crossing anterior to the common hepatic duct[7,8]
	Double cystic artery/accessory cystic artery[9]
	Cystic artery seen more anteriorly than posteriorly in relation to Mascagni's lymph node[7,9]
	A constant vessel found on the postero-lateral margin of gallbladder bed[6,9]
	Cystic artery coming from gastroduodenal artery, passing outside Calot's triangle[6,9]
Patient-related factors	Overweight and pathological obesity[1]
	History of biliary surgery or endoscopic procedures[1]
	Underlying liver disease[1]
Gallbladder pathology	Acute or chronic cholecystitis[1-3]
	Gallbladder anomalies (gallbladder duplication, gallbladder agenesia, left-side gallbladder)[1-3]
Surgical experience	Learning curve[1,2]
	Inadequate exposure[1,2,6]
	Failure to recognize anatomical landmarks[2,6]

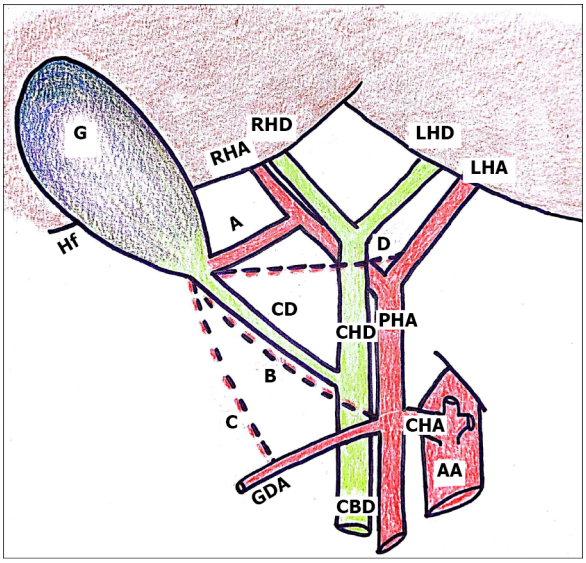

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Figure 1 Anatomic illustration of the most common variants of cystic artery. Common variants of cystic artery. A: Cystic artery originating from the right hepatic artery in the classical position[6-8]; B: Long cystic artery seen anteriorly to the cystic duct[6,7]; C: Cystic artery coming from the gastroduodenal artery, passing outside Calot's triangle[6,9]; D: Long single cystic artery not from the right hepatic artery crossing anterior to the common hepatic duct[6,9]. RHA: Right hepatic artery; LHA: Left hepatic artery; PHA: Proper hepatic artery; CHA: Common hepatic artery; GDA: Gastroduodenal artery; G: Gallbladder; CHD: Common hepatic duct; CD: Cystic duct; CBD: Common bile duct; RHD: Right hepatic duct; LHD: Left hepatic duct; AA: Abdominal aorta.

artery ligation can sometimes cause ischemic hepatic necrosis or liver atrophy. RHA injury is frequently encountered in association with bile duct injury, even if the true incidence of RHA injury without concomitant bile duct injury is not clear[11]. In a cadaveric study, Halasz[12] reported that the incidence of injury to the RHA or its branches was only 7%. All patients survived at least one year after cholecystectomy, and they had normal livers. For this reason, the decision to immediately repair the lesion remains controversial. RHA injuries always occur in two ways: the first is when the fundus-first approach for laparoscopic cholecystectomy is performed in the presence of severe inflammation[13]; the

second is in the presence of vascular anomalies, as in the case of caterpillar hump of the RHA, where the hepatic artery may be wrongly mistaken for the cystic artery[4,5]. The most important complication of RHA injury is massive bleeding during dissection, which always leads to conversion to open surgery in inexperienced hands. In some cases, laparoscopic repair is feasible and safe[11] by suturing in cases of intra-operative bleeding or direct end-to-end anastomosis when possible in cases of ligation or clipping of the RHA.

Hepatic artery pseudoaneurysm represents another important complication after RHA injury, and it may occur in the early or late postoperative course after LC. Approximately 10% of all the reported cases of hemobilia are secondary to iatrogenic cystic artery or hepatic artery pseudoaneurysms as a consequence of an opening of cystic or RHA pseudoaneurysm within the biliary tree[14]. The exact mechanism of hepatic pseudoaneurysm formation is yet unclear: The most accredited hypotheses concern the mechanical or thermal damage during surgical dissection. Transarterial embolization represents the best therapeutic solution for hepatic artery aneurysm with a high success rate, and surgical repair should be performed in cases where the embolization attempt has failed. In many patients, an open approach in an emergency setting is performed[14], even if a laparoscopic approach is used in some cases[15].

HEPATIC VEINS, PORTAL VEIN AND MAJOR RETROPERITONEAL VESSEL INJURIES

Venous bleeding is less common than arterial bleeding. Bleeding from hepatic vein injury commonly comes from the liver bed during detachment of the gallbladder. Between 10% and 15% of patients may present a large branch of the middle hepatic vein adherent to the liver bed, leading to an increased risk of venous injury during cholecystectomy. In 1999, Misawa *et al*[16] first proposed an ultrasonographic assessment of the risk of injury to branches of the middle hepatic vein during laparoscopic cholecystectomy by analyzing the middle hepatic vein distance from the gallbladder bed before laparoscopy. Currently, there is controversy about the risk of injury to the branch of the middle hepatic vein during LC[17]. In a previous study, Zhang *et al*[18] analyzed the anatomical relationship between the gallbladder bed and the branches of the middle hepatic vein in 143 healthy volunteers by color Doppler ultrasound and found that, in most subjects, the branch of the middle hepatic vein and the gallbladder bed were well separated. Only patients with large branches of the middle hepatic vein running very close to the gallbladder bed are at risk of bleeding during laparoscopic cholecystectomy. The diameter of the distal branch of the middle hepatic vein close to the gallbladder bed is reported to vary from 0.9 mm to 3.2 mm and in some cases over 5 mm[17,19,20]. Moreover, according to Ball *et al*[19], the presence of chronic cholecystitis and fibrous tissue may increase the risk of significant bleeding from the liver bed. Concerning the treatment of venous injuries, bleeding from the middle hepatic vein branch during the operation can only be stopped by direct hemostatic stitches; it can be performed by laparoscopy in experienced hands or can often require conversion to open surgery[21]. In general, we strongly recommend careful dissection during the final steps of laparoscopic cholecystectomy, especially for training surgeons, when dissection becomes easier, and the surgeon may relax.

Portal vein injuries are frequently associated with biliary and RHA injuries. Compared with arterial injury after cholecystectomy, there are very few reports of isolated portal vein injury without associated biliary lesions[22]. Furthermore, as a result of its rarity, the pathogenesis of this type of injury remains unclear. The surgical repair of portal vein lesions is very difficult, often complicated by massive hemorrhage, and seldom successfully managed. When the portal vein is injured during surgery, it should be reconstructed immediately by an experienced hepato-biliary surgeon if the patient is hemodynamically stable. However, the most important complication after surgical repair of a portal vein injury is represented by acute portal thrombosis, often leading to liver infarction. For this reason, anticoagulation therapy should be started as soon as possible to avoid the progression of acute portal vein thrombosis. Liver transplantation is a salvage therapy that should only be considered in end-stage liver disease[22].

Injuries of major retroperitoneal vascular structures are uncommon but potentially life-threatening complications of laparoscopy[23-25]. Inferior vena cava and aorta injuries are frequently associated with trocar or Veress needle insertion during laparoscopic surgery. Early diagnosis and immediate conversion are mandatory for the proper management of these important injuries to minimize morbidity and mortality. Some authors have also described occasional injuries to the right renal artery with the formation of a pseudoaneurysm and consequent renal-vena cava fistula[26,27]. This often represents a late complication following laparoscopic cholecystectomy.

Another important medical complication associated with vena cava injury is venous air embolism [28]; the cardiovascular, pulmonary, and central nervous systems may all be affected, with severity ranging from no symptoms to immediate cardiovascular collapse.

CLASSIFICATION OF VASCULAR INJURIES

Several attempts have been made to uniformly classify vascular lesions, so they are always underreported, as summarized in Table 2. In early 2000, Schäfer *et al*[29] proposed a working classification from the Swiss Association of Laparoscopic and Thoracoscopic Surgery (SALTS) by defining vascular injuries during laparoscopy into intraoperative and postoperative bleeding complications. In 2007, Bektas *et al* [30] proposed the Hannover classification by underlining the importance of including additional vascular injury and the location of the biliary lesion at or above the bifurcation of the hepatic duct, as they were found to have a major impact on the extent of surgical intervention for iatrogenic bile duct injury. The Neuhaus and Strasberg-Bismuth classifications for biliary injuries do not consider vascular involvement.

In 2010, Kaushik[31] suggested a new classification system, wherein vascular injuries were divided into major and minor injuries based on the need for conversion, additional surgical procedures, or blood transfusions.

The European Association for Endoscopic Surgery (EAES) recently proposed a new classification named ATOM, including the anatomy of damage and vascular injury (A), timing of detection (To), and mechanism of damage (M)[32].

VASCULO-BILIARY INJURY

Vascular injury, in particular to the RHA, is found in approximately 12% to 61% of iatrogenic bile duct lesions, leading to high morbidity and mortality associated with altered quality of life[33-35]. It is very important to know preoperatively if a vascular lesion occurs along with a biliary lesion because the poor vascularization of the common bile duct may result in anastomotic strictures after surgical biliary tract repair, recurrent cholangitis and secondary biliary cirrhosis[33]. For these reasons, appropriate knowledge of the vascular lesion represents an important condition when the patient is referred to a specialized hepato-biliary center. In most cases, the surgical repair of biliary and vascular injuries is performed simultaneously. There are no guidelines for the timing of repair, whereas few studies have compared early *vs* late repair of bile duct injury[34,36,37]. In a multicenter study of the European-African Hepato Pancrea to Biliary Association (E-AHPBA), the timing of biliary reconstruction after bile duct injury with hepaticojejunostomy was not correlated with the occurrence of severe postoperative complications, re-intervention or liver-related mortality[34]. In another multicenter study, the most favorable outcomes were more frequently observed in the immediate (within the first 72 h) and (after 6 wk) reconstruction of biliary injury, and type E4 injury was found to be an independent factor of worse outcome[36]. In general, if a major bile duct transection occurs (types E1-E2 according to the Strasberg classification), the integrity of the hepatic artery, especially the RHA, should always be examined meticulously to plan early vascular reconstruction if technically possible. If revascularization is not technically feasible, biliary reconstruction close to the hilar plate is mandatory in order to minimize the possibility of anastomotic complications[38]. If the vascular lesion is discovered late, in a minority of cases, hepatectomy is needed as a salvage strategy[39,40].

DIAGNOSIS AND SURGICAL MANAGEMENT

The diagnosis of intra-operative bleeding during dissection may be obvious, but it should be correctly identified, and surgeons must choose the best therapeutic option to quickly repair the vascular lesion, depending on their own experience and medical center resources. At present, there is no clear consensus on the most suitable type or time to perform the repair, especially when vascular injury occurs in centers not specialized in complex hepato-biliary surgery; thus, the management of these complications is still a much debated topic[33]. In a recent multicenter retrospective study, the authors analyzed the management of vascular injuries during laparoscopic cholecystectomy, focusing on referral to specialized centers, time to perform the repair, and different treatment option outcomes[33]. In a cohort of 104 patients with vascular injuries, 29 patients underwent vascular repair (27.9%), 13 (12.5%) liver resection, and 1 liver transplant as a first treatment. The majority of vascular and biliary injuries occurred in non-specialized centers, and more than half were immediately transferred. The authors concluded that the management of complex vascular and biliary lesions should be mandatory in specialized centers and that late vascular repair is not necessarily associated with worse outcomes[33]. Another interesting study by Li *et al*[38] analyzed the effects of vascular reconstruction and hepatic re-arterialization when technically possible. In this study, successful early arterial reconstruction with or without a vascular graft (within 4 d) allowed recovery from hepatic ischemia, without any evidence of hepatic atrophy or necrosis during follow-up.

Table 2 Classifications of vascular injuries during laparoscopic cholecystectomy

Ref.	Definition of vascular injury
Schäfer *et al* [29], 2000	Major injury: Injury to any of the following vessels: Aorta, vena cava, portal vein, hepatic artery and splenic artery, iliac vessels, mesenteric, omental and renal vessels; the vascular injury is classified in: Intra-operative; local haemorrhage within the abdominal cavity, retroperitoneum or abdominal wall; post-operative: Bleeding occurring within 24 h after surgery
Bektas *et al* [30], 2007	Vascular involvement in different biliary injuries grades (types C and D): Type C tangential injury of the common bile duct: with or without vascular lesion; Type D complete transection of the common bile duct: with or without vascular lesion
Kaushik[31], 2010	Major injury: Any bleeding involving cystic artery, right hepatic artery, portal vein, superior mesenteric vein, suprahepatic veins, inferior vena cava, aorta that requires conversion to open surgery to control/repair; additional surgical procedures; need for blood transfusions
Fingerhut *et al* [32], 2013	Vasculo-biliary involvement by reporting the type of injured vessel
Our study	Major vascular injury: Any bleeding involving right hepatic artery, portal vein, suprahepatic veins, inferior vena cava that always requires conversion to open surgery for control/repair; need for blood transfusions; associated biliary injury; need for transfer to tertiary center

CONCLUSION

Vascular injuries represent a life-threatening complication, and they should be carefully evaluated along with biliary lesions during laparoscopic cholecystectomy. The recognition of these lesions must occur as early as possible, and the surgeon must choose the best therapeutic option for the patient according to available medical resources. Currently, the management of referrals to specialized hepato-biliary centers for multidisciplinary approaches is mandatory.

FOOTNOTES

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Country/Territory of origin: Italy

ORCID number: Antonio Pesce 0000-0002-7560-551X; Nicolò Fabbri 0000-0001-7039-3717; Carlo Vittorio Feo 0000-0003-0699-5689.

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ORIGINAL ARTICLE

Basic Study

Differential expression and significance of 5-hydroxymethylcytosine modification in hepatitis B virus carriers and patients with liver cirrhosis and liver cancer

Yue-Cui Li, Wei-Yue Hu, Cheng-Hang Li, Li-Li Zhang, Xiang-Wei Xu, Jin Li, Hong-Xia Luo

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Yue-Cui Li, Wei-Yue Hu, Cheng-Hang Li, Li-Li Zhang, Xiang-Wei Xu, Jin Li, Hong-Xia Luo, Department of Infectious Diseases, The First People's Hospital of Yongkang, Jinhua 321300, Zhejiang Province, China

Corresponding author: Yue-Cui Li, MBChB, Chief Physician, Department of Infectious Diseases, The First People's Hospital of Yongkang, No. 599 Jinshan West Road, Yongkang, Jinhua 321300, Zhejiang Province, China. liyuecui02@yeah.net

Abstract

BACKGROUND

The relationship between hepatitis B surface antigen (HBsAg)-positive carrier status and liver cancer has been extensively studied. However, the epigenetic changes that occur during progression from HBsAg-positive carrier status or cirrhosis to liver cancer are unknown. The epigenetic modification of DNA hydroxymethylation is critical in tumor development. Further, 5-hydroxymethylcytosine (5hmC) is an important base for DNA demethylation and epigenetic regulation. It is also involved in the assembly of chromosomes and the regulation of gene expression. However, the mechanism of action of 5hmC in HBsAg-positive carriers or patients with cirrhosis who develop liver cancer has not been fully elucidated.

AIM

To investigate the possible epigenetic mechanism of HBsAg-positive carriers and hepatocellular carcinoma (HCC) progression from cirrhosis.

METHODS

Forty HBsAg-positive carriers, forty patients with liver cirrhosis, and forty patients with liver cancer admitted to the First People's Hospital of Yongkang between March 2020 and November 2021 were selected as participants. Free DNA was extracted using a cf-DNA kit. cfDNA was extracted by 5hmC DNA sequencing for principal component analysis, the expression profiles of the three groups of samples were detected, and the differentially expressed genes (DEGs) modified by hydroxymethylation were screened. Bioinformatic analysis was used to enrich DEGs, such as in biological pathways.

RESULTS

A total of 16455 hydroxymethylated genes were identified. Sequencing results showed that 32 genes had significant 5hmC modification differences between HBsAg carriers and liver cancer patients, of which 30 were upregulated and 2 downregulated in patients with HCC compared with HBsAg-positive carriers. Significant 5hmC modification differences between liver cirrhosis and liver cancer patients were identified in 20 genes, of which 17 were upregulated and 3 were downregulated in patients with HCC compared with those with cirrhosis. These genes may have potential loci that are undiscovered or unelucidated, which contribute to the development and progression of liver cancer. Analysis of gene ontology enrichment and Kyoto Encyclopedia of Genes and Genomes showed that the major signaling pathways involved in the differential genes were biliary secretion and insulin secretion. The analysis of protein interactions showed that the important genes in the protein-protein interaction network were phosphoenolpyruvate carboxykinase and solute carrier family 2.

CONCLUSION

The occurrence and development of liver cancer involves multiple genes and pathways, which may be potential targets for preventing hepatitis B carriers from developing liver cancer.

Key Words: Hepatitis B surface antigen; 5-hydroxymethylcytosine; Hepatocellular carcinoma; Liver cancer; DNA sequencing; Differentially expressed genes

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Core Tip: Major signaling pathways involved in differentially expressed genes are biliary secretion and insulin secretion. Abnormal secretion of bile and insulin in tumor cells may promote or symbolize the occurrence and development of liver cancer. *SLC2A2* and *PCK1* are the central nodes of the differential genes, which may be most closely related to the occurrence of liver cancer. *FABP1, APOC3, SI, KRT20, SLC5A1, SLC10A2, RBP2,* and *AKR1B10* may be key genes in the protein regulatory network, and these genes may play regulatory roles after modification by 5-hydroxymethylcytosine (5hmC). Therefore, we suggest that the difference in 5hmC modification levels is related to the occurrence and progression of liver cancer.

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INTRODUCTION

Primary liver cancer, mainly hepatocellular carcinoma (HCC), is a solid tumor generated from the malignant transformation of hepatocytes or intrahepatic bile duct cells and is one of the most common malignancies in China[1]. Additionally, the number of hepatitis B virus (HBV) carriers in China is high. If patients develop an infection, chronic HBV infection, liver cirrhosis, and even HCC may occur. The relationship between hepatitis B surface antigen (HBsAg)-positive carriers and liver cancer has been reported in many studies[2]. There is consensus that liver cirrhosis can progress to liver cancer. Although great progress has been made in the prevention and treatment of hepatitis B in China, including a reduction in the transmission rate of HBV, effective treatments for HBV carriers are still lacking. Drugs such as nucleotide analogs, including entecavir, cannot rapidly reduce HBV titers in the short term. Additionally, administration of these drugs to HBV carriers remains controversial in clinical practice[3]. At present, the mechanisms underlying the transformation from the HBsAg-positive state or liver cirrhosis to liver cancer is not entirely clear, especially the potential mechanism of epigenetic changes in the occurrence and progression of these diseases. Therefore, the differences in epigenetic modifications between the HBsAg-positive state, liver cirrhosis, and liver cancer must be explored.

DNA hydroxymethylation is a process in which 5-methylcytosine is oxidized to 5-hydroxymethylcytosine (5hmC) by ten-eleven translocation enzymes during DNA methylation[4]. Further, 5hmC is an important base in DNA demethylation as well as in epigenetic regulation. Some studies suggest that 5hmC is the sixth genome base and is involved in the assembly of chromosomes and regulation of gene expression[5]. Studies have shown that the level of hydroxymethylation in tumors and other diseases is significantly different from that in the normal state, and the difference gradually increases with the

progression of diseases, indicating that the epigenetic modification of hydroxymethylation is essential in the development of tumors[6]. However, the mechanism of 5hmC in HBsAg-positive carriers or patients with cirrhosis that develops into liver cancer has not yet been fully elucidated. 5hmC sequencing is a new technology that constructs free nucleic acid fragments containing 5hmC using polymerase chain reaction (PCR) technology and detects the 5hmC sequence using second-generation DNA sequencing technology. Because the number of 5hmC modifications is far less than the number of DNA methylations, 5hmC sequencing has a higher cost performance, efficiency, accuracy, and economy, as well as extensive clinical application value. In this study, we analyzed differentially expressed genes (DEGs) in HBsAg-positive carriers, patients with liver cirrhosis, and patients with liver cancer using 5hmC sequencing technology and further annotated the function of DEGs to explore the similarities and differences in gene hydroxymethylation between HBsAg-positive carriers, patients with liver cirrhosis, and patients with liver cancer and the regulatory role of signaling pathways.

MATERIALS AND METHODS

Participants

Forty HBsAg-positive carriers, forty patients with liver cirrhosis, and forty patients with liver cancer admitted to the First People's Hospital of Yongkang between March 2020 and November 2021 were selected as participants. This study was approved by the medical ethics committee of the hospital. The diagnostic criteria for liver cirrhosis were based on the International Guidelines for the Diagnosis and Treatment of Liver Cirrhosis updated in 2021[7]. There were no differences in baseline data, such as sex and age, between the three groups of patients. Inclusion criteria for primary liver cancer were as follows [8]: Body mass index of 20–30 kg/m^2 in men and 19–34 kg/m^2 in women; complete results of general biochemical indexes such as liver function; imaging data such as tumor computed tomography/magnetic resonance imaging and serological indexes; a history of hepatitis B; no history of diabetes or other systemic diseases; no history of other infectious diseases; and no pregnancy or lactation.

Detection with 5hmC sequencing

cfDNA extraction: Blood samples from HBsAg-positive carriers, patients with liver cirrhosis, and patients with liver cancer were collected at the time of diagnosis and sent to Zhongke Jinzhen Co., Ltd. for DNA extraction, pyrolysis of specimen precipitate after centrifugation, and extraction of cfDNA from plasma using the Quick-cfDNA Serum & Plasma Kit (Zymo).

DNA quality test and results: Qubit accurately quantified the DNA concentration, and Q-sep analyzed the size, distribution, and relative quantification of DNA fragments. After the sample was quantified, the DNA of the sample was first repaired, a tail was added to the 3' end, and the sequencing joint was connected. Biotins were connected by a transglycosylation reaction and click chemistry. The DNA fragment containing 5hmC was captured using streptavidin beads, and PCR amplification was performed to complete the entire library construction. After the library quality inspection, different libraries were sequenced using Nova6000 according to the effective concentration and target data volume. After obtaining the original sequence (sequenced reads), the original gene fragments were returned to the correct human reference genome position to calculate the gene expression of each sample.

Principal component analysis

Principal component analysis (PCA) is an unsupervised multivariate statistical analysis method that can generally reflect the overall differences between samples and the variation between samples within the group. It is commonly used to evaluate sample differences between groups and consistency within groups. PCA was used for dimensionality reduction of all 5hmC gene sequencing results. After data visualization, outlier samples or sample clusters with high similarity were identified.

Screening of DEGs modified by 5hmC

Through the analysis of the significant difference in the 5hmC modification expression matrix of all samples, functional gene modification differences among HBsAg-positive carriers, patients with liver cirrhosis, and patients with liver cancer were found. In this study, the differences in 5hmC expression were analyzed using normalization, discrete estimation, and significance tests. Normalization and discrete estimation mainly remove the influence of sample sequencing depth differences and reduce the false-positive rate through homogenization. DEGs were further detected using DEseq2 and PossionDis algorithms. DEGs were screened according to the log2FoldChange ≥ 0.26, gene 5hmC modified expression value, and adjusted *P* value ≤ 0.05. The sample classification of this analysis included three groups: HBsAg-positive carriers, patients with liver cirrhosis, and patients with liver cancer, with 40 patients in each group. In the three types of samples, the differences between the liver cirrhosis group and liver cancer group, HBsAg-positive carrier group, and liver cancer patient group were analyzed. Lists of all differential genes are in the original data.

Functional enrichment analysis

Based on the results of gene ontology (GO) and gene pathway annotation, the DEGs were enriched and classified according to the aforementioned functions and pathways. GO enrichment analysis was used for functional classification, and the Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis was used for pathway classification. GO enrichment analysis was performed from three aspects: cellular component (CC), biological process (BP), and molecular function (MF). KEGG is a database used for analyzing gene functions, linking multiple genes with specific pathways and functions, and classifying genes according to the pathways involved. STRING (https://string-db.org/) is currently the largest protein interaction database. DEGs were imported into the STRING database, and the homology, literature, and co-expression relationship of known proteins in the database were used to determine the interaction between the imported encoded proteins to construct a protein-protein interaction (PPI) network analysis.

Statistical analysis

Pearson correlation analysis was performed between each pair of samples using the Cor function in *R* software; $P < 0.05$ was considered statistically significant. The expression of 5hmC modified genes obeyed a Poisson distribution after standardization. The *P* value was calculated using the Wald test and corrected using multiple hypothesis tests. Statistical significance was set at $P < 0.05$.

RESULTS

Analysis of 5hmC sequencing results

The Nova6000 platform was used to measure samples from the three groups of patients. Each group contained 40 patients, and 16455 genes were detected. The percentages of principal components (PC) 1 and 2 in the PCA plot of all genes in HBsAg-positive carriers and patients with liver cancer were 24.933% and 12.06% (Figure 1A), respectively. The percentages of PC1 and PC2 in the PCA plot of differential genes were 46.351% and 14.927% (Figure 1B), respectively, suggesting that differential genes can distinguish HBsAg-positive carriers from patients with liver cancer.

Similarly, when detecting the same number of genes, the percentages of PC1 and PC2 in the PCA plot of all genes in patients with liver cirrhosis and liver cancer were 21.998% and 11.076% (Figure 1C), respectively, and the percentages of PC1 and PC2 in the PCA plot of differential genes were 59.621% and 12.27% (Figure 1D), respectively, suggesting that differential genes have the ability to distinguish between liver cirrhosis and liver cancer.

Analysis of DEG expression level

Differences between patients with liver cirrhosis and those with liver cancer and differences between HBsAg-positive carriers and patients with liver cancer were analyzed. According to the levels of 5hmC modified genes in each sample, DEGs between HBsAg-positive carriers and patients with liver cirrhosis or liver cancer were screened. The results showed 32 DEGs between HBsAg-positive carriers and patients with liver cancer, of which 30 were upregulated and 2 genes were downregulated by 5hmC modification. The distribution of DEGs is shown by a volcanic and thermal map in Figure 2A and C. All DEGs upregulated and downregulated in HBsAg-positive carriers and liver cancer groups are shown in Table 1. There were 20 DEGs between patients with liver cirrhosis and those with liver cancer, of which 17 were upregulated and 3 genes were downregulated by 5hmC modification. The distribution of the DEGs is shown by a volcanic and thermal map (Figure 2B and D). All DEGs that were upregulated and downregulated in patients with liver cirrhosis and liver cancer are shown in Table 2.

GO and KEGG enrichment analysis of DEGs in HBsAg carriers and patients with liver cancer

According to the results of DEG detection, GO enrichment analysis was used for the functional annotation of the 5hmC sequences. After the difference analysis between HBsAg carrier and liver cancer groups, the top 10 enriched GO terms related to BP, CC, and MF were used as the main functions of differential hydroxymethylation genes between HBsAg carriers and patients with liver cancer. The main pathways involved are shown in Figure 3A. The numbers of genes involved in the GO BP of TOP3 were 4, 4, and 4, respectively, which were mainly related to digestion, homophilic cell adhesion *via* plasma membrane adhesion membrane, and cellular lipid catabolic processes. The numbers of genes included in the MF of TOP3 were 3, 2, and 2, respectively, which were related to the activities of secondary active transmembrane transporter activity, alcohol binding, and solute:cation symporter activity. The numbers of genes in TOP3 cell components were 5, 4, and 2, respectively, which were mainly related to the apical part of the cell, apical plasma membrane, and cell cortex region. These three kinds of gene function together suggest that the main differences between HBsAg-positive carriers and patients with liver cancer may be digestive function and cell information transmission.

From the perspective of pathway enrichment, 92 pathways were found to be closely related to KEGG enrichment in HBsAg carriers and patients with liver cancer. The main pathways are shown in

Table 1 Differential genes between hepatitis B surface antigen-positive carriers and patients with liver cancer after 5-hydroxymethylcytosine sequencing

Symbol	Ensembl	log2FoldChange	padj
SI	ENSG00000090402	0.849003917	0.000172596
FAM83B	ENSG00000168143	0.532487323	0.00425853
PCK1	ENSG00000124253	0.519299173	0.006848676
KCNN2	ENSG00000080709	-0.510730422	0.011078186
FAT1	ENSG00000083857	0.47499449	0.02542581
FGF19	ENSG00000162344	0.428605733	0.036854977
FABP1	ENSG00000163586	0.427372957	0.025268146
SLC10A2	ENSG00000125255	0.417559665	0.005504835
ISX	ENSG00000175329	0.391889896	0.005936182
APOC3	ENSG00000110245	0.374978715	0.017711634
NOVA1	ENSG00000139910	0.367147827	0.006848676
KRT20	ENSG00000171431	0.361001798	0.049694505
DUSP1	ENSG00000120129	0.341097702	0.001523335
RBP2	ENSG00000114113	0.330491105	0.049694505
PCLO	ENSG00000186472	0.307272826	0.000520372
BRINP3	ENSG00000162670	0.297534011	0.001107995
SLC2A2	ENSG00000163581	0.297032232	0.006630228
AKR1B10	ENSG00000198074	0.296134756	0.012660193
SEMA3A	ENSG00000075213	0.295498456	7.92E-05
SLC5A1	ENSG00000100170	0.295343232	0.027331533
ROBO1	ENSG00000169855	0.294408057	0.026805139
ROPN1B	ENSG00000114547	-0.292505301	0.002291301
PRR16	ENSG00000184838	0.291799543	0.049694505
TNFSF15	ENSG00000181634	0.286998557	0.01533013
CDH17	ENSG00000079112	0.284940571	0.001204498
MUC17	ENSG00000169876	0.284637524	0.022168549
PCDH7	ENSG00000169851	0.284173648	0.00131498
FOS	ENSG00000170345	0.28075648	0.008754834
GABRA2	ENSG00000151834	0.27973066	0.049694505
NRCAM	ENSG00000091129	0.270536808	0.047702973
DPP10	ENSG00000175497	0.268657512	0.005504835

Figure 3B. Among them, the number of pathways related to digestive secretion, such as carbohydrate digestion and absorption, insulin and bile secretion, galactose metabolism, and the glucagon signaling pathway, were most significant. The peroxisome proliferator-activated receptor and mitogen-activated protein kinase (MAPK) signaling pathways were also significantly enriched in differentially hydroxymethylated genes. These results indicate that the main difference between HBsAg carriers and patients with liver cancer lies in their digestive function. Soluble carrier family 2 member 2 (*SLC2A2*) and Fos proto-oncogene, AP-1 transcription factor subunit (*FOS*) were involved in the most enriched pathways. *SLC2A2* is mainly enriched in insulin and bile secretion, the prolactin signaling pathway, and central carbon metabolism in cancer. *FOS* is mainly enriched in the prolactin, MAPK, and B-cell receptor signaling pathways and the PD-L1/PD-1 pathway, suggesting that *SLC2A2* is related to liver-digestive function and *FOS* is related to immune signal transduction.

Table 2 Differential genes between patients with liver cirrhosis and those with liver cancer after 5-hydroxymethylcytosine sequencing

Symbol	Ensembl	log2FoldChange	padj
MUC8	NA	-0.61023	0.048721
PROX1	ENSG00000117707	0.510971	0.047662
TBX3	ENSG00000135111	0.380857	0.04644
DSC2	ENSG00000134755	0.366222	0.021397
PSME1	ENSG00000092010	0.340336	0.036054
C2orf72	ENSG00000204128	0.339959	0.015473
PTP4A1	ENSG00000112245	0.33768	0.043273
KCTD12	E0NSG00000178695	0.325745	0.016818
FMO2	ENSG00000094963	0.320229	0.040782
LGALS9C	ENSG00000171916	-0.29776	0.040782
CYP3A5	ENSG00000106258	0.292488	0.048557
SNAPC5	ENSG00000174446	0.290892	0.020989
TMEM176A	ENSG00000002933	0.285556	0.04535
SMPDL3A	ENSG00000172594	0.283335	0.036054
TNFSF10	ENSG00000121858	0.281624	0.009552
CYP27A1	ENSG00000135929	0.275649	0.038131
FAM20A	ENSG00000108950	0.275255	0.040338
CCDC67	NA	0.268828	0.036054
IL37	ENSG00000125571	-0.26789	0.021397
RBM47	ENSG00000163694	0.267243	0.038605

GO and KEGG enrichment analysis of DEGs in the liver cirrhosis and liver cancer groups

After the difference analysis between the liver cirrhosis and liver cancer groups, the main pathways involved in the GO enrichment analysis were determined, as shown in Figure 4A. Among them, the numbers of genes involved in the GO BP of TOP3 were 2, 2, and 2, respectively, which were mainly related to the bile acid biosynthetic process, ectodermal placode development, and ventricular cardiac muscle tissue development. The numbers of genes included in the MF of TOP3 were 3, 3 and 3, respectively, which were related to monooxygenase activity, oxidoreductase activity, acting on paired donors, and cofactor binding. The numbers of genes contained in the TOP3 cell components were 1, 1, and 1, respectively, which were mainly related to the hydrolysis of short peptides, ubiquitination and protein synthesis. These three types of gene functions jointly suggest that the main differential functions between liver cirrhosis and liver cancer may be bile acid metabolism and oxidoreductase activity.

The KEGG enrichment results of the liver cirrhosis and liver cancer groups differed from those of the above enrichment pathways. The results showed that 22 pathways were closely related; the main pathways involved are shown in Figure 4B. Among them, pathways related to the metabolism of various biological components were enriched, but specific pathways were different, such as primary bile acid biosynthesis, cholesterol metabolism, retinol metabolism, and drug metabolism (cytochrome P450), as well as cell death-related signaling pathways such as cytotoxicity, apoptosis, and necrotizing apoptosis mediated by natural killer cells, which were also significantly enriched in differentially hydroxymethylated genes. These results indicate that the main difference between liver cirrhosis and liver cancer is first reflected in the metabolic disorders of various active substances, and that the death behavior of tumor cells is different from that of non-tumor cells.

PPI analysis of proteins encoded by DEGs

Proteins usually perform biological functions by binding to one another. According to the https://string-db.org/ STRING protein interaction database, DEGs were analyzed using PPI, and the results are shown in Figure 5A, which shows the PPI network of DEGs in HBsAg carriers and patients with liver cancer. *PCK1* and *SLC2A2* were most closely related to each protein. Protein interactions were mainly concentrated between genes such as *FABP1*, *APOC3*, *SI*, *KRT20*, *SLC5A1*, *SLC10A2*, *RBP2*, and *AKR1B10*; Figure 5B displays the PPI network of patients with liver cirrhosis and those with liver cancer. It shows that only *PROX1* and *TBX3* have potential protein interactions, and the relationship between other

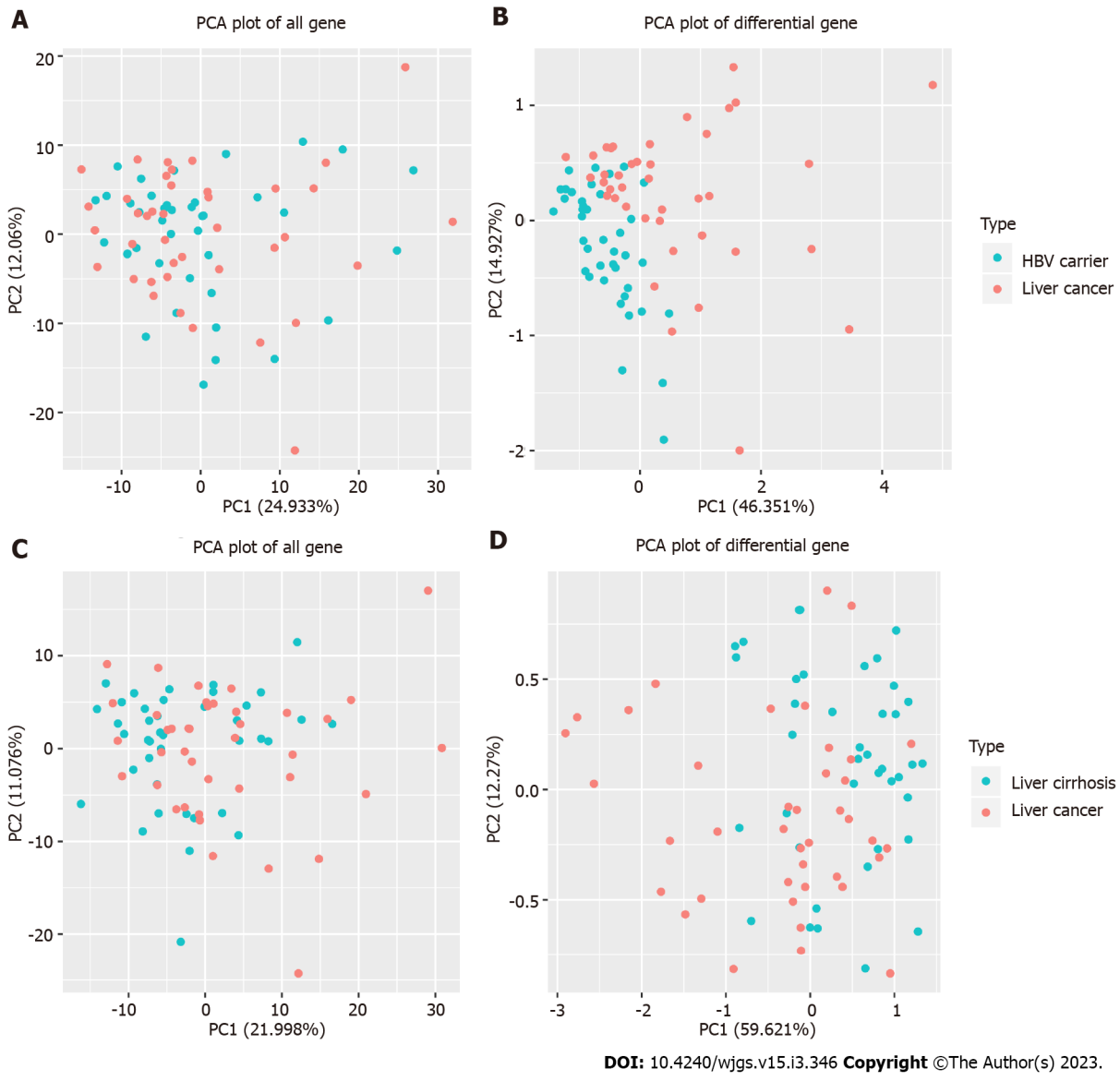

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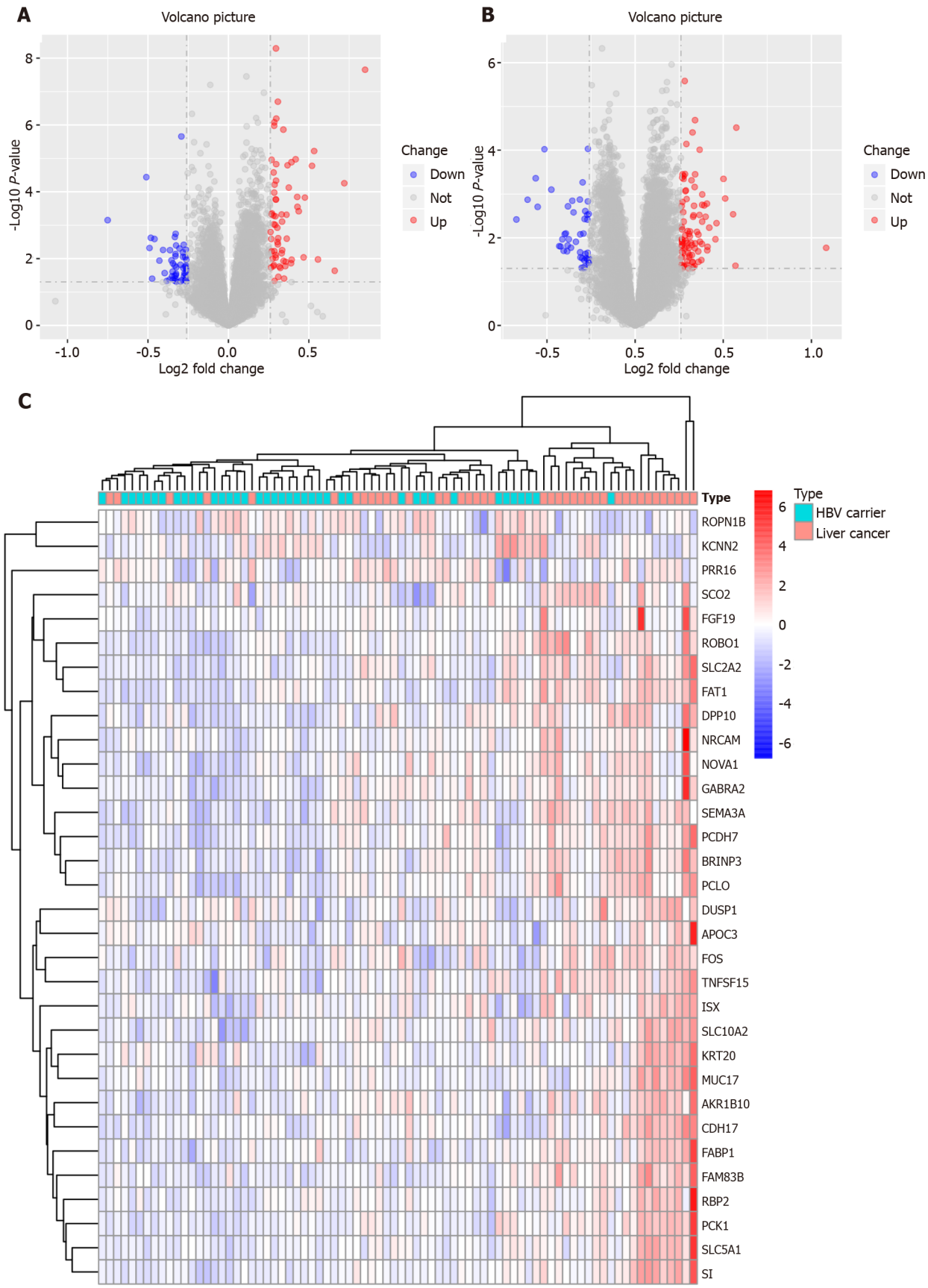
Figure 1 Principal component analysis after 5-hydroxymethylcytosine sequencing of hepatitis B surface antigen-positive carriers, patients with liver cirrhosis, and patients with liver cancer (40 cases per group). A: Principal component analysis (PCA) plot of all genes in hepatitis B surface antigen (HBsAg)-positive carriers and patients with liver cancer; B: PCA plot of differential genes between HBsAg-positive carriers and patients with liver cancer; C: PCA plot of all genes in patients with liver cirrhosis and those with liver cancer; D: PCA plot of differential genes between patients with liver cirrhosis and those with liver cancer. PCA: Principal component analysis; HBV: Hepatitis B virus.

proteins is unclear.

DISCUSSION

China has the most frequent occurrences of liver cancer, accounting for 47% of cases globally. Liver cancer ranks third among malignant tumors in China. In 2018, the number of newly diagnosed patients with liver cancer in China was 390000, and the number of deaths was 360000. Therefore, it remains a major threat to the health of the Chinese population[9]. Although many basic and clinical studies have explored the mechanisms of liver cancer formation and development, it remains unclear, and there are limited studies on epigenetic modifications in the occurrence and development of liver cancer, especially on the regulation of hydroxymethylation. To further define the potential relationship between HBsAg carrier status, liver cirrhosis, and liver cancer in the epigenetic modification of hydroxymethylation, serum samples from 40 HBsAg carriers, 40 patients with liver cirrhosis, and 40 patients with liver cancer were collected in our hospital. The bioinformatics method of 5hmC sequencing was used to conduct an in-depth analysis of these datasets, and DEGs were screened for 5hmC; the genes and pathways closely related to them were identified through bioinformatic analysis.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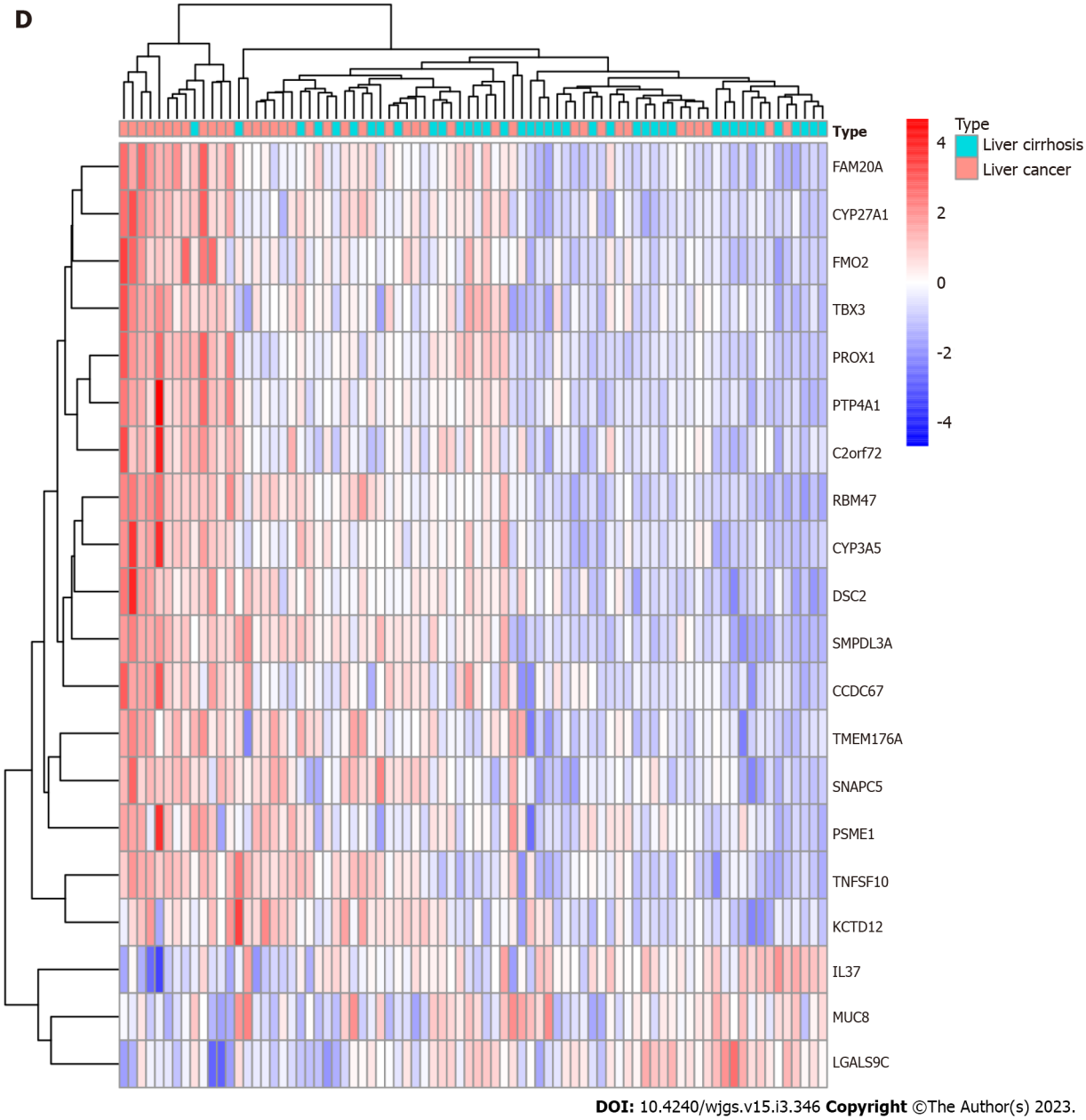

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Figure 2 Analysis of 5-hydroxymethylcytosine differences after sequencing. A, B: The gene volcano maps of hepatitis B surface antigen (HBsAg)-positive carriers and patients with liver cancer (A) and of patients with liver cirrhosis and those with liver cancer (B). The blue point indicates that the change of gene hydroxymethylation log2 fold is less than -0.26, and the red point indicates that the change of gene hydroxymethylation log2 fold is more than 0.26; C, D: Gene hot maps for HBsAg-positive carriers and patients with liver cancer (C) and for patients with liver cirrhosis and those with liver cancer (D). The blue block colors indicate a lower level of gene hydroxymethylation, and the red block colors indicate a higher level of gene hydroxymethylation. HBV: Hepatitis B virus.

In this study, 16455 hydroxymethylated genes were identified. Sequencing showed that 32 genes had significant differences in 5hmC modifications between HBsAg carriers and patients with liver cancer, and 20 genes had significant differences in 5hmC modifications between patients with liver cirrhosis and liver cancer. These genes may have potential loci that have not been discovered or clearly studied, leading to the occurrence and development of liver cancer, which is congruent with the findings of previous studies on epigenetic modifications[10]. Studies have shown that multiple DEGs of 5hmC are upregulated and downregulated in HBsAg carriers, patients with liver cirrhosis, and patients with liver cancer, involving multiple cellular signaling pathways and biological processes[11].

GO enrichment analysis showed that 32 DEGs were enriched in both HBsAg carriers and patients with liver cancer, indicating that liver cancer progression is the result of multiple pathways. For example, in GO BP analysis, the digestion and cellular lipid catabolic processes are enriched; digestion is one of the most important functions of the liver, and lipid catabolism is part of the digestive link and is responsible for one of the most basic biological processes[12]. In GO MF, the enrichment of secondary active transmembrane transporters and cation symporter activity was the most obvious, indicating that transmembrane transporters and ion transporters are involved in the digestive function of liver cells and

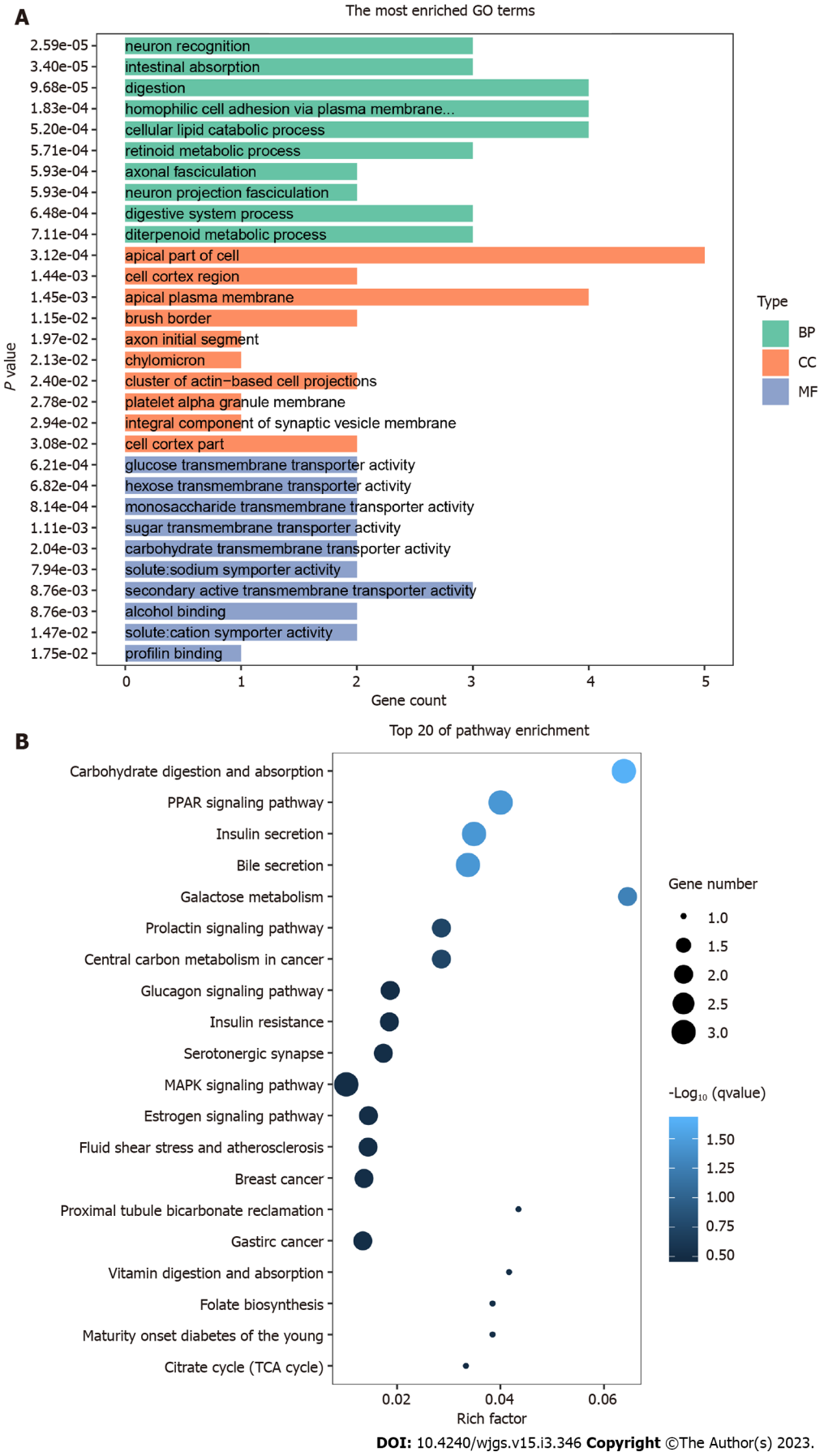

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Figure 3 Results of 5-hydroxymethylcytosine sequencing differential gene enrichment analysis between hepatitis B surface antigen carriers and patients with liver cancer. A: Gene ontology enrichment analysis of 5-hydroxymethylcytosine (5hmC) sequencing differentially expressed genes

(DEGs); B: Kyoto Encyclopedia of Genes and Genomes enrichment analysis of 5hmC sequencing DEGs. GO: Gene ontology; CC: Cellular component; BP: Biological process; MF: Molecular function.

may affect the progression of liver cancer[13]. In GO CC analysis, the apical part of the cell and apical plasma membrane were enriched, suggesting that the interaction between cells mainly occurs on the cell membrane[14]. Interestingly, in the GO BP analysis of the liver cirrhosis and liver cancer groups, the most obvious enrichment was bile acid biosynthesis and metabolic processes. Bile acid can increase the contact area of lipase by emulsification of fat, improve the activity of pancreatic and lipoprotein lipases, and promote intestinal fat transport to promote fat metabolism[15]. In the GO MF analysis, oxidation-related enzymes were enriched, indicating that the redox function of liver cirrhosis was further affected after liver cancer progression, which is consistent with the results of Chen *et al*[16]. In GO CC analysis, the enrichment of the proteasome complex further supports the results of these molecular functions. Minor *et al*[17] also pointed out that HBV proteins can promote the occurrence and development of HCC by forming a ubiquitinated proteasome complex.

KEGG analysis showed that the DEGs between HBsAg carriers and liver cancer groups had the largest number of genes enriched in the series of digestive and metabolic pathways, and the genes enriched in liver digestive function-related pathways accounted for the largest proportion of DEGs. Most genes are involved in digestive processes such as insulin and bile secretion, galactose metabolism, and the glucagon signaling pathway. In addition to these pathways, DEGs in the liver cirrhosis and liver cancer groups were also related to death processes, such as apoptosis and necrotizing apoptosis. Normal liver cells often develop abnormal metabolic behavior during their gradual development into tumor cells. This abnormal behavior affects the normal function of the liver, which can be considered a progressive feature of liver cancer. However, most previous studies concluded that no obvious pathological changes appeared in the liver of HBV carriers without disease. A few studies pointed out that the secretion of digestive juice in HBsAg-positive carriers might be related to the occurrence and development of liver cancer. An increasing number of researchers believe that the normal transaminase levels of HBsAg-positive carriers do not indicate fibrosis or inflammatory necrosis in the liver, which may also show different degrees of hepatocyte degeneration, necrosis, and even fibrosis[18]. In the liver tissue of HBV carriers with normal alanine aminotransferase (ALT) levels and without treatment, the proportion of liver inflammation grade G2-3 was 25.0%, which was higher than that in the group with a slight increase in ALT, and HBV carriers were accompanied by different degrees of liver fibrosis[18]. Studies have shown that insulin inhibits HBsAg expression in hepatocytes[19]. Moreover, the presence of insulin resistance-related diseases during entecavir treatment is associated with a slower decline in HBsAg expression[20]. Researchers have found that, while lovastatin is used to block the p21Ras signaling pathway of insulin, it also inhibits the secretion of HBsAg in Hep3B cells, which may be caused by the instability of lipid rafts due to the depletion of cholesterol from the membrane[21]. Therefore, it is reasonable to believe that changes in liver digestive function-related pathways are closely related to the progression of liver cancer.

PPI analysis showed that protein interactions were mainly concentrated among genes with *PCK1* and *SLC2A2* as the central nodes, and protein interactions were mainly concentrated among genes such as *FABP1*, *APOC3*, *SI*, *KRT20*, *SLC5A1*, *SLC10A2*, *RBP2*, and *AKR1B10*. Most of them are involved in the regulation of cellular insulin, glucocorticoids, glucagon, and other signaling pathways and play a key role in glucose metabolism and gluconeogenesis. The *PCK1* gene, encoding cytosolic phosphoenolpyruvate carboxykinase (PEPCK-C), functions as a glucoamylase in the liver and kidneys[22]. Studies have found that the type 2 diabetes phenotypes, such as obesity, fat malnutrition, fatty liver, and even death in serious circumstances, appear in mice after knockout of systemic and tissue-specific *PCK1* genes[23]. In this study, *PCK1* was highly expressed in liver cancer tissues (log2FC = 0.519299173). Considering that the 5hmC modification of *PCK1* may affect the transcription and translation of the PEPCK-C isoenzyme, it is necessary to verify the effect of 5hmC on its protein expression and explore the relationship between *PCK1* and the occurrence and development of liver cancer. *SLC2A2* is a membrane glycoprotein that encodes liver cells, pancreatic β cells, and intestinal and renal epithelial cells and mediates easy bidirectional glucose transport. Owing to its low affinity for glucose, it is a glucose sensor rather than the main transporter of glucose. This gene mutation is reportedly related to susceptibility to Fanconi–Bickel syndrome and non-insulin-dependent diabetes[24]. It participates in many processes, such as cell proliferation, differentiation, and apoptosis, by regulating glucose metabolism[25,26]. This study found that the 5hmC modification level of *SLC2A2* was slightly increased (log2FC = 0.297032232); however, whether the 5hmC modification affects the function of *SLC2A2* requires further confirmation. The valuable information obtained in the PPI network construction of liver cirrhosis and liver cancer groups is limited, and we can only infer that PROX1-TBX3 may have molecular interactions and a role in the progression of liver cirrhosis to liver cancer.

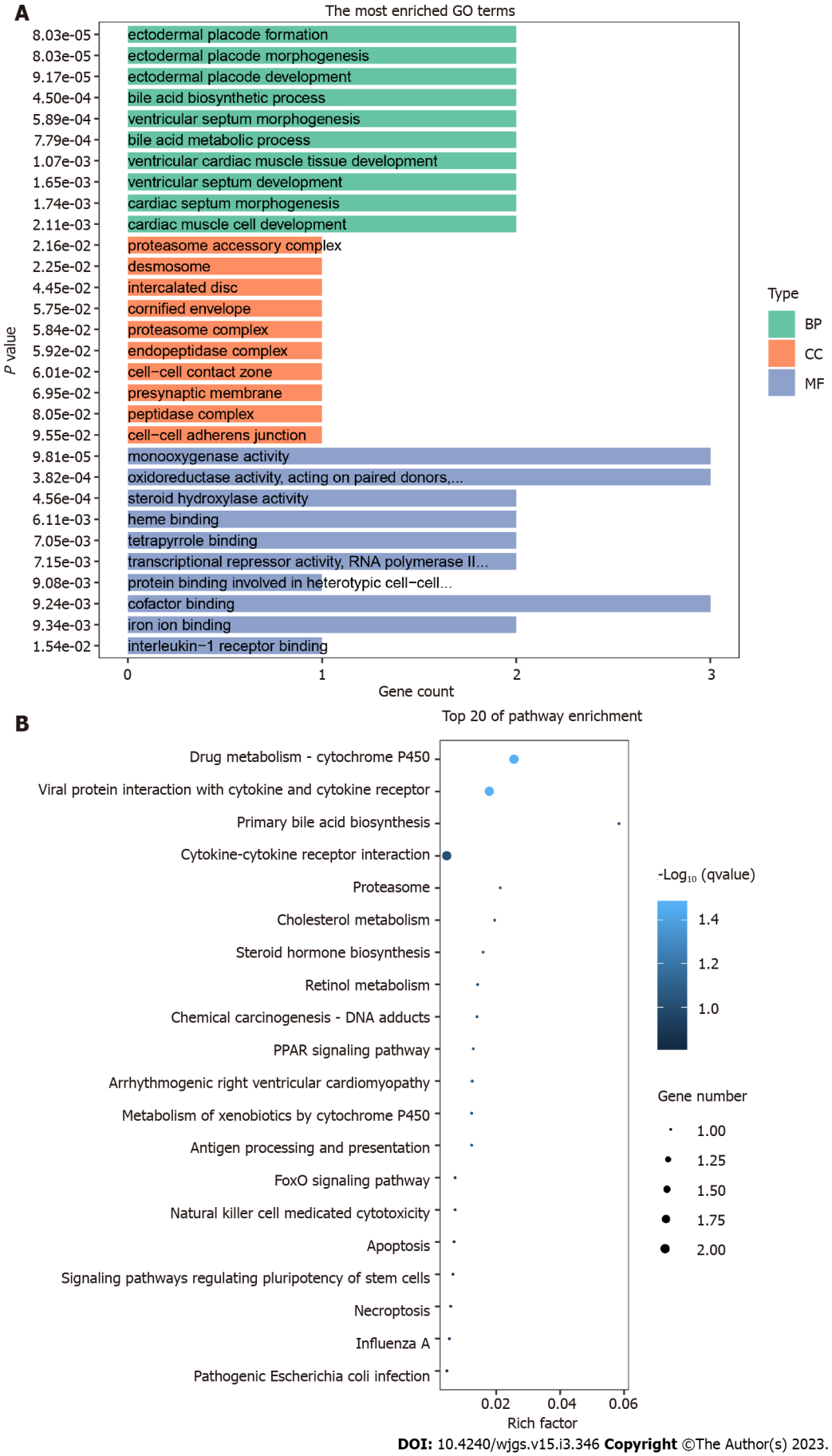

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Figure 4 Enrichment analysis results of 5-hydroxymethylcytosine sequencing differential genes between patients with liver cirrhosis and

those with liver cancer. A: Gene ontology enrichment analysis of 5-hydroxymethylcytosine (5hmC) sequencing differentially expressed genes (DEGs); B: Kyoto Encyclopedia of Genes and Genomes enrichment analysis of 5hmC sequencing DEGs. GO: Gene ontology; CC: Cellular component; BP: Biological process; MF: Molecular function.

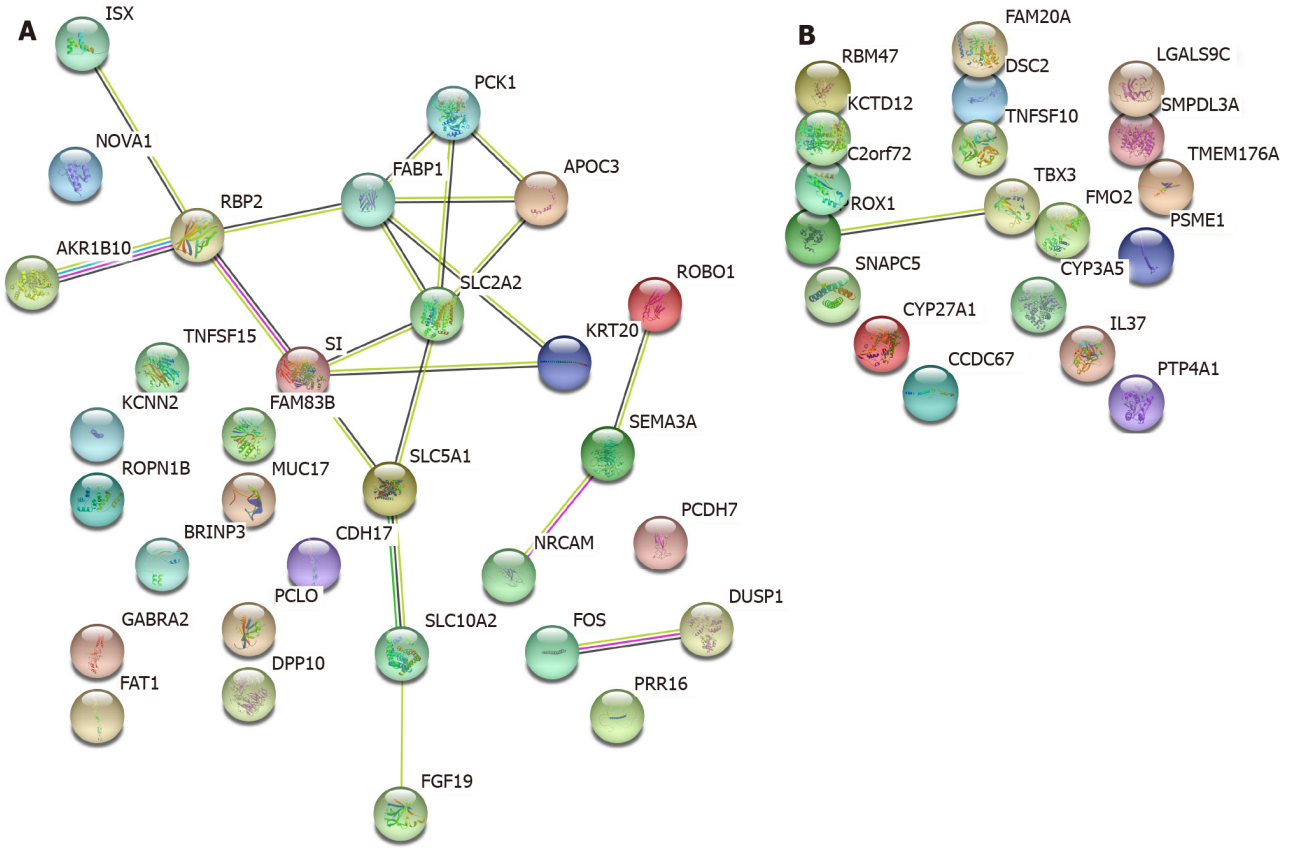

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Figure 5 Protein-protein interaction network analysis of differentially expressed genes. A: Protein-protein interaction (PPI) network of differentially expressed genes (DEGs) in hepatitis B surface antigen carriers and patients with liver cancer; B: PPI network of DEGs in patients with liver cirrhosis and those with liver cancer.

CONCLUSION

This study showed that the 5hmC modification of genes in the liver digestion-related pathway may be closely related to the occurrence and development of liver cancer. Abnormal bile and insulin secretion by tumor cells may promote or symbolize the occurrence and development of liver cancer. *SLC2A2* and *PCK1* are the central nodes of the DEGs, which may be most closely related to the occurrence of liver cancer. *FABP1*, *APOC3*, *SI*, *KRT20*, *SLC5A1*, *SLC10A2*, *RBP2*, and *AKR1B10* may be the key genes in the protein regulatory network. 5hmC modification of these genes alters their transcription and other functions and plays a regulatory role. These differences in the 5hmC modification levels of DEGs provide further insights into the development and progression of liver cancer. We plan to verify the 5hmC modification levels of these genes to further explore the mechanisms of liver cancer.

ARTICLE HIGHLIGHTS

Research background

As an important base in DNA demethylation, 5-hydroxymethylcytosine (5hmC) is also involved in epigenetic regulation, specifically in the assembly of chromosomes and the regulation of gene expression. However, the mechanism of action of 5hmC in hepatitis B surface antigen (HBsAg)-positive carriers and during the transition from cirrhosis to liver cancer remains unclear.

Research motivation
This study investigated the relationship between HBsAg-positive carriers, patients with cirrhosis, and patients with hepatocellular carcinoma using their serum samples and to identify potential genes and signaling pathways of DNA hydroxymethylation in order to understand the possible developmental mechanisms.

Research objectives
Using 5hmC sequencing technology, we analyzed the differentially expressed genes (DEGs) of HBsAg-positive carriers, patients with liver cirrhosis, and patients with liver cancer. The function of DEGs was further elucidated to explore the differences and similarities in gene hydroxymethylation and the regulatory role of signaling pathways in these groups.

Research methods
Using 5hmC DNA sequencing technology, we detected the expression profile of the samples, and the DEGs modified by DNA hydroxymethylation were screened. Bioinformatic analysis was used to enrich the DEGs.

Research results
The 5hmC DNA sequencing results showed that 30 genes were upregulated and 2 genes were downregulated in patients with hepatocellular carcinoma compared with HBsAg positive carriers. Further, 17 genes were upregulated and 3 genes were downregulated in hepatocellular carcinoma, compared with cirrhosis. Abnormal secretion of bile and insulin in tumor cells may promote or symbolize the occurrence and development of liver cancer. *SLC2A2* and *PCK1* are the central nodes of the differential genes, which may be most closely related to the occurrence of liver cancer. *FABP1*, *APOC3*, *SI*, *KRT20*, *SLC5A1*, *SLC10A2*, *RBP2*, and *AKR1B10* may be the key genes in the protein regulatory network that play a regulatory role through 5hmC modification.

Research conclusions
The occurrence and development of liver cancer are related to several 5hmC-modified pathway genes and metabolic pathways, which may be potential therapeutic targets to prevent the progression of liver cancer in hepatitis B carriers.

Research perspectives
The differences and similarities in gene hydroxymethylation in HBsAg positive carriers, patients with cirrhosis, and patients with liver cancer and the regulatory role of signaling pathways were revealed by 5hmC sequencing technology.

FOOTNOTES

Author contributions: Li YC and Hu WY conceived the experimental ideas; Hu WY and Li CH performed the data collection; Zhang LL, Xu XW, Li J and Luo HX completed data sorting and analysis; Li YC wrote this manuscript.

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

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

Data sharing statement: No additional data are available.

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Country/Territory of origin: China

ORCID number: Yue-Cui Li 0000-0002-3147-1724; Wei-Yue Hu 0000-0002-5266-7638; Cheng-Hang Li 0000-0001-9286-5375; Li-Li Zhang 0000-0002-5080-6091; Xiang-Wei Xu 0000-0003-1352-0294; Jin Li 0000-0003-3978-0086; Hong-Xia Luo

0000-0002-5378-3446.

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Retrospective Cohort Study

Compliance with enhanced recovery after surgery predicts long-term outcome after hepatectomy for cholangiocarcinoma

Chaowasaporn Jongkatkorn, Vor Luvira, Chalisa Suwanprinya, Kantaruthai Piampatipan, Natwutpong Leeratanakachorn, Theerawee Tipwaratorn, Attapol Titapun, Tharatip Srisuk, Suapa Theeragul, Apiwat Jarearnrat, Vasin Thanasukarn, Ake Pugkhem, Narong Khuntikeo, Chawalit Pairojkul, Supot Kamsa-Ard, Vajarabhongsa Bhudhisawasdi

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Chaowasaporn Jongkatkorn, Vor Luvira, Chalisa Suwanprinya, Kantaruthai Piampatipan, Theerawee Tipwaratorn, Attapol Titapun, Tharatip Srisuk, Suapa Theeragul, Apiwat Jarearnrat, Vasin Thanasukarn, Ake Pugkhem, Narong Khuntikeo, Vajarabhongsa Bhudhisawasdi, Department of Surgery, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand

Natwutpong Leeratanakachorn, Department of Surgery, Saraburi Hospital, Saraburi 18000, Thailand

Chawalit Pairojkul, Department of Pathology, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand

Supot Kamsa-Ard, Department of Epidemiology and Biostatistics, Faculty of Public Health, Khon Kaen University, Khon Kaen 40002, Thailand

Corresponding author: Vor Luvira, FRCS (Gen Surg), MD, Associate Professor, Doctor, Surgical Oncologist, Department of Surgery, Faculty of Medicine, Khon Kaen University, Mittraphap Road, Muang Khon Kaen, Khon Kaen 40002, Thailand. vor_110@yahoo.com

Abstract

BACKGROUND

Enhanced recovery after surgery (ERAS) program has been proved to improve postoperative outcome for many surgical procedures, including liver resection. There was limited evidence regarding the feasibility and benefit of ERAS in patients who underwent liver resection for cholangiocarcinoma.

AIM

To evaluate the feasibility of ERAS in patients who underwent liver resection for cholangiocarcinoma and its association with patient outcomes.

METHODS

We retrospectively analyzed 116 cholangiocarcinoma patients who underwent hepatectomy at Srinagarind Hospital, Khon Kaen University between January 2015 and December 2016. The primary outcome was the compliance with ERAS.

To determine the association between ERAS compliance and patient outcomes. the patients were categorized into those adhering more than and equal to 50% (ERAS ≥ 50), and below 50% (ERAS < 50) of all components. Details on type of surgical procedure, preoperative and postoperative care, tumor location, postoperative laboratory results, and survival time were evaluated. The compliance with ERAS was measured by the percentage of ERAS items achieved. The Kaplan-Meier curve was used for survival analysis.

RESULTS

The median percentage of ERAS goals achieved was 40% (± 12%). Fourteen patients (12.1%) were categorized into the ERAS ≥ 50 group, and 102 patients were in the ERAS < 50 group. Postoperative hospital stay was significantly shorter in the ERAS ≥ 50 group [8.9 d, 95% confidence interval (CI): 7.3-10.4 d] than in the ERAS < 50 group (13.7 d, 95%CI: 12.2-15.2 d) (P = 0.0217). No hepatobiliary-related complications or in-hospital mortality occurred in the ERAS ≥ 50 group. Overall survival was significantly higher in the ERAS ≥ 50 group. The median survival of the patients in the ERAS < 50 group was 1257 d (95%CI: 853.2-1660.8 d), whereas that of the patients in the ERAS ≥ 50 group was not reached.

CONCLUSION

Overall ERAS compliance for patients who underwent liver resection for cholangiocarcinoma is poor. Greater ERAS compliance could predict in-hospital, short-term, and long-term outcomes of the patients.

Key Words: Enhanced recovery program after surgery; Cholangiocarcinoma; Hepatectomy; Survival; Enhanced recovery after surgery; Outcome

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Core Tip: The present study is the first and the largest study demonstrating the enhanced recovery program after surgery (ERAS) compliance and its association with short-term and long-term outcomes of cholangiocarcinoma patients. This study demonstrated that overall ERAS compliance in patients who underwent liver resection for cholangiocarcinoma was poor. The patients with high ERAS compliance were significantly associated with shorter postoperative hospital stay, and, interestingly, longer overall survival.

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INTRODUCTION

Enhanced recovery after surgery (ERAS) program has been proven to be beneficial and become the standard of care in colorectal surgery. Over the years, it gains considerable momentum and has been implemented in other surgical specialties[1], even in emergency settings[2]. Since liver resection is a relatively complex surgery, with unique perioperative procedures and complications[3,4], ERAS in liver resection may be more difficult to implement and has different considerations from other abdominal operations. There are several recommendations and evidence supporting ERAS in liver resection procedures[5-7].

Despite a large amount of evidence supporting using ERAS in liver surgery, most of them did not focus specifically on liver resection for cholangiocarcinoma, which has several unique features including: (1) The requirement of anatomic major liver resection; (2) Being non-cirrhotic but having a tense liver from various degree of biliary obstruction; and (3) The requirement of biliary-enteric anastomosis in selected cases[8,9]. There was limited evidence regarding the feasibility and benefit of ERAS in patients who underwent hepatic resection for cholangiocarcinoma. Although the feasibility of applying ERAS in patients who underwent hepatic resection for cholangiocarcinoma has been demonstrated by Yip *et al*[10] and Quinn *et al*[8], the association between ERAS compliance and patient outcomes, both in short and long term, has not been reported. We, therefore, aimed to evaluate the feasibility of ERAS in patients who underwent hepatic resection for cholangiocarcinoma, and determine

its association with outcomes of the patients.

MATERIALS AND METHODS

Study population

All patients undergoing hepatic resection for cholangiocarcinoma at Srinagarind Hospital, Khon Kaen University (Khon Kaen, Thailand) between January 2015 and December 2016 were included in this comparative study. We retrospectively reviewed the prospectively maintained medical and pathological records of 116 patients with histologically-confirmed cholangiocarcinoma. During the study period, our team was aware of ERAS of all abdominal operations but did not fully implement a formal ERAS protocol for hepatobiliary surgery.

Preoperative preparation

All patients with radiologically diagnosed cholangiocarcinoma received a common preoperative protocol, which included: (1) Resectability evaluation by reviewing cross-sectional imaging and patient status. The criteria for resectability included: (a) Good performance status (ECOG 0-1); (b) Absence of distant organ or lymph node metastasis on preoperative imaging; and (c) Sufficient volume of expected future liver remnant; (2) Blood examination: Complete blood count, liver tests, coagulogram, hepatitis panels, and tumor markers; and (3) Preoperative biliary drainage of future liver remnants, either endoscopically or percutaneously, in patients with obstructive jaundice with the aim to reduce serum total bilirubin to below 10 mg/dL. All patients were admitted to the hospital at least one day before the operation. All clinical, laboratory, and radiological data were rechecked at the time of the admission.

Operative procedure

During the study period, we performed all liver resection by open surgery. Mirror-L incision was used in all cases. The type of liver resection was determined by the extent of the tumor, with plans to achieve at least all gross tumor removal. To optimize the surgical margin, surgeons preferred major hepatic resection to minor hepatic resection, which was performed only in patients with intraoperatively found limited future liver function. Liver parenchyma transection techniques and method of vascular inflow occlusion depended on the surgeon's preference. Biliary-enteric anastomosis, if needed, encompassed ante-colic hepatico-jejunostomy in all cases.

Postoperative care plan

After surgery, all patients were admitted to the intensive care unit until their conditions were stable and able to be extubated. Patients were allowed to be discharged from the hospital when they were on a full oral diet, received adequate pain controls, and demonstrated acceptable clinical and laboratory results. All patients were followed up in the hepatobiliary clinic with their respective attending surgeon at 2 wk after discharge.

ERAS compliance assessment

Adherence to ERAS components was recorded. During the study period, our hepatobiliary team had not fully implemented a formal ERAS protocol. Our protocol, as detailed in Table 1, contained 17 components, including preoperative counseling, preoperative fasting and preoperative carbohydrate load, pre-anesthetic anxiolytic, venous thromboembolism (VTE) prophylaxis, antimicrobial prophylaxis and skin preparation, prophylactic nasogastric intubation, preventing intraoperative hypothermia, fluid management, prophylactic abdominal drainage, early mobilization, postoperative glycemic control, preventing postoperative nausea and vomiting (PONV), multimodal analgesia, initial oral analgesic drug at postoperative day 1 (POD1), early nasogastric (NG) tube removal at POD 1, postoperative nutrition and early oral intake, and removal of urinary catheter at POD 2. Patients were then categorized into those who adhered to more than and equal to 50% (ERAS ≥ 50), and below 50% (ERAS < 50) of all ERAS components.

Data collection and statistical analysis

The primary outcome of this study was the compliance with ERAS, which was measured by the percentage of ERAS items achieved. We also investigated the association between the ERAS compliance and long-term outcomes of the patients. Descriptive analyses were performed and presented as appropriate. Continuous data were analyzed using student's *t*-test. Categorical data were compared using the Pearson χ^2 test. Survival analysis was presented using the Kaplan-Meier curve. Comparisons amongst groups were analyzed using a log-rank test. A *P*-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using STATA version 13 (Lakeway, TX, United States).

Table 1 Hepatic resection enhanced recovery program after surgery pathway

ERAS item	Goals
Preoperative counseling	Patients receive dedicated education, full care pathway, details of operation and associated complication, and estimated length of hospital stay with clear verbal and wriinstruction
Preoperative fasting and preoperative carbohydrates load	Preoperative fasting 6 h for solids and 2 h for liquids. Carbohydrate loading evening before the day of surgery and 2 h before induction of anesthesia
Pre-anesthetic anxiolytic	Short-acting anxiolytics prior to the induction of anesthesia
VTE prophylaxis	Low-molecular weight heparin or unfragmented heparin administration 2-12 h before surgery
Antimicrobial prophylaxis and skin preparation	Single dose intravenous antibiotics administration before skin incision and less than 1 h before hepatectomy
Prophylactic nasogastric intubation	No use of prophylactic nasogastric intubation
Preventing intraoperative hypothermia	Maintenance of perioperative normothermia using forced air blankets and controlling temperature of the operating room
Fluid management (CVP monitoring)	The maintenance of low CVP (below 5 cm H_2O) with close monitoring during liver transection phase
Prophylactic abdominal drainage	None or minimize the use of prophylactic abdominal drainage
Early mobilization	Begin to walk around the ward at least 3 times a day
Postoperative glycemic control	Insulin therapy to maintain normoglycemia before full oral intake
Preventing PONV	Patients should receive PONV prophylaxis with 2 anti-emetic drugs until POD3
Multimodal analgesia	Multimodal analgesia combined with wound infusion analgesia or intrathecal opiates. Removal of epidural analgesia before POD3
Initial oral analgesic drug at POD1	Initial oral analgesic drug at POD1
Early NG tube removal at POD1	Removal of NG tube at POD1 unless there was > 400 mL/d drainage
Postoperative nutrition and early oral intake	Patients can eat soft diet at POD2
Removal of urinary catheter POD2	Removal of urinary catheter POD2

VTE: Venous thromboembolism; POD: Postoperative day; ERAS: Enhanced recovery program after surgery; PONV: Postoperative nausea and vomiting; NG: Nasogastric; CVP: Central venous pressure.

Ethical consideration

The Institutional Review Board, Office of Human Research Ethics, Khon Kaen University reviewed and approved this study (No. HE611590).

RESULTS

There were 116 cholangiocarcinoma patients who underwent hepatic resection during the study period. The median age was 63 ± 9.5 years. Male patients outnumbered female patients (62.1% *vs* 37.9%). None of the patients achieved ERAS goal of at least 80%. The median percentage of ERAS goals achieved was 40% ± 12%. Only 14 patients (12.1%) achieved at least 50 percent of ERAS goal and were categorized into the ERAS ≥ 50 group. The remaining were categorized into the ERAS < 50 group. All of the patients of this cohort achieved goals in three components, including preoperative counseling, antimicrobial prophylaxis and skin preparation, and preventing intraoperative hypothermia. None of the patients achieved goals in preoperative fasting and preoperative carbohydrate load, avoiding NG intubation, avoiding abdominal drainage, and early mobilization. The ERAS items that had a difference in goal achievement between two groups included: Early removal of Foley catheter, early oral dietary intake, early NG tube removal, initiate oral analgesic drug, postoperative glycemic control, prevention of PONV, multimodal analgesia, VTE prophylaxis, pre-anesthetic anxiolytic, and fluid management, as detailed in Figure 1. There were no differences in patients' clinical and operative characteristics between groups, except for a higher percentage of male patients in the ERAS < 50 group (65.7% *vs* 35.7%, P = 0.03), and a higher proportion of intrahepatic tumor location (85.7% *vs* 39.2%, P = 0.027) and higher preoperative serum cholesterol level (P = 0.0445) in the ERAS ≥ 50 group (Table 2).

ERAS and postoperative outcome

The postoperative outcomes are shown in Table 3. There were no hepatobiliary related complications in

Table 2 Characteristics of the patients according to enhanced recovery program after surgery compliance

Variable	*n* (%) or mean (SD)				*P* value[1]
	ERAS < 50 (*n* = 102)		ERAS ≥ 50 (*n* = 14)		
Age	62.1	7.9	61.8	11.0	0.905
Gender (male)	67	65.7	5.0	35.7	0.031
Location					0.027
Intrahepatic	40	39.2	12.0	85.7	
Bismuth I	0	0.0	0.0	0.0	
Bismuth II	2	2.0	0.0	0.0	
Bismuth IIIA	38	37.3	1.0	7.1	
Bismuth IIIB	17	16.7	1.0	7.1	
Bismuth IV	5	4.9	0.0	0.0	
Type of CCA					0.442
MF	10	9.8	2.0	14.3	
PI/FN	31	30.4	2.0	14.3	
IG/PP	61	59.8	10.0	71.4	
Procedure					0.285
Right hepatectomy	38	37.3	9.0	64.3	
Extended right hepatectomy	18	17.7	0.0	0.0	
Right trisectionectomy	12	11.8	0.0	0.0	
Left hepatectomy	25	24.5	4.0	28.6	
Extended left hepatectomy	3	2.9	0.0	0.0	
Left trisectionectomy	2	2.0	0.0	0.0	
Other	4	3.9	1.0	7.1	
Vascular resection	7	6.9	1.0	7.1	0.969
Vascular inflow occlusion	39	38.2	7.0	50.0	0.399
EBL (mL)	647.1	490.5	446.4	273.5	0.138
Preoperative laboratory investigation					
TB	2.1	2.6	0.8	0.7	0.070
AST	365.9	359.0	215.8	122.7	0.139
ALT	253.6	250.6	166.0	96.0	0.216
ALP	141.3	106.0	84.8	39.4	0.060
Alb	2.8	0.7	3.0	0.6	0.257
Cholesterol	133.7	39.7	156.9	29.7	0.045

[1]$P < 0.05$ by chi squared or *t*-test where appropriate.

MF: Mass-forming; PI: Periductal infiltrating; FN: Flat-nodular; IG: Intraductal growth; PP: Papillary polypoid; ERAS: Enhanced recovery program after surgery; CCA: Cholangiocarcinoma; EBL: Estimated blood loss; TB: Total bilirubin; AST: Aspartate aminotransferase; ALT: Alanine transaminase; ALP: Alkaline phosphatase; Alb: Albumin.

the ERAS ≥ 50 group. Postoperative hospital stay was significantly shorter in the ERAS ≥ 50 group [8.9 d, 95% confidence interval (CI): 7.3-10.4 d] than in the ERAS < 50 group (13.7 d, 95%CI: 12.2-15.2 d) (P = 0.0217). There were no differences in postoperative laboratory results between the two groups, except for serum cholesterol level at POD3 and POD5.

There was no 30-d mortality in this cohort. There were three patients with 60-d mortality, all of which were in the ERAS < 50 group. The patients died on POD 21, 37, and 45 from bleeding aneurysm of right hepatic artery stump, severe pneumonia, and postoperative liver failure, respectively. With a median follow-time of 1241 d, the median survival of this cohort was 1302 d (95%CI: 1130.6-1473.4 d). There was

Table 3 Postoperative outcomes

Variable	*n* (%) or mean (95%CI)				*P* value[1]
	ERAS < 50 (*n* = 102)		ERAS ≥ 50 (*n* = 14)		
Overall morbidity	51	50.0%	4	28.6%	0.132
Hepatobiliary complications					0.281
Post-hepatectomy liver failure	14	13.7%	0	0%	
Bile leakage	4	3.9%	0	0%	
Stricture/cholangitis	1	0.9%	0	0%	
Transient hyperbilirubinemia	9	8.8%	0	0%	
General complications					
Wound complications	18	18.8%	0	0%	0.076
Pulmonary complications	9	8.8%	2	14.3%	0.513
Cardiac complication	5	4.9%	0	0%	0.397
Acute kidney injury	2	1.9%	0	0	0.597
Post-operative stay (d)	13.7	12.2-15.2	8.9	7.3-10.4	0.022
Cholesterol					
Postoperative day 1	131.5	123.9-138.9	151.1	141.2-160.9	0.057
Postoperative day 3	107.3	101.5-113.1	127.7	116.7-138.7	0.013
Postoperative day 5	96.6	90.8-102.5	118.1	109.1-127.2	0.009
Serum albumin					
Postoperative day 1	3.0	2.9-3.1	3.1	2.9-3.3	0.271
Postoperative day 3	2.9	2.8-2.9	3.0	2.9-3.2	0.224
Postoperative day 5	2.8	2.7-2.9	2.9	2.8-3.1	0.425
Total bilirubin					
Postoperative day 1	3.2	2.4-3.9	1.6	1.1-2.2	0.142
Postoperative day 3	2.7	2.1-3.4	1.4	0.9-2.0	0.171
Postoperative day 5	2.8	2.0-3.5	1.3	0.9-1.6	0.157
Alanine aminotransferase					
Postoperative day 1	294.9	242.6-347.2	231.1	166.9-295.3	0.376
Postoperative day 3	169.4	142.6-196.3	177.6	124.1-231.1	0.829
Postoperative day 5	89.7	74.5-104.9	97.1	72.5-121.8	0.726
Aspartate aminotransferase					
Postoperative day 1	386.5	323.4-449.7	285.2	196.4-373.9	0.247
Postoperative day 3	169.4	142.6-196.3	177.6	124.1-231.1	0.829
Postoperative day 5	89.7	74.5-104.9	97.1	72.5-121.8	0.726
International normalized ratio (PT/INR)					
Postoperative day 1	1.27	1.2-1.35	1.27	1.18-1.35	0.939
Postoperative day 3	1.42	1.37-1.47	1.34	1.24-1.45	0.293
Postoperative day 5	1.39	1.3-1.49	1.26	1.17 -1.35	0.295
Postoperative mortality					
30 d	0	0%	0	0%	
60 d	3	2.9%	0	0%	
Survival (95%CI)					0.019

Median (d)	1257	853.2-1660.8	Not reached	
1-yr survival	77.5%	63.1-89.1	100%	
3-yr survival	50.9%	37.1-67.9	85.7	53.9-96.2

[1]*P* < 0.05 by chi squared or t-test where appropriate.
ERAS: Enhanced recovery program after surgery; CI: Confidence interval; PT: Prothrombin time; INR: International normalized ratio.

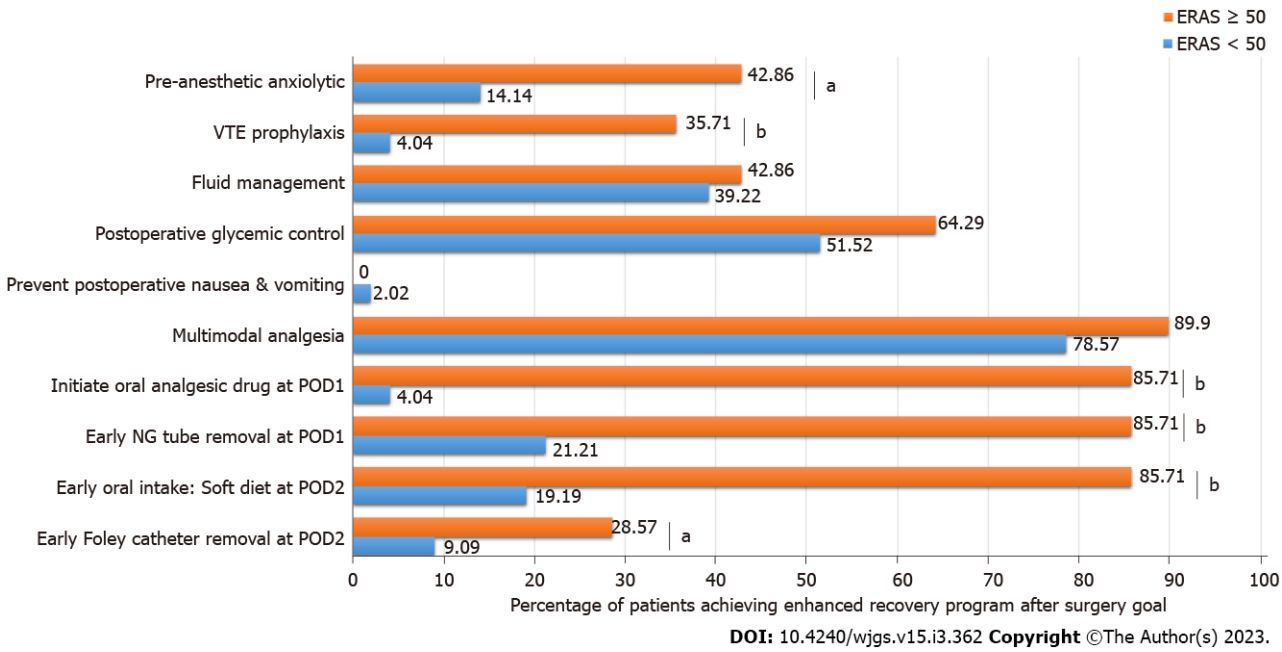

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Figure 1 Comparison of enhanced recovery program after surgery compliance between enhanced recovery program after surgery ≥ 50 and enhanced recovery program after surgery < 50 groups. The numbers indicate the percentage of patients achieving enhanced recovery program after surgery goal in each component. [a]*P* < 0.05, [b]*P* < 0.001. VTE: Venous thromboembolism; POD: Postoperative day ERAS: Enhanced recovery program after surgery.

a statistically significant difference in overall survival between the two groups (*P* = 0.0187) (Figure 2A). The median survival of the patients in the ERAS < 50 group was 1257 d (95%CI: 853.2-1660.8 d), whereas that of the patients in the ERAS ≥ 50 group was not reached - more than 50% of the patient with ERAS ≥ 50 were still alive at the time of the last follow-up. The respective 1- and 3-year survival rate of the patients in the ERAS < 50 was 77.5% (95%CI: 63.1-89.1) and 50.9% (95%CI: 37.1-67.9), and that of the patients in the ERAS ≥ 50 group was 100% and 85.7% (95%CI: 53.9-96.2). The survival between the groups seem to differ in both intrahepatic (Figure 2B) and extrahepatic tumors (Figure 2C), but the difference was not statistically significant.

DISCUSSION

This study demonstrated that overall ERAS compliance in patients who underwent liver resection for cholangiocarcinoma was poor. The patients with ERAS ≥ 50 were significantly associated with shorter postoperative hospital stay, and, interestingly, longer overall survival.

Postoperative care for liver resection has many unique challenges that have a large impact on the physiologic outcomes, such as having a large abdominal incision that requires the use of spinal anesthesia, significant intraoperative hemodynamic disturbance, and having a decreased liver volume postoperatively. These factors explain why overall ERAS compliance is lower compared to other abdominal operations, despite the fact that this group of patients might gain the most benefit from ERAS implementation. We initially intended to use 80% ERAS adherence as the cut point for categorizing the patients. However, at the time of the study, there was poor compliance to the ERAS protocol and none of the cases were able to achieve more than 80% of ERAS components. Consequently, a cut point at 50% ERAS was used instead. In the future, when ERAS is more routinely adopted, a higher cut point for components achieved may result in more tiers and more pronounced difference in patient outcomes. It should be noted that some ERAS components might not be suitable for cholangiocarcinoma resection, including the omission of nasogastric tube and abdominal drainage[8]. In our

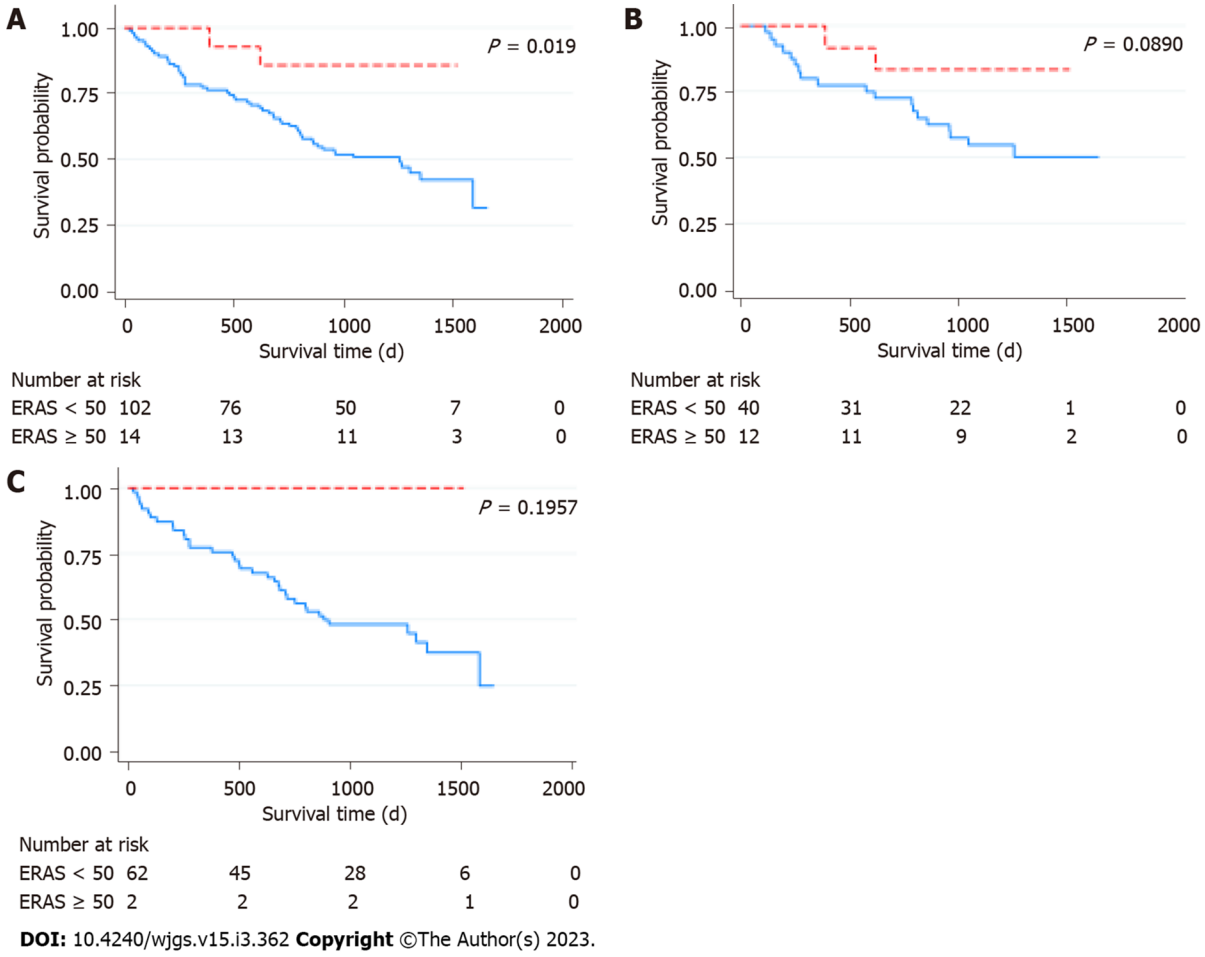

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Figure 2 Kaplan-Meier survival curves stratified by percentage of enhanced recovery program after surgery goal achievement. A: All cohort; B: Intrahepatic cholangiocarcinoma; C: Extrahepatic cholangiocarcinoma. ERAS: Enhanced recovery program after surgery.

study, none of the patients achieved these component goals. Gastric dilation during the operation would preclude a good exposure of the operative field. Liver transection created a large raw surface of the liver that could cause postoperative bleeding and bile collection, therefore placement of abdominal drainage is almost unavoidable. Instead, several intraoperative manners should be further evaluated and considered to be ERAS components, such as intraoperative vascular inflow occlusion, controlling of central venous pressure, and inferior vena cava clamping[9,11]. These make liver transection safer, and would enhance patient recovery. We found that ERAS components that showed difference in compliance between the groups were mostly related to analgesic and dietary-related components. This finding is compatible with a previous study[12]. These components could be modified easily without any additional costs, and should be prioritized for implementation. Effective pain management might be a key to successfully enhancing recovery after liver resection. Lower postoperative pain, incorporated with early removal of Foley catheter, leads to early mobilization and, subsequently, early returns of bowel movement[8]. The delayed oral intake in the patients with extrahepatic cholangiocarcinoma, who require biliary-enteric anastomosis, preclude enhanced recovery. This leads to several delays, including oral analgesia, NG tube removal, mobilization, and, ultimately, recovery. This explains why we found a higher proportion of extrahepatic cholangiocarcinoma in the ERAS < 50 group. Improvement of ERAS for liver resection is crucial. Since a number of cases are required for achieving the optimal recovery and compliance[13], the large center with a high number of cholangiocarcinoma cases should be the initiator of ERAS development. Since 2016, we have been able to consistently apply these ERAS components: Pre-anesthetic anxiolytic, VTE prophylaxis, preventing intraoperative hypothermia, preventing PONV, early NG tube removal at POD1, and early oral intake. Moreover, we started to perform minimally invasive surgery for liver resection procedure.

Another way in which operative outcomes could be improved is through laparoscopic surgery, as previous studies have shown that laparoscopic liver resection is associated with shorter length of stay [14]. Therefore, ERAS in laparoscopic liver resection should be considered separately from open liver resection. Since laparoscopic liver resection is typically performed in selected patients that require less complicate operative procedure, our study was intentionally conducted when all cholangiocarcinoma cases, at our center, received open resection in order to minimize selection bias.

Recent evidence from other randomized controlled trials reaffirmed that the ERAS protocol for patients who underwent liver resection was associated with decreased length of hospital stay and lower overall morbidity[15-17]. Our study confirmed that these findings are also valid in cholangiocarcinoma patients. We found that the patients with higher ERAS compliance had significantly shorter length of hospital stay. This is comparable with a previous report, which stated that patients undergoing major liver resection that were on ERAS protocol experienced the greatest benefit in terms of decreased length of hospital stay and decreased rate of 30-d complications[12]. Alteration of postoperative liver tests could be used as an indicator for liver recovery and risk of postoperative liver failure[4]. In our study, the postoperative serum cholesterol level was significantly higher in the ERAS ≥ 50 group. It might indirectly indicate that liver recovery is faster in this group. Other explanations include: (1) The patients in this group already had higher cholesterol level preoperatively; and (2) Higher proportion of intrahepatic tumors, which require less extensive liver resection. None of our patients in the ERAS ≥ 50 group experienced hepatobiliary-related complications. There might be synergistic effects between absence of complications and achieving ERAS goals. Both of them promote patient recovery and, ultimately, shorten length of hospital stay. One study reported that even in high risk or with major postoperative complications, high ERAS compliance was achievable[8]. However, it is safe to say that achievement of ERAS ≥ 50 can be used to predict in-hospital, postoperative hepatobiliary-related complications, especially postoperative liver failure.

Although ERAS protocol has been proven to be beneficial amongst patients who underwent liver resection in terms of short-term outcomes[6,7,12], there was no study demonstrating these associations with long-term outcomes. We demonstrated the association between higher ERAS achieving and longer survival of the patients. This issue had been addressed in other cancers[18,19]. ERAS improved survival through various ways: (1) Reduction of postoperative stress leads to better immunologic function against the remaining tumor micro-metastases; and (2) Promoting quick recovery prevents the delay of adjuvant treatment. However, since there is no solid evidence of benefit of postoperative adjuvant chemotherapy for resectable cholangiocarcinoma[20-22], and cholangiocarcinoma is a heterogeneous disease with various progression pathways[23,24], it could not be concluded that improvement of ERAS compliance leads to an improvement of overall survival of cholangiocarcinoma patients. Even so, higher ERAS achievement could at least be used as a marker of better survival of cholangiocarcinoma patients.

To the best of our knowledge, our study was the first to demonstrate the association between greater ERAS achievement and long-term outcome of the patients who underwent liver resection. Moreover, this study was the largest study that focused only on cholangiocarcinoma patients who underwent liver resection by various hepatobiliary surgeons. However, there were several limitations that should be acknowledged. Bias might be introduced due to the following: (1) Being retrospective in nature; (2) Having a short interval of study period when a standard, full-ERAS protocol has not completely been developed. Due to the aforementioned limitations, only a correlation between better ERAS compliance and better outcome can be drawn; we were unable to interpret that better ERAS achievement caused better outcome; and (3) The sample size of the ERAS ≥ 50 group is quite small and could cause a significant type 2 error. Future prospective study should be conducted with full implementation of ERAS protocol specifically for the cholangiocarcinoma patients to demonstrate this association.

CONCLUSION

Overall ERAS compliance for cholangiocarcinoma is poor. There is a room for improvements of ERAS in patients who underwent liver resection for cholangiocarcinoma. Greater ERAS compliance could predict not only in-hospital, short-term outcomes but also long-term outcomes of the patients.

ARTICLE HIGHLIGHTS

Research background

Enhanced recovery after surgery (ERAS) protocol has shown to be beneficial to patient outcomes in various abdominal surgeries, including hepatectomy. However, no previous study has demonstrated this association for hepatectomy in cholangiocarcinoma patients.

Research motivation

The present study explored the ERAS compliance and its association with outcomes of the patients who underwent open liver resection for cholangiocarcinoma during the first period of ERAS implementation.

Research objectives

To demonstrate the association between good ERAS compliance and short-term and long-term outcomes in cholangiocarcinoma patients.

Research methods

Cholangiocarcinoma patients who underwent open hepatectomy between January 2015 and December 2016 were retrospectively analyzed. Patient's compliance to ERAS was measured by the percentage of ERAS items achieved and categorized into more than and equal to 50% (ERAS ≥ 50), and below 50% (ERAS < 50) of of all ERAS components. Details on operative procedure, patient care, and survival were analyzed.

Research results

A total of 116 patients were identified - 14 patients (12.1%) were categorized into the ERAS ≥ 50 group, and 102 patients were in the ERAS < 50 group. Postoperative hospital stay was significantly shorter in the ERAS ≥ 50 group [8.9 d, 95% confidence interval (CI): 7.3-10.4 d] than in the ERAS < 50 group (13.7 d, 95%CI: 12.2-15.2 d) (P = 0.0217). No hepatobiliary-related complications or in-hospital mortality occurred in the ERAS ≥ 50 group. Overall survival was significantly higher in the ERAS ≥ 50 group.

Research conclusions

Good ERAS compliance is associated with decreased length of hospital stay, decreased morbidity, and better survival.

Research perspectives

Current overall ERAS compliance is poor. Future improvements in ERAS compliance could result in better short-term and long-term outcomes.

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FOOTNOTES

Author contributions: All the authors contributed to this paper.

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Country/Territory of origin: Thailand

ORCID number: Vor Luvira 0000-0001-7333-2936; Ake Pugkhem 0000-0002-0882-9740; Narong Khuntikeo 0000-0001-9305-0688.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Pain management in patients with hepatocellular carcinoma after transcatheter arterial chemoembolisation: A retrospective study

Yan Guan, Ye Tian, Ya-Wei Fan

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Yan Guan, Ye Tian, Ya-Wei Fan, Hepatic Surgery Center, Department of Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, Hubei Province, China

Corresponding author: Ya-Wei Fan, MD, Nurse, Hepatic Surgery Center, Department of Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, No. 116 Zhuodaoquan South Road, Hongshan District, Wuhan 430030, Hubei Province, China. fanyaweitj2022@163.com

Abstract

BACKGROUND

Pain after transcatheter arterial chemoembolisation (TACE) can seriously affect the prognosis of patients and the insertion of additional medical resources.

AIM

To develop an early warning model for predicting pain after TACE to enable the implementation of preventive analgesic measures.

METHODS

We retrospectively collected the clinical data of 857 patients (from January 2016 to January 2020) and prospectively enrolled 368 patients (from February 2020 to October 2022; as verification cohort) with hepatocellular carcinoma (HCC) who received TACE in the Hepatic Surgery Center of Tongji Hospital. Five predictive models were established using machine learning algorithms, namely, random forest model (RFM), support vector machine model, artificial neural network model, naive Bayes model and decision tree model. The efficacy of these models in predicting postoperative pain was evaluated through receiver operating characteristic curve analysis, decision curve analysis and clinical impact curve analysis.

RESULTS

A total of 24 candidate variables were included in the predictive models using the iterative algorithms. Age, preoperative pain, number of embolised tumours, distance from the liver capsule, dosage of iodised oil and preoperative prothrombin activity were closely associated with postoperative pain. The accuracy of the predictive model was compared between the training [area under the curve (AUC) = 0.798; 95% confidence interval (CI): 0.745-0.851] and verification (AUC = 0.871; 95%CI: 0.818-0.924) cohorts, with RFM having the best

predictive efficiency (training cohort: AUC = 0.869, 95%CI: 0.816-0.922; internal verification cohort: AUC = 0.871; 95%CI: 0.818-0.924).

CONCLUSION

The five predictive models based on advanced machine learning algorithms, especially RFM, can accurately predict the risk of pain after TACE in patients with HCC. RFM can be used to assess the risk of pain for facilitating preventive treatment and improving the prognosis.

Key Words: Hepatocellular carcinoma; Transcatheter arterial chemoembolization; Pain; Machine learning algorithm; Prediction

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Core Tip: Machine learning-based pre-warning models can be used to predict post-transcatheter arterial chemoembolisation (TACE) pain for hierarchical management of patients at high risk of moderate and severe pain after TACE. In particular, random forest model (RFM) combined with preoperative predictors (*i.e.,* age, preoperative pain, distance from liver capsule ≤ 2 cm, prothrombin activity, iodine oil dose and increased number of emboli) has optimal discriminating power and high predictive accuracy. Therefore, RFM can be used for early prediction of the risk of pain, which can facilitate prompt pain management after TACE and improve the prognosis of patients.

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INTRODUCTION

As a first-line treatment for patients with mid-stage hepatocellular carcinoma (HCC), transcatheter arterial chemoembolisation (TACE) is especially suitable for patients with multifocal HCC who are not eligible for radical treatment[1,2]. Compared with the classic supportive treatment, TACE can significantly improve the quality of life and prolong the survival time of patients[3]. However, because TACE can block the blood supply of main blood vessels and lead to local liver tissue swelling and tumour necrosis, most patients experience pain of varying intensity after receiving TACE[4]. Previous studies have shown that the incidence of pain in patients with HCC after TACE is 60%-80%, and approximately 20%-40% of patients have severe pain, prolonged bed rest time and increased likelihood of postoperative complications, resulting in increased medical costs[5-7]. Therefore, prompt and effective pain management and nursing care are of great significance for improving the prognosis and quality of life of patients receiving TACE.

Early pain management can not only significantly reduce the incidence of pain but also improve the quality of life of patients receiving TACE. Therefore, identifying predictive factors related to postoperative pain may help to assess the risk of pain after TACE to implement pain relief interventions in advance[8]. Previous studies have shown that age, portal vein tumour thrombosis and tumour diameter are associated with an increased risk of pain after TACE[9]. In addition, preoperative anxiety, depression and other psychological factors can promote postoperative pain[10,11]. However, no effective scoring strategy is available for evaluating the risk of pain in patients with HCC after TACE. Developing such strategies may facilitate hierarchical management of patients with HCC with different degrees of pain.

In recent years, scholars have constructed nomographs for quantitative scoring by integrating multi-dimensional pain-related variables. Nomographs are based on traditional logic algorithms, which can help to indicate the risk of pain in patients with HCC receiving TACE[9]. However, with the continuous innovation and improvement of machine learning algorithms, several advanced algorithms have been gradually applied to the medical field for improving the accuracy and robustness of risk stratification [12-14]. To the best of our knowledge, an early warning model integrating machine learning algorithms and clinical indicators of post-TACE pain has not yet been developed for the management of pain in patients with HCC. Therefore, in this study, we constructed a machine learning-based model to predict post-TACE pain for early identification and prompt treatment of high-risk patients in clinical settings.

MATERIALS AND METHODS

Study population

We retrospectively included 857 patients with HCC who received TACE in the Hepatic Surgery Center of Tongji Hospital from January 2016 to January 2020 through the electronic record system of the hospital. Additionally, we prospectively included 368 patients with HCC who underwent TACE in the hospital from February 2020 to October 2022 as the external verification cohort. The inclusion criteria were as follows: (1) Patients aged > 18 years; (2) Patients diagnosed with HCC *via* histopathological examination; (3) Patients receiving traditional TACE; and (4) The patients received corticosteorids as part of the protocol and the pain-management protocols has not changed between 2016 and 2022. The exclusion criteria were as follows: (1) Patients with incomplete medical records; and (2) Patients who underwent other surgeries and those with long-term use of painkillers before surgery. This study was approved by the Ethics Committee of Tongji Hospital, Tongji Medical College, and Huazhong University of Science and Technology and complies with the Declaration of Helsinki (2013 version). All patients with HCC who participated in this study signed an informed consent form. Figure 1 demonstrates the process of patient selection and construction of predictive models.

Selection of predictive factors

We retrospectively collected the perioperative clinical data of patients: (1) Demographic data, including age, sex and body mass index; (2) History of TACE and hepatobiliary surgery; (3) Relevant preoperative imaging data, including maximum tumour diameter, number of embolised tumours, location of embolised tumours, portal vein tumour thrombosis and distance from the liver capsule; (4) Surgery-related data, including preoperative pain (PrP) perception, Child-Pugh classification, surgical duration, use of embolic supplement (except for iodised oil, gelatin sponge, blank microspheres, polyvinyl alcohol and other granular embolic agents) and iodised oil dosage; and (5) Preoperative biochemical data, including the levels of albumin, total bilirubin, alanine aminotransferase and aspartate aminotransferase; prothrombin time; prothrombin activity and platelet count. The quality control standards for retrospective data were as follows: Variables with missing data in ≤ 5% of the total number of cases were considered for inclusion in the analysis (the missing value is filled in using median interpolation); however, those with missing data in > 5% of cases were excluded to avoid bias caused by filling the missing value.

Evaluation criteria for postoperative pain intensity

The intensity of postoperative pain was evaluated by trained professionals using the numeric rating scale. The subjective feelings of patients were considered the main observation index. Patients were evaluated every 2 h after receiving TACE and scored as follows: 0 points, no pain; 1-3 points, mild pain; 4-6, moderate pain; 7-10, severe pain. Patients with scores of ≥ 4 points are identified as having moderate and severe pain, and opioids should be considered for analgesic treatment. We considered moderate and severe pain within 24 h after surgery as the outcome variables. Patients with pain scores of ≥ 4 points within 24 h of surgery were included in the pain group, whereas those with < 4 points were included in the non-pain group.

Establishment of predictive models for post-TACE pain

Five common machine learning algorithms were used to develop predictive models: Random forest model (RFM), support vector machine model (SVMM), artificial neural network model (ANNM), decision tree model (DTM) and naive Bayes model (NBM). The efficacy of these models in predicting postoperative pain was evaluated through receiver operating characteristic analysis and decision curve analysis (DCA). In addition, continuous correction curves were plotted to evaluate the robustness of predictive models, and clinical impact curves (CICs) were plotted to evaluate the differentiation efficiency of the optimal predictive model (RFM). All predictive models were tested in the internal training, internal verification and external verification cohorts.

Statistical analysis

Statistical analysis was performed using the R software (https://www.r-project.org/). For descriptive analysis, the median (interquartile range) and frequency (%) of continuous variables and categorical variables were evaluated, respectively. Pearson correlation coefficients were evaluated to measure the degree of correlation between variables, and least absolute shrinkage and selection operator (LASSO) regression was performed for selecting significant variables for models. For variable screening and inter-group comparison (pain *vs* non-pain group), *P*-values of < 0.05 were considered significant.

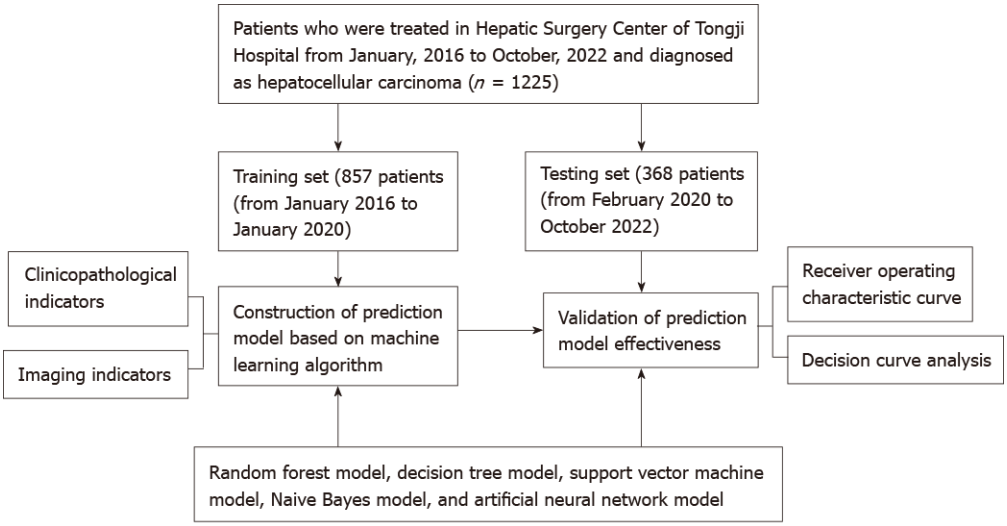

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Figure 1 Flow chart of patient inclusion and prediction model construction.

RESULTS

Baseline characteristics of patients with or without postoperative pain

Patients were divided into pain and non-pain groups based on whether they had moderate or severe pain within 24 h of TACE. Among 1225 patients, 205 (16.73%) had pain after TACE. The cumulative incidence of moderate and severe post-TACE pain at < 6 h, 6-12 h and 12-24 h after TACE was 15.12%, 17.26% and 13.15%, respectively, in the training cohort, and 14.86%, 18.26% and 15.11%, respectively, in the external verification cohort.

On comparing the baseline data of patients with HCC between the pain and non-pain groups, significant differences ($P < 0.05$) were observed in age, PrP, maximum tumour diameter, number of embolised tumours (NOETs), distance from the liver capsule (DFLS), use of embolic supplements and dosage of iodised oil. On comparison of biochemical indicators, post-TACE pain was found to be significantly associated with prothrombin activity and platelet count ($P < 0.05$). The detailed baseline data of the two groups are summarised in Table 1.

Selection of predictors of postoperative pain

According to the distribution of Pearson correlation coefficients, postoperative pain was considered an 'outcome variable', and its correlation with 24 candidate variables was examined (Figure 2A). Postoperative pain was significantly correlated with age, PrP, NOET, DFLS, dosage of iodised oil (LOD) and preoperative prothrombin activity (PTA). Similarly, LASSO regression was used to determine the optimal penalty coefficient (Figures 2B and 2C) to screen for candidate variables for the predictive models. For four models, age, PrP, NOET, DFLS, LOD and PTA were identified as significant predictive factors, which was consistent with the results obtained by generalized linear modelthrough univariate and multivariate logistic regression analyses (Figure 2D). Altogether, these results indicate that age, PrP, NOET, DFLS, LOD and PTA can efficiently predict postoperative pain in patients with HCC.

Construction of predictive models for postoperative pain

RFM and DTM were constructed based on the principle of 'branching' to discriminate and classify each included variable (Figure 3 and Supplementary Table 1). Age, PrP, NOET, DFLS, LOD and PTA were the major variables included in RFM, whereas the 'branch' variable in the decision tree included only PTA and DFLS. In addition, ANNM was constructed based on the algorithms of the 'input layer', 'hidden layer' and 'output layer' (Figure 4). After iteration of the input and hidden layers, age, tumour size and pathological type could accurately stratify the pain risk. Consistent with the candidate variables included in ANNM, SVMM was based on a class of generalised linear classifiers that categorise data in a binary way according to supervised learning, which can convert the problem into a convex quadratic programming problem. Furthermore, age, NOET, DLFS, LOD and PTA were the major variables included in NBM. These results suggest that predictive models of postoperative pain can be developed using the abovementioned variables, and the contribution of the intersecting variables among these models cannot be ignored.

Effectiveness of the five predictive models

DCA was performed to evaluate the differentiation efficiency and robustness of the five predictive

Table 1 Baseline demographic and clinicopathological characteristics of patients with hepatocellular carcinoma

Variables	Training set			*P* value	Testing set
	Overall (*n* = 857)	Pain (*n* = 139)	No-pain (*n* = 718)		Overall (*n* = 368)
Age (%), yr					
≤ 50	199 (23.2)	119 (85.6)	80 (11.1)	< 0.001	86 (23.4)
> 50	658 (76.8)	20 (14.4)	638 (88.9)		282 (76.6)
Gender (%)					
Male	445 (51.9)	74 (53.2)	371 (51.7)	0.806	151 (41.0)
Female	412 (48.1)	65 (46.8)	347 (48.3)		217 (59.0)
BMI [median (IQR)], kg/m^2	24.00 (21.10, 27.10)	23.70 (21.10, 27.45)	24.00 (21.02, 27.08)	0.658	24.00 (21.20, 26.70)
Pathogeny (%)					
Hepatitis B	218 (25.4)	31 (22.3)	187 (26.0)	0.089	104 (28.3)
HCV	226 (26.4)	28 (20.1)	198 (27.6)		88 (23.9)
Alcoholic liver	214 (25.0)	39 (28.1)	175 (24.4)		95 (25.8)
Others	199 (23.2)	41 (29.5)	158 (22.0)		81 (22.0)
ECOG (%)					
0	417 (48.7)	63 (45.3)	354 (49.3)	0.443	187 (50.8)
1	440 (51.3)	76 (54.7)	364 (50.7)		181 (49.2)
TACE (%)					
Yes	445 (51.9)	70 (50.4)	375 (52.2)	0.756	169 (45.9)
No	412 (48.1)	69 (49.6)	343 (47.8)		199 (54.1)
HHS (%)					
Yes	414 (48.3)	73 (52.5)	341 (47.5)	0.321	195 (53.0)
No	443 (51.7)	66 (47.5)	377 (52.5)		173 (47.0)
PrP (%)					
Yes	204 (23.8)	130 (93.5)	74 (10.3)	< 0.001	91 (24.7)
No	653 (76.2)	9 (6.5)	644 (89.7)		277 (75.3)
MDT (%), cm					
≤ 10	416 (48.5)	76 (54.7)	340 (47.4)	0.137	193 (52.4)
> 10	441 (51.5)	63 (45.3)	378 (52.6)		175 (47.6)
LOET (%)					
Left	437 (51.0)	80 (57.6)	357 (49.7)	0.11	189 (51.4)
Right	420 (49.0)	59 (42.4)	361 (50.3)		179 (48.6)
NOET (%)					
Single	683 (79.7)	21 (15.1)	662 (92.2)	< 0.001	280 (76.1)
Multiple	174 (20.3)	118 (84.9)	56 (7.8)		88 (23.9)
PVTT (%)					
Yes	438 (51.1)	72 (51.8)	366 (51.0)	0.932	185 (50.3)
No	419 (48.9)	67 (48.2)	352 (49.0)		183 (49.7)
DFLS (%), cm					
> 2	646 (75.4)	16 (11.5)	630 (87.7)	< 0.001	268 (72.8)
≤ 2	211 (24.6)	123 (88.5)	88 (12.3)		100 (27.2)
CTPG (%)					

Grade A	442 (51.6)	75 (54.0)	367 (51.1)	0.602	176 (47.8)
Grade B	415 (48.4)	64 (46.0)	351 (48.9)		192 (52.2)
OpD (%), h					
≤ 1	452 (52.7)	83 (59.7)	369 (51.4)	0.088	184 (50.0)
> 1	405 (47.3)	56 (40.3)	349 (48.6)		184 (50.0)
ES (%)					
Yes	437 (51.0)	72 (51.8)	365 (50.8)	0.908	187 (50.8)
No	420 (49.0)	67 (48.2)	353 (49.2)		181 (49.2)
LOD (%), mL					
≤ 10	630 (73.5)	21 (15.1)	609 (84.8)	< 0.001	260 (70.7)
> 10	227 (26.5)	118 (84.9)	109 (15.2)		108 (29.3)
Albumin [median (IQR)], g/L	36.12 (33.45, 38.63)	36.11 (33.50, 38.81)	36.12 (33.43, 38.57)	0.688	36.03 (33.42, 38.73)
PT [median (IQR)], s	12.70 (12.30, 13.20)	12.60 (12.30, 13.10)	12.70 (12.30, 13.20)	0.559	12.70 (12.30, 13.10)
PTA [median (IQR)], %	82.25 (77.12, 86.60)	90.20 (87.26, 93.18)	80.33 (76.45, 84.36)	< 0.001	82.29 (77.81, 86.83)
TBIL [median (IQR)], g/L	16.17 (12.95, 19.37)	16.20 (13.34, 19.27)	16.16 (12.88, 19.39)	0.972	16.12 (13.25, 19.23)
ALT [median (IQR)], U/L	33.00 (27.00, 40.00)	34.00 (24.50, 40.00)	33.00 (27.00, 40.75)	0.446	34.00 (26.00, 41.00)
AST [median (IQR)], U/L	42.00 (35.00, 48.00)	44.00 (35.00, 49.00)	41.00 (35.00, 48.00)	0.091	42.00 (34.00, 48.25)
PLT [median (IQR)], 10^9	136.00 (104.00, 163.00)	138.00 (104.00, 160.00)	135.50 (104.00, 164.00)	0.749	130.50 (100.00, 160.25)

IQR: Interquartile range; BMI: Body mass index; ECOG: Eastern cooperative oncology group; HHS: History of hepatobiliary surgery; PrP: Preoperative_pain; MTD: Maximum tumor diameter; LOET: Location of embolized tumor; NOET: Number of embolized tumors; PVTT: Portal vein tumor thrombus; DFLS: Distance from liver capsule; CTBG: Child-pugh grade; OpD: Operation_duration; ES: Embolization supplement; LOD: Iodine oil dosage; PT: Prothrombin time; PTA: Prothrombin activity; TBIL: Total bilirubin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; PLT: Platelet count.

models. The predictive efficiency of RFM was most optimal, followed by DTM. The predictive efficiency of ANNM and SVMM was better than that of NBM (Figure 5). The area under the curve (AUC) values of RFM were 0.869 [95% confidence interval (CI): 0.816-0.922) and 0.871 (95%CI: 0.818-0.924) in the training and internal verification sets, respectively. Additionally, the prediction accuracy of DTM, ANNM, SVMM, and NBM in the training cohort was between (AUC = 0.798; 95%CI: 0.745-0.851) and (AUC = 0.871; 95%CI: 0.818-0.924) (Table 2). These results indicate that although the candidate variables used in the five predictive models were similar, the predictive efficiency of the models was significantly different, with RFM having the best predictive efficiency.

Clinical evaluation of the optimal predictive model

CIC curves were plotted to verify the predictive efficiency of RFM. As shown in Supplementary Figure 1, RFM significantly distinguished between high- and low-risk patients in the training, internal verification and external verification sets, and its stratification effect was very stable. These results suggest that RFM as a predictive tool for evaluating post-TACE pain has clinical significance and can be used to guide early management of pain hierarchically.

DISCUSSION

At present, TACE is considered the first-line non-surgical treatment for HCC. TACE can effectively control the growth of HCC cells, significantly prolong the survival of patients and benefit patients with HCC; therefore, it is the first therapeutic option and the most effective treatment for patients with advanced HCC who are not eligible for surgical resection[15,16]. Although the trauma of TACE is minor, several adverse reactions may occur postoperatively[17]. Pain is one of the common postoperative complications; however, its pathophysiological mechanism remains unclear[18]. It may be caused by acute liver parenchyma ischaemia, liver capsule tension caused by transient liver swelling and chemical damage of hepatic arteries[19]. Previous studies have shown that pain can prolong the length of hospital stay, reduce the quality of life of patients and harm the physiology and psychology of patients[19,20]. Therefore, early treatment of postoperative pain is necessary for improving the

Table 2 The receiver operating characteristic curve analyses for pain risk in each machine learning-based model

Model	Training set		Testing set	
	AUC mean	AUC 95%CI	AUC mean	AUC 95%CI
RFM	0.869	0.816-0.922	0.871	0.818-0.924
DTM	0.861	0.808-0.914	0.864	0.811-0.917
ANNM	0.826	0.773-0.879	0.827	0.774-0.880
SVMM	0.803	0.750-0.856	0.808	0.755-0.861
NBM	0.798	0.745-0.851	0.803	0.750-0.856

RFM: Random forest model; SVMM: Support vector machine model; DTM: Decision tree model; ANNM: Artificial neural network model; NBM: Naive Bayesian model; AUC: Area under curve; 95%CI: 95% confidence interval.

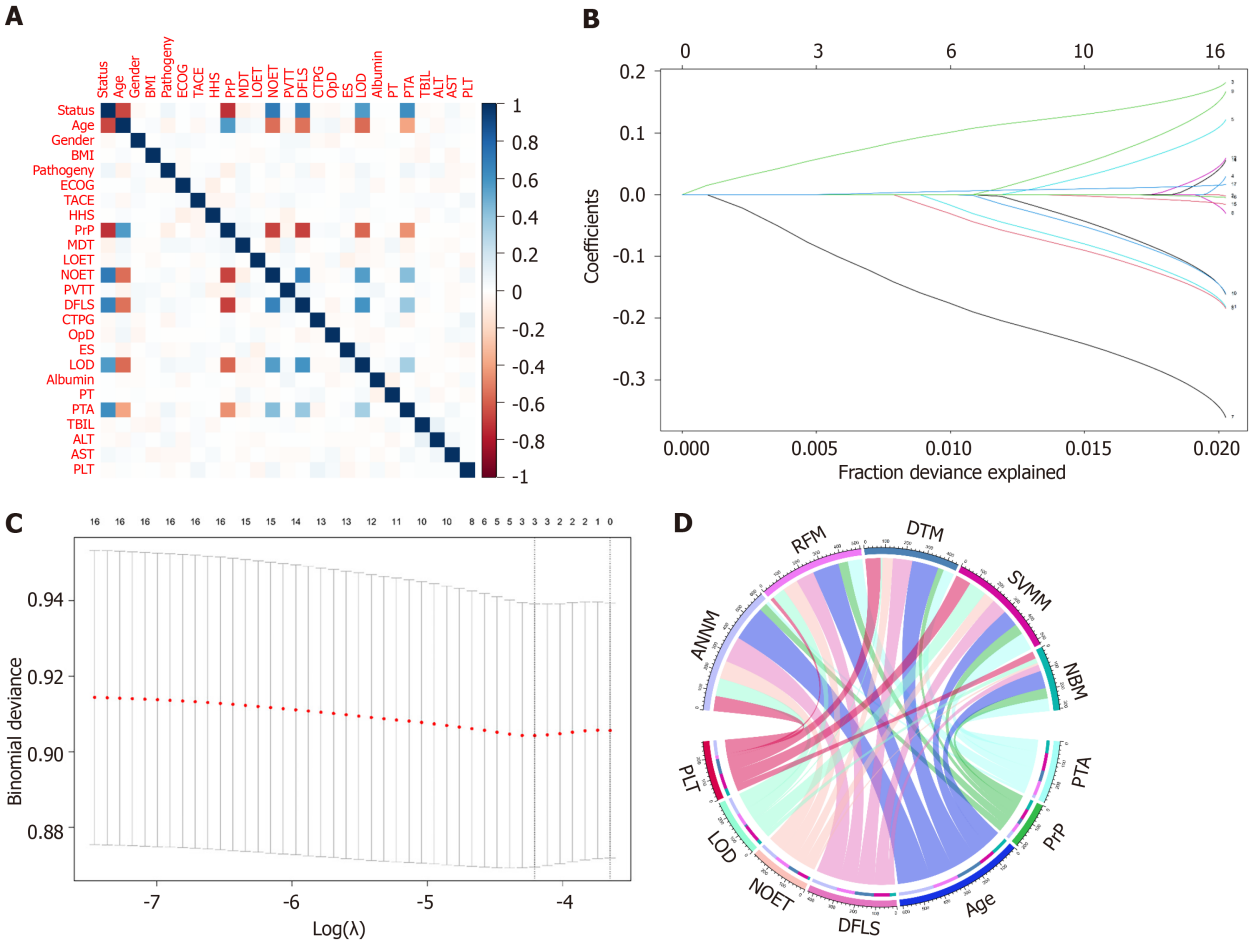

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Figure 2 Variable screening and weight allocation. A: Correlation matrix analysis of candidate features; B and C: Feature selection by least absolute shrinkage and selection operator regression; D: The weight distribution of the candidate variables of each ML-based model. BMI: Body mass index; ECOG: Eastern Cooperative Oncology Group; TACE: Transcatheter arterial chemoembolisation; HHS: History of hepatobiliary surgery; PrP: Preoperative pain; MDT: Maximum tumor diameter; LOET: Location of embolized tumor; NOET: Number of embolised tumours; PVTT: Portal vein tumor thrombus; DFLS: Distance from the liver capsule; CTPG: Child-pugh grade; OpD: Operation_duration; ES: Embolization supplement; LOD: Iodine oil dosage; PT: Prothrombin time; PTA: Prothrombin activity; TBIL: Total bilirubin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; PLT: Platelet count; RFM: Random forest model; DTM: Decision tree model; SVMM: Support vector machine model; NBM: Naive Bayes model; ANNM: Artificial neural network model.

prognosis of patients with HCC. To the best of our knowledge, this study is the first to use machine learning algorithms to build a multi-course model for predicting post-TACE pain. The model can help to assess the risk of post-TACE pain objectively in order to improve clinical diagnosis and treatment.

Previous studies have shown that the incidence of pain is high among patients with HCC after 6-12 h of TACE[19,21,22]. However, this study showed that the incidence of moderate and severe pain in

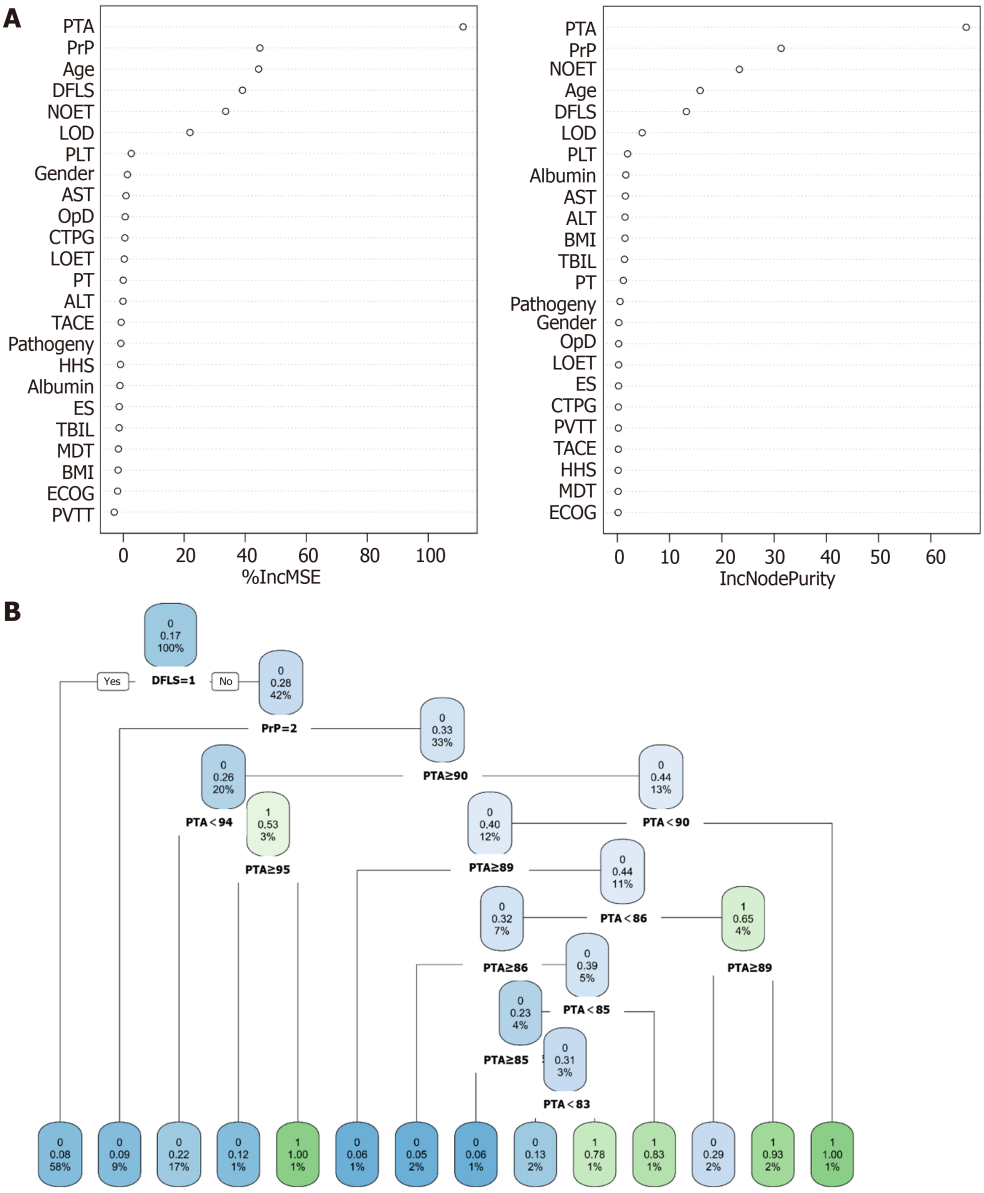

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Figure 3 Predictive model visualization based on machine learning-based algorithm. A: Random forest model; B: Decision tree model. The candidate factors associated with fracture risk were ordered *via* random forest algorithm (A) and (B) prediction node and weight were allocated *via* decision tree algorithm. BMI: Body mass index; ECOG: Eastern Cooperative Oncology Group; TACE: Transcatheter arterial chemoembolisation; HHS: History of hepatobiliary surgery; PrP: Preoperative pain; MDT: Maximum tumor diameter; LOET: Location of embolized tumor; NOET: Number of embolised tumours; PVTT: Portal vein tumor thrombus; DFLS: Distance from the liver capsule; CTPG: Child-pugh grade; OpD: Operation_duration; ES: Embolization supplement; LOD: Iodine oil dosage; PT: Prothrombin time; PTA: Preoperative prothrombin activity; TBIL: Total bilirubin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; PLT: Platelet count; RFM: Random forest model; DTM: Decision tree model; SVMM: Support vector machine model; NBM: Naive Bayes model; ANNM: Artificial neural network model.

patients with HCC was 16.73% within 24 h of TACE. Based on the analysis of pain occurrence at various time points, the incidence of pain was highest at 6 h after TACE. A possible reason is that postoperative pain is mostly caused by tumour tissue embolism and necrosis, the liver volume increases, and the right upper quadrant pain is caused by pulling the capsule. In this study, patients with HCC were uniformly administered preventive analgesic drugs before surgery, thus delaying the occurrence of pain. However, medical staff should strengthen the early inspection of patients with HCC, pay close attention to the symptoms and signs of patients and implement preventive measures, whenever necessary, to alleviate postoperative pain symptoms.

In this study, machine learning-based models were developed to predict post-TACE pain, and candidate predictors were identified based on the clinical baseline data of patients before surgery. The results were consistent with those of previous studies[20,23,24]. For example, this study showed that age of > 50 years was an independent risk factor for moderate-to-severe pain after TACE. The reason for the high incidence of postoperative pain in young patients is that the pain threshold of the human body

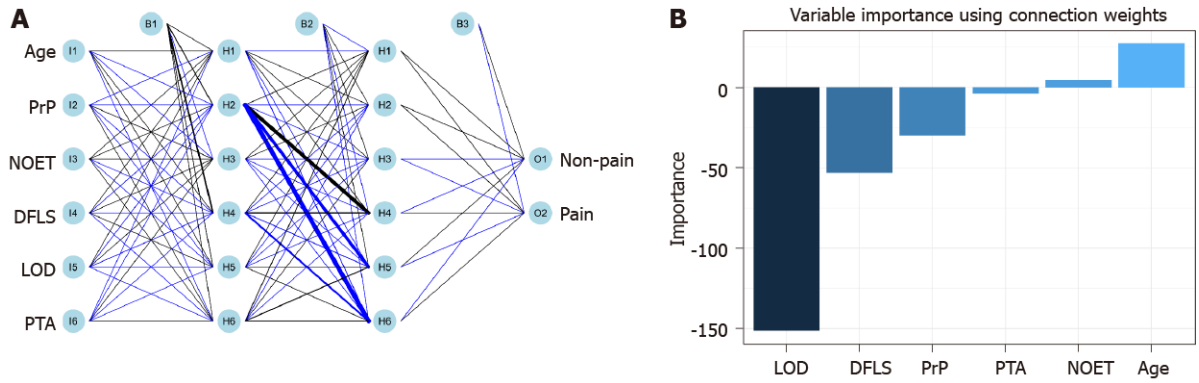

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Figure 4 Predictive model visualization based on artificial neural network model algorithm. A: Artificial neural network model; B: Variable importance using connection weight. PrP: Preoperative pain; NOET: Number of embolised tumours; DFLS: Distance from the liver capsule; LOD: Iodine oil dosage; PTA: Preoperative prothrombin activity.

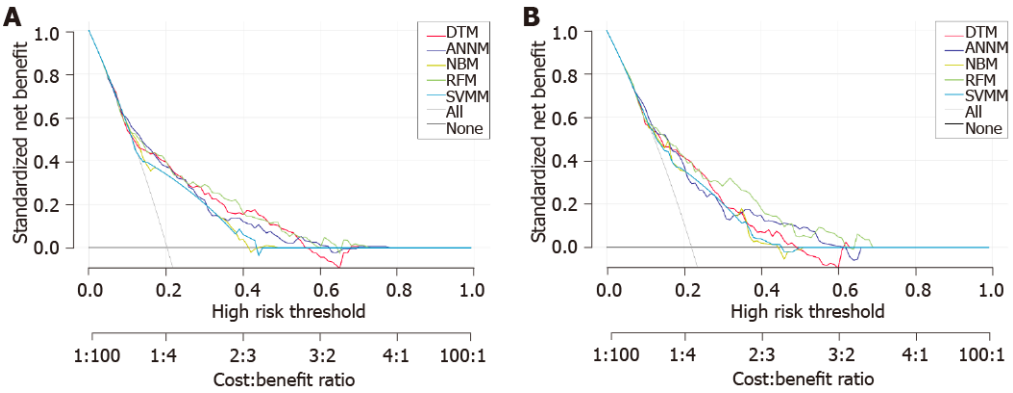

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Figure 5 Prediction pain risk performance of candidate models based on machine learning-based algorithm. A: Decision curve analysis (DCA) for five machine learning (ML)-based models in the training set; B: DCA for five ML-based models in the testing set. DTM: Decision tree model; ANNM: Artificial neural network model; NBM: Naive Bayes model; RFM: Random forest model; SVMM: Support vector machine model.

increases with age, and the sensitivity of elderly patients to pain is lower than that of young patients, resulting in changes in pain tolerance[25]. Therefore, medical staff should closely observe the symptoms and signs of young patients after surgery, and if necessary, pre-emptive analgesia should be implemented to reduce the incidence of postoperative pain. Furthermore, PrP was also identified as an important predictor of moderate-to-severe pain after TACE, which is consistent with the results of previous studies[26,27]. A meta-analysis reported that PrP is an important predictor of postoperative pain[26]. A possible reason is that the influx of PrP signals can enhance the excitability of spinal dorsal horn neurons and their responsiveness to pain transmission, which can be further maintained through transcriptional changes[28]. For example, cyclooxygenase-2 is induced to produce prostaglandin E2, which leads to postoperative pain[21]. Therefore, selective cyclooxygenase-2 inhibitors should be administered to high-risk patients preoperatively to reduce the incidence of moderate and severe pain postoperatively.

Furthermore, the distance between the tumour and liver capsule (≤ 2 cm), presence of multiple embolic tumours and dosage of lipiodol greater than 10 mL were also identified as risk factors for moderate-to-severe pain after TACE, which is consistent with the results of previous studies[10,29]. If the tumour tissue is close to the liver capsule, it may become necrotic and oedematous after hepatic arterial chemoembolisation, leading to increased tension in the liver capsule. Consequently, the patient is more likely to feel pain and discomfort. Moreover, if more tumours are embolised, more iodised oil is required, and a larger embolised area may increase the pain caused by tumour necrosis. we speculated that embolization of nodules close to the gallbladder might also be an alternative cuase of pain, especially if cystic artery vessels provided bllod to the nodules and had to be embolized. Prothrombin activity is an important indicator of liver coagulation because high prothrombin activity often indicates that the body is in a hypercoagulable state[30,31]. High prothrombin activity may be a primary cause of postoperative pain. Alternatively, injured tissue cells release a large amount of thromboplastin during surgery, which can also lead to a temporary hypercoagulable state in the early postoperative period[32,

33]. Consequently, the blood flow is slow, and the risk of postoperative micro-thrombosis and pain is increased. Therefore, medical staff should promptly evaluate the liver function of patients, detect changes in prothrombin time and control the abnormal indicators of coagulation function for effective pain management.

Although the candidate variables included in this study can be used to develop different machine learning-based predictive models, the predictive accuracy of the models may differ. In this study, RFM was found to have the best prediction efficiency, which is consistent with the results reported in previous studies[34,35]. RFM can realise multiple iterations of subsequent variables based on the 'bagging' algorithm, which signifies that the predictive efficiency of the included variables can be optimised after adding numerous 'branches' and 'pruning'[35,36]. Although ANNM can be used for risk stratification of patients with post-TACE pain, its predictive efficiency is slightly inferior to that of RFM, which reflects the practicability of the input- and hidden-layer algorithms in this study. However, the algorithm requires to be constantly updated to reflect the robustness of its 'output layer'[37]. The predictive performance of machine learning algorithms is undoubtedly better than that of logical regression algorithms because machine learning has incomparable advantages in terms of the number of iterations. Altogether, in this study, we developed an efficient predictive model based on candidate variables that can be adopted clinically. The model can be used for stratifying the risk of post-TACE pain to facilitate early management and improve the prognosis of patients.

However, this study has some limitations. First, this study had a retrospective design and only focused on patients undergoing traditional lipiodol-based embolisation, while the latter focused on patients using drug-eluting microspheres for embolisation. Therefore, the results may have been affected by selection bias. Second, although some clinical variables were included in this study, the psychological status and psychosocial factors of patients were not included, and no suggestion was made to further improve the predictive model by adding these factors. Third, this study relied on only single-centre internal verification; therefore, external spatial verification is required to accurately evaluate the predictive efficiency of the predictive models. Fourth, this study included only patients receiving traditional TACE; therefore, patients undergoing different types of TACE should be included in future studies to improve the universality of the predictive model.

CONCLUSION

Machine learning-based pre-warning models can be developed to predict post-TACE pain for hierarchical management of patients at high risk of moderate and severe pain after TACE. In particular, RFM combined with preoperative predictors (*i.e.*, age, PrP, DFLS ≤ 2cm, prothrombin activity, iodine oil dose and presence of multiple emboli) has optimal discriminating power and high predictive accuracy. Therefore, RFM can be used for early prediction of the risk of postoperative pain, which can facilitate prompt pain management after TACE and improve the prognosis of patients.

ARTICLE HIGHLIGHTS

Research background

Pain after transcatheter arterial chemoembolisation (TACE) can seriously affect the prognosis of patients and the insertion of additional medical resources.

Research motivation

To develop a practical model for predicting pain after TACE.

Research objectives

This study aimed to predict pain after TACE to enable the implementation of preventive analgesic measures.

Research methods

Of 857 patients (from January 2016 to January 2020) and prospectively enrolled 368 patients (from February 2020 to October 2022; as verification cohort) with hepatocellular carcinoma (HCC) who received TACE were collected from the Hepatic Surgery Center of Tongji Hospital. Five predictive models were established using machine learning algorithms were used to predicting postoperative pain and receiver operating characteristic curve analysis, decision curve analysis and clinical impact curve analysis were used to evaluate the effectiveness of the model.

Research results

Of 24 candidate variables were to build prediction model, among them, the age, preoperative pain,

number of embolised tumours, distance from the liver capsule, dosage of iodised oil and preoperative prothrombin activity were closely associated with postoperative pain. The random forest model (RFM) had the best predictive efficiency [training cohort: Area under the curve (AUC) = 0.869, 95% confidence interval (CI): 0.816-0.922; internal verification cohort: AUC = 0.871; 95%CI: 0.818-0.924].

Research conclusions

The five prediction models based on advanced machine learning algorithms are extremely suitable for the pain management of liver cancer patients after TACE, especially the RFM can accurately classify the pain risk of patients.

Research perspectives

Machine learning-based pre-warning models can be developed to predict post-TACE pain for hierarchical management of patients at high risk of moderate and severe pain after TACE. Alarmingly, the RFM can be used for early prediction of the risk of postoperative pain, which can facilitate prompt pain management after TACE and improve the prognosis of patients.

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FOOTNOTES

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Country/Territory of origin: China

ORCID number: Ya-Wei Fan 0000-0002-4101-7488.

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Retrospective Study

Risk factors and prediction model for inpatient surgical site infection after elective abdominal surgery

Jin Zhang, Fei Xue, Si-Da Liu, Dong Liu, Yun-Hua Wu, Dan Zhao, Zhou-Ming Liu, Wen-Xing Ma, Ruo-Lin Han, Liang Shan, Xiang-Long Duan

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Jin Zhang, Fei Xue, Si-Da Liu, Dong Liu, Yun-Hua Wu, Zhou-Ming Liu, Wen-Xing Ma, Ruo-Lin Han, Xiang-Long Duan, Second Department of General Surgery, Shaanxi Provincial People's Hospital, Xi'an 710068, Shaanxi Province, China

Fei Xue, Xiang-Long Duan, Institute of Medical Research, Northwestern Polytechnical University, Xi'an 710072, Shaanxi Province, China

Fei Xue, Xiang-Long Duan, Second Department of General Surgery, Third Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710068, Shaanxi Province, China

Dan Zhao, Computer Science School, Universiti Sains Malaysia, Penang 11800, Malaysia

Liang Shan, Medical Service, Shaanxi Provincial People's Hospital, Xi'an 710068, Shaanxi Province, China

Corresponding author: Liang Shan, MD, Attending Doctor, Medical Service, Shaanxi Provincial People's Hospital, No. 256 West Youyi Road, Beilin District, Xi'an 710068, Shaanxi Province, China. 584710525@qq.com

Abstract

BACKGROUND

Surgical site infections (SSIs) are the commonest healthcare-associated infection. In addition to increasing mortality, it also lengthens the hospital stay and raises healthcare expenses. SSIs are challenging to predict, with most models having poor predictability. Therefore, we developed a prediction model for SSI after elective abdominal surgery by identifying risk factors.

AIM

To analyse the data on inpatients undergoing elective abdominal surgery to identify risk factors and develop predictive models that will help clinicians assess patients preoperatively.

METHODS

We retrospectively analysed the inpatient records of Shaanxi Provincial People's Hospital from January 1, 2018 to January 1, 2021. We included the demographic data of the patients and their haematological test results in our analysis. The attending physicians provided the Nutritional Risk Screening 2002 (NRS 2002)

scores. The surgeons and anaesthesiologists manually calculated the National Nosocomial Infections Surveillance (NNIS) scores. Inpatient SSI risk factors were evaluated using univariate analysis and multivariate logistic regression. Nomograms were used in the predictive models. The receiver operating characteristic and area under the curve values were used to measure the specificity and accuracy of the model.

RESULTS

A total of 3018 patients met the inclusion criteria. The surgical sites included the uterus (42.2%), the liver (27.6%), the gastrointestinal tract (19.1%), the appendix (5.9%), the kidney (3.7%), and the groin area (1.4%). SSI occurred in 5% of the patients (n = 150). The risk factors associated with SSI were as follows: Age; gender; marital status; place of residence; history of diabetes; surgical season; surgical site; NRS 2002 score; preoperative white blood cell, procalcitonin (PCT), albumin, and low-density lipoprotein cholesterol (LDL) levels; preoperative antibiotic use; anaesthesia method; incision grade; NNIS score; intraoperative blood loss; intraoperative drainage tube placement; surgical operation items. Multivariate logistic regression revealed the following independent risk factors: A history of diabetes [odds ratio (OR) = 5.698, 95% confidence interval (CI): 3.305-9.825, P = 0.001], antibiotic use (OR = 14.977, 95%CI: 2.865-78.299, P = 0.001), an NRS 2002 score of ≥ 3 (OR = 2.426, 95%CI: 1.199-4.909, P = 0.014), general anaesthesia (OR = 3.334, 95%CI: 1.134-9.806, P = 0.029), an NNIS score of ≥ 2 (OR = 2.362, 95%CI: 1.019-5.476, P = 0.045), PCT ≥ 0.05 μg/L (OR = 1.687, 95%CI: 1.056-2.695, P = 0.029), LDL < 3.37 mmol/L (OR = 1.719, 95%CI: 1.039-2.842, P = 0.035), intraoperative blood loss ≥ 200 mL (OR = 29.026, 95%CI: 13.751-61.266, P < 0.001), surgical season (P < 0.05), surgical site (P < 0.05), and incision grade I or III (P < 0.05). The overall area under the receiver operating characteristic curve of the predictive model was 0.926, which is significantly higher than the NNIS score (0.662).

CONCLUSION

The patient's condition and haematological test indicators form the bases of our prediction model. It is a novel, efficient, and highly accurate predictive model for preventing postoperative SSI, thereby improving the prognosis in patients undergoing abdominal surgery.

Key Words: Surgical site infections; Risk factors; Abdominal surgery; Prediction model

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Core Tip: Herein, we retrospectively analysed the data, including patient personal information, test indicators, and surgical information, of patients undergoing elective abdominal surgery and used univariate and multivariate logistic regression analyses to assess risk factors for surgical site infection (SSI) in hospitalised patients. Nomograms were used in the prediction models. Subject working characteristics and area under the curve were used to measure the accuracy of the model up to 97%. R language was used to create a web page for dynamic predictive analysis of abdominal SSIs. A new predictive approach for preventing abdominal SSIs is made easier and more precise.

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INTRODUCTION

Surgical site infection (SSI) is the commonest healthcare-associated infection[1] that helps determine patient prognosis. SSIs occur in 2%-5% of inpatients undergoing surgery in the United States[2]. The incidence of SSI ranges from 2% to 10% in Europe[3-5], while in China, it ranges from 4% to 6%[6,7]. Patients undergoing complex surgeries associated with high-risk factors are more likely to develop SSI [8]. SSI results in a prolonged hospital length of stay (LOS). It burdens patients physically, psychologically, and economically[9].

Patients with abdominal symptoms requiring abdominal surgeries, such as gastric surgery, colorectal surgery, appendix surgery, *etc*., have a higher incidence of postoperative infection because the human gastrointestinal tract is a cavity that communicates with the outside world, comprising a wide variety of

intestinal flora, which can cause infections[10,11]. The National Quality Partnership, as part of the Surgical Care Improvement Project (SCIP), aims to prevent postoperative SSI. Several preoperative quality indicators, namely preoperative oxygen inhalation, normal body temperature maintenance, adequate circulating glucose, sterile drapes, surgical gowns, wound-protection devices, antimicrobial-coated sutures, incisional wound irrigation, and prophylactic negative-pressure wound therapy, lower the risk of SSI[12]. Despite these efforts, the LOS remained high, and the SSI remained unaffected. The National Nosocomial Infections Surveillance (NNIS) risk index is a traditional tool used to predict SSI [13]. The model comprises the American Society of Anaesthesiologists' preoperative assessment score, incision grade, and surgery time, with the score ranging from 0 to 3. These three elements, however, are insufficient to construct a prediction model. Grant *et al*[14] later developed a prediction model with an area under the receiver operating characteristic curve (AUROC) of 0.65, higher than that of the NNIS. Despite its ease of use, this model could only be applied to colorectal surgery. Therefore, our goal was to establish a novel, efficient, and highly accurate predictive model to prevent postoperative SSI in patients undergoing abdominal surgery.

MATERIALS AND METHODS

Inclusion and exclusion criteria

The clinical data of 3018 patients who underwent abdominal surgeries from January 2018 to January 2021 at Shaanxi Provincial People's Hospital were retrospectively analysed. We included patients aged > 18 years and < 100 years in the study. This study was performed in accordance with the Declaration of Helsinki. Informed consent was obtained from the patients and their families before surgery. SSI was diagnosed if one of the following occurred: Incision infection, deep incision infection, and organ-space infection[15]. The infection prevention and control staff manually diagnosed SSI. This study was approved by the Ethics Committee of Shaanxi Provincial People's Hospital.

Data collection

The hospital information system (HIS) was used to obtain the following patient-related data: Basic information: Age, gender, marital status, place of residence, and a history of diabetes and hypertension.

Scores: Nutritional Risk Screening 2002 (NRS 2002) and NNIS.

Preoperative biochemical index: Red blood cell, white blood cell (WBC), haemoglobin, procalcitonin (PCT), albumin (ALB), triglyceride, low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol, and total cholesterol levels.

Hospitalisation information: Preoperative duration (days from admission to surgery), preoperative antibiotic use, surgical season, anaesthesia method (general anaesthesia or non-general anaesthesia), incision grade (I, II, or III), intraoperative blood loss, intraoperative irrigation, tension reduction suture, incision drainage, multiple tissue excision, and the surgical site.

Statistical methods

The 22.0 and R 4.2.1 were used to perform statistical analyses. The chi-square test or Fisher's exact test was used to compare enumeration data, and the *t*-test was used to compare measurement data. SSI was the dependent variable, and the other variables were the independent variables. Significant indicators of SSI after abdominal surgery ($P < 0.05$) were identified using the univariate analysis, and multivariate logistic regression was used to identify independent risk factors for SSI after abdominal SSI ($P < 0.05$). The "rms" package in R 4.2.1 was used to display the prediction model as a nomogram based on independent risk factors. A nomogram was used to calculate the probability of SSI after abdominal surgery. Scores are assigned to each index. Higher probabilities were associated with a higher score. Receiver operating characteristic curves were constructed, and the area under the curve (AUC) values were calculated. The higher the value, the higher the model's accuracy. The datasets analysed in the current study are not publicly available due to the hospital's restrictions on public resources and confidentiality requirements; however, they are available from the corresponding author upon reasonable request.

RESULTS

A total of 3018 patients were included in this study. Of these, 150 patients were diagnosed with SSI, and 2868 were diagnosed with nonsurgical site infection. The median age of the patients was 45 years. Of the 3018 patients, 900 (29.8%) were males, 2118 (70.2%) were females, 1622 (53.7%) patients lived in urban areas, and 1396 (46.3%) patients lived in rural areas. A total of 539 (17.8%) patients had hypertension, and 402 (13.3%) patients had diabetes. The surgical site distribution was as follows: The uterus (42.2%), the liver (27.6%), the gastrointestinal tract (19.1%), the appendix (5.9%), the kidney (3.7%), and the groin area (1.4%).

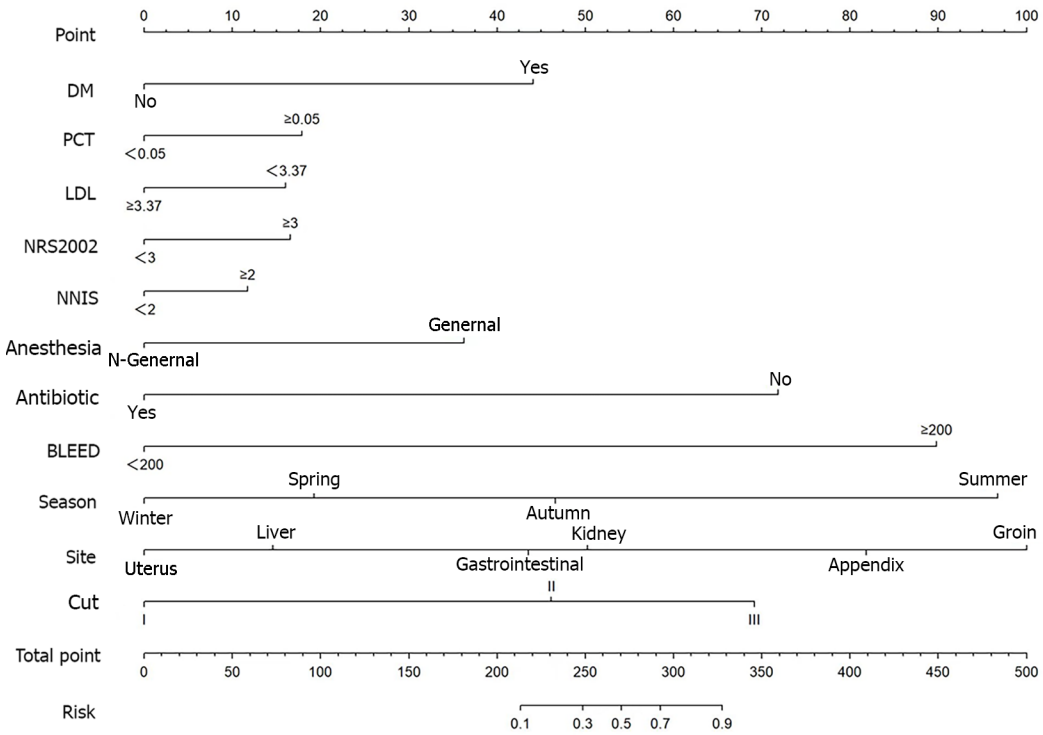

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Figure 1 The nomogram to construct a predictive model of abdominal surgical site infection. PCT: Procalcitonin; LDL: Lipoprotein cholesterol; NNIS: National Nosocomial Infections Surveillance.

Univariate and multivariate logistic regression analyses were performed on SSI development after abdominal surgery. Univariate analyses revealed that gender; age; marital status; place of residence; history of diabetes; the NRS 2002 score; the NNIS score; preoperative WBC, PCT, ALB, and LDL; preoperative antibiotic use; anaesthesia method, incision grade; intraoperative blood loss; intraoperative drainage; multiple tissue excision; surgical season; and surgical site were significantly associated with postoperative abdominal incision infection ($P < 0.05$) (Table 1).

Multivariate analysis revealed that diabetes [odds ratio (OR) = 5.698, 95% confidence interval (CI): 3.305-9.825, $P = 0.001$]; antibiotic use (OR = 14.977, 95%CI: 2.865-78.299, $P = 0.001$); an NRS 2002 score of ≥ 3 (OR = 2.426, 95%CI: 1.199-4.909, $P = 0.014$); an NNIS score of ≥ 2 (OR = 2.362, 95%CI: 1.019-5.476, $P = 0.045$); PCT ≥ 0.05 μg/L (OR = 1.687, 95%CI: 1.056-2.695, $P = 0.029$); LDL < 3.37 mmol/L (OR = 1.719, 95%CI: 1.039-2.842, $P = 0.035$); surgical sites, such as the gastrointestinal tract (OR = 3.646, 95%CI: 1.097-12.121, $P = 0.035$), appendix (OR = 23.056, 95%CI: 6.944-76.548, $P < 0.001$), kidney (OR = 6.256, 95%CI: 1.377-29.361, $P < 0.020$), and the groin area (OR = 53.589, 95%CI: 10.354-277.357, $P < 0.001$); surgical seasons, including summer (OR = 18.948, 95%CI: 9.537-37.648, $P < 0.001$), autumn (OR = 2.648, 95%CI: 1.454-4.823, $P = 0.001$), and winter (OR = 0.481, 95%CI: 0.266-0.872, $P = 0.016$); incision grade III (OR = 11.226, 95%CI: 1.689-74.630, $P = 0.012$); general anaesthesia (OR = 3.334, 95%CI: 1.134-9.806, $P = 0.029$); intraoperative blood loss > 200 mL (OR = 29.026, 95%CI: 13.751-61.266, $P < 0.001$) were independent risk factors for SSI (Table 2).

The multivariate analysis results were incorporated into the nomogram to construct a predictive model of SSI after abdominal surgery using R 4.2.1 (Figure 1). The following points were assigned to the patients based on the nomogram: 0 points for patients without a history of diabetes and 43 points for patients with a history of diabetes; 0 points for patients with a PCT level within the normal range and 19 points for patients with an abnormal PCT level; 0 points for patients with an LDL of ≥ 3.37 mmol/L and 16 points for patients with an LDL of < 3.37 mmol/L; 0 points for patients with an NRS 2002 score of < 2 and 17 points for patients with an NRS 2002 score of ≥ 3; 0 points for patients with an NNIS score of < 2 and 12 points for patients with an NNIS score of ≥ 2; 0 points for patients who received non-general anaesthesia and 38 points for patients who received general anaesthesia; 0 points for preoperative antibiotic use and 71 points for no preoperative antibiotic use; 0 points for patients with an intraoperative blood loss of < 200 mL and 91 points for patients with an intraoperative blood loss of ≥ 200 mL; 0 points if the surgical season was winter, 20 points if the surgical season was spring, 45 points if the surgical season was autumn, and 96 points if the surgical season was summer; in terms of the surgical site, the points were assigned as follows: 0 points for the uterus, 15 points for the liver, 45 points for the stomach, 51 points for the kidney, 82 points for the appendix, and 98 points for the groin area; in terms of the incision grade the points were assigned as follows: 0 points for grade I incision, 48 points for

Table 1 Univariate analysis of risk factors associated with surgical site infection

Factors		SSI (*n* = 150)	NSSI (*n* = 2868)	X^2	*P* value
Gender	Male	85	815	54.356	< 0.001
	Female	65	2053		
Age	< 70 yr	83	2145	27.927	< 0.001
	≥ 70 yr	67	723		
Marriage	Married	132	2678	10.006	0.007
	Single	7	108		
	Others	11	82		
Residence	Rural	83	1313	5.232	0.022
	Urban	67	1555		
Antibiotic use	Yes	14	66	27.316	< 0.001
	No	136	2802		
Hypertension	Yes	20	519	2.204	0.138
	No	130	2349		
Diabetes	Yes	46	356	41.137	< 0.001
	No	104	2512		
Preoperative duration	< 7 d	108	2248	3.391	0.066
	≥ 7 d	42	620		
NRS 2002	< 3	104	2652	44.853	< 0.001
	≥ 3	46	216		
NNIS	< 2	80	2420	96.634	< 0.001
	≥ 2	70	448		
RBC (10^{12}/L)	< 4	86	1565	0.44	0.507
	≥ 4	64	1303		
WBC (10^9/L)	< 10	86	1943	7.017	0.008
	≥ 10	64	925		
HB (g/L)	< 120	67	1473	2.555	0.11
	≥ 120	83	1395		
PCT (μg/L)	< 0.05	58	1824	37.748	< 0.001
	≥ 0.05	92	1044		
ALB (g/L)	< 35	105	1344	30.574	< 0.001
	≥ 35	45	1524		
TG (mmol/L)	< 1.7	124	1503	0.433	0.511
	≥ 1.7	26	365		
LDL (mmol/L)	< 3.37	95	1456	9.011	0.003
	≥ 3.37	55	1412		
HDL (mmol/L)	< 1.55	79	1722	3.222	0.073
	≥ 1.55	71	1146		
TC (mmol/L)	< 6.45	117	2149	0.718	0.397
	≥ 6.45	33	719		
Blood loss (mL)	< 200	87	2401	65.118	< 0.001
	≥ 200	63	467		

Drainage	Yes	103	1129	50.661	< 0.001
	No	47	1739		
Tension suture	Yes	7	72	Fisher	0.112
	No	143	2796		
Flushing	Yes	86	1596	0.164	0.685
	No	64	1272		
Item	Single	41	1443	30.12	< 0.001
	Multiple	109	1425		
Anesthesia	General	133	1969	26.525	< 0.001
	N-general	17	899		
Incision	I	8	95	228.143	< 0.001
	II	103	2702		
	III	39	71		
Season	Spring	36	825	301.157	< 0.001
	Summer	41	68		
	Autumn	42	382		
	Winter	31	1593		
Surgical site	Uterus	22	1252	188.267	< 0.001
	Liver	12	821		
	Gastrointestinal	76	501		
	Appendix	27	152		
	Kidney	5	107		
	Groin	8	35		

SSI: Surgical site infection; NNIS: National Nosocomial Infections Surveillance; NRS 2002: Nutritional Risk Screening 2002; RBC: Red blood cell; WBC: White blood cell; HB: Hemoglobin; PCT: Procalcitonin; ALB: Albumin; TG: Triglyceride; LDL: Lipoprotein cholesterol; HDL: High-density lipoprotein; TC: Total cholesterol.

grade II incision, and 68 points for grade III incision. The total score was 500. The predictive value of SSI after abdominal surgery was 90% when the score was > 328. Overall, the predictive model had a significantly higher AUC value (0.926) than that of the NNIS (0.662) (Figure 2). SSI occurrence was significantly associated with the SSI risk score obtained on logistic regression. Particularly, the model was associated with an increased incidence of SSI (30%, 70%, 90%, and 100% for score cut-offs of 210-250, 250-290, 290-330, and > 330, respectively) as the SSI score increased in the validation cohort (Figure 3). Based on these results, we set up an online tool to better predict SSI risk after abdominal surgery established on the nomogram in this study (https://drzhangjinssi.shinyapps.io/DynNo/mapp/).

DISCUSSION

SSI after abdominal surgery results in prolonged hospital LOS and significant hospitalisation costs[16]. A survey reported that the additional expenditure *per* SSI patient could support the hospitalisation costs of 13 normal surgical patients[8]. Therefore, the significance of SSI for hospitals, countries, and patients is obvious[17]. Over the past few years, several SSI prediction models have been developed to help clinicians identify high-risk patients who might benefit from early intervention. Due to its simplicity and convenience, the NNIS risk index is currently the method that is most frequently used. Its three variables, however, are insufficient for a precise evaluation[18,19]. Mu *et al*[20] established an SSI prediction model based on patient data from 39 countries between 2006 and 2008 [area under the receiver operating characteristic curve (AUROC) = 0.67]. An accurate prediction model might be created using data from 39 additional; however, using such a model in clinical settings could be inconvenient. Although Van Walraven *et al*[21] established a prediction model with an AUROC of 0.80; this model required substantial patient information. Medical personnel are overworked in settings where electronic

Table 2 Multivariate analysis of risk factors associated with surgical site infection

Factors	OR	95%CI		*P* value
The history of diabetes	5.698	3.305	9.825	0.001
The use of antibiotic	14.977	2.865	78.299	0.001
NRS 2002 ≥ 3	2.426	1.199	4.909	0.014
NNIS ≥ 2	2.362	1.019	5.476	0.045
PCT ≥ 0.05 μg/L	1.687	1.056	2.695	0.029
LDL < 3.37 mmol/L	1.719	1.039	2.842	0.035
General anesthesia	3.334	1.134	9.806	0.029
Blood loss ≥ 200 mL	29.026	13.751	61.266	< 0.001
Surgical site				
Uterus	Ref.			
Gastrointestinal	3.646	1.097	12.121	0.035
Appendix	23.056	6.944	76.548	< 0.001
Kidney	6.256	1.377	29.361	0.020
Groin	53.589	10.354	277.357	< 0.001
Incision				
I	Ref.			
III	11.226	1.689	74.630	0.012
Season				
Spring	Ref.			
Summer	18.948	9.537	37.648	< 0.001
Autumn	2.648	1.454	4.823	0.001
Winter	0.481	0.266	0.872	0.016

PCT: Procalcitonin; LDL: Lipoprotein cholesterol; NNIS: National Nosocomial Infections Surveillance; NRS 2002: Nutritional Risk Screening 2002; OR: Odds ratio; CI: Confidence interval.

medical records are not being used. Therefore, it is necessary to construct a prediction model which is accurate and easy to use. In this study, the SSI prediction model is relatively novel and efficient. It can be used to predict SSI after abdominal surgery, and the necessary information involved is within the scope of implementation, making it applicable. In this study, the SSI-related factors were retrospectively examined from the perspectives of fundamental preoperative patient data, preoperative blood test indicators, surgery-related data, and the overall patient condition score, including age, gender, marital status, WBC count, and intraoperative blood loss. Additionally, we included various comprehensive and representative factors, including the NRS 2002 and NNIS scores. Our model is innovative compared with other models[22,23]. Besides objective test indicators and the patient's personal information, the doctor can establish overall control and evaluate the patient's condition. This model is more practical and credible, as shown by the entire procedure and the AUROC result.

The predictability of the SSI prediction model was comprehensively evaluated using univariate regression, multivariate logistic regression, and R 4.2.1 "rms". Identifying patients at high risk for SSI is important; however, intervention should be the primary action following identification. The SCIP items must first be completed, albeit not all of them need to be covered[24,25]. Furthermore, when patients undergo elective surgeries, the model should be used comprehensively to determine the probability of infection. SSI is more likely to occur when the prediction score is high, and precautions must be taken accordingly. Improving the patient's nutrition, appropriate anaesthesia methods, and reducing intraoperative blood loss will help prevent SSIs. Patients with an SSI monitor for post-discharge wound surveillance could help identify and manage the condition at the earliest using intelligent identification programs available in some developed regions of the world. This would improve the effectiveness of hospital visits and foster better communication between doctors and patients[26,27]. Additionally, a preoperative plan devised by a multidisciplinary team could lower the occurrence of SSI, particularly in critically ill patients, as well as help in a comprehensive assessment and symptomatic treatment[28].

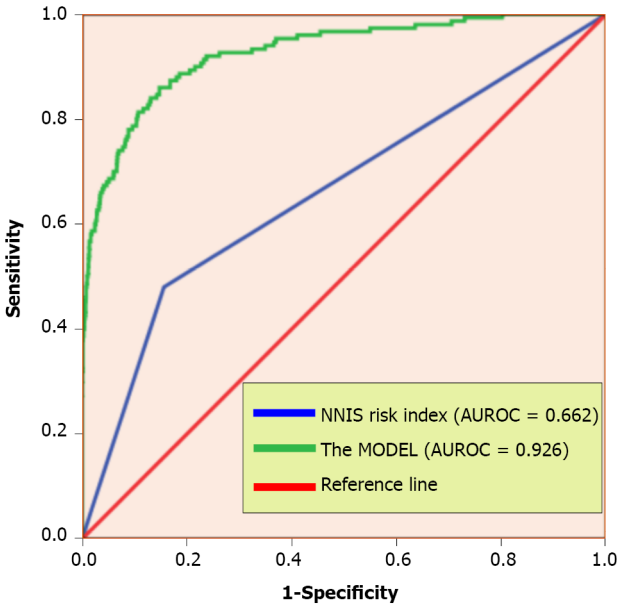

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Figure 2 The receiver operating characteristic curve of prediction model compared with National Nosocomial Infections Surveillance risk index in the validation cohort. AUROC: Area under the receiver operating characteristic curve; NNIS: National Nosocomial Infections Surveillance.

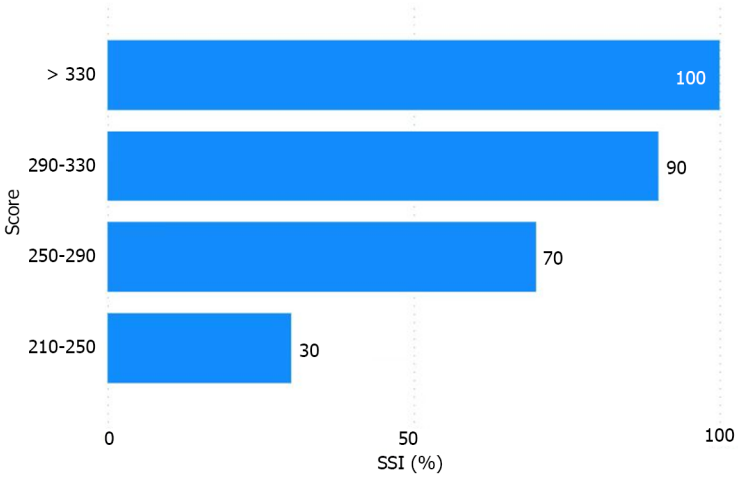

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Figure 3 Surgical site infection scores by the incidence. SSI: Surgical site infection.

There are four aspects to predicting SSI preoperatively: Assessment, intervention, diagnosis, and treatment, which are equally essential for managing SSI[29]. Multidisciplinary discussions and comprehensive step-by-step assessments can help lower the incidence of SSI, thereby improving patient satisfaction and recovery indexes.

The efficacy of our model has been verified; however, it has a few limitations. First, professionals diagnosed and selected the patients for this study; however, there may still be artificial errors that affect our model. Second, as the study was a retrospective analysis, potential selection bias could exist. The prediction model was created based on a broad cohort of patients undergoing abdominal surgery. The model needs constant improvement to be clinically used because the data were only from one institution, and the sample size was insufficient. This challenge could be categorised under clinical big data analysis, as reported by Ejaz *et al*[16]. Lastly, in terms of data analysis, several missing variables were excluded, and the model establishment expression form needs improvement.

The following will be considered in our future studies: (1) As a result of the promotion of diagnosis-related groups payment system for hospitalised patients[30], the International Classification of Diseases code[31] will become increasingly standardised as it can be used to screen cases; (2) More validation cohorts need to be included, and patient information can be collected from different regions of the country and globally, making the model more convincing and resilient; (3) The patients' missing data

needs to be handled appropriately. Chen *et al*[1] suggested that other variables can be used to replace the factors with too many missing values. As a fundamental step, clinicians need to strengthen their ability to write medical records; and (4) The text content in the model will be embedded later and then applied to the entire HIS, making the process more efficient and accurate.

CONCLUSION

SSI prediction models are useful for hospitalised patients and have recently undergone continuous development. However, they lack reliability due to their complex and dynamic nature. Herein, we established a novel model for predicting SSI after abdominal surgery and verified its efficiency and accuracy in preventing postoperative SSI. We anticipate that our study will help improve patient prognosis after abdominal surgery.

ARTICLE HIGHLIGHTS

Research background

Surgical site infections (SSIs) can increase mortality and prolong the length of hospital stay, thereby increasing healthcare costs. Therefore, it is much necessary to develop a prediction model after elective abdominal surgeries in order to identify risk factors of SSI.

Research motivation

To establish a predictive model for SSI which is more easily assess the risk of it. And provide timely interventions for high-risk patients to improve the quality of care so as to reduce medical costs and ease the burden on patients.

Research objectives

The present study aimed to develop a realistic, feasible, valid and unique model for predicting the risk of elective abdominal SSI.

Research methods

This observational study was conducted from January 1, 2018 to January 1, 2021 using patient demographic data and haematological test results. Inpatient SSI risk factors were evaluated using univariate analysis and multivariate logistic regression. Nomograms were used in the predictive models. The receiver operating characteristic and area under the curve values were used to measure the specificity and accuracy of the model.

Research results

The key findings indicated that the surgical sites included the uterus (42.2%), the liver (27.6%), the gastrointestinal tract (19.1%), the appendix (5.9%), the kidney (3.7%), and the groin area (1.4%). SSI occurred in 5% of the patients (n = 150). Multivariate logistic regression revealed the following independent risk factors: A history of diabetes, antibiotic use, a Nutritional Risk Screening 2002 score of ≥ 3, general anaesthesia, a National Nosocomial Infections Surveillance (NNIS) score of ≥ 2, procalcitonin ≥ 0.05 μg/L, low-density lipoprotein cholesterol < 3.37 mmol/L, intraoperative blood loss ≥ 200 mL, surgical season, surgical site, and incision grade (all P < 0.05. The overall area under the receiver operating characteristic curve of the predictive model was 0.926, which was significantly higher than that of the NNIS (0.662).

Research conclusions

The patient's condition and haematological test indicators formed the bases of our prediction model. It is a novel, efficient, and highly accurate predictive model for preventing postoperative SSI, thereby improving the prognosis in patients undergoing abdominal surgery.

Research perspectives

This study developed the accurate model for predicting the risk of elective abdominal SSI. We plan to make larger multi-centre and large sample studies in order to obtain more realistic and valid data results.

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FOOTNOTES

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Country/Territory of origin: China

ORCID number: Jin Zhang 0000-0002-7302-6477; Si-Da Liu 0000-0003-4766-3111; Liang Shan 0000-0002-6482-0919.

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ORIGINAL ARTICLE

Retrospective Study

Percutaneous management in hepatic alveolar echinococcosis: A sum of single center experiences and a brief overview of the literature

Suat Eren, Sonay Aydın, Mecit Kantarci, Volkan Kızılgöz, Akın Levent, Düzgün Can Şenbil, Okan Akhan

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Suat Eren, Department of Radiology, Faculty of Medicine, Atatürk University, Erzurum 25100, Turkey

Sonay Aydın, Mecit Kantarci, Volkan Kızılgöz, Akın Levent, Düzgün Can Şenbil, Department of Radiology, Faculty of Medicine, Erzincan Binali Yıldırım University, Erzincan 24100, Turkey

Okan Akhan, Department of Radiology, Hacettepe University, Ankara 06090, Turkey

Corresponding author: Düzgün Can Şenbil, MD, Academic Research, Doctor, Research Assistant, Department of Radiology, Faculty of Medicine, Erzincan Binali Yıldırım University, Hacı Ali akın Street, Erzincan 24100, Turkey. senbilcan@gmail.com

Abstract

BACKGROUND

Hepatic alveolar echinococcosis (HAE) is a serious zoonotic infection that affects humans. It may have a tumor-like appearance at times. Percutaneous treatment of HAE patients is extremely relaxing for them. HAE is a significant human zoonotic infection caused by the fox tapeworm *Echinococcus Multilocularis* larvae. It possesses the characteristics of an invasive tumor-like lesion due to its infiltrative growth pattern and protracted incubation period. The disease is endemic over central Europe, Asia, and North America.

AIM

To characterize HAE patients who were treated percutaneously, their outcomes, and the major technical features of percutaneous treatment in HAE.

METHODS

Patients who were treated with percutaneous cyst drainage and/or percutaneous biliary drainage were included in the study. Uncorrected abnormal coagulation values and solid or non-infected HAE with minor necrotic change were excluded.

RESULTS

Thirty-two patients underwent percutaneous cyst drainage, two patients underwent percutaneous biliary drainage, and four patients underwent percutaneous biliary drainage alone. Interventional radiology is utilized to drain echinococcal necrosis and abscesses within/without the liver, as well as diseased

and clogged bile ducts.

CONCLUSION
Percutaneous drainage of cyst contents and/or biliary channels using a minimally invasive technique is a very beneficial. Percutaneous cyst drainage with albendazole therapy improves quality of life in patients who are unable to undergo surgery, even when the mass resolves with long-term treatment.

Key Words: Interventional; Radiology; Treatment; Alveolar echinococcosis; Liver

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Core Tip: Interventional radiology is utilized to drain echinococcal necrosis and abscesses within/without the liver either as palliative operations or as a bridge to radical resection. Percutaneous cyst drainage with albendazole therapy improves quality of life in patients who are unable to undergo surgery, even when the mass resolves with long-term treatment.

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INTRODUCTION

Hepatic alveolar echinococcosis (HAE) is a significant human zoonotic infection caused by the fox tapeworm *Echinococcus Multilocularis* larvae (EM). It possesses the characteristics of an invasive tumor-like lesion due to its infiltrative growth pattern and protracted incubation period. The disease is endemic over central Europe, Asia, and North America[1,2].

Percutaneous sterilization procedures, surgery, medication treatment, a "wait-and-see" approach, or a combination of these are available for management. In comparison, the clinical signs of alveolar echinococcosis (AE) are similar to those of a malignant, silently progressive liver disease, with local tissue infiltration and metastasis. Structured treatment is critical for AE management, which involves WHO staging, pharmacological therapy, and at least a decade of follow-up[3].

While excision of lesions or liver transplantation (LT) is the most successful treatment option when operable, the majority of patients require palliative care prior to open surgery due to the presence of comorbidities. Typically, the disease is identified at an irreversible stage. In certain instances, invasion of the bile ducts and arteries, as well as necrosis in the lesion's center, result in serious consequences such as cholangitis and liver abscesses. Palliative surgery has been shown to have little advantage in terms of care, while percutaneous and endoscopic techniques have increased in popularity. In these patients, percutaneous draining of the complex cyst and biliary tree may be employed as a minimally invasive technique[2,4-6].

The purpose of this study is to characterize the methods to treat HAE patients, the outcomes of the treatment options, and the major technical features of percutaneous treatment in HAE.

MATERIALS AND METHODS

Patients and diagnosis

Electronic archives were retrospectively evaluated to define the treatment options of the HAE patients between January 2012-December 2021. Patients were classified under two main subgroups: (1) surgical treatment: complete surgical excision and antihelmintic therapy, partial resection and antihelmintic therapy, LT; and (2) Interventional radiologic treatment: percutaneous cyst drainage, percutaneous cyst drainage with percutaneous biliary drainage, percutaneous biliary drainage only.

The first diagnosis was made mostly on the basis of conventional imaging findings such as computed tomography (CT) scans in three phases (hepatic artery, portal vein, and hepatic vein); ultrasound (US); immunoserologic testing with enzyme-linked immunosorbent assay; and, in some cases, magnetic resonance imaging (MRI).

Age, gender data and the presence/frequency of the complications were noted.

Interventional radiologic treatment: Uncorrected abnormal coagulation values and solid or non-infected HAE with minor necrotic change were the main contraindications for interventional radiologic treatment. The big necrotic cyst or infected cyst with or without mass effect on the biliary tree and surrounding arteries were the selection criteria for percutaneous cyst drainage.

All cases were reviewed for percutaneous access to the cyst, application route, and selection of the appropriate imaging modality for guidance prior to draining. Generally, we preferred US entry advice. We chose CT guidance for cysts that were difficult to visualize with US (due to thick calcification of the cyst wall or conspicuous gas within the cyst). Patients with abnormal coagulation parameters were handled as soon as possible after hematologic correction. In situations of cholangitis or biliary obstruction due to mass invasion, percutaneous biliary drainage was performed. Seldinger's method was used to install drainage catheters (8-10 Fr). We employed both intercostal and subcostal techniques.

Statistical analysis

The Statistical Package for Social Sciences for Windows 20 software was used to analyze the data (IBM SPSS Inc., Chicago, IL, United States). The Kolmogorov-Smirnov test was used to determine whether the data conformed to a normal distribution. Numerical variables with a normal distribution were represented as mean ± SD values and categorical variables as number (n) and percentage values (%). Age was compared across groups using the student's t test, and the frequency of complications was analyzed using the Chi-square test according to subgroups.

RESULTS

Patients

The current study included 125 patients, 67 (53.6%) of whom were female and 58 (46.4%) of whom were male. Mean age of the population was 53.6 ± 8.4 years, median age was 63 years (min-max; 41-82 years).

Table 1 shows the detailed distribution of patients based on treatment options.

Surgical treatment

Mean age of the patients was 48.8 ± 3.4 years. 45 patients (51.7%) were female and 42 (48.2%) patients were male.

Complications were discovered in 15 (17.2%) patients: Fever (8 patients), hemorrage (4 patients), subphrenic infection (2 patient), bile leakage (1 patient).

Figures 1 and 2 demonstrate the significant radiologic findings of surgically treated patients.

Interventional radiologic treatment

Mean age of the patients was 64.5 ± 6.1 years, 20 patients (52.6%) were female and 18 (47.3%) patients were male.

Twenty-eight lesions mostly located in the right lobe (73.6 %) and 9 lesions primarily located in the left lobe (32.1%). There was bilateral involvement in one case (2.6%). Cyst infection was detected at 11 (28.9%) cases.

Intercostal route was used in six patients (15.7 %), whereas subcostal approach was preferred in the rest. All cysts were effectively drained, and no significant complications associated with catheter drainage were observed during follow-up. Complication rate was significantly higher in surgical treatment group than interventional radiologic treatment (P = 0.001). Catheters were replaced due to blockage or stenosis in six patients. All patients admitted prophylactic antibiotics and albendazole.

Figure 3 demonstrates the significant findings of interventional radiologic treatment. Table 2 contains further information about the patients covered.

Extrahepatic findings

There were no cases of extrahepatic alveolar echinococcosis in the surgical therapy group. Whereas, in the interventional radiologic treatment subgroup, six patients were diagnosed with extrahepatic alveolar echinococcosis: three in the lung, one in the adrenal gland, one in the brain (Figure 4), and one in the peritoneal cavity.

DISCUSSION

Alveolar echinococcosis is one of the most dangerous and potentially fatal zoonoses on the planet, and it appears to be spreading across Europe[1,7]. In 97 percent of patients, lesions begin in the liver. Due to the larva's slow growth rate, it behaves similarly to a slow-growing invasive tumor that eventually invades the liver parenchyma, arteries, and bile ducts. In severe HAE, the mass may invade all neighboring organs and spread hematogenously to distant organs such as the lungs and brain[8,9].

Table 1 Distribution of patients based on treatment options, *n* (%)

Surgical treatment		Interventional radiologic treatment	
Complete surgical excision and antihelmintic therapy	60 (48)	Percutaneous cyst drainage	32 (25.6)
Partial resection and antihelmintic therapy	23 (18.4)	Percutaneous cyst drainage with percutaneous biliary drainage	2 (1.6)
Liver transplantation	4 (3.2%)	Percutaneous biliary drainage only	4 (3.2)
Total	87 (69.6)	Total	38 (30.4)

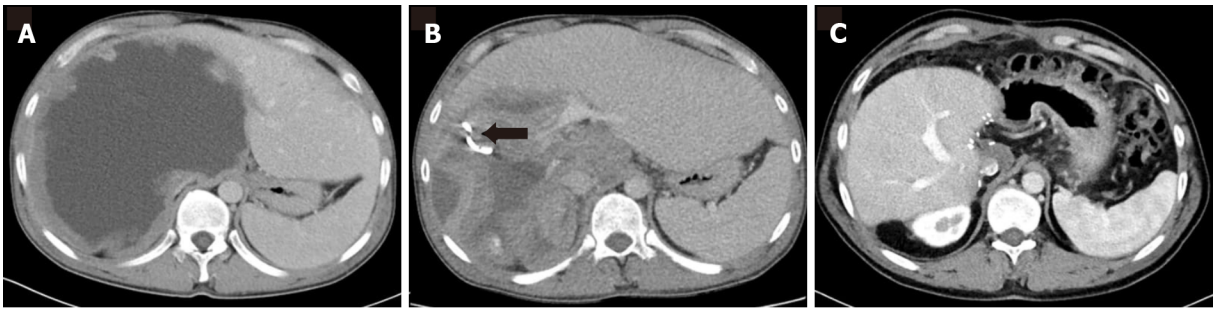

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Figure 1 Male, 28 years old. Hepatic alveolar echinococcosis is a serious infection that requires liver replacement. A: On axial portal venous phase contrast enhanced computed tomography, a large cystic mass is visible; B: After percutaneous treatment, the lesion's size has decreased, and a drainage catheter is visible (arrow); C: Percutaneous drainage was unable to heal the lesion, and liver transplantation was undertaken.

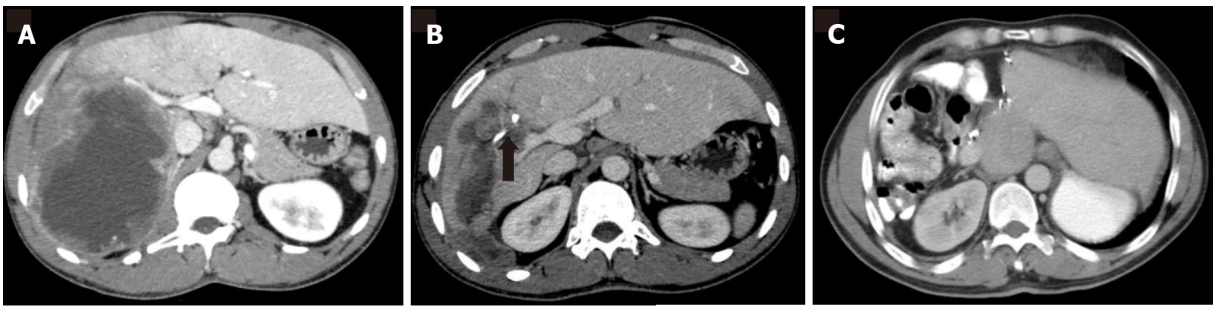

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Figure 2 Female, 50-year-old. Treatment of hepatic alveolar echinococcosis with right hepatectomy. A: On axial portal venous phase contrast enhanced computed tomography, a large cystic mass is visible; B: After percutaneous treatment, the lesion's size has decreased, and a drainage catheter is visible (arrow); C: Percutaneous drainage was unable to heal the condition, and a right hepatectomy was performed.

There are studies in the literature that show that familial factors may influence susceptibility to alveolar echinococcosis[10]. However, family clustering is extremely uncommon in alveolar echinococcus. The rate of blood ties between patients was found to be 13% in a study of 153 people. As a result, in the event of alveolar echinococcosis, the family should be screened with US[11].

Immunoserologic studies based on the use of EM are useful in diagnosing and determining the EM agent. In the United States, HAE lesions frequently present as ill-defined heterogeneous infiltrations. While necrosis and infection cause hypoechoic foci inside the mass, hyperechoic zones are associated with fibro-parasitic tissue and dispersed calcifications. CT demonstrates the invading mass's characteristic calcifications more clearly. Triphasic contrast enhanced CT imaging is very beneficial for determining the vascular and biliary extension and invasion of neighboring tissue. With its high sensitivity to soft tissue, MRI is extremely useful for detecting satellite liver lesions, invasions, and central nervous system lesions, as well as examining the biliary tract[12].

Due to the sluggish growing rate of cysts, there is typically an asymptomatic phase before diagnosis of several years. The clinical appearance is similar to that of slow-growing liver cancer, and severe illness almost always involves invasion of the biliary and vascular walls. Although it is always fatal if not properly treated, early detection and treatment offer a better prognosis[13,14].

Although radical liver resection is the preferred method of treatment in order to prevent palliative surgical procedures, total excision of the mass is frequently not possible. LT should be regarded as a viable option for life-saving treatment. LT, on the other hand, is not always feasible and is contrain-

Table 2 Details of the included patients

No.	Age/gender	Location of cyst	Cystic content	Percutaneous treatment	Surgery
1	35/M	RL	Infected	PD	LT
2	47/F	LL	Non-infected	PD	No
3	58/F	RL	Non-infected	PD-PBD	No
4	60/F	LL	Non-infected	PD	No
5	37/M	RL	Non-infected	PD	Right lobectomy
6	66/F	RL	Non-infected	PD	No
7	33/F	RL	Non-infected	PD	LT
8	36/F	RL	Non-infected	PD	LT
9	36/M	RL	Non-infected	PD	LT
10	52/F	RL	Infected	PD-PBD	LT
11	57/M	RL	Non-infected	PD	LT
12	33/F	RL	Infected	PD	Right lobectomy
13	26/F	RL	Infected	PD	Right lobectomy
14	62/M	RL	Non-infected	PD	No
15	39/M	LL	Infected	PD	No
16	59/M	LL	Non-infected	PD	No
17	66/F	LL	Non-infected	PD	No
18	21/F	LL	Infected	PD	Left lobectomy
19	24/M	RL	Non-infected	PD	LT
20	35/M	RL	Non-infected	PD	LT
21	51/M	RL	Non-infected	PD	Right lobectomy
22	44/F	RL	Non-infected	PD	No
23	28/M	RL	Infected	PD	LT
24	57/F	RL	Non-infected	PD	LT
25	71/F	RL	Non-infected	PD	No
26	17/M	RL	Non-infected	PD	No
27	39/F	RL	Non-infected	PD	No
28	71/F	RL	Infected	PD	No
29	50/F	RL	Infected	PD	Right lobectomy
30	34/M	Bilateral	Non-infected	PD	No
31	28/M	RL	Non-infected	PD	No
32	50/M	LL	Non-infected	PD	Left lobectomy
33	15/M	LL	Infected	PD	Inoperable
34	61/M	RL	Infected	PD	Inoperable
35	45/F	LL	Non-infected	PBD	No
36	53/F	RL	Non-infected	PBD	LT
37	25/F	RL	Non-infected	PBD	LT
38	43/F	RL	Non-infected	PBD	LT

PD: Percutaneous drainage of cyst; PBD: Percutaneous biliary drainage; RL: Right lobe of liver; LL: Left lobe of liver; M: Male; F: Female.

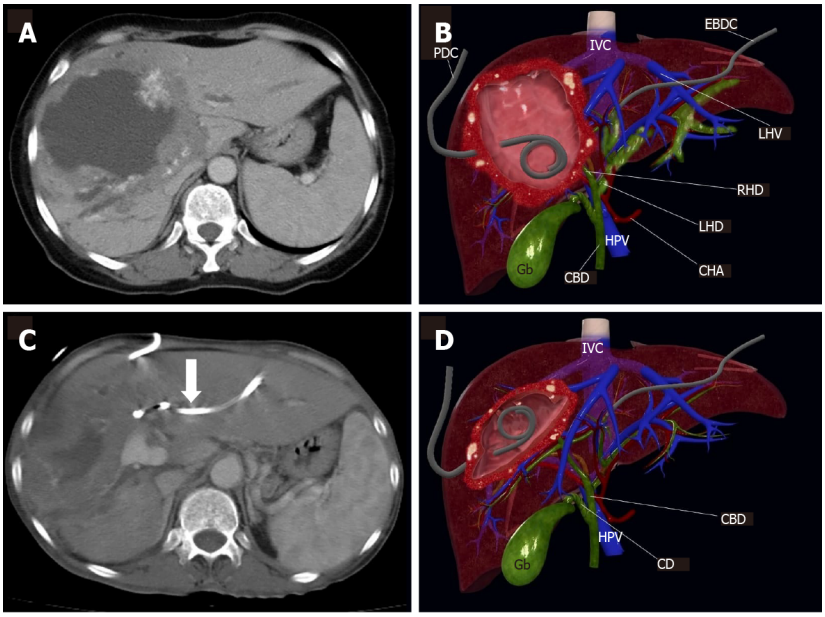

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Figure 3 Female, 32-year-old. A: Alveolar Echinococcosis at right liver lobe, with typical peripheral calcifications and large central necrosis; B: 3D image in the coronal plane illustrates the location of the percutaneous drainage catheter and the external biliary drainage catheter in the patient; C: Drainage catheter can be seen in within the lesion (arrow); D: The shrunken lesion cavity and the regression of the dilatation in the left intrahepatic bile ducts are illustrated by 3D coronal plane image. PDC: Percutaneous drainage catheter; IVC: Inferior vena cava; EBDC: External biliary drainage catheter; LHV: Left hepatic vein; RHD: Right hepatic duct; LHD: Left hepatic duct; CHA: Common hepatic artery; HPV: Hepatic portal vein; CBD: Common biliary duct; Gb: Gallbladder; CD: Cystic duct.

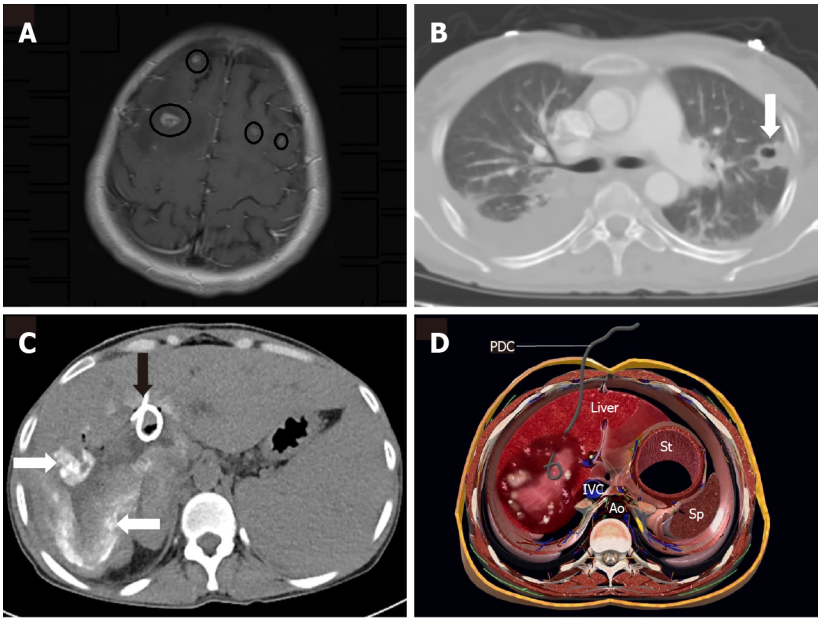

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Figure 4 Male, 45 years old. A and B: Axial magnetic resonance imaging demonstrates enhancing brain lesions associated with alveolar echinococcosis (circles). Alveolar Echinococcosis is also prevalent in the parenchyma of the left lung (arrow); C: Percutaneous drainage was performed; typical calcifications (white arrow) are visible, as is the drainage catheter (black arrow); D: 3D axial plane cross sectional illustration image shows the percutaneous drainage catheter placement in the lesion cavity. PDC: Percutaneous drainage catheter; IVC: Inferior vena cava; Ao: Abdominal aorta; IVC: Inferior vena cava; St: Stomach; Sp: Spleen.

dicated in patients with residual or metastatic HAE[15,16]. Depending on the degree of liver surgery, documented complication rates ranged from 15% to 36%, and fatality rates after excision ranged from 3% to 4.2%[17]. Similarly to the literature, the complication rate of surgical treatment in our sample was 17.2%, but we identified no issues in the interventional radiologic treatment subgroup, despite having a higher mean age. This suggests that interventional radiological therapy may be a viable treatment option for alveolar echinococcosis.

Despite all major surgical procedures, only half of the patients recovered completely. Interventional radiological treatments have been developed over time and have replaced palliative surgeries[18,19]. Drugs that inhibit parasitic growth are also crucial in the treatment of alveolar echinococci. In a series of 37 patients, Bresson-Hadni *et al*[14] used a multidisciplinary approach. In comparison to the past, only one patient received a liver transplant, and palliative surgery rates dropped by 80% in the literature.

HAE lesions are divided into three types: solid, pseudocystic, and mixed. While percutaneous cyst drainage can be performed in pseudocystic and mixed forms, percutaneous biliary drainage can be performed in any form as a palliative treatment for biliary stasis[20].

Cyst enlargement may result in compression or obstruction of the circulatory and biliary systems. Cyst necrosis and infection are two primary factors that contribute to fast cyst growth. The mass's inadequate vascularization frequently results in necrosis in the center portion of the lesion. Necrosis increases the intra-cystic pressure and mass effect, which may result in biliary stasis, cysto-biliary fistula, or necrotic cyst content rupture into the peritoneal and/or pleural space. With lower intracystic pressure, catheter drainage of necrotic material minimizes these problems[21].

Cyst infection is a significant consequence of HAE and may present acutely as cholangitis and septicemia, mimicking a liver abscess. Catheter drainage of infected cysts, such as liver abscess, should be performed until favorable conditions for major surgery are achieved. Because surgical therapy is contraindicated in acutely infected cysts, transcatheter drainage of a life-threatening bacterial or fungal infection within the cyst may be performed as a bridge operation in symptomatic patients prior to a curative surgical procedure. Catheter drainage can alleviate both the symptoms associated with abscess and the compressive symptoms on the arteries and biliary tree[8,21]. Eleven of our patients with infected cystic content were successfully treated with drainage.

In cases of infectious manifestations of centro-parasitic abscess or cholangitis, radiological interventional procedures are extremely useful. Percutaneous drainage of massive centro-parasitic abscesses, combined with systemic antibiotics, significantly improves the patient's clinical status. It is especially useful in elderly patients for whom a partial hepatectomy is not an option. Radiological interventional procedures are also very helpful in cases of cholangitis caused by parasitic tissue infiltration of the biliary tree and the resulting fibro-inflammatory reaction[22].

Biliary blockage symptoms typically emerge as a result of direct invasion of the major bile ducts or as a result of HAE's mass effect. Cholangitis symptoms may also be present as a result of parasite mass connection with bile ducts or pigment stones accumulating above a parasitic biliary stenosis[8]. Biliary blockage and cholangitis result in a more rapid decline in liver function, as well as mass destruction of the liver tissue. In these instances, if the patient has a large necrotic mass, we choose cyst drainage to alleviate tension on the biliary tree and major arteries. In certain cases, biliary stasis symptoms may improve with cyst draining alone due to the cyst's reduction in size. If biliary invasion and extensive cysto-biliary fistulas are present, the bile content of the cyst can be drained concurrently with the cyst content without extra biliary drainage. If these individuals benefit just from cyst drainage, this approach may be beneficial in avoiding the use of several catheters and may be sufficient in the interim till surgery. If patients have not demonstrated sufficient benefit from cyst draining, catheterization of one or two sides of the biliary tree should alleviate symptoms of biliary stasis.

In patients who are unable to undergo surgery, percutaneous cyst drainage and/or percutaneous biliary drainage with albendazole medication are the only treatment options available to protect these patients from re-infection, rupture, and to alleviate compressive symptoms. Biliary stenting may be combined with percutaneous biliary drainage or cyst draining if necessary[2]. We also have examples extrahepatic alveolar echinococcosis. Percutaneous cyst draining was used to treat one incidence of metastases to peritoneal cavity due to infected cystic material. Another case with cerebral metastases was treated with percutaneous draining of the infected cyst and albendazole (10 mg/kg) medical treatment. Extrahepatic involvement was not uncommon in patients treated with interventional radiologic procedures, according to our patient sample. The relevance of the radiologic workup before deciding on the sort of treatment is highlighted at this point. Extensive exams for extrahepatic involvement, particularly with CT or MRI, can aid in determining the best course of treatment.

Although percutaneous drainage is extremely beneficial in HAE patients, our cases had certain restrictions. Transcatheter draining of alveolar cysts is more challenging than conventional cyst drainage. To begin, we generally opted to apply US instructions. Nonetheless, the cyst's appearance was obscured in some cases due to significant calcification or strong fibrosis. In some patients, CT guidance for needle entry and catheter placement may be required. Second, the cyst capsule proved difficult to puncture due to its rigid nature. As a result, we are required to employ a thick needle for entrance and to dilate the tract prior to catheter drainage installation. Prior to catheter implantation, it is beneficial to lower positive pressure within the cyst *via* cystic content aspiration to minimize peritoneal seeding in these circumstances. Nonetheless, catheter exchange is required in the majority of patients undergoing follow-up.

CONCLUSION

Interventional radiology is utilized to drain echinococcal necrosis and abscesses within/without the liver, as well as diseased and clogged bile ducts, in HAE cases, either as palliative operations or as a bridge to radical resection. These techniques not only relieve pressure on the hepatic arteries and biliary path, but also make surgical resection easier by minimizing peripheral granulation tissue. In acutely infected patients, percutaneous drainage of cyst contents and/or biliary channels using a minimally invasive technique is a very beneficial, if not required, surgery that can save lives in some circumstances. Percutaneous cyst drainage with albendazole therapy improves quality of life in patients who are unable to undergo surgery, even when the mass resolves with long-term treatment.

ARTICLE HIGHLIGHTS

Research background

Alveolar echinococcus is a zoonotic infection that can be fatal in humans. In our study, we conducted a brief assessment of the role of interventional radiology in the treatment of alveolar echinococcus.

Research motivation

Despite radical surgical procedures, the rate of complete recovery from alveolar echinococcus is quite low. Patients can benefit greatly from an increase in the success rates of treatments performed with interventional radiology.

Research objectives

The goal of our research is to compare the success rates of interventional radiological methods to surgical methods.

Research methods

Our clinic's experience and those mentioned in the literature, as well as surgical methods, were compared.

Research results

Interventional radiology can be used to treat infected alveolar echinococci in particular.

Research conclusions

Interventional radiology can be used to treat infected alveolar echinococci in particular. Palliative surgery rates may thus fall.

Research perspectives

In our study, it was aimed to provide convenience for the patient and save time and money by advancing interventional radiological treatment methods in the treatment of alveolar echinococcus.

FOOTNOTES

Author contributions: Eren S, Aydın S and Kantarcı M contributed with data acquisition; Kızılgöz V performed the statistical analysis; Levent A, Senbil DC and Akhan O contributed to study design; Eren S and Kızılgöz V contributed to critical analysis; Senbil DC and Aydın S contributed to writing and critical review of the manuscript; All authors read and approved the final manuscript.

Institutional review board statement: The Ethics and Research Board of the Erzincan Binali Yıldırım University faculty of medicine approved the study, No. EBYU-KAEK-2020-001-297.

Informed consent statement: Written informed consent was obtained from the participants.

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

Data sharing statement: Data used in this study is available from the corresponding author on reasonable request.

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Country/Territory of origin: Turkey

ORCID number: Sonay Aydın 0000-0002-3812-6333; Mecit Kantarci 0000-0002-1043-6719; Düzgün Can Şenbil 0000-0003-0233-7371.

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ORIGINAL ARTICLE

Retrospective Study

Clinical features of acute esophageal mucosal lesions and reflux esophagitis Los Angeles classification grade D: A retrospective study

Chikamasa Ichita, Akiko Sasaki, Sayuri Shimizu

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Chikamasa Ichita, Akiko Sasaki, Department of Gastroenterology Medicine Center, Shonan Kamakura General Hospital, Kamakura 247-8533, Kanagawa, Japan

Chikamasa Ichita, Sayuri Shimizu, Department of Health Data Science, Yokohama City University, Yokohama 236–0027, Kanagawa, Japan

Corresponding author: Chikamasa Ichita, MD, Doctor, Department of Gastroenterology Medicine Center, Shonan Kamakura General Hospital, 1370-1 Okamoto, Kamakura 247-8533, Kanagawa, Japan. ichikamasa@yahoo.co.jp

Abstract

BACKGROUND

Acute esophageal mucosal lesions (AEMLs) are an underrecognized and largely unexplored disease. Endoscopic findings are similar, and a higher percentage of AEML could be misdiagnosed as reflux esophagitis Los Angeles classification grade D (RE-D). These diseases could have different pathologies and require different treatments.

AIM

To compare AEML and RE-D to confirm that the two diseases are different from each other and to clarify the clinical features of AEML.

METHODS

We selected emergency endoscopic cases of upper gastrointestinal bleeding with circumferential esophageal mucosal injury and classified them into AEML and RE-D groups according to the mucosal injury's shape on the oral side. We examined patient background, blood sampling data, comorbidities at onset, endoscopic characteristics, and outcomes in each group.

RESULTS

Among the emergency cases, the AEML and RE-D groups had 105 (3.1%) and 48 (1.4%) cases, respectively. Multiple variables exhibited significantly different results, indicating that these two diseases are distinct. The clinical features of AEML consisted of more comorbidities [risk ratio (RR): 3.10; 95% confidence interval (CI): 1.68–5.71; $P < 0.001$] and less endoscopic hemostasis compared with RE-D (RR: 0.25; 95%CI: 0.10–0.63; $P < 0.001$). Mortality during hospitalization was

higher in the AEML group (RR: 3.43; 95%CI: 0.82–14.40; P = 0.094), and stenosis developed only in the AEML group.

CONCLUSION

AEML and RE-D were clearly distinct diseases with different clinical features. AEML may be more common than assumed, and the potential for its presence should be taken into account in cases of upper gastrointestinal bleeding with comorbidities.

Key Words: Acute esophageal mucosal lesion; Comorbidities; Esophageal reflux; Black esophagus; Acute necrotizing esophagitis

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Core Tip: The pathogenesis of acute esophageal mucosal lesion (AEML) is uncertain and is frequently misdiagnosed as reflux esophagitis Los Angeles classification grade D (RE-D). Therefore, we compared the clinical features of AEML and RE-D using a single-center retrospective study. These esophageal diseases were distinguished based on the oral shape of the esophageal mucosal injury. Our results suggest AEML cases may be more prevalent than previously thought, as twice as many AEML cases were observed than RE-D cases. We found clear differences between these diseases and recommend that AEML is considered in cases of upper gastrointestinal bleeding.

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INTRODUCTION

Acute esophageal mucosal lesion (AEML) is proposed in Japan and other Asian countries as a disease concept that unites black and non-black esophagus[1]. The proportion of black esophagus is quite rare, accounting for 0.2% and 3% in upper and emergency endoscopy for upper gastrointestinal bleeding, respectively[2,3]. A severe case of AEML is considered a black esophagus[4]. AEML is observed mainly in older males with severe comorbidities presenting with upper gastrointestinal bleeding[5-7]. Circulatory insufficiency and gastric acid reflux have been suggested as factors associated with AEML [6-8]. However, the actual pathogenesis of AEML remains uncertain, and the disease has many indistinct aspects, including its clinical characteristics.

The endoscopic features of AEML include circumferential diffuse mucosal injury of the lower esophagus and sharp changes at the squamocolumnar junction[5]. This finding is similar to reflux esophagitis Los Angeles classification grade D (RE-D). Consequently, AEML is frequently misdiagnosed as RE-D. Although reports have compared AEML with reflux esophagitis Los Angeles classification grade C (RE-C) and RE-D[1], no studies have compared AEML with RE-D.

Therefore, this study aimed to clarify that AEML and RE-D are different diseases and to investigate the clinical features of AEML by comparing them with those of RE-D, which is a relatively established disease concept. Furthermore, since only a few studies have investigated the necessity for endoscopic hemostasis and outcomes such as stenosis development and in-hospital mortality, we also examined subjects with these outcomes.

MATERIALS AND METHODS

Study design

This was a single-center, retrospective study.

Patients

We assessed the medical records of all patients who underwent emergency upper endoscopy at Shonan Kamakura General Hospital in Kanagawa, Japan, between October 2016 and May 2022. Emergency upper endoscopy was defined as endoscopy performed within 24 h of the request. We included patients with diffuse circumferential mucosal injury of the esophagus and excluded patients with corrosive

esophagitis, radiation esophagitis, infectious esophagitis, eosinophilic esophagitis, esophageal pemphigoid, and systemic sclerosis. We also excluded obstructive symptoms caused by tumors or ileus or post-upper gastrointestinal tract surgery.

Definitions

We categorized the patients into groups based on the esophageal mucosal injury's shape on the oral side [1]. The RE-D group was defined as esophageal mucosal injuries that tapered off radially toward the oral side (Figure 1). In contrast, the AEML group was defined as esophageal mucosal injuries untapered radially toward the oral side and extended circumferentially (Figure 2). In the AEML group, black esophagus was defined as black esophageal mucosa appearing circumferentially (Figure 3A). We diagnosed black esophagus if a small amount of the black component was discovered (Figure 3B). However, the mucosa that did not meet this definition was considered non-black esophagus. These endoscopic findings were confirmed by two expert endoscopists (CI and AS), who were assigned to each group if their diagnoses were both consistent. Cases that did not match the two endoscopists' diagnoses were excluded from this study. If multiple upper endoscopies were performed on the same patient, only the first episode of the most severe disease was used for analysis.

Sample size

We did not set the case number in this study since the prevalence of AEML remains uncertain.

Variables and outcomes

We compared the following factors between these two groups: Age, sex, chief complaint (hematemesis, black vomit, and black stool), presence of shock vitality, underlying conditions (hypertension, diabetes mellitus, chronic kidney disease, coronary artery disease, liver cirrhosis, and previous malignancy), medications (nonsteroidal anti-inflammatory drugs), antithrombotic drugs, steroids, antibiotics, and acid inhibitors, comorbidities at onset, blood sampling data (white blood cell, C-reactive protein, hemoglobin, blood urea nitrogen, creatinine, albumin, blood glucose, and lactate), endoscopic findings (need for hemostasis, esophageal hiatal hernia, gastric ulcer, duodenal ulcer, and atrophic gastritis), and other outcomes (presence of stenosis post-onset and mortality during hospitalization).

Shock vitality was defined as a shock index of > 1 at the time of presentation[9,10]. Blood sampling data were collected at the time of admission. Previous malignancy was defined as a previous diagnosis of malignant disease, regardless of the degree of progression, and those currently inactive. Acid inhibitors included proton-pump inhibitors (PPI), histamine H2-receptor antagonists, and potassium-competitive acid blockers. Comorbidities at onset indicated diseases that were simultaneously observed when the patient presented with an episode of upper gastrointestinal bleeding, and treatment for malignancy was defined as a non-surgical treatment for malignancy, such as chemotherapy. Prerenal failure was defined as a creatinine level of > 1.5 mg/dL and fractional excretion of sodium of < 1% or urea nitrogen of < 35%[11]. Esophageal hiatal hernia was defined as an indirect finding of an esophageal hiatus widened by two or more scopes in the retroflex view (Figure 4)[12]. Atrophic gastritis, where a mucosal change was caused by *Helicobacter pylori* infection, was diagnosed by the vascular pattern associated with loss of gastric mucosal glands and loss of folds[13,14]. Patients with esophageal stenosis were considered to have stenosis when it was difficult to pass the upper endoscope (GIF-H260 or GIF-H290Z; Olympus, Tokyo, Japan) within 6 mo.

Statistical analysis

Parametric and non-parametric continuous values were reported using mean ± standard deviation and median and interquartile ranges, respectively. Categorical variables are reported using numbers and percentages. Continuous and categorical values were compared using the Mann–Whitney U test and Fisher's exact test, respectively. A two-sided P value of < 0.05 was considered statistically significant. Risk ratios (RRs), including 95% confidence intervals (CIs), and effect sizes (r) were calculated for binary and continuous outcomes, respectively[15]. All statistical analyses were performed using EZR version 1.55[16], which is a package for R statistical software (https://www.r-project.org/). Specifically, it is a modified version of the R commander designed to add statistical functions that are frequently used in biostatistics. The statistical methods of this study were reviewed by Sayuri Shimizu from the Department of Health Data Science, Yokohama City University.

RESULTS

Upper endoscopies were performed in 47254 cases, of which 3362 (7.1%) were emergency upper endoscopies. Of the emergency upper endoscopies, diffuse circumferential mucosal injury of the esophagus occurred in 209 cases (6.2%). Forty-nine cases were excluded based on the exclusion criteria. The expert endoscopists did not match the diagnosis in seven cases. The patients were classified into the AEML (n = 105) and RE-D (n = 48) groups. Among all upper endoscopic cases, AEML and RE-D accounted for 0.2% and 0.1%, respectively, whereas among all emergency upper endoscopic cases,

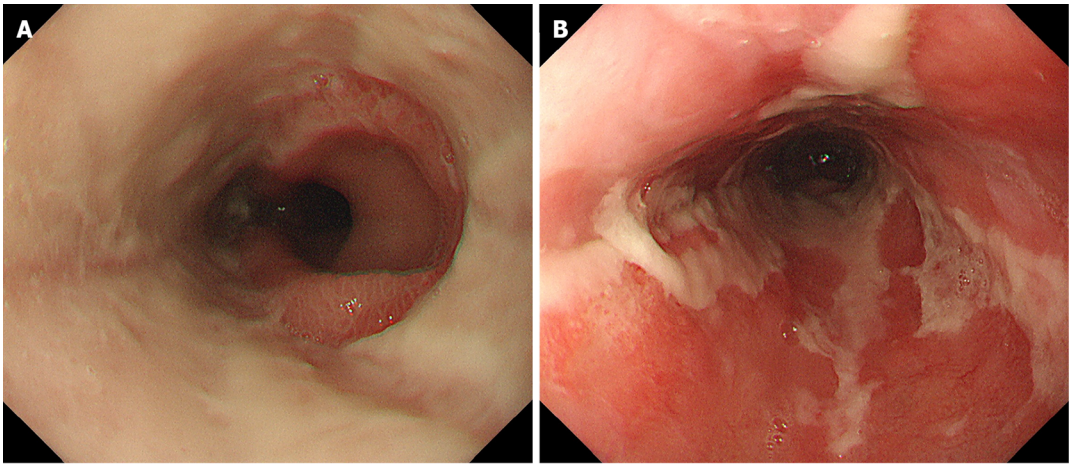

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Figure 1 Visual definition of endoscopic findings regarding reflux esophagitis Los Angeles classification grade D. A: In the lower esophagus; fused; the circumferential mucosal injury; B: Oral mucosal injury radially tapered off toward the oral side.

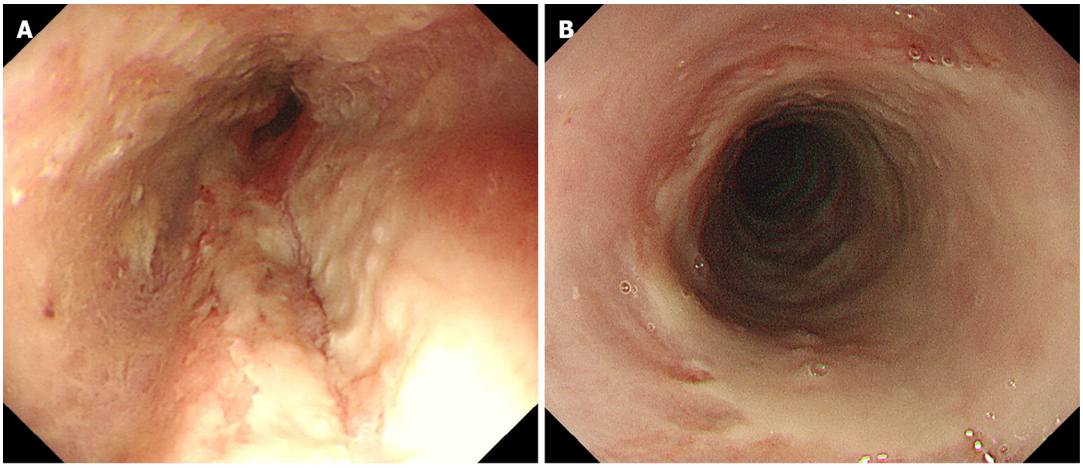

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Figure 2 Visual definition of the endoscopic findings regarding the acute esophageal mucosal lesion. A: In the lower esophagus; fused; the circumferential mucosal injury; B: Oral mucosal injury was not spiny-shaped.

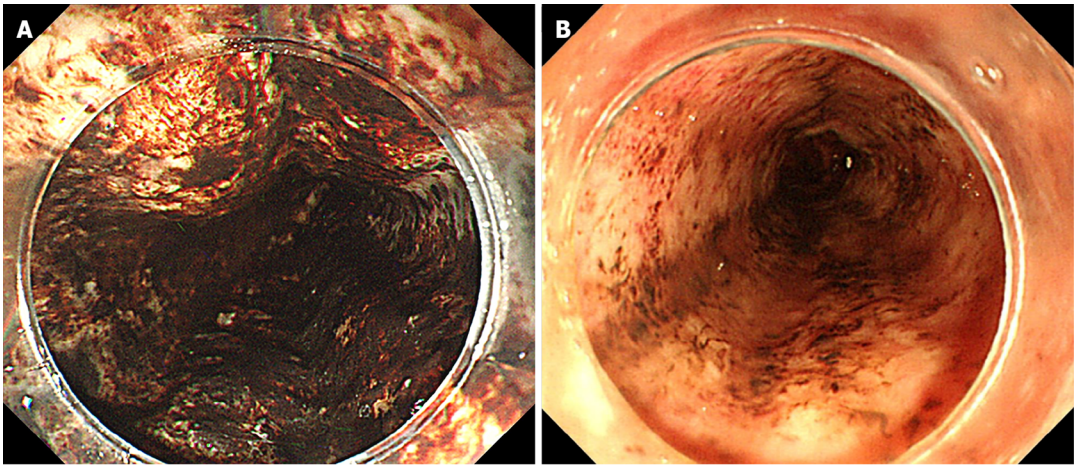

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Figure 3 Visual definition of endoscopic findings regarding black esophagus. A: In the acute esophageal mucosal lesions group, black esophagus was defined as circumferentially appearing black esophageal mucosa; B: Even with a small amount of black component, we diagnosed black esophagus.

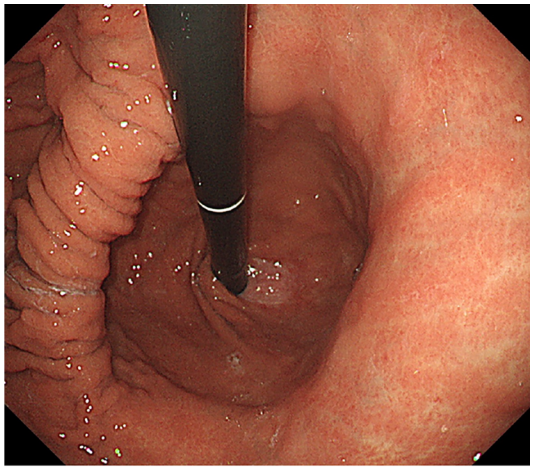

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Figure 4 Visual definition of a hiatal hernia. Esophageal hiatal hernia was defined as a widening of the hilum with two or more scopes in the retroflex view of the endoscope.

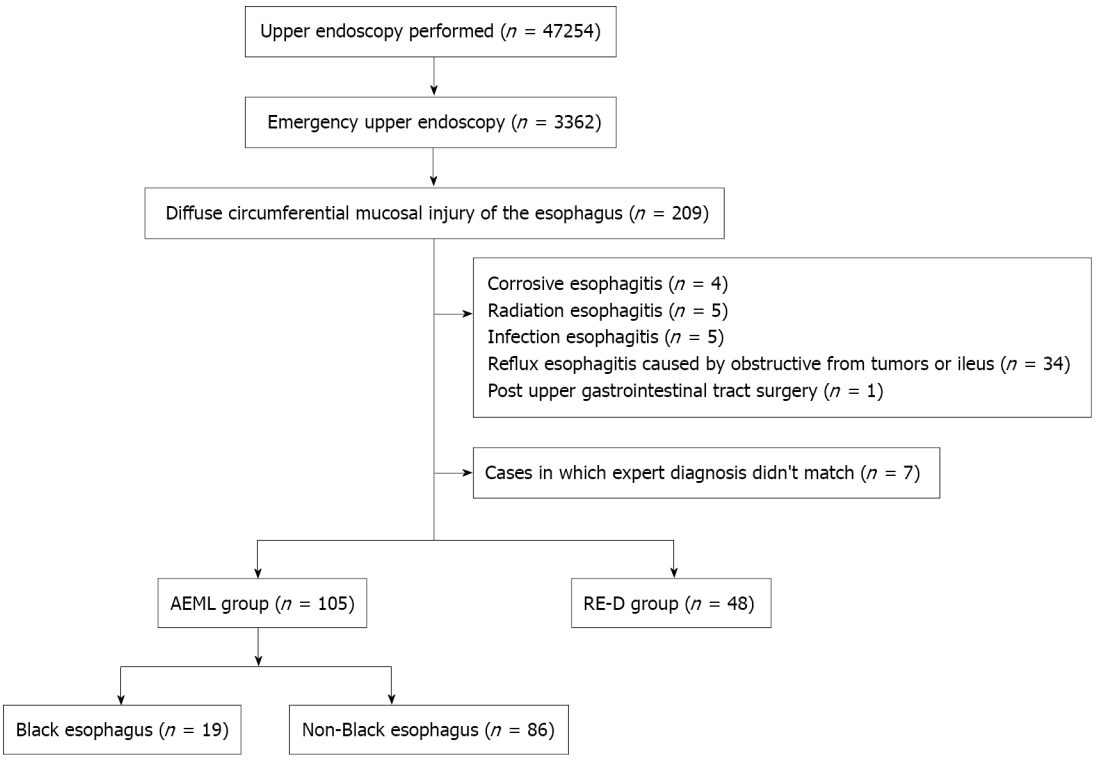

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Figure 5 Flow diagram of patient inclusion and exclusion. AEML: Acute esophageal mucosal lesions; RE-D: Reflux esophagitis Los Angeles classification grade D.

AEML and RE-D accounted for 3.1% and 1.4%, respectively. In the AEML group, black and non-black esophagus accounted for 19 (18%) and 86 (82%) cases, respectively (Figure 5). Patient characteristics are shown in Table 1. AEML was more common in a younger age group (AEML group *vs* RE-D group; median 75.0 years *vs* 87.0 years; $P < 0.001$) and in male patients (58.1% *vs* 27.1%; RR: 2.15; 95%CI: 1.31–3.51; $P < 0.001$). Although no significant differences were observed regarding main complaints or the presence of shock vitality (27.6% *vs* 16.7%; RR: 1.66; 95%CI: 0.82–3.35; $P = 0.16$), patients with AEML were significantly more likely to have an underlying condition of diabetes mellitus (22.1% *vs* 8.3%; RR: 2.63; 95%CI: 0.96–7.18; $P = 0.043$) and previous malignancy (28.6% *vs* 10.4%; RR: 2.74; 95%CI: 1.13–6.63; $P = 0.013$). No significant difference was found in the type of medication administered. The blood sampling data showed significant differences in all collected items except for albumin levels (Table 2).

Table 1 Patient background and medications, *n* (%)

Parameter	AEML (*n* = 105)		RE-D (*n* = 48)	Risk ratio (95%CI)	*P* value
	Black esophagus (*n* = 19)	Non-black esophagus (*n* = 86)			
Age in yr, median (IQR)	75.0 (65.0–85.0)		87.0 (78.0–91.3)	0.34	< 0.001
	83.0 (71.5–86.0)	75.0 (65.0–84.0)			
Male	61 (58.1)		13 (27.1)	2.15 (1.31–3.51)	< 0.001
	11 (57.9)	50 (58.1)			
Chief complaint					0.713
Hematemesis	30 (28.3)		16 (33.3)		
	6 (31.6)	24 (27.9)			
Black vomiting	65 (61.0)		26 (54.2)		
	10 (52.6)	54 (62.8)			
Black stools	11 (10.5)		6 (12.5)		
	3 (15.8)	8 (9.3)			
Presence of shock vitality	29 (27.6)		8 (16.7)	1.66 (0.82–3.35)	0.16
	6 (31.6)	23 (26.7)			
Underlying conditions					
Hypertension	49 (46.7)		23 (47.9)	0.97 (0.68–1.39)	1
	13 (68.4)	36 (41.9)			
Diabetes mellitus	23 (22.1)		4 (8.3)	2.63 (0.96–7.18)	0.043
	4 (21.1)	19 (22.4)			
Chronic kidney disease	19 (18.3)		7 (14.6)	1.24 (0.56–2.75)	0.649
	5 (26.3)	14 (16.5)			
Coronary artery disease	13 (12.4)		1 (2.1)	5.94 (0.8–44.14)	0.065
	3 (15.8)	10 (11.6)			
Liver cirrhosis	3 (2.9)		2 (4.2)	0.69 (0.12–3.97)	0.649
	0 (0.0)	3 (3.5)			
Previous malignancy	30 (28.6)		5 (10.4)	2.74 (1.13–6.63)	0.013
	7 (36.8)	23 (26.7)			
Medications					
NSAIDs	13 (12.4)		2 (4.2)	2.97 (0.70–12.66)	0.148
	3 (15.8)	10 (11.6)			
Antithrombotic	28 (26.7)		17 (35.4)	0.75 (0.46–1.24)	0.339
	3 (15.8)	25 (29.1)			
Steroids	4 (3.8)		1 (2.1)	1.83 (0.21–15.93)	1
	0 (0.0)	4 (4.7)			
Antibiotics	8 (7.6)		1 (2.1)	3.66 (0.47–28.4)	0.274
	2 (10.5)	6 (7.0)			
Acid blockers	42 (40.4)		15 (31.2)	1.28 (0.79–2.07)	0.368
	10 (52.6)	32 (37.6)			

Age was calculated with an effect size *r* because the risk ratio could not be calculated. 95%CI: 95% confidence interval; AEML: Acute esophageal mucosal

lesion; IQR: Interquartile range; NSAIDs: Nonsteroidal anti-inflammatory drugs; RE-D: Reflux esophagitis Los Angeles classification grade D.

Table 2 Blood sampling data

Parameter	AEML (*n* = 105)		RE-D (*n* = 48)	Effect size, *r*	*P* value
	Black esophagus (*n* = 19)	Non-black esophagus (*n* = 86)			
White blood cell in μL, median (IQR)	11650 (8300–14700)		8700 (6750–10925)	0.26	< 0.001
	13100 (8750–16700)	11200 (8225–14500)			
Hemoglobin in g/dL, (mean ± SD)	10.70 (3.47)		9.45 (2.81)	0.2	0.026
	10.53 (3.58)	10.78 (3.46)			
Albumin in g/dL, (mean ± SD)	3.11 (0.97)		3.00 (0.74)	0.06	0.483
	2.91 (1.14)	3.15 (0.93)			
BUN in mg/dL, median (IQR)	36.60 (20.50–62.40)		28.05 (16.90–37.92)	0.21	0.009
	35.10 (18.95– 67.85)	39.20 (20.65–61.90)			
Creatinine in mg/dL, median (IQR)	1.10 (0.87– 2.32)		0.80 (0.63–0.94)	0.37	< 0.001
	1.34 (0.90–2.63)	1.09 (0.84–2.10)			
Glucose in mg/dL, median (IQR)	141 (110–196)		124.00 (99.00–147.00)	0.20	0.015
	137 (106–172)	145 (111–203)			
CRP in mg/dL, median (IQR)	1.59 (0.35–5.22)		0.45 (0.23–1.93)	0.24	0.003
	1.37 (0.31–4.68)	1.64 (0.38–5.48)			
Lactate in mmol/L, median (IQR)	3.18 (1.96–5.14)		1.81 (1.38–2.38)	0.40	< 0.001
	3.45 (2.76–6.31)	3.02 (1.94–4.75)			

The following blood sampling data were not measured: albumin level in one case in the acute esophageal mucosal lesion (AEML) group (1 in the non-black esophagus); glucose level in six cases in the AEML group (one and five cases of the black and non-black esophagus, respectively) and three cases in the reflux esophagitis Los Angeles classification grade D (RE-D) group; C-reactive protein level in one case in the AEML group (1 in the non-black esophagus); and lactate level in 23 cases in the AEML group (5 and 18 cases of the black and non-black esophagus, respectively) and 15 cases in the RE-D group. BUN: Blood urea nitrogen; IQR: Interquartile range; SD: Standard deviation.

The AEML group had significantly more comorbidities at admission (57.5% *vs* 18.8%; RR: 3.10; 95%CI: 1.68–5.71; $P < 0.001$), with infection being the leading cause (21.7% *vs* 10.4%), followed by treatment for malignancy (8.5% *vs* 0%), prerenal failure (7.5% *vs* 2.1%), and after surgery (6.6% *vs* 2.1%) (Table 3).

The need for endoscopic hemostasis and endoscopic findings is shown in Table 4. RE-D showed more cases requiring endoscopic hemostasis (5.7% *vs* 22.9%; RR: 0.25; 95%CI: 0.10–0.63; $P = 0.004$). Esophageal hiatal hernias were significantly more frequent in the RE-D group (74.8% *vs* 97.9%; RR: 0.76; 95%CI: 0.68–0.86; $P < 0.001$). However, the percentage of atrophic gastritis was not significantly different (36.8% *vs* 31.2%; RR: 1.19; 95%CI: 0.73–1.94; $P = 0.586$), but gastric ulcers (29.2% *vs* 2.1%; RR: 14.17; 95%CI: 1.99–100.79; $P < 0.001$) and duodenal ulcers (19.8% *vs* 6.2%; RR: 3.20; 95%CI: 1.00–10.21; $P = 0.033$) were more significantly common in the AEML group.

The outcomes for each group are shown in Table 5. Mortality during hospitalization tended to be higher in the AEML group (14.2% *vs* 4.2%; RR: 3.43; 95%CI: 0.82–14.40; $P = 0.094$), and esophageal stenosis was not significantly different (3.8% *vs* 0%; $P = 0.309$). However, esophageal stenosis occurred only in the AEML group, specifically in those with non-black esophagus (0% in black esophagus *vs* 4.7% in non-black esophagus). Esophageal stenosis developed at an average onset of 27 d. Furthermore, endoscopic dilatation was performed in two cases, while central venous nutrition was performed in two other cases (Figure 6).

DISCUSSION

This study aimed to investigate whether AEML and RE-D are different diseases by distinguishing the

Table 3 Comorbidities at onset, *n* (%)

	AEML (*n* = 105)		RE-D (*n* = 48)	Risk ratio (95%CI)	*P* value
	Black esophagus (*n* = 19)	Non-black esophagus (*n* = 86)			
Comorbidities	61 (57.5)		9 (18.8)	3.10 (1.68–5.71)	< 0.001
Infection	23 (21.7)		5 (10.4)		
	3 (15.8)	20 (23.0)			
Treatment for malignancy	9 (8.5)		0 (0.0)		
	4 (21.1)	5 (5.7)			
Prerenal failure	8 (7.5)		1 (2.1)		
	1 (5.3)	7 (8.0)			
After surgery	7 (6.6)		1 (2.1)		
	1 (5.3)	6 (6.9)			
Stroke	4 (3.8)		1 (2.1)		
	0 (0.0)	4 (4.6)			
Alcoholic ketoacidosis	4 (3.8)		0 (0.0)		
	0 (0.0)	4 (4.6)			
Diabetic ketoacidosis/Hyperosmolar hyperglycemic syndrome	2 (1.9)		0 (0.0)		
	1 (5.3)	1 (1.1)			
Pulmonary embolism	1 (0.9)		0 (0.0)		
	0 (0.0)	1 (1.1)			
Peripheral arterial disease	1 (0.9)		0 (0.0)		
	0 (0.0)	1 (1.1)			
Duodenal ulcer	1 (0.9)		0 (0.0)		
	0 (0.0)	1 (1.1)			
Liver disease	1 (0.9)		0 (0.0)		
	1 (5.3)	0 (0.0)			
Heart failure	0 (0.0)		1 (2.1)		
	0 (0.0)	0 (0.0)			

AEML: Acute esophageal mucosal lesion; RE-D: Reflux esophagitis Los Angeles classification grade D; 95%CI: 95% confidence interval.

two esophageal diseases according to the oral shape of the esophageal mucosal injury. Here, approximately twice as many AEML cases were observed than RE-D cases. Multiple variables in this study exhibited significantly different results, indicating that the two diseases may be attributed to different pathologies. The AEML group was significantly less likely to require endoscopic hemostasis. Although no significant differences were detected, mortality during hospitalization was higher in the AEML group than in the RE-D group. Stenosis was observed in three cases, only in the AEML group.

This study is similar to previous research that compared AEML with RE-C and D regarding patient background, endoscopic findings, and blood sampling data[1]; however, several differences were observed. The AEML group was younger, had more comorbidities at onset, more patients with diabetes mellitus or previous malignancy as an underlying condition, and less need for endoscopic hemostasis. Mortality during hospitalization was also at a high percentage, although not significantly different.

Diabetes mellitus and previous malignancy history were highly prevalent in the AEML group because they were associated with comorbidities, such as increased susceptibility to infection[17]. Comorbidities deteriorate the general condition, resulting in microcirculatory disturbances. Although gastric acid reflux and impaired peripheral circulation were considered possible etiologies of AEML[1,5-7], this study's results, which included blood sampling data, strongly suggested an association with impaired peripheral circulation. The possible cause of the higher mortality observed in the AEML group

Table 4 Need for endoscopic hemostasis and endoscopic findings, *n* (%)

	AEML (*n* = 105)		RE-D (*n* = 48)	Risk ratio (95%CI)	*P* value
	Black esophagus (*n* = 19)	Non-black esophagus (*n* = 86)			
Need of endoscopic hemostasis	6 (5.7)		11 (22.9)	0.25 (0.10–0.63)	0.004
	0 (0.0)	6 (7.0)			
Hiatus hernia	77/103 (74.8)		46/47 (97.9)	0.76 (0.68–0.86)	< 0.001
	14/18 (77.8)	64/85 (74.4)			
Gastric atrophy	39 (36.8)		15 (31.2)	1.19 (0.73–1.94)	0.586
	5 (26.3)	34 (39.1)			
Gastric ulcer	31 (29.2)		1 (2.1)	14.17 (1.99–100.79)	< 0.001
	8 (42.1)	23 (26.4)			
Duodenal ulcer	21 (19.8)		3 (6.2)	3.20 (1.00–10.21)	0.033
	5 (26.3)	16 (18.4)			

AEML: Acute esophageal mucosal lesion; RE-D: Reflux esophagitis Los Angeles classification grade D; 95%CI: 95% confidence interval.
Hiatus hernia could not be evaluated in 2 cases in the AEML group (1 in black esophagus, 1 in non-black esophagus) and 1 case in the RE-D group.

Table 5 Outcomes in patients, *n* (%)

	AEML (*n* = 106)		RE-D (*n* = 48)	Risk ratio (95%CI)	*P* value
	Black esophagus (*n* = 19)	Non-black esophagus (*n* = 87)			
Mortality during hospitalization	15 (14.2)		2 (4.2)	3.43 (0.82–14.40)	0.094
	5 (26.3)	10 (11.5)			
Esophageal stenosis	4 (3.8)		0 (0.0)		0.309
	0 (0.0)	4 (4.6)			

AEML: Acute esophageal mucosal lesion; RE-D: Reflux esophagitis Los Angeles classification grade D; 95%CI: 95% confidence interval.

may also be related to the high prevalence of comorbidities. Additionally, the RE-D group had more elderly patients because more older women with kyphosis tend to have reflux esophagitis[18-21]. Elderly age is reportedly to be a high-risk factor for bleeding with reflux esophagitis[22], which may be associated with the need for endoscopic hemostasis.

Notably, this is the largest study to investigate the characteristics of AEML. In contrast to previous research, our study included only emergency cases presenting with upper gastrointestinal bleeding and used RE-D, which is an appropriate comparator for AEML. This study indicates that the incidence of AEML is higher than that of RE-D, suggesting that many AEML cases could be misdiagnosed as RE-D.

Although esophageal mucosal injury in AEML improves relatively quickly with the treatment of comorbidities, RE-D, which is caused by chronic gastric acid reflux, requires long-term acid-blocker therapy. Therefore, differentiating AEML from RE-D can prevent the unnecessary administration of acid blockers[1]. Although a stenosis risk of approximately 3.4% has been reported in reflux esophagitis cases[22], this study confirms that stenosis also develops in AEML cases. Several reports have shown that stenosis develops in black esophagus[23-25] and that black esophagus has a higher prevalence of stenosis than non-black esophagus[4]. However, this study indicated that stenosis could also develop in non-black esophagus. Stenosis was observed after approximately 1-mo; therefore, appropriate endoscopic follow-up is necessary even for non-black esophagus.

This study had some limitations. First, it was an observational study, and some of the possible information related to the outcomes, such as the duration of PPI administration and the history of treatment of varices with endoscopic variceal ligation, was not fully obtained. However, this is the largest study of AEML, adopting the more idealistic RE-D as a comparison. As a result, it may be possible to evaluate outcomes that could not be obtained in previous studies, such as the occurrence of stenosis. Second, the differences between AEML and RE-D in terms of endoscopic findings are not yet definitive. Although the present study was based on a previous report, further investigation is warranted.

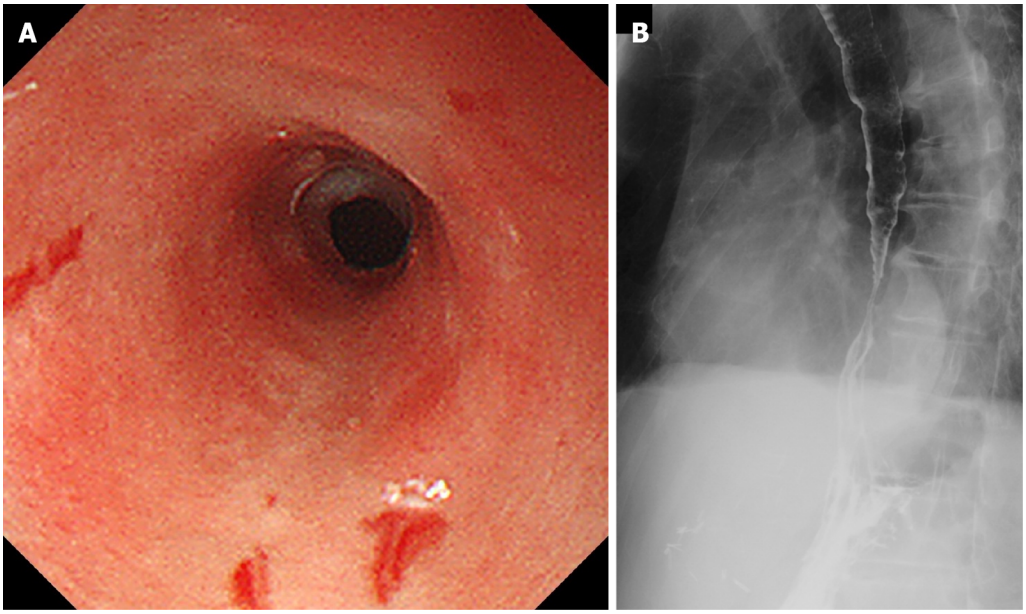

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Figure 6 A case of esophageal stenosis. A 75-year-old male patient developed non-black esophagus acute esophageal mucosal lesions during chemotherapy for colorectal cancer. The patient could not eat on the 27th day of onset. Upper endoscopy and esophagography showed esophageal stenosis. Symptoms improved after five endoscopic balloon dilatations. A: Upper endoscopy; B: Esophagography.

CONCLUSION

In conclusion, AEML and RE-D were clearly distinct diseases with different clinical features. AEML develops about twice as frequently as RE-D and may be a more familiar disease. Therefore, the possibility of AEML should be considered in cases of upper gastrointestinal bleeding with comorbidities.

ARTICLE HIGHLIGHTS

Research background

Recently, the concept of acute esophageal mucosal lesions (AEML), which encompasses both Black Esophagus and its milder variant, has been proposed, particularly in the Asian region.

Research motivation

The clinical manifestations of AEML remain inadequately understood and have been misdiagnosed as reflux esophagitis Los Angeles classification grade D (RE-D).

Research objectives

This study aimed to differentiate AEML from RE-D and to elucidate the clinical features of AEML.

Research methods

We selected emergency endoscopic cases of upper gastrointestinal bleeding characterized by circumferential esophageal mucosal injury and classified them into AEML and RE-D groups based on the shape of mucosal injury observed on the oral side. We subsequently examined patient demographics, blood sampling data, comorbidities at onset, endoscopic characteristics, and outcomes in each group.

Research results

Among the emergency cases, the incidence of AEML and RE-D were 3.1% and 1.4%, respectively. A comparison of multiple variables revealed significant differences, suggesting that these two conditions are distinct. The clinical features of AEML were characterized by a higher prevalence of comorbidities [risk ratio (RR): 3.10; $P < 0.001$] and a lower rate of endoscopic hemostasis compared with RE-D (RR: 0.25; $P < 0.001$). Additionally, in-hospital mortality was higher in the AEML group (RR: 3.43; $P = 0.094$), and stenosis was observed exclusively in the AEML group.

Research conclusions

AEML and RE-D were clearly distinct diseases with different clinical features. AEML may be more prevalent than previously thought, and the potential for its presence should be taken into account in cases of upper gastrointestinal bleeding accompanied by comorbidities.

Research perspectives

In the future, we aim to conduct studies on a larger sample size across multiple institutions.

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FOOTNOTES

Author contributions: Ichita C, Sasaki A, and Shimizu S contributed equally to this work; Ichita C contributed to the planning, data gathering, literature review, as well as writing and editing of this article; Shimizu S provided epidemiological advice and reviewed the statistical analysis; Sasaki A contributed to this study as an expert endoscopist; All authors commented on draft versions and approved the final version of the manuscript.

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Country/Territory of origin: Japan

ORCID number: Chikamasa Ichita 0000-0001-9210-7371; Akiko Sasaki 0000-0003-4219-554X; Sayuri Shimizu 0000-0003-0661-1171.

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ORIGINAL ARTICLE

Retrospective Study

Positive correlation between latent Epstein-Barr virus infection and severity of illness in inflammatory bowel disease patients

Hong-Tao Wei, Xiao-Wei Xue, Qing Ling, Peng-Yan Wang, Wei-Xun Zhou

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Hong-Tao Wei, Department of Gastroenterology, Beijing Friendship Hospital, Capital Medical University, Beijing 100050, China

Xiao-Wei Xue, Qing Ling, Peng-Yan Wang, Wei-Xun Zhou, Department of Pathology, Molecular Pathology Research Center, Peking Union Medical College Hospital, Chinese Academy of Medical Science, Beijing 100730, China

Corresponding author: Wei-Xun Zhou, MD, PhD, Chief Physician, Professor, Department of Pathology, Molecular Pathology Research Center, Peking Union Medical College Hospital, Chinese Academy of Medical Science, No. 1 Shuaifuyuan, Dongcheng District, Beijing 100730, China. zweixun@163.com

Abstract

BACKGROUND

Emerging studies indicate the critical involvement of microorganisms, such as Epstein-Barr virus (EBV), in the pathogenesis of inflammatory bowel disease (IBD). Immunosuppressive therapies for IBD can reactivate latent EBV, complicating the clinical course of IBD. Moreover, the clinical significance of EBV expression in B lymphocytes derived from IBD patients' intestinal tissues has not been explored in detail.

AIM

To explore the clinical significance of latent EBV infection in IBD patients.

METHODS

Latent EBV infection was determined by double staining for EBV encoded RNA and CD20 in colon specimens of 43 IBD patients who underwent bowel resection. Based on the staining results, the patients were divided into two groups, according to their latent EBV infection states - negative (n = 33) and positive (n = 10). Illness severity of IBD were assigned according to Crohn's disease activity index (ulcerative colitis) and Mayo staging system (Crohn's disease). The clinic-pathological data were analyzed between the two different latent EBV groups and also between the mild-to-moderate and severe disease groups.

RESULTS

Systolic pressure (P = 0.005), variety of disease (P = 0.005), the severity of illness (P = 0.002), and pre-op corticosteroids (P = 0.025) were significantly different between the EBV-negative and EBV-positive groups. Systolic pressure (P = 0.001),

variety of disease (P = 0.000), pre-op corticosteroids (P = 0.011) and EBV infection (P = 0.003) were significantly different between the mild-to-moderate and severe disease groups.

CONCLUSION

IBD patients with latent EBV infection may manifest more severe illnesses. It is suggested that the role of EBV in IBD development should be further investigated, latent EBV infection in patients with serious IBD should be closely monitored, and therapeutic course should be optimized.

Key Words: Epstein-Barr virus; Epstein-Barr virus encoded RNA; Inflammatory bowel disease; Crohn's disease; Ulcerative colitis

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Core Tip: Inflammatory bowel disease (IBD) patients with latent Epstein-Barr virus (EBV) infection may manifest more severe illnesses. It is suggested that the role of EBV in IBD development should be further investigated, latent EBV infection in patients with serious IBD should be closely monitored, and therapeutic course should be optimized.

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INTRODUCTION

Inflammatory bowel disease (IBD) collectively refers to the chronic inflammation of the intestinal lining due to the altered immune response of the gut microbiota. The cases of IBD are increasing globally at an alarming rate in the 21st century[1]. Two major types of IBD, namely Crohn's disease (CD) and ulcerative colitis (UC) are the most commonly occurring ones, seriously threatening global health burden. Therefore, understanding the pathogenesis of IBD plays an important role in the prevention and disease management. Emerging studies have indicated the critical involvement of microorganisms in the IBD pathogenesis and progression[2].

Epstein-Barr virus (EBV), also called human herpesvirus 4, infection accounts for one of the leading viral infections (approximately 90%) in humans. While most infections have been found to be involved in the oral route, other infection pathways like sexual transmission, transmission during blood transfusion, and organ transplantation have also been noted. EBV primarily targets resting B lymphocytes inducing their proliferation and polyclonal activities. Under this condition, adaptive immunity-associated cytotoxic T cells play important roles in regulating the EBV infection in the host. Notably, acutely infected individuals may present with infectious mononucleosis in a small cohort. Mostly, EBV integrates its DNA element into the memory B lymphocytes and establishes a lifelong latent infection status. While the virus can enter the lytic stage in individuals with compromised immune systems. In such cases, EBV may be reactivated, promoting the onset of virus-related malignancies, including Burkitt's lymphoma, Hodgkin's lymphoma, gastric cancer, and nasopharyngeal cancer subtypes[3]. In addition, EBV infection is associated with autoimmune diseases, such as multiple bone marrow fibrosis[4].

Moreover, the pathological connection between EBV and IBD has been receiving increasing attention in recent times[5,6]. Notably, immunosuppressive therapies, including anti-tumor necrosis factor alpha therapy, have been found to induce IBD pathogenesis and reactivate latent EBV[7], thereby increasing the susceptibility toward lymphocyte proliferation diseases. There is currently a lot of controversy regarding the direct involvement of EBV in inducing IBD and whether to include the EBV screening prior to IBD treatment initiation[8,9]. On the other hand, EBV co-infection may complicate the clinical course of IBD by aggravating the severity, chronicity, refraction to therapy, and increasing the recurrence rate of IBD[10]. However, most studies on EBV infection and IBD severity included a relatively small number of cases[6,11], and the clinical significance of EBV expression in B lymphocytes in the diseased intestinal tissue of IBD patients has not been discussed in detail.

Based on the findings from previous studies and the mode of EBV pathogenesis in relation to IBD, in this study, we examined 43 patients who underwent surgical resection, using EBV encoded RNA (EBER) and B lymphocyte (CD20) double staining technique to correlate the latent EBV infection and clinic-pathological data of IBD patients. Furthermore, we explored the clinical value of latent EBV

infection in predicting the severity of IBD.

MATERIALS AND METHODS

Sample collection

This study involved the retrospective review of 43 IBD patients' demographics and basic clinical information, including characteristics, medical history, clinical data, biochemical data, and pathological information. The enrolled patients underwent bowel resection surgery in the Department of Surgery at Peking Union Medical College Hospital between July 2010 and September 2013. These patients were diagnosed with either CD or UC by both pathological and clinical examinations. Exclusion criteria of the study included: (1) Extraintestinal chronic diseases, such as chronic renal insufficiency, heart failure, cirrhosis and severe chronic obstructive pulmonary disease, *etc*.; (2) Medical history of immunodeficiency diseases, such as chronic infections and/or history of inflammatory diseases, including vasculitis, systemic lupus erythematosus, and rheumatologic condition; and (3) History of synchronous malignancies.

Collection data included the following parameters, patient age at the time of surgery, gender, past medical history, variety and severity of disease, cause of surgery, surgery procedure, symptoms, signs, complications, accompanying diseases, treatment course, and biochemical data. Illness severity of CD and UC were assigned according to CD activity index and Mayo staging system.

Detection of EBV latent infection

EBV latent infection was diagnosed based on the results of double staining of EBER and CD20 (specific biomarker of B lymphocytes) markers. The double staining was performed following the pre-optimized staining protocol. Briefly, the IBD samples were fixed in 10% buffered formalin, dehydrated in alcohol, and embedded in paraffin. Paraffin blocks were sectioned at 4 μm thickness. Routine hematoxylin and eosin staining was performed for histopathological examinations. For double staining with EBER and CD20, *in situ* hybridization (ISH) using 3,3'-diaminobenzidine (DAB) chromogen was first performed, followed by immunohistochemistry (IHC) for CD20 using Fast Red DAB chromogen. IHC was performed on an automated immunostainer (BOND-MAX, Leica Microsystems), according to the manufacturer's protocols (Bond Polymer Refine RNA ISH protocol and Bond Polymer Refine Red IHC protocol, Leica Microsystems).

For each test sample, a second section (consecutive section wherever possible) was hybridized with a mixture of sense (non-complimentary) EBER probe as the negative control. The number of EBER positive cells, which were stained in the cell nucleus, were manually counted in the high-power field (HPF) for each optical field. B-lymphocytes cytomembrane showed positive staining for CD20 expression in IHC analysis.

Statistical analysis

Based on the double staining results, patients from the EBV latent infection (EBER positive) and EBV non-latent infection (EBER negative) were compared in terms of demographics, clinical characteristics, and biochemical findings. The clinic-pathological results were also compared between the patients with mild-to-moderate and severe disease symptoms. To analyze categorical variables, the χ^2 test was used. Measurement data that met the normal distribution were compared using the *t*-test between the two groups, and measurement data that did not conform to the normal distribution were compared using the Mann-Whitney *U* test between the two groups. To perform statistical analyses, SPSS 25.0 (SPSS for Window, SPSS Inc, Chicago, IL) was adopted. A $P < 0.05$ indicated significant differences.

RESULTS

The clinico-pathological characteristics of patients

All clinic-pathological data are detailed in Table 1 and Table 2. Among the 43 IBD patients recruited to this study, there were 34 male- and 9 female patients. The age of the patients ranged from 13 to 70 years, and the mean age was 43.6 years. Among these patients, 20 patients had a history of smoking, and 17 patients had an alcohol drinking habit. Twenty-seven patients were diagnosed with CD and 16 patients with UC. The number of mild, moderate and severely affected patients were 10, 21, and 12, respectively. Three patients underwent surgery as they were seriously required, 9 patients were non-responsive to internal medicine therapy, and the other patients were medically required. Regarding the surgical procedures, 14 patients received laparoscopic partial enterectomy, and the other 29 patients had partial enterectomy through open surgery. The mean heart rate of these patients was 87.2 times/min, the median systolic pressure was 101 mmHg, and the mean diastolic pressure was 66.2 mmHg. At admission, 17 patients complained of fever, 42 patients reported abdominal pain, 29 patients had diarrhea, 20 patients had fecal occult blood, 15 patients had mucus or bloody purulent stool, 39 patients

Table 1 Basic information on patients (*n* = 43)

Variables	Data
Characteristics	
Sex (Male/female)	34/9
Age (yr), mean ± SD	43.6 ± 2.7
Smoking (No/Yes)	23/20
Drinking (No/Yes)	26/17
Clinical data	
Crohn's disease/ulcerative colitis	27/16
Location	
Crohn disease (L1/L2/L3/L4)	9/0/18/0
Ulcerative colitis (E1/E2/E3)	0/2/14
Severity of illness (Mild/moderate/severe)	10/21/12
Cause of surgery	
Patient required	3
Non-response to intern medicine therapy	9
Medical required	31
Intestinal obstruction	18
Fistula	5
Definite diagnosis requires	1
Gastrointestinal bleeding	3
Intestinal stenosis	1
Gastrointestinal perforation	2
Carcinogenesis	1
Pre-op aminosalicylic acid (No/Yes)	8/35
Pre-op corticosteroids (No/Yes)	24/19
Pre-op immunosuppressive therapy (No/Yes)	34/9
Surgical procedures (Laparoscopic/open surgery)	14/29
Course (d), mean ± SD	73.6 ± 11.7
Indicators to be explored	
Latent Epstein-Barr virus infection (Negative/positive)	33/10

had a history of losing weight, 14 patients had abdominal mass, 2 patients had toxic megacolon, 14 patients had a gastrointestinal hemorrhage, 24 patients had intestinal obstruction, 9 patients had intestinal perforation, 8 patients had a perianal disease, and 16 patients had extraintestinal manifestations. Before surgery, 35 patients received aminosalicylic acid, 19 patients had corticosteroids, and 9 patients undertook immunosuppressive therapy. The mean treatment course was 73.6 d.

Histochemical double staining results of EBER and CD20 in IBD colon tissues

EBER positive staining, mainly distributed in the nucleus of B lymphocytes, suggested that the EBV latent infection status in the diagnosed patients. We found ten cases (23.3%) of IBD with EBV positive diagnosis, including 2 (7.4%) CD and 8 (50%) UC patients. Figure 1A, D and G show the normal control colon tissue.

In two cases of CD patients with EBV latent infection, numbers of EBER-positive B lymphocytes ranged from 8 to15 cells per HPF, and the positively stained cells were scattered throughout the field, accounting for 80%-90% EBER-positive B lymphocytes. The CD pathology was manifested as the full-wall inflammation, but EBER-positive B lymphocytes were mainly concentrated in the mucosa and submucosa (Figure 1B, E, and H).

Table 2 Vital signs, clinical manifestations and biochemical data of the patients (*n* = 43)

Variables	Data
Vital signs	
Heart rate (time/min), mean ± SD	87.2 ± 3.1
Systolic pressure (mmHg), median (Q1, Q3)	101.0 (94.5, 113.0)
Diastolic pressure (mmHg), mean ± SD	66.2 ± 1.7
Clinical manifestations	
Fever (No/Yes)	26/17
Abdominal pain (No/Yes)	1/42
Diarrhea (No/Yes)	14/29
Fecal occult blood (No/Yes)	23/20
Mucus or bloody purulent stool (No/Yes)	28/15
Lose weight (≥ 5 kg) (No/Yes)	4/39
Abdominal mass (No/Yes)	29/14
Toxic megacolon (No/Yes)	41/2
Gastrointestinal hemorrhage (No/Yes)	29/14
Intestinal obstruction (No/Yes)	19/24
Intestinal perforation (No/Yes)	34/9
Perianal disease (No/Yes)	35/8
Extraintestinal manifestations (No/Yes)	27/16
Oral ulcer (Yes)	13
Pyoderma gangrenosum (Yes)	1
Peripheral spondyloarthritis (Yes)	6
Others (Yes)	2
Biochemical data	
White blood cell (× 10^9/L), mean ± SD	6.7 ± 0.6
Neutrophil count (× 10^9/L), mean ± SD	4.6 ± 0.5
Hemoglobin (g/L), mean ± SD	103.6 ± 4.5
Platelets (× 10^9/L), mean ± SD	343.2 ± 25.7
Alanine aminotransferase (U/L), median (Q1, Q3)	11.0 (8.0, 14.0)
Aspartate aminotransferase (U/L), median (Q1, Q3)	14.0 (10.3, 18.8)
Albumin (g/L), mean ± SD	30.6 ± 1.5
Lactate dehydrogenase (U/L), median (Q1, Q3)	127.0 (102.0, 140.0)
Creatinine (μmol/L), mean ± SD	60.7 ± 3.0
Potassium (mmol/L), mean ± SD	3.8 ± 0.1
Prothrombin time (s), mean ± SD	12.2 ± 0.2
Activated partial thromboplastin time (s), median (Q1, Q3)	29.3 (26.5, 32.9)
C-reactive protein (g/L), median (Q1, Q3)	26.3 (16.3, 71.4)

In cases of 8 UC patients with EBV latent infection, numbers of EBER-positive B lymphocytes ranged from13 to 60 cells/HPF, and with a random distribution of the EBER-positive cells, accounting for 30%-70% cells per HPF. Like CD patients, EBER-positive B lymphocytes in UC patients were also concentrated in the mucosa and submucosa (Figure 1C, F, and I). Importantly, all cases of UC with EBV latent infection showed a full colon type pathology.

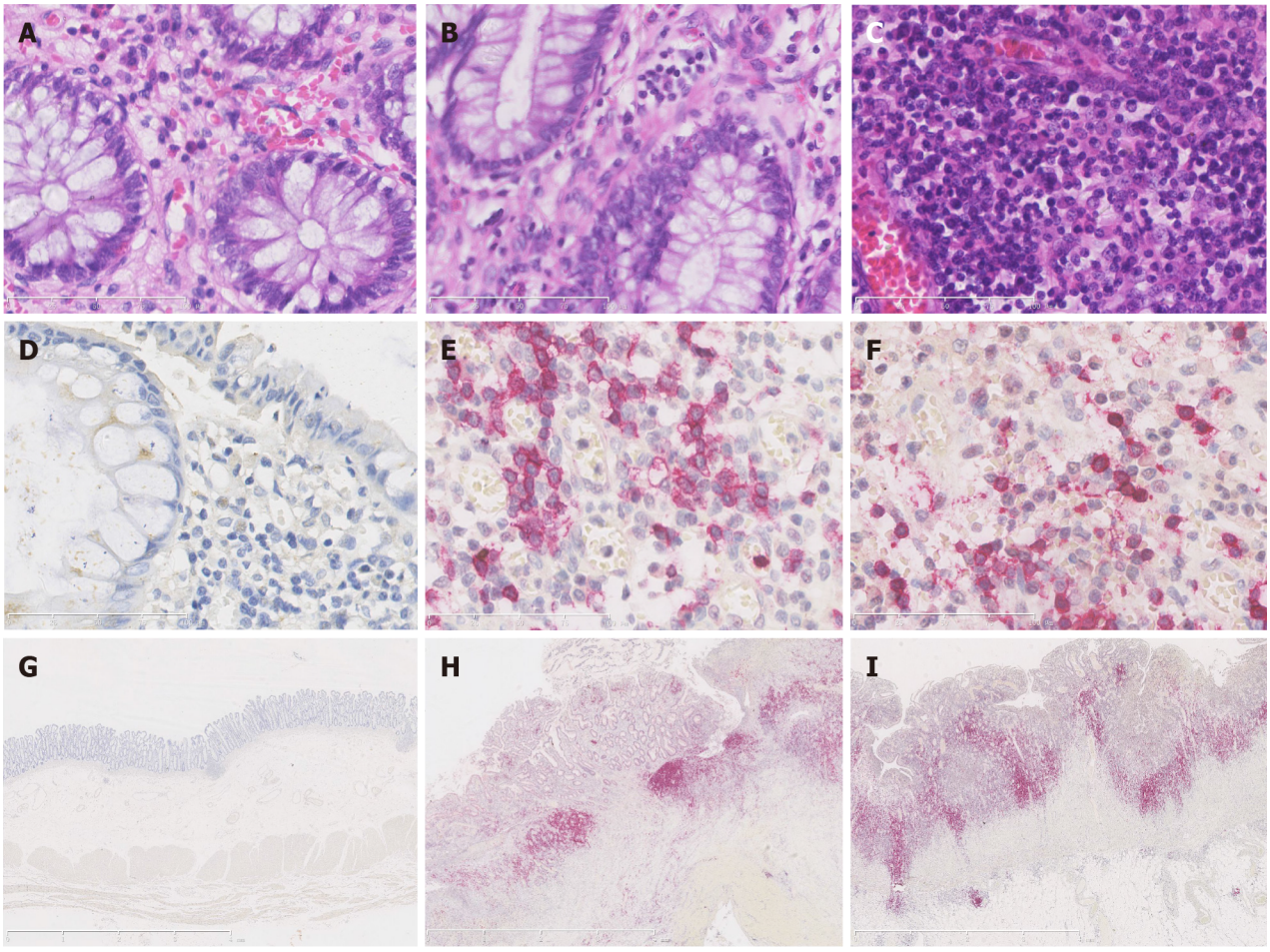

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Figure 1 Normal control colon tissue and latent Epstein-Barr virus infection in Crohn's disease and ulcerative colitis-affected colon tissues. A, D, G: Normal control colon tissue; B, E, H: Colon tissue in Crohn's disease patients; C, F, I: Colon tissue in ulcerative colitis patients. A-C: Hematoxylin and eosin staining, ×400; D-F: CD20 and Epstein-Barr virus-encoded RNA (EBER) double staining, ×400; G-I: CD20 and EBER double staining, ×12.5.

Correlation between latent EBV infection and clinic-pathological features

Clinico-pathological data of all patients were compared between the EBER-positive and EBER-negative expressions in B lymphocyte groups, according to the IHC results, as demonstrated in Table 3. Systolic pressure (P = 0.005), variety of disease (P = 0.005), the severity of illness (P = 0.002), and pre-op corticosteroids (P = 0.025) were significantly different between the two groups. While no significant difference was found between the two groups in terms of other characteristics, clinical and biochemical data.

Correlation between severity of disease and basic medical information

Clinico-pathological data of all patients were also compared between the mild-to-moderate and severe patient groups, as demonstrated in Table 4. Systolic pressure (P = 0.001), variety of disease (P = 0.000), pre-op corticosteroids (P = 0.011) and latent EBV infection (P = 0.003) were significantly different between the two groups, and no significant difference was found between the two groups in terms of other categories of characteristics, clinical and biochemical data.

DISCUSSION

After excluding some confounding factors, our results showed that the latent EBV infection detected in colon tissue of IBD patients was positively related to the severity of the disease, and patients with latent EBV infection in their colon tissues were severely ill. Studies have confirmed that EBV can cause immune disorders, and IBD is one of the autoimmune diseases. Therefore, we hypothesized that EBV infection could aggravate the severity of IBD through complex immune mechanisms. In addition, advanced stage IBD patients with altered immune response and immunosuppressive therapy could also show increased susceptibility to EBV. Eventually, the immune imbalance following EBV infection and the resulting deterioration of the IBD stage are most likely to be mutually causal, leading to a vicious

Table 3 Summary of factors related to latent Epstein-Barr virus infection

Variables	Epstein-Barr virus-negative (n = 33)	Epstein-Barr virus-positive (n = 10)	Statistical value (t/χ^2)	P value
Systolic pressure (mmHg), mean ± SD	106.56 ± 11.51	94.33 ± 7.71	2.991 (t)	0.005[1]
Variety of disease			7.965 (Adjusted)	0.005[1]
Crohn disease	25	2		
Ulcerative colitis	8	8		
Severity of illness			12.293 (Likelihood ratio)	0.002[1]
Mild	8	2		
Moderate	20	1		
Severe	5	7		
Pre-op corticosteroids			5.017 (Adjusted)	0.025[1]
No	22	2		
Yes	11	8		

[1]Significant differences.

Table 4 Data comparison between patients with mild/moderate or severe inflammatory bowel disease

Variables	Mild/moderate (n = 31)	Severe (n = 12)	Statistical value (t/χ^2)	P value
Systolic pressure (mmHg), mean ± SD	107.33 ± 11.698	94.45 ± 7.71	3.482 (t)	0.001[1]
Variety of disease			12.542 (Adjusted)	0.000[1]
Crohn disease	25	2		
Ulcerative colitis	6	10		
Pre-op corticosteroids			6.408	0.011[1]
No	21	3		
Yes	10	9		
Latent Epstein-Barr virus infection			8.911 (Adjusted)	0.003[1]
Negative	28	5		
Positive	3	7		

[1]Significant differences.

cycle of disease aggressiveness and poor prognosis. However, unlike the effect of EBV on multiple myeloma, we observed that not all the patients with severe IBD had EBV-positive diagnosis, which led us to postulate that EBV infection could be one of the critical factors in inducing severe IBD symptoms, but was not an indispensable etiological factor. In addition to the involvement of EBV, the severity of IBD must have involved other complex pathophysiological mechanisms. Based on our findings, we suggest that patients with latent EBV infection should be closely monitored, and the effect of EBV infection on the IBD patients should be given attention, and the pathogenesis between them should be clearly defined.

The clinic-pathological relationship between EBV and IBD has always attracted the attention of researchers and clinicians. For example, Dimitroulia *et al*[12], and Li *et al*[13], have shown that the prevalence of EBV in the intestinal tissue of patients with IBD is significantly higher than that in the control group. Moreover, patients with a high prevalence of EBV infection exhibit worsening disease symptoms, as compared to non-EBV infected patients who present remission incidences, suggesting that the severity of IBD may be related to the EBV infection[12,13]. In addition, it has also been found that the positive expression of EBV in IBD patients is higher in refractory patients than in the control group. Further, the higher EBV positive expression has been linked to the mucous damage and high clinical indexes of activity[6,11,14]. Our results were consistent with these findings, suggesting that the positive expression of EBV in latent infection might be related to the severity of IBD. However, most of the above

studies used specimens from patients' serum or colonoscopy biopsies, while the specimens used in our study were specimens removed from bowel surgery. Relative to the determination of EBV in serum, EBV in bowel resection specimens can better reflect the direct role of EBV in the IBD pathology. In addition, compared to the EBV determination in colonoscopy biopsy specimens, the EBV of the bowel resection specimens can better reflect the EBV infiltration of the entire layer of the bowel wall. Therefore, our results based on the bowel resection specimens were more reliable and precise. We also obtained morphological data of EBV by IHC analysis of the colon wall of IBD patients to determine the exact location of EBV in the B lymphocytes of intestinal tissue, which was also the verification and supplementary to the previous studies.

In our study, we found that latent EBV infection rates were related to the pre-op corticosteroid administration. Crosstalk between EBV-positivity and corticosteroid administration has also been found in another study[14]. We thought two aspects should be considered to explain these reasons. Firstly, latent EBV infection might be related to the severity of the disease, and the disease severity was directly proportional to the increasing dose of corticosteroids, indicating EBV infection was related to corticosteroids. Secondly, following the corticosteroid therapy, the immunosuppressive condition of patients might have increased their susceptibility toward EBV infection. However, the exact reason is needed to be confirmed by cohort research in the future.

Interestingly, we also found that the proportion of latent EBV infection in UC patients was higher than that in CD patients. In addition, all UC patients with latent EBV infection exhibited full colon type pathology. The reason for the difference in the proportion of EBV latent infection in the UC and CD patients and the relationship between latent EBV infection and subtypes in UC patients are worthy of further research and discussion.

So far, there is no consensus on whether all IBD patients mandatorily require EBV infection testing at the early stage. At present, the detection of EBV infection in IBD patients is mainly focused on patients who require azathioprine treatment, which may increase the activation of EBV and the incidence of related lymphatic system proliferative diseases. Studies suggest that before starting to use azathioprine, detection of EBV serology should be performed first, following the counting of natural killer cells during treatment to determine whether the patient has the risk of developing an abnormally serious primary EBV infection and EBV-related malignancies[5,8,15-17]. But other studies have also shown that the activation of EBV has no direct connection with the impact of immunosuppressive therapy[13,18]. Notably, the exposure to EBV in adulthood is almost universal, and the incidences of hematological malignancies in IBD are rare. In the cost-benefit analysis, it seems that the value of EBV detection before the IBD patient starts treatment is limited[9,19-21]. Our results suggest that it is important not only to consider the activation of EBV by immunosuppressive drugs that can lead to related malignant tumors but also to understand the relationship between EBV infection and the severity of IBD. With regard to the question of whether to carry out EBV testing first in IBD patients, we suggest that determination should be made after the role of EBV infection on IBD progression rate and deterioration are clarified, or it can be used in high-risk patient populations (such as patients with full colon UC or those who require corticosteroid therapy for the disease).

In addition to the aforementioned obstacles, there are still several unsolved questions about the relation of EBV infection with IBD severity. For example, whether IBD patients with latent EBV infection should be treated for EBV. And recent studies have shown that different EBV strains have inconsistent pathogenic effects on nasopharyngeal carcinoma[22]. However, the exact causal relationship between different EBV strains and the progression of IBD is not clear yet.

Small sample size and one-center study were also considerable drawbacks of this retrospective study. A large sample size and multi-center studies to explain the serious relationship between latent EBV infection and the condition of IBD patients are needed for detailed investigation in the future.

CONCLUSION

In conclusion, our findings indicated that IBD patients with latent EBV infection might manifest severe symptoms. We suggest that the role of EBV in IBD development should be further investigated, and latent EBV infection in patients with serious IBD should be closely monitored and optimized treatment.

ARTICLE HIGHLIGHTS

Research background

Emerging studies indicate the critical involvement of microorganisms, such as Epstein-Barr virus (EBV), in the pathogenesis of inflammatory bowel disease (IBD). Immunosuppressive therapies for IBD can reactivate latent EBV, complicating the clinical course of IBD.

Research motivation

This study explored the clinical significance of EBV expression in B lymphocytes derived from IBD patients' intestinal tissues in detail.

Research objectives

This study aimed to explore the clinical significance of latent EBV infection in IBD patients.

Research methods

Double staining for EBV encoded RNA and CD20 to determine latent EBV infection. The clinic-pathological data were analyzed between the two different latent EBV groups and also between the mild-to-moderate and severe disease groups.

Research results

Systolic pressure, variety of disease, the severity of illness, and pre-op corticosteroids were significantly different between the EBV-negative and EBV-positive groups. Systolic pressure, variety of disease, pre-op corticosteroids and EBV infection were significantly different between the mild-to-moderate and severe disease groups.

Research conclusions

Latent EBV infection is positively related to severity of IBD illness.

Research perspectives

The role of EBV in IBD development should be further investigated; latent EBV infection in patients with serious IBD should be closely monitored.

FOOTNOTES

Author contributions: Wei HT made a major contribution to the study design, data analysis, and manuscript writing; Xue XW and Zhou WX had the same contribution to the manuscript by providing advice for the study design and giving suggestions to improve the manuscript writing; Ling Q and Wang PY collected and reviewed the experimental data; and all authors read and approved the final version of the manuscript.

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Country/Territory of origin: China

ORCID number: Hong-Tao Wei 0000-0001-7394-7447; Xiao-Wei Xue 0000-0002-9174-8211; Peng-Yan Wang 0000-0002-8967-986X; Wei-Xun Zhou 0000-0002-7459-7343.

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ORIGINAL ARTICLE

Clinical Trials Study

Efficacy and outcome of extensive intraoperative peritoneal lavage plus surgery *vs* surgery alone with advanced gastric cancer patients

En-Dong Song, Heng-Bo Xia, Li-Xiang Zhang, Jun Ma, Pan-Quan Luo, Lai-Zhi Yang, Ben-Hong Xiang, Bai-Chuan Zhou, Lei Chen, Hui Sheng, Yin Fang, Wen-Xiu Han, Zhi-Jian Wei, A-Man Xu

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En-Dong Song, Lai-Zhi Yang, Ben-Hong Xiang, Yin Fang, Department of General Surgery, The First People's Hospital of Wuhu City, Wuhu 241000, Anhui Province, China

Heng-Bo Xia, Li-Xiang Zhang, Pan-Quan Luo, Bai-Chuan Zhou, Wen-Xiu Han, Zhi-Jian Wei, A-Man Xu, Department of General Surgery, The First Affiliated Hospital of Anhui Medical University, Hefei 230032, Anhui Province, China

Jun Ma, Department of Surgical Oncology, Anqing Municipal Hospital, Anqing 246000, Anhui Province, China

Lei Chen, Department of General Surgery, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou 325000, Zhejiang Province, China

Hui Sheng, Department of Obstetrics and Gynecology, East Hospital Area of Wuhan Fourth Hospital, Wuhan 430030, Hubei Province, China

Corresponding author: A-Man Xu, MD, Doctor, Department of General Surgery, The First Affiliated Hospital of Anhui Medical University, Ji-Xi Road, Hefei 230032, Anhui Province, China. xuaman@ahmu.edu.cn

Abstract

BACKGROUND

Gastric cancer (GC) is one of the most common malignant tumors. After resection, one of the major problems is its peritoneal dissemination and recurrence. Some free cancer cells may still exist after resection. In addition, the surgery itself may lead to the dissemination of tumor cells. Therefore, it is necessary to remove residual tumor cells. Recently, some researchers found that extensive intraoperative peritoneal lavage (EIPL) plus intraperitoneal chemotherapy can improve the prognosis of patients and eradicate peritoneal free cancer for GC patients. However, few studies explored the safety and long-term outcome of EIPL after curative gastrectomy.

AIM

To evaluate the efficacy and long-term outcome of advanced GC patients treated with EIPL.

METHODS

According to the inclusion and exclusion criteria, a total of 150 patients with advanced GC were enrolled in this study. The patients were randomly allocated to two groups. All patients received laparotomy. For the non-EIPL group, peritoneal lavage was washed using no more than 3 L of warm saline. In the EIPL group, patients received 10 L or more of saline (1 L at a time) before the closure of the abdomen. The surviving rate analysis was compared by the Kaplan-Meier method. The prognostic factors were carried out using the Cox appropriate hazard pattern.

RESULTS

The basic information in the EIPL group and the non-EIPL group had no significant difference. The median follow-up time was 30 mo (range: 0-45 mo). The 1- and 3-year overall survival (OS) rates were 71.0% and 26.5%, respectively. The symptoms of ileus and abdominal abscess appeared more frequently in the non-EIPL group ($P < 0.05$). For the OS of patients, the EIPL, Borrmann classification, tumor size, N stage, T stage and vascular invasion were significant indicators. Then multivariate analysis revealed that EIPL, tumor size, vascular invasion, N stage and T stage were independent prognostic factors. The prognosis of the EIPL group was better than the non-EIPL group ($P < 0.001$). The 3-year survival rate of the EIPL group (38.4%) was higher than the non-EIPL group (21.7%). For the recurrence-free survival (RFS) of patients, the risk factor of RFS included EIPL, N stage, vascular invasion, type of surgery, tumor location, Borrmann classification, and tumor size. EIPL and tumor size were independent risk factors. The RFS curve of the EIPL group was better than the non-EIPL group ($P = 0.004$), and the recurrence rate of the EIPL group (24.7%) was lower than the non-EIPL group (46.4%). The overall recurrence rate and peritoneum recurrence rate in the EIPL group was lower than the non-EIPL group ($P < 0.05$).

CONCLUSION

EIPL can reduce the possibility of perioperative complications including ileus and abdominal abscess. In addition, the overall survival curve and RFS curve were better in the EIPL group.

Key Words: Extensive intraoperative peritoneal lavage; Advanced gastric cancer; Prognosis; Recurrence; Overall survival

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Core Tip: It has been found that extensive intraoperative abdominal lavage (EIPL) combined with abdominal chemotherapy can improve the prognosis of patients with gastric cancer. However, few studies have explored the safety and long-term efficacy of EIPL after therapeutic gastrectomy. This randomized study evaluated the efficacy and long-term outcome of advanced gastric cancer patients with extensive intraoperative peritoneal lavage.

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INTRODUCTION

Gastric cancer (GC) is one of the most common malignant tumors. Its morbidity and mortality in China have been increasing in recent years[1,2]. Despite great advances in surgery and other treatment, the 5-year survival rate of GC is low[3,4]. After resection, one of the major problems is its peritoneal dissemination and recurrence. Peritoneal recurrence is more likely to occur in advanced GC patients. Although chemotherapy is applied, the prognosis of these patients remains poor[5].

Some free cancer cells may still exist after resection. In addition, the surgery itself may lead to the dissemination of tumor cells[6,7]. Therefore, it is necessary to remove residual tumor cells. Recently, extensive intraoperative peritoneal lavage (EIPL) has received more attention. It is a useful treatment that can wash the abdominal cavity completely using 10 L of physiological saline (up to 10 times). Based on a previous study, EIPL is a safe and simple procedure[8]. Some researchers found that EIPL plus intraperitoneal chemotherapy can improve the prognosis of patients[9]. This technique can eradicate peritoneal free cancer, which is beneficial for the recurrence-free survival (RFS) of GC patients[7,10]. However, few studies explored the safety and long-term outcome of EIPL after curative gastrectomy.

In this study, we explored the efficacy and 3-year outcome of advanced GC patients with the technique of EIPL and analyzed the possible mechanism.

MATERIALS AND METHODS

Patients

The study population was advanced GC patients with clinically T3 or T4 and M0 disease according to computed tomographic scans and ultrasonographic gastroscopy. The seventh American Joint Committee was used for the tumor, node and metastasis stage. Each patient signed the informed consent, and this study was approved by the institutional review board of The First Affiliated Hospital of Anhui Medical University, Anqing Municipal Hospital and The First Affiliated Hospital of Wenzhou Medical University.

Inclusion and exclusion criteria

According to the inclusion and exclusion criteria, patients were included in the research. The inclusion criteria included: (1) All patients were confirmed GC with T3/4NanyM0; (2) The surgery was definite and complete resection of cancer; (3) These patients did not have heart disease or any important organ failure; and (4) The patient was available for follow-up. The exclusion criteria included: (1) The patient had previous malignant tumors or various primary tumors; and (2) The patient had accepted radiation treatment or chemotherapy treatment previously.

Procedure

If patients were confirmed with cT3 or cT4 and M0 disease and were suitable for radical gastrectomy, they were formally included in the study and then randomized. Patients were randomized to the EIPL group or non-EIPL group in a 1:1 ratio. Allocation was performed using sealed opaque envelopes that contained computer-generated random numbers and the procedure to which patients were allocated. Research participants were randomized to the EIPL arm or non-EIPL arm based on random permuted blocks with a varying block size of four, assuming equal allocation between treatment arms. The cytological examination was performed by introducing saline into the cavity. The cytological statuses were negative. After the exploratory operation, the envelopes were opened to determine whether EIPL was applied. A total, proximal or distal gastrectomy was completed depending on the primary tumor location. Total gastrectomy or partial resection with D2 lymphadenectomy was performed by the guidelines of the Japanese Research Society[11]. All patients received laparotomy, which reduced the influence of surgical methods. In addition, after clinical preoperative evaluation, the patient's preoperative nutritional status was good.

For the non-EIPL group, peritoneal lavage was washed using no more than 3 L of warm saline. In the EIPL group, patients received 10 L or more of saline (1 L at a time) before the closure of the abdomen. Patients were excluded if the stage was not detected as T3 or T4 and M0. In the end, 100 patients were finally included in this study between March 2016 and March 2017. The external population included 50 GC patients who were hospitalized at The First Affiliated Hospital of Wenzhou Medical University and Anqing Municipal Hospital from March 2016 to November 2017, and the methods and procedures were consistent with our group (Supplementary Figure 1).

Data collection and follow-up

The patient's demographic and clinicopathological data were recorded, including age, sex, tumor location, tumor size, differentiation grade, pathological type, *etc*. The routine laboratory data including neutrophil, lymphocyte, platelet, carcinoembryonic antigen (CEA), *etc* were collected.

Peripheral blood tests were obtained within 1 wk before surgery and on the 2nd day after surgery. The cutoff value of CEA was determined according to the normal level. We determined the following indexes: neutrophil-to-lymphocyte ratio (NLR); neutrophil count; and lymphocyte count. These two variables were grouped into the low group and high group according to the optimal cutoff values, which were calculated based on the Youden index [maximum (sensitivity + specificity-1)][12].

Tumor location was classified into five subgroups according to the anatomy of the stomach: gastric cardia; fundus of stomach; body of stomach; gastric antrum; and pylorus. Among them, upper means cardia and fundus of stomach. Middle means body of stomach. Low means gastric antrum and pylorus. To prevent the influence of esophageal cancer on the results of this study, gastroesophageal junction tumors were not included in our research. The postoperative complications, the length of hospital stay and other outcomes were also recorded. The complications included abscess, leakage, bleeding, *etc*.

After the operation, the patients received eight 3-wk cycles of oral S-1 plus intravenous oxaliplatin. Diagnosis of recurrence was made by abdominal ultrasound, computed tomography, magnetic resonance imaging, gastroscopy and pathology tests. We collected follow-up data through telephone and outpatient visits every 90 d until December 2020.

Statistical analysis

The baseline characteristics analysis of the non-EIPL group and EIPL group patients was performed including age, sex, body mass index (BMI), smoking status, tumor location, differentiated grade, T stage, N stage, tumor size, Borrmann classification, CEA, neutrophil count, lymphocyte count, NLR and platelet count. The outcome after surgery was analyzed, including type of surgery, the time from surgery to first flatus, postoperative hospital stays, abdominal pain, ileus, abdominal abscess, leakage, bleeding, neutrophil count, lymphocyte count, NLR and platelet count. Continuous variables were expressed as mean ± SD and were analyzed by the Student's *t*-test. Categorical values were identified by count (percent) and were analyzed by χ^2 test or Fisher exact test. The Kaplan-Meier method and Log-rank test were used to compare the prognosis of the non-EIPL group and EIPL group. In addition, variables including sex, age, EIPL/non-EIPL, tumor size, type of surgery, tumor location, Borrmann classification, differentiated grade, T stage, N stage and vascular invasion were enrolled into the univariate analysis using the Cox proportional hazards model to determine the factors influencing the GC patient's overall survival (OS). Subsequently, risk factors screened by univariate analysis ($P < 0.05$) were enrolled into the multivariate analysis using the Cox proportional hazards model to determine the independent risk factors influencing the OS. The SPSS app (17.0 version) was used for statistical analysis.

RESULTS

Baseline characteristics

The baseline characteristic analysis of the 150 patients was shown in Table 1. Among them, 109 (72.67%) were male, and 41 (27.33%) were female. The median age was 67 years (range: 35-80 years). The basic information in the EIPL group and the non-EIPL group had no significant difference. The median follow-up time was 30 mo (range: 0-45 mo). The 1- and 3-year OS rates were 71.0% and 26.5%, respectively.

Surgical outcome after gastrectomy

Table 2 presented the results of surgery. There was no significant difference in time (surgery to first flatus), postoperative hospital stay, abdominal pain, bleeding, leakage or another blood index between the two groups ($P > 0.05$), but the symptoms of ileus and abdominal abscess appeared more frequently in the non-EIPL group ($P < 0.05$).

OS of patients

Risk factors of OS were shown in Table 3. The result showed that the EIPL, Borrmann classification, tumor size, N stage, T stage and vascular invasion were significant indicators. Then multivariate analysis revealed that EIPL, tumor size, vascular invasion, N stage and T stage were independent prognostic factors (Table 4). The survival curve (Figure 1A) revealed that the prognosis of the EIPL group was better than the non-EIPL group ($P < 0.001$). The 3-year survival rate of the EIPL group (38.4%) was higher than the non-EIPL group (21.7%).

RFS of patients

The risk factor of RFS included EIPL, N stage, vascular invasion, type of surgery, tumor location, Borrmann classification and tumor size (Supplementary Table 1). EIPL and tumor size were independent risk factors (Supplementary Table 2). The RFS curve of the EIPL group was better than the non-EIPL group ($P = 0.004$) (Figure 1B), and the recurrence rate of the EIPL group (24.7%) was lower than the non-EIPL group (46.4%).

Patterns of recurrence

The recurrence rate of lymph node, node and other organs in the EIPL group and the non-EIPL group were not significantly different ($P > 0.05$), but the overall recurrence rate and peritoneum recurrence rate in the EIPL group was lower than the non-EIPL group ($P < 0.05$) (Supplementary Table 3).

DISCUSSION

Positive peritoneal lavage cytology and peritoneal recurrence are associated with the prognosis of GC [13,14]. Previous research has reported that EIPL combined with intraperitoneal treatment is an effective treatment for GC patients[9] that can reduce the recurrence rate of advanced patients. However, the safety and effect of EIPL alone remained unclear. Therefore, this study explored the clinical value of EIPL.

Table 1 The baseline characteristic analysis of the patients

Variables	Non-EIPL group, *n* = 75	EIPL group, *n* = 75	*P* value
Age in yr	66.93 ± 9.38	64.55 ± 8.22	0.099
Sex			0.200
Male	51	58	
Female	24	17	
BMI in kg/m^2	21.51 ± 2.29	21.64 ± 3.34	0.786
Smoking status			0.373
Yes	55	50	
No	20	25	
Tumor location			0.260
Upper	21	14	
Middle	11	17	
Low	43	44	
Differentiated grade			0.121
High	0	0	
Middle	55	45	
Low	20	30	
T stage			0.405
T3	4	2	
T4	71	73	
N stage			0.112
N0	13	24	
N1	18	12	
N2	14	17	
N3	30	22	
Tumor size in cm	5.52 ± 2.21	5.37 ± 2.32	0.671
Borrmann classification			0.100
II	7	14	
III	68	61	
CEA in g/L	16.21 ± 78.06	14.13 ± 35.88	0.834
Neutrophil count as 10^9/L	3.49 ± 1.32	4.71 ± 8.39	0.215
Lymphocyte count as 10^9/L	1.35 ± 0.47	1.76 ± 2.48	0.164
NLR	3.02 ± 1.96	3.03 ± 2.20	0.989
Platelet as 10^9/L	202.52 ± 61.39	226.19 ± 90.94	0.064

BMI: Body mass index; CEA: Carcinoembryonic antigen; EIPL: Extensive intraoperative peritoneal lavage; NLR: Neutrophil to lymphocyte ratio.

Our results indicated that the OS curve and RFS curve of the EIPL group were better than the non-EIPL group, and the technique of EIPL was a significant factor in OS and RFS in advanced GC patients. EIPL may reduce the recurrence rate of the tumor and improve the outcome for patients. Yamamoto *et al* [6] also conducted a randomized controlled trial (RCT) of EIPL with pancreatic cancer patients and found similar conclusions. Based on these studies, the technique of EIPL needs to be applied to abdominal cancers.

Intraoperative bleeding and surgery can lead to residual tumor cells in the abdominal cavities, which may increase the risk of peritoneal metastasis. In our study, intraoperative blood loss between two groups was not significantly different. In the non-EIPL group, intraperitoneal lavage does not exceed 3

Table 2 Outcomes after surgery

Variables	Non-EIPL group, *n* = 75	EIPL group, *n* = 75	*P* value
Type of surgery			0.242
Total	55	61	
Distal	20	14	
Time, surgery to first flatus in d	4.19 ± 0.99	3.95 ± 0.87	0.108
Postoperative hospital stay in d	15.26 ± 3.10	14.48 ± 1.97	0.072
Abdominal pain	10/75	5/75	0.174
Ileus	15/75	3/75	0.003
Abdominal abscess	9/75	1/75	0.009
Leakage	5/75	2/75	0.246
Bleeding	6/75	3/75	0.302
Neutrophil count as 10^9/L	10.36 ± 3.32	10.03 ± 3.56	0.552
Lymphocyte cell as 10^9/L	1.02 ± 0.63	1.00 ± 0.60	0.817
NLR	13.48 ± 8.55	11.87 ± 5.22	0.169
Platelet as 10^9/L	171.00 ± 59.98	179.73 ± 60.38	0.381

EIPL: Extensive intraoperative peritoneal lavage; NLR: Neutrophil to lymphocyte ratio.

Table 3 Univariate analysis of overall survival

Variable	β	HR (95%CI)	*P* value
Sex	0.514	1.671 (0.983-2.841)	0.058
Age	0.024	1.025 (0.994-1.056)	0.114
EIPL/Non-EIPL	-0.991	0.371 (0.218,0.631)	0.000
Tumor size	0.192	1.211 (1.088-1.348)	0.000
Type of surgery	0.185	1.203 (0.653-2.214)	0.553
Tumor location	0.075	0.928 (0.689-1.250)	0.622
Borrmann classification	-1.474	0.229 (0.072-0.731)	0.013
Differentiated grade	0.491	0.612 (0.351-1.067)	0.083
T stage	1.250	3.489 (1.094-11.130)	0.035
N stage	0.535	1.707 (1.339-2.176)	0.000
Vascular invasion	-0.954	0.385 (0.235-0.632)	0.000

EIPL: Extensive intraoperative peritoneal lavage; HR: Hazard ratio.

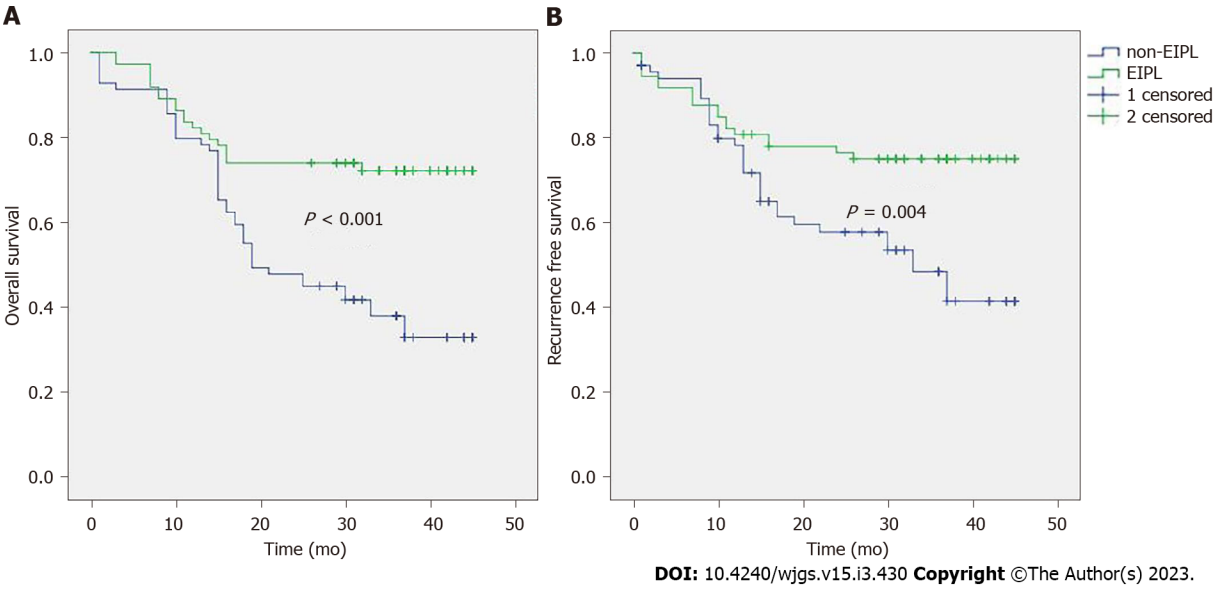
L of saline, which may make it difficult to remove free peritoneal cancer cells. The technique of EIPL can remove free cancer cells and blood in the abdominal cavity with plenty of washing (10 L or more of saline), which can prevent free cancer cells from attaching to the peritoneum[15].

In recent years, several reports[15-17] have shown that inflammation was linked to poor survival. Inflammation can stimulate the proliferation of malignant tumors cells, promote metastasis and destroy the adaptive immune response[16]. In this study, we found that the preoperative inflammatory index of NLR in the non-EIPL group was lower than in the EIPL group. However, the level of postoperative NLR in the non-EIPL group was higher than in the EIPL group. As for patients with high levels of NLR, the anti-tumor immune response of T cells and natural killer cells in the system may be surrounded by several neutrophils, which may decrease the opportunity to contact tumor cells[17,18]. Therefore, the free peritoneal cancer cells may survive in this course.

Table 4 Multivariate analysis of overall survival

Variable	β	HR (95%CI)	*P* value
EIPL/Non-EIPL	-0.861	0.423 (0.246-0.727)	0.002
Tumor size	0.139	1.149 (1.025-1.289)	0.017
Borrmann classification	-0.268	0.765 (0.211-2.775)	0.684
T stage	1.395	4.034 (1.255-12.971)	0.019
N stage	0.313	1.368 (1.034-1.811)	0.029
Vascular invasion	-0.608	0.545 (0.317-0.935)	0.027

EIPL: Extensive intraoperative peritoneal lavage; HR: Hazard ratio.



DOI: 10.4240/wjgs.v15.i3.430 **Copyright** ©The Author(s) 2023.

Figure 1 Kaplan-Meier curve of overall survival and recurrence-free survival in the non-extensive intraoperative peritoneal lavage and extensive intraoperative peritoneal lavage groups. A: Overall survival; B: Recurrence-free survival. EIPL: Extensive intraoperative peritoneal lavage.

This study concluded that the symptoms of ileus appeared more in the non-EIPL group than in the EIPL group. In addition, EIPL can reduce the possibility of abdominal abscess, but the complications of bleeding and leakage have no significant difference. Indeed, EIPL is similar to the so-called limiting dilution method[19]. This technique can clean up the peritoneal effusion and reduce the risk of infection. The ten washes of regular warm saline can promote intestinal motility and functional recovery, and this may be helpful for surgeons to find the bleeding location.

All patients received laparotomy, which reduced the influence of different surgical methods. The patients also had good preoperative nutritional statuses, which made no obvious difference. As for the factors of type of surgery, when the proximal resection margin ranged from 3 to 5 cm, there was no significant difference between distal gastrectomy and total gastrectomy for the 5-year OS of GC patients [20]. We concluded that EIPL can reduce the possibility of perioperative complications including ileus and abdominal abscess, and the technique of EIPL may be beneficial for perioperative complications to make patients more comfortable after the operation. This conclusion was consistent with a previous study[8].

Although EIPL could not reduce the recurrence rate of lymph nodes, nodes and other organs, the overall recurrence rate and peritoneum recurrence rate in the EIPL group were lower than in the non-EIPL group. The OS curve and RFS curve were better in the EIPL group. Currently, only three RCTs are ongoing to explore the long-term efficacy of EIPL in advanced GC. Kuramoto *et al*[9] concluded that the peritoneal recurrence rate of the EIPL group was significantly lower than that of the non-EIPL (6.7% *vs* 45.8%, $P = 0.013$). There was no difference in recurrence rate for liver transfer, lymph node and other organ transfer cases between the two groups, which was similar to our study. Among 88 patients who had positive cytology, EIPL-intraperitoneal chemotherapy (IPC) greatly improved the 5-year survival of patients (44%) compared with 0% in patients with surgery alone. The prognosis of patients is poorer than in our study because the recruited patients of their study had positive cytology.

Another advantage is that IPC was not used in our study. It may remove side effects associated with chemotherapy and confound the effect of EIPL. Misawa *et al*[21] conducted an RCT indicating that peritoneal RFS was not significantly different between the EIPL group and the non-EIPL group. The 3-year OS rate and RFS rate were better than our study, and the reason is that the proportion of T4 (49.5%) and N3 (28.1%) was smaller than our study population (T4: 96.0%, N3: 34.7%).The value of EIPL may be related to the stage of T status and N status. The patients of our study (more cases of T4 and N3) had a higher risk of recurrence, and the reduction of recurrence rate was significant in the EIPL group. One RCT based in Singapore is still ongoing[22]. Eligible patients having cT3 or cT4 with M0 disease are also in their criteria, but our study collected more clinical information and explored the safety and efficacy of the EIPL group. Our study showed that the technique of EIPL can reduce the perioperative complications of patients.

Our study had several limitations. First, we analyzed only advanced GC patients, which is not representative of all patients. Second, the sample size was relatively small, and more cases are needed to verify our results.

CONCLUSION

In conclusion, EIPL can reduce the possibility of perioperative complications including ileus and abdominal abscess. The OS curve and RFS curve were better in the EIPL group. This technique is easy and inexpensive. Therefore, EIPL can benefit advanced GC patients and would be a promising therapeutic strategy in the future.

ARTICLE HIGHLIGHTS

Research background

After resection, one of the major problems is the peritoneal dissemination and recurrence of gastric cancer (GC). It is necessary to remove residual tumor cells. Recently, a study found that extensive intraoperative peritoneal lavage (EIPL) plus intraperitoneal chemotherapy can improve the prognosis of patients and eradicate peritoneal free cancer for GC patients.

Research motivation

The efficacy and outcome of advanced GC patients treated with EIPL has not been determined.

Research objectives

Evaluating the efficacy and long-term outcome of advanced GC patients treated with EIPL.

Research methods

A total of 150 patients with advanced GC were enrolled in this study according to the inclusion and exclusion criteria and randomly allocated to 2 groups. For the non-EIPL group, peritoneal lavage was performed using no more than 3 L of warm saline. In the EIPL group, patients received 10 L or more of saline (1 L at a time) before the closure of the abdomen. The surviving rate analysis was compared by the Kaplan-Meier method. Using the Cox appropriate hazard pattern was used to screen the prognostic factors.

Research results

The basic information in the EIPL group and the non-EIPL group had no significant differences. The symptoms of ileus and abdominal abscess appeared more frequently in the non-EIPL group. The multivariate analysis revealed that EIPL, tumor size, vascular invasion, N stage and T stage were independent prognostic factors for the overall survival of patients. The prognosis of the EIPL group was better than the non-EIPL group, and the 3-year survival rate of the EIPL group was higher than the non-EIPL group. For the recurrence-free survival (RFS) of patients, the risk factor included EIPL, N stage, vascular invasion, type of surgery, tumor location, Borrmann classification and tumor size. EIPL and tumor size were independent risk factors. The RFS curve of the EIPL group was better than the non-EIPL group (P = 0.004), and the recurrence rate of the EIPL group was lower than the non-EIPL group. The overall recurrence rate and peritoneum recurrence rate in the EIPL group was lower than the non-EIPL group.

Research conclusions

The overall survival curve and RFS curve were better in the EIPL group. The possibility of perioperative complications, including ileus and abdominal abscess, could be reduced by EIPL.

Research perspectives

EIPL could benefit advanced GC patients because it is inexpensive and easy and would be a promising therapeutic strategy in the future.

FOOTNOTES

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Country/Territory of origin: China

ORCID number: A-Man Xu 0000-0003-1210-7430.

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ORIGINAL ARTICLE

Randomized Controlled Trial

Endoscopic mucosal resection with double band ligation versus endoscopic submucosal dissection for small rectal neuroendocrine tumors

Jia-Lan Huang, Ri-Yun Gan, Ze-Han Chen, Ruo-Yu Gao, De-Feng Li, Li-Sheng Wang, Jun Yao

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Jia-Lan Huang, Ri-Yun Gan, Ze-Han Chen, Department of Gastroenterology, The Second Clinical Medical College, Jinan University, Shenzhen 518020, Guangdong Province, China

Ruo-Yu Gao, Department of Gastroenterology, Shenzhen Luohu People's Hospital, Shenzhen 518020, Guangdong Province, China

De-Feng Li, Li-Sheng Wang, Jun Yao, Department of Gastroenterology, Shenzhen People's Hospital (The Second Clinical Medical College, Jinan University; The First Affiliated Hospital, Southern University of Science and Technology), Shenzhen 518020, Guangdong Province, China

Corresponding author: Jun Yao, MD, PhD, Associate Chief Physician, Associate Professor, Department of Gastroenterology, Shenzhen People's Hospital (The Second Clinical Medical College, Jinan University; The First Affiliated Hospital, Southern University of Science and Technology), 1017 East Gate Road, Shenzhen 518020, Guangdong Province, China.
yao.jun@szhospital.com

Abstract

BACKGROUND

Endoscopic resection remains an effective method for the treatment of small rectal neuroendocrine tumors (NETs) (≤ 10 mm). Moreover, endoscopic mucosal resection (EMR) with double band ligation (EMR-dB), a simplified modification of EMR with band ligation, is an alternative strategy to remove small rectal NETs.

AIM

To evaluate the feasibility and safety of EMR-dB for the treatment of small rectal NETs (≤ 10 mm).

METHODS

A total of 50 patients with small rectal NETs, without regional lymph node enlargement or distant metastasis confirmed by endoscopic ultrasound, computerized tomography scan, or magnetic resonance imaging, were enrolled in the study from March 2021 to June 2022. These patients were randomly assigned into the EMR-dB (n = 25) group or endoscopic submucosal dissection (ESD) group (n = 25). The characteristics of the patients and tumors, procedure time, devices cost, complete resection rate, complications, and recurrence outcomes were

analyzed.

RESULTS

There were 25 patients (13 males, 12 females; age range 28-68 years old) in the EMR-dB group, and the ESD group contained 25 patients (15 males, 10 females; age range 25-70 years old). Both groups had similar lesion sizes (EMR-dB 4.53 ± 1.02 mm, ESD 5.140 ± 1.74 mm; P = 0.141) and resected lesion sizes(1.32 ± 0.52 cm *vs* 1.58 ± 0.84 cm; P = 0.269). Furthermore, the histological complete resection and *en* bloc resection rates were achieved in all patients (100% for each). In addition, there was no significant difference in the complication rate between the two groups. However, the procedure time was significantly shorter and the devices cost was significantly lower in the EMR-dB group. Besides, there was no recurrence in both groups during the follow-up period.

CONCLUSION

The procedure time of EMR-dB was shorter compared with ESD, and both approaches showed a similar curative effect. Taken together, EMR-dB was a feasible and safe option for the treatment of small rectal NETs.

Key Words: Small rectal neuroendocrine tumor; Endoscopic submucosal dissection; Endoscopic mucosal resection; Ligation; complete resection rate; Complication

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Core Tip: Endoscopic mucosal resection (EMR) with double band ligation (EMR-dB), a simplified modification of EMR with band ligation, is an alternative strategy to remove small rectal neuroendocrine tumors (NETs). Our study first evaluates the feasibility and safety of EMR-dB and endoscopic submucosal dissection (ESD) for the treatment of small rectal NETs (≤ 10 mm). We discovered that the EMR-dB technique took less time than ESD, and displayed a similar curative effect to ESD. If no lymph nodes and distant metastases are revealed by either endoscopic ultrasound or computerized tomography, EMR-dB is a feasible and safe option for the treatment of small rectal NETs.

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INTRODUCTION

With the wide application of screening colonoscopy, the incidence of neuroendocrine tumors (NETs) has increased in the past few decades. The gastrointestinal (GI) tract is the most frequent site for NETs [1]. Rectal NETs represent 34% of all diagnosed GI NETs and are the most common NETs behind small bowel NETs[2]. Most GI NETs do not cause clinical symptoms. Therefore, they are only found by colonoscopy accidentally[3]. Rectal tumors of 10-19 mm in diameter have a metastatic rate of 4%-30%[4, 5], whereas over 80% of tumors measuring more than 20 mm in diameter are associated with lymph nodes or liver metastases. Well-differentiated NETs ≤ 10.0 mm in diameter and limited to the submucosal layer are reported to be associated with a low frequency of lymph nodes and distant metastases. These NETs are good candidates for endoscopic resection (ER)[6,7], because ER can achieve high resection(R0) resection rates like many minimally invasive techniques[8], and it has reduced costs, morbidity, and mortality[9] compared with conventional surgery. However, the consensus about the optimal endoscopic treatment modality for rectal NETs has not been established yet.

ER, including conventional endoscopic mucosal resection (EMR), modified EMR (m-EMR), and endoscopic submucosal dissection (ESD), is a safe and effective modality for the treatment of small and localized early rectal NETs[2]. However, although conventional EMR can remove small rectal NETs in a minimally invasive manner, it is difficult to achieve deep resection margins because most rectal NETs invade the submucosal layer[10]. Therefore, various modified methods of EMR have been developed. m-EMR includes EMR with cap[11], EMR with band ligation (EMR-B)[12], (EMR-L)[13], EMR with circumferential incision[14], and so on. These strategies have all been proven to be safe and effective for removing rectal NETs. However, according to previous reports, EMR-B and EMR-L show a histological complete R0 rate that varies from 82.8% to 95.5% in treating rectal NETs[12,13,15]. The positive basal margins may be attributed to the insufficient distance from lesion to the resection margin. To overcome

the shortcomings of the EMR-B and EMR-L, we presented a new EMR technique. EMR with double band ligation (EMR-dB), a simplified modification of EMR-B, could achieve a deeper vertical resection margin compared with EMR-B. However, the safety and efficacy of such m-EMR technique in treating small rectal NETs has not been determined. Therefore, in the present study, we compared the safety and efficacy of EMR-dB and ESD in the treatment of rectal NETs. Moreover, we aimed to evaluate the feasibility of EMR-dB for the treatment of small rectal NETs (≤ 10 mm) in comparison to ESD.

MATERIALS AND METHODS

Study design and participants

EMR-dB and ESD were performed in 50 patients with rectal NETs in the Gastroenterology Unit of Shenzhen People's Hospital from March 2021 to June 2022. These patients were randomly assigned into the EMR-dB (n = 25) group or ESD group (n = 25). The inclusion criteria were as follows: (1) Rectal NETs confirmed by histological diagnosis; (2) Tumors were ≤ 10 mm in diameter by endoscopic ultrasound (EUS); and (3) EUS and computerized tomography(CT) of the thorax/abdomen/pelvis were negative for lymph node and distant metastases. The study protocol was approved by the ethics committee of the hospital, and all patients gave their informed consent before the procedures (Clinical trial registration number: ChiCTR2200063871).

Randomization strategy

A researcher who was unaffiliated with this trial created a randomization list. Specific software (www.randomizer.org) was used, and the participants were randomly allocated at a 1:1 ratio to the EMR-dB group or the ESD group. Outcomes assessor was blinded after assignment to interventions.

Endoscopic devices and procedures

A wide (14.9 mm in diameter), soft, straight, transparent cap with an inside rim (D-201-11802, Olympus) was fitted onto the tip of a standard single-channel endoscope (GIF-260, Olympus).

A ligating device with a 110-cm maximum Multiple Band Ligator (M00542251, Boston Scientific) was inserted into the accessory channel of the endoscope.

Other devices included a dual knife, injection needles, snares, hot biopsy forceps from Olympus, and a high-frequency generator (ICC-200, ERBE).

EMR-dB procedure (Figure 1): (1) Endoscopy showing a rectal carcinoid (Figure 1A); (2) Marking dots were on the lesion with an electric snare tip(KD-650Q, Olympus, Tokyo, Japan) (Figure 1B); (3) When the lesion was suctioned into the ligating device, the first band was deployed to ligate the lesion and increase luminal protuberance (Figure 1C); Then the second band was deployed below the first one after endoscopic suctioning of the tumor into the cap (Figure 1D); (4) The lesion resection was performed *via* electrocautery below the second band (Figure 1E); (5) Wound after resection (Figure 1F); and (6) The wound was closed with clips (Figure 1G); Subsequently, the resection specimen was entirely flattened (Figure 1H).

ESD procedure: ESD was performed using a single-channel endoscope with a short transparent cap attached to the tip of the endoscope. (1) Submucosal solution was injected as described above, and the circumferential mucosa of the lesion was incised using a dual knife. The mucosal incisions were placed at least 2-3 mm from the lesion periphery to create a sufficient tumor-free lateral resection margin; (2) Circumferential incision and submucosal dissection were carried out as previously described[16]; and (3) The wound was treated as described above.

Two experienced endoscopists (Yao J and Wang LS) conducted all procedures. All patients were subjected to food deprivation for 1 d after the operation.

Outcomes and definition

The efficacy was evaluated by assessing the rates of histological complete R0, *en* bloc resection, and operation success, and the safety was evaluated by assessing the complications.

The primary outcome was the histological complete R0 rate. Histological complete resection was defined as a complete single-piece (*en* bloc) resection of the lesion with a tumor-free margin in both the lateral and vertical margins.

Secondary outcomes included: *En* bloc resection rate: *En* bloc resection was defined as a complete single resection of the targeted lesion, regardless of whether the basal and lateral tumor margins were infiltrated or undetermined. Complications: The primary complications included bleeding and perforation. Immediate bleeding was defined as an evident hemorrhage during the procedure that could not be controlled by endoscopic hemostasis. Delayed bleeding was defined as bleeding that caused hemoglobin to drop ≥ 2 g/dL or hematochezia, which required endoscopic and/or radiologic hemostasis or transfusions within 14 d after the procedure. Perforation was defined as the wall defect

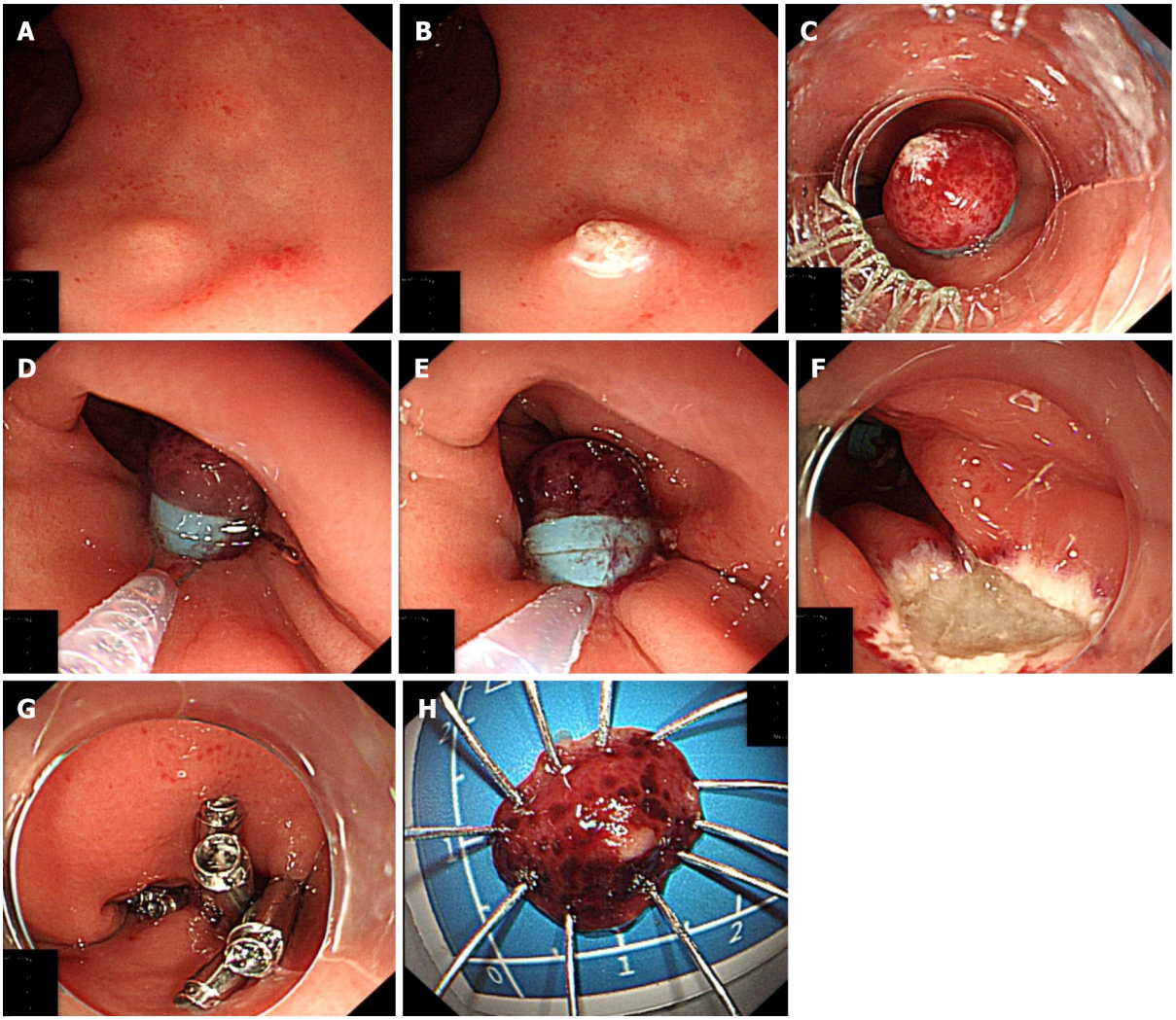

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Figure 1 Utilizing Endoscopic mucosal resection with double band ligation to remove the rectal neuroendocrine tumors. A: Endoscopy showing a rectal neuroendocrine tumors; B: Marking dots were made approximately 2-3 mm on the lesion with an electric snare tip; C: When the lesion was sucked into the ligating device, the first band was deployed to ligate the lesion; D: The second band was deployed below the first one after endoscopic suctioning of the tumor into the cap; E: The resection of the lesion was performed *via* electrocautery below the second band; F: Wound after resection; G: The wound was closed with clips; H: Endoscopic resection of the intact tumor and the fully flattened specimen.

identified by endoscopy or free air in the abdominal cavity detected by radiological examinations (such as plain abdominal X-ray and/or abdominal CT) after the procedure. Procedure time was counted from the time of submucosal injection to the end of complete resection of the targeted lesion. Devices cost was defined as the cost of the required use of clips and the ligation devices in EMR-dB or dual knife using in ESD procedures, except the cost of other endoscopic procedures. Histopathologic grade included NET grade(G) 1, NET G2, NET G3, and neuroendocrine carcinomas according to the 2019 World Health Organization classification[17].

Follow-up

All patients were followed up by colonoscopy at 3 mo after endoscopic treatment to detect the recovery of the surgical wound and local recurrence. The patients with vertical and/or lateral margin involvement were recommended to undergo additional treatment.

Statistical analysis

All statistical analyses were performed using Statistical Product and Service Solutions statistics version 26. Continuous data were described as mean ± standard deviation, or median and range. Categorical data were expressed as numbers (*n*) and percentages (%). Chi-square or Fisher's exact tests were performed for comparative analysis of categorical variables. Continuous variables were analyzed using Student's t-test. $P < 0.05$ was considered statistically significant.

RESULTS

Characteristics of patients and tumors

There were 25 patients (13 males, 12 females; age range 28-68 years old) in the EMR-dB group, and the ESD group contained 25 patients (15 males, 10 females; age range 25-70 years old). The average age of the EMR-dB and ESD groups was comparable between the two groups (47.04 ± 10.58 *vs* 42.92 ± 10.93, $P = 0.182$). There was no statistical difference in the location (average distance from anus) between the EMR-dB group and the ESD group (7.96 ± 3.52 cm *vs* 7.36 ± 2.83 cm; $P = 0.509$). Sex and age distribution were similar between the two groups. Moreover, both groups had identical mean lesion sizes (4.53 ± 1.02 mm *vs* 5.140 ± 1.74 mm; $P = 0.141$) and resected lesion diameters (1.32 ± 0.52 cm *vs* 1.58 ± 0.84 cm; $P = 0.001$). Table 1 shows the characteristics and tumor sizes of the patients in the two groups.

Intervention outcomes

The histological complete resection and *en* bloc resection rates were the same in the two groups (100% for each). No significant difference in the complication rate between the two groups [delayed bleeding occurred in 0 patients in the EMR-dB group and two patients in the ESD group (8.0%) ($P = 0.47$), and no perforation was observed in either group]. However, the procedure time was significantly shorter in the EMR-dB group (6.28 ± 0.75 min) compared with the ESD group (14.30 ± 1.51 min) ($P < 0.001$) and the devices cost was significantly lower in the EMR-dB group than in the ESD group ($ 494.04 ± $ 85.47 *vs* $ 808.98 ± $ 143.67, $P < 0.05$). The pathological results were similar between the two groups ($P > 0.99$). All tumors were classified as NET G1 grade according to the staging system for NETs of the American Joint Committee on Cancer, absence of lymphovascular invasion, negative horizontal margin (pHM0) and negative vertical margin (pVM0) (Figure 2). Table 2 shows the therapeutic outcomes of ER in the two groups. In the two cases with delayed bleeding, bloody stool appeared on the 1st day and the 7th day after the ESD procedure, respectively. A colonoscopy revealed that the postoperative wound was bleeding, hemostasis was well managed using endoscopy, and no blood transfusion or surgical intervention was necessary. All patients were followed up after 3 mo of the treatment. Again, a colonoscopy was performed, and a postoperative scar was seen.

Follow-up outcomes

No local remnant lesions or recurrences were observed during the follow-up period in both groups.

DISCUSSION

NETs of the rectum are a heterogeneous group of tumors. The pathological types mainly include NET, neuroendocrine carcinoma, mixed gland neuroendocrine carcinoma, and site-specific and functional NETs[18,19]. Less than 2% and 0.7% of rectal NETs < 10 mm in diameter are related to lymph nodes and distant metastases, respectively[10]. According to the current European Neuroendocrine Tumor Society guidelines, ER is considered curative for tumors smaller than 10 mm and well differentiated[20]. EMR has the advantages of simple and rapid operation and low complication rate[21-23], while its high recurrence rate of residual lesions is a limiting factor for its application[10]. On the other hand, ESD is an effective method with a higher complete resection rate, while its technical requirements and the rate of complications are relatively high[12,24,25]. The consensus about the optimal endoscopic treatment modality for rectal NETs has not yet been established.

Previous studies have proved that EMR using a band-ligation device (EMR-B) (EMR-L) is sufficient for tumors ≤ 10 mm in diameter[12,13,15]. However, the histopathological examination shows a positive margin for some lesions that have invaded the submucosa or deeper layers of the rectal wall. Therefore, we presented the EMR-dB technique, a new approach derived from EMR-B, containing an extra band below the first one. With EMR-dB, the second band could lengthen the distance from the lesion to the vertical resection margin, especially for some flat lesions and tumors that invaded the submucosa or deeper layers of the rectal wall. Therefore, this approach might better improve the complete resection rate and reduce the risk of residual tumors. However, there have been no more research reports about the EMR-dB technique.

The present study was the first randomized controlled trial to compare the safety and efficacy of EMR-dB with ESD for treating small rectal NETs. To remove the tumor completely, we carried out a series of optimization and improvement on operation steps. Firstly, we marked the head-end of the tumor to avoid deflecting the tumor during the ligation, making it easier to be suctioned it into the ligating device completely. Secondly, a submucosal injection was given to completely lift the submucosal layer of the tumor and set the basal layer of the tumor apart from the muscularis propria. This procedure could achieve a better complete resection and prevent the muscularis propria from being suctioned into the cap leading to perforation. Thirdly, given intestinal inflation when the NETs and part of the muscularis propria layer were ligated by band ligation, the muscularis propria layer will fall out of the band ligation over time due to the ductility of muscularis propria layer, leaving only the mucosal layer and submucosa, which may reduce the risk of perforation during resection.

Table 1 Characteristics and tumor sizes of the patients in the two groups

	EMR-dB (*n* = 25)	ESD (*n* = 25)	*P* value
Age	47.04 ± 10.58	42.92 ± 10.93	0.182
Sex (Male/Female)	13/12	15/10	0.569
Tumor size (mm)	4.53 ± 1.02	5.140 ± 1.74	0.141
Location (distance from anus) (cm)	7.96 ± 3.52	7.36 ± 2.83	0.509
Resected lesion size (cm)	1.32 ± 0.52	1.58 ± 0.84	0.269

Values are *n* or mean ± standard deviation. EMR-dB: Endoscopic mucosal resection with double band ligation; ESD: Endoscopic submucosal dissection.

Table 2 Therapeutic outcomes of endoscopic resection in the two groups

	EMR-dB (*n* = 25)	ESD (*n* = 25)	*P* value
Histological complete resection, *n* (%)	25 (100)	25 (100)	> 0.99
En bloc resection, *n* (%)	25 (100)	25 (100)	> 0.99
Resection time (min)	6.28 ± 0.75	14.30 ± 1.51	< 0.001
Delayed bleeding perforation	0	2	0.470
Perforation	0	0	> 0.99
Devices cost	$ 494.04 ± $ 85.47	$ 808.98 ± $ 143.67	< 0.001
Histopathological classification			> 0.99
NET G1, *n* (%)	25 (100)	25 (100)	
NET G2	0	0	
NET G3	0	0	
NEC	0	0	
Recurrence follow-up	0	0	> 0.99

Values are *n* (%) or mean ± standard deviation. EMR-dB: Endoscopic mucosal resection with double band ligation; ESD: Endoscopic submucosal dissection; NET: Neuroendocrine tumor; NEC: Neuroendocrine carcinomas; G: Grade.

EMR-dB showed an *en* bloc resection of all lesions with a tumor-free margin in both the lateral and vertical margins. Moreover, no complications occurred, and there were free of local remnant lesions or recurrence during the follow-up period, indicating similar efficacy with ESD. However, the procedure time of the EMR-dB group was significantly shorter compared with the ESD group (6.28 ± 0.75 min *vs* 14.30 ± 1.51 min) and the devices cost was significantly lower in the EMR-dB group than in the ESD group ($ 494.04 ± $ 85.47 *vs* $ 808.98 ± $ 143.67). When compared with EMR-B, the use of the Multiple Band Ligators for continuous ligations at one time in EMR-dB procedure may resulted in a little increase in technical difficulty, cost, and procedure time, and the size of the resection specimen might enlarge. However, it could better reduce residual tumor infiltration within vertical and lateral margins and potentially reduce recurrence rates. Recently, a case of rectal NET removal using the EMR-dB technique has been reported[26], and the pathological examination reveals a G1 NET with a negative margin and without complications, indicating that EMR-dB could work more significantly, which is consistent with our result.

In addition, the EMR-dB technique has several other advantages. Firstly, the tightening of the elastic band in EMR-dB could shrink the wound size. Therefore, the required use of clips is less. Secondly, as demonstrated in our study, the cost of the devices in the EMR-dB group was much lower compared with the ESD group. It is mainly attributed to the fact that the cost of the ligation device of EMR-dB is lower than that of ESD group using a dual knife. Moreover, EMR-dB requires fewer clips, which leads to the reduction of the operation and hospitalization cost. Moreover, there was no complication in the EMR-dB group. In contrast, two cases in the ESD group had delayed bleeding and needed further treatment, which also increased the hospitalization cost and days, bringing more physical and mental pain to patients.

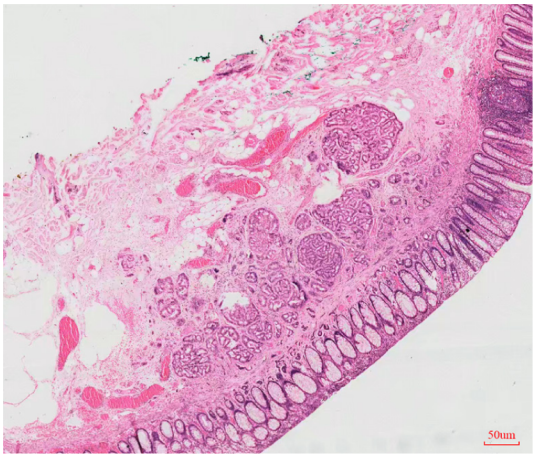

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Figure 2 Pathological examination reveals a grade 1 neuroendocrine tumors with negative vertical and lateral margins.

The present study has some limitations. First, this study was a single-center study with limited sample size. In addition, considering that rectal NET is a slow-growing tumor, further prospective studies with a long-term follow-up period are needed to verify our findings.

In conclusion, our study demonstrated that the EMR-dB technique took less time than ESD, and it displayed a similar curative effect to ESD. If no lymph nodes and distant metastases are revealed by either EUS or CT, EMR-dB is a feasible and safe option for the treatment of small rectal NETs.

CONCLUSION

In conclusion, our study demonstrated that the EMR-dB technique took less time than ESD, and it displayed a similar curative effect to ESD. If no lymph nodes and distant metastases are revealed by either EUS or CT, EMR-dB is a feasible and safe option for the treatment of small rectal NETs.

ARTICLE HIGHLIGHTS

Research background

Endoscopic resection remains an effective method for the treatment of small rectal neuroendocrine tumors (NETs) (≤ 10 mm). However, the consensus about the optimal endoscopic treatment modality for rectal NETs has not been established yet.

Research motivation

To overcome the shortcomings of endoscopic mucosal resection(EMR) with band ligation (EMR-B)(EMR-L), we presented a new EMR technique. EMR with double band ligation (EMR-dB), a simplified modification of EMR-B, could achieve a deeper vertical resection margin compared with EMR-B. However, the safety and efficacy of EMR-dB technique in treating small rectal NETs has not been determined.

Research objectives

In the present study, we compared the safety and efficacy of EMR-dB and endoscopic submucosal dissection (ESD) in the treatment of rectal NETs. We aimed to evaluate the feasibility of EMR-dB for the treatment of small rectal NETs (≤ 10 mm) in comparison to ESD.

Research methods

A randomized controlled trial comparing EMR-dB and ESD was conducted. The primary outcome was the histological complete resection rate; secondary outcomes included *en* bloc resection rate, procedure time, complications and so on. Follow-up was also performed.

Research results

A total of 50 patients were analyzed and were 25 patients in each group. The demographic and baseline characteristics of the participants were similar between the two groups, including age, gender, lesion

location (average distance from anus), lesion sizes, and resected lesion sizes. histological complete resection and *en* bloc resection were achieved in all 50 patients. No significant difference in the complication rate between the two groups [delayed bleeding occurred in 0 patients in the EMR-dB group and two patients in the ESD group (8.0%) (P = 0.47)], indicating that EMR-dB is non-inferior to ESD with a similar complete resection rate and complication rate. However, the procedure time was significantly shorter in the EMR-dB group (6.28 ± 0.75 min) compared with the ESD group (14.30 ± 1.51 min) (P < 0.001) and the devices cost was significantly lower in the EMR-dB group than in the ESD group ($ 494.04 ± $ 85.47 *vs* $ 808.98 ± $ 143.67, P < 0.05), which demonstrated that EMR-dB had shorter procedure duration time and lower operation costs. No local remnant lesions or recurrences were observed during the follow-up period in both groups, further prospective studies with a long-term follow-up period are needed to verify our findings.

Research conclusions

EMR-dB, a new EMR technique presented in our study, took less time than ESD, and displayed a similar curative effect to ESD. If no lymph nodes and distant metastases are revealed by either endoscopic ultrasound or computerized tomography, EMR-dB is a feasible and safe option for the treatment of small rectal NETs.

Research perspectives

First, this study was a single-center study with limited sample size. In addition, considering that rectal NET is a slow-growing tumor, further prospective studies with a long-term follow-up period are needed to verify our findings. Moreover, statistical analysis between EMR-B and EMR-dB can be further investigate.

FOOTNOTES

Author contributions: Yao J was responsible for design of the study and reviewed the manuscript; Huang JL drafted the manuscript; Huang JL, Gan RY, Chen ZH and Gao RY contributed to data acquisition, analysis, and interpretation; Yao J, Li DF and Wang LS were responsible for revising manuscript; All authors have read and approved the final manuscript.

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Clinical trial registration statement: This study is registered at Chinese Clinical Trial Registry. The registration identification number is ChiCTR2200063871.

Informed consent statement: All study participants provided informed written consent prior to study enrollment.

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

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at yao.jun@szhospital.com. Participants gave informed consent for data sharing.

CONSORT 2010 statement: The authors have read the CONSORT 2010 statement, and the manuscript was prepared and revised according to the CONSORT 2010 statement.

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Country/Territory of origin: China

ORCID number: Jia-Lan Huang 0000-0001-5590-7118; Ri-Yun Gan 0000-0003-0441-8810; Ze-han Chen 0000-0003-3754-5795; Ruo-Yu Gao 0000-0002-7721-2314; De-Feng Li 0000-0003-3118-6840; Li-Sheng Wang 0000-0002-7418-6114; Jun Yao 0000-0002-3472-1602.

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SYSTEMATIC REVIEWS

Preoperative risk modelling for oesophagectomy: A systematic review

James Paul Grantham, Amanda Hii, Jonathan Shenfine

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James Paul Grantham, Department of General Surgery, Modbury Hospital, Adelaide 5092, South Australia, Australia

Amanda Hii, Department of General Surgery, Modbury Hospital, Modbury 5092, South Australia, Australia

Jonathan Shenfine, General Surgical Unit, Jersey General Hospital, Saint Helier JE1 3QS, Jersey, United Kingdom

Corresponding author: James Paul Grantham, MBBS, MSc, Doctor, Department of General Surgery, Modbury Hospital, Smart Road, Adelaide 5092, South Australia, Australia. jamespgrantham91@gmail.com

Abstract

BACKGROUND

Oesophageal cancer is a frequently observed and lethal malignancy worldwide. Surgical resection remains a realistic option for curative intent in the early stages of the disease. However, the decision to undertake oesophagectomy is significant as it exposes the patient to a substantial risk of morbidity and mortality. Therefore, appropriate patient selection, counselling and resource allocation is important. Many tools have been developed to aid surgeons in appropriate decision-making.

AIM

To examine all multivariate risk models that use preoperative and intraoperative information and establish which have the most clinical utility.

METHODS

A systematic review of the MEDLINE, EMBASE and Cochrane databases was conducted from 2000-2020. The search terms applied were ((Oesophagectomy) AND (Risk OR predict OR model OR score) AND (Outcomes OR complications OR morbidity OR mortality OR length of stay OR anastomotic leak)). The applied inclusion criteria were articles assessing multivariate based tools using exclusively preoperatively available data to predict perioperative patient outcomes following oesophagectomy. The exclusion criteria were publications that described models requiring intra-operative or post-operative data and articles appraising only univariate predictors such as American Society of Anesthesiologists score, cardiopulmonary fitness or pre-operative sarcopenia. Articles that exclusively assessed distant outcomes such as long-term survival were excluded as were

publications using cohorts mixed with other surgical procedures. The articles generated from each search were collated, processed and then reported in accordance with PRISMA guidelines. All risk models were appraised for clinical credibility, methodological quality, performance, validation, and clinical effectiveness.

RESULTS

The initial search of composite databases yielded 8715 articles which reduced to 5827 following the deduplication process. After title and abstract screening, 197 potentially relevant texts were retrieved for detailed review. Twenty-seven published studies were ultimately included which examined twenty-one multivariate risk models utilising exclusively preoperative data. Most models examined were clinically credible and were constructed with sound methodological quality, but model performance was often insufficient to prognosticate patient outcomes. Three risk models were identified as being promising in predicting perioperative mortality, including the National Quality Improvement Project surgical risk calculator, revised STS score and the Takeuchi model. Two studies predicted perioperative major morbidity, including the predicting postoperative complications score and prognostic nutritional index-multivariate models. Many of these models require external validation and demonstration of clinical effectiveness.

CONCLUSION

Whilst there are several promising models in predicting perioperative oesophagectomy outcomes, more research is needed to confirm their validity and demonstrate improved clinical outcomes with the adoption of these models.

Key Words: Oesophagectomy; Risk model; Oesophageal cancer; Preoperative; Morbidity; Mortality

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Core Tip: The undertaking of an oesophagectomy incurs a high morbidity rate and can lead to mortality. It is therefore incumbent upon the surgeon to appropriately select and counsel prospective patients on anticipated risks. Multivariate clinical decision-making tools can be a powerful adjunct in improving this process when utilised preoperatively. In a world of countless proposed surgical risk models, choosing which model to use can prove challenging. This systematic review represents the largest and most comprehensive effort to determine which model is most relevant, valid and accurate in forecasting perioperative outcomes following oesophagectomy.

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INTRODUCTION

Oesophageal cancer is the eighth most commonly diagnosed cancer worldwide and remains the sixth leading cause of cancer-related deaths globally[1]. The mainstay of curative treatment is surgical resection, an oesophagectomy, often in combination with neoadjuvant chemotherapy or chemoradiotherapy[2]. There are various surgical approaches when performing an oesophagectomy, these are broadly classified as open, hybrid and minimally invasive techniques[3]. Irrespective of the approach an oesophageal resection is a major surgical undertaking; often taking hours to perform, with a significant period of single lung ventilation[4,5]. Post-operative complications are common, occurring in approximately half of all patients[6]. These are most frequently respiratory in nature, which occur in 20%-40% of all patients[7,8]. Anastomotic leak, which can occur in 10%-20% of cases, is perhaps the most feared due to the associated high mortality[9]. The reported rates of mortality in high-volume centres is recognised to lie between 2% and 8%[10]. However, even non-life threatening complications can lead to significant morbidity which can exact a devastating toll on patient outcomes[7].

The substantial associated morbidity and mortality emphasises the critical role of the preoperative assessment in selecting suitable patients for oesophagectomy. Patients require a preoperative assessment to assess if they are fit enough to withstand the physiological strain of the surgery but also enables an opportunity to counsel patients about the risks of surgical treatment. It also permits the identification of higher-risk patients for whom more intense resource allocation may be warranted in

the post-operative setting. In recent decades, surgeons have begun to turn to cognitive aids such as surgical risk prediction tools to help guide the decision-making process[11]. Several studies have demonstrated that the utilisation of predictive modelling to augment decision making is superior to isolated subjective clinical judgement[12,13]. By selecting more appropriate surgical candidates, informing patients more accurately and deploying the resources in a more tailored fashion, these tools are designed to improve patient outcomes.

There are many available tools, some of which are generic surgical risk predictors whilst others have been specifically developed and validated for patients undergoing oesophagectomy. Some are based on preoperatively available data and others rely on intraoperative data. Naturally, only tools based exclusively on preoperative data can aid selection of appropriate surgical candidates or be used to better inform patients of their risk status. The clear advantages of utilising these multivariate risk prediction models framed against the proliferating multitude of these models has created a significant conundrum for surgeons attempting to determine which one to adopt. There have been two systematic reviews undertaken to aid surgeon choice of the best tool to utilise. The first, by Findlay *et al*[14], also assessed the quality of scientific rigor in the development studies from which the models were constructed. Their review concluded that none of the preoperative models evaluated accurately predicted morbidity or mortality. Warnell *et al*[15] also concluded that none of the existing models could be confidently applied to clinical practice. Despite the disheartening results, many new multivariate risk prediction models have since been developed.

The aim of this research is to conduct an up to date, systematic review assessing which of the pre-operative multivariate data risk models most accurately predict outcomes following oesophagectomy. The primary outcome will be their ability to predict perioperative mortality. The secondary outcomes of the review will focus on their predictive capacity for major morbidity, overall morbidity and index complications such as anastomotic leak and adverse cardiorespiratory events. The working hypothesis is that this systematic review will aid surgeons to use the most accurate preoperative prediction model to select appropriate patients for oesophagectomy, and to aid informed consent for patients in relation to their individual surgical risks and thus allocate resources more appropriately to high-risk patients.

MATERIALS AND METHODS

Search strategy and article selection

A systematic review of the existing literature was undertaken, incorporating the MEDLINE, EMBASE and Cochrane review databases. The search terms applied were ((Oesophagectomy) AND (Risk OR predict OR model OR score) AND (Outcomes OR complications OR morbidity OR mortality OR length of stay OR anastomotic leak)). The articles generated from each search were collated and processed with reporting in accordance with the PRISMA model[16]. Duplicates were excluded, then preliminary screening of titles and abstracts for potentially relevant publications was conducted by the first author. Potentially relevant texts were then assessed in full for eligibility with reference to the inclusion and exclusion criteria by two authors. No pre-existing protocol for a systematic review on this topic was found.

Inclusion and exclusion criteria

The inclusion criteria applied were articles which assessed multivariate based tools using exclusively pre-operatively available data to predict perioperative patient outcomes following oesophagectomy. The perioperative period was defined as any duration whilst an inpatient from the index oesophagectomy admission and no more than 90 d post-operative if the patient had been discharged. Given the significant reduction in morbidity and mortality in recent decades, only articles published in English from 2000 onward were included. The exclusion criteria were publications that described models requiring intra-operative or post-operative data and articles appraising only univariate predictors such as American Society of Anesthesiologists score, cardiopulmonary fitness or pre-operative sarcopenia. Articles that exclusively assessed distant outcomes such as long-term survival or disease-free survival were excluded as were publications using cohorts mixed with other surgical procedures. Studies which presented insufficient data for meaningful analysis, such as calibration measures in the form or *P*-values or area under the receiver operating characteristic curve (AUC) and/or discrimination statistics, were also excluded. Abstracts that were superseded by full articles were excluded. Abstracts from conference proceedings not subsequently published in full were considered eligible for inclusion, provided it included sufficient data for meaningful analysis as outlined above.

Data extraction and synthesis

The essential study characteristics extracted included the study period, geographical location, data source including the number of centres involved, sample size and case mix descriptors such as type of operation. Patient characteristics including the proportion of neoadjuvant therapy use and histological subtype were also extracted. For each article, we recorded the model or models which were tested within and essential performance metrics such as discrimination and calibration. Outcome measures

such as definitions of perioperative mortality and morbidity were also extracted. Heterogeneity of surgical method was considered by identifying and classifying surgical technique into either transthoracic, transhiatal, hybrid or totally minimally invasive oesophagectomy for each article. Heterogeneity in outcome definitions was minimised by considering the broad outcomes of mortality, major morbidity as defined as grade three or four by the Clavien-Dindo classification, overall morbidity and respiratory complications[17]. Index outcomes such as anastomotic leak, readmission, return to theatre and length of stay were also considered when specifically reported. All risk prediction models were analysed in the following five domains: Clinical credibility, methodological quality, external validation, model performance and clinical effectiveness.

Clinical credibility

Clinical credibility is whether the characteristics of the prognostic model encourage clinicians to utilise the system[18-20]. This was first outlined in the systematic review of clinical prediction models in 2011 and applied to the appraisal of oesophageal resection risk models in 2014[14,21]. There are seven components addressed in the assessment of clinical credibility and each is scored in the affirmative, partially or negative. These include whether the model uses oesophageal specific factors and avoids using thresholds for data categorisation. It also considers whether the data is available prior to the time of clinical decision-making, if the data is objective and how easily the data required to generate the outcome can be obtained. The last two factors consider whether the model can be rendered in a way understandable to the clinician and if it effectively stratifies the risk of a particular outcome in a clinically useful fashion. A full description of the methods applied to assessing clinical credibility has been supplied in the Supplementary materials.

Methodological quality

We adopted the quality assessment framework of Minne *et al*[21] to ensure a high standard of methodological quality of the examined studies and to minimise the risk of bias[22-24]. This utilises a framework of twenty points with eight points allotted to study participation characteristics, four points to prognostic factor and outcome measurement characteristics and the remaining eight points to the methodological integrity of the study analysis[24]. Models which satisfied a particular component were awarded one point, partial satisfaction conveyed half a point and no points were awarded if the relevant component was not satisfied. A detailed outline of this assessment criteria can be found within the Supplementary materials.

External validation

We assessed whether the included studies reported a new model or externally validated an existing model. We subsequently analysed if a given model had been externally validated within a separate population.

Model performance

The performance of each model was compared based on discrimination and calibration metrics. Discrimination is the ability of the model to discern between those that will and will not develop an outcome, in this case post-operative complications[25]. The accuracy with which a predictive model discriminated between outcomes was measured in terms of area under the receiver operating characteristics (ROC) curve or c-statistic. In the instance of the model having no discriminative ability, the c-statistic will be 0.5, whereas a c-statistic of 1 suggests perfect discrimination[26]. The threshold for acceptable discriminative capacity has been previously defined as a c-statistic exceeding 0.7[27]. Calibration pertains to the fidelity between the actual and the predicted frequency of an outcome[25]. This is represented in terms of Hosmer and Lemeshow goodness of fit *P*-values and observed to expected outcome (O:E) ratios. A *P*-value of greater than 0.05 indicates adequate calibration on goodness of fit when applied to linear regression models and an O:E ratio of 1 indicates perfect calibration[28]. An O:E ratio of < 1 indicates that the model overestimates the predicted outcome, whereas a ratio of > 1 indicates it underestimates the frequency of the predicted outcome measure[28]. Where adequate data reporting allowed, weighted AUC discrimination metrics were generated for each model by calculating the mean across individual studies with weighted reference to the study cohort size.

Clinical effectiveness

We also assessed all studies for evidence that the application of any of the individual models has been clinically proven to improve patient outcomes.

RESULTS

Search results

The initial search of composite databases yielded 8715 articles which reduced to 5827 following the deduplication process. After title and abstract screening, 197 potentially relevant texts were retrieved for detailed review. Of these, a total of 27 articles satisfied the inclusion and exclusion criteria. The rationale for exclusion of the 170 articles omitted is illustrated (See Figure 1). In total, thirteen articles were developing new predictive risk models for oesophagectomy[29-41] (Table 1). Two of these studies, by Filip *et al*[36] and Wan *et al*[41] respectively, also served to externally validate other existing models. The remaining 14 articles exclusively externally validated existing models on new data sets[42-55] (Table 2). Many studies sought to test the performance of multiple models within the same dataset. These 27 articles appraised the use of a total of 21 different preoperative multivariate risk prediction models in oesophagectomy. As stated above, thirteen of the twenty-one models had their development study within the list of retrieved articles. The remaining eight models were developed for predicting outcomes in patients not initially undergoing oesophagectomy but were subsequently validated in an oesophagectomy cohort[56-63]. A reference key for the various abbreviations used in relation to the models is provided in Figure 2.

Study characteristics

The included studies were published over a fourteen year period and originated from four different continents. Ten studies arose from North America, nine from Europe, six from Asia and two, both involved Europe with the second databases arising from North America and Australia respectively. All multivariate models utilised logistical regression of retrospective patient cohort data. The thirteen articles developing a new predictive model had a median study population size of 1172 (range 90-10826). The fourteen articles exclusively validating existing models had a median study population size of 246 (range 43-1039).

There was significant heterogeneity in operative approach and technique within the studies. Twenty-two of the articles incorporated open oesophagectomy, all included an open transthoracic procedure (Ivor-Lewis, left thoracolumbar or McKeown), fifteen of which utilised a transhiatal approach, and eight included minimally invasive oesophagectomy with three incorporating patients undergoing a hybrid oesophagectomy approach. Only two studies exclusively dealt with patients undergoing minimally-invasive oesophagectomy. Three studies of large national multicentre databases failed to detail the operative strategy.

In total, 24 of the 27 studies reported the overall rate of neoadjuvant therapy, including two studies for which this was an exclusion criteria. The rates observed varied significantly between studies, ranging from 3.6% to 87.0%. The total combined samples had 33.6% receiving neoadjuvant therapy. The histological subtype of oesophageal cancer was reported in 16 of the 27 studies, including three studies originating from Asia and thirteen from Western nations. Overall, where reported, 56.3% of patients had adenocarcinoma compared to 37.9% with squamous cell carcinoma. Across the studies 5.8% had another histological tumour type. These characteristics are reported across Tables 1 and 2.

Clinical credibility

The median clinical credibility score, out of 7, was 5.5 (range 4.5-6) (Table 3). Six models scored highest at 6 out of 7: The Rotterdam, Philadelphia, Amsterdam, prognostic nutritional index (PNI), and the original and revised STS models[30-33,37,56]. Twelve of these twenty-one preoperative models were oesophageal-specific and all models provided timely data for clinical decision making. Three of these models used subjectively reported patient health questionnaire data. Seventeen of the twenty-one preoperative models were considered easy to generate with the other four reliant on pre-operative spirometry, which may not be routinely performed. Three of the 21 preoperative models were considered challenging to understand. Sixteen of the twenty-one preoperative models were found to generate a useful scoring range to prognosticate patient outcomes.

Methodological quality - study participation

Only 20 of the models were able to be appraised for methodological quality, with the prognostic nutritional index original development study being unavailable in English[56]. Overall, the median score was 7.5 out of 8 (range 6-8). Of the model development studies, all but the Geriatric Nutrition Risk Index model sufficiently outlined the setting and period in which the study was conducted[59]. Five of the model development studies failed to outline their exclusion criteria appropriately. All studies detailed their patient mix and number of patients. Just one of the development studies had fewer than 100 patients and one model failed to report the mortality rate of patients. Sixteen models reported the characteristics of their cohort sufficiently and one scored partial marks in this area. Seven development studies did not utilise a sample patient group representative of the population to which the model would be applied. These omissions often related to a single gender within the sample, neoadjuvant treatment being an exclusion criteria or patients being selected based on age requirements.

Table 1 Development studies of preoperative multivariate models

Ref.	Period + number	Sample region	Operation	Characteristics	Source of data	Models tested	Outcomes tested
Schröder *et al* [29], 2006	1997-2002 (126)	Germany	TT	N: 46/126; H: 68 AC/54 SCC	Single centre	Cologne score	Morbidity
Steyerberg *et al*[30], 2006	1980-2002 (3592)	Unites States/Netherlands	TT/TH	N: 878/3592; H: 2118 AC/1307 SCC	SEER database + two centres	Rotterdam score	Mortality
Ra *et al*[32], 2008	1997-2003 (1172)	United States	TT/TH	N: N/A; H: N/A	SEER database	Philadelphia score	Mortality
Lagarde *et al* [31], 2008	1993-2005 (663)	Netherlands	TT/TH	N: 114/663; H: 476 AC/187 SCC	Single centre	Amsterdam score	Morbidity
Wright *et al* [33], 2009	2002-2007 (2315)	United States	TT/TH/MIE	N: 1016/2315; H: N/A	STSGTS database (164 centres)	Original STS model	Major morbidity + mortality
Ferguson *et al* [34], 2011	1980-2009 (516)	United States	TT/TH/hybrid/MIE	N: 167/516; H: 261 AC/137 SCC	Single centre	Ferguson score	Respiratory complications
Takeuchi *et al* [35], 2014	2011-2011 (5354)	Japan	Not stated	N: 1268/5354; H: N/A	National database	Tackeuchi model	Mortality
Filip *et al*[36], 2015	2008-2012 (167)	Italy	TT/TH/MIE	N: 131/167; H: 105 AC/62 SCC	Single centre	PNI-multivariate: PNI; CCI; ACCI; POSSUM; Amsterdam score	Morbidity + major morbidity (PNI-multivariate only)
Raymond *et al*[37], 2016	2011-2014 (4321)	United States	TT/TH/MIE	N: 2930/4321; H: N/A	STSGTS database (164 centres)	Revised STS model	Major morbidity + mortality
Reeh *et al* [38], 2016	1994-2007 (498)	Germany	TT/TH	N: 0/498; H: 253 SCC/245 AC	Single centre	PER score	Morbidity + mortality
Saito *et al* [39], 2019	2007-2015 (90)	Japan	MIE	N: 29/90; H: 87 SCC/3 AC	Single centre	PPCS model	Major morbidity
Ohkura *et al* [40], 2020	2011-2012 (10826)	Japan	Not stated	N: 2717/10826;H: N/A	National database (4105 centres)	JNCD model	Anastomotic leak
Wan *et al* [41], 2022	2006-2017 (10602)	United States	Not reported	N: N/A; H: N/A	National (NSQIP)	RAI-revised (CC): RAI-A; RAI-revised; 5 Factor MFI	Morbidity + mortality

TT: Transthoracic; TH: Transhiatal; MIE: Minimally invasive esophagectomy; N: Neoadjuvant chemotherapy; H: Histopathology subtype; SCC: Squamous cell carcinoma; AC: Adenocarcinoma; ACCI: Age-adjusted charlson comorbidity index; CCI: Charlson comorbidty index; POSSUM: Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity; RAI-A: Administrative risk analysis index; MFI: Modified frailty index; STS: Society of Thoracic Surgeons Oesophagectomy Composite Score; PNI: Prognostic nutritional index; PPCS: Predicting postoperative complications score; JNCD: Japanese National Clinical Database; PER: Perioperative esophagectomy risk score.

Methodological quality - prognostic factor and outcome measurement

The majority of the development studies available for analysis performed well in defining their prognostic factors and outcome measurements. The median score was 4 out of 4 (range 3-4). The lowest performing models achieved three out of a possible four points and this occurred in four models. All development studies defined their prognostic factors and model type, as well as their outcomes. Four of the models failed to outline their handling of missing data and a further two only did so in part.

Methodological quality - analysis

The median score for methodological quality of analysis was 5.75 out of 8 (range 4-8). All studies which developed preoperative models had adequate reporting on their evaluation measures, model building strategy and testing method. Seven failed to test or report the model's discriminatory capacity and fourteen also failed in reporting calibration. Only six studies also tested model performance on a testing set. Five studies had insufficient data to appraise the quality of their analysis fully and there were two instances of selective reporting found. One quarter of the preoperative models were compared to existing predictive tools within their development study.

Table 2 Validation studies of preoperative models

Ref.	Period + number	Sample region	Operation	Characteristics	Source of data	Models tested	Outcomes tested
Zingg *et al* [42], 2009	1990-2007 (346)	Switzerland/Australia	TT	N: 140/346; H: 259 AC/71 SCC	Two centres	Rotterdam score; Philadelphia score	Mortality
Grotenhuis *et al*[43], 2010	1991-2008 (777)	Netherlands	TT/TH	N: 221/777; H: N/A	Single centre	Amsterdam score	Morbidity
Bosch *et al* [44], 2011	1991-2007 (278)	Netherlands	TT	N: 10/278; H: 235 AC/43 SCC	Single centre	ACCI; CCI; O-POSSUM; P-POSSUM	Mortality
Ferguson *et al* [45], 2011	1980-2009 (514)	United States	TT/TH/hybrid/MIE	N: 167/514; H: 261 AC/137 SCC	Single centre	Amsterdam score	Morbidity + major morbidity
Filip *et al*[46], 2014	2004-2013 (43)	Romania	TT/TH	N: 22/43; H: 33 SCC/9 AC	Single centre	ACCI; CCI; POSSUM; O-POSSUM; P-POSSUM	Mortality
Yamana *et al* [47], 2015	2005-2013 (251)	Japan	TT/MIE	N: 150/251; H: N/A	Single centre	GNRI; PNI; E-PASS; POSSUM	Respiratory complications
Lindner *et al* [48], 2016	2005-2009 (94)	Germany	TT	N: 54/94; H: 94 AC/0 SCC	Single centre	Cologne score	Morbidity
Reinersman *et al*[49], 2016	2009-2012 (136)	United States	TT/TH/hybrid/MIE	N: 110/136; H: 118 AC/18 SCC	Single centre	Ferguson score	Respiratory complications
Xing *et al*[50], 2016	2008-2010 (217)	China	TT/TH	N: 0/217; H: 162 SCC/50 AC	Single centre	Ferguson score	Respiratory complications
Takeuchi *et al* [51], 2018	2000-2016 (438)	Japan	TT	N: 208/438; H: 398 SCC/27 AC	Single centre	Takeuchi model	Mortality
D'Journo *et al* [52], 2017	2004-2013 (1039)	France	TT/TH	N: 420/1039; H: N/A	National database	Rotterdam score	Mortality
Gray *et al*[53], 2020	2016-2018 (240)	United States	TT/TH/MIE	N: N/A; H: N/A	Single centre	NSQIP SRC	Morbidity
Peng *et al*[54], 2020	2012-2019 (218)	United States	MIE	N: 189/218; H: N/A	Single centre	NSQIP SRC	Morbidity + mortality
Ravindran *et al*[55], 2020	2013-2017 (100)	United States	TT	N: 87/100; H: 75 AC/21 SCC	Single centre	NSQIP SRC	Morbidity + mortality

TT: Transthoracic; TH: Transhiatal; MIE: Minimally invasive esophagectomy; N: Neoadjuvant chemotherapy; H: Histopathology subtype; SCC: Squamous cell carcinoma; AC: Adenocarcinoma; N/A: Not available; NSQIP SRC: National Surgical Quality Improvement Program Surgical Risk Calculator; ACCI: Age-adjusted charlson comorbidity index; CCI: Charlson comorbidty index; POSSUM: Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity; O-POSSUM: Operative - Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity; P-POSSUM: Portsmouth - Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity; GNRI: Geriatric nutritional risk index; PNI: Prognostic nutritional index; E-PASS: Estimation of physiologic and surgical stress.

Methodological quality - overall performance

Overall, the average score of methodological quality for the 20 studies appraised was 16.7 out 20. The median and mode score achieved was 16.5. The lowest scoring models were the Charlson comorbidity index, Cologne score and geriatric nutritional risk index, all of which scored fourteen[29,57,59]. The best scoring risk prediction models in this group for methodological quality were the PNI-multivariate score and the RAI-revised score, each scoring nineteen out of 20[36,63]. The overall methodological quality of the preoperative models is outlined in Table 4.

External validation

Eight of the twenty-one preoperative prediction models had been previously developed and were externally validated within this group of articles. Of the thirteen preoperative risk models that were development studies within the collated articles, six were subsequently externally validated. In total 14 out of 21 preoperative models have been externally validated. These findings are outlined in Figure 3.

Model performance - perioperative mortality

Fourteen of the twenty-seven included studies had an outcome measure related to perioperative

Table 3 Clinical credibility of preoperative models

Ref.	Model	Oesophageal specific	No thresholds	Timely data	Reliable data	Easy to generate	Understandable	Useful range	Total
Onodera *et al* [56], 1984	PNI	No	Yes	Yes	Yes	Yes	Yes	Yes	6
Charlson *et al* [57], 1987	CCI	No	No	Yes	Yes	Yes	Yes	Yes	5
Charlson *et al* [58], 1994	ACCI	No	No	Yes	Yes	Yes	Yes	Yes	5
Bouillanne *et al* [59], 2005	GNRI	No	Yes	Yes	Yes	Yes	Yes	Partly	5.5
Schröder *et al* [29], 2006	Cologne	Yes	No	Yes	Yes	Partly	Yes	No	4.5
Steyerberg *et al* [30], 2006	Rotterdam	Yes	No	Yes	Yes	Yes	Yes	Yes	6
Ra *et al*[32], 2008	Philadelphia	Yes	No	Yes	Yes	Yes	Yes	Yes	6
Lagarde *et al* [31], 2008	Amsterdam	Yes	Partly	Yes	Yes	Partly	Yes	Yes	6
Wright *et al*[33], 2009	Original STS	Yes	No	Yes	Yes	Yes	Yes	Yes	6
Ferguson *et al* [34], 2011	Ferguson	Yes	No	Yes	Yes	Partly	Yes	Yes	5.5
Bilimoria *et al* [60], 2013	NSQIP SRC	No	Partly	Yes	Yes	Yes	Yes	Yes	5.5
Takeuchi *et al* [35], 2014	Takeuchi	Yes	No	Yes	Yes	Yes	Partly	Yes	5.5
Filip *et al*[36], 2015	PNI multivariate	Yes	No	Yes	Yes	Yes	Partly	Yes	5.5
Raymond *et al* [37], 2016	Revised STS	Yes	No	Yes	Yes	Yes	Yes	Yes	6
Reeh *et al*[38], 2016	PER	Yes	No	Yes	Yes	Partly	Yes	No	4.5
Hall *et al*[61], 2017	RAI-A	No	No	Yes	Partly	Yes	Yes	Yes	4.5
Subramaniam *et al*[62], 2018	5 Factor MFI	No	Yes	Yes	Yes	Yes	Yes	Partly	5.5
Saito *et al*[39], 2019	PPCS	Yes	No	Yes	Yes	Yes	Yes	Partly	5.5
Ohkura *et al*[40], 2020	JNCD	Yes	No	Yes	Yes	Yes	Partly	Yes	5.5
Arya *et al*[63], 2020	RAI-revised	No	No	Yes	Partly	Yes	Yes	Yes	4.5
Wan *et al*[41], 2022	RAI-revised (CC)	No	No	Yes	Partly	Yes	Yes	Yes	4.5

CCI: Charlson comorbidity index; ACCI: Age-adjusted charlson comorbidity index; GNRI: Geriatric nutritional risk index; NSQIP SRC: National Surgical Quality Improvement Program Surgical Risk Calculator; RAI-A: Administrative risk analysis index; MFI: Modified frailty index; STS: Society of Thoracic Surgeons Oesophagectomy Composite Score; PNI: Prognostic nutritional index; PPCS: Predicting postoperative complications score; JNCD: Japanese National Clinical Database; PER: Perioperative esophagectomy risk score.

mortality, but the mortality endpoints varied across studies, with some considering inpatient mortality and others selecting a post-operative time frame, typically 30 or 90 d. Multiple papers appraised two or more performance models, leading to a total of twenty instances of a preoperative risk model being tested for predicting mortality. Overall, thirteen of the twenty-one preoperative prediction models were tested against mortality. Eleven of the models utilised discrimination, represented through area under the ROC curve. Three models had a weighted average exceeding 0.70, thereby indicating clinical utility. These included the Takeuchi score, the revised STS model and the National Quality Improvement

Table 4 Methodological quality (overall performance) for preoperative models

Model	Study participation (out of 8)	Measurements (out of 4)	Analysis (out of 8)	Total (out of 20)
PNI	N/A	N/A	N/A	N/A
CCI	6	4	5	14
ACCI	6	4	4.5	14.5
GNRI	6.5	3	4.5	14
Cologne	7	3	4	14
Rotterdam	7.5	4	6	17.5
Philadelphia	7.5	4	5	16.5
Amsterdam	8	3.5	7	18.5
Original STS	8	4	5.5	17.5
Ferguson	7.5	4	5	16.5
NSQIP SRC	7.5	3.5	6	16.5
Takeuchi	8	3	7	18
PNI multivariate	8	4	7	19
Revised STS	8	4	4.5	16.5
PER	7	4	4	15
RAI-A	7	4	6.5	17.5
5 Factor MFI	6.5	3	6.5	16
PPCS	7	4	5.5	16.5
JNCD	8	4	6.5	18.5
RAI-revised	7	4	8	19
RAI-revised (CC)	8	4	6.5	18.5

CCI: Charlson comorbidity index; ACCI: Age-adjusted charlson comorbidity index; GNRI: Geriatric nutritional risk index; NSQIP SRC: National Surgical Quality Improvement Program Surgical Risk Calculator; RAI-A: Administrative risk analysis index; MFI: Modified frailty index; STS: Society of Thoracic Surgeons Oesophagectomy Composite Score; PNI: Prognostic nutritional index; PPCS: Predicting postoperative complications score; JNCD: Japanese National Clinical Database; PER: Perioperative esophagectomy risk score.

Project (NSQIP) surgical risk calculator[35,37,60]. Calibration was represented more heterogeneously, the majority used Hosmer-Lemeshow goodness of fit or O:E ratios but of the fourteen studies which tested models against mortality on twenty occasions, calibration was reported in just eight instances. The calibration was adequate in all instances. The best performing preoperative calibration model in terms of calibration was the Rotterdam score[30]. This was adequately calibrated to mortality in each of the three instances it was tested[30,42,52]. The Philadelphia score was also adequately calibrated in both studies it was tested[31,42]. The overall performance of these models in relation to predicting mortality outcomes is illustrated in Table 5.

Model performance - perioperative major morbidity

Five of the twenty-seven studies had an outcome measure related to perioperative major morbidity all based on a grade three Clavien-Dindo complication or higher. All five preoperative multivariate models reported discrimination statistics in the form of area under the ROC curve. Two preoperative models had a weighted mean exceeding 0.7: The predicting postoperative complications score (PPCS) model and the PNI multivariate[36,39]. Neither model has been externally validated in a second cohort as reaching the utility threshold. Only on one occasion was calibration reported in predicting major morbidity, namely the PNI-multivariate model, which was found to be sufficiently calibrated[36]. Model performance in relation to major morbidity outcomes is summarised in Table 6.

Model performance - overall perioperative morbidity

Eleven out of the twenty-seven studies measured outcomes in relation to overall perioperative morbidity, not specified to respiratory complications. There were seventeen instances of a preoperative models being tested in predicting overall morbidity found. Eleven different models were tested for these complications, with nine having discriminatory performance represented through area under the

Table 5 Summary of the performance for all preoperative models in predicting perioperative mortality

Ref.	Predictive model	Discrimination	Calibration	Outcome
Bosch *et al*[44], 2011	CCI (2)	AUC = 0.567	HL *P* value (0.659)	Mortality
Filip *et al*[46], 2014		AUC = 0.736	Not reported	Mortality
Bosch *et al*[44], 2011	ACCI (2)	AUC = 0.684	HL *P* value (0.270)	Mortality
Filip *et al*[46], 2014		AUC = 0.744	Not reported	Mortality
Steyerberg *et al*[30], 2006	Rotterdam score (3)	AUC = 0.70	"Excellent"	Mortality
Zingg *et al*[42], 2009		*P* value = 0.003	HL *P* value (0.266)	Mortality
D'Journo *et al*[52], 2017		AUC = 0.64	Fair (overpredicts)	Mortality
Ra *et al*[32], 2008	Philadelphia score (2)	"Effective"	"Good"	Mortality
Zingg *et al*[42], 2009		*P* value = 0.001	HL *P* value (0.735)	Mortality
Wright *et al*[33], 2009	Original STS model	AUC = 0.621	Not reported	Major morbidity or mortality
Peng *et al*[54], 2020	NSQIP SRC (2)	AUC = 0.627	O:E = 1.13	Mortality
Ravindran *et al*[55], 2020		AUC = 0.880	Not reported	Mortality
Takeuchi *et al*[35], 2014	Takeuchi model (2)	AUC = 0.766	Not reported	Mortality
Takeuchi *et al*[51], 2018		AUC = 0.697	Not reported	Mortality
Raymond *et al*[37], 2016	Revised STS model	AUC = 0.71	Not reported	Mortality
Reeh *et al*[38], 2016	PER score	P = 0.001	Not reported	Mortality
Wan *et al*[41], 2022	RAI-A	AUC = 0.58	Not reported	Mortality
	5 Factor MFI	AUC = 0.58	Not reported	Mortality
	RAI-revised	AUC = 0.62	Not reported	Mortality
	RAI-revised (CC)	AUC = 0.60	Not reported	Mortality

AUC: Area under the receiver operating characteristic curve; HL: Hosmer-Lemeshow; O:E: Observed:expected ratio; CCI: Charlson comorbidity index; ACCI: Age-adjusted charlson comorbidity index; NSQIP SRC: National Surgical Quality Improvement Program Surgical Risk Calculator; RAI-A: Administrative risk analysis index; STS: Society of Thoracic Surgeons Oesophagectomy Composite Score; PNI: Prognostic nutritional index; PER: Perioperative esophagectomy risk score.

Table 6 Summary of the performance for all preoperative models in predicting perioperative major morbidity

Ref.	Predictive model	Discrimination	Calibration	Outcome
Ferguson *et al*[45], 2011	Amsterdam score	AUC = 0.653	Not stated	Major morbidity
Wright *et al*[33], 2009	Original STS model	AUC = 0.621	Not reported	Major morbidity or mortality
Filip *et al*[36], 2015	PNI multivariate	AUC = 0.80	HL *P* value (0.67)	Major morbidity
Raymond *et al*[37], 2016	Revised STS model	AUC = 0.63	Not reported	Major morbidity
Saito *et al*[39], 2019	PPCS model	AUC = 0.798	Not reported	Major morbidity

AUC: Area under the receiver operating characteristic curve; HL: Hosmer-Lemeshow; O:E: Observed:expected ratio; PPCS: Predicting postoperative complications score; STS: Society of Thoracic Surgeons Oesophagectomy Composite Score; PNI: Prognostic nutritional index.

ROC curve. No model possessed a weighted mean that reached the threshold for clinical utility. The best performance was the Amsterdam model with a weighted AUC of 0.64[32]. Only eight of the seventeen instances in which the models were tested for predicting overall complications reported calibration with it being sufficient calibration on five occasions. The Amsterdam model was well calibrated in all three studies in which it was reported[32,36,43]. The NSQIP was appropriately calibrated in one out of two studies and the Prognostic Nutritional Index was sufficiently calibrated in the sole study it was reported[36,53,54]. A summary of model performance in predicting perioperative morbidity outcomes is presented in Table 7.

Table 7 Summary of the performance for all preoperative models in predicting perioperative morbidity

Ref.	Predictive model	Discrimination	Calibration	Outcome
Filip *et al*[36], 2015	PNI	AUC = 0.65	HL *P* value (0.85)	Morbidity
Filip *et al*[36], 2015	CCI	AUC = 0.59	Pearson *P* value (0.48)	Morbidity
Filip *et al*[36], 2015	ACCI	AUC = 0.61	Pearson *P* value (0.17)	Morbidity
Schröder *et al*[29], 2006	Cologne score (2)	*P* value ≤ 0.001	Not reported	Morbidity
Lindner *et al*[48], 2016		*P* value = 0.010	Not reported	Morbidity
Lagarde *et al*[31], 2008	Amsterdam score (4)	AUC = 0.65	HL *P* value (0.366)	Morbidity
Grotenhuis *et al*[43], 2010		AUC = 0.64	HL *P* value (0.84)	Morbidity
Ferguson *et al*[45], 2011		AUC = 0.639	Not stated	Morbidity
Filip *et al*[36], 2015		AUC = 0.60	HL *P* value (0.55)	Morbidity
Gray *et al*[53], 2020	NSQIP SRC (3)	AUC = 0.553	"Insufficient"	Morbidity
Peng *et al*[54], 2020		AUC = 0.600	O:E = 1.89	Morbidity
Ravindran *et al*[55], 2020		AUC = 0.628	Not reported	Morbidity
Reeh *et al*[38], 2016	PER score	*P* ≤ 0.001	Not reported	Morbidity
Wan *et al*[41], 2022	RAI-A	AUC = 0.54	Not reported	Morbidity
Wan *et al*[41], 2022	5 Factor MFI	AUC = 0.57	Not reported	Morbidity
Wan *et al*[41], 2022	RAI-revised	AUC = 0.54	Not reported	Morbidity
Wan *et al*[41], 2022	RAI-revised (CC)	AUC = 0.51	Not reported	Morbidity

AUC: Area under the receiver operating characteristic curve; HL: Hosmer-Lemeshow; O:E: Observed:expected ratio; CCI: Charlson comorbidity index; ACCI: Age-adjusted charlson comorbidity index; NSQIP SRC: National Surgical Quality Improvement Program Surgical Risk Calculator; RAI-A: Administrative risk analysis index; PNI: Prognostic nutritional index; PER: Perioperative esophagectomy risk score.

Model performance - perioperative respiratory complications/anastomotic leak/readmission/return to theatre

Four articles appraised five instances of three different model's performance in predicting respiratory complications. These included the Ferguson score, the geriatric nutritional risk index and the prognostic nutritional index, however, none of these reached a weighted mean c-statistic of clinical utility[34,56,59]. The Ferguson score was the best performing in terms of discrimination, reaching significance in two out of the three studies in which it was tested but only had a weighted-average c-statistic of 0.669[34,49,50]. The Ferguson model was appropriately calibrated in both studies for which this was reported[34,49]. None of the other models had reporting of calibration. A single study by Ohkura *et al*[40] assessed model performance in predicting anastomotic leak rate but this failed to reach sufficient discrimination and did not report calibration. Only the NSQIP surgical risk calculator was tested specifically for the prediction of readmission and return to theatre rates[53-55]. For return to theatre, this model was poorly calibrated and was unable to discriminate outcomes in all studies[53-55]. The surgical risk calculator demonstrated utility and good calibration for predicting readmission in a single study but overall performed poorly in this area too[55]. A summary of model performance for these secondary outcome measures is illustrated in Table 8.

Model performance - overall comments

The summary of all the models and their performance for each outcome against which they were tested has been outlined for preoperative models (Tables 5-8). The weighted average area under the ROC curve is presented in each of the major four outcomes for every model in which these were reported (Figure 4). Meaningful subgroup analysis of model performance based on surgical approach was not feasible as many articles incorporated multiple surgical approaches and did not delineate model performance for each technique. Similar limitations also prevented subgroup analyses of model performance on the basis of histological subtype and the administration of neoadjuvant chemotherapy.

Clinical effectiveness

None of the models were tested prospectively in terms of whether adoption of the model in clinical decision making would lead to improved clinical outcomes.

Table 8 Summary of the performance for all preoperative models in predicting respiratory complications, return to theatre, readmission and anastomotic leak

Ref.	Predictive model	Discrimination	Calibration	Outcome
Yamana *et al*[47], 2015	PNI	AUC = 0.609	Not reported	Respiratory complications
Yamana *et al*[47], 2015	GNRI	AUC = 0.651	Not reported	Respiratory complications
Ferguson *et al*[34], 2011	Ferguson score (3)	AUC = 0.708	HL *P* value (0.16)	Respiratory complications
Reinersman *et al*[49], 2016		AUC = 0.726	HL *P* value (0.2394)	Respiratory complications
Xing *et al*[50], 2016		AUC = 0.539	Not reported	Respiratory complications
Gray *et al*[53], 2020	NSQIP SRC (3)	AUC = 0.533	Insufficient	Return to theatre
		AUC = 0.625	Insufficient	Readmission
Peng *et al*[54], 2020		AUC = 0.558	O:E = 0.48	Return to theatre
		AUC = 0.558	O:E = 1.11	Readmission
Ravindran *et al*[55], 2020		AUC = 0.584	Not reported	Return to theatre
		AUC = 0.767	Not reported	Readmission
Ohkura *et al*[40], 2020	JNCD model	AUC = 0.531	Not reported	Anastomotic leak

AUC: Area under the receiver operating characteristic curve; HL: Hosmer-Lemeshow; O:E: Observed:expected ratio; PNI: Prognostic nutritional index; GNRI: Geriatric nutritional risk index; NSQIP SRC: National Surgical Quality Improvement Program Surgical Risk Calculator; JNCD: Japanese National Clinical Database.

Overall performance

The overall performance of each model within the five domains is outlined in Table 9.

DISCUSSION

This systematic review included twenty-seven articles utilising twenty-one different preoperative risk prediction models deemed to forecast outcomes after oesophagectomy. Twelve of these were specifically devised for oesophageal resection and fourteen models have been externally validated. The clinical credibility of the development studies of these models was generally strong. The methodological quality of the majority of the studies was also sound, with more recent studies trending better in this assessment. Only one model's development study was not available for analysis. However, with respect to model performance, the findings were underwhelming and there were only a few instances in which models demonstrated clinical utility.

Across the breadth of the articles, just three preoperative risk models possessed a weighted mean of discriminatory capacity sufficient to be of clinical utility in predicting perioperative mortality. These three models were the NSQIP surgical risk calculator, the Takeuchi score and the revised STS model[35,37,60]. It must be noted that of the two occasions that the NSQIP surgical risk calculator and Takeuchi score were tested, both reached clinical utility on only one of the two occasions[35,51,54,55]. Furthermore, the revised STS model is yet to be externally validated. Calibration was not reported for the Takeuchi score or revised STS model but the NSQIP surgical risk calculator reported calibration once, and performed well[54]. A handful of other models displayed clinically useful discrimination in one of the two studies in which they were tested but failed to meet this threshold in the weighted mean. These included the Charlson comorbidity index, the age-adjusted Charlson comorbidity index and Rotterdam scores[30,46]. All three of these models performed well with respect to calibrating expected mortality in the studies in which this was reported[30,42,44,52].

In terms of the preoperative prediction of non-fatal complications, the performance of the models was also underwhelming. Only two models demonstrated clinical utility forecasting perioperative major morbidity: The PPCS model and the PNI-multivariate[36,39]. The PNI-multivariate model had good calibration in its only study whereas the PPCS model calibration remains unreported in the literature [36]. The clinical credibility of both were strong and the methodological quality of the PNI-multivariate was sound[36]. However, neither of these models have been externally validated. No preoperative risk model demonstrated adequate performance in discriminating overall morbidity. The best performer in this area was the Amsterdam score which calibrated well but was unable to sufficiently discriminating outcomes[32]. Similarly, no model consistently displayed clinical utility in predicting respiratory complications. The most promising model was the Ferguson pulmonary score, developed specifically

Table 9 Summary of the preoperative models across the five categories

Ref.	Model	Clinical credibility (out of 7)	Methodological quality (out of 20)	Model performance (overall utility)	External validation	Clinical effectiveness
Onodera *et al*[56], 1984	PNI	6	N/A	No	Yes	No
Charlson *et al*[57], 1987	CCI	5	14	No	Yes	No
Charlson *et al*[58], 1994	ACCI	5	14.5	No	Yes	No
Bouillanne *et al*[59], 2005	GNRI	5.5	14	No	Yes	No
Schröder *et al*[29], 2006	Cologne	4.5	14	No	Yes	No
Steyerberg *et al*[30], 2006	Rotterdam	6	17.5	No	Yes	No
Ra *et al*[32], 2008	Philadelphia	6	16.5	No	Yes	No
Lagarde *et al*[31], 2008	Amsterdam	6	18.5	No	Yes	No
Wright *et al*[33], 2009	Original STS	6	17.5	No	No	No
Ferguson *et al*[34], 2011	Ferguson	5.5	16.5	No	Yes	No
Bilimoria *et al*[60], 2013	NSQIP SRC	5.5	16.5	Mortality	Yes	No
Takeuchi *et al*[35], 2014	Takeuchi	5.5	18	Mortality	Yes	No
Filip *et al*[36], 2015	PNI multivariate	5.5	19	Major morbidity	No	No
Raymond *et al*[37], 2016	Revised STS	6	16.5	Mortality	No	No
Reeh *et al*[38], 2016	PER	4.5	15	No	No	No
Hall *et al*[61], 2017	RAI-A	4.5	17.5	No	Yes	No
Subramaniam *et al*[62], 2018	5 Factor MFI	5.5	16	No	Yes	No
Saito *et al*[39], 2019	PPCS	5.5	16.5	Major morbidity	No	No
Ohkura *et al*[40], 2020	JNCD	5.5	18.5	No	No	No
Arya *et al*[63], 2020	RAI-revised	4.5	19	No	Yes	No
Wan *et al*[41], 2022	RAI-revised (CC)	4.5	18.5	No	Yes	No

PNI: Prognostic nutritional index; GNRI: Geriatric nutritional risk index; NSQIP SRC: National Surgical Quality Improvement Program Surgical Risk Calculator; JNCD: Japanese National Clinical Database; RAI: Risk analysis index; PPCS: Predicting postoperative complications score; MFI: Modified frailty index; RAI-A: Administrative risk analysis index; PER: Perioperative esophagectomy risk score; STS: Society of Thoracic Surgeons Oesophagetomy Composite Score.

for predicting respiratory outcomes[34]. In two of three studies, it performed well in discrimination and calibration, but the weighted mean was adversely affected by a poor performance in the third study[34,49,50]. Discouragingly, no preoperative risk model could predict anastomotic leak, readmission or return to theatre.

The results of this systematic review are consistent with the major findings of previous systematic reviews in this area. Findlay *et al*[14] concluded that no preoperative model predicted post-operative morbidity or mortality with sufficient accuracy and Warnell *et al*[15] concluded that no models could be applied to clinical practice with any confidence. The models identified in our review as having clinical promise in predicting mortality and major complications were developed subsequent to these reviews. The reasons for vast majority of these models failing to sufficiently predict outcomes are multifactorial. Most clinical prediction tools are generated from outcome data from the same cohort on which the

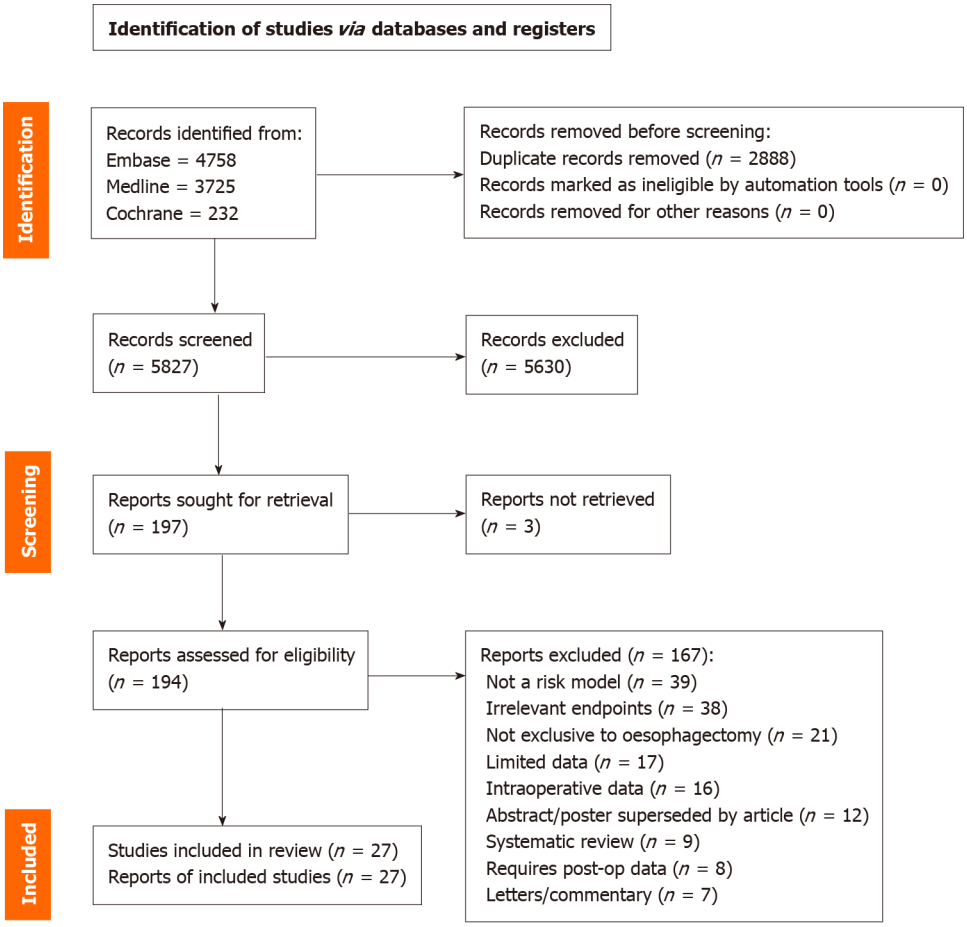

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Figure 1 PRISMA 2020 flow diagram.

PNI = Prognostic nutritional index
CCI = Charlson comorbidity index
ACCI = Age-adjusted charlson comorbidity index
GNRI = Geriatric nutritional risk index
Cologne = Cologne Score
Rotterdam = Rotterdam Score
Philadelphia = Philadelphia Score
Amsterdam = Amsterdam Score
Original STS = Society of Thoracic Surgeons Oesophagectomy Composite Score
Ferguson = Ferguson Pulmonary Risk Score
NSQIP SRC = National Surgical Quality Improvement Program Surgical Risk Calculator
Takeuchi = Takeuchi Risk Model
PNI Multivariate = Prognostic nutritional index multivariate score
Revised STS = Revised Society of Thoracic Surgeons Oesophagectomy Composite Score
PER = Preoperative esophagectomy risk score
RAI-A = Administrative risk analysis index
5 Factor MFI = 5 Factor modified frailty index
PPCS = Predicting postoperative complications score
JNCD = Japanese National Clinical Database Model
RAI-revised = Revised risk analysis index
RAI-revised (CC) = Revised risk analysis index (cancer corrected)

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Figure 2 Reference key for list of abbreviated model names.

model is subsequently tested[23]. This predisposes the models to bias through overfitting to the development data set and thus subsequently poor performance when applied to an external population dataset[23]. In addition, several models were developed from a single centre with a relatively small dataset that further confounded their ability to predict uncommon clinical outcomes especially considering the relative rarity of mortality or major morbidity post-oesophagectomy. Larger

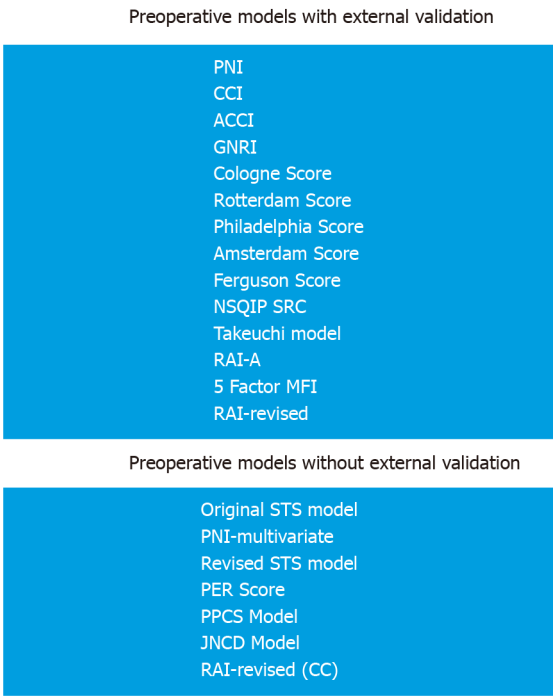

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Figure 3 External validation status of pre-operative models. CCI: Charlson comorbidity index; ACCI: Age-adjusted comorbidity index; GNRI: Geriatric nutritional risk index; NSQIP SRC: National Surgical Quality Improvement Program Surgical Risk Calculator; RAI-A: Administrative risk analysis index; MFI: Modified frailty index; STS: Society of Thoracic Surgeons Oesophagectomy Composite Score; PNI: Prognostic nutritional index; PPCS: Predicting postoperative complications score; JNCD: Japanese National Clinical Database.

development models are therefore required to reliably predict these events.

Aside from the studied multivariate risk models, there are a plethora of single factor prognostic indicators researched over this period. There have been three studies of the discriminatory capacity of cardiopulmonary fitness testing (CPEX), often represented through anaerobic threshold and VO_2 maximum[64]. In each study CPEX fell short of reaching clinical utility thresholds in predicting major complications following oesophagectomy[65,66]. Preoperative sarcopenia, represented through grip strength or volumetric psoas muscle analysis, has also been highlighted as a prognostic marker for perioperative and long-term outcomes following oesophagectomy. But again, the performance of sarcopenia in predicting outcomes following oesophagectomy has been highly variable[67]. A systematic review conducted in 2020 by Papaconstantinou *et al*[67] found a statistically significant relationship between preoperative sarcopenia and overall perioperative morbidity, respiratory complications and anastomotic leaks. However, the same study failed to demonstrate correlative significance for sarcopenia and perioperative mortality or major complications (Clavien-Dindo grade III or higher)[67].

There are a number of strengths to this review. The review was conducted thoroughly and reported in accordance with the PRISMA method, outlining the study search and selection strategy. There was no iterative manipulation of the search terms or strategy to allow for selective inclusion or exclusion or specific articles. To the knowledge of the authors, this is the third systematic review to appraise multivariate risk models in the prediction of perioperative outcomes following oesophagectomy. It just the second to incorporate qualitative analysis of the risk models involve. This review is the first to consider the issue since 2015 and over the intervening period, there has been a substantial proliferation of multivariate risk models in the literature. Therefore, this systematic review is the largest of its kind. Although somewhat peripheral to the scope of this review, the temporal gap between this review and the preceding systematic review means this review can uniquely consider the performance of these multivariate risk models against the burgeoning list of other recently developed clinical predictors as outlined above. In contrast to a previous related effort, this review has not excluded low-volume centres in the analysis. Perhaps the greatest strength of this submission is that it is the first to isolate models which exclusively use preoperative variables. This is important because by their very nature, only preoperative risk prediction models can assist surgeons in selecting appropriate surgical candidates and appropriately counselling these patients of their risks prior to an operation.

Despite this, a number of common challenges were encountered. The quality of the results generated was limited by the completeness of reporting in the original publications added to which is a risk of positive finding publication bias. We limited our search to articles published in English and from the year 2000 onward, which whilst pragmatic, could have led to the exclusion of valuable publications. This review also did not consider long-term survival or patient reported quality of life outcomes, both of

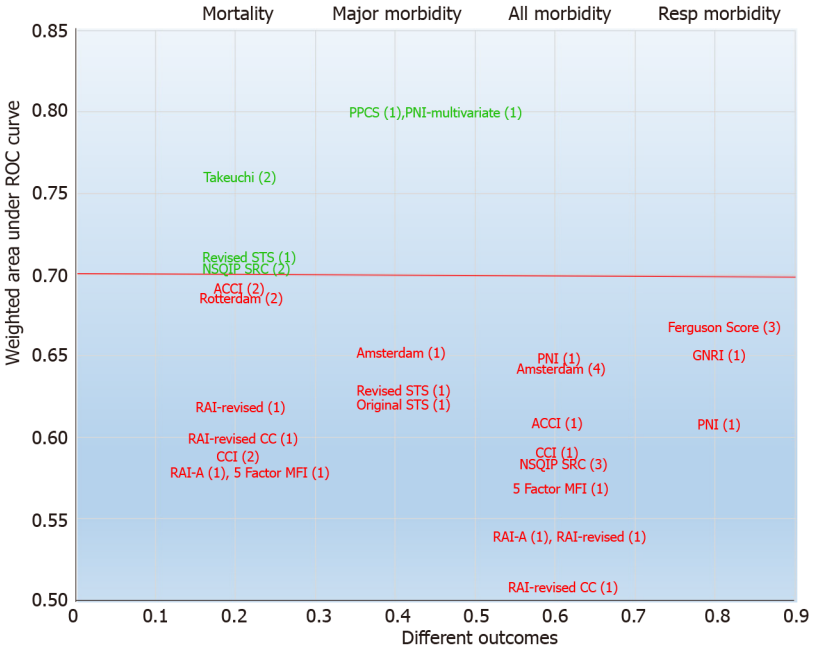

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Figure 4 Weighted mean of c-statistics for each major outcome. CCI: Charlson comorbidity index; ROC: Receiver operating characteristic; ACCI: Age-adjusted comorbidity index; GNRI: Geriatric nutritional risk; NSQIP SRC: National Surgical Quality Improvement Program Surgical Risk Calculator; RAI-A: Administrative risk analysis index; MFI: Modified frailty index; STS: Society of Thoracic Surgeons Oesophagectomy Composite Score; PNI: Prognostic nutritional index; PPCS: Predicting postoperative complications score.

which may influence the decision whether to undertake surgical intervention. Qualitative analysis of the risk prediction models, whilst deemed a source of strength, can sometimes be subjective. There were also several challenges unique to this topic, many of which were also encountered during the preceding systematic reviews. Across the studies, there was significant heterogeneity in clinical practice and methodology in outcome measurements. Much of this related to the regional and temporal variance observed in the treatment of oesophageal cancer within the studies.

These limitations also highlight areas in which further research could be focused. A few preoperative prediction models do show promise but have not yet been externally validated. If these models were tested in a different population group, it would certainly strengthen the case for their application. Owing to the low risk of mortality following oesophagectomy, any attempt to demonstrate clinical improvement would require a large multicentre, long-term prospective clinical trial, this likely contributes to why none of the studies have been used to show prospective improvement in clinical outcomes. If a model was demonstrated to lead to better outcomes, it would encourage surgeons to utilise such model in everyday practice. Finally, with an increasing emphasis on individualised medicine, future research should also seek to develop and define models that also focus on long-term survival and patient reported quality of life outcomes.

CONCLUSION

A large number of clinical multivariate risk models have been developed or adapted to use in predicting perioperative outcomes including morbidity, major morbidity and mortality following oesophagectomy. By being based on preoperative variables, they are designed to aid in patient selection for surgical resection and to guide informed preoperative counselling of patients. This study has demonstrated that most models are clinically credible and were constructed with sound methodological quality, but their performance was often insufficient to prognosticate patient outcomes. In total, three models were identified as being capable in discriminating patients for mortality: The NSQIP surgical risk calculator, the revised STS score and the Takeuchi model. Two models predicted postoperative major morbidity: The PPCS model and PNI-multivariate model. However, most of these models are not externally validated and none have shown clinical effectiveness in improving outcomes. Further research is needed before prediction models can be confidently applied to clinical practice in selecting appropriate surgical candidates, counselling patients on surgical risk and guiding postoperative resource allocation.

ARTICLE HIGHLIGHTS

Research background

Oesophageal cancer is the eighth most common type of cancer and sixth leading cause of cancer-related death worldwide. If it is detected in the early stages, an oesophagectomy can be undertaken with realistic curative intent. Unfortunately, this surgery comes with a significant morbidity burden and can result in fatal outcomes, making appropriate selection of surgical candidates imperative. Numerous multivariate risk prediction models have been devised to augment this decision-making with ongoing conjecture as to which risk prediction tool is most reliable. This publication is the first systematic review in seven years to attempt to resolve which model most accurately predicts perioperative outcomes following oesophagectomy.

Research motivation

The identification of the best preoperative risk prediction model would allow surgeons apply this to clinical practice. Such a tool may assist in augmenting clinical decision making to better identify and counsel appropriate surgical candidates for oesophagectomy. It is expected that improved patient selection would lead to overall improved perioperative outcomes for patients suffering from oesophageal cancer.

Research objectives

The objective of this research is to conduct a contemporary systematic review assessing which preoperative multivariate risk model best predicts perioperative oesophagectomy outcomes. The primary objective relates to appraising predictive performance for mortality outcomes. The secondary objectives are to assess the ability of the multivariate models in forecasting major morbidity, overall morbidity and specific key complications such as respiratory complications and anastomotic leak.

Research methods

A systematic review incorporating the MEDLINE, Embase and Cochrane databases was conducted from 2000-2020. Applied search terms were ((Oesophagectomy) AND (Risk OR predict OR model OR score) AND (Outcomes OR complications OR morbidity OR mortality OR length of stay OR anastomotic leak)). Only multivariate based tools which utilised exclusively data available preoperatively to predict perioperative outcomes following oesophagecotmy were included with articles generated, collated and then reported in accordance with PRISMA guidelines. All risk models were appraised across the five domains of clinical credibility, methodological quality, model performance, external validation and clinical effectiveness.

Research results

The initial search yielded 8715 articles which was reduced to 197 potentially relevant texts after deduplication, title and abstract screening. Following detailed assessment of these articles, 27 published studies were ultimately included with these examining 21 multivariate preoperative risk prediction models. The majority of models were clinically credible with sound methodological quality but many models still require external validation and none had yet proven clinical effectiveness with their adoption. Three models adequately predicted perioperative mortality (National Surgical Quality Improvement Program surgical risk calculator, revised Society of Thoracic Surgeons oesophagectomy composite score and Takeuchi model) whilst two (predicting postoperative complications score and prognostic nutritional index-multivariate model) predicted major morbidity sufficiently.

Research conclusions

There are a few well-constructed and credible multivariate risk prediction models that demonstrate promise in forecasting perioperative mortality and major morbidity outcomes. However, more research is required in the sphere of external validation and to demonstrate improved clinical outcomes with the adoption of these models in preoperative surgical patient selection.

Research perspectives

There is a research gap in externally validating some of these models which have yet to be assessed outside of their development cohort. Ultimately, the direction of future research should involve the development of a prospective randomised controlled trial in which one group would utilise clinical discretion with the other applying one of the promising preoperative risk prediction models in determining appropriate surgical candidates. In such a trial, clinical effectiveness with the adoption of a risk prediction model could be demonstrated if improved patient outcomes were observed. This would provide compelling evidence for the broader application of such a risk prediction model in patient selection for oesophagectomy.

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FOOTNOTES

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Country/Territory of origin: Australia

ORCID number: James Paul Grantham 0000-0002-5267-5646; Amanda Hii 0000-0003-3056-0087; Jonathan Shenfine 0000-0002-1862-4693.

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

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META-ANALYSIS

Effect of music therapy on chemotherapy-induced nausea and vomiting in gastrointestinal cancer: A systematic review and meta-analysis

Fang-Ping Zhong, Jun Zhong, Ming-Yan Zhong

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Fang-Ping Zhong, Ming-Yan Zhong, Department of Oncology, Pingxiang Second People's Hospital, Pingxiang 337000, Jiangxi Province, China

Jun Zhong, School of Biomedical Engineering, Guangzhou Medical University, Guangzhou 511436, Guangdong Province, China

Corresponding author: Fang-Ping Zhong, CCST, MS, RN, Associate Chief Nurse, Department of Oncology, Pingxiang Second People's Hospital, No. 18-301 Athenian Century Garden, Anyuan Town, Anyuan District, Pingxiang 337000, Jiangxi Province, China.
zz23181113441123@163.com

Abstract

BACKGROUND

Chemotherapy is the primary treatment for patients with advanced gastrointestinal cancer, but it has many adverse reactions, particularly nausea and vomiting. Music therapy can reduce anxiety symptoms, avoid the response to the human body under various stress conditions through psychological adjustment, and improve the adverse reactions of chemotherapy.

AIM

To investigate the impact of music therapy on relieving gastrointestinal adverse reactions in chemotherapy for patients with digestive tract cancer by meta-analysis.

METHODS

EMBASE, PubMed, OVID, WoS, CNKI, CBM, and VIP database were all used for searching relevant literature, and the efficacy after treatment was combined for analysis and evaluation.

RESULTS

This study included seven articles. The results of meta-analysis indicated that music therapy could reduce the nausea symptom score of patients after chemotherapy [mean difference (MD) = -3.15, 95% confidence interval (CI): -4.62 to -1.68, Z = -4.20, P < 0.0001]. Music therapy could reduce the vomiting symptom score of patients after chemotherapy (MD = -2.28, 95%CI: -2.46 to -2.11, Z = -25.15, P < 0.0001). Furthermore, music therapy could minimize the incidence of grade I and above nausea or vomiting in patients after chemotherapy (odds ratio = 0.38,

95%CI: 0.26-0.56, Z = -4.88, P < 0.0001). Meta-regression analysis found that publication year was not a specific factor affecting the combined results. There was no significant publication bias (P > 0.05).

CONCLUSION

Music therapy can significantly improve the scores of nausea and vomiting symptoms in patients with digestive system cancer during chemotherapy and reduce the incidence of grade I and above nausea and vomiting after chemotherapy, making it an effective psychological intervention method worthy of clinical promotion.

Key Words: Music therapy; Gastrointestinal cancer; Nausea and vomiting; Gastrointestinal reactions

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Core Tip: Music therapy bases on the theories and methods of psychotherapy. It helps human body to react positively under various stress conditions through psychological adjustment, interest improving, and anxiety symptoms reduction. Music therapy plays a role in improving the negative emotions of cancer patients. However, whether it could reduce nausea and vomiting caused by chemotherapy still remains unknown. In this meta-analysis, we searched the public databases for relevant articles and pooled the results of the symptom scores and incidence of chemotherapy-induced nausea and vomiting to further discussion.

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INTRODUCTION

The basic types of gastrointestinal malignant tumors include esophageal cancer, liver cancer, and pancreatic cancer. Surgery is the first option for the treatment of the disease. However, most patients are in the late stage of the tumor at the time of treatment and lose the chance of surgical treatment. Chemotherapy has become the standard treatment, but many adverse reactions, such as bone marrow suppression, gastrointestinal reactions, neurotoxicity, *etc*, directly affect the digestion and absorption function of patients, resulting in malnutrition. Chemotherapy-induced nausea and vomiting gastrointestinal reactions are among the most common adverse reactions during chemotherapy in cancer patients[1,2]. Various clinical data confirmed that even if the latest antiemetics are used during chemotherapy, 60% of chemotherapy patients experience nausea and vomiting. Severe nausea and vomiting reduce the quality of life of cancer patients and affect the progress of chemotherapy courses [3]. Therefore, timely and effective prevention and relief of nausea and vomiting caused by chemotherapy are of great significance to improving the quality of life of cancer patients and ensuring the smooth progress of chemotherapy. Music therapy can reduce anxiety symptoms, avoid the response to the human body under various stress conditions through psychological adjustment, and has a positive effect on improving the adverse reactions of chemotherapy[4,5]. Music therapy has been used in treating primary cancers such as lung cancer and breast cancer and plays a huge role in relieving anxiety before surgery and reducing the dosage of anesthetics[6,7]. However, the research on nausea and vomiting caused by chemotherapy for gastrointestinal cancer remains controversial. Thus, we implemented this meta-analysis study as it is an effective method to resolve the above controversy.

MATERIALS AND METHODS

Databases and keywords

The relevant articles on this topic were obtained in October 2022 by searching EMBASE, PubMed, OVID, WoS, CNKI, CBM, and VIP database and selecting the publication deadline of October 2022. The keywords used in the search strategy were “music therapy”, or “music intervention”, or “audio program”, or “chemotherapy-induced nausea and vomiting”, or “CINV”.

The following literature was included based on the PICOS principle: (1) Study types: Randomised controlled trials were preferred, but a retrospective cohort study was also performed; (2) Study subjects: Gastrointestinal cancer was the primary disease of all study subjects, which could be any of esophageal cancer, colorectal cancer, and pancreatic cancer, where patients were treated with chemotherapy; (3) Intervention group: Music therapy, which was adopted could be performed before chemotherapy, or throughout the chemotherapy process, and the selected repertoire, duration, and treatment methods were different according to different studies, and other relaxation methods could be superimposed, such as massage, aroma therapy, and other relaxation methods; (4) Control group: Routine intervention was adopted; (5) Outcome indicators: The scores of nausea and vomiting symptoms assessed using the scale as well as the number and proportion of nausea and vomiting grade I and above after chemotherapy[8].

Literature exclusion criteria

Patients with non-primary gastrointestinal cancer, such as lung cancer, breast cancer, uterine cancer, *etc*, non-chemotherapy patients; literatures in which music therapy is not used in the intervention measures, or music therapy is only used as an adjuvant will be excluded; study types of investigation, case analysis, and review were excluded.

Literature quality evaluation and bias risk assessment

The risk of bias in the literature was evaluated using the Cochrane risk of bias V2.0[9] provided by Cochrane Collaboration, which included six levels, with each level assigned "low", "some concern of risk" and "high" for risk evaluation.

Data extraction

Two authors independently extracted data, which included title, author name, publication year, number of participants, gender, grouping, and outcome indicators. Gastrointestinal reactions were graded in some studies as follows: (1) Grade 0: No nausea or vomiting; (2) Grade I: Mild nausea and vomiting, no effect on eating, vomiting frequency not more than once a day; (3) Grade II: Significant nausea and vomiting, affecting eating, vomiting frequency 2-5 times a day; (4) Grade III: Severe nausea and vomiting, persistent attacks, unable to eat, vomiting frequency > 5 times a day; and (5) Grade IV: Nausea and vomiting could not be controlled. The number of cases of nausea and vomiting in grade I and above shall predominate in the statistical results.

Synthetic analysis

Odds ratio (OR) was used for dichotomous variables, and SMD was used for continuous variables as the analysis statistic. Descriptive statistics were compared using forest plots. For heterogeneity, the Q test was used. For $P < 0.05$, heterogeneity among studies was considered. The I^2 test was used for quantitative analysis of inconsistency among different studies. If $I^2 < 50\%$, a fixed effect model was used, else the random effect model was used. Subgroup analysis method is adopted to investigate the heterogeneity, and if there is no heterogeneity, a descriptive method is used to investigate the heterogeneity between articles. Investigating factors meaningful for effect size by using meta-regression. The articles were eliminated one by one, and the combined effect size of the remaining articles was calculated to determine the greatest impact on the results. Egger's test was used to detect the publication bias, and a funnel plot was used for the presentation.

RESULTS

Literature retrieval results

Finally, seven articles were screened by search. Figure 1 depicts the retrieval results, whereas Table 1 presents the baseline information of these articles.

Quality evaluation

The article was grouped by order of admission and did not strictly follow the random sequence process [15], and there may be a large bias. All other articles described the generation method of random sequence. The allocation concealment method and blinding method were not described in those articles [11-14,16], and there was a potential bias of "deviation from established intervention". Except for one article[10], no dropout cases were recorded as there may be data assessment bias shown in Figure 2.

Meta-analysis results

Effect of music therapy on reducing nausea symptom scores: Among the reports, nausea symptom score after the intervention was reported in two articles[10,16], with statistical heterogeneity between them ($I^2 = 98\%$, $P < 0.01$). Meta-analysis indicated that music therapy could reduce nausea symptom scores after chemotherapy [mean difference (MD) = -3.15, 95% confidence interval (CI): -4.62 to -1.68, Z

Table 1 Baseline information of literature

Ref.	Number of cases	Number (E/C)	Age (yr)	Primary cancer type	Intervention measures	Control intervention	Outcome indicators
Dadkhah *et al*[10], 2019	60	30/30	56 ± 8.84	Gastrointestinal neoplasm	Relaxing music 45 min before chemotherapy	Conventional treatment	Scale score
Xue *et al* [11], 2017	94	47/47	54.1 ± 10.7	Gastric cancer	Music therapy was performed 2 h before each chemotherapy, twice a day, 30 min/time, with muscle relaxation training according to the patient's characteristics	Conventional treatment	Number of nausea and vomiting
Jiao *et al* [12], 2018	156	78/78	54.8 ± 17.20	Gastrointestinal neoplasm	Light music and instrumental music are the main ones, supplemented by patient's self-selection	Conventional treatment	Number of nausea and vomiting
Wang and Liu[13], 2016	220	110/110	58.02 ± 6.18	Colorectal cancer	Choose natural light music during chemotherapy and combine it with aromatherapy	Conventional treatment	Number of nausea and vomiting
Chen[14], 2013	68	35/33	55.9	Esophageal cancer	Light and soft music played continuously for four weeks before chemotherapy	Conventional treatment	Number of nausea and vomiting
Huang[15], 2012	68	34/34	40-78	Colorectal cancer	Gentle music played before chemotherapy	Conventional treatment	Number of nausea and vomiting
Li[16], 2022	60	30/30	65.51 ± 1.99	Gastric cancer	Group music therapy mode with aerobic exercise	Conventional treatment	Scale score

E/C: Experiment/control.

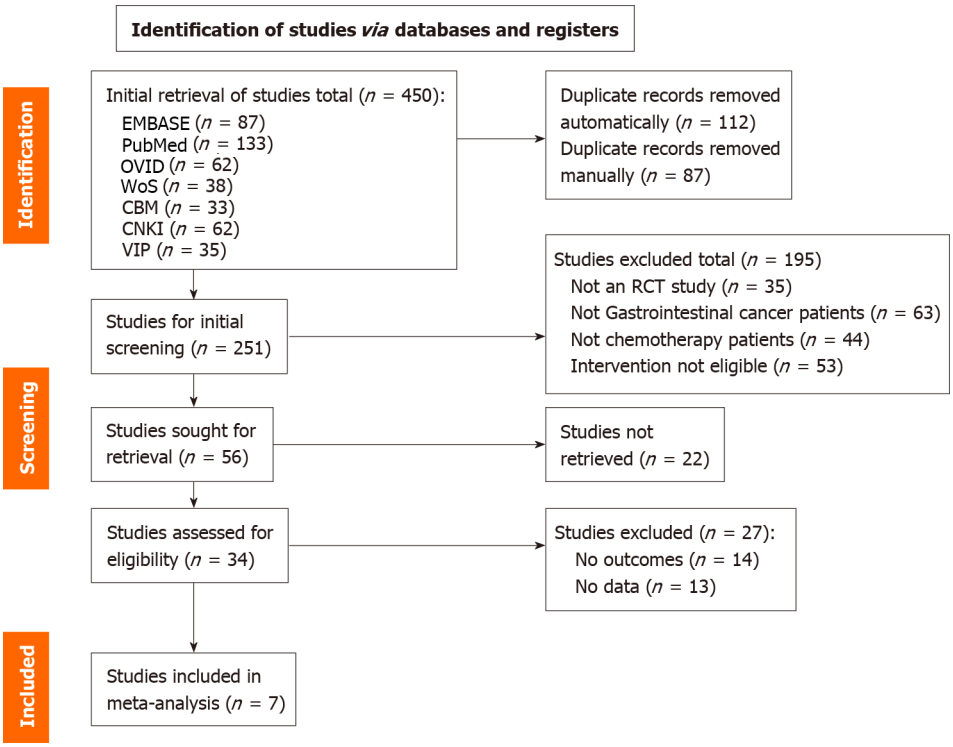

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Figure 1 Literature selection flow chart. RCT: Randomized control trial.

= -4.20, $P < 0.0001$] by random effect model, as shown in Figure 3A.

Effect of music therapy on reducing vomiting symptom scores: Among the reports, vomiting symptom score after the intervention was found in two articles[10,16], without statistical heterogeneity (I^2 = 15%, P = 0.28). Meta-analysis indicated that music therapy could reduce vomiting symptom scores after chemotherapy in patients (MD = -2.28, 95%CI: -2.46 to -2.11, Z = -25.15, $P < 0.0001$) by fixed effect mode,

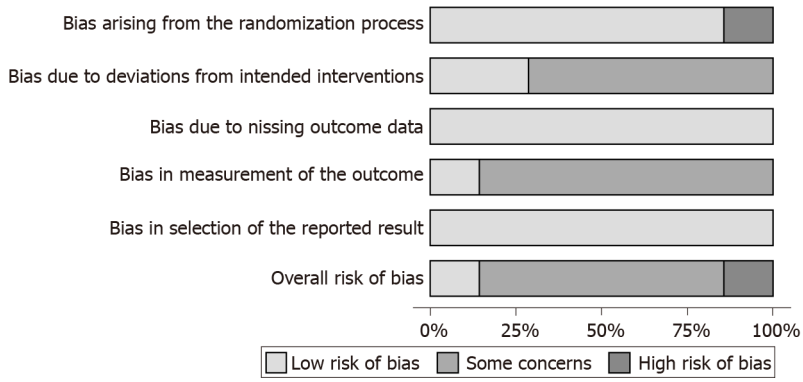

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Figure 2 Bias analysis based on ROB 2.0.

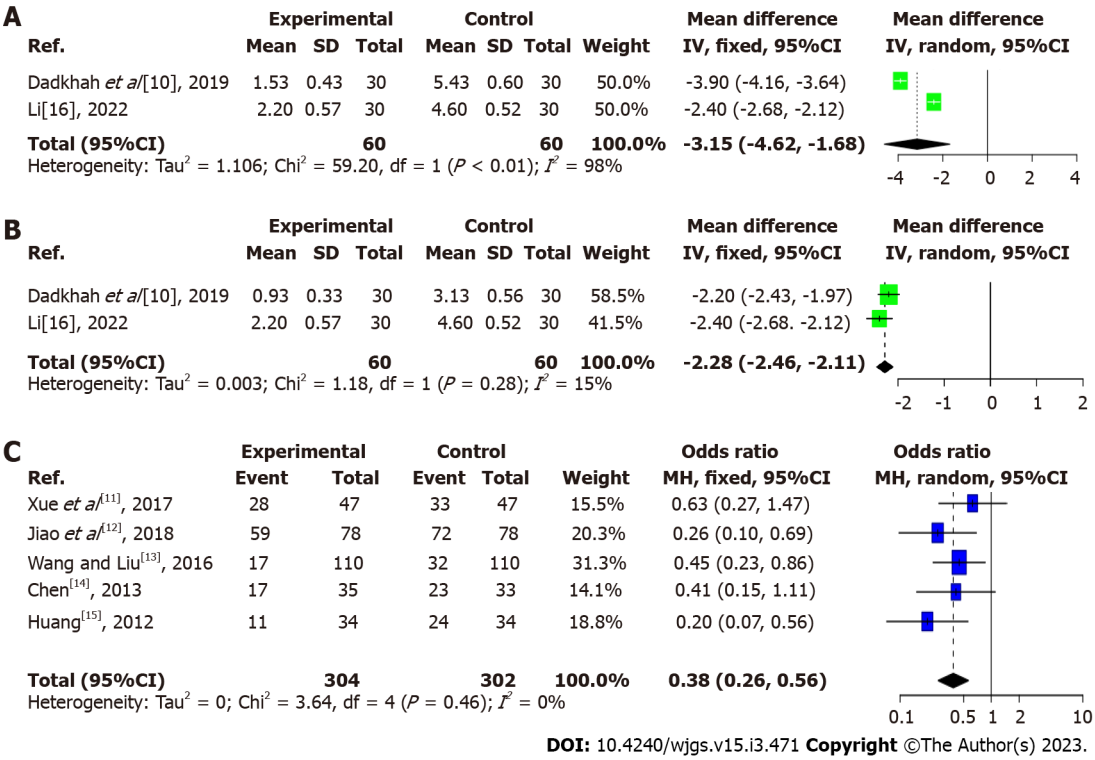

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Figure 3 Effect of music therapy on nausea symptom score, vomiting symptom scores, and the number of cases of nausea and vomiting after chemotherapy. A: Nausea symptom score; B: Vomiting symptom scores; C: The number of cases of nausea and vomiting. CI: Confidence interval.

as shown in Figure 3B.

Effect of music therapy on reducing the incidence of nausea and vomiting (grade I and above): Five articles reported the incidence rate of grade I nausea or vomiting or above after intervention, without statistical heterogeneity between articles (I^2 = 0%, P = 0.46)[11-15]. Meta-analysis indicated that music therapy could reduce the incidence rate of grade I nausea or vomiting or above after chemotherapy (OR = 0.38, 95%CI: 0.26-0.56, Z = -4.88, P < 0.0001) by fixed effect mode, as shown in Figure 3C.

Investigation of heterogeneity: Subgroup analysis could not be performed due to the small number of articles. The two included articles showed heterogeneity in the statistics of nausea symptom scores, which could be attributed to the different scales adopted by the two articles for nausea and vomiting symptoms.

Meta-regression analysis: In analyzing the incidence of nausea and vomiting indicators, we used the "publication year of the literature" to regress pooled effect size. We found that this factor had no statistically significant effect on the results (P = 0.68), implying that the results of this indicator were not related to the publication year and month of the literature, as shown in Figure 4.

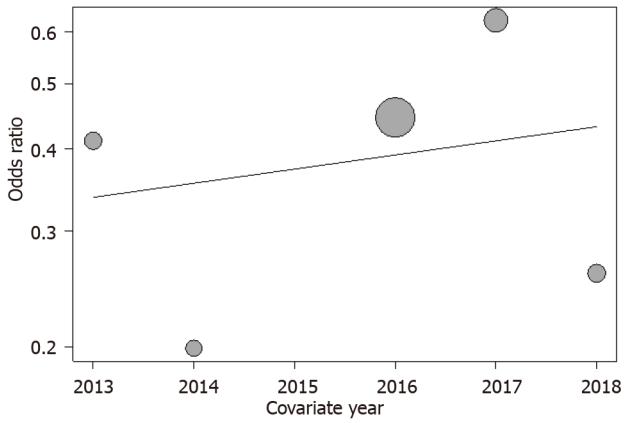

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Figure 4 Meta-regression analysis of incidence indicators for nausea and vomiting: Publication year factor (*P* = 0.68).

Sensitivity analyses: No significant deviations were found after removing each study during the analysis of incidence indicators of nausea and vomiting, indicating that the final pool results were stable.

Publication bias analysis: Egger' *t* test was used to detect the publication bias during the analysis of nausea and vomiting incidence indicators, t = -1.20, P = 0.30. There was no asymmetry in the funnel plot, as shown in Figure 5.

DISCUSSION

Music therapy is not yet a well-defined science that uses music to promote physical and mental health based on its practical functions[17,18]. Chemotherapy is one of the important means to treat malignant tumors. Chemotherapy kills tumor cells while also bringing many adverse physical and psychological reactions to patients, such as bone marrow suppression, nausea, vomiting, anxiety, and depression, reducing the quality of life of patients[19]. Psychosocial intervention helps to alleviate the adverse reactions of chemotherapy and improve the quality of life of patients. Music therapy is a psychological intervention method that can improve the physical and mental health of cancer patients without causing adverse reactions[20-22].

Seven articles were included in this study to explore the effect of music therapy on adverse reactions during chemotherapy for primary cancer of the digestive system. The results indicated that music therapy could significantly improve nausea and vomiting symptom scores during chemotherapy of patients with digestive system cancer and reduce the incidence of nausea and vomiting after chemotherapy (grade I and above), which was a good psychological intervention method.

The frequency, rhythm, and regular acoustic vibration of music are physical energies that can produce harmonious resonance phenomena in human tissue cells, resulting in excitation or inhibition of the corresponding organs. Simultaneously, music can improve the excitability of God meridian cells and secrete some beneficial and healthy hormones, enzymes, acetylcholine, and other substances *via* neurohumoral regulation, all of which contribute to improved blood circulation and strengthening metabolism. Furthermore, music stimulation can inhibit adjacent pain centers while stimulating the auditory center and reducing pain because the auditory center on the cerebral cortex is adjacent to the pain center. Music can also stimulate the body to release endorphins, increase the content of endorphins in the blood, and achieve the effect of relaxing the body and mind and relieving pain[23,24]. Subcortical centers like the hypothalamus control emotions such as joy, anger, mourning, and music, as a special language, can act directly on subcortical centers such as the hypothalamus through the auditory system plays a role in regulating emotions[25,26]. Music stimulation of the limbic system of the brain can also cause people to remember or consider related events, resonate in music therapy, and release adverse emotions and catharsis. Therefore, the psychological effects of music therapy on people mainly achieve a good psychological state of patients by regulating emotions[27]. Relaxation training with light music can counteract the negative effects of psychological and physical stress, restore balance and coordination of people's physical and psychological spirits, which help individuals deal with life challenges more healthily, make involuntary reactions of the human body, such as heartbeat, respiration, and blood pressure, and epinephrine secretion in spontaneous control, and reduce the severity of adverse reactions caused by chemotherapy[28].

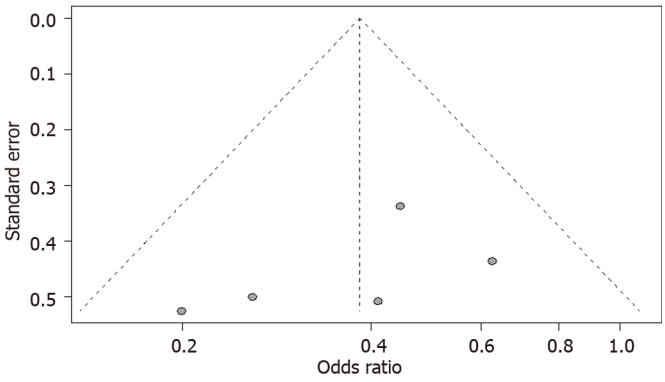

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Figure 5 Funnel plot for nausea and vomiting incidence indicators.

The music can be chosen by the healer or by the patient himself. Some studies suggest that music therapy should be patient-centered, and music selection should be individualized to meet everyone's preference for music. The included article adopted the method used in this study where the investigators selected music primarily, whereas the patients self-selected music as a supplement and achieved good results[11]. Music therapy can also be combined with other intervention methods, such as progressive music and muscle relaxation training[11]. Aromatherapy is applied in music therapy in another study[13], and the group music therapy model is also adopted[16], combined with moderate aerobic exercise.

Although the results of the combined analysis indicated that music therapy had a significant effect on adverse reactions to chemotherapy, it must be recognized that music therapy is only a psychological intervention rather than a treatment for adverse reactions such as nausea and vomiting and patients receiving chemotherapy for moderately and highly emetogenic cancer, drugs such as 5-HT3 receptor antagonists should be given before chemotherapy to prevent serious gastrointestinal reactions.

Furthermore, this study has limitations due to insufficient evidence. First, too few included studies were related to the current low number of reports on this topic. Second, there were inconsistencies in the reported indicators. Some articles used the incidence of gastrointestinal reactions as an indicator, others used the symptom score as an indicator, and some others used the quality of life as an evaluation indicator. Although the articles, Dadkhah *et al*[10] and Li[16] reported the symptom scores of nausea and vomiting in patients after the intervention, the scoring tables adopted were different, which made the results heterogeneous. Only one of the seven included articles had a low risk of bias, indicating that the rest are of poor quality and have a high risk of bias. Therefore, further research on this topic is required. Music therapy could significantly improve nausea and vomiting symptom scores in patients with digestive system cancer during chemotherapy and reduce the incidence of grade I and nausea and vomiting after chemotherapy, making it an effective psychological intervention method.

CONCLUSION

This meta-analysis included a total of 726 patients in 7 articles. The result is that music therapy can significantly improve the score of nausea and vomiting symptoms in patients with digestive system cancer during chemotherapy, reduce the incidence of nausea and vomiting at grade I and above after chemotherapy, and is a good psychological intervention method. However, due to the small number of articles included in this study, the evidence is not good enough. This subject still needs to be further explored by larger number of randomized controlled studies.

ARTICLE HIGHLIGHTS

Research background

Music therapy can reduce anxiety symptoms, avoid the response to the human body under various stress conditions through psychological adjustment, and has a positive effect on improving the adverse reactions of chemotherapy. Music therapy has been used in treating primary cancers such as lung cancer and breast cancer and plays a huge role in relieving anxiety before surgery and reducing the dosage of anesthetics.

Research motivation
Music therapy plays a role in improving the negative emotions of cancer patients. However, whether it could reduce nausea and vomiting caused by chemotherapy still remains to be explored.

Research objectives
To explore whether music therapy has a positive impact on the improvement of nausea and vomiting symptoms in patients with gastrointestinal cancer during chemotherapy.

Research methods
A few relevant articles of this subject have been searched from the public databases. The data of the outcome indicators have been extracted from the articles. A meta-analysis has been performed for the pooling results.

Research results
Music therapy could reduce the nausea and vomiting symptom score of patients after chemotherapy, also it could reduce the incidence of grade I and above nausea or vomiting in patients after chemotherapy.

Research conclusions
Music therapy is a good adjuvant therapy for improving the adverse reactions of chemotherapy.

Research perspectives
Indicators for chemotherapy-induced nausea and vomiting have been determined and a meta-analysis has been performed for the pooling results of the indicators. The evidence was withdrawn from the process.

FOOTNOTES

Author contributions: Zhong FP and Zhong J contributed equally to this work; Zhong MY designed the study; Zhong FP contributed to the analysis of the manuscript; Zhong J involved in the data and writing of this article; and all authors have read and approved the final manuscript.

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Country/Territory of origin: China

ORCID number: Fang-Ping Zhong 0000-0003-0099-5020; Jun Zhong 0000-0002-9873-0460; Ming-Yan Zhong 0000-0002-4785-851X.

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L-Editor: A
P-Editor: Wang JJ

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CASE REPORT

Immunotherapy in combination with chemotherapy for Peutz-Jeghers syndrome with advanced cervical cancer: A case report

Xiang-Cheng Hu, Chen-Xiao Gan, Hui-Min Zheng, Xue-Ping Wu, Wen-Sheng Pan

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Xiang-Cheng Hu, Hui-Min Zheng, Department of Gastroenterology, Bengbu Medical College, Bengbu 233000, Anhui Province, China

Chen-Xiao Gan, Xue-Ping Wu, Wen-Sheng Pan, Department of Gastroenterology, Zhejiang Provincial People's hospital, Hangzhou 310014, Zhejiang Province, China

Corresponding author: Wen-Sheng Pan, MD, Doctor, Department of Gastroenterology, Zhejiang Provincial People's Hospital, No. 158 Shangtang Road, Gongshu District, Hangzhou 310014, Zhejiang Province, China. wspan223@163.com

Abstract

BACKGROUND

Peutz-Jeghers syndrome (PJS) is a rare autosomal dominant disorder, and female patients may develop gynecologic tumours. The prognosis for such patients is poor and the specific pathogenesis remains uncertain. Therefore, there are currently no uniform treatment options.

CASE SUMMARY

Herein, we introduce the case of a 45-year-old female who was diagnosed with PJS for 45 years and cervical cancer for 3 years. Postoperative pathological examination showed metastases in the right external iliac lymph nodes. The patient was initially treated with a combination of doxorubicin and carboplatin chemotherapy and pelvic magnetic resonance showed that the metastases had grown. Subsequently, we performed whole exome sequencing in this patient and identified the relevant causative gene. In addition to the chemotherapy regimen, sindilizumab was administered and the patient was followed up. After 4 cycles of treatment, the metastases were substantially reduced and were not enlarged after six months of follow-up. This case report suggests that patients with PJS combined with cervical cancer may have a sustained response to immune-combination chemotherapy regimens.

CONCLUSION

Clinicians should be aware of the importance of immunotherapy in patients with PJS combined with advanced cervical cancer.

Key Words: Peutz-Jeghers syndrome; Cervical cancer; Programmed cell death protein 1; Chemotherapy; Case report

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Core Tip: Peutz-Jeghers syndrome (PJS) is a rare genetic disease with cancerous potential. In this case, the patient was diagnosed with PJS combined with progressive cervical cancer and she initially received doxorubicin and carboplatin; however, the right parietal iliac vessel metastases did not shrink. This case suggests that the use of programmed cell death protein 1 (PD-1) inhibitors was helpful in this patient and that PD-1 inhibitors combined with chemotherapy may be a good choice for treating this disease.

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INTRODUCTION

Peutz-Jeghers syndrome (PJS) is a rare autosomal dominant-inherited disorder. The incidence of this syndrome ranges from 1 in 25000 to 1 in 28000 people per year[1]. Current research indicates that this disease is caused by a mutation of the *STK11* gene on chromosome 19p13.3(1). Patients with PJS are characterized by dark spots on the skin mucosa and hamartomatous polyps in the digestive tract[2]. At the same time, studies have indicated a higher incidence of malignancy in patients with PJS than in the general population. The cumulative incidence of gastrointestinal cancers is 55%, with colorectal cancer at 39%, pancreatic cancer at 36%-40%, and small bowel cancer at 13%[3,4]. The risk of cancers of the nongastrointestinal tract is also increased, with a cumulative incidence of 32%-54% for breast cancer, 21% for ovarian cancer, and 7% for lung cancer at age 60[5-8]. Cisplatin has been the standard chemotherapy for cervical cancer with distant metastases, and recent evidence supports the use of platinum-based dual therapy rather than cisplatin alone[9-11]. However, in patients with PJS combined with uterine malignancy, the pathogenesis may be more complex and unclear, and there is no standard treatment protocol. We report a patient with PJS combined with progressive cervical cancer. A regimen using a programmed cell death protein 1 (PD-1) inhibitor in combination with chemotherapy may be a good option for treating this disease.

CASE PRESENTATION

Chief complaints

A 45-year-old Chinese female was admitted to the hospital with mucous membrane black spots on the lips, intermittent abdominal pain for more than forty years and recurrent cervical cancer for three years.

History of present illness

Forty years prior, the patient visited several hospitals for lip pigmentation and abdominal pain and was finally diagnosed with PJS by gastroscopy (Figure 1A and B). The patient later underwent three "partial small bowel resections" and two "intestinal polypectomies" for intestinal obstruction. Three years ago, the patient was diagnosed with cervical cancer and underwent "extensive hysterectomy and bilateral adnexal resection". Postoperative pathology suggested an endogenous cervical (size 5.4 cm × 3.5 cm) highly differentiated adenoma with metastasis to the right external iliac vessels (Figure 1C). The patient was treated with six cycles of chemotherapy with a carboplatin-doxorubicin (CD) (doxorubicin 30 mg/m^2 and carboplatin area under the curve = 5) regimen before admission.

History of past illness

The patient reported no remarkable history of past illness.

Personal and family history

The patient's mother, brother, sister and daughter all had PJS. Her mother died of colon cancer at the age of forty. Genetic mapping was recorded (Figure 2).

Physical examination

A surgical scar of approximately 5 cm was visible below the umbilicus. Other physical examinations showed no important abnormalities.

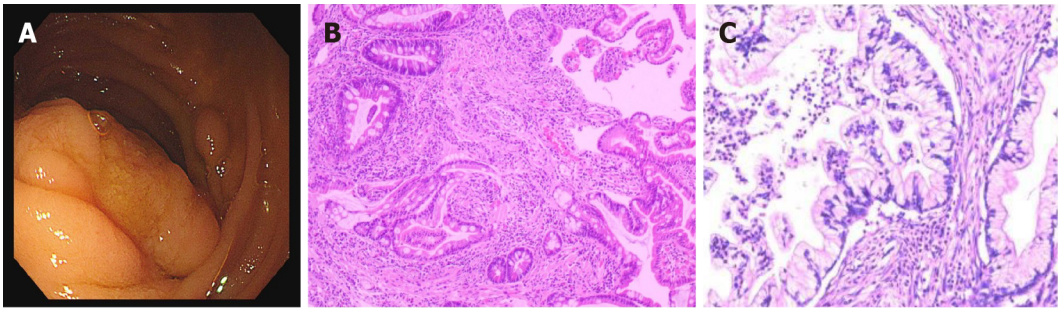

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Figure 1 Transoral single-balloon enterosocpy results and cervical cancer histopathological results. A: The images show a polypoid tissue measuring 2 cm × 3 cm was identified 1.5 m below the flexural ligament and was biopsied; B: The pathology of the polyp showed a dendritic extension of the mucosal muscle layer into the central part of the polyp, with the glands forming a villi-like structure. The surface of the polyp was covered with normal epithelium and the interstitium showed no obvious inflammatory lesions; C: Pathological findings of cervical cancer revealed a highly differentiated adenocarcinoma of the cervix, partly with microscopic adenocarcinomatous changes, infiltrating into the deep mesenchymal layer near the outer membrane, with visible vascular tumour plugs and metastases or infiltrations in the right external iliac lymph nodes.

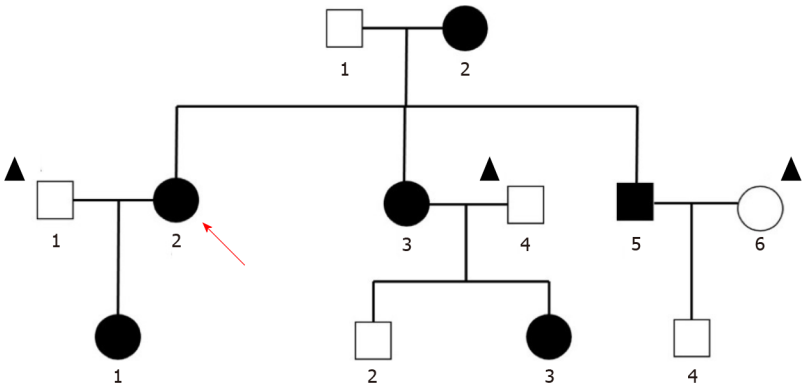

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Figure 2 Pedigree of the family with Peutz–Jeghers syndrome. Black symbols denote individuals with mucocutaneous pigmentations. Circles and squares indicate females and males, respectively, while the arrow indicates the reported patient and one with the triangle is nonfamily members.

Laboratory examinations

The leukocytes, bilirubin, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, infectious disease screening and serum tumour markers were within normal limits, but the carbohydrate antigen-199 (CA199) level was elevated (71.2).

Imaging examinations

After admission, 18F-fluorodeoxyglucose positron emission tomography (PET)/computed tomography (CT) indicated multiple small metastases next to the right iliac vessels [the largest was approximately 0.5 cm × 0.5 cm; the regular scan maximum standardized uptake value (SUVmax) = 1.4; delayed scan SUVmax = 3.2].

FINAL DIAGNOSIS

Based on the patient's transoral single-balloon enteroscopy findings and the patient's surgical report, we diagnosed her with PJS combined with advanced cervical cancer.

TREATMENT

The patient was hospitalized to complete PET-CT and transoral single-balloon enteroscopy and did not continue chemotherapy due to financial reasons. In September 2021, pelvic magnetic resonance (MR) suggested a substantially larger right iliac metastasis than before, with CA199 = 146.8 U/mL. The patient then underwent a four-cycle CD chemotherapy protocol. In January 2022, pelvic MR suggested

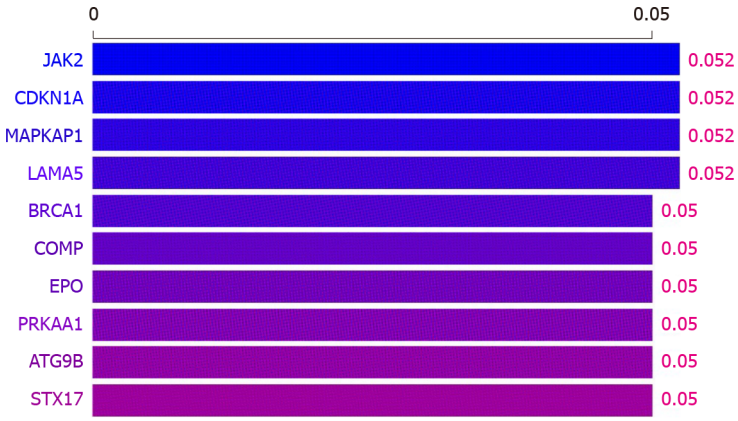

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Figure 3 Whole exome-sequencing findings of blood. *JAK2*, *CDKN1A*, *MAPKAP1*, and *LAMA5* genes are slightly associated with Peutz–Jeghers syndrome and cervical cancer.

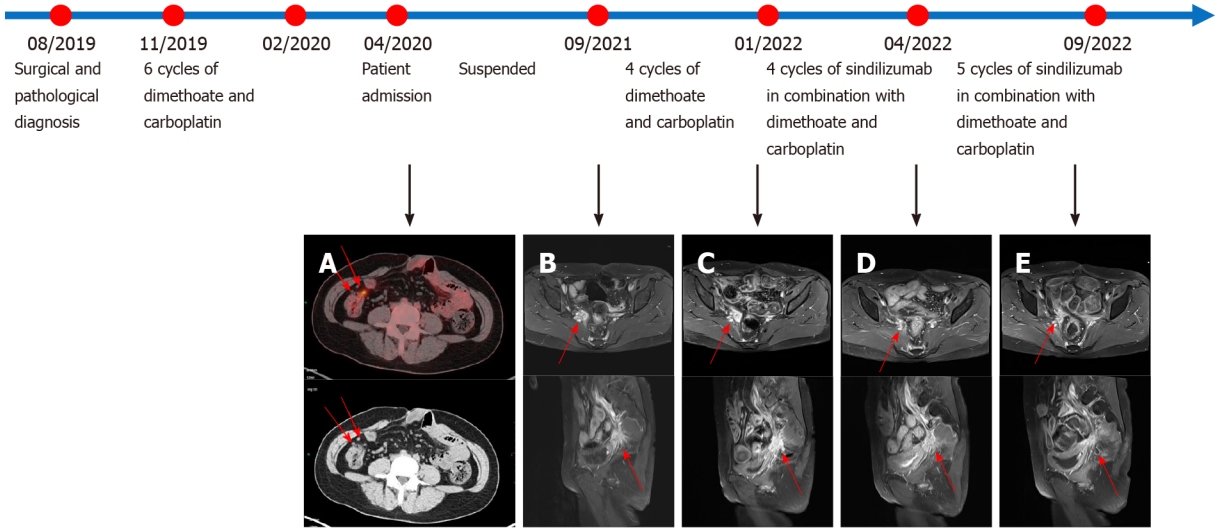

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Figure 4 Pelvic magnetic resonance imaging scans before and after the use of sindilizumab and timeline of treatment. Before the use of sindilizumab. A: The red arrows in the positron emission tomography-computed tomography images revealed multiple small nodular foci in the right pelvic wall and anterior sacral space with mildly increased fluorodeoxyglucose metabolism, which was considered to be due to tumor metastasis; B: The red arrow revealed an abnormal signal of about 22 mm × 24 mm mass is shown next to the right iliac vessels; C: After using 4 cycles of doxorubicin and carboplatin, the red arrow revealed the abnormal signal foci beside the right iliac vessels were slightly larger than before, with a size of 25 mm × 38 mm, which was considered to be caused by tumor recurrence. After the use of sindilizumab in combination with doxorubicin and cisplatin; D: The red arrow revealed the abnormal signal foci next to the right iliac vessels were significantly smaller than before, with a size of 17 mm × 12 mm; E: The red arrow revealed a small mass of abnormal signal foci, 17 mm × 12 mm in size, was observed next to the right iliac vessels, similar to the previous one. The timeline showed the whole process of diagnosis and treatment of this patient.

that the metastases continued to increase in size and CA199 was 160.8 U/mL. The patient's platelet count was 42 × 10^9/L, suggesting a risk of bleeding, so the patient was not directly punctured to test the expression of PD-L1 on the surface of the tumour cells. In addition, considering that the patient had both PJS and cervical cancer, whole exome sequencing (WES) was performed on the patient's blood and showed a mild correlation between Janus kinase-2 (JAK2) and the development of the disease (Figure 3). The patient was then treated for the first time with a PD-1 inhibitor (sindilizumab 200 mg, 21 d per cycle) in combination with the CD chemotherapy regimen[12]. In April 2022, pelvic MR suggested that the lesion had decreased greatly and CA199 was 29.8 U/mL, so the treatment was continued with the above regimen. In September 2022, pelvic MR showed no progression of metastases and CA199 was 27.1 U/mL. The whole treatment process was documented (Figure 4), and the overall health parameters during treatments were recorded (Table 1).

Table 1 Overall health parameters during treatments records

Time	April, 2020		September, 2021	January, 2021	November, 2021	December, 2021	January, 2022	February, 2022	March, 2022	April, 2022	May, 2022	June, 2022	July, 2022	August, 2022	September, 2022
Treatment	Admission	Suspend	4 cycles of doxorubicin and carboplatin				9 cycles of sindilizumb in combination with doxorubicin and carboplatin								
Temp/°C	37.1	NA	36.2	37	36.5	36.8	36.5	36.3	37.1	36.8	NA	36.8	36.9	37.2	36.9
HR/min	86	NA	76	84	75	79	82	78	82	81	NA	79	75	79	77
RR/min	19	NA	19	18	19	19	19	18	19	17	NA	18	19	18	19
BP/kPa	16.1/7.5	NA	15.4/8.5	18.7/9.7	18.4/11.1	16.9/11.9	16.5/9.3	16.5/9.7	16.0/9.5	14.0/8.4	NA	12.0/8.0	12.5/8.7	13.2/9.6	13.1/8.0
Weight/kg	56	NA	49	51	51.5	52	53.8	52	51.3	50.9	NA	50.5	51	52.3	53
WBC/10^9/L	5.11	NA	5.4	5.91	5.03	3.6	3.34	2.91	3.23	4.02	NA	4.42	4.51	4.43	4.52
Hb/g/L	133	NA	124	114	105	96	102	102	106	109	NA	111	112	112	113
Alb/g/L	39.9	NA	38.5	42	40.3	36.9	45.6	NA	44.2	43.4	NA	43.1	40.7	37.6	35.3
ALT/U/L	34	NA	20	17	17	16	20	21	22	23	NA	24	36	47	54
AST/U/L	29	NA	25	24	17	8.3	26	NA	27	28	NA	28	37	43	47
CEA/μg/L	1	NA	0.8	1.2	1.1	0.9	1	0.8	0.9	0.8	NA	0.8	0.9	0.8	0.8
CA125/U/mL	11.1	NA	14.4	19.3	14.6	8.9	10.2	10.3	9.7	9.1	NA	9	9.3	9.7	10.7
CA199/U/mL	71.2	NA	146.8	151.5	153.6	154.3	160.8	37.8	32.6	29.8	NA	22.3	24.3	25.6	27.1
CA153/U/mL	4.9	NA	5.6	11.1	9.4	7.3	8.4	9	6.1	5.2	NA	4.6	4.6	4.5	4.5
CA724/U/mL	2.3	NA	2.7	5.7	8.5	14.3	1.5	5.6	3.4	3.8	NA	2.4	2.3	2.2	2.1

HR: Heart rate; RR: Respiratory rate; BP: Blood pressure; WBC: White blood cell; Hb: Haemoglobin; Alb: Albumin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CEA: Carcinoma embryonic; CA: Carbohydrate antigen; NA: Not available.

OUTCOME AND FOLLOW-UP

Studies have found that sindilizumab-treated patients often suffer from adverse effects such as fever (38%), anaemia (74.1%) and elevated aspartate aminotransferase (41%) and alanine aminotransferase (40.6%)[13,14]. At the same time, carcinoma embryonic antigen (CEA), CA199 and cancer antigen-125 (CA125) are useful markers for detecting cervical cancer and monitoring the clinical course. In particular, CA199 and CA125 have been shown to be particularly useful in patients with adenocarcinoma[15]. In our case, after two months of follow-up, the patient's temperature, heart rate, respiratory rate, blood pressure, white blood cell, haemoglobin concentration, liver function and tumour markers (including CA199, CA125 and CEA) were within the normal ranges (Table 2).

Table 2 Laboratory examinations of the patient after two months of follow-up

Time	Temp/°C	HR/min	RR/min	BP/kPa	Weight/kg	WBC/109/L	Hb/g/L	Alb/g/L	ALT/U/L	AST/U/L	CEA/μg/L	CA125/U/mL	CA199/U/mL	CA153/U/mL	CA724/U/mL
January, 2022	36.5	92	17	14.2/9.6	44.7	5.99	118	43.1	19	17	2.8	32	23	13.6	18.3
November, 2022	37	87	19	14.7/10.4	45.2	6.45	115	35.8	18	23	2.3	31.7	24.6	15.6	19.3

HR: Heart rate; RR: Respiratory rate; BP: Blood pressure; WBC: White blood cell; Hb: Haemoglobin; Alb: Albumin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CEA: Carcinoma embryonic; CA: Carbohydrate antigen.

DISCUSSION

We introduced a case of PJS combined with advanced cervical cancer. After the use of a PD-1 inhibitor combined with a CD chemotherapy regimen, the patient's right iliac metastases were markedly reduced in volume to a stable state, and a more satisfactory result was achieved.

PJS is a rare autosomal dominant disorder characterized by gastrointestinal malformations and skin pigmentation. Mutations in the *STK11* gene can be detected in 50% to 80% of patients. Other related causative genes include the possible gene in the 19q13.4 region, the *Brg1* gene and the *IFTTM1* gene[16]. Patients with PJS are more prone to various malignancies, among which gastrointestinal and reproductive tract and endocrine tumours are the most common. Cervical adenocarcinoma is a common malignancy among patients with PJS (46.8%)[17]. Patients with PJS combined with cervical cancer often present with symptoms such as menstrual irregularities, endocrine disorders and abnormal vaginal bleeding, but there is no uniform treatment protocol. In 2008, Li *et al*[18] first reported a case of PJS complicated by cervical adenocarcinoma and small bowel malignancy in which the patient underwent total hysterectomy after neoadjuvant chemotherapy (paclitaxel 120 mg/dL and carboplatin 350 mg/dL 1 d per week for 6 wk, and the tumour markers returned to normal after three months. However, the patient was not followed up. In 2008, Kilic-Okman *et al*[19] reported a case of PJS combined with stage IIIB cervical cancer in which the patient received six cycles of combination chemotherapy (5-fluorouracil, adriamycin, and cyclophosphamide) and radiotherapy. That patient died of cervical adenocarcinoma progression within one month after the completion of radiotherapy. In 2019, Kim *et a*l [20] reported a case of PJS combined with gastric-type mucinous cervical adenocarcinoma. As the mass was confined to the cervix and no peripheral lymph node metastasis was present in this patient, the patient achieved recovery after radical cervical surgery followed by adjuvant radiotherapy. In 2021, Vu Dinh *et al*[21] reported a case of PJS combined with stage IIIC gastric cervical mucinous adenocarcinoma. After adjuvant radiotherapy, the disease was stable with no recurrence at one year of follow-up.

PD-1 (also known as CD279) is a coreceptor expressed on the surface of antigen-stimulated T cells. PD-1 and its ligand (PD-L1) belong to the immune checkpoint pathway. Cervical cancer patients can exhibit PD-L1 expression. In 2018, Feng *et al*[22] reported that 59.1% of cervical cancer patients exhibited PD-L1 expression. Additionally, increased incidents of abortion and childbearing can also enhance PD-L1 expression in tumour cells. The study confirmed that PD-1 in tumour-invasive lymphocytes (TILs) and PD-L1 and TILs in cancer cells together constitute the PD-1/PD-L1 pathway, and the imbalance of this pathway is one of the mechanisms of tumour development and cellular immune escape. In

addition, Meng *et al*[23] revealed that 60.82% of patients had PD-L1 expression, and PD-L1 overexpression was associated with vascular invasion and lymph node metastasis in cervical cancer.

JAK2 is a nonreceptor tyrosine kinase that plays key roles as the intracellular signalling effector of the cytokine receptor[24]. JAK2 was also found to regulate the expression of PD-L1. In 2016, Ikeda *et al*[25] found that the PD-L1 protein is upregulated by the simultaneous amplification of the PD-L1 and JAK2 genes through JAK-STAT signalling in non-small cell lung cancer. In 2017, Garcia-Diaz *et al*[12] discovered that interferon-γ could induce PD-L1 expression *via* the interferon-γ-JAK1/JAK2-STAT1/STAT2/STAT3-IRF1 axis in tumour cells, leading to immune escape and cancer induction.

Based on the above studies and the WES in this case, JAK2 was mildly associated with the development of the disease, and we used sindilizumab in combination with carboplatin and doxorubicin for the treatment of PJS combined with advanced cervical carcinoma[12,22-25]. A more satisfactory result was achieved based on the comparison of the right parietal iliac metastases on pelvic MR before and after drug administration, which showed a substantial reduction.

The unique feature of this case is that PJS is a rare disease about which there are only a few international reports, and there is no uniform treatment protocol. We performed WES, identified the relevant causative genes, and treated the patient with sindilizumab in combination with chemotherapy for the first time. The metastases were substantially reduced and the CA199 was greatly decreased after the treatment, which may suggest that immune-combination chemotherapy may be one of the future treatment directions for PJS combined with progressive cervical cancer.

CONCLUSION

We reported a case of PJS combined with advanced cervical cancer. Protein 1 inhibitor combined with a CD chemotherapy regimen substantially decreased the size of the patient's metastases showing that the aforementioned protocol could be a good choice for such patients.

FOOTNOTES

Author contributions: Hu XC and Gan CX assembled, analysed, and interpreted the patient's data and case presentation; Zheng HM and Wu XP prepared the original manuscript; Pan WS edited and critically revised the manuscript; All authors contributed to writing the manuscript; All authors read and approved the final manuscript.

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Country/Territory of origin: China

ORCID number: Xue-Ping Wu 0000-0002-9614-1638; Wen-Sheng Pan 0000-0002-2347-1695.

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CASE REPORT

Xanthogranulomatous inflammation requiring small bowel anastomosis revision: A case report

William Wang, Maria Korah, Kovi E Bessoff, Jeanne Shen, Joseph D Forrester

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William Wang, Department of Biology, Stanford University, Stanford, CA 94305, United States

William Wang, Department of Bioengineering, Stanford University, Stanford, CA 94305, United States

Maria Korah, Kovi E Bessoff, Joseph D Forrester, Division of General Surgery, Department of Surgery, Stanford University, Stanford, CA 94305, United States

Jeanne Shen, Center for Artificial Intelligence in Medicine and Imaging, Stanford University, Palo Alto, CA 94304, United States

Jeanne Shen, Department of Pathology, Stanford University School of Medicine, Stanford, CA 94305, United States

Corresponding author: Joseph D Forrester, FACS, MD, MSc, Assistant Professor, Attending Doctor, Director, Surgeon, Division of General Surgery, Department of Surgery, Stanford University, 300 Pasteur Drive, H3591, Stanford, CA 94305, United States. jdf1@stanford.edu

Abstract

BACKGROUND

Xanthogranulomatous inflammation (XGI) is an uncommon process involving an accumulation of inflammatory cells, commonly lipid-laden macrophages. XGI has been described to occur throughout the body but only rarely in the lower gastrointestinal tract. We describe a case of XGI contributing to chronic obstructive symptoms in the terminal ileum, in which the patient had an initial diagnostic laparoscopy, continued to have symptoms, then proceeded to have the definitive treatment. To our knowledge, this is the first report of XGI associated with a prior small bowel anastomosis.

CASE SUMMARY

We report the case of a 42-year-old female who presented with intermittent epigastric pain and subjective fevers. She had undergone a laparoscopic small bowel resection for Meckel's diverticulum five years prior. Her workup was notable for computed tomography scan demonstrating mild inflammation and surrounding stranding at the level of the prior anastomosis. She underwent a laparotomy, resection of the prior anastomosis and re-anastomosis, with final histopathological examination findings consistent with mural XGI.

CONCLUSION

XGI can occur at the site of a prior bowel anastomosis and cause chronic obstructive symptoms.

Key Words: Xanthogranulomatous inflammation; Chronic obstructive symptoms; Terminal ileum; Bowel anastomosis; Bowel resection; Case report

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Core Tip: Xanthogranulomatous inflammation (XGI) is an uncommon inflammatory condition characterized by foamy histiocytes and other inflammatory cells. We report a rare case of XGI that occurred in the terminal ileum. Moreover, this is the first reported case of XGI associated with a prior bowel anastomosis. This case enhances our understanding of XGI and provides more insight into the pathophysiology of the condition.

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INTRODUCTION

Xanthogranulomatous inflammation (XGI) is a rare benign condition involving an inflammatory response that can occur in multiple areas throughout the body[1,2]. Clinical presentations and imaging are generally nonspecific since XGI symptoms can vary depending on the organ system; as such, histopathological examination is necessary for a definitive diagnosis[3,4].

Though XGI is a benign process, it is important to consider this diagnosis in the differential for atypical masses because XGI can be challenging to distinguish from cancer, which may lead to avoidable radical treatments[1,3,5]. Therefore, a better understanding of the characteristics of XGI is urgently needed.

Herein, we present a case of a 42-year-old female with XGI at a prior small bowel anastomosis. While XGI has been reported in many organs[1,6], only a few cases of XGI in the lower gastrointestinal (GI) tract have been reported[1,7]. In addition, there have been no cases reported for XGI associated with a bowel anastomosis.

CASE PRESENTATION

Chief complaints

Intermittent mid-epigastric abdominal pain.

History of present illness

A 42-year-old female started having intermittent recurrent mid-epigastric abdominal pain episodes that resulted in multiple emergency department (ED) visits. Six months prior, she had presented to the ED with two days of intermittent epigastric pain and subjective fevers. At that time, she had no nausea or vomiting, her last bowel movement was the day prior to presentation, and she was passing flatus. On exam, she was hemodynamically stable with a benign physical exam. Her abdomen was soft, slightly distended, with moderate tenderness to palpation in the epigastric region, with no evidence of peritonitis. Her white blood cell count was 8.0 K/μL. She had a computed tomography (CT) scan of her abdomen and pelvis (AP) without contrast demonstrating her prior bowel anastomosis was focally dilated, with abnormal surrounding inflammatory stranding, along with mesenteric swirling around the anastomosis which raised suspicion for possible obstruction due to internal hernia. She underwent a diagnostic laparoscopy where an adhesive band of omentum to the prior small bowel anastomosis was lysed. All bowel was viable.

Following that surgery, her epigastric pain recurred, along with some nausea and vomiting. She had *Helicobacter pylori (H. pylori)* serum and stool antigen and antibody tests that were negative, and an abdominal radiograph demonstrated non-obstructive bowel gas pattern. Esophagogastroduodenoscopy (EGD) demonstrated a few localized non-bleeding erosions in the gastric antrum, with no stigmata of recent bleeding. A CT AP with intravenous contrast given after premedication demonstrated no acute pathologies that could explain her ongoing abdominal pain. She was discharged after she started tolerating oral intake and her pain improved. At a postoperative clinic visit a week later, her pain had

completely resolved, and she was tolerating a regular diet without issues.

Unfortunately, her symptoms returned months later and led to multiple ED visits. During these episodes, she had no nausea or vomiting and no particular precipitating factors. She had been having dark stools, which had resolved after stopping ibuprofen, and otherwise had normal stools and flatus. Her recurrent symptoms prompted a thorough outpatient work-up.

History of past illness

Her past history was notable for depression, anxiety, iron deficiency anemia, cystitis, infectious mononucleosis, *H. pylori* infection, an unprovoked pulmonary embolism for which she had previously been on warfarin for a year, and prior Epstein-Barr virus (EBV) infection. Five years prior, she had a laparoscopic small bowel resection with a stapled side-to-side anastomosis for Meckel's diverticulum. She also had a history of left ovarian cyst removal and bilateral inguinal hernia repairs. Three years prior, she had a colonoscopy and EGD performed for bright red blood per rectum, heartburn, epigastric and lower abdominal pain, nausea, and bilious emesis. These studies demonstrated very small internal hemorrhoids and erosive gastropathy but were otherwise normal.

Personal and family history

The patient had never smoked, had used methamphetamine previously but quit 13 years prior, and drank one glass of wine a week. Her family history was notable for diabetes and stroke in her parents. She was allergic to penicillins, iodinated contrast media, and fish-containing products.

Physical examination

Her vital signs during her ED visits were within normal limits. Her abdominal exam was unremarkable at office visits when she was not experiencing an abdominal pain episode, but during her symptomatic episodes, she had mid-epigastric tenderness to palpation with no rebound or guarding.

Laboratory examinations

During each ED visit, she was noted to have mild leukocytosis (11.8-15.9 K/μL), with otherwise overall unremarkable laboratory findings.

Imaging examinations

During one ED visit, a CT AP demonstrated mild inflammation and surrounding stranding at the level of the prior anastomosis (Figure 1A and B), along with small bowel fecalization (Figure 1C) concerning for possible infectious or inflammatory enteritis with nonspecific prominent mesenteric nodes.

FINAL DIAGNOSIS

The patient underwent a lower double-balloon enteroscopy, where neither a double nor single enteroscope could be advanced beyond the terminal ileum (TI), though the examined colon and visualized approximately 3 cm of TI appeared normal (Figure 2).

TREATMENT

Given that she failed nonoperative attempts to access her possible stricture, she underwent a laparotomy, resection of her prior small bowel anastomosis, and had a handsewn re-anastomosis.

Histopathologic examination of the resected small bowel segment demonstrated a 7.5 cm × 5.3 cm × 4 cm portion of small bowel, with smooth, tan-brown serosa and tan-green mucosa with normal appearing folds (Figure 3). The prior anastomosis site was tan-pink with puckered area of mucosa. There was a cystic cavity abutting the prior anastomosis, which was tan-yellow with copious yellow-tan, viscous purulent cystic material, suggesting significant chronic inflammation underlying the anastomosis site. Microscopic analysis revealed significant infiltration by foamy macrophages, lymphocytes, and plasma cells with no neoplastic cells concerning for carcinoma (Figures 4 and 5). Overall, the histopathological examination findings were consistent with mural XGI.

OUTCOME AND FOLLOW-UP

Postoperatively, she developed ileus that self-resolved and was discharged eight days after surgery. At her postoperative clinic visit three weeks later, she was tolerating oral intake, having normal bowel movements, and only having some incisional pain with no obstructive symptoms. Eight months after that follow-up, she developed an incisional hernia that was repaired with mesh. At an outpatient

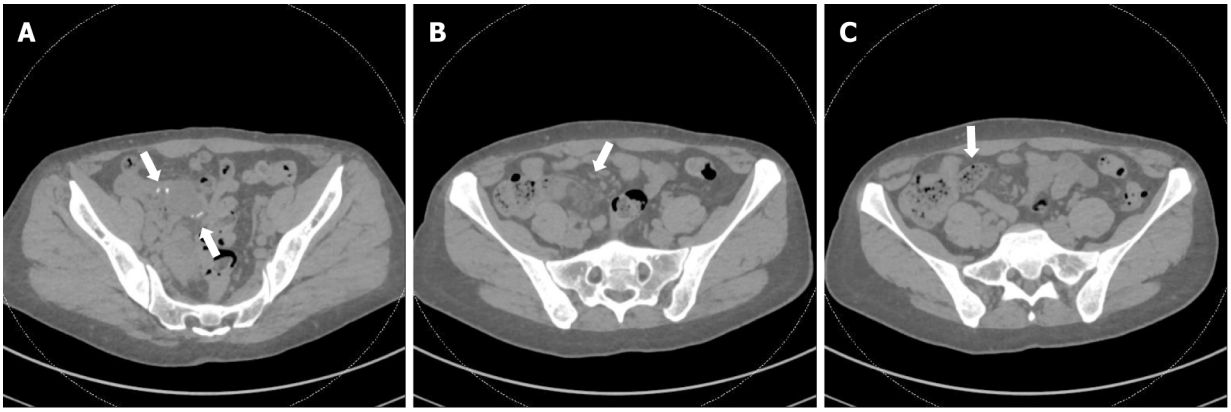

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Figure 1 Computed tomography scan of her abdomen and pelvis without contrast. A: Prior anastomotic suture line is visualized (arrows) and appeared intact; B: Mild surrounding inflammatory stranding (arrow) seen near the prior anastomosis; C: Fecalization (arrow) noted in small bowel adjacent to anastomosis.

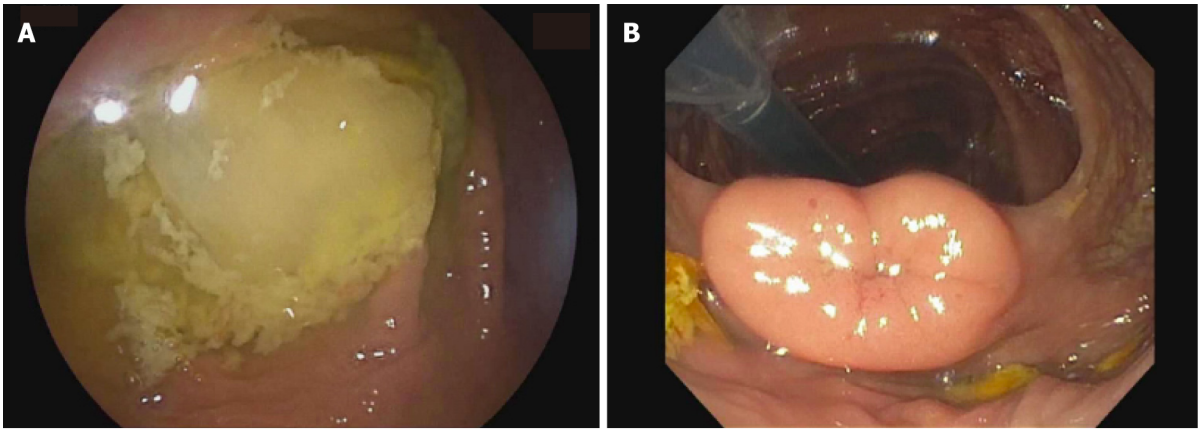

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Figure 2 Double balloon enteroscopy. A: The entire examined colon appeared normal, including the cecum; B: The ileocecal valve. The terminal ileum (TI) was only marginally intubated and could not be advanced further. The visualized portion of the TI (approximately 3 cm) appeared normal.

follow-up clinic visit two weeks after the hernia repair surgery, she had some incisional pain but continued to have no obstructive symptoms.

DISCUSSION

XGI is a rare inflammatory process that requires histopathological examination for definitive diagnosis. Specifically, XGI usually presents, as it did in our patient, with yellow lesions on gross pathologic examination and is histologically defined by foamy histiocytes and various inflammatory cells, including activated plasma cells, lymphocytes, and sometimes multinucleated giant cells[6,8].

Although XGI has been reported in many organs, the majority of reported cases of XGI have been in the gallbladder, followed by occasional cases in the kidney and less commonly in the GI tract or other organs, such as the female genital tract or the head and neck[1,6]. Only a few cases of XGI in the lower GI tract have been reported[1,7]. In one, a patient presented with chronic abdominal pain mimicking appendiceal cancer on abdominal CT[1]. In that case, laparoscopic hemicolectomy revealed several golden-yellow and brown lesions, and histology confirmed XGI in the TI[1]. Interestingly, pathogenesis was attributed to chronic inflammation caused by microscopic perforations from a possible fish bone [1]. In another report, a patient presented with abdominal pain with ultrasound findings concerning for acute appendicitis. Diagnostic laparoscopy and midline laparotomy revealed an ileocecal mass concerning for invasive cancer. The mass was resected *via* hemicolectomy followed by a primary side-to-side anastomosis and was revealed to be XGI upon histologic examination. In that case presentation, no clear pathogenesis was established[7].

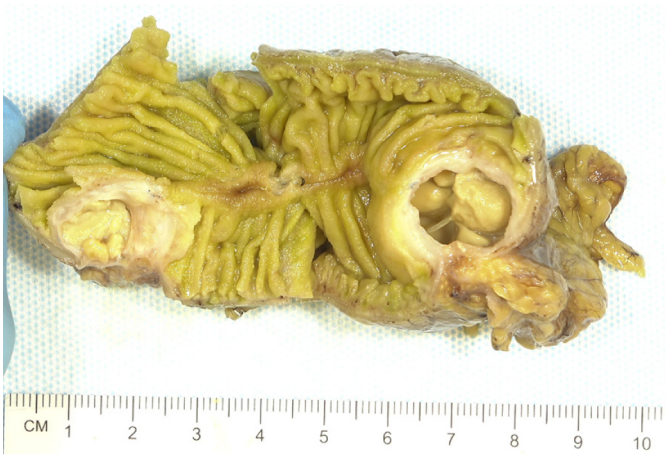

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Figure 3 Gross specimen. Gross examination revealed a 7 cm long region of cystically dilated small intestine immediately adjacent to the anastomosis, which was filled with abundant intraluminal pus.

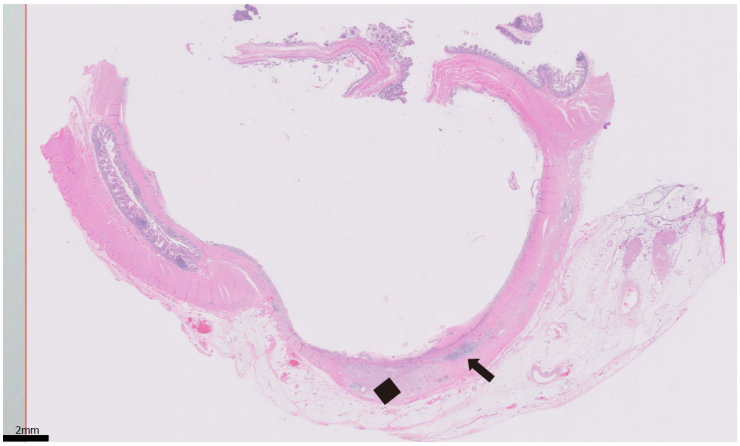

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Figure 4 Low-magnification section of the specimen. Microscopic (0.5 × objective magnification) cross section of the cystically dilated small intestine with mucosal ulceration (diffusely involving the luminal surface) and chronic inflammation (arrow), fibrosis, and xanthogranulomatous inflammation (black diamond) of the underlying wall.

The exact pathophysiology of XGI is currently unknown, and various theories have been proposed, including abscess, hemorrhage, and necrosis, which may instigate the XGI response[2]. Chronic infection, abnormal lipid transport, and immunological disorders may also play a role[9]. Furthermore, recurrent inflammation due to a foreign body and obstruction has also been hypothesized and may have played a role in our patient[1,9].

Our patient's XGI lesion was in the TI, and it is especially unique because the lesion was associated with a prior anastomosis. Though the exact mechanism by which this patient's XGI developed is unclear, she had multiple risk factors that may have acted as triggers that elicited this response. For example, as described earlier, foreign body has been hypothesized to play a role in the development of XGI by causing microperforations leading to chronic inflammation and tissue damage[1]. In this patient's case, the anastomosis itself may have triggered a foreign body response that led to XGI.

To our knowledge, there are no other cases where a stapled anastomosis was associated with XGI. However, it is possible the patient's immune system reacted to the staples in such a way as to trigger XGI. This unusual reaction to the foreign body may be related to the patient's prior EBV infection, which can impact the immune system, lead to inflammation, and trigger several autoimmune diseases [10,11]. It is unknown if performing a hand-sewn anastomosis initially could have prevented this. In fact, meta-analyses comparing both anastomosis techniques in emergency laparotomy and colorectal surgery have generally demonstrated little significant difference in outcomes[12,13]. However, further studies are needed to understand specific variations in foreign body responses that may be triggered by the two different techniques[12,13].

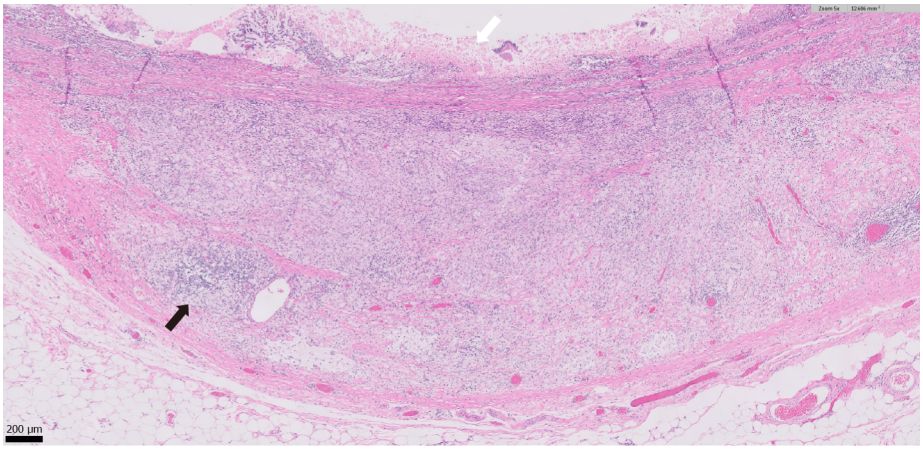

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Figure 5 High-magnification section of the specimen. Higher magnification (5 × objective magnification) image showing mucosal ulceration (white arrow) with abundant infiltration of the underlying small intestinal wall by collections of foamy, lipid-laden histiocytes (xanthogranulomatous inflammation), along with lymphocytes and plasma cells (example highlighted by black arrow).

Another potential explanation for our patient's XGI is that an obstructive process triggered it, perhaps from stricture at the anastomosis independent of the XGI lesion. Obstruction is recognized as a cause of xanthogranulomatous appendicitis, pyelonephritis, and cholecystitis[9]. On the other hand, the large inflammatory XGI mass may have formed as a response to another process, and the lesion then may have then led to this patient's obstructive symptoms rather than the XGI lesion being a consequence of obstruction.

CONCLUSION

In conclusion, XGI is an uncommon inflammatory condition characterized by foamy histiocytes and other inflammatory cells. XGI occurs very rarely in the lower GI tract, and we describe such a case in the TI. To our knowledge, this is the first case report describing XGI associated with a prior anastomosis. This case is also an example where repeated pain and obstructive symptoms may necessitate anastomosis revision for definitive diagnosis and clinical resolution.

FOOTNOTES

Author contributions: Wang W and Korah M contributed to manuscript writing and editing; Forrester JD was in charge of conceptualization, manuscript preparation and the patient case; Shen J contributed the gross and histopathologic images and descriptions; Wang W, Korah M, Bessoff KE, Shen J, and Forrester JD contributed to analysis; All authors have read and approved the final manuscript.

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Country/Territory of origin: United States

ORCID number: William Wang 0000-0002-0878-1257; Maria Korah 0000-0001-9328-3908; Kovi E Bessoff 0000-0002-5626-4027; Jeanne Shen 0000-0002-1519-0308; Joseph D Forrester 0000-0002-8558-6180.

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