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MINIREVIEWS

Transarterial chemoembolization failure/refractoriness: A scientific concept or pseudo-proposition

Shen Zhang, Bin-Yan Zhong, Lei Zhang, Wan-Sheng Wang, Cai-Fang Ni

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Abstract

Multi-session transarterial chemoembolization (TACE) is usually needed for the treatment of intermediate-stage hepatocellular carcinoma (HCC), but it may not always have a positive influence on prognosis due to high heterogeneity of HCC. To avoid ineffective repeated TACE, the concept of TACE failure/refractoriness has been proposed by several organizations and is being addressed using tyrosine kinase inhibitors. The concept of TACE failure/refractoriness is controversial due to ambiguous definitions and low evidence-based data. To date, only a few studies have examined the rationality concerning the definition of TACE failure/refractoriness, although the concept has been introduced and applied in many TACE-related clinical trials. This review focuses on some of the issues related to different versions of TACE failure/refractoriness, the rationality of related definitions, and the feasibility of continuing TACE after so-called failure/refractoriness based on published evidence. A suggestion to re-define TAEC failure/refractoriness is also put forward.

Key Words: Hepatocellular carcinoma; Transarterial chemoembolization; Failure; Refractoriness

Core Tip: The definitions in the current concept of transarterial chemoembolization (TACE) failure/refractoriness are not capable of guiding clinical practice. A persistent viable tumor lesion is a well-accepted item of TACE failure/refractoriness, but that is not the case when it comes to new lesions, portal vein tumor thrombosis or extrahepatic spread. Patients with recurrent hepatocellular carcinoma after TACE constitute a heterogenous group and the treatment modalities need to be individualized.

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INTRODUCTION

According to the Barcelona Clinic Liver Cancer (BCLC) staging system, transarterial chemoembolization (TACE) is the standard approach for patients with intermediate stage (BCLC-B) hepatocellular carcinoma (HCC)[1-3]. Nevertheless, the overall prognosis for patients undergoing TACE varies considerably due to the high heterogeneity of BCLC-B stage HCC[4]. In addition, repeated TACE courses are associated with an increase in angiogenesis and embolization-related liver damage, all of which may negate the benefits achieved in the tumor or even adversely affect overall survival (OS)[4-6]. Thus, many investigations have been carried out in order to identify a turning point where subsequent repeated TACE is not any more beneficial than alternative treatments or best supportive care for patients[7,8]. With the clinical application of tyrosine kinase inhibitors (TKIs), some scholars have proposed a new treatment paradigm where patients with intermediate stage HCC should switch to TKIs monotherapy when tumor progression occurs after TACE procedures[9,10], and as a consequence, the concept of TACE failure/refractoriness was introduced and proposed.

REVIEW OF DIFFERENT DEFINITIONS OF TACE FAILURE/REFRACTORINESS

The concept of TACE failure/refractoriness was initially proposed by the Japan Society of Hepatology (JHS) in 2010[11] and revised by the JSH-Liver Cancer Study Group of Japan (LCSGJ) in 2014 (Table 1) during a consensus meeting[6]. According to the definition, persistent viable treated lesions, consecutive emergence of new intrahepatic tumors and disease stage progression as well as continuous elevation of tumor markers were scenarios for terminating repeated TACE. However, Korean scholars did not take the same view and they concluded that 3 conditions, namely 3 or more TACE procedures within 6 mo, advancing to portal vein tumor thrombosis (PVTT) and extrahepatic spread (EHS) was TACE failure/refractoriness[12]. These suggestions were also supported by the International Association for the Study of the Liver (Table 1)[13]. Notably, the concept from Europeans seems to be more reliable in clinical practice (Table 1)[14]. They suggested that the determination of TACE failure/refractoriness should be in line with the indications of TACE. If stable disease (SD) of HCC is achieved when TACE is used as a palliative therapy it is regarded as effective. Conversely, when TACE acts as a curative treatment, the outcome of SD or progressive disease is identified as TACE failure/refractoriness. Currently, the concept of TACE failure/refractoriness has been widely introduced, especially in clinical trials for HCC[5,9,10,15,16]. However, these concepts require further discussion due to low evidence-based data. This article attempts to provide a comprehensive understanding concerning the omissions in the current definitions based on published evidence.

COMPREHENSIVE ANALYSES OF THE ENDPOINTS FOR TACE IN TACE FAILURE/REFRACTORINESS

Persistent viable targeted lesion(s) after consecutive treatments

When insufficient response in intrahepatic tumor occurs after multi-session TACE, it is sensible to define TACE failure/refractoriness and to stop TACE. The peripheral region as well as the capsular region of HCC nodules may be nourished by both the hepatic artery and portal vein and, as a result, substantial tumor necrosis by arterial embolization is not always guaranteed[17-19]. It has been reported that nourishing vessels of residual tumors may change from the hepatic artery to the portal vein after repeated TACE[20]. In addition, repeated chemoembolization increases pressure in the tumor microenvironment and may lead to phenotypic variation in surviving tumor cells, which tend to be more malignant and chemoembolization-resistant[21-23]. It has been reported that locally recurrent HCC after TACE has a significantly shorter doubling time than primary HCC nodules[24].

The number of TACE sessions performed before abandoning TACE in the case of insufficient tumor necrosis is a crucial issue. Georgiades *et al*[25] reported that 47% of non-responders to the first TACE ultimately achieved partial response (PR) or complete response (CR) after the second procedure, and median OS between patients who achieved response at the first or the second chemoembolization was comparable. Some experts suggested that if target nodule(s) show no response after at least two consecutive sessions of TACE, it is reasonable to define TACE-failure and trigger treatment stage

Table 1 Different concepts of transarterial chemoembolization failure/refractoriness

Guidelines/articles	Contents
JSH-LCSGJ criteria 2014 [6]	(1) Intrahepatic lesion: Two or more consecutive insufficient responses of the treated tumor (viable lesion > 50%) even after changing the chemotherapeutic agents and/or reanalysis of the feeding artery seen on response evaluation CT/MRI at 1-3 mo after having adequately performed selective TACE; two or more consecutive progressions in the liver (tumor number increases as compared with tumor number before the previous TACE procedure) even after having changed the chemotherapeutic agents and/or reanalysis of the feeding artery seen on response evaluation CT/MRI at 1-3 mo after having adequately performed selective TACE; (2) Continuous elevation of tumor markers immediately after TACE even though a slight transient decrease is observed; (3) Appearance of vascular invasion; and (4) Appearance of extrahepatic spread
International Association for the Study of the Liver [13]	No response after 3 or more TACE procedures within a 6 mo period, to the same area.
Europe[14]	Depending on the purpose of TACE, if TACE is used as palliative therapy, stable lesions can be regarded as effective. Conversely, if TACE is used as a curative therapy, stable lesions are considered TACE-failure

JSH-LCSGJ: JSH-Liver Cancer Study Group of Japan; TACE: Transarterial chemoembolization; CT: Computed tomography; MRI: Magnetic resonance imaging.

migration[2,4,16,26]. Based on a large cohort study of 4154 patients with HCC, Chen *et al*[27] found that HCC nodules became insensitive to chemoembolization after 3 sessions of TACE, with an objective response rate (ORR) < 10%. Furthermore, patients with tumors eventually attaining CR or PR within the first 3 TACE sessions had a longer median OS than those who did not (43.4 mo *vs* 16.6 mo, $P < 0.001$). As a consequence, three sessions were recommended before abandoning TACE.

However, residual tumors with persistent viability may not be an absolute indication for systemic monotherapy owing to the unsatisfactory anti-tumor effect[28]. Other locoregional interventional methods, with curative potential, are preferred options once tumor size meets the indications. Chen *et al*[17] reported that subsequent microwave ablation (MWA) yielded a better survival time than sorafenib in patients with incomplete remission of targeted lesions after multiple sessions of TACE, with a longer progression-free survival (PFS) time (9.0 mo *vs* 2.8 mo, $P = 0.006$) and OS (not reached *vs* 16.6 mo, $P = 0.001$). In addition, Yttrium-90 radioembolization and Iodine-125 (^{125}I) seed brachytherapy have been adopted to control target lesions[29-31]. TACE combined with systemic therapy or loco-regional therapy revealed favorable outcomes and good tolerance[15,31,32].

New intrahepatic lesion(s) appearing after consecutive treatments

Vascular endothelial growth factor (VEGF), which is regulated by hypoxia-inducible factor-1α, has been demonstrated to be the most important element in neovascularization[33]. Substantial evidence has been elucidated on the intrinsic connection between the transient upregulation of VEGF after TACE and intrahepatic metastasis. Tumor recurrences are frequently reported after TACE, whereas it is arbitrary to describe this scenario as an absolute contraindication to repeated TACE[34,35]. First, TACE is traditionally recognized as a palliative, loco-regional therapy and it is unreasonable to define the occurrence of new lesions outside treated areas as disease progression[4,27,35]. Second, frequent intrahepatic metastasis is the inherent nature of HCC and it occurs in the very early-stage. A clinicopathologic study found that nearly 19% of small HCC patients (solitary nodule with a diameter no more than 3 cm) had satellite lesions, located 2 cm or less from the main tumor and were 1 mm to 5 mm in diameter[36]. Although these undetectable and untypical micro-metastases are too small to be diagnosed as tumors according to the European Association for the Study of the Liver (EASL)[3], they possess enormous potential to develop into typical tumor lesions and appear as local recurrence or intrahepatic metastases[37]. In addition, the malignancy of HCC is positively associated with tumor size. It has been reported that approximately 51.3% of HCC nodules (with an average size of 5 cm) had microvascular invasion (MVI) and 42.4% of the nuclei were severely atypical[38]. For patients with intermediate- or advanced-stage HCC, early tumor progression after locoregional therapy was almost inevitable due to heavy tumor burden and frequent MVI[15,32,39]. Combination therapy was expected to delay tumor recurrence[16]. Even the supporters of TACE failure/refractoriness are ambivalent on the issue of whether new lesion(s) after TACE is a condition of TACE failure/refractoriness[6,16,35]. In the TACTICS trial, the first randomized control trial (RCT) demonstrating the superiority of TACE plus sorafenib compared to TACE monotherapy in unresectable HCC, "TACE failure/refractoriness" was one of the major endpoints for TACE treatment. However, the study simultaneously emphasized that multicentric occurrence and intrahepatic recurrence/metastases were the unique biological features of HCC[35], and therefore it was reasonable to perform demand TACE to control new tumor lesions[40]. To date, there is still no convincing evidence to conclude that new intrahepatic tumor lesions attribute to the biological features of HCC, whereas consecutive intrahepatic metastasis should be defined as TACE failure/refractoriness.

On-demand TACE for new intrahepatic lesions is safe and efficient in selected patients[12,41]. In a large cohort study, 264 patients with intermediate-stage HCC underwent TACE with "on demand" mode (range: 1-13 times; mean: 3 times)[12]. During the follow-up, patients experiencing intrahepatic metastasis or a total target tumor diameter increase of 20% were defined as having progressive disease (PD), while those having PVTT invasion or EHS were defined as having stage progression (SP). The results showed that median OS was comparable between patients in the PD (-) and SP (-) group (36.6 mo) and in the PD (+) and SP (-) group (35.5 mo). However, evidence from these studies only supports the feasibility of repeated TACE in new lesions, but by no means indicates that TACE can be implemented unrestrainedly. Liver function deterioration and hypoxia-induced pressure on residual HCCs have a great influence on patients' survival. Additional systemic therapies including TKIs may prolong the interval between two TACE sessions and hamper intrahepatic micro-metastases[16,42]. Hence, the treatment decision has to be individualized according to expert evaluation. Several nomograms have been established to identify patients who may benefit from repeated TACE, but the rationality of these nomograms is still controversial[7,8,43].

Continuous elevation of tumor markers

On-schedule tumor marker assessment is a crucial adjuvant method for evaluating tumor response and monitoring tumor recurrence. A sudden increase in α-fetoprotein (AFP), AFP-L3 and/or des-gamma-carboxy prothrombin after treatment was thought to show tumor progression or greater malignancy of the tumor[44,45]. However, that does not indicate a definitive correlation with TACE failure/refractoriness. On the one hand, a well-designed control study is expected to clarify the superiority of TKIs to TACE in patients who experienced tumor marker flare after TACE. Although previous evidence has shown that rapid reductions in tumor markers were positive predictors of TACE and vice versa[46], subsequent treatments to deal with elevated tumor markers were not explored and recommended. Up to now, all TKIs targeting HCC, except ramucirumab which demonstrated apparent benefits in patients with AFP ≥ 400 ng/mL, are not designed for the biomarker-selected population[47]. On the other hand, the significance of the tumor marker trends has not yet been fully elucidated in the management of HCC and the relationship between different tumor markers and morphological changes is unclear[21,46]. As shown by the EASL clinical practice guideline, the use of changes in serum biomarker levels for assessment of response (*i.e.*, AFP levels) is under investigation[3]. Hence, when tumor markers are increased after TACE, subsequent treatment should be codetermined by tumor burden, liver function and tumor response to previous TACE, rather than abandoning TACE blindly[3,48]. Furthermore, "continuous elevation" is a vague definition and an immature quantification of "elevation" brings many factors into the clinical decision. Ogasawara *et al*[10] suggested an increase in the level of AFP of 20% from baseline as a cut-off value. However, other researchers have different opinions[8,45].

Appearance of vascular invasion or extrahepatic spread

Neither the EASL nor the American Association for the Study of Liver Disease guidelines recommend TACE for the treatment of HCC with PVTT or EHS[1,3]. However, according to the BRIDGE study that documented real-world clinical practice in HCC, TACE was still the most frequent first treatment in advanced-stage HCC[49]. A national questionnaire conducted in Korea also indicated that nearly half of clinicians would not abandon TACE in the case of PVTT or EHS due to the heterogeneity of HCC[48]. Outcomes from the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) and Oriental clinical trials and the corresponding subgroup analyses showed a marginal improvement for sorafenib over placebo in terms of PVTT with/without EHS[28,50-52]. Lenvatinib exhibited a promising short-term anti-tumor effect compared with sorafenib in patients suffering PVTT with/without EHS [Hazard ratio (HR): 0.64; 95% confidence interval (CI): 0.54-0.77], while the long-term prognosis was undefined (HR: 0.87; 95%CI: 0.73-1.04). It is worth stressing that although the BCLC stage system recommends systemic therapy as the initial treatment for advanced-stage HCC, a special profile of an individual patient may induce a different option in clinical practice[48,49,53-55].

Vascular invasion

With the development of embolization techniques, TACE has been safely and effectively performed in some patients with adequate collateral pathways around the occluded portal vein[15,48,55-58]. These advanced stage populations were defined as "Quasi-C" patients (segmental PVTT, Child-Pugh A, and acceptable performance status). A meta-analysis showed that TACE conferred a longer OS in patients with branch PVTT than those with main trunk PVTT (11 mo *vs* 5 mo, $P < 0.001$)[59]. Significantly, for PVTT invading the main trunk, initial portal vein re-canalization using irradiation and a stent with subsequent selective TACE was effective in hampering disease progression, with a median stent patency of 8 mo and median OS of 12.5 mo[60]. Wang *et al*[61] introduced modified ^{125}I seed brachytherapy to treat main trunk PVTT and exhibited favorable outcomes when combined with TACE (median OS: 9.8 mo). In addition, combination therapy of TACE and TKIs demonstrated better results for selected patients with PVTT[62]. According to a large cohort study, compared with sorafenib monotherapy, TACE combined with sorafenib showed a trend towards significant risk reduction in patients (n = 1136) with vascular invasion (HR: 0.78; 95%CI: 0.59-1.02)[63]. Recently, a RCT conducted

by Ding *et al*[62] reported that TACE plus lenvatinib had a more favorable efficacy *vs* TACE plus sorafenib in patients with PVTT, especially those with Vp1-3 type (HR: 0.12; 95%CI: 0.03-0.42, $P < 0.01$) or heavy tumor burden (HR: 0.30; 95%CI: 0.15-0.61, $P < 0.01$). It should be emphasized that PVTT is a complex system and the optimal treatment strategy is individual rather than univocal. For patients whose tumor thrombus involves a segment of the portal vein or above, surgery is a potential option once tumor burden is downstaged to the Milan criteria in the liver; for patients who miss curative treatment, TACE, TKIs and other modalities may play a complementary role in controlling disease progression[57]. So far, many novel treatment strategies for PVTT have been investigated and have yielded exciting results, providing patients with more treatment options[30,57,60,64,65].

Extrahepatic spread

Subgroup analysis from the SHARP clinical trial revealed that sorafenib only conferred an additional survival time of 0.6 mo compared with placebo[52]. Due to the fact that more than two-thirds of patients with EHS died of intrahepatic tumor progression rather than extrahepatic disease, aggressive treatment targeting intrahepatic disease might be beneficial in selected patients with EHS[15,53,63]. The results from Kirstein *et al*[53] suggested that TACE was not inferior to sorafenib in patients with limited EHS of HCC, with a median OS of 8.8 mo *vs* 7.0 mo for sorafenib *vs* TACE ($P = 0.312$) before propensity score matching (PSM) analysis and 4.0 mo *vs* 8.0 mo after PSM ($P = 0.613$). In another large cohort study of 186 patients with EHS, TACE appeared to be more beneficial in patients aged below 60 years (HR: 0.58, 95%CI: 0.37-0.91, $P = 0.017$) or complicated with PVTT (HR: 0.44, 95%CI: 0.25-0.79, $P < 0.001$)[66]. Choi *et al*[55] compared combination treatment (TACE plus sorafenib) with sorafenib alone in advanced stage patients. The combination group demonstrated a more significant survival benefit than monotherapy both in time to progression (2.7 mo *vs* 2.1 mo, $P = 0.011$) and median OS (8.9 mo *vs* 5.9 mo; $P = 0.009$). Subgroup analysis revealed that combination therapy was more efficacious in patients who had good liver function and EHS. Hence, although systemic therapy is recommended as the first choice for patients with EHS, TACE may still be a potential alternative in selected patients.

SUGGESTIONS TO DEFINE TACE FAILURE/REFRACTORINESS

For patients with intermediate-stage HCC, multidisciplinary treatment is compulsory to overcome the vast heterogeneity in HCC and different treatment modalities are cooperators rather than competitors. The term "failure" or "refractoriness" was initially derived from systemic chemotherapy in oncology where the current chemotherapeutic strategy failed to prevent overall tumor progression including tumor recurrences and new lesions. TACE is only a locoregional therapy but disease progression of HCC involves intrahepatic areas and extrahepatic tissues. In the absence of prospective well-designed studies, a persuasive definition of TACE failure/refractoriness should largely rely on the nature of the treatment, that is, a locoregional therapy. In 2020, a nationwide online survey of 257 clinicians in 184 hospitals was conducted to recognize TACE failure/refractoriness among clinicians treating HCC in China[67]. The survey showed that 89.1% ($n = 229$) of participants deemed TACE as a palliative therapy although sometimes could be a curative modality. While the outcome of TACE was full of variation ($n = 244$), almost all the participants ($n = 252$) would still choose TACE as the first choice for intermediate-stage HCC. In terms of TACE failure/refractoriness, nearly three-quarters ($n = 199$) acknowledged the rationality of the concept, whereas 91.4% ($n = 235$) of the respondents did not agree with the current definitions. A clear majority of clinicians would perform TACE combined with therapy in patients with segmental PVTT ($n = 242$) or EHS ($n = 253$) if liver function was well preserved. In addition, only 42 (16.3%) respondents unequivocally stated that new intrahepatic tumor lesions were an indication of TACE failure/refractoriness; and 36.6% ($n = 94$) gave an equivocal answer. Among the remaining 121 respondents who answered "No" to the question, most preferred combination therapy, including TACE ($n = 80$) and ablation ($n = 80$), to control new lesions. Additionally, 166 (64.6%) participants agreed that repeated TACE can be performed if tumor necrosis was insufficient and feeding arteries were available. Whereas, 150 participants (58.4%) believed that repeated TACE on pre-treated lesions should be limited to 3 times. Notably, 98.1% ($n = 252$) of the respondents expressed a strong desire for the improvement of TACE, including preferable embolization agents, chemotherapeutic drugs followed by embolization technique and more advanced microcatheters. Based on the above discussion and evidence, if intrahepatic targeted lesions are well controlled by appropriate TACE regimens, TACE should not be indiscriminately abandoned in the context of disease progression including new lesions, PVTT and EHS. However, if three consecutive insufficient tumor responses in targeted lesions occur, TACE should not be repeated and TACE failure/refractoriness proposed.

FUTURE OF TACE FAILURE/REFRACTORINESS

Treatment modalities for unresectable HCC have undergone profound changes and TACE faces

unprecedented challenges, where novel treatment strategies may substitute for TACE as the first treatment option in selected patients with intermediate-stage HCC (ABC-HCC, NCT04803994; RENOTACE, NCT04777851). As a consequence, the concept of TACE failure/refractoriness may be expanded or re-defined as other proposals, for example, TACE unsuitability and TACE impossible. However, such concepts should not be overemphasized before substantial evidence is published, as the management of unresectable HCC is no longer the conversion between various monotherapies in the era of comprehensive therapy. The evolution of TACE will continue and many options are being investigated, including new embolic or chemotherapeutic agents in order to ensure complete tumor necrosis, and combination treatments with newly-developed immune checkpoint inhibitors (LEAP-012, NCT04246177; EMERALD-1, NCT03778957; CheckMate74W, NCT04340193; IMMUTACE, NCT03572582). In the near future, the outcomes of these RCTs may re-position the role of TACE in the management of HCC.

CONCLUSION

TACE failure/refractoriness is a scientific proposal for HCC but certain definitions in current concepts are debatable. Tumor progression after TACE is due to high heterogeneity and therefore subsequent treatment is an individual profile rather than a univocal recommendation. We put forward new opinions concerning TACE failure/refractoriness which might be more reasonable in clinical practice.

FOOTNOTES

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MINIREVIEWS

Indications for the surgical management of pancreatic trauma: An update

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Abstract

Pancreatic trauma is rare compared to other abdominal solid organ injuries, accounting for 0.2%-0.3% of all trauma patients. Moreover, this type of injury may frequently be overlooked or not readily appreciated on initial clinical examinations and investigations. The organ injury scale determines the severity of the trauma. Nonetheless, there are conflicting recommendations for the best strategy in severe cases. Overall, conservative management of induced severe traumatic pancreatitis is adequate. Modern imaging modalities such as ultrasound scanning and computed tomography scanning can detect injuries in fewer than 60% of patients. However, magnetic resonance cholangiopancreatography and endoscopic retrograde cholangiopancreatography (ERCP) have diagnostic accuracies approaching 90%-100%. Thus, management options include ERCP and stent placement or distal pancreatectomy in cases of complete gland transection and wide drainage only for damage control surgery, which can prevent mortality but increases the risk of morbidity. In the majority of cases, surgical intervention is not required and should be reserved for only severe grade III to grade V injuries.

Key Words: Pancreas; Acute pancreatitis; Abdominal trauma; Pancreatic traumatic injury; Emergency surgery; Damage control surgery

Core Tip: Pancreatic trauma management should be individualized based on the exact grade of injury. Damage control surgery is the best approach for severe life-threatening cases. However, in such cases, the presence of severe acute pancreatitis makes safe resection impossible. Endoscopic stent placement into the ruptured pancreatic duct is the best alternative after the acute phase. In cases in which local conditions allow, pancreaticojejunostomy can be performed.

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INTRODUCTION

The location of the pancreas behind the posterior peritoneum contributes to the rarity of pancreatic trauma, which accounts for 0.2%-0.3% of all trauma patients[1,2]. This type of trauma usually occurs in conjunction with other organ injuries, mainly to the duodenum. In cases of blunt abdominal trauma, a reasonable mechanism of injury is crushing between the action force and the vertebral column. Less rare but more severe penetrating traumas (gunshot wounds, stab wounds) are common in North America and South Africa. Morbidity and mortality rates are high in cases of gunshot injuries to the pancreas[3,4].

It should be stressed that pancreatic trauma may frequently be overlooked in injured patients with multiple injuries, resulting in a delay in diagnosing severe traumatic pancreatitis[5].

Of the modern imaging techniques, magnetic resonance cholangiopancreatography and endoscopic retrograde cholangiopancreatography (ERCP) have superior diagnostic accuracy (90%-100%) compared to ultrasound scanning and computed tomography scanning (less than 60%)[6-8].

Elevated serum amylase levels (required time 4-6 h) and a high C-reactive protein level above 150 mg/dL contribute to the diagnosis of severe pancreatitis.

A recent large multicenter national cohort study from Japan showed that the Organ Injury Scaling of the American Association for Surgery for Trauma (grade III/IV severe), revised trauma scale score on arrival, age, and the coexistence of severe abdominal injury aside from pancreatic injury are prognostic factors of mortality after pancreatic trauma. Among 743 patients, 84.8% had blunt injuries, and 15% had penetrating injuries. The severity of the injuries was classified as follows: grade I: 45.4%; grade II: 8.9%; grade III: 24%; grade IV: 8.3%; and grade V: 13.5%[9].

The aim of this manuscript is to present an updated clinical analysis of the available knowledge on the detection, classification and optimal management of pancreatic trauma. For this minireview, we selected and focused on the most relevant recent articles from PubMed.

STAGING SYSTEM

Optimal management depends on the exact staging of the injury. The organ injury scale by the American Association for Surgery of Trauma for pancreatic injury severity described in Moore *et al*[10] and Søreide *et al*[1] is shown in Table 1.

The revised trauma scale score to predict mortality on arrival used in Shibahaski *et al*[9] and Jeong *et al*[11] is shown in Table 2.

CONSERVATIVE MANAGEMENT

Conservative management is adequate for grade I and grade II injuries, which represent the majority of cases, and includes proper conservative management of induced severe traumatic pancreatitis[1]. Close monitoring, no oral feeding to rest the pancreas, intravenous fluids and electrolytes, analgesics, antibiotics, total parenteral nutrition and, in the case of peripancreatic collections, percutaneous drainage are the basic proposed measures. The use of somatostatin in its original form or its chemical analog sandostatin is indicated for cases of persistent pancreatic fistula with an output above 500 mL per day. In the rare case in which the patient develops compartment syndrome and increased intraabdominal pressure, urgent lifesaving laparotomy and wide drainage are mandatory.

Table 1 Pancreatic injury scale

Grade	Type of injury	Description of injury	Abbreviated injury score
I	Hematoma	Minor contusion without duct injury	2
	Laceration	Superficial laceration without duct injury	2
II	Hematoma	Major contusion without duct injury or tissue loss	2
	Laceration	Major laceration without duct injury or tissue loss	3
III	Laceration	Distal transection or parenchymal injury with duct injury	3
IV	Laceration	Proximal transection or parenchymal injury involving the ampulla	4
V	Laceration	Massive disruption of the pancreatic head	5

Table 2 Modification of the revised trauma score

Revised trauma score				New trauma score		
Glasgow coma scale	Systolic blood pressure (mmHg)	Respiratory rate	Coded value	Glasgow coma scale	Systolic blood pressure (mmHg)	Oxygen saturation (%)
13-15	> 89	10-29	4	3-15	110-149	≥ 94
9-12	76-89	> 29	3		≥ 150	80-93
6-8	50-75	6-9	2		90-109	60-79
4-5	1-49	1-5	1		70-89	40-59
3	0	0	0		< 70	< 40

INDICATIONS AND OPTIONS FOR SURGICAL MANAGEMENT

Much debate exists regarding the best strategy for severe grade III to grade V injuries. The management options include ERCP and stent placement into the major pancreatic duct, distal pancreatectomy in cases of complete gland transection, and wide drainage only for damage control surgery, which can prevent mortality but increases the risk of morbidity.

However, pancreatic trauma management should be individualized based on the exact grade of injury. Damage control surgery is the best alternative for severe life-threatening cases. In such cases, the presence of severe acute pancreatitis makes safe resection impossible. Endoscopic stent placement into the ruptured pancreatic duct is the best alternative after the acute phase. In cases in which local conditions allow, pancreaticojejunostomy can be performed[9].

Another study recommended resection surgery rather than drainage for grade IV pancreatic injuries, thus avoiding the need for reoperation[12].

A recent multicenter national survey in Japan showed that serum amylase levels and ERCP can more accurately indicate injury to the main pancreatic duct in hemodynamically stable patients. Poor outcomes were reported in patients with long-standing injuries who were initially managed nonoperatively[13].

Early pancreatic resection is recommended when possible for grade IV pancreatic duct injuries; otherwise, the development of peripancreatic fluid collections requires drainage[14].

In difficult cases, damage control surgery is the best alternative[4,15].

A recent multicenter trial showed that the updated management strategy should include earlier endoscopic evaluation and pancreatic duct stenting. However, a completely transected major pancreatic duct will likely require surgery, which can improve long-term outcomes[16].

Conservative management of pancreatic trauma is often feasible and effective. When surgical management is needed, the options should be resection or a more limited approach. A distal pancreatectomy with splenectomy can be performed safely, but proximal injuries require a stage-specific approach[17].

When possible, primary repair of the pancreatic duct can be attempted[18]. A comparison between blunt and penetrating trauma showed that the latter type of injury is worse[19].

The risk factors determined by regression analysis include other intraabdominal injury, hypovolemia, and penetrating injury[20,21].

The characteristics of pancreatic injuries among trauma patients have been studied in detail[22].

An analysis of immediate, intermediate and long-term outcomes of grade IV injuries showed that resection should be chosen when possible. The majority of patients who undergo drainage procedures

will require additional interventions[12].

In a systematic review and meta-analysis of pancreatic trauma occurring in children, most patients could initially be managed conservatively. In addition, ERCP was found to offer high diagnostic accuracy and to facilitate the repair of ductal injuries[23] in both children and adults[24].

Modern imaging techniques[25] as well as radiological and endoscopic interventions have changed the perception that surgery is mandatory for abdominal solid organ injuries; a more selective surgical strategy is now considered[26,27]. Multidisciplinary collaboration among surgeons, endoscopists, radiologists and intensivists is crucial for managing pancreatic trauma[28]. However, more complex conditions exist in severe hepatopancreatobiliary trauma[29,30].

For isolated grade III pancreatic duct injury, a Roux-en-Y pancreatojejunostomy is feasible[31].

According to the aforementioned, the anatomic location of the pancreas and its close relationship with major vascular structures such as mesenteric vessels, portal vein, and aorta, as well as the duodenum, predisposes for co-existing injuries. Therefore, the severe pancreatic trauma would be combined with major vascular injuries at 28% of the incidence[32]. Penetrating traumas more likely need emergency surgery compared with blunt traumas[33]. It should be emphasized that when pancreatic trauma is accompanied by hemorrhage due to major vascular injury or peritonitis caused by gastrointestinal tract perforation, urgent laparotomy is mandatory, regardless of the grade of pancreatic injury. For the latter, damage control surgery may be sufficient and related with improved outcomes [33], given the recent advancements in imaging modalities that make nonoperative management of pancreatic trauma possible at a later stage[4,5]; otherwise, a more detailed imaging modality is required after the acute phase to identify overlooked pancreatic injury. Thus, modern multidisciplinary management approaches have decreased mortality[34], and the majority of cases can be managed conservatively. ERCP, which determines the anatomical integrity of the main pancreatic duct and the possibility for stent placement, may be used to avoid surgical intervention in most cases[35-37]. Patients with severe traumatic pancreatitis in the subacute phase should be mainly managed nonoperatively[1].

CONCLUSION

Pancreatic trauma is rare, and its management requires an individualized approach. Conservative management is sufficient for the majority of patients with low-grade injuries. In severe cases with pancreatic duct involvement, much controversy over the optimal patient management strategy still exists. Damage control surgery is the best option for such cases and should be used when indicated. Modern radiologic and endoscopic interventions have allowed select patients to avoid reoperation.

FOOTNOTES

Author contributions: Pavlidis TE designed the research, contributed new analytic tools and analyzed the data; Pavlidis ET performed the research and wrote the paper; Psarras K, Symeonidis NG, Geropoulos G analyzed the data and reviewed the data.

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MINIREVIEWS

Clinical application and research progress of extracellular slow wave recording in the gastrointestinal tract

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Abstract

The physiological function of the gastrointestinal (GI) tract is based on the slow wave generated and transmitted by the interstitial cells of Cajal. Extracellular myoelectric recording techniques are often used to record the characteristics and propagation of slow wave and analyze the models of slow wave transmission under physiological and pathological conditions to further explore the mechanism of GI dysfunction. This article reviews the application and research progress of electromyography, bioelectromagnetic technology, and high-resolution mapping in animal and clinical experiments, summarizes the clinical application of GI electrical stimulation therapy, and reviews the electrophysiological research in the biliary system.

Key Words: Gastrointestinal tract; Slow wave; Electromyography; High-resolution mapping; Bioelectromagnetic technology

Core Tip: The motility pattern of the gastrointestinal (GI) tract is fundamental in studying functional GI disorders. Extracellular recording has been used to characterize the generation and propagation of slow waves and abnormalities that may lead to GI motility disorders. This review focuses on the application and progress of extracellular recording techniques in the physiological and pathological state of the alimentary system.

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INTRODUCTION

The gastrointestinal (GI) tract is a complex organ that efficiently processes nutrients and waste. These tasks are facilitated by the phasic contractions resulting from a cyclical depolarization-repolarization cycle, known as electrical slow waves. The slow wave potential of the GI tract is generated by interstitial cells of Cajal (ICCs) distributed in the submucosa and smooth muscle layer of the GI wall and spreads to smooth muscle cells (SMCs), causing excitation-contraction coupling[1]. SMCs and ICCs are also electrically coupled with platelet-derived growth factor receptor alpha-positive (PDGFRα$^+$) cells, forming an integrated unit called the SMC-ICC-PDGFRα$^+$ cells (SIP) syncytium[2,3]. SIP cells provide pacemaker activity, propagation pathways for slow waves, transduction of inputs from motor neurons, and mechanosensitivity[4,5].

Alvarez *et al*[6] and Berkson *et al*[7] first recorded the extracellular slow wave potential of the stomach and small intestine, and proved the consistency between the frequency of slow wave and the rhythm of GI contraction. Over the past century, extracellular electrical recording technology has become one of the most critical methods to characterize the generation and propagation of slow wave and GI motility disorders[8]. The milestone research of GI extracellular slow wave recording is provided in Table 1. The limitation of electromyography (EMG) is the lack of temporal-spatial features of slow wave propagation, which has been proved to be an essential indicator of GI dysfunction[9]. In recent years, research on high-resolution (HR) mapping of GI mucosal slow wave using array matrix electrodes *in vivo* and a bioelectromagnetic technique for recording the magnetic field produced by GI electrical activity, has provided more accurate and reliable support for research on the role of GI dysrhythmia in digestive diseases.

This review explores the application and progress of extracellular recording techniques in the physiological and pathological states of the alimentary system.

GI ELECTROPHYSIOLOGY

In the GI tract, SMCs form gap junctions with two types of interstitial cells, ICCs and PDGFRα$^+$ cells, creating a highly integrated electrical SIP syncytium. Electrical coupling makes it very difficult to deduce the specific functions of one component in intact tissues, so the functions of SIP cells have benefitted from studies of particular cell types[10]. ICCs are organized into networks in the pacemaker regions of the GI tract[11]. Spontaneous electrical activity is generated by ICCs, which are electrically coupled to the SMCs[12,13]. Once a slow wave is generated, it regenerates and propagates actively through the ICC network. Depolarization of SMCs by slow wave enhances the open probability of L-type voltage-dependent calcium (Ca^{2+}) channels, resulting in the generation of Ca^{2+} action potentials, which are superimposed upon the peaks of slow waves. Slow waves are actively propagated in GI muscle tissues, enabling the recruitment of thousands of SMCs to contract together or in sequence to generate segmental and peristaltic contractions. In normal condition, the PDGFRα$^+$ cells network runs parallel or even intercalates with that formed by the ICC network. PDGFRα$^+$ cells express small conductance calcium-activated potassium channel 3 (SK3) channels and P2Y1 receptors[14,15]. These proteins are essential for the purinergic inhibitory regulation of GI motility[5,16,17]. GI motility patterns are highly integrated behaviors requiring coordination between SMCs and utilizing regulatory inputs from interstitial cells (ICCs and PDGFRα$^+$ cells), neurons, and endocrine and immune cells[11,18].

Disorders of gastroduodenal function without an apparent organic cause, defined by the Rome IV criteria, are common, including functional dyspepsia, chronic nausea and vomiting, belching, and rumination disorders[19]. The resultant inefficiencies contribute to vast health and economic burden, considering societal prevalence rates of > 10% for functional dyspepsia and > 2% for chronic nausea and vomiting[20-22]. Diagnosing GI functional disorders remains challenging. Slow waves are omnipresent in GI organs, and motor activity is controlled, in part, by modulation of the frequency, amplitude, and

Table 1 Milestone research of extracellular gastrointestinal slow wave recording

Ref.	Year	Research type	Methods	Part of GI	Major advances
Alvarez *et al*[6]	1922	Rabbits	Monopolar electrode	Small intestine	First record the SW
Alvarez[32]	1922	Human	EGG	Abdominal wall	First electrogastrogram recording
Code and Marlett [89]	1974	Dogs	Multi-electrode	Stomach	First report gastric arrhythmia
Code *et al*[29]	1975	Dogs	Multi-electrode	Stomach and small intestine	Define the MMC
Hinder and Kell [54]	1977	Human	Multi-electrode	Stomach	First locate the gastric pacemaker
Di Luzio *et al*[90]	1989	Human	MGG	Stomach and small intestine	Noninvasively investigate the activity of the GI system
Miranda *et al*[91]	1992	Human	ACB	Stomach	Study stomach emptying model
Bradshaw *et al* [92]	2003	Rabbits	MGG	Stomach	Investigate gastric electrical activity under normal and vagotomized condition
Corá *et al*[76]	2005	Human	ACB	Stomach	Obtain a comprehensive knowledge of the behavior of pharmaceutical forms in the GI tract
Lammers *et al*[93]	2008	Dogs	HR mapping	Stomach	First observe the spatial origin and propagation patterns of SW arrhythmias
Bradshaw *et al* [68]	2009	Human	MGG	Stomach	Obtain spatiotemporal parameters of the gastric SW
Du *et al*[62]	2009	Pigs	HR mapping	Stomach	Design a new sterilized PCB electrode
O'Grady *et al*[66]	2009	Pigs and human	HR mapping	Stomach	Design a novel laparoscopic device for HR mapping
O'Grady *et al*[55]	2010	Human	HR mapping	Stomach	The most comprehensive study of the gastric conduction system
Farajidavar *et al* [52]	2012	Dogs	Multi-wireless modules	Stomach	Design a bidirectional wireless system for SW recording
Calabresi *et al*[72]	2015	Rats	ACB	Stomach	Assess gastric motility
Gharibans *et al* [94]	2017	Electrophysiology model	HR-EGG	Stomach	Address the spatial limitations of the EGG
Gharibans *et al* [95]	2019	Human	HR-EGG	Stomach	Achieve comprehensive spatial analytics of gastric far-field gastric potentials

ACB: Alternate current biosusceptometry; EGG: Electrogastrogram; GI: Gastrointestinal tract; HR: High-resolution; MGG: Magnetogastrogram; MMC: Migrating motor complex; PCB: Printed circuit board; SW: Slow wave.

duration of slow waves[23,24]. ICC loss and injury are now a significant research focus, as it is recognized as a hallmark of several functional GI motility disorders[25]. Hence, coupling between slow waves and contractions is vital in understanding GI motility and developing concepts about what might lead to motility disorders. It requires techniques to record and model the patterns of slow wave generation and propagation.

EMG

Since 1922, when Alvarez *et al*[6] first recorded the slow wave of an experimental animal using bioelectric recording devices, EMG has gradually developed into a technique for recording bioelectric signals produced by nerve-muscle activity, using electrical stimulation to detect nerve and muscle excitation conduction function, and has assisted in the diagnosis and treatment of diseases[26]. In the field of GI electrophysiology, the most commonly used electrodes are monopole electrodes and surface electrodes.

Monopolar electrode

The monopole electrode records the action potential (AP) of the muscle fiber adjacent to the electrode so that the signal of AP amplitude is reliable and prominent[27]. Szurszewski *et al*[28] investigated the

myoelectric activity of the small intestine in conscious healthy dogs by implanting a monopolar electrode in the muscular layer of the small intestine and found that the periodic AP activity spreads slowly from the duodenum to the end of the ileum. This regular electrical activity only occurs during fasting. In follow-up research, Code *et al*[29] divided the periodic GI myoelectric activity, namely, the migrating motor complex (MMC), into four typical stages (I-IV). Phase I is the quiescent phase with no contractions, phase II is characterized by random contractions, phase III has a sudden onset and ends with a burst of contractions with maximal amplitude and duration, and phase IV is characterized by the rapid decrease of contractions. The human GI tract also has regular MMCs, and is regulated by circadian rhythms, hormones, nerves, and other factors[24].

As monopolar electrode implantation is an invasive operation, the main complications are pain, bleeding, infection, and perforation[27,30,31]. Moreover, the reference electrode is routinely placed on the surface of the skin near the tested tissue or organ, so the recorded myoelectric signal has many interferences and poor baseline stability. Therefore, the monopolar electrode is rarely used in the clinical diagnosis and treatment of diseases of the digestive system.

Electrogastrography

Electrogastrography (EGG) is a non-invasive technique for recording GI myoelectric activity using a surface electrode placed on the abdominal wall[32]. Many early studies have shown a good correlation between EGG and EMG, which was recorded with a monopolar electrode[33,34]. Familonie *et al*[35] recorded the surface EGG and intragastric EMG of postoperative patients and healthy subjects, respectively. They found that EGG could not only detect normal slow wave and electrical rhythm but also successfully detected abnormal EGGs in patients with clinical GI symptoms.

EGG is currently regarded as an auxiliary diagnostic examination in the clinic, which is used to evaluate nausea, vomiting, and other GI rhythm disorders, eventually exploring the mechanism of functional GI disease[36,37]. Chen *et al*[38] found that approximately 75% of gastroparesis patients had preprandial or postprandial abnormal signal patterns following EGG examination of healthy subjects and gastroparesis patients. About 60% of patients with functional dyspepsia have an abnormal EGG, including delayed gastric emptying and slow wave reduction[39]. A prospective study that compared the EGG of mechanical, vascular, and paralytic intestinal obstruction, combined with inflammatory indices, indicated that EGG has a high sensitivity in evaluating vascular and paralytic intestinal obstruction, even though its specificity is low. However, the significant correlation between EGG and plasma levels of interleukin-6 and procalcitonin supports the role of inflammation in the pathogenesis of impaired gastric electrical activity in patients with intestinal obstruction[40].

EGG also shows potential in clinical pharmacological research, digestive system development, GI function evaluation, and treatment safety evaluation. A case-control study that studied the EGG changes in patients with esophageal variceal bleeding during treatment with octreotide found that octreotide could inhibit gastric electrical activity and was positively correlated with its hemostatic effect. Therefore, EGG can be used as a predictive index to evaluate the efficacy of octreotide in treating esophageal variceal bleeding[41]. Ortigoza *et al*[42] simultaneously used EGG, abdominal near-infrared spectroscopy, and intestinal tinnitus acoustics to monitor the development of the GI tract in premature infants, evaluate the safety of enteral feeding, and reduce the morbidity and mortality of premature infants.

Because the relative position of the electrode affixed to the body surface is easy to deviate from the stomach, it is difficult for the recording system to obtain stable and repeatable data. The main parameter of EGG analysis is the frequency of slow wave, which cannot fully reflect the function of the GI tract. Therefore, the value of EGG in clinical diagnosis is limited[43].

GI electrical stimulation

The GI myoelectric abnormalities observed in the models of gastroparesis, intractable nausea and vomiting, and intestinal obstruction provide a theoretical basis for the development of GI electrical stimulation (GIES) therapy[38,44]. According to the location of electrical stimulation, GIES can be divided into inhibitory electrical stimulation and excitatory electrical stimulation[45]. Inhibitory electrical stimulation can inhibit the contractile movement of the normal GI tract by placing the electrode near the tail end of the GI tract to send stimulation signals, forcing GI myoelectric activity and movement to reverse propagation[46,47]. Excitatory electrical stimulation, also known as "electrical pacing," promotes GI peristalsis by implanting electrodes into the area near the physiological pacemaker to send electrical stimulation signals[48,49].

Recently, many clinical studies have shown that GIES can improve the physiological function of the GI tract and relieve clinical symptoms by setting different parameters and electrical stimulation sites (Table 2). However, as a treatment modality, GIES is still in the exploratory stage. A meta-analysis based on case-control studies found that GIES had a significant "placebo effect" in the treatment of gastroparesis. Therefore, GIES therapy requires further clinical studies to prove its safety and efficacy and related animal models to explore the pathogenic mechanism[50]. Although GIES is still controversial, it has great potential to improve and treat GI motility disorders[51,52].

Table 2 Clinical research on gastrointestinal electrical stimulation

Ref.	Methods	Sample size	Indications	Location of GIES	Stimulation parameters	Duration	Results
Gastric electrical stimulation							
McCallum *et al*[96]	Multicenter, double-blind, RCT	32	Idiopathic gastroparesis	Stomach	14 Hz, 5 mA, 330 μs	3 mo	Significant decrease in vomiting and days of hospitalization
Teich *et al* [97]	Prospective study	16 (children)	Chronic nausea andvomiting	Stomach	14 Hz, 5 V, 330 μs	0.5-23 mo	Significant improvement in severity and frequency of vomiting, frequency, and severity of nausea
Morales-Conde *et al* [98]	Randomized, multicenter trial	47	Obesity	Stomach	/	24 mo	Limited weight regain with strong safety outcomes
Ducrotte *et al*[99]	RCT	172	Refractory vomiting	Stomach	14 Hz, 5 mA, 330 μs	8 mo	Effectively reduced the frequency of refractory vomiting in patients with and without diabetes, although it did not accelerate gastric emptying or increase the quality of life
Intestinal electrical stimulation							
Norton *et al* [100]	RCT	90	Fecal incontinence	Anus	35 Hz, 300 ms	8 wk	Improved bowel control to a modest extent
Daram *et al* [101]	Case report	1	Roux stasis syndrome	Jejunum	14 Hz, 5 mA, 330 μs	5 d	Effective relief of the symptom of stasis post-Roux-en-Y anastomosis
Cadeddu *et al*[102]	Randomized trial	81	Idiopathic constipation	Anus	2 Hz, 30-35V, 360-960 μs	6 times	Continuous improvement of constipation symptoms and anorectal function
Nerve electrical stimulation							
Fassov *et al* [103]	RCT	20	IBS	Sacral nerve	14 Hz, 0.1-4.0 V, 210 μs	3 wk	Reduced symptoms of diarrhea-predominant and mixed IBS
Stakenborg *et al*[104]	Pilot study	18	Post-colectomy surgery	Abdominal vagus nerve	5, 20 Hz, 2.5 mA, 0.5, 1, 2 ms	2 times (preparation, postoperation)	Inhibition of IL-6 and IL-8 induced by lipopolysaccharide to prevent postoperative intestinal obstruction
Zhang *et al* [105]	Pilot study	42	Major abdominal surgeries	Acupoints ST36 and PC6	25 Hz, 2-10 mA, 0.5 ms	3 d	Improved major postoperative symptoms
Teckentrup *et al*[106]	RCT	22	Healthy subjects	Vagus nerve	25 Hz, 0.3-0.9 mA	2 d	Reduced the frequency of gastric myoelectricity and did not affect resting energy consumption

GIES: Gastrointestinal electrical stimulation; IBS: Irritable bowel syndrome; IL: Interleukin; RCT: Randomized controlled trial.

HR MAPPING

In clinical practice, the myoelectric signal obtained directly from the surface of the GI tract is still the most reliable method for analyzing GI myoelectricity. However, both EMG and EGG are highly dependent on equipment hardware, filtering technology, and the size and material of recording electrodes. They could only obtain low-resolution GI myoelectric recordings, which have limited value for analyzing slow wave propagation mode and speed of the GI tract. By placing multiple arrays of electrodes on the serous surface of the GI tract to record GI myoelectric signals, HR mapping can accurately analyze GI myoelectric signals and electrical rhythm disorders under pathological conditions [53].

Gastric pacing region

Alvarez *et al*[6] first studied the pacing region of the human stomach and proposed the hypothesis that the "pacing region" may be located in the lesser curvature of the gastric cardia. Hinder *et al*[54] roughly located the "gastric pacing region" in the greater curvature of the middle gastric corpus by implanting multiple pairs of monopolar electrodes. Through HR mapping research of the stomach in patients with normal gastric function, O'Grady *et al*[55] found that the slow wave of the stomach originated from a "special region" in the middle and upper part of the great curvature of the stomach, which was consistent with the results of Hinder's work. They also found significant regional spread of slow waves from the pacing area to the distal gastric antrum. However, the pacing region lacked specialized

anatomical tissue or cellular structures and was labile in that if it was to be removed, a neighboring region would become the apparent site of initiation[56].

Gastric conduction system

HR mapping studies in humans and large animal healthy stomach models have shown that slow waves arise from the defined pacemaker region and are quickly propagated in a circular waveform from the pacing area to the antrum[55,57-59]. In the human stomach, the annular slow waves are propagated longitudinally at a velocity of 3 $mm \cdot s^{-1}$ until the distal antrum is continuously moving at a higher velocity (almost > 7 $mm \cdot s^{-1}$) at the greater *vs* lesser curvature and eventually terminate in the pylorus [55]. Interestingly, slow waves do not normally excite the gastric fundus[60].

HR mapping technology has apparent advantages in diagnosing and treating GI motility disorders. In an HR mapping study, O'Grady *et al*[61] found that approximately 50% of experimental pigs with abnormal gastric function had abnormal rhythms, including incomplete and complete conduction block, escape rhythm competing, ectopic pacemakers, and functional re-entry. Subsequently, Du *et al*[62] designed and optimized a flexible printed circuit board that can be sterilized repeatedly, which can be used for HR mapping of the slow wave of the GI tract in an experimental animal model and shows excellent spatiotemporal accuracy, thus providing a low cost and stable alternative for clinical GI myoelectric detection. A recent clinical study comparing EGG and HR mapping showed that gastric slow waves exhibit pacing and conduction abnormalities in patients with gastroparesis, but their frequency is not significantly abnormal, resulting in the missed detection of abnormal gastric myoelectricity on the EGG, indicating that earlier studies likely underestimated both the prevalence and complexity of gastric dysrhythmia[63]. Berry *et al*[64] found that ectopic pacing of the remnant stomach after laparoscopic sleeve gastrectomy is one of the possible mechanisms leading to postoperative chronic gastric dyskinesia. Mapping studies also revealed how anisotropic propagation, re-entry, and conduction block contribute to motility disruption during dysrhythmia[61,63,65]. These works have enabled several novel clinically relevant insights into the features and mechanisms of gastric arrhythmias.

However, due to the limitations of invasive examination, HR mapping is rarely applied in the clinic. A clinical study attempted to detect and analyze the rhythm and propagation pattern of gastric slow wave reliably through trocars in the limited area of the gastric mucosa (limited by the number of trocars, usually less than four) during laparoscopic surgery[66]. Implanting temporary electrodes in the GI mucosa through the endoscope may be the direction of its future development.

BIOELECTROMAGNETIC TECHNOLOGY

Compared with EMG and HR mapping technology, bioelectromagnetic technology has the advantages of non-invasiveness, non-ionizing radiation, and low risk, which provides a new direction for the research of GI tract dynamics. Until now, the bioelectromagnetic techniques used in GI research are mainly based on the alternate current biosusceptometry (ACB) of tracking the movement of magnetic tracers in the GI tract after ingestion and magnetogastrography (MGG) to detect the magnetic field produced by the electrical activity of GI smooth muscle[67,68].

ACB

ACB is a bioelectromagnetic technique that records the changes in the magnetic flux of magnetic tracers ingested *in vivo* with the movement of the GI tract by placing induction coils and reference coils *in vitro*. This technique has the advantages of simplicity, easy operation, and low cost in investigating gastric emptying time and dynamic activity of the GI tract in humans or experimental animals[69]. An animal experiment studying the effect of triple immunosuppressive therapy on GI function found that both ACB and EGG can accurately monitor the contraction frequency and amplitude of the GI tract. Américo *et al*[70] implanted magnetic markers and monopole electrodes under the serosa of the distal stomach and proximal ascending colon in beagle dogs. Compared with EMG, these works proved that ACB could safely and effectively record the contractile activity of GI smooth muscle *in vitro*. The ACB image could visualize intrasegmental tracer distribution and the automated scan of the GI motility segments [71-73]. In two animal experiments, analysis of the relationship between ACB and the strain-gauge signal amplitude showed that ACB may serve as an accurate and sensitive technique for GI motility research[74,75].

In the field of pharmacological research, Corá *et al*[76] obtained a magnetic image of the disintegration of drug tablets in the human stomach using ACB, which shows that the ACB has sufficient sensitivity and spatial resolution in evaluating drug dosage forms *in vivo*. It provides a new research method for comprehensively understanding the metabolic model of drug dosage forms in the human GI tract and developing a new drug delivery system to improve and control the bioavailability and effectiveness of drugs. Another study developed a biomagnetic cellulose gel composed of polymeric nanocapsules containing ferrite nanoparticles, which can be substantially retained in the stomach walls, and consequently has the potential to be used as a traceable drug delivery system for gastric diseases

[77].

However, the measurement of ACB is easily affected by the magnetic tracer, the shape and position of the coils, and the spatial position of the tracer relative to the coils. Bruno *et al*[78] combined ultrasound and ACB to overcome its overdependence on the position and distribution of magnetic tracers in magnetic inductors. Above all, ACB has apparent advantages in recording gastric emptying, which reflects the unique superiority of ACB in GI function evaluation[79].

MGG

MGG is a bioelectromagnetic technique based on a superconducting quantum interferometer to detect the extracellular magnetic field produced by the slow wave of the GI tract, which is highly related to EGG[69]. Several studies have shown that MGG is less affected by the difference in electrical conductivity of the tissue, so it is easier to reflect the physiological characteristics of slow waves in the GI tract[68,69,80]. Based on a study of the effect of erythromycin on gastric motility, Somarajan *et al*[81] compared the differences among MGG, EGG, and EMG, proving that MGG could objectively indicate gastric dysrhythmia and quantify the therapeutic effect in patients with functional gastropathy. In addition, MGG can reliably detect spatial parameters such as propagation velocity and mode of GI slow wave. Recently, Bradshaw *et al*[82] measured EGG and MGG in seven healthy subjects and seven patients with diabetic gastroparesis. The parameters such as dominant frequency, percentage of power distribution, and propagation characteristics were compared. They found that MGG could detect the pathological slow wave of gastroparesis. Above all, MGG shows unique advantages in detecting transmission speed and propagation mode, which provides a new method for studying the pathological myoelectric characteristics of digestive diseases.

ELECTROPHYSIOLOGICAL RESEARCH ON THE GALLBLADDER AND BILIARY TRACT

Early studies on MMC have shown that rhythmic myoelectric activity also exists in the biliary system, which is regulated by many factors such as cholecystokinin, cholinergic receptor agonists, and intestinal peristalsis[83]. Romański *et al*[84] found that the minute rhythm occurs regularly in the entire ovine small intestine and gallbladder, which is controlled by nicotinic receptors and muscarinic receptor subtypes. In benign gallbladder diseases, research on biliary dysfunction, especially smooth muscle in the biliary tract and the sphincter of Oddi, is from animal experiments. Abell *et al*[85] designed an annular electrode to detect Oddi sphincter EMG without damaging the Oddi sphincter wall, which has the advantages of less trauma, convenient placement, accurate location, and high repeatability. In the guinea pig lithogenic model, EMG was used to detect the myoelectric difference in the Oddi sphincter at different stages under a high cholesterol diet, indicating that Oddi sphincter dysfunction caused by a high cholesterol diet may be one of the pathogenic mechanisms of cholesterol gallstones[86]. Liu *et al*[87] also found Oddi sphincter dysfunction in rabbits with chronic cholangitis and proved that the intracellular calcium mobilization pathway was involved in the relaxation of the sphincter under pathological conditions.

To date, there is still little research on gallbladder myoelectricity. It may be because of the weak gallbladder myoelectricity or signal close to the heart or respiration, making it difficult for researchers to obtain stable myoelectric signals. Therefore, the gallbladder myoelectric activity detection method needs to be continuously optimized and improved. Recently, we detected gallbladder EMG in guinea pigs with acute acalculous cholecystitis (AAC) using a bipolar electrode, which showed that the slow wave frequency in the control group was 10.66 ± 0.51 cpm, in the AAC 12 h group was 7.13 ± 0.20 cpm (mean ± standard deviation; $P < 0.001$), in the AAC 24 h group was 6.46 ± 0.16 cpm, and in the AAC 48 h group was 5.75 ± 0.43 cpm (unpublished data). There was no significant difference among the AAC 12 h, AAC 24 h, and AAC 48 h groups. This suggests that inflammation may first affect the function of gallbladder ICCs, then decrease gallbladder slow wave frequency, and eventually lead to a decline in gallbladder function.

With a deeper understanding of the electrophysiology of the biliary system, clinicians have begun to re-examine the necessity of gallbladder function evaluation for benign gallbladder diseases. Currently, the primary methods for evaluating gallbladder function are gallbladder angiography, three-dimensional ultrasonic detection, cholescintigraphy, and Oddi sphincter manometry, which indirectly evaluate gallbladder function through parameters such as gallbladder emptying and biliary pressure [88]. There is still a lack of direct methods to evaluate biliary function in the clinic. The advantages of EMG, bioelectromagnetic technology, and HR mapping in the study of the physiological function of the GI tract provide a new research direction for the evaluation of biliary system function, especially for gallbladder function. We believe that gallbladder EMG is the most concise, reliable, and direct method for evaluating gallbladder function. However, there is still a lack of research on gallbladder EMG under physiological and pathological conditions. Compared with EMG, HR mapping can directly detect the myoelectricity of the gallbladder and provide a spatiotemporal model of the origin and propagation pattern of gallbladder myoelectricity. This will enable a more comprehensive understanding of the origin and spread of myoelectric activity in gallbladder pathophysiology and may provide new

evaluation methods for the diagnosis and treatment of benign gallbladder diseases. Nevertheless, because EMG and HR mapping are invasive examinations, non-invasive low-risk bioelectromagnetic technology may be the best method for clinical gallbladder function evaluation in the future.

CONCLUSION

The rhythmic slow wave in the GI tract is the basis for the realization of the physiological function of the digestive system. EMG detects the GI electrical signals by placing electrodes on the GI serosa or mucosal surface and has been widely used to study the normal physiological rhythm of the GI tract and the mode of dyskinesia under pathological conditions. Because EMG is an invasive technique, which limits its application in clinical diagnosis and treatment, it is mainly used in clinical scientific research and electrical stimulation therapy. Therefore, non-invasive detection technologies such as EGG and bioelectromagnetic technology are gaining more and more attention from scientific researchers and clinical workers. EGG collects GI electrical signals through the surface electrode of the abdominal wall, but it is easily affected by the difference in tissue conductivity. ACB and MGG, which are based on bioelectromagnetic technology, could not only accurately record the frequency and distribution of GI slow wave, but also provide their time-space variation parameters. HR mapping is also an invasive technique for detecting GI myoelectric signals. Unlike EMG, HR mapping uses array electrodes to obtain the myoelectric signal of the GI serosa surface, which can accurately obtain the spatial propagation model. Given the lack of electrophysiological research on the gallbladder, it will be an important research direction in the field of GI electrophysiology in the future.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Cohort Study

Predicting the outcome of closed-loop small bowel obstruction by preoperative characteristics

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Abstract

BACKGROUND

Closed-loop small bowel obstruction (CL-SBO) can threaten the viability of the intestine by obstructing a bowel segment at two adjacent points. Prompt recognition and surgery are crucial.

AIM

To analyze the outcomes of patients who underwent surgery for CL-SBO and to evaluate clinical predictors.

METHODS

Patients who underwent surgery for suspected CL-BSO on computed tomography (CT) at a single center between 2013 and 2019 were evaluated retrospectively. Patients were divided into three groups by perioperative outcome, including viable bowel, reversible ischemia, and irreversible ischemia. Clinical and laboratorial variables at presentation were compared and postoperative outcomes were analyzed.

RESULTS

Of 148 patients with CL-SBO, 28 (19%) had a perioperative viable small bowel, 86 (58%) had reversible ischemia, and 34 (23%) had irreversible ischemia. Patients with a higher age had higher risk for perioperative irreversible ischemia [odds ratio (OR): 1.03, 95% confidence interval (CI): 0.99-1.06]. Patients with American Society of Anaesthesiologists (ASA) classification ≥ 3 had higher risk of perioperative irreversible ischemia compared to lower ASA classifications (OR: 3.76, 95%CI: 1.31-10.81). Eighty-six patients (58%) did not have elevated C-reactive protein (> 10 mg/L), and between-group differences were insignificant. Postoperative in-hospital stay was significantly longer for patients with irre-

versible ischemia (median 8 d, P = 0.001) than for those with reversible ischemia (median 6 d) or a viable bowel (median 5 d). Postoperative morbidity was significantly higher in patients with perioperative irreversible ischemia (45%, P = 0.043) compared with reversible ischemia (20%) and viable bowel (4%).

CONCLUSION

Older patients or those with higher ASA classification had an increased risk of irreversible ischemia in case of CL-SBO. After irreversible ischemia, postoperative morbidity was increased.

Key Words: General surgery; Laparoscopy; Laparotomy; Critical care; Intestinal obstruction; Morbidity

Core Tip: We studied the preoperative characteristics and postoperative outcomes of 148 patients with closed-loop small bowel obstruction, based on the perioperative small bowel viability (viable, reversible ischemia, or irreversible ischemia). Retrospective evaluation found that older age or an American Society of Anesthesiologists classification of 3 or higher increased the risk of perioperative irreversible ischemia. C-reactive protein (CRP) that is not increased above normal levels does not assure the presence of a viable bowel, and 55.83% of patients with ischemia had normal CRP levels. Perioperative irreversible ischemia significantly increased postoperative morbidity. These risks should be mentioned in preoperative consultations.

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INTRODUCTION

Small bowel obstructions (SBOs) are a common cause of (sub)acute abdominal pain in patients presenting to the emergency department, and account for approximately 300000 hospitalizations in the United States annually[1]. Simple SBOs that occur at one site because of a single adhesion may allow conservative treatment without surgery[2-4]. However, in about 10% of SBOs, the intestine is occluded at two separate sites at one anatomic location because of adhesions, internal herniation, or torsion of the small bowel[5-7]. Such closed-loop SBOs (CL-SBOs) present with (sub)acute abdominal pain, vomiting, abdominal distension, and sometimes obstipation[6,8,9].

In cases of CL-SBO, viability of the small bowel is threatened by the possibility of strangulation. Three factors increase the risk of strangulation and indicate emergency surgery, external compression of the vascular pedicle of the closed loop at the obstruction site, distension of the closed loop, and/or volvulus of the closed loop with twisting of its mesentery[5]. If a strangulated small bowel is not surgically released, bowel wall ischemia and necrosis can occur, which increase the risk of septic shock and other complications[10]. Prompt recognition and surgery are crucial to achieve a good patient outcome and to preserve the involved bowel.

To date, most studies have evaluated patients with SBOs by comparing surgical *vs* conservative treatments[2]. Studies for CL-SBOs have mostly focused on aspects of computed tomography (CT) imaging[5,11-13]. The perioperative findings of previous studies vary and there is often a lack information on the postoperative outcomes. The aim of this single-center study was to analyze the perioperative and postoperative outcomes of patients with CT imaging consistent with CL-SBOs, and to evaluate clinical predictors.

MATERIALS AND METHODS

Patients and study design

A series of Dutch patients who underwent surgery for suspected CL-SBOs between September 2013 and September 2019 were included. Potential patients were retrieved from a medical records database that included all abdominal surgeries involving the small bowel. Patients with a preoperative CT scan that diagnosed CL-SBO, defined as an SBO with two contiguous caliber changes at a single anatomic

location, were eligible for inclusion. Patients with bowel obstructions caused by external abdominal herniation (*e.g.*, inguinal or umbilical hernia) or malignancy, or with a history of bariatric surgery or surgery with Roux-and-Y reconstruction were excluded. Patients with Roux-and-Y surgery were excluded because of the difference in clinical presentation with intermittent and subacute pain, and difference in perioperative aetiology, *i.e.* small bowel herniation through an iatrogenic defect created in the mesentery[14,15].

The regional Medical Ethical Testing Committee evaluated the study protocol and declared that the law on medical scientific research concerning humans was not applicable because of the non-invasive and retrospective nature of the study. The scientific board of our hospital approved the study, and the need for written informed consent was waived. However, every patient file was checked for notes of refusal to participate in scientific research. No patients were excluded on that basis.

Patient characteristics

Age, sex, American Society of Anesthesiologists (ASA) classification[16], body mass index and history of abdominal surgery were obtained from medical records. The presence of abdominal pain, vomiting, obstipation (no stool for > 24 h), and abdominal guarding, as well as vital signs, including tachycardia (> 100 beats/min), tachypnoea (> 20 breaths/min), and fever (body temperature > 38.5 °C) had been recorded at the initial evaluation. Blood and laboratory tests at presentation included measures of hematocrit, thrombocyte and white blood cell (WBC) count, C-reactive protein (CRP), creatinine, urea, lactate dehydrogenase, creatine kinase, albumin, and glucose.

Patients were divided into three groups based on the perioperative findings, including viable bowel, reversible bowel wall ischemia, and irreversible bowel wall ischemia. The small bowel was considered viable when the affected region between the two sites of obstruction did not show signs of discoloration before the obstruction was released. Reversible ischemia required that a discolored portion of the small bowel regained normal color within 5 min after surgical release and repositioning of the bowel. If there was no evident return to viable bowel in 5 min, but a clear increase in color did occur, we waited a maximum of 20 min, as previously described[17]. If recoloration did not occur after release of the obstruction, the ischemia was considered irreversible and the affected bowel was resected. The type of surgery (laparoscopy/laparotomy), whether a resection was performed, and type of anastomosis (hand sutured/stapled) was recorded. The intervals between the onset of symptoms and CT imaging and between CT imaging and the start of surgery were recorded in hours of time. Postoperative data collected were length of hospital stay (days) and postoperative complications, which were recorded following the Clavien–Dindo classification[18].

Imaging

For all included patients, CT imaging was performed with or without contrast and including the arterial and/or portal venous phase. The original radiology reports were scored for suspicion of small bowel ischemia because of CL-SBO and graded as no suspicion of ischemia, inconclusive, or strong suspicion of ischemia. Grades were based on suspicion of ischemia in the original radiology report. Imaging features reported in the original radiology report, such as decreased enhancement of mesenterial vessels and the bowel wall and the presence of peritoneal fluid or pneumatosis intestinalis, were taken into account.

Statistical analysis

The statistical analysis was performed with SPSS version 22 (IBM Corp., Armonk, NY, United States). Categorical data were reported as numbers and percentages. Differences between proportions were compared with chi-square or Fisher's exact tests, as appropriate. Continuous data with a significantly skewed distribution were reported as medians and were compared using Kruskal–Wallis test. Univariate analysis was performed to identify whether any clinical characteristics were associated with specific perioperative outcomes. For characteristics with significant between-group differences, odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated trough logistic regression. The significance level was set at $P < 0.05$.

RESULTS

Patients

A series of 148 patients included in a database of 763 patients (19.40%) with abdominal surgery of the small bowel between September 2013 and September 2019 met the inclusion criteria. In total, 28 patients (18.92%) had perioperative viable small bowel, 86 patients (58.11%) had reversible ischemia, and 34 patients (22.97%) had irreversible ischemia and resection. The baseline characteristics are shown in Table 1. Fifty-eight percent of patients (86/148) had previous abdominal surgery. Between-group differences were not significant. The median ages of the groups were significantly different, and the patients with irreversible ischemia were the oldest. Patients with irreversible ischemia were significantly

Table 1 Baseline characteristics of patients in the three study groups

Baseline characteristics	Total, *n* = 148	Viable bowel, *n* = 28	Reversible ischemia, *n* = 86	Irreversible ischemia, *n* = 34	*P* value
Male, *n* (%)	64 (43.24)	13 (46.43)	41 (47.67)	10 (29.41)	0.18
Age in yr, median (range)	68 (15–98)	57 (35–98)	68 (15–93)	76 (23–92)	0.04
ASA classification (%)					0.01
1–2	82 (55.41)	18 (64.29)	53 (61.63)	11 (32.35)	
≥ 3	66 (44.59)	10 (35.71)	33 (38.37)	23 (67.65)	
BMI in kg/m^2, median (range)	24 (16–35)	23 (17–31)	24 (16–35)	23 (18–30)	0.89
Previous abdominal surgery, median (%)	86 (58.11)	19 (67.86)	45 (52.33)	22 (64.71)	0.24

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

more frequently classified as ASA ≥ 3. The ORs of these two characteristics are shown in Table 2.

All 148 patients presenting to the emergency department with CL-SBO had abdominal pain that was accompanied by vomiting in 112 (75.68%) and obstipation in 43 (29.05%). Fifteen patients (10.14%) presented with abdominal guarding and four (2.82%) presented with fever (body temperature > 38.5 ^{o}C); between-group differences were not significant (Table 3). Tachycardia was reported in 26 patients (17.67%) and tachypnoea in 30 of the 75 patients with that information (40.00%). The occurrence of tachycardia and tachypnoea on admission did not differ significantly in the three study groups (Table 3).

Blood and laboratory results

One hundred patients (67.57%) had elevated WBC counts and sixty-six patients (44.90%) had an elevated CRP, but between-group differences were not significant (Table 4). The median values of the other laboratory results (Table 5) were within the normal ranges and no significant between-group differences were observed. Arterial blood gases were analyzed in only 9 patients; hence, no conclusions could be drawn.

CT imaging

The baseline evaluation of the CT scans included no suspicion of ischemia in 18 of the 28 patients (64.29%) with a perioperative viable bowel. The reports for the other 10 patients were inconclusive (Table 6). When ischemia was found during surgery, more than half of the radiology reports had been inconclusive for the suspicion of ischemia (78/148, 52.70%). Strong suspicion of ischemia was reported in only 13.96% of the patients with reversible ischemia (12/86) and 38.24% of patients with irreversible ischemia (13/34).

Timing

Although the interval between the onset of symptoms and surgery was very variable (2–264 h), the differences in the median hours for the three groups were not significant (Table 7).

Surgery

In all 34 patients with irreversible ischemia, the affected bowel was resected. The median length of the resected bowel was 45 (range: 30-100) cm. In 30 patients (88.24%), bowel continuity was restored with either a hand-sutured (53.33%) or stapled (46.67%) anastomosis. In 3 patients (9.00%), a temporary ileostomy was constructed. A laparotomy was performed in 128 of the 148 patients (86.49%). In 5 of the patients with viable bowel (17.86%), the obstruction was relieved laparoscopically. Laparoscopic procedures were performed in 13 patients (15.11%) with reversible ischemia and in 2 (5.88%) with irreversible ischemia.

Postoperative course

The median postoperative hospital stay was 5 (range: 2–13) d for patients with a viable bowel, 6 (range: 2–45) d for those with reversible ischemia, and 8 (range: 3–45) d for those with irreversible ischemia (P = 0.001). Only 32 of 148 patients (21.62%) had postoperative complications (Table 8). Only 1 of those patients was in the viable bowel group. Postoperative morbidity was reported in 44.11% (15/34) of patients with irreversible ischemia and resection, which was significantly higher (P = 0.043) than the frequency in those with reversible ischemia (19.77%, 17/86) and viable bowel (3.57%, 1/28). With reference to the patients with preoperative viable bowel, the ORs for postoperative complications was

Table 2 Logistic regression of predictors of perioperative ischemia

Patient characteristics	Viable bowel, OR (95%CI)	Reversible ischemia, OR (95%CI)	Irreversible ischemia, OR (95%CI)
Age	Ref.	1.01 (0.98-1.03)	1.03 (0.99-1.06)
ASA classification			
1-2	Ref.	Ref.	Ref.
≥ 3	Ref.	1.12 (0.46–2.72)	3.76 (1.31-10.81)

ASA: American Society of Anaesthesiologists; CI: Confidence interval; OR: Odds ratio.

Table 3 Clinical symptoms and vital signs at presentation

Signs at presentation	Overall, *n* = 148	Viable bowel, *n* = 28	Reversible ischemia, *n* = 82	Irreversible ischemia, *n* = 34	*P* value
Vomiting, *n* (%)					0.07
No	36 (24.32)	9 (32.14)	15 (17.44)	12 (35.29)	
Yes	112 (75.68)	19 (67.86)	71 (82.56)	22 (64.71)	
Obstipation[1], *n* (%)					0.60
No	105 (70.95)	22 (78.57)	60 (69.77)	23 (67.65)	
Yes	43 (29.05)	6 (21.43)	26 (30.23)	11 (32.35)	
Abdominal guarding, *n* (%)					0.35
No	133 (89.86)	27 (96.43)	77 (89.53)	29 (85.29)	
Yes	15 (10.14)	1 (3.57)	9 (10.47)	5 (14.71)	
Heart rate[2], *n* (%)					0.42
Bradycardia	2 (1.35)	0 (0.00)	1 (1.16)	1 (2.94)	
Normocardia	120 (81.08)	26 (92.86)	67 (77.91)	27 (79.41)	
Tachycardia	26 (17.67)	2 (7.14)	18 (20.93)	6 (17.65)	
Respiratory rate[3,4], *n* (%)					0.50
Normopnoea	45 (60.00)	9 (69.23)	27 (64.29)	9 (45.00)	
Tachypnea	30 (40.00)	4 (30.77)	15 (35.71)	11 (55.00)	
Fever[5], *n* (%)					0.52
No	138 (97.18)	25 (96.15)	79 (96.34)	34 (100.00)	
Yes	4 (2.82)	1 (3.85)	3 (3.66)	0 (0.00)	

[1]Obstipation: No defecation > 24 h.
[2]Bradycardia: ≤ 50 beats/min; Normocardia: 50-100 beats/min; Tachycardia: > 100 beats/min.
[3]Normopnoea: < 20 breaths/min; Tachypnoea: > 20 breaths/min.
[4]11 patients missing, *n* = 137.
[5]Fever: > 38.5 °C body temperature.

6.65 (95%CI: 0.84-52.47) in patients with reversible ischemia and 19.89 (95%CI: 2.40-164.42) in those with irreversible ischemia.

Severe Clavien–Dindo classification ≥ IIIa complications occurred in 12 patients (14%) with reversible ischemia and in 10 (30%) with irreversible ischemia. Twelve re-exploration procedures were performed during postoperative recovery; one was for an intra-abdominal abscess with ileus in a patient in the viable bowel group. Three patients with reversible ischemia required re-exploration for a suspected perforation, which was not confirmed. Hence, no additional small bowel resection was performed. Two re-exploration procedures resulted in small bowel resection after initial surgery with irreversible ischemia; one was performed because of intra-abdominal bleeding and the other because of an ischemic colostomy that required reversion. In addition, 2 patients developed respiratory insufficiency and 1 patient was septic; no explanation was found during re-exploration.

Table 4 Patient characteristics and findings of perioperative ischemia

Infection parameters at presentation	Overall, *n* = 148	Viable bowel, *n* = 28	Reversible ischemia, *n* = 86	Irreversible ischemia, *n* = 34	*P* value
WBC, median (%)					
4.5-11 × 10^9/L	48 (32.43)	9 (32.14)	31 (36.05)	8 (23.53)	0.42
> 11 × 10^9/L	100 (67.57)	19 (67.86)	55 (63.95)	26 (76.47)	
CRP, median (%)					0.92
1–10 mg/L	82 (55.10)	15 (53.57)	49 (56.47)	18 (52.94)	
11–74 mg/L	38 (25.85)	7 (25.00)	23 (27.06)	8 (23.53)	
> 75 mg/L	28 (19.05)	6 (21.43)	14 (16.47)	8 (23.53)	

CRP: C-reactive protein; WBC: White blood cell.

Table 5 Blood and laboratory results in the three study groups

Laboratory results at presentation	Overall, median (range)	Viable bowel, median (range)	Reversible ischemia, median (range)	Irreversible ischemia, median (range)	*P* value
Haematocrit, L/L	0.43 (0.31-0.59)	0.43 (0.37-0.52)	0.44 (0.34-0.59)	0.42 (0.31-0.53)	0.34
Thrombocytes × 10^9/L	263.00 (145.00-687.00)	280.50 (161.00-687.00)	266.00 (145.00-650.00)	235.50 (148.00-511.00)	0.20
WBCs × 10^9/L	11.80 (4.0-27.2)	12.40 (4.80-21.30)	11.55 (4.00-25.00)	12.00 (5.50-27.20)	0.33
CRP, mg/L	6.00 (1.00-630.00)	6.00 (1.00-216.00)	5.50 (1.00-630.00)	5.00 (1.00-434.00)	0.84
Creatinine, μmol/L	80.00 (38.00-785.00)	81.00 (53.00-141.00)	80.00 (38.00-785.00)	81.00 (45.00-258.00)	0.97
Urea, mmol/L	6.60 (2.30-30.60)	5.95 (2.70-23.10)	6.40 (2.30-30.60)	7.60 (3.00-20.70)	0.33
LDH, U/L	208.00 (109.00-333.00)	184.00 (142.00-309.00)	210.00 (109.00-309.00)	208.00 (151.00-333.00)	0.15
CK, U/L	112.00 (24.00-472.00)	107.50 (30.00-207.00)	127.50 (51.00-472.00)	95.00 (24.00-192.00)	0.47
Albumin, g/L	44.00 (36.00-52.00)	43.00 (36.00-50.00)	44.00 (37.00-52.00)	40.50 (37.00-51.00)	0.10
Glucose, mmol/L	8.00 (5.00-15.60)	7.40 (5.40-12.20)	8.00 (5.00-15.60)	8.20 (5.10-15.00)	0.19

CK: Creatine kinase; CRP: C-reactive protein; LDH: Lactate dehydrogenase; WBC: White blood cell.

Table 6 Suspicion of ischemia on computed tomography imaging in the three study groups

Grading of initial radiology reports	Viable bowel, *n* = 28	Reversible ischemia, *n* = 86	Irreversible ischemia, *n* = 34
No suspicion of ischemia, *n* (%)	18 (64.29)	23 (26.74)	4 (11.76)
Inconclusive, *n* (%)	10 (36.71)	51 (59.30)	17 (50.00)
Strong suspicion of ischemia, *n* (%)	0	12 (13.96)	13 (38.24)

Ten patients (6.76%) died during their hospital stay following surgery, including seven of eight-six with reversible ischemia (8.14%) and three of thirty-four with irreversible ischemia (8.82%). None of the patients with perioperative viable small bowel died after surgery. The causes of death were multiorgan failure because of postoperative systemic inflammatory response syndrome, aspiration, and pneumonia with congestive heart failure.

Table 7 Intervals between onset of symptoms and computed tomography and surgery in the three study groups

Intervals	Viable bowel, *n* = 28	Reversible ischemia, *n* = 86	Irreversible ischemia, *n* = 34	*P* value
Onset of symptoms to CT, median (range)	16.50 h (2.00–120.00 h)	20.50 h (1.00–260.00 h)	18.00 h (2.00–120.00 h)	0.79
CT to surgery, median (range)	4.00 h (1.00–65.00 h)	4.00 h (1.00–51.00 h)	4.00 h (1.00–71.00 h)	0.98
Onset of symptoms to surgery, median (range)	23.00 h (3.00–124.00 h)	26.00 h (2.00–264.00 h)	25.50 h (5.00–126.00 h)	0.91

CT: Computed tomography.

Table 8 Clavien–Dindo classification of complications and perioperative findings

Clavien–Dindo	Overall, *n* = 148	Viable bowel, *n* = 28	Reversible ischaemia, *n* = 86	Irreversible ischaemia, *n* = 34
No complications, *n* (%)	115 (77.70)	27 (96.43)	69 (80.23)	19 (55.88)
Grade I, *n* (%)	3 (2.03)	0 (0.00)	2 (2.33)	1 (2.94)
Grade II, *n* (%)	7 (4.73)	0 (0.00)	3 (3.49)	4 (11.76)
Grade III, *n* (%)				
a	1 (0.68)	0 (0.00)	1 (1.16)	0 (0.00)
b	10 (6.76)	1 (3.57)	3 (3.49)	6 (17.65)
Grade IV, *n* (%)				
a	1 (0.68)	0 (0.00)	1 (1.16)	0 (0.00)
b	1 (0.68)	0 (0.00)	0 (0.00)	1 (2.94)
Grade V, *n* (%)	10 (6.76)	0 (0.00)	7 (8.14)	3 (8.82)

Grade I: Complication without pharmacological, surgical, endoscopic, or radiologic treatment (anti-emetics, antipyretics, analgesics, diuretics, electrolytes and physiotherapy were acceptable); Grade II: Complication requiring pharmacological management including blood transfusion or total parenteral nutrition; Grade IIIa: Complication requiring intervention under local anaesthesia; Grade IIIb: Complication requiring general or epidural anaesthesia; Grade IVa: Single organ dysfunction (including dialysis); Grade IVb: Multiorgan dysfunction; Grade V: Patient death.

DISCUSSION

CL-SBO is a serious clinical diagnosis that can be fatal if left untreated or undiagnosed. Despite the significance of the condition, diagnosis remains a challenge. In this study, a large cohort of patients with surgery for CL-BSO was retrospectively analyzed. Most patients in our cohort presented with abdominal pain that was accompanied with vomiting in 76% of cases, consistent with the 66% to 81% of cases in other studies[19,20]. We believe that obstipation does not often accompany CL-SBO because colon movements usually continue during an obstruction of the small bowel and because CL-SBO is considered a (sub)acute entity. In this cohort, 29% of the patients reported obstipation, as did 22% of the patients in another study[20]. Possibly the definition of obstipation, *i.e.* no stool for > 24 h, was not sufficiently specific, as not all patients have bowel movements every 24 h, and a change in their bowel movement pattern was not noted. With regard to patient characteristics, 42% had no history of abdominal surgery, which is noteworthy and more than reported in previous studies that included smaller cohorts[2,21]. Even in patients without a history of abdominal surgery presenting with abdominal pain and vomiting without fever, a CT should be performed to rule out CL-BSO.

Patients with CL-SBO and irreversible ischemia were significantly older and had higher ASA classifications than those in the other study groups. Older patients also had an increased risk of 3% *per* year for perioperative irreversible ischemia. Patients with an ASA classification of > 3 had an increased risk (OR of 3.76) of perioperative irreversible ischemia. Other studies have not reported a correlation between age or ASA classification and intraoperative outcome in CL-SBO patients[11,12]. To the best of our knowledge, this is the first study to report an association of comorbidities and ASA classification in patients with surgery for CL-BSO. The finding is very important for guiding the surgical approach and expectations of treatment for such high-risk patients.

Some studies reported that a WBC count of > 10×10^9 cells/L was predictive of perioperative bowel ischemia[2,19]. In our CL-BSO series, the WBC count was increased in most patients and was highest in patients with irreversible ischemia (77%), but the differences in WBC count were not significant. Another study reported a WBC count of > 10×10^9 and a CRP concentration of > 75 mg/L as two out of

six variables indicating the need for surgery with resection for ischemia. The reported sensitivity was 67.7% and the specificity was 90.8%[11]. CRP is an acute-phase reactant and considered a predictor of vascular compromise and bacterial translocation severity[22]. Contrary to a study by Schwenter *et al* [11], only 43% of the patients in our cohort with reversible ischemia and 48% with irreversible ischemia had an elevated CRP. That might have been a result of the short interval between the onset of symptoms and presentation. However, the results in our large patient cohort indicate that a CRP concentration within the normal range does not ensure the absence of ischemia in patients who present with signs of CL-SBO.

CT imaging is reported to have high interobserver agreement for the diagnosis of CL-SBO. However, small bowel ischemia can be much more difficult to predict, and has poor-to-moderate interobserver agreement[23,24]. Radiologists have a significant role in recognizing signs that require immediate surgical exploration. In studies of small cohorts, increased unenhanced bowel wall attenuation was reported to be predictive of (irreversible) ischemia[12,13,25,26].

When the need for surgery is determined, the choice between a laparotomy or laparoscopic procedure is made by the surgeon. In most of the literature on CL-SBOs, the type of surgical procedure is not discussed[2,19,21]. Most comparisons have found that recovery and in-hospital stays are longer after a laparotomy than after laparoscopic surgery and with less postoperative morbidity after laparoscopic surgeries[27]. Therefore, the type of surgical approach was taken into account in our dataset. Laparoscopic procedures comprised only 13% (20/148) of the procedures performed in this study. The percentage of laparoscopic procedures was the highest in patients with a perioperative viable bowel (17%, 5/28). This type of abdominal surgery will be performed more and more frequently by specialized gastrointestinal surgeons in the acute setting, which may lead to more laparoscopic procedures, with better postoperative morbidity and shorter in-hospital stay.

During surgery, 120 patients (81%) were found to have ischemia, which was reversible in 86 (58%). Although resection was not necessary in that group, 30-d morbidity was 20% and mortality was 8%. After surgery for irreversible ischemia, morbidity increased to 45% and mortality was 9%, consistent with the 39% and 9% rates reported in other study populations[5,21]. High morbidity and mortality in patients with CL-SBO and ischemia show that we have to pay close attention to patients who present with CL-SBO that requires emergent surgery. In this cohort, 2 of 86 patients (2.33%) with perioperative reversible ischemia required re-exploration and additional small bowel resection, suggestive of more advanced ischemia than initially expected. We have to pay close postoperative attention to patients with reversible ischemia.

Although surgery *vs* conservative treatment of complicated SBOs has been widely studied, to the best of our knowledge this is the first study to compare patients with absent, reversible, and irreversible ischemia, and the largest patient cohort to include only CL-SBO cases. We assessed patient characteristics, clinical presentation, blood values, and initial radiology reports as predictors of ischemia. Postoperative outcomes were taken into account. This relatively large cohort of 148 patients in a single center was analyzed retrospectively, with a focus on the clinical characteristics and blood results that were able to predict perioperative ischemia and postoperative outcomes.

CONCLUSION

In conclusion, a diagnosis of CL-SBO should not be ignored in patients with no history of abdominal symptoms. In patients with CL-SBO, older age and an ASA classification ≥ 3 were predictive of irreversible ischemia, and urgent surgery is indicated. Patients should be informed of the relatively high chance of morbidity, longer in-hospital stay, and mortality after resection. Lastly, a CRP concentration within the normal range in patients with suspected CL-SBO does not ensure that ischemia is not present.

ARTICLE HIGHLIGHTS

Research background

Closed-loop small bowel obstruction (CL-SBO) can threaten the viability of the intestine by obstruction of a bowel segment at two adjacent points. Prompt recognition of CL-SBO, followed by surgery, is crucial. Clinical predictors of perioperative ischemia and postoperative outcome have not been previously analyzed in a cohort as large as this one.

Research motivation

To date, most studies have evaluated patients with SBOs by comparing surgical *vs* conservative treatments. Studies for CL-SBOs have mostly focused on aspects of computed tomography imaging. The perioperative findings of previous studies vary and there is often a lack information on the postoperative outcomes.

Research objectives

The aim of this study was to analyze perioperative characteristics and postoperative outcomes of patients with surgery for CL-SBO and to evaluate clinical predictors.

Research methods

The medical records of a cohort of 148 patients who underwent surgery for CL-SBO were analyzed retrospectively. Univariate analysis was performed to identify clinical characteristics that were associated with specific perioperative outcomes. The odds ratios for those that were significantly associated with outcomes were analyzed by logistic regression.

Research results

Of 148 patients with CL-SBO, 28 (19%) had a perioperative viable small bowel, 86 (58%) had reversible ischemia and 34 (23%) had irreversible ischemia. Median age and American Society of Anesthesiologists (ASA) classification were significantly higher in patients with irreversible ischemia (P = 0.042 and 0.008, respectively). Postoperative morbidity was significantly higher in patients with perioperative irreversible ischemia (45%, P = 0.043) than in those with reversible ischemia (20%) and a viable bowel (4%).

Research conclusions

Older patients and those with an ASA classification ≥ 3 had an increased risk of irreversible ischemia. C-reactive protein within the normal range did not ensure the absence of ischemia. After irreversible ischemia, postoperative morbidity was increased.

Research perspectives

The study results are relevant to preoperative informed consent procedures in patients with CL-SBO. Close attention should be paid to patients with perioperative ischemia for the prompt detection of postoperative complications.

FOOTNOTES

Author contributions: Toneman MK, de Kok BM, Zijta FM, Oei S, van Acker GJD, Westerterp M and van der Pool AEM designed the report; Toneman MK collected the patient's clinical data, analyzed the data and wrote the paper; de Kok BM, Zijta FM, Oie S, van Acker GJD, Westerterp M and van der Pool AEM revised the paper for important intellectual content; van der Pool AE supervised the report.

Institutional review board statement: The Institutional Review Board of Haaglanden Medical center provided approval for this study, No. 2018-105.

Informed consent statement: The scientific board of our hospital approved the study. Because the law on medical scientific research concerning humans was not applicable due of the non-invasive and retrospective nature of the study, the need for written informed consent was waived. However, it was required that every patient file was checked for notes of refusal to participate in scientific research.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Transjugular intrahepatic portosystemic shunt with radioactive seed strand for main portal vein tumor thrombosis with cirrhotic portal hypertension

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Abstract

BACKGROUND

Patients with hepatocellular carcinoma complicated with main portal vein tumor thrombosis (mPVTT) and cirrhotic portal hypertension (CPH) have an extremely poor prognosis, and there is a lack of a clinically effective treatment paradigm.

AIM

To evaluate the efficacy and safety of transjugular intrahepatic portosystemic shunt (TIPS) combined with radioactive seed strand for the treatment of mPVTT patients with CPH.

METHODS

The clinical data of 83 consecutive patients who underwent TIPS combined with ^{125}I seed strand placement for mPVTT and CPH from January 2015 to December 2018 were retrospectively reviewed. Procedure-related data (success rate, relief of portal vein pressure and CPH symptoms, and adverse events), PVTT response, and patient survival were assessed through a 2-year follow-up.

RESULTS

The success rate was 100.0% without perioperative death or procedure-related severe adverse events. The mean portal vein pressure was significantly decreased after the procedure (22.25 ± 7.33 mmHg *vs* 35.12 ± 7.94 mmHg, t = 20.61, P < 0.001). The symptoms of CPH were all effectively relieved within 1 mo. The objective response rate of PVTT was 67.5%. During a mean follow-up of 14.5 ± 9.4 mo (range 1-37 mo), the cumulative survival rates at 6, 12 and 24 mo were 83.1%, 49.7%, and 21.8%, respectively. The median survival time was 12.0 ± 1.3 mo (95% confidence interval: 9.5-14.5). In multivariate Cox regression analysis, body mass index, Child-Pugh grade, cTNM stage, and PVTT response were independent prognostic factors (P < 0.05).

CONCLUSION

TIPS combined with radioactive seed strand might be effective and safe in treating mPVTT patients with CPH.

Key Words: Transjugular intrahepatic portosystemic shunt; Radioactive seed strand; Portal vein tumor thrombosis; Hepatocellular carcinoma; Cirrhotic portal hypertension; Cirrhosis

Core Tip: We adequately evaluated whether transjugular intrahepatic portosystemic shunt combined with radioactive seed strand placement was safe in adverse events and effective in portal vein tumor thrombosis response and prolonging survival time for the treatment of patients with main portal vein tumor thrombosis and cirrhotic portal hypertension through a retrospective cohort study with 2 years of follow-up.

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INTRODUCTION

Portal vein tumor thrombosis (PVTT) is common in patients with hepatocellular carcinoma (HCC), with an incidence of 44.0%-62.2%[1]. Main PVTT (mPVTT) is defined as PVTT invading the main trunk of the portal vein, accounting for approximately 19.5%-35.2% of PVTT[2-4]. The prognosis of patients with PVTT is poor and the median overall survival is only 2.7-4.0 mo without treatment[5].

HCC is mostly based on cirrhosis, and is usually complicated with cirrhotic portal hypertension (CPH). The decompensated stage of CPH is often accompanied by high-mortality events, *e.g.*, esophagogastric variceal bleeding (EGVB) and refractory ascites/hydrothorax. EGVB is associated with a mortality of 10%-20% at 6 wk[6], and refractory ascites is associated with a reduction in the survival rate to 50% at 6 mo[7]. Once PVTT is combined with cirrhosis-related decompensated events, it would worsen the disease and accelerate the death of patients.

The treatment strategies for PVTT include palliative surgical resection, transarterial chemoembolization (TACE), external radiotherapy, chemotherapy, and targeted therapy[2,8,9], but these treatments are usually infeasible and unsatisfactory in patients with decompensated CPH. Transjugular intrahepatic portosystemic shunt (TIPS) is an effective treatment for CPH[10,11] and eliminates pylemphraxis with the covered stent, but the stent has no substantial therapeutic effect on mPVTT and results in PVTT progression and stent stenosis.

In recent years, the application of radioactive seed placement, such as the low-energy radionuclide ^{125}I [12-14], has attracted attention and achieved promising efficacy when combined with portal vein stents. Radioactive seed strand placement is one method of endovascular brachytherapy. The purpose of this study was to retrospectively analyze the clinical efficacy of TIPS combined with radioactive seed strand placement for mPVTT patients with CPH from January 2015 to December 2018.

MATERIALS AND METHODS

Participants

The study was approved by the Ethics Committee and Institutional Review Board of Peking University Ninth School of Clinical Medicine. A consecutive cohort of 83 patients with HCC who underwent TIPS combined with ^{125}I seed strand placement for mPVTT and CPH from January 2015 to December 2018 was retrospectively reviewed. Patients with incomplete clinical data or loss to follow-up were excluded from the analysis. Among 81 patients, 70 (84.3%) were males and 13 (15.7%) were females, aged 35-79 years (mean 56.46 years). There were 62 (74.7%) cases of EGVB, 14 (16.9%) cases of refractory ascites/hydrothorax, and 7 (8.4%) cases of both. Child–Pugh grading included 23 (27.7%) cases with grade A, 52 (62.7%) cases with grade B, and 8 (9.6%) cases with grade C. According to cTNM staging, 55 (66.3%) cases were stage IIIB, 19 (22.9%) cases were stage IVA, and 9 (10.8%) cases were stage IVB. The baseline characteristics of the patients are presented in Table 1.

Study design

Procedure-related data [success rate, relief of portal vein pressure (PVP) and CPH symptoms, and adverse events], mPVTT response, and patient survival were assessed through a 2-year follow-up. The success rate was defined by the planned stent and seed successfully placed. PVTT response was determined according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST)[15] by experienced radiologists: (1) Complete response (CR) was defined as disappearance of PVTT; (2) Partial response (PR) was a ≥ 30% reduction of the PVTT lesion compared with baseline; (3) Progressive disease (PD) was defined as ≥ 20% enlargement of the PVTT lesion than baseline; (4) Stable disease (SD) referred to the PVTT lesion that did not reach the standard of PR and PD. The objective response rate (ORR) of PVTT was the sum of CR and PR. Patient survival was defined as the period from the day of operation to patient death from any cause or to the last follow-up time point.

Adverse events were classified as shunt-related adverse events and radiation-related adverse events. Shunt-related adverse events consisted of post-TIPS hepatic encephalopathy (HE), the recurrence of CPH, shunt stenosis, and shunt-induced potential distant metastasis. The recurrence of CPH was determined as recurrent EGVB or hepatic ascites/hydrothorax, which principally resulted from shunt or intra-stent stenosis. Shunt stenosis was indicated by the recurrence of CPH events and confirmed by imaging [*e.g.*, enhanced computed tomography (CT) or portal venography]. Shunt-induced potential distant metastasis was defined as new-onset hematogenous metastasis after shunt opening of TIPS, which was diagnosed by systemic imaging or pathology. Radiation-related adverse events included radiation injury and seed strand or ^{125}I seed translocation.

TIPS combined with transcatheter radioactive seed strand placement

All patients were fully evaluated before the procedure: (1) The severity of esophagogastric varices (EGV) was graded by gastroscopy; (2) The degree of ascites was graded by ultrasound examination[16]; (3) Child-Pugh was used for evaluation of liver function; (4) Tumors were staged according to both the international Barcelona Clinic Liver Cancer (BCLC) staging system[17] and cTNM staging system[18]; and (5) intrahepatic tumor size was determined as the sum of the longest viable tumor diameters of typical intrahepatic target lesions according to mRECIST[15], measured by experienced radiologists.

The indications for the procedure were as follows: (1) mPVTT secondary to HCC, as confirmed by percutaneous biopsy or enhanced CT/magnetic resonance imaging /positron emission tomography imaging; (2) Intrahepatic CPH confirmed by imaging examinations and hepatic venous pressure gradient (HVPG) measurement; (3) Failure of prior conservative treatment for cirrhosis-related decompensated events such as EGVB or refractory ascites/hydrothorax; and (4) Life expectancy > 2 mo. The contraindications were any one of the following: (1) Uncomplicated prehepatic portal hypertension; (2) Severe cardiac, cerebral, respiratory, renal insufficiency or other systemic malignancy; (3) Rapid progression in hepatic insufficiency; (4) Intrahepatic tumor hampering the procedure; (5) Allergy to contrast agent; and (6) Pregnancy or lactation. The operation was performed by interventional physicians with more than 15 years of experience. The benefits and potential risks of the procedure were explained thoroughly to all patients and their families, and then, written informed consent was signed.

During the procedure, the right internal jugular vein was punctured routinely under local anesthesia. After intubation to the inferior vena cava and hepatic vein, HVPG was measured, and then RUPS-100 (Cook Inc., United States) was inserted. According to preoperative imaging and angiography, the appropriate position and angle were determined to puncture the intrahepatic portal vein from the hepatic vein or inferior vena cava of the hepatic segment. After successful puncture, an angiographic

Table 1 Baseline characteristics of patients

Characteristics	*n* (%)/mean ± SD/M (P_{25}-P_{75})
Gender (male/female)	70/13 (84.3/15.7)
Age (yr)	56.46 ± 8.97
BMI	22.83 ± 2.99
Etiology of cirrhosis (HBV/HCV/alcoholic/other)	66/8/4/5 (79.5/9.6/4.8/6.0)
Cirrhosis-related decompensated events (EGVB/Refractory ascites or hydrothorax/Both)	62/14/7 (74.7/16.9/8.4)
EGV degree (mild/moderate/severe)	7/36/40 (8.4/43.4/48.2)
Ascites degree (no/mild/moderate-severe)	8/24/51 (9.6/28.9/61.4)
Preoperative HVPG (mmHg)	19.96 ± 9.01
Child–Pugh grade (A/B/C)	23/52/8 (27.7/62.7/9.6)
Intrahepatic HCC morphology (unifocal/multifocal)	47/36 (56.6/43.4)
Sum of longest viable tumor diameters (cm)	6.62 ± 2.77
≤ 5/5-8/> 8	23/44/16 (27.7/53.0/19.3)
BCLC stage (C/D)	75/8 (90.4/9.6)
cTNM stage (IIIB/IVA/IVB)	55/19/9 (66.3/22.9/10.8)
PLT (10^9/L)	108.24 ± 86.09
PT (s)	14.89 ± 3.89
ALT (U/L)	31.40 ± 29.29
AST (U/L)	49.63 ± 45.00
TBil (μmol/L)	31.74 ± 17.68
Albumin (g/L)	35.08 ± 4.85
AFP (ng/mL)[1]	769.49 (16.69-2345.11)
Log_{10}(AFP)	2.40 ± 1.26
Combined TACE/RFA/targeted therapy	83/52/41 (100/62.7/49.4)

[1]Skewness distribution. The upper limit of AFP detection is 20000 ng/mL. BMI: Body mass index; HBV: Hepatitis B virus; HCV: Hepatitis C virus; EGVB: Esophagogastric variceal bleeding; EGV: Esophagogastric varices; HVPG: Hepatic venous pressure gradient; HCC: Hepatocellular carcinoma; PLT: Platelet; PT: Prothrombin time; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; TBil: Total bilirubin; AFP: Alpha-fetoprotein; TACE: Transarterial chemoembolization; RFA: Radiofrequency ablation.

catheter was inserted for portal venography, and the puncture set was placed into the intrahepatic portal vein.

Before shunting, PVP was measured, and then PVTT was grabbed and aspirated as much as possible. Two ultrasmooth guidewires were inserted through the outer sheath of RUPS-100, one of which was retained in the splenic vein, and the other introduced a 4-5F single-bend or cobra catheter that was selected to the distal end of branch PVTT. Then, a 6F guiding catheter was replaced, and a radioactive seed strand was implanted *via* the guiding catheter. Next, a 6-8 mm balloon was introduced through the outer sheath to dilate the shunt, and then a 7-8 mm Fluency covered stent (Bard Inc., United States) was placed. According to the extent of mPVTT, a distal 10-12 mm covered stent was placed for the entire coverage of mPVTT.

The radioactive seed (Isotope & Radiation Corp., China) was fully loaded into a 4F catheter in vitro, creating the radioactive seed strand (Figure 1). Then, the radioactive seed strand was placed outside the stents *via* a 6F guiding catheter (by the guidewire retained in the splenic vein). The radioactive seed strand was compressed and fixed to the portal vein by the stents. The length of the radioactive seed strand was usually more than 10 mm at both ends of the PVTT. Finally, PVP after shunting was measured, and portal venography was performed again (Figure 2).

Treatment for HCC

TACE was used for intrahepatic tumors and PVTT lesions every 1-3 mo by using an embolic agent (lipiodol 3-30 mL) and chemotherapy drugs (epirubicin 10-20 mg and hydroxycamptothecine 5-15 mg).

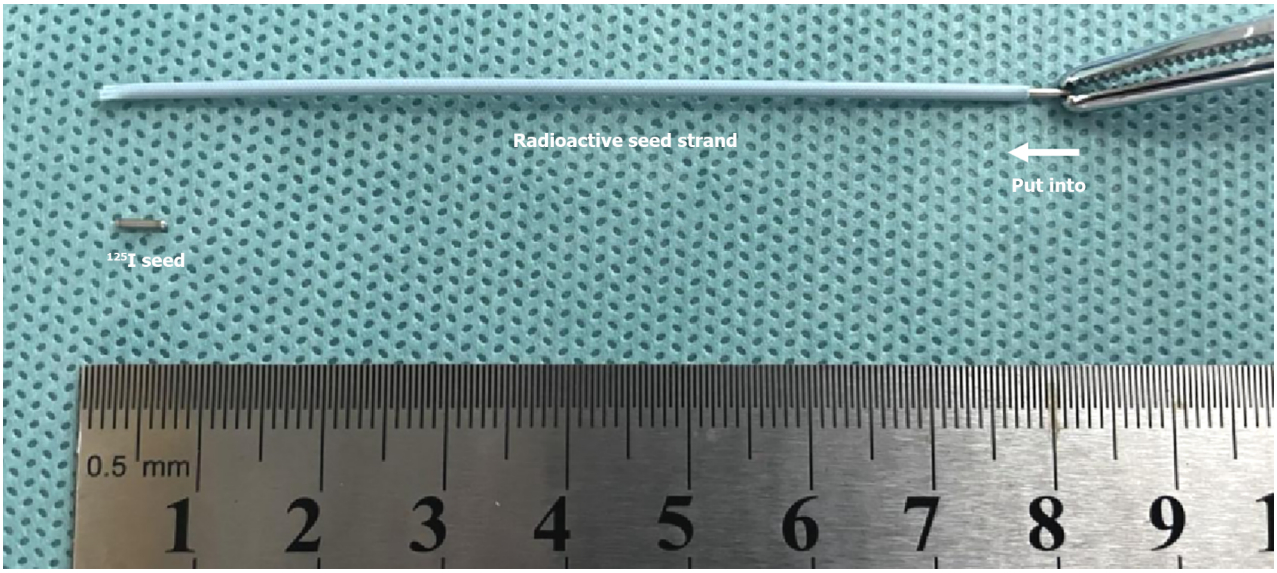

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Figure 1 Assembly of a radioactive seed strand *in vitro*.

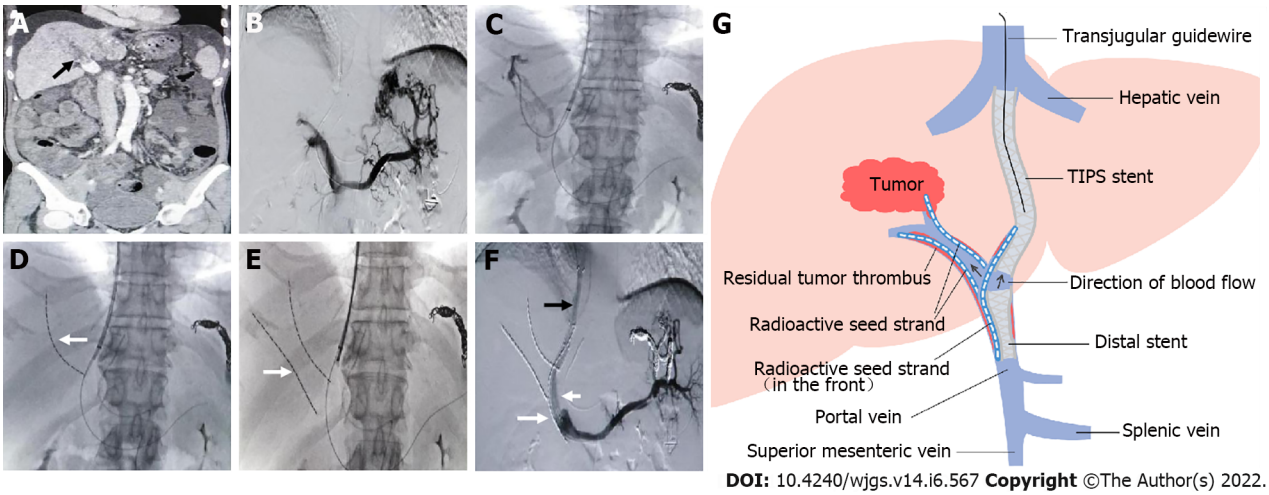

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Figure 2 Representative case. A: Filling defect in the main portal vein (black arrow), suggesting main portal vein tumor thrombosis; B: Most of the intrahepatic branches did not develop under contrast, and several short gastric veins were obviously varicose; C and D: A guidewire was retained in the splenic vein, a catheter was directed into the secondary branch of the right portal vein, and then a radioactive seed strand (white arrow) was implanted; E: Another radioactive seed strand (white arrow) was implanted into another secondary branch of the right portal vein; F: A shunt of transjugular intrahepatic portosystemic shunt (black arrow) was established, a distal stent (short white arrow) was placed, and then a radioactive seed strand (long white arrow) was implanted. Portal venography showed unobstructed blood flow in the shunt and obvious reduction in the varicose veins; G: Schematic diagram. TIPS: Transjugular intrahepatic portosystemic shunt.

TACE was performed in all patients (ranging from 1-12 times per patient and an average of 4.2 times).

Radiofrequency ablation (RFA) was also carried out for intrahepatic tumors in patients with good coagulation function and platelet count and the inability to sequentially undergo TACE due to arterial occlusion after repeated arterial intervention. The RFA equipment was WHK-IB, Beijing Welfare Electronics Co., China. 52 of 83 patients underwent RFA (ranging from 1-3 times per patient and an average of 1.6 times).

According to patients' specific conditions and wishes, 41 patients received targeted therapy such as sorafenib or lenvatinib.

Follow-up

All patients were followed up by telephone at a 4-6-wk interval postoperatively until death or their last follow-up. At 3, 6, 12, and 24 mo after the operation, patients were required to undergo a hospital revisit to assess PVTT response and adverse events. Sequential TACE or RFA was performed on the intrahepatic primary lesions. In addition, positive and timely management was given for adverse events such as post-TIPS HE, shunt stenosis, and recurrence of CPH.

Statistical analysis

Continuous variables conforming to a normal distribution are presented as the mean ± SD and median (interquartile range) [M (P_{25}-P_{75})] for those with a nonnormal distribution. Categorical variables are presented as percentages (%). The mean values of two related samples were compared by using the paired samples *t* test. In survival analysis, the Kaplan-Meier curve was performed for description, the log-rank test was utilized for comparison, and Cox regression was carried out for correlated factor analysis. Variables satisfying the proportional hazards assumption were included in the multivariate analysis using Cox regression. $P < 0.05$ was considered a statistically significant difference. IBM SPSS software version 26.0 was used for statistical analysis.

RESULTS

Procedure-related data

The success rate of the procedure was 100.0% (83/83), without perioperative death or procedure-related serious adverse events. The number of implanted seeds ranged from 29 to 95, with an average of 47 per patient. The mean PVP was significantly decreased after the procedure (22.25 ± 7.33 mmHg *vs* 35.12 ± 7.94 mmHg, $t = 20.61$, $P < 0.001$). The symptoms of CPH, including EGVB and/or refractory ascites/hydrothorax, were all effectively relieved within 1 mo.

The mean follow-up period was 14.5 ± 9.4 mo (range 1-37 mo). HE developed in a total of 16 patients (19.3%) after the procedure, most of whom had mild HE in clinical stages 1-2. The cumulative recurrence rates of CPH at 6, 12, and 24 mo were 9.6% (8/83), 22.9% (19/83), and 33.7% (28/83), respectively. The cumulative rates of shunt stenosis at 6, 12, and 24 mo were 13.3% (11/83), 28.9% (24/83), and 38.6% (32/83), respectively (Table 2). During follow-up, no seed strand shift or ^{125}I seed fall-off and translocation occurred, and no radiation injury (such as radiation-induced liver disease or gastrointestinal ulceration) was observed.

PVTT response

Four patients failed to be assessed on account of death within 2 mo. The ORR of PVTT was 67.5% (Table 3). Among patients who presented PD, all 6 cases related to PVTT exceeded the distal portal system, *e.g.*, the mesenteric vein or splenic vein.

Patient survival

The Kaplan-Meier survival curve is shown in Figure 3. The median survival time was 12.0 ± 1.3 mo [95% confidence interval (CI): 9.5-14.5]. The cumulative survival rates at 6, 12, and 24 mo were 83.1%, 49.7%, and 21.8%, respectively.

In the stratification analysis using the survival curves and log-rank test, patients with age < 60, Child-Pugh grade A or B, BCLC stage C, cTNM stage IIIB or IVA, and PVTT response had significant survival benefits ($P < 0.05$) in the comparison of their respective groups (Figure 4 and Table 4). Notably, cTNM staging showed a more detailed stratification capability than BCLC staging.

In Cox regression analysis, the relevant parameters including body mass index (BMI), Child-Pugh grade, cTNM stage, and PVTT response, were independent prognostic factors as indicated in the multivariate Cox regression model (Table 5).

DISCUSSION

With the development of multidisciplinary teamwork, HCC complicated with PVTT has attracted increasing interest and research. Owing to the biological characteristics of HCC and anatomical features of the liver, HCC cells tend to invade the intrahepatic vasculature, especially the portal venous system [19]. In the past few years, the application of ^{125}I seeds[12-14] has provided a new therapy for advanced HCC. In our study, the ORR of PVTT reached 67.5% after ^{125}I seed strand placement. In multivariate survival analysis, PVTT response had a significant effect on patient survival, which could reduce the risk of death [hazard ratio (HR) = 0.472]. Additionally, no radiation injury was observed during postoperative follow-up. In short, radioactive seed strand placement may be an effective approach for the local treatment of PVTT.

It is a biological effect of ionizing radiation that ^{125}I relies on by continuously releasing low-energy γ rays to kill tumor cells and then achieve the purpose of treatment. With a half-value layer of only 17 mm in equivalent tissue, ^{125}I rarely involves adjacent tissues or organs. Thus, radioactive seed strand placement has the advantages of a high local dose to the tumor thrombus and less damage to normal tissues.

In addition, radioactive seed strands also have the following advantages: first, the length of the seed strand can be determined according to the length of the tumor thrombus, and the seeds in the catheter are arranged neatly; second, the seed strand implanted in the portal vein branch does not shift, nor does

Table 2 Summary of long-term efficacy and safety

Items	6 mo	12 mo	24 mo
Cumulative survival rate (%)	83.1	49.7	21.8
Cumulative rate of shunt stenosis (%)	13.3	28.9	38.6
Cumulative recurrence rate of CPH (%)	9.6	22.9	33.7

CPH: Cirrhotic portal hypertension.

Table 3 Summary of portal vein tumor thrombosis response in short-term efficacy

PVTT response	CR	PR	SD	PD	Response (ORR)
Number (%)	15 (18.1)	41 (49.4)	17 (20.5)	6 (7.2)	56 (67.5)

PVTT: Portal vein tumor thrombosis; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease; ORR: Objective response rate.

Table 4 Summary of survival comparison of different stratification factors

Stratification indicator	Log-rank χ^2	*P* value
Gender	0.448	0.503
Age group	5.311	0.021
EGV degree	0.448	0.600
Ascites degree	1.308	0.520
Child-Pugh grade	15.810	< 0.001
Intrahepatic HCC morphology	0.174	0.677
Group of tumor diameters	1.685	0.431
BCLC stage	10.883	< 0.001
cTNM stage	51.774	< 0.001
Combined with RFA	0.275	0.600
Combined with targeted therapy	0.001	0.978
PVTT response	22.617	< 0.001
Post-TIPS HE	0.255	0.613
Shunt stenosis	0.027	0.868
Recurrence of CPH	0.235	0.628

EGV: Esophagogastric varices; HCC: Hepatocellular carcinoma; BCLC: Barcelona Clinic Liver Cancer; RFA: Radiofrequency ablation; PVTT: Portal vein tumor thrombosis; TIPS: Transjugular intrahepatic portosystemic shunt; HE: Hepatic encephalopathy; CPH: Cirrhotic portal hypertension.

the seed strand that is fixed in the main portal vein by stents; and finally, radioactive seed have antitumor and anti-intimal hyperplasia effects, which can prevent stent stenosis. However, as a drawback of this approach, when the diameter of the tumor thrombus is large, the effective radiation dose may not be achieved.

In clinical practice, the management of HCC patients with PVTT often neglects the effective diagnosis and treatment of CPH. PVTT patients complicated with CPH usually have an extremely poor prognosis. TIPS is an established treatment for CPH and its decompensated events by establishing a shunt between the intrahepatic portal vein and the hepatic vein or inferior vena cava. In our study, PVP was significantly reduced, and the symptoms of CPH were efficaciously relieved in mPVTT patients with CPH after combined TIPS. Moreover, survival analysis showed that the severity of EGV and the degree of ascites had no significant impact on survival, which indirectly indicated the therapeutic effect of TIPS on decompensated CPH.

Table 5 Correlative factors for survival in univariate and multivariate analyses

Variable	Univariate analysis			Multivariate analysis		
	HR	95%CI	*P* value	HR	95%CI	*P* value
Gender (female/male)	1.237	0.650-2.355	0.518			
Age (years)	1.039	1.011-1.068	0.006			
BMI	0.781	0.701-0.871	< 0.001	0.861	0.768-0.965	0.010
EGV degree (mild/moderate/severe)	1.130	0.796-1.605	0.493			
Ascites degree (no/mild/moderate-severe)	1.055	0.760-1.464	0.748			
Preoperative HVPG (mmHg)	1.006	0.979-1.034	0.668			
Child-Pugh grade			< 0.001			
A/B	1.856	1.068-3.225	0.028	2.243	1.270-3.961	0.005
A/C	4.999	2.099-11.907	< 0.001	7.308	2.898-18.425	< 0.001
Intrahepatic HCC morphology (unifocal/multifocal)	0.909	0.570-1.447	0.687			
Sum of longest viable tumor diameters (cm)	1.070	0.988-1.158	0.097			
BCLC stage (C/D)	3.216	1.509-6.851	0.002			
cTNM stage (IIIB/IVA/IVB)	3.269	2.228-4.795	< 0.001	2.745	1.726-4.366	< 0.001
PLT (10^9/L)	1.000	0.997-1.003	0.917			
PT (s)	1.006	0.959-1.056	0.802			
ALT (U/L)	1.004	0.994-1.013	0.465			
AST (U/L)	1.003	0.998-1.008	0.173			
TBil (μmol/L)	1.022	1.008-1.035	0.001			
Albumin (g/L)	0.929	0.886-0.974	0.002			
Log_{10}(AFP) (ng/mL)	1.341	1.097-1.639	0.004			
Combined RFA (no/yes)	0.885	0.552-1.419	0.612			
Combined targeted therapy (no/yes)	0.994	0.627-1.574	0.978			
Reduction of PVP (mmHg)	1.025	0.983-1.069	0.247			
PVTT response (nonresponse/response)	0.302	0.176-0.516	< 0.001	0.472	0.259-0.859	0.014
Post-TIPS HE (no/yes)	0.864	0.482-1.551	0.625			
Shunt stenosis (no/yes)	1.039	0.650-1.662	0.873			
Recurrence of CPH (no/yes)	1.122	0.694-1.814	0.639			

BMI: Body mass index; EGV: Esophagogastric varices; HVPG: Hepatic venous pressure gradient; HCC: Hepatocellular carcinoma; PLT: Platelet; PT: Prothrombin time; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; TBil: Total bilirubin; AFP: Alpha-fetoprotein; RFA: Radiofrequency ablation; PVP: Portal vein pressure; PVTT: Portal vein tumor thrombosis; TIPS: Transjugular intrahepatic portosystemic shunt; HE: Hepatic encephalopathy; CPH: Cirrhotic portal hypertension.

In addition, TIPS still has the following effects: first, it can improve liver functional reserve by improving portal blood supply to normal liver tissue and then prevent fatal liver failure caused by PVTT and provide favorable conditions for the subsequent treatment of intrahepatic primary lesions; next, the covered stent of TIPS plays a part in covering and compressing PVTT; and last, TIPS is able to resolve portal hypertension not only caused by cirrhosis but also due to the combination of intrahepatic cirrhosis and prehepatic PVTT[20,21].

TIPS combined with radioactive seed strand placement and sequential TACE/RFA for mPVTT with CPH may reduce the mortality risk from decompensated events of CPH (*i.e.*, nonneoplastic mortality risk) as well as reduce neoplastic mortality risk by controlling PVTT and primary lesions, prolonging survival. In our study, the median survival time of patients was 12.0 ± 1.3 mo (95%CI: 9.5-14.5), and the cumulative survival rates at 6, 12 and 24 mo were 83.1%, 49.7% and 21.8%, respectively. In a systematic

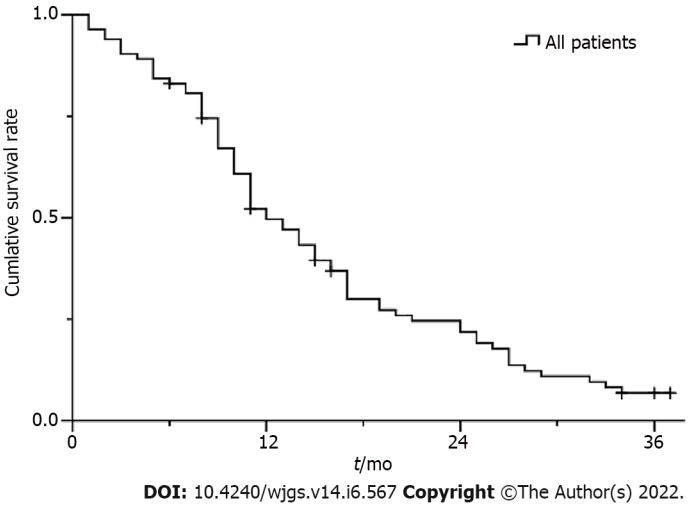

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Figure 3 Kaplan-Meier survival curve for all patients.

review[13] of 6 retrospective studies involving mPVTT patients whose CPH was unclear, after percutaneous transhepatic ^{125}I seed strand with stent placement combined with TACE, the median survival time was 10.3 mo (range 4.9-12.5 mo), and the cumulative survival rates at 6, 12 and 24 mo were 74.5% (range 61.8%-88.9%), 48.7% (range 32.4%-54.5%) and 20.1% (range 14.1%-26.1%), respectively. Huo *et al*[22] reported that in mPVTT patients partly mixed with CPH, the 2-year cumulative survival rate after palliative resection was 17.1%. Our results were similar to theirs. Despite similar survival results, it is necessary to differentiate and treat CPH in the management of PVTT or mPVTT patients.

In regard to postoperative long-term complications, our results showed that the cumulative rates of shunt stenosis at 6, 12 and 24 mo were 13.3%, 28.9% and 38.6%, respectively. Luo *et al*[23] and Yu *et al*[24] reported that after ^{125}I seed strand with stent placement combined with TACE, the cumulative stent patency rates were 43.2% and 46.5% at 12 mo and 26.1% and 25.7% at 24 mo, respectively. Our results were clearly superior to theirs, which might be related to the following reasons: TIPS dredging the blood flow of the portal vein, full use of covered stents, and our postoperative anticoagulation treatment.

Furthermore, by survival analysis, shunt-related adverse events, including post-TIPS HE, shunt stenosis and recurrence of CPH, had no significant influence on survival, which might be related to the timely management of these complications, such as removal of HE inducements, balloon dilatation and/or stent reimplantation for shunt stenosis.

Regarding shunt-induced potential distant metastasis, 5 new cases of pulmonary metastasis and 1 new case of adrenal metastasis were observed. This small number of cases observed might be related to the censoring of death and the nonadherence of patients to the revisit and systematic examination. Further study is needed to expand the sample. However, it cannot be ignored that distant metastasis may be reduced to some extent by PVTT grab and aspiration before shunting, the entire coverage of mPVTT using covered stents, the PVTT response obtained by radioactive seed strand, and active intervention for intrahepatic lesions.

Among other factors that affected survival, cTNM staging showed a more detailed stratification capability than BCLC staging and showed an independent significant association with survival, with an increased risk of death for each increase in cTNM stage (HR = 2.745). Child-Pugh grade was an important factor affecting survival throughout, and the mortality risk in patients with grade C (HR = 7.308) and grade B (HR = 2.243) was much higher than those with grade A. Combining the Child-Pugh liver function grade and the cTNM tumor stage may be of great significance for the assessment of prognosis and survival.

Concerning other tumor-related factors, intrahepatic HCC morphology had no significant effect on survival, and the sum of longest viable tumor diameters approached significance, which might be related to active interventional treatment for intrahepatic primary lesions. Combined RFA was not significant, which might be related to RFA as an additional therapy after TACE for intrahepatic lesions. Combined targeted therapy was also not significant, and some high-quality studies[25,26] showed that targeted therapy did not achieve satisfactory outcomes in the treatment of HCC with PVTT.

BMI exerted a significant influence on survival (HR = 0.861). Patients with advanced HCC and decompensated cirrhosis often present malnutrition, so attention should be given to improving nutrition.

In addition, radioembolizaton was not used in combination therapy because it was not approved during the time of the study, but it could be considered for treatment in the future.

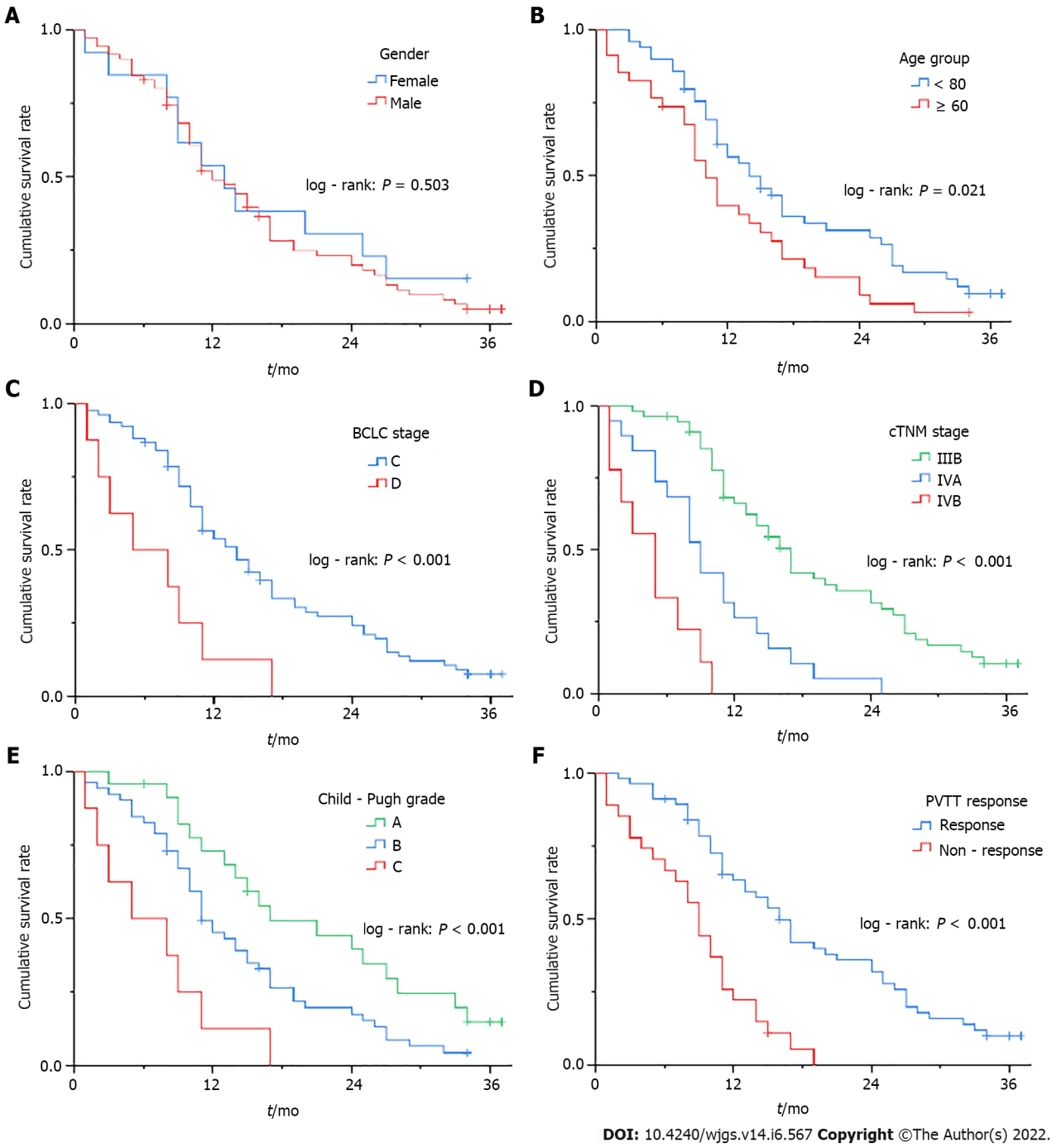

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Figure 4 Kaplan-Meier survival curve for different stratification factors. A: Gender group; B: Age group; C: Barcelona Clinic Liver Cancer stage; D: cTNM stage; E: Child-Pugh grade; F: Portal vein tumor thrombosis response). BCLC: Barcelona Clinic Liver Cancer; PVTT: Portal vein tumor thrombosis.

This single-arm retrospective cohort study has inherent limitations. Further relevant studies are warranted to follow and expand on the findings.

CONCLUSION

In conclusion, the key points of this initial study may be summarized as follows: (1) TIPS combined with radioactive seed strand placement might be effective and safe in treating mPVTT with CPH, which could effectively alleviate symptoms of portal hypertension and prolong patient survival time; (2) In the management of PVTT or mPVTT patients, it is necessary to differentiate and effectively treat CPH; (3) Combining Child-Pugh liver function grade and cTNM tumor stage may be of guiding significance for the assessment of prognosis and survival.

ARTICLE HIGHLIGHTS

Research background

Main portal vein tumor thrombosis (mPVTT) is common in patients with hepatocellular carcinoma (HCC). Mostly based on cirrhosis, HCC is usually complicated with cirrhotic portal hypertension (CPH), which is often accompanied by high-mortality decompensated events such as esophagogastric variceal bleeding and refractory ascites/hydrothorax.

Research motivation

HCC patients with PVTT have a poor prognosis with median survival of only 2.7-4.0 mo. Once mPVTT is combined with cirrhotic decompensated events, it would deteriorate the disease and accelerate the death of patients. However, there is a lack of a clinical treatment paradigm for mPVTT patients with CPH.

Research objectives

This cohort study is to evaluate the efficacy and safety of transjugular intrahepatic portosystemic shunt (TIPS) combined with radioactive seed strand for the treatment of mPVTT complicated with CPH. It might contribute new perspectives into clinical treatment management.

Research methods

The clinical data of 83 consecutive patients who underwent TIPS combined with ^{125}I seed strand placement for mPVTT and CPH from January 2015 to December 2018 were retrospectively reviewed, and the efficacy and safety were adequately evaluated by a 2-year follow-up.

Research results

There was universal improvement in CPH and apparent relief of its decompensated complications after operation. The majority of patients had at least a decrease in the extent of PVTT and the objective response rate of PVTT was 67.5%. The cumulative rate of shunt stenosis and recurrence rate of CPH were low within the first year. The median survival time was 12.0 ± 1.3 mo (95% confidence interval: 9.5-14.5).

Research conclusions

TIPS combined with radioactive seed strand might be effective and safe in the treatment of mPVTT with CPH, which could effectively alleviate symptoms of portal hypertension and prolong patient survival time.

Research perspectives

In the management of HCC patients with PVTT or mPVTT, it is necessary to differentiate and effectively treat CPH. The treatment of mPVTT with CPH is still a clinical difficulty and requires multidisciplinary teamwork. Future studies may require randomized controlled trials to verify our results.

FOOTNOTES

Author contributions: Liu FQ designed the research; Yue ZD, Zhao HW, Wang L, Fan ZH, Wu YF, Meng MM, Zhang K, Jiang L, Ding HG, Zhang YN and Yang YP performed the research; Yan XH analyzed the data and wrote the paper; Liu FQ reviewed and edited the manuscript; all authors read and approved the manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Prognostic significance of the preoperative hemoglobin to albumin ratio for the short-term survival of gastric cancer patients

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Abstract

BACKGROUND

Hemoglobin and albumin are associated with the prognosis of gastric cancer (GC) patients. However, the prognostic value of the hemoglobin to albumin ratio (HAR) for the short-term survival of GC patients with D2 radical resection has not been studied.

AIM

To investigate the significance of the HAR in evaluating the short-term survival of GC patients after D2 radical resection and to construct a nomogram to predict the prognosis in GC patients after surgery, thus providing a reference for the development of postoperative individualized treatment and follow-up plans.

METHODS

Cox regression and Kaplan-Meier analysis was used for prognostic analysis. Logistic regression was used to analyze the relationships between HAR and the clinicopathological characteristics of the GC patients. A prognostic nomogram model for the short-term survival of GC patients was constructed by R software.

RESULTS

HAR was an independent risk factor for the short-term survival of GC patients. GC patients with a low HAR had a poor prognosis ($P < 0.001$). Low HAR was markedly related to high stage [odds ratio (OR) = 0.45 for II *vs* I; OR = 0.48 for III *vs* I], T classification (OR = 0.52 for T4 *vs* T1) and large tumor size (OR = 0.51 for ≥ 4 cm *vs* < 4 cm) (all $P < 0.05$). The nomogram model was based on HAR, age, CA19-9, CA125 and stage, and the C-index was 0.820.

CONCLUSION

Preoperative low HAR was associated with short-term survival in GC patients. The prognostic nomogram model can accurately predict the short-term survival of

GC patients with D2 radical resection.

Key Words: Gastric cancer; Hemoglobin to albumin ratio; Short-term survival; Prognosis; Nomogram

Core Tip: Hemoglobin and albumin are associated with the prognosis of gastric cancer (GC) patients. However, the prognostic value of the hemoglobin to albumin ratio (HAR) for the short-term survival of GC patients with D2 radical resection has not been studied. HAR was an independent risk factor for the short-term survival of GC patients. GC patients with a low HAR had a poor prognosis. Low HAR was markedly related to high stage, T classification and tumor size. The nomogram model was based on HAR, age, CA19-9, CA125 and stage and can accurately predict the short-term survival of D2 radical resection GC patients.

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INTRODUCTION

For resectable gastric cancer (GC), radical surgery and adjuvant therapy are the standard therapies[1,2]. Postoperative prognosis is evaluated by the American Joint Committee on Cancer TNM classification system[3,4]. However, prognostic factors such as age, tumor size and tumor location are not considered in the prediction of individual survival. Moreover, the prognosis of patients in the same stage with similar treatment regimens varies greatly[5,6]. Therefore, it is necessary to develop a comprehensive and accurate prognostic evaluation system to predict the prognosis of GC patients, which is of great significance in selecting individualized treatment plans for these patients.

In addition, studies have shown that the prognosis of cancer is not only correlated with tumor characteristics but also to the nutritional status and systemic inflammation of patients[7,8]. The systemic inflammatory response can affect the progression and metastasis of tumors[9]. Recently, studies also found that malnutrition is associated with decreased immunity, which increases the incidence of complications and mortality postoperatively, leading to poor postoperative prognosis in cancer patients [10,11].

Hemoglobin and albumin are used as the two most common indicators of nutritional status. Various perioperative nutritional parameters have been confirmed as independent prognostic factors in GC patients who underwent D2 radical resection[12]. Low hemoglobin levels can lead to tumor hypoxia, which can accelerate tumor growth and promote the angiogenesis of tumor cells[13]. Low serum albumin concentration was an independent risk factor affecting the survival of GC patients[14]. In addition, low serum albumin levels can impair cellular immune function, leading to poor prognosis in cancer patients[15]. Studies have demonstrated that preoperative low serum albumin and hemoglobin levels are closely associated with the poor prognosis of malignant tumors[16,17]; the high preoperative C-reactive protein to albumin ratio was related to poor outcome in patients with GC[18,19].

However, the clinical value of the hemoglobin to albumin ratio (HAR) in the prognosis of GC patients with D2 radical resection has not been reported. Nomogram can provide the overall probability of specific outcomes for individual patients and provide more accurate predictions than the traditional TNM staging system, thereby improving personalized treatment decisions[20,21]. Therefore, the aim of this study was to investigate the significance of the HAR in evaluating the short-term survival of GC patients after D2 radical resection and to construct a nomogram to predict the prognosis in GC patients after surgery, thus providing a reference for the development of postoperative individualized treatment and follow-up plans.

MATERIALS AND METHODS

Patient characteristics

The clinical and follow-up data of 312 GC patients who underwent D2 radical resection in our hospital were collected from January 2017 to January 2019. Tumor markers, serum albumin and fibrinogen levels and blood cell counts, including hemoglobin, neutrophils, platelets and lymphocytes, were extracted at

the first admission. The HAR, platelet to hemoglobin ratio, platelet to lymphocyte ratio (PLR), platelet to albumin ratio (PAR), fibrinogen to lymphocyte ratio (FLR), albumin to fibrinogen ratio, hemoglobin to fibrinogen ratio (HFR), platelet to fibrinogen ratio, neutrophil to lymphocyte ratio (NLR) and albumin to lymphocyte ratio were calculated. According to the median HAR value, GC patients were divided into a high HAR group and a low HAR group. The stage of postoperative patients was based on the American Joint Committee on Cancer TNM classification system. Survival time was calculated from the day of surgery to the last follow-up. After surgery, all patients were followed up every 3 mo for the first 2 years and then every 6 mo until 5 years. The last follow-up date was March 1, 2020.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) Patients with GC were diagnosed by pathology after surgery; and (2) Neoadjuvant chemoradiotherapy was not performed before surgery. The exclusion criteria were as follows: (1) Patients with a history of surgery 2 mo before admission; (2) Patients with a history of blood transfusion; (3) Patients using hemostatic and anticoagulant drugs; (4) Patients with bleeding, thrombotic disease or splenectomy; and (5) Patients with pregnancy, chronic disease, acute infection, relapse or other distant organ metastases and those who were lost to follow-up or had incomplete information.

Statistical analysis

Prognostic analysis was performed using Kaplan-Meier and Cox regression analyses. The Mann-Whitney *U* test was used for comparisons between two groups. The relationships between HAR and clinicopathological characteristics were determined by logistic regression. The receiver operating characteristic curve was used to evaluate the ability of a single factor or combined factors to predict the short-term survival of GC patients. The RMS package of R software was used to construct a prognostic nomogram model for the short-term survival of GC patients, and the scores of various indicators were obtained. In addition, Harrell's concordance index (C-index) was calculated to evaluate the performance of the model's prediction results[22]. A *P* value less than 0.05 was considered to indicate a statistically significant result. Analyses were performed by SPSS 22.0 for Windows (SPSS Inc., Chicago, IL, United States) and R (version x64 3.6.1).

RESULTS

Prognostic analysis of GC patients with D2 radical resection

The factors associated with prognosis were as follows: age, CEA, CA19-9, CA125, HAR, platelet to hemoglobin ratio, PLR, PAR, FLR, HFR, tumor size, vascular infiltration, nerve infiltration and stage (all $P < 0.05$). Multivariate Cox regression analysis found that age, HAR and stage were independent risk factors affecting prognosis (all $P < 0.05$) (Table 1). Kaplan-Meier analysis found that the difference in the survival time of GC patients with a low HAR and high HAR was statistically significant ($P = 0.003$), indicating that GC patients with low HAR had a poor prognosis (Figure 1).

Association between HAR and clinicopathological characteristics

To analyze the association between HAR and clinicopathological characteristics, we performed logistic regression analysis. HAR was associated with stage, T classification and large tumor size (all $P < 0.05$) (Figure 2). Logistic regression analysis showed that a low HAR was effectively related to high stage [odds ratio (OR) = 0.45 for II *vs* I; OR = 0.48 for III *vs* I], T classification (OR = 0.52 for T4 *vs* T1) and large tumor size (OR = 0.51 for ≥ 4 cm *vs* < 4 cm) (all $P < 0.05$) in GC patients (Table 2). These results indicate that GC patients with a low HAR were more likely to have advanced GC.

Comparison between the low HAR group and the high HAR group

To further analyze the relationships between HAR and prognostic factors, we divided the GC patients into a low HAR group and a high HAR group according to the median HAR value. The factors with statistically significant differences between the two groups were sex, CA125, platelet to hemoglobin ratio, PLR, PAR, FLR, HFR, platelet to fibrinogen ratio, NLR, albumin to lymphocyte ratio, large tumor size, stage and T classification (all $P < 0.05$), suggesting that patients with a low HAR had high stage, T classification, CA125, FLR, PAR, PLR, large tumor sizes and low HFR (Table 3 and Figure 3).

Receiver operating characteristic curve analysis

To evaluate the ability of HAR or combined factors to predict the short-term survival of GC patients, we performed receiver operating characteristic curve analysis. The area under the curve (AUC) of HAR alone in predicting the 1-year survival of GC patients was 0.656, the sensitivity was 78.19%, and the specificity was 52.94%, while the AUC of predicting the 2.5-year survival was 0.804, the sensitivity was 85.29%, and the specificity was 74.95%. The AUC of HAR combined with age, CA19-9, CA125 and stage to predict the 1-year survival of GC patients was 0.833, the sensitivity was 86.83%, and the specificity

Table 1 Prognostic analysis of clinical characteristics in patients with gastric cancer

Clinical variable	*n*	Univariate analysis		Multivariate analysis	
	312	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Age (yr)	62 (54-68)	1.046 (1.015-1.077)	0.003	1.049(1.017-1.081)	0.002
Sex (male/female)	225/87	0.715 (0.400-1.280)	0.259		
BMI (kg/m^2)	21.55 (19.53-23.55)	0.983 (0.911-1.062)	0.670		
Smoking (yes/no)	64/248	0.442 (0.189-1.034)	0.060		
Drinking (yes/no)	49/263	1.316 (0.641-2.701)	0.454		
CEA (ng/mL)	2.94 (1.85-5.29)	1.006 (1.003-1.009)	0.000		
CA19-9 (U/mL)	13.26 (7.36-23.70)	1.001 (1.000-1.002)	0.003		
CA125 (U/mL)	8.50 (5.90-13.80)	1.008 (1.000-1.016)	0.049		
CA72-4 (IU/mL)	1.81 (1.17-4.46)	1.004 (0.990-1.018)	0.57		
HAR	3.18 (2.68-3.44)	0.425 (0.278-0.650)	0.000	0.466 (0.301-0.720)	0.001
PHR	1.86 (1.40-2.58)	1.371 (1.194-1.575)	0.000		
PLR	157.74 (114.06-211.23)	1.003 (1.001-1.006)	0.004		
PAR	5.75 (4.51-7.48)	1.184 (1.088-1.288)	0.000		
FLR	2.05 (1.49-2.89)	1.171 (1.018-1.347)	0.028		
AFR	13.16 (10.36-16.85)	0.970 (0.912-1.033)	0.344		
HFR	42.52 ± 17.83	0.974 (0.955-0.993)	0.007		
PFR	77.41 (57.84-101.46)	1.005 (0.998-1.012)	0.135		
NLR	2.47 (1.76-3.59)	1.100 (0.974-1.242)	0.124		
ALR	26.25 (22.16-35.08)	1.008 (0.986-1.030)	0.489		
Tumor size (cm)	4.0 (2.5-5.5)	1.167 (1.079-1.262)	0.000		
Vascular infiltration (present/absent)	168/144	3.230 (1.695-6.153)	0.000		
Nerve infiltration (present/absent)	149/163	2.974 (1.651-5.359)	0.000		
Histological grade (G1/G2/G3)	6/120/186	0.920 (0.553-1.530)	0.748		
Stage (I/II/III)	88/75/149	4.154 (2.291-7.531)	0.000	4.112 (2.225-7.602)	0.000
Survival status (death/survival)	53/259				
Follow-up time (d)	531 (440-691)				

BMI: Body mass index; PHR: Platelet to hemoglobin ratio; PLR: Platelet to lymphocyte ratio; PAR: Platelet to albumin ratio; FLR: Fibrinogen to lymphocyte ratio; AFR: Albumin to fibrinogen ratio; HFR: Hemoglobin to fibrinogen ratio; PFR: Platelet to fibrinogen ratio; NLR: Neutrophil to lymphocyte ratio; ALR: Albumin to lymphocyte ratio. HR: Hazard ratio; CI: Confidence interval; HAR: Hemoglobin to albumin ratio.

was 84.77%, while the AUC of predicting the 2.5-year survival was 0.832, the sensitivity was 87.87%, and the specificity was 72.18% (Figure 4). These results indicate that HAR combined with prognostic factors can accurately predict the short-term survival of patients with GC.

Construction of the prognostic nomogram

To predict the short-term survival probability of GC patients after surgery, we used the rms package to construct a logistic regression model of HAR combined with age, CA19-9, CA125 and stage, and the C-index evaluated by this model was 0.820, indicating that this prediction model had certain accuracy. Then, the plotting function was employed, and the nomogram was plotted (Figure 5). A score of HAR ≥ 3.18 was 0 points, while a score of HAR < 3.18 was 37 points. A score of age ≥ 62 years was 13 points, while a score of age < 62 years was 0 points. A score of CA19-9 ≥ 13.255 U/mL was 26 points, while a score of CA19-9 < 13.255 U/mL was 0 points. A score of CA125 ≥ 8.5 U/mL was 18 points, while a score of CA125 < 8.5 U/mL was 0 points. A score of stage I was 0 points, a score of stage II was 63 points, and a score of stage III was 100 points. The highest score was 194 points, indicating that the 1-year survival

Table 2 Hemoglobin to albumin ratio value associated with clinical pathological characteristics

Clinical characteristics	Total (*n*)	Odds ratio in HAR value	*P* value
Age (≥ 62 yr *vs* < 62 yr)	312	0.78 (0.50-1.21)	0.264
Size (≥ 4 cm *vs* < 4 cm)	312	0.51 (0.32-0.80)	0.004
Histological grade			
(G2 *vs* G1)	126	0.91 (0.16-5.06)	0.905
(G3 *vs* G1)	192	1.00 (0.18-5.52)	1.000
Vascular infiltration (yes *vs* no)	312	1.14 (0.73-1.79)	0.552
Nerve infiltration (yes *vs* no)	312	1.00 (0.64-1.56)	0.988
Stage			
(II *vs* I)	163	0.45 (0.24-0.83)	0.012
(III *vs* I)	237	0.48 (0.28-0.81)	0.007
T classification			
(T2 *vs* T1)	106	0.61 (0.27-1.39)	0.243
(T3 *vs* T1)	112	0.62 (0.28-1.35)	0.227
(T4 *vs* T1)	236	0.52 (0.29-0.91)	0.022
N classification			
(N1 *vs* N0)	169	0.76 (0.33-1.74)	0.518
(N2 *vs* N0)	201	0.56 (0.30-1.04)	0.067
(N3 *vs* N0)	226	0.68 (0.39-1.16)	0.160

HAR: Hemoglobin to albumin ratio.

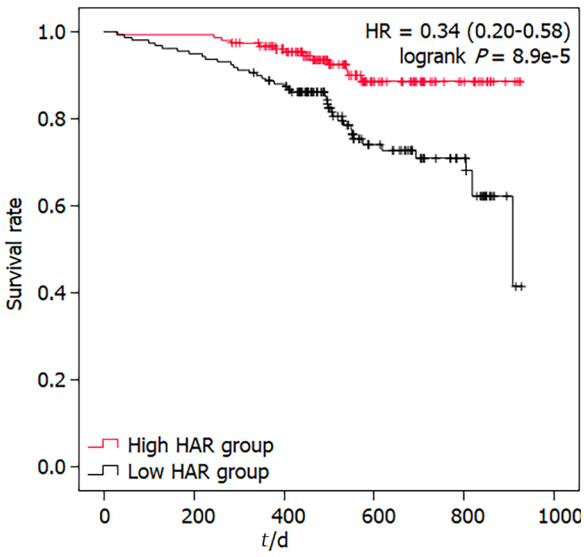

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Figure 1 Survival curve of gastric cancer patients with low hemoglobin to albumin ratio and high hemoglobin to albumin ratio. HAR: Hemoglobin to albumin ratio; HR: Hazard ratio.

probability of GC patients was 60%-65% and that the 5-year survival probability was < 10%. According to the total points, the probability of the short-term survival of GC patients can be predicted.

Table 3 Comparison of the relevant factors between the high hemoglobin to albumin ratio group and low hemoglobin to albumin ratio group

Factors	High HAR group (*n* = 158)	Low HAR group (*n* = 154)	*P* value
Age (yr)	61 (53-67)	63 (54-69)	0.266
Sex (*n*)			0.000
Male	132	93	
Female	26	61	
BMI (kg/m^2)	21.81 (19.90-23.82)	21.30 (19.32-23.33)	0.154
Smoking (*n*)			0.468
Yes	35	29	
No	123	125	
Drinking (*n*)			0.322
Yes	28	21	
No	130	133	
CEA (ng/mL)	2.89 (1.87-5.23)	2.97 (1.83-5.44)	0.581
CA19-9 (U/mL)	12.63 (7.43-21.52)	13.38 (7.23-24.20)	0.658
CA125 (U/mL)	8.30 (5.68-11.30)	9.15 (6.08-16.80)	0.034
CA72-4 (IU/mL)	1.91 (1.19-4.46)	1.73 (1.14-4.46)	0.396
PHR	1.55 (1.25-1.95)	2.29 (1.71-3.36)	0.000
PLR	138.71 (98.29-188.22)	177.27 (134.34-252.12)	0.000
PAR	5.49 (4.36-6.86)	6.04 (4.70-8.20)	0.002
FLR	1.83 (1.39-2.62)	2.26 (1.57-3.11)	0.001
AFR	13.73 (10.92-16.83)	12.62 (9.69-16.93)	0.162
HFR	48.46 ± 14.63	36.42 ± 18.78	0.000
PFR	73.48 (57.12-92.62)	79.78 (60.16-112.23)	0.040
NLR	2.32 (1.74-3.36)	2.89 (1.92-3.78)	0.024
ALR	24.40 (19.05-32.52)	27.87 (23.08-35.77)	0.000
Tumor size (cm)	3.5 (2.4-5.0)	4.5 (3.0-6.1)	0.009
Vascular infiltration (*n*)			0.507
present	88	80	
absent	70	74	
Nerve infiltration (*n*)			0.918
present	75	74	
absent	83	80	
Histological grade (*n*)			0.682
G1	3	3	
G2	59	61	
G3	96	90	
Stage (*n*)			0.036
I	56	32	
II	32	43	
III	70	79	
T classification (*n*)			0.037

T1	44	27	
T2	18	17	
T3	20	21	
T4	76	89	
N classification (*n*)			0.141
N0	79	63	
N1	14	13	
N2	25	34	
N3	40	44	

HAR: Hemoglobin to albumin ratio; BMI: Body mass index; PHR: Platelet to hemoglobin ratio; PLR: Platelet to lymphocyte ratio; PAR: Platelet to albumin ratio; FLR: Fibrinogen to lymphocyte ratio; AFR: Albumin to fibrinogen ratio; HFR: Hemoglobin to fibrinogen ratio; PFR: Platelet to fibrinogen ratio; NLR: Neutrophil to lymphocyte ratio; ALR: Albumin to lymphocyte ratio.

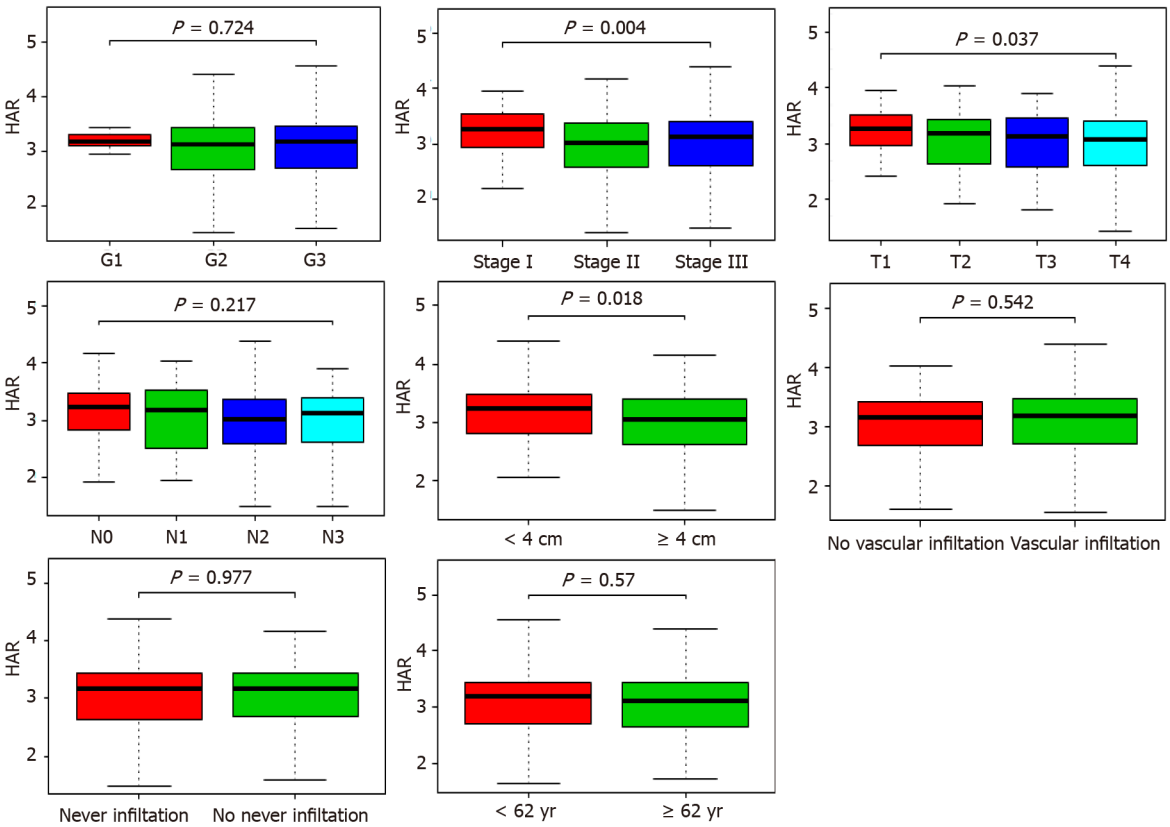

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Figure 2 Association between hemoglobin to albumin ratio and clinicopathological characteristics, including grade, stage, T classification, N classification, tumor size, vascular infiltration, nerve infiltration and age. HAR: Hemoglobin to albumin ratio.

DISCUSSION

The systemic inflammatory response and malnutrition are markedly related to the prognosis of cancer [10,11,13]. Neutrophils, lymphocytes, platelets and fibrinogen may play important roles in tumor-induced systemic inflammatory responses[23,24]. Hemoglobin and albumin are the two most common indicators of nutritional status. At the same time, serum albumin can also reflect the inflammation of patients. Various scores and indicators based on inflammation and nutritional status have been produced to predict the prognosis of cancer, such as the controlling nutritional status score, C-reactive protein to albumin ratio, NLR, PLR, prognostic nutrition index and systemic immune inflammation index[25-27].

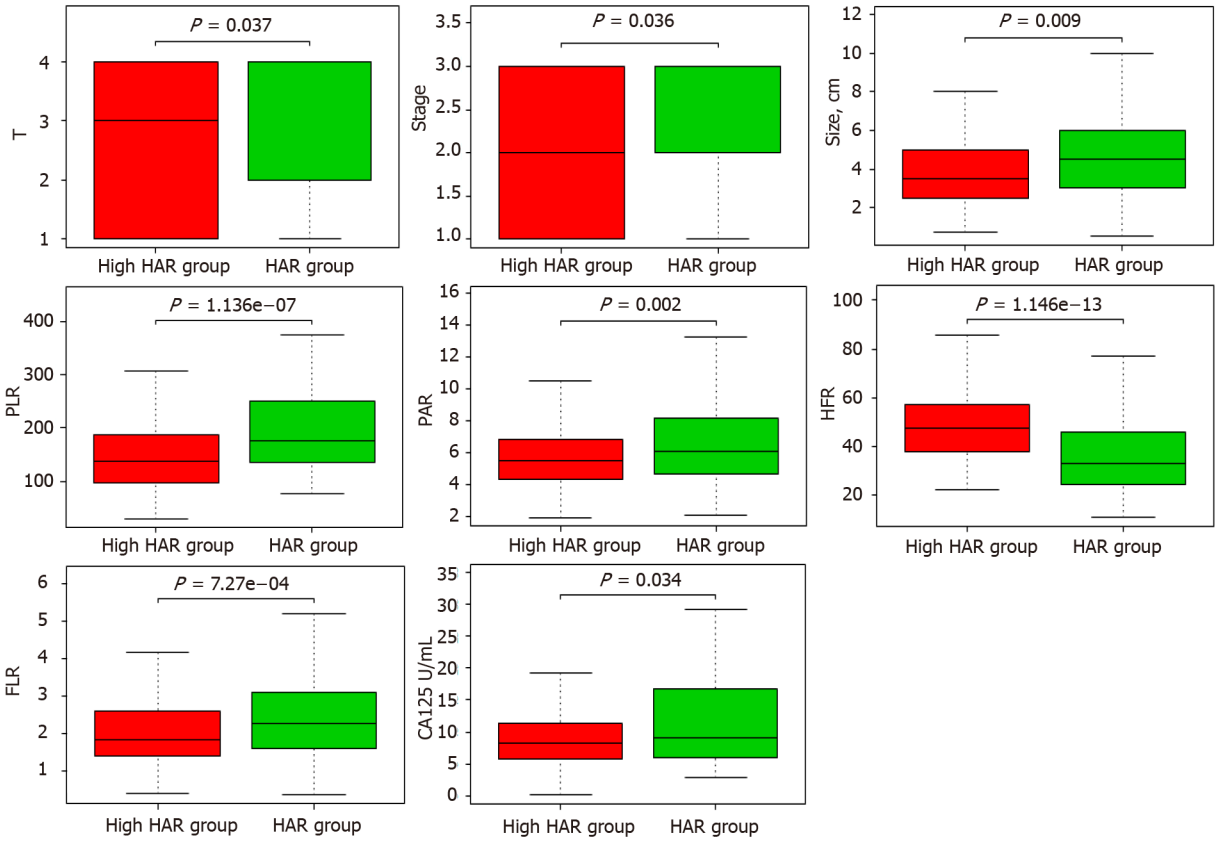

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Figure 3 Relationships between hemoglobin to albumin ratio and prognostic factors, including stage, T classification, and tumor size, CA125, fibrinogen to lymphocyte ratio, platelet to albumin ratio, platelet to lymphocyte ratio and hemoglobin to fibrinogen ratio. HAR: Hemoglobin to albumin ratio; FLR: Fibrinogen to lymphocyte ratio; HFR: Hemoglobin to fibrinogen ratio; PAR: Platelet to albumin ratio; PLR: Platelet to lymphocyte ratio.

Deng *et al*[28] showed that the preoperative PLR was significantly associated with poor prognosis in GC patients with surgical resection. Gu *et al*[29] also found that GC patients with elevated PLR had poor overall survival. Sun *et al*[30] indicated that the combination of NLR and PLR was an independent risk factor for the overall survival of stage III GC patients undergoing radical resection. In addition, Suzuki *et al*[31] found that high plasma fibrinogen was related to tumor progression and poor overall survival in GC patients. Huang *et al*[32] showed that elevated FLR was a high risk factor for peritoneal metastasis in patients with GC. This study also showed that PLR and FLR were significantly related to the prognosis of GC patients.

Hemoglobin is used to determine anemia. Hypoxia caused by anemia, on the one hand, may accelerate tumor angiogenesis to promote tumor progression; on the other hand, it may make tumor cells resistant to radiotherapy and chemotherapy through proteomics and genomic changes[13,33,34]. Moreover, it is well known that hypoxia-inducible factor 1 can regulate gene products that promote tumor progression, and hypoxia increases its expression[35]. However, the molecular mechanisms of hypoxia need to be further elucidated. Previous studies have found that anemia was an independent risk factor for poor prognosis in patients with malignant tumors[36,37].

Huang *et al*[38] found that GC patients with low hemoglobin levels before surgery had poor survival. Liu *et al*[39] demonstrated that preoperative low hemoglobin concentrations were significantly related to not only large tumor sizes but also poor 5-year overall survival and high postoperative complication rates in advanced GC patients. Shen *et al*[40] suggested that preoperative anemia was markedly related to large tumor sizes, deep invasion depths and high stages and showed that stage I and II GC patients with anemia before surgery had a low long-term survival rate compared with patients without anemia before surgery.

Malnutrition and inflammation can inhibit albumin synthesis. Serum albumin was an independent prognostic indicator of malignant tumors[14,41]. Lien *et al*[42] showed that serum albumin was effectively associated with the 5-year survival of GC patients. Moreover, relevant studies have indicated that low albumin levels are related to poor prognosis in GC[14,43]. However, Crumley *et al*[14] demonstrated that GC patients with low albumin levels had a poor prognosis compared with those with high albumin levels, but this factor was not an independent predictor of prognosis. Moreover, Toyokawa *et al*[44] believed that C-reactive protein to albumin ratio was an independent prognostic

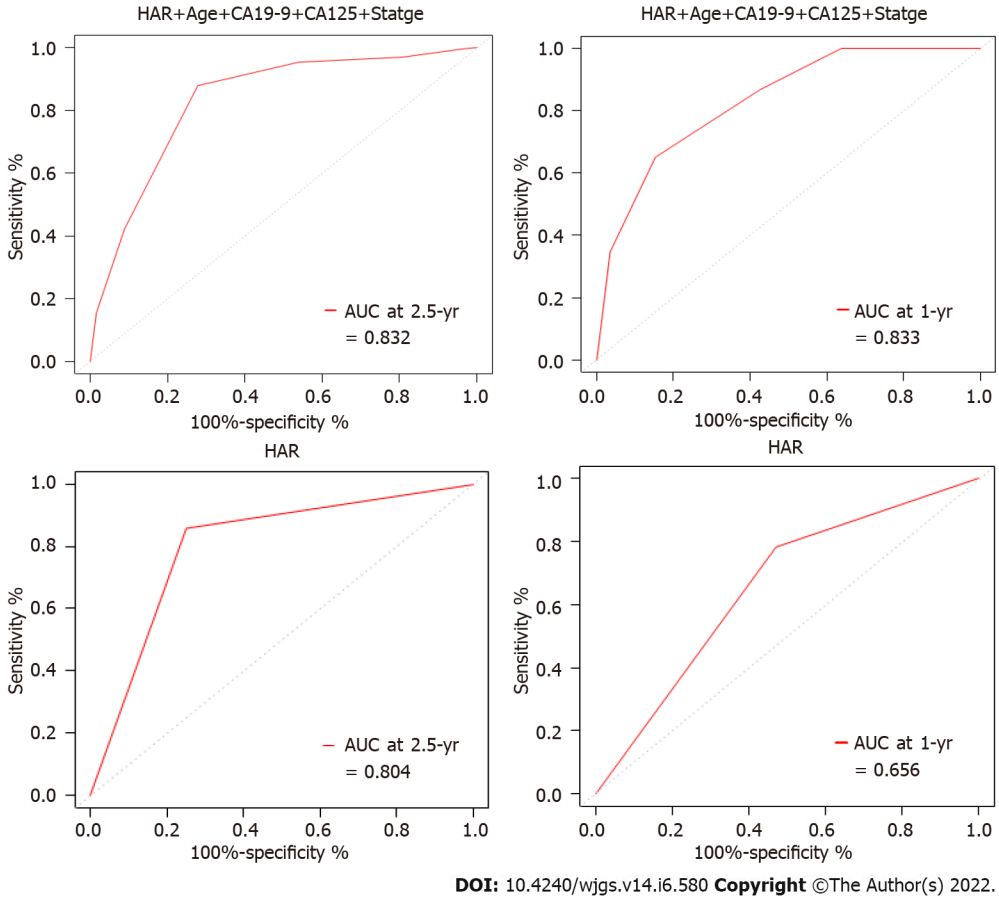

Figure 4 Receiver operating characteristic curve of hemoglobin to albumin ratio or combined factors to predict the short-term survival of gastric cancer patients. HAR: Hemoglobin to albumin ratio; AUC: Area under the curve.

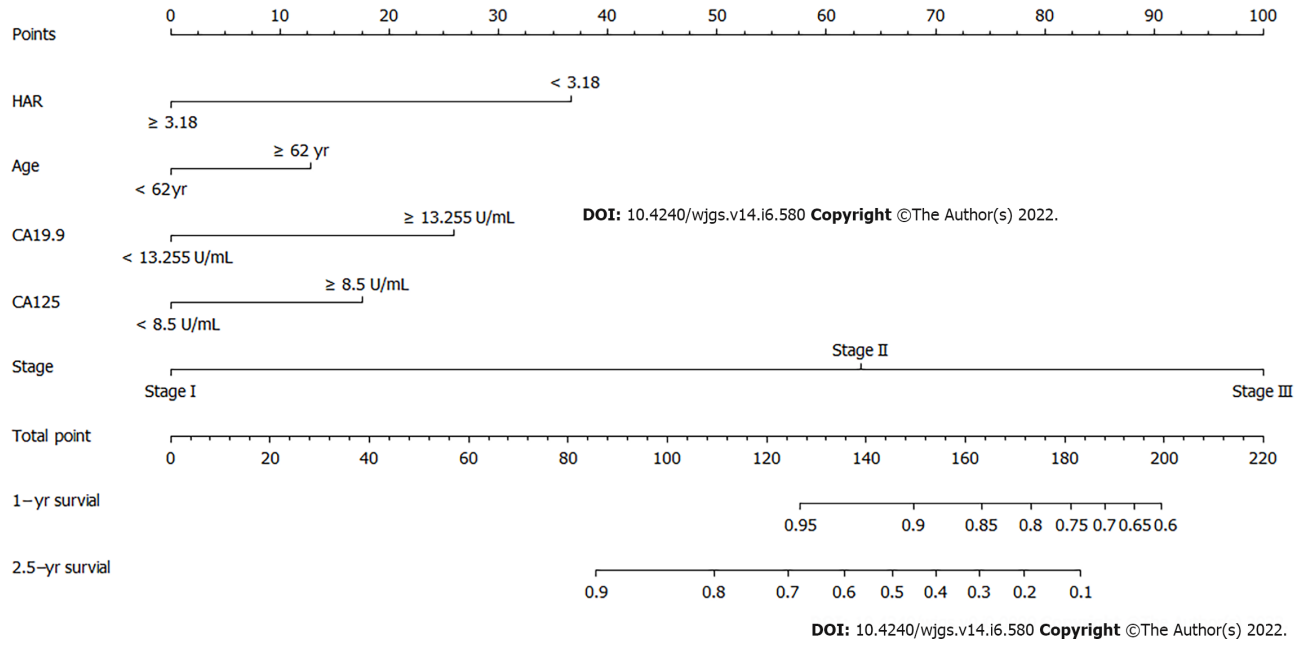

Figure 5 Nomogram of the logistic regression model. HAR: Hemoglobin to albumin ratio.

factor for overall survival in patients who underwent R0 resection for stage III gastric cancer.

This study indicated that HAR, stage and age were independent risk factors for the short-term survival of GC patients. Logistic regression analysis showed that a low HAR was markedly correlated with high stage, T classification and large tumor size in GC patients. To further analyze the relationships

between HAR and prognostic factors, we divided GC patients into a low HAR group and a high HAR group according to the median HAR value, and the results showed that patients with low HAR had high stage, T classification, CA125 and large tumor size. In addition, Kaplan-Meier analysis indicated that low HAR was related to short survival in GC patients.

Serum tumor markers can be used to predict the prognosis of cancer. Previous studies have found that elevated CEA, CA19-9 and CA125 levels were related to the prognosis of GC[45-47]. Related studies have also indicated that preoperative CEA and CA19-9 levels are related to tumor invasion depth and stage and can be used to predict prognosis[48,49]. Kochi *et al*[50] indicated that serum CA125 and CA19-9 were independent predictors of GC prognosis. This study also showed that CEA, CA19-9 and CA125 were associated with the prognosis of GC patients. The prognosis of patients with GC was evaluated mainly according to the American Joint Committee on Cancer TNM classification system[3,4]. However, this system has some limitations in clinical application.

Currently, nomograms combining prognostic factors have been developed, and it has been found that nomograms including inflammation and tumor markers can predict the prognosis of cancer more accurately than the traditional TNM classification system[51-53]. In this study, HAR, stage, age, CA19-9 and CA125 were used to construct a nomogram model for the short-term survival of GC patients, and the C-index for model evaluation was 0.820. The accuracy, sensitivity and specificity of this model for predicting the 1-year survival of GC patients were 83.30%, 86.83% and 84.77%, respectively, and the accuracy, sensitivity and specificity of the model for predicting the 2.5-year survival of GC patients were 83.20%, 87.87% and 72.18%, respectively, indicating that the model had a certain validity in predicting the short-term survival of patients with GC.

This study has some limitations. First, this was a single-center, small-sample retrospective study. Second, several other inflammatory markers correlated with prognosis were not included. Therefore, multicenter large-scale prospective randomized controlled trials are necessary.

In conclusion, this is the first study to apply HAR to predict the prognosis of GC patients with D2 radical resection and to construct a short-term survival prognostic nomogram for GC patients. Preoperative low HAR was associated with short survival in GC patients. The prognostic nomogram model based on HAR, stage, age, CA19-9 and CA125 can correctly predict the short-term survival of GC patients with D2 radical resection, thus providing a reference for the development of personalized postoperative treatment and follow-up plans.

CONCLUSION

Preoperative low HAR was associated with short survival in GC patients. The prognostic nomogram model can accurately predict the short-term survival of GC patients with D2 radical resection.

ARTICLE HIGHLIGHTS

Research background

Hemoglobin and albumin are associated with the prognosis of gastric cancer (GC) patients. However, the prognostic value of the hemoglobin to albumin ratio (HAR) for the short-term survival of GC patients with D2 radical resection has not been studied.

Research motivation

The clinical value of the HAR in the prognosis of GC patients with D2 radical resection has not been reported. Nomogram can provide the overall probability of specific outcomes for individual patients and provide more accurate predictions than the traditional TNM staging system, thereby improving personalized treatment decisions.

Research objectives

The aim of this study was to investigate the significance of the HAR in evaluating the short-term survival of GC patients after D2 radical resection and to construct a nomogram to predict the prognosis in GC patients after surgery.

Research methods

Cox regression and Kaplan-Meier analysis was used for prognostic analysis. Logistic regression was used to analyze the relationships between HAR and the clinicopathological characteristics of the GC patients. A prognostic nomogram model for the short-term survival of GC patients was constructed by R software.

Research results

HAR was an independent risk factor for the short-term survival of GC patients. GC patients with a low HAR had a poor prognosis ($P < 0.001$). Low HAR was markedly related to high stage [odds ratio (OR) = 0.45 for II *vs* I; OR = 0.48 for III *vs* I], T classification (OR = 0.52 for T4 *vs* T1) and large tumor size (OR = 0.51 for ≥ 4 cm *vs* < 4 cm) (all $P < 0.05$). The nomogram model was based on HAR, age, CA19-9, CA125 and stage, and the C-index was 0.820.

Research conclusions

Preoperative low HAR was associated with short survival in GC patients. The prognostic nomogram model can accurately predict the short-term survival of GC patients with D2 radical resection.

Research perspectives

The significance of the HAR in evaluating the short-term survival of GC patients after D2 radical resection and to construct a nomogram to predict the prognosis in GC patients after surgery may provide a reference for the development of postoperative individualized treatment and follow-up plans.

FOOTNOTES

Author contributions: Hu BE and Hu CG designed the study and contributed equally to this work; Hu BE, Hu CG and Zhu JF collected the clinical data; Hu BE analyzed the data and wrote the manuscript with contributions from all authors; Zhu ZM and Huang C provided critical comments for this paper; All authors read and approved the final version of the paper.

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META-ANALYSIS

Comparison between laparoscopic uncut Roux-en-Y and Billroth II with Braun anastomosis after distal gastrectomy: A meta-analysis

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Abstract

BACKGROUND

Conventional Billroth II (BII) anastomosis after laparoscopic distal gastrectomy (LDG) for gastric cancer (GC) is associated with bile reflux gastritis, and Roux-en-Y anastomosis is associated with Roux-Y stasis syndrome (RSS). The uncut Roux-en-Y (URY) gastrojejunostomy reduces these complications by blocking the entry of bile and pancreatic juice into the residual stomach and preserving the impulse originating from the duodenum, while BII with Braun (BB) anastomosis reduces the postoperative biliary reflux without RSS. Therefore, the purpose of this study was to compare the efficacy and safety of laparoscopic URY with BB anastomosis in patients with GC who underwent radical distal gastrectomy.

AIM

To evaluate the value of URY in patients with GC.

METHODS

PubMed, Embase, Web of Science, Cochrane Library, Chinese National Knowledge Infrastructure, Wanfang, Chinese Biomedical Database, and VIP Database for Chinese Technical Periodicals (VIP) were used to search relevant studies published from January 1994 to August 18, 2021. The following databases were

also used in our search: Clinicaltrials.gov, Data Archiving and Networked Services, the World Health Organization International Clinical Trials Registry Platform Search Portal (https://www.who.int/clinical-trials-registry-platform/the-ictrp-search-portal), the reference lists of articles and relevant conference proceedings in August 2021. In addition, we conducted a relevant search by Reference Citation Analysis (RCA) (https://www.referencecitationanalysis.com). We cited high-quality references using its results analysis functionality. The methodological quality of the eligible randomized clinical trials (RCTs) was evaluated using the Cochrane Risk of Bias Tool, and the non-RCTs were evaluated using the Newcastle-Ottawa scale. Statistical analyses were performed using Review Manager (Version 5.4).

RESULTS

Eight studies involving 704 patients were included in this meta-analysis. The incidence of reflux gastritis [odds ratio = 0.07, 95% confidence interval (CI): 0.03-0.19, $P < 0.00001$] was significantly lower in the URY group than in the BB group. The pH of the postoperative gastric fluid was lower in the URY group than in the BB group at 1 d [mean difference (MD) = -2.03, 95%CI: (-2.73)-(-1.32), $P < 0.00001$] and 3 d [MD = -2.03, 95%CI: (-2.57)-(-2.03), $P < 0.00001$] after the operation. However, no significant difference in all the intraoperative outcomes was found between the two groups.

CONCLUSION

This work suggests that URY is superior to BB in gastrointestinal reconstruction after LDG when considering postoperative outcomes.

Key Words: Gastric cancer; Laparoscopy; Uncut Roux-en-Y; Anastomosis; Meta-analysis; Conventional Billroth II

Core Tip: No consensus is available in the literature regarding the more beneficial technique between laparoscopic Uncut Roux-en-Y (URY) and Billroth II combined Braun (BB) anastomosis for radical distal gastrectomy. This is the first systematic review and meta-analysis comparing URY and BB anastomosis. These two techniques were investigated in terms of surgical outcomes, postoperative recovery, and postoperative complications.

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INTRODUCTION

Gastric cancer (GC) is the fifth most common cancer worldwide and the third most common cause of death from cancer[1]. The latest update from 2018 showed that GC accounted for 5.7% of all cancer cases, 8.2% of all deaths related to cancer, and approximately 782685 total deaths, representing a serious threat to human life and health[2]. The development of the treatments used to cure cancer revealed that radiotherapy as well as neoadjuvant and adjuvant chemotherapy may improve the outcomes, but surgery (*e.g.*, traditional open surgery and laparoscopic surgery) is the primary option for an effective cure[3].

Laparoscopic distal gastrectomy (LDG) was reported for the first time in Japan in 1994[4], when it was performed in combination with Billroth I (BI) gastroduodenostomy in a patient with GC at an early stage. It has been subsequently applied in Asia, due to its low trauma and rapid recovery of the patient. To date, a growing number of studies demonstrated that LDG is an oncologic safe alternative to open distal gastrectomy (ODG) in the treatment of early and advanced GC[5-7]. However, the choice of the most appropriate type of gastrointestinal reconstruction after LDG is still under debate.

Gastrointestinal reconstruction is an important part of GC surgery as well as tumor resection and lymph node dissection, since it is necessary to maintain a satisfactory nutritional status and quality of life, with a postoperative morbidity as low as possible[8]. BI reconstruction has the physiological advantage of allowing food passage through the duodenum[9] and reducing the postoperative weight loss[10]. However, the incidence of short-term complications, such as gastrointestinal fistulas classified

as Clavien-Dindo grade IIIa or higher, is high in the BI group due to excessive anastomotic tension[11-13]. BII anastomosis resolves the anastomotic tension, but is prone to postoperative complications potentially associated to residual GC such as postoperative biliary reflux, alkaline reflux gastritis, and esophagitis[14]. Roux-en-Y (RY) anastomosis does not cause anastomotic tension, and the gastric content enters directly into the jejunum, reducing the duodenal lumen pressure and the development of delayed gastric emptying and reflux gastritis. However, Roux-Y stasis syndrome (RSS) has an incidence of 10%-30% due to the abnormal activity in the distal jejunum of the anastomosed stomach[15]. On the other hand, postoperative biliary reflux without RSS can be reduced by performing BII with Braun (BB) anastomosis[16,17]. In addition, a new method of reconstructing the digestive tract, "uncut Roux-en-Y (URY) anastomosis", was introduced in 1988, which is an improvement of the RY anastomosis, since it can effectively prevent the development of RSS, reflux gastritis, and reflux esophagitis[18,19].

Therefore, this systematic review and meta-analysis were performed by including the most recent and comprehensive studies, to systematically evaluate the safety and efficacy of the two approaches (URY and BB) for the reconstruction surgery of distal gastrectomy.

MATERIALS AND METHODS

This systematic review and meta-analysis were performed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis statement[20].

Literature search strategy

A systematic literature search was performed from January 1994 to August 18, 2021 using PubMed, Embase, Web of science, Cochrane Library, China National Knowledge Infrastructure, Wanfang, Chinese Biomedical Database, and Chinese Science and Technology Journal Database (VIP). The following databases were also used in our search: Clinicaltrials.gov (https://clinicaltrials.gov), Data Archiving and Networked Services, the World Health Organization International Clinical Trials Registry Platform Search Portal (https://www.who.int/clinical-trials-registry-platform/the-ictrp-search-portal), and the reference lists of articles and relevant conference proceedings in August 2021. In addition, we conducted a relevant search by Reference Citation Analysis (RCA) (https://www.referencecitationanalysis.com). We cited high-quality references using its results analysis functionality. The search strategy used a combination of the Mesh terms and free terms, such as: "Stomach neoplasms" and "laparoscopy or laparoscopes" and "gastroenterostomy" and "gastric bypass"[21]. All the identified studies were imported into Endnote X9 to identify duplicates and screen eligible studies.

Eligibility criteria

Randomized clinical trials (RCTs) and non-RCTs comparing the outcomes of URY with those of BB anastomosis in the treatment of patients with GC were included in this study. In case of two or more studies from the same author or institution and the overlap of the study intervals or patients involved, the most recent study or the study with the largest sample size was selected. No language restriction was considered in including the studies. The exclusion criteria were the following: (1) Studies that did not include outcomes of interest; (2) Studies that did not show the statistical analysis necessary to perform the meta-analysis; (3) Studies with mixed LDG and ODG groups, unless the LDG-related data were presented separately; (4) Studies that did not specify the type of reconstruction; and (5) Posters, review articles, commentaries, and abstract-only articles. Two reviewers independently evaluated the titles and abstracts and read the full text to identify the eligible studies according to the inclusion and exclusion criteria[22]. A third reviewer could be involved in case of disagreement between the two reviewers.

Definitions

Bile reflux means the reflux of bile into the stomach. Bile can easily enter the stomach after gastrectomy, causing a series of discomforts such as acid regurgitation, which can lead to reflux gastritis over time. Inflammation and bleeding may occur in the gastric mucosa, as observed using gastroscopy. The definition of reflux gastritis varies from study to study; whenever a postoperative complication in a study reports alkaline reflux gastritis or bile reflux gastritis, it is directly categorized as reflux gastritis. Postoperative gastroparesis is a disorder characterized by delayed gastric emptying of solid food in the absence of a mechanical obstruction of the stomach, resulting in the cardinal symptoms of early satiety, postprandial fullness, nausea, vomiting, belching, and bloating[23]. Postoperative ileus is a transient interruption of coordinated bowel motility after surgical intervention, which prevents the effective transit of the intestinal contents or tolerance of oral intake[24].

Data extraction and quality assessment

Two reviewers independently extracted the data from the eligible studies using a standardized form including the first author, year of publication, number of patients, study design, participant characteristics, operative details, and outcomes. The surgical outcomes included the operative time, time to

perform the anastomosis, number of removed lymph nodes, and intraoperative blood loss. Postoperative recovery indicators included the postoperative hospital stay, time to first passage of flatus or defecation, postoperative gastric fluid pH, and time to first solid diet at days 1 and 3 post operation. Postoperative complications included reflux gastritis, gastroparesis, anastomotic leakage, and ileus. If an outcome was observed at different times in the study, the data at the time of the last observation were extracted.

Risk of bias assessment

The risk of bias for all the included RCTs was assessed using the Cochrane Risk of Bias Tool[25]. The domain included the random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other bias. As regards the non-RCTs, the quality of the studies was evaluated using the modified Newcastle-Ottawa scale (NOS)[26] according to three main factors: (1) Selection of the studied groups; (2) Comparability among groups; and (3) Determination of the outcomes. Each study was scored on an NOS of 0-9, with eligible studies with a score of 6 and high quality studies with a score of 8 and above[27].

Statistical analysis

The meta-analysis was performed using Review manager (Version 5.4). The results of the dichotomous data are expressed as an odds ratio (OR) with 95% confidence interval (CI), while the effect size of the continuous outcomes was measured as the weighted mean difference (MD) with 95%CI. Heterogeneity was assessed by the χ^2 test and I^2 statistics and was classified as low (I^2 < 25%), moderate (25%< I^2 < 50%), and high heterogeneity (I^2 > 50%)[28]. When the I^2 value was less than 50%, a fixed effects model was used; otherwise, a random effects model was used. Evaluation of publication bias was not conducted because less than ten studies were included. Subgroup analysis was conducted to explore the sources of heterogeneity according to the type of study (RCTs and non-RCTs). The considered information was extracted from the published articles; thus, the authors were not contacted for asking the data. A P value < 0.05 was considered statistically significant.

RESULTS

Study selection

A total of 908 potentially relevant articles were identified, and among these, 36 were selected to read the full text. A total of eight studies were finally included and among them[29-36], three were RCTs[30,31,34] and five were non-RCTs[29,32,33,35,36]. Two reviewers indicated that the techniques of the two anastomosis methods were sufficiently similar so that the results could be pooled. No disagreement occurred between the two reviewers during the study selection process, and all the included articles were chosen after discussion and mutual agreement. The flow diagram of the study selection demonstrating the details of the selection process is shown in Figure 1[37].

Characteristics of the studies and quality assessment

The included articles described investigations performed in China and published between 2017 and 2021, and the type of procedure was laparoscopy in all of them. A total of 704 patients were included, and among them, 354 underwent URY and 350 underwent BB. In addition, among them, 272 (38.6% of all the included cases) were from the three included RCTs, and 136 (38.4% of all the URY cases) were in the URY group. The information regarding the characteristics of the included studies is summarized in Table 1. The quality assessment of the RCTs is shown in Table 2. The included RCTs of surgical interventions had certain problems with blinding[38]. The quality of non-RCTs studies had scores between 6 and 8, with a mean of 7.4 (Table 1).

Meta-analysis: Surgical outcomes

Operative time: Seven studies reported the operative time of the two procedures[29-34,36]. A fixed-effect model was used (χ^2 = 1.05, P = 0.98, I^2 = 0%) for meta-analysis, revealing that there was no significant difference between the two groups [MD = 1.22, 95%CI: (-4.16)-6.60, P = 0.66] (Figure 2A). The subgroup analysis also revealed no significant difference between the RCTs [MD = 0.93, 95%CI: (-5.87)-7.73, P = 0.79] and non-RCTs subgroups [MD = 1.71, 95%CI: (-7.09)-10.05, P = 0.70] (Table 3).

Reconstruction time: Six studies compared the reconstruction time necessary to perform URY and BB [29,30,32-35]. A high heterogeneity (I^2 = 81%) was observed among inter-studies; thus, a random effects model was used. The results demonstrated that the reconstruction time was similar between the URY group and BB group [MD = 0.90, 95%CI: (-2.05)-3.85, P = 0.55] (Figure 2B). Moreover, the subgroup analysis did not find any statistically significant difference between the two subgroups [RCTs: MD = 3.32, 95%CI: (-3.85)-10.49, P = 0.36; non-RCTs: MD = -0.41, 95%CI: (-3.85)-3.03, P = 0.81] (Table 3).

Table 1 Characteristics of the included studies

Ref.	Study type	Country	Period	Number (URY/BB)	Gender (M/F)	Age (URY/BB)	BMI	ASA (I/II/III)	Tumor stage (I/II/III/IV)	Differentiation (H/M/L)	Matched factors[1]	NOS score
Chen[30], 2018	RCT	China	2016.5-2017.9	URY 30, BB 30	17/13, 16/14	55.00 ± 5.40, 53.50 ± 7.56	22.89 ± 4.23, 21.38 ± 2.02	NR	3/10/17/0, 4/12/14/0	5/15/10, 4/14/12	1, 2, 3, 4, 7, 8, 12	NA
Gao and Xiang [29], 2018	Retro	China	2014.1-2017.1	URY 26, BB 34	17/9, 21/13	60.61 ± 11.14, 59.72 ± 10.79	21.58 ± 1.86, 21.35 ± 1.93	NR	0/5/14/7, 0/7/18/9	8/7/11, 10/11/13	1, 2, 3, 5, 6, 9, 10, 11, 12, 13	8
Li *et al*[32], 2017	Retro	China	2010.1-2016.1	URY 30, BB 33	21/9, 21/12	52.81 ± 5.39, 52.09 ± 6.47	21.66 ± 2.54, 21.81 ± 2.62	NR	NG	8/11/11, 9/12/12	1, 2, 3, 5, 6, 9, 12	7
Ren *et al*[31], 2020	RCT	China	2015.6-2016.12	URY 44, BB 44	30/14, 28/16	59.61 ± 11.14, 59.72 ± 10.79	21.51 ± 1.86, 21.38 ± 1.93	NR	0/8/25/11, 0/9/23/12	14/13/17, 13/14/17	1, 3, 5, 6, 9, 10, 11, 13	NA
Wang *et al*[36], 2018	Retro	China	2015.3-2017.6	URY 81, BB 58	52/29, 46/12	56 (30-79), 56.5 (24-77)	NR	NR	41/20/17/0, 28/13/16/0	NR	1, 3, 4, 5, 6, 9	8
Wang *et al*[34], 2021	RCT	China	2017.1-2018.5	URY 62, BB 62	44/18, 44/18	54.84 ± 8.31; 54.69 ± 10.07	22.43 ± 3.07, 22.46 ± 3.17	27/28/7, 16/41/5	NG	NR	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12	NA
Wu *et al*[33], 2021	Retro	China	2016.1-2019.4	URY 45, BB 50	27/18, 31/19	59.1 ± 6.2, 59.1 ± 6.3	23.3 ± 3.0, 23.2 ± 2.9	NR	45/0/0/0, 50/0/0/0	7/15/23, 8/19/23	1, 2, 3, 4, 5, 9, 10, 11, 12, 13	6
Zhou *et al*[35], 2018	Retro	China	2010.6-2015.4	URY 36, BB 39	22/14, 24/15	61 ± 5, 61 ± 8	23 ± 3, 22 ± 4	21/15/0, 23/16/0	36/0/0/0, 39/0/0/0	11/16/9, 10/19/10	2, 3, 4, 5, 6, 9, 10, 13	8

[1]Outcomes: (1) Operative time; (2) Reconstruction times; (3) Intraoperative bleeding; (4) Total number of harvested lymph nodes; (5) Time to first passage of flatus or defecation; (6) Time to first solid diet; (7) Mean gastric pH at day 1; (8) Mean gastric pH at day 3; (9) Post-operative hospitalization time; (10) Anastomotic leakage; (11) Ileus; (12) Reflux gastritis; and (13) Gastroparesis.

ASA: American Society of Anesthesiologists score; BMI: Body mass index; NOS: Newcastle-Ottawa Scale; NR: Not reported; Retro: Retrospective observational study; NA: Not applicated; RCT: Randomised controlled trial; URY: Uncut Roux-en-Y; BB: BII combined Braun; NG: Not given.

Intraoperative blood loss: The intraoperative blood loss was reported in all studies. The evidence suggested a small difference in the intraoperative blood loss between the URY and BB groups [MD = 0.84, 95%CI: (-2.21)-3.90, P = 0.59] (Figure 2C). The meta-analysis among the RCTs indicated no significant difference in the intraoperative blood loss between the two groups [MD = 3.87, 95%CI: (-7.02)-14.75, P = 0.49] with low statistical heterogeneity (P = 0.49, I^2 = 45%). The pooled data in the non-RCTs revealed a similar result [MD = 0.58, 95%CI: (-2.60)-3.77, P = 0.72] with the absence of statistical heterogeneity (P = 0.91, I^2 = 0%) (Table 3).

Total number of harvested lymph nodes: Five articles reported the total number of harvested lymph nodes[30,33-36]. A fixed effect model was used, which showed a low statistical heterogeneity (I^2 = 0%). The pooled result revealed no significant difference between the two groups [MD = 1.01, 95%CI: (-0.20)-2.22, P = 0.10] (Figure 2D). The subgroup analysis showed no evident statistical difference in the total number of harvested lymph nodes between the URY and BB groups in both the RCT and non-RCT

Table 2 Results of risk of bias assessment (randomised controlled trials)

Ref.	Sequence generation	Allocation concealment	Blind of participant and personnel	Blind of assessment	Outcome of incomplete data	Selective report	Other bias
Chen[30], 2018	Low	Unclear	High	Unclear	Low	Unclear	Unclear
Ren *et al* [31], 2020	Low	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Wang *et al* [34], 2021	Low	Low	Low	Unclear	Low	Low	Unclear

The level of bias was determined as follows: "High" indicating a risk of bias; "Unclear" indicating an uncertain risk of bias; and "Low" indicating no risk of bias.

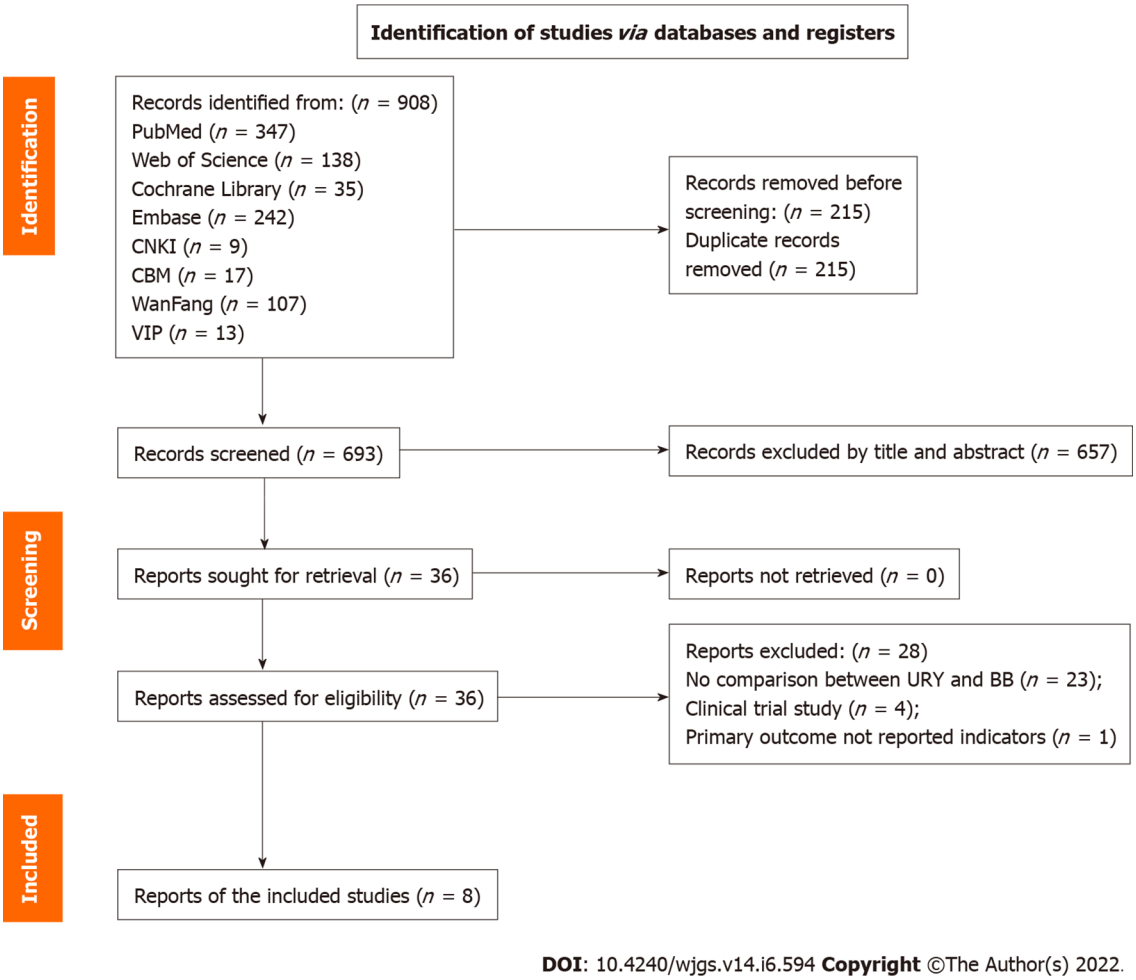

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Figure 1 Study flow diagram. URY: Uncut Roux-en-Y; BB: BII combined Braun; CNKI: Chinese National Knowledge Infrastructure; CBD: Chinese Biomedical Database.

subgroups [RCTs: MD = 0.15, 95%CI: (-1.86)-2.16, P = 0.88; non-RCTs: MD = 1.90, 95%CI: (-0.14)-3.95, P = 0.05] (Table 3).

Postoperative recovery

Time to first passage of flatus or defecation: Seven studies involving 644 patients reported the time to first passage of flatus or defecation[29,31-36]. The meta-analysis revealed that URY was associated with a shorter time to first passage of flatus or defecation than BB [MD = -0.26, 95%CI: (-0.51)-(-0.02), P = 0.03] (Figure 3A). A significant heterogeneity was observed among studies (χ^2 = 17.34, P = 0.008, I^2 = 65%); thus, a random effects model was used. However, no significant difference was found after performing the subgroup analysis between the non-RCT and RCT subgroups [RCTs: MD = -0.26, 95%CI: (-0.87)-0.34,

Table 3 Subgroup analysis of all the outcomes according to study type

Subgroup	Type	No. of studies	No. of patients		Meta-analysis results		Assessment of heterogeneity	
			URY	BB	OR/MD (95%CI)	*P* value	I^2	*P* value
Operative time	RCTs	3	136	136	0.93 [(-5.87)-7.73]	0.79	0	0.95
	Non-RCTs	4	182	175	1.71 [(-7.09)-10.51]	0.70	0	0.82
Reconstruction time	RCTs	2	92	92	3.32 [(-3.85)-10.49]	0.36	0.92	0.0005
	Non-RCTs	4	137	156	-0.41 [(-3.85)-3.03]	0.81	0.74	0.0009
Intraoperative blood loss	RCTs	3	136	136	3.87 [(-7.02)-14.75]	0.49	0.45	0.16
	Non-RCTs	4	218	214	0.58 [(-2.60)-3.77]	0.72	0	0.91
Total number of harvested lymph nodes	RCTs	2	92	92	0.15 [(-1.86)-2.16]	0.88	0	0.98
	Non-RCTs	3	163	147	1.90 [(-0.14)-3.94]	0.07	0	0.39
Time to first passage of flatus or defecation	RCTs	2	106	106	-0.26 [(-0.87)-0.34]	0.40	0.77	0.04
	Non-RCTs	5	218	214	-0.29 [(-0.59)-0.01]	0.05	0.56	0.06
Time to first solid diet	RCTs	1	44	44	-0.05 [(-1.14)-1.04]	0.93	Not applicable	
	Non-RCTs	4	173	164	-0.29 [(-0.53)-(-0.05)]	0.02	0	0.67
Postoperative hospitalization time	RCTs	2	106	106	-0.01 [(-0.16)-0.14)]	0.87	0	0.84
	Non-RCTs	5	218	214	-0.26 [(-0.78)-0.26]	0.32	0	0.63
Reflux gastritis	RCTs	2	92	92	0.03 (0.01-0.11)	< 0.00001	0	0.70
	Non-RCTs	3	193	209	0.15 (0.03-0.66)	0.01	0	0.77
Anastomotic leakage	RCTs	2	106	106	0.73 (0.15-3.48)	0.69	Not applicable	
	Non-RCTs	3	107	123	1.16 (0.23-5.87)	0.85	0	0.85

URY: Uncut Roux-en-Y; BB: BII combined Braun; RCTs: Randomised controlled trials; OR: Odds ratio; MD: Mean difference; CI: Confidence interval.

P = 0.40; non-RCTs: MD = -0.29, 95%CI: (-0.59)-0.01, *P* = 0.05] (Table 3).

Time to first solid diet: Five studies contributed to the meta-analysis regarding this parameter[29,31,32,35,36]. A fixed effects model was used due to a low heterogeneity (I^2 = 0%). The meta-analysis results showed a significant difference in the time to first solid diet between the URY and BB groups [MD = -0.28, 95%CI: (-0.51)-(-0.05), *P* = 0.02] (Figure 3B). The subgroup analysis revealed that the URY group had a shorter time to first solid diet than the BB [MD = -0.29, 95%CI: (-0.53)-(-0.05), *P* = 0.02] in the non-RCTs subgroup, while no statistically significant difference between the two groups was found in the RCT subgroup [MD = -0.05, 95%CI: (-1.14)-1.04, *P* = 0.93] (Table 3).

Postoperative gastric fluid pH: Two RCTs reported the postoperative pH of the gastric fluid[30,34]. The pooled result on days 1 and 3 revealed that this parameter was superior in the URY than in BB [day 1: MD = -2.03, 95%CI: (-2.73)-(-1.32), *P* < 0.00001 (Figure 3C); day 3: MD = -2.30, 95%CI: (-2.57)-(-2.03), *P* < 0.00001 (Figure 3D)]. However, a high heterogeneity was observed in the postoperative gastric fluid pH between days 1 and 3 (I^2 = 92% and I^2 = 40%, respectively).

Postoperative length of hospital stay: Seven articles reported the postoperative length of hospital stay [29,31-36]. A fixed effects model was used because no significant heterogeneity was present among studies (I^2 = 0%). The meta-analysis revealed no significant difference between the two groups [MD = -0.18, 95%CI: (-0.62)-0.25, *P* = 0.41] (Figure 3E). The subgroup analysis also showed no statistically significant difference between the URY and BB groups in both the non-RCT subgroup [MD = -0.26,

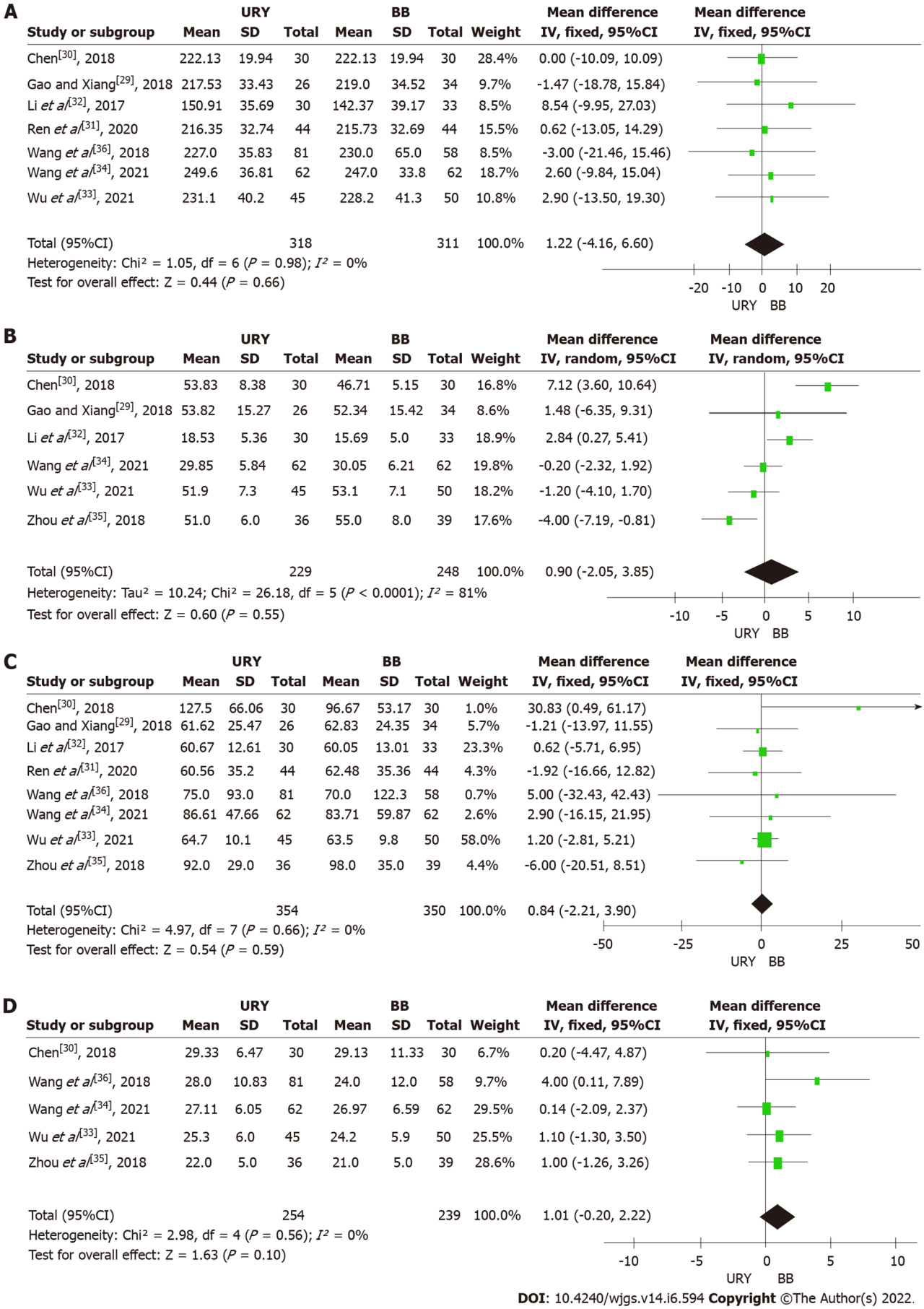

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Figure 2 Results of meta-analysis. A: Operative time; B: Reconstruction time; C: Intraoperative blood loss; D: Total number of harvested lymph nodes. URY: Uncut Roux-en-Y; BB: Billroth II combined Braun; CI: Confidence interval.

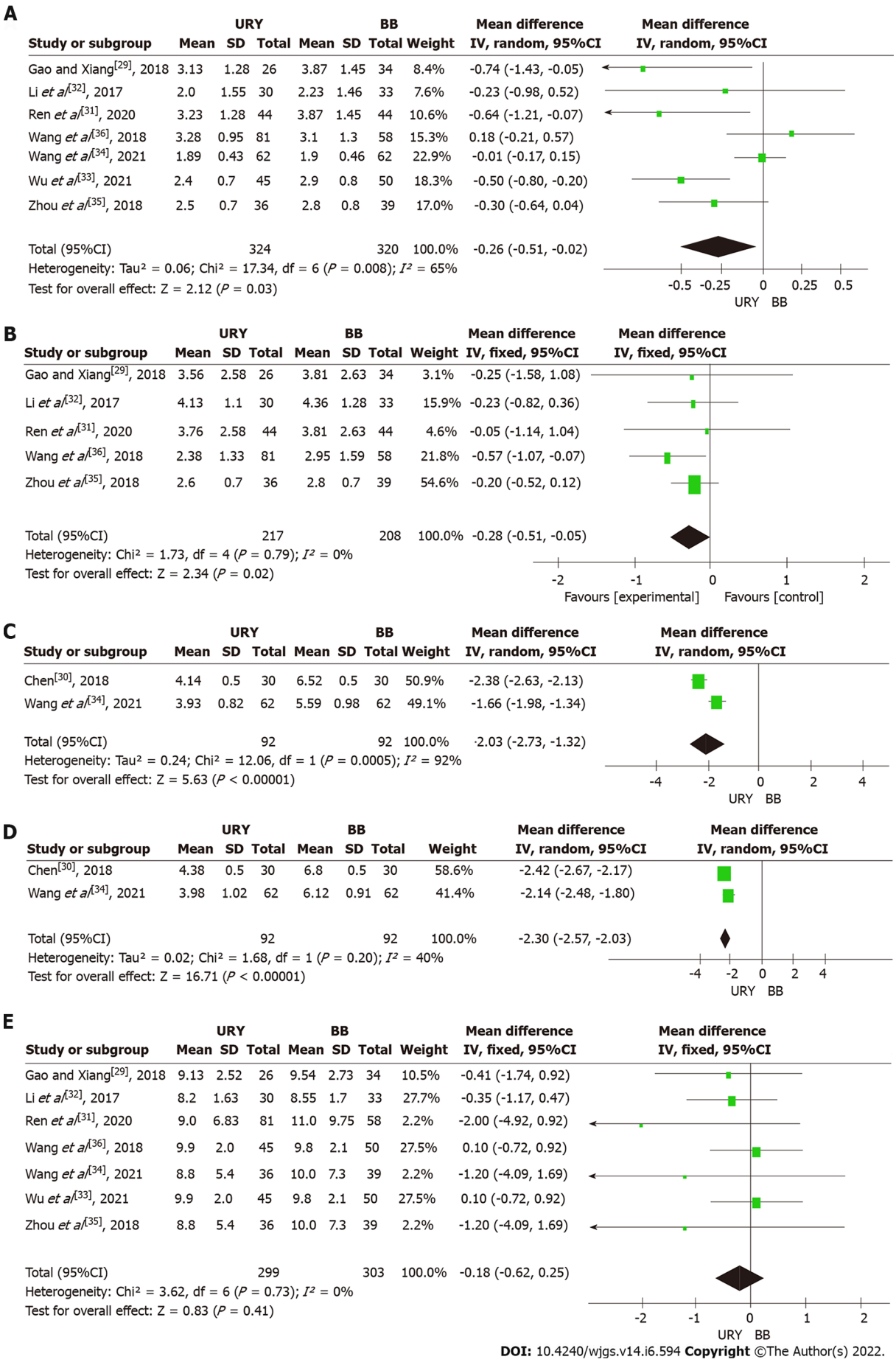

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Figure 3 Results of meta-analysis of postoperative recovery. A: Time to first passage of flatus or defecation; B: Time to first solid diet; C: Mean gastric pH

at day 1; D: Mean gastric pH at day 3; E: Postoperative hospitalization time. URY: Uncut Roux-en-Y; BB: BII combined Braun; CI: Confidence interval.

95%CI: (-0.78)-0.26, P = 0.32] and RCT subgroup [MD = -0.01, 95%CI: (-0.16)-0.14, P = 0.87] (Table 3).

Postoperative complications

Anastomotic leakage: Five studies reported the presence of anastomotic leakage[29,31,32-35]. A fixed effects model was used (I^2 = 0%) due to a low heterogeneity. The incidence of postoperative anastomotic leakage was similar between the URY and BB groups (OR = 0.91, 95%CI: 0.30-2.80; P = 0.88) (Figure 4A). The subgroup analysis between RCTs and non-RCTs indicated no significant difference in postoperative anastomotic leakage between the two groups (RCTs: OR = 0.73, 95%CI: 0.15-3.48, P = 0.69; non-RCTs: OR = 1.16, 95%CI: 0.23-5.87, P = 0.85) (Table 3).

Ileus: Four articles reported the incidence of postoperative ileus[29,31,33,34]. The meta-analysis showed no statistically significant difference between the two groups (OR = 0.26, 95%CI: 0.04-1.62, P = 0.15). However, a low heterogeneity (I^2 = 22%) was observed among studies, and a fixed effects model was used (Figure 4B).

Reflux gastritis: Five studies compared the reflux gastritis between the two groups[29,30,32-34]. A fixed effects model was used due to a low heterogeneity (I^2 = 0%). The incidence of reflux gastritis was significantly lower in the URY group than in the BB group (OR = 0.07; 95%CI: 0.03-0.19; P < 0.00001) (Figure 4C). The subgroup analysis showed that the incidence of reflux gastritis was lower in the URY group than in the BB group, regardless of the subgroup RCT or non-RCT (RCTs: OR = 0.03, 95%CI: 0.01-0.11, P < 0.00001; non-RCTs: OR = 0.15, 95%CI: 0.03-0.66, P = 0.01) (Table 3).

Gastroparesis: A total of four studies reported the incidence of postoperative gastroparesis[29,31,33,35], and among them, two had an incidence of 0[29,33]. The meta-analysis revealed that the incidence of postoperative gastroparesis was not significantly different between the two groups (OR = 0.68, 95%CI: 0.11-4.17, P = 0.68), and it was without significant heterogeneity (I^2 = 0%) (Figure 4D).

Sensitivity analysis

In the present study, a sensitivity analysis was performed on the operative time, intraoperative bleeding, reconstruction time, total number of harvested lymph nodes, time to first passage of flatus or defecation, time to first solid diet, postoperative hospitalization time, anastomotic leakage, and reflux gastritis to explore the stability of the included studies by the removal of each study from the meta-analysis and then examining the impact of the removed study on the overall composite estimate. After the exclusion of the relevant studies, when the CIs were within 95%, no significant effect was observed on the overall combined results.

DISCUSSION

No consensus exists on the most appropriate method to reconstruct the digestive tract for reducing complications and improving the quality of life after LDG. BII reconstruction has been a commonly used anastomosis method nowadays. However, bile reflux occurs frequently after BII due to the structural defects of this type of reconstruction. Therefore, BB's anastomosis was designed specifically to reduce the flow of bile into the stomach[17], actually also reducing ileus and postoperative gastrointestinal symptoms[16]. URY reconstruction was first reported by Van Stiegman *et al*[39] in 1988. URY gastrojejunostomy is an improved technique composed of the BII procedure and the BB anastomosis, which includes the additional step of closing the jejunal lumen proximal to the gastrojejunostomy[40]. At the end of distal gastrectomy, a gastrojejunostomy is performed between the residual stomach and the jejunum, approximately 30 cm away from the ligament of Treitz. The side-to-side or end-to-side gastrojejunostomy is performed more often selecting the greater curvature of the residual stomach. Then, a side-to-side jejunojejunostomy is established between the afferent and efferent jejunal limbs, approximately 20 cm distal from the ligament of Treitz and 40 cm distal from the gastrojejunostomy site. Finally, the jejunal lumen is occluded at a site 5 cm proximal to the gastrojejunostomy using different methods[40]. The common methods of jejunal occlusion without transection are the following: Stapling with non-bladed six-row linear staplers or four-row staplers (knifeless GIA, Covidien), placement of four or five tightly tied 3-0 polypropylene seromuscular stitches circularly around the jejunal wall, and jejunal ligature with No. 7 silk and reinforcement by suturing the serosal layers of the upper and lower jejunum at the occlusion site. This anastomosis is considered as a controversial but promising method for gastrointestinal reconstruction after distal gastrectomy. Therefore, this systematic review and meta-analysis were performed to evaluate and compare the safety and efficacy of URY reconstruction (Figure 5A) and BB reconstruction (Figure 5B) after distal gastrectomy.

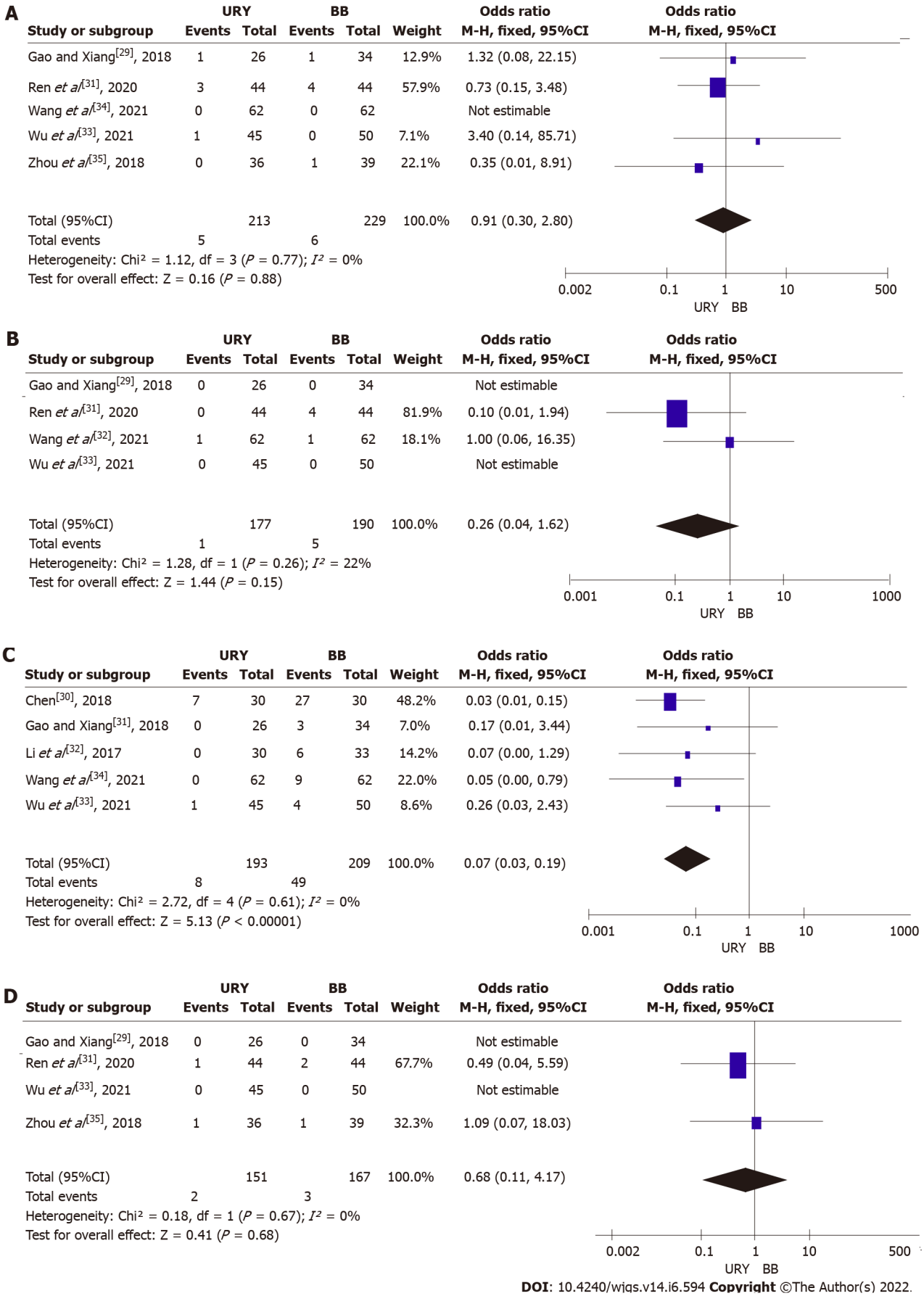

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Figure 4 Results of meta-analysis. A: Anastomotic leakage; B: Ileus; C: Reflux gastritis; D: Gastroparesis. URY: Uncut Roux-en-Y; BB: BII combined Braun; CI: Confidence interval.

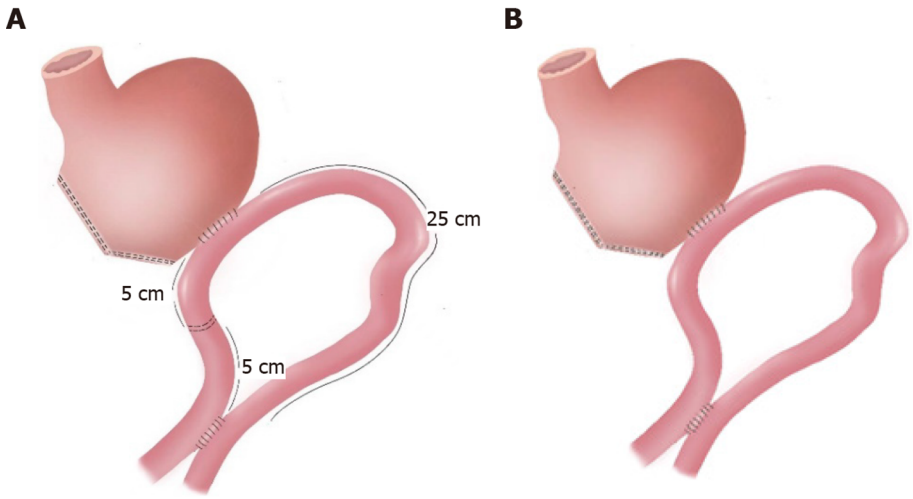

Figure 5 Anastomosis method. A: Uncut Roux-en-Y; B: Billroth II with Braun.

Eight studies involving 704 patients were included in this meta-analysis, divided into 354 who received URY and 350 who received BB[29-36]. No statistical difference in surgical outcomes between the two groups was observed in terms of operative time, intraoperative bleeding, reconstruction time, and lymph node dissection. Our analysis revealed that the reconstruction time had a high degree of heterogeneity both in the total and subgroup analyses, which might be due to factors such as study design, proficiency of the surgeon in performing anastomosis, and cooperation within the surgical team. Our results were like those of a previous study[41], except for the fact that URY in our study had a shorter operative time as well as reconstruction time. This might be due to differences in surgical experience among different reconstructive procedures that might lead to biased results and inconsistent reconstructive approaches (*in vivo* or *ex vivo*).

During the postoperative recovery, the mean gastric pH at days 1 and 3 post operation and time to first solid diet were significantly shorter in the URY group than in the BB group. However, the heterogeneity of these observations in our study was high. This might be related to Chen[30]'s study because the author did not use a new negative pressure drainage tube in a timely manner at the beginning of the study to measure the postoperative gastric fluid, leading to a large error in measuring the pH of the gastric fluid in the experimental group in the early stage. The sensitivity analysis of the time to first passage of flatus or defecation, time to first solid diet, and post-operative hospitalization time showed consistency. In addition, URY did not increase the postoperative length of stay compared to BB, which was consistent with the results of Park and Kim[41] and Chen *et al*[42]. The time to first passage of flatus or defecation in the URY group was shorter than that in the BB group. However, the subgroup analysis showed significance only in the non-RCTs with high heterogeneity, and it was also highly subjective; thus, our results should be interpreted with caution.

In terms of postoperative complications, the URY group had a lower incidence of postoperative reflux gastritis. This result is probably due to the fact that duodenal secretions are diverted to the distal jejunum though the jejunojejunostomy after URY anastomosis compared to BB anastomosis[16]. The uncut limb during the URY procedure preserved the original normal electrical conduction and direction of conduction[40]. This dual action promotes the normal recovery of the postoperative intestinal motility. Reflux gastritis is commonly observed in patients who underwent DG. Endoscopy remains the cornerstone of the diagnosis; the characteristic endoscopic features are adherent mucus, edema, mucosal friability, and erosions. The medical treatment includes antacids and cholestyramine alone or together. Severe cases require surgical treatment. Our study shows that URY is a good way to avoid postoperative reflux gastritis in patients subjected to LDG. Noh *et al*[43] reported that uncircumcised gastrojejunal RY anastomosis prevents RSS and reduces the alkaline reflux gastritis compared with conventional surgery. A recent clinical study by Park and Kim[41] also indicated that sufficient evidence is available to demonstrate that URY anastomosis reduces postoperative gastritis, duodenal secretion reflux, and gastric residuals. No significant difference in the probability of anastomotic leakage, gastroparesis, or ileus was found in the postoperative period between the two groups. Ma *et al*[44] demonstrated that URY does not increase the occurrence of postoperative anastomotic leakage and gastrointestinal motility dysfunction for conventional anastomoses.

Although gastrojejunostomy RY anastomosis is an effective method to prevent bile reflux gastritis after DG surgery, the incidence of postoperative RSS is high, seriously affecting the quality of life of patients. URY is a reliable anastomosis after distal radical GC surgery, resulting in few postoperative complications[45], with a lower incidence of RSS compared to RY[18,46,47]. URY gastrojejunostomy

reduces RSS by maintaining jejunal continuity (through normal conduction of myoelectric pulses), thereby maintaining the conduction of duodenal pacemaker activity[47]. BI reconstruction is one of the most popular reconstructive procedures after DG, and the incidence of postoperative complications is low; thus, it is considered a good option for surgeons[48]. However, it is not suitable for severe GC cases that require extensive dissection of the stomach, since this approach can lead to excessive anastomotic tension[11]. Our study also demonstrated that the postoperative complication rates after URY were significantly lower than those after BB. Thus, URY might be considered the primary option for reducing the incidence of reflux gastritis and RSS.

Our meta-analysis has several advantages. First, it is the first study comparing URY with BB anastomosis. Second, unlike the comparison of the procedures in previous works, our work considered BB because the URY gastrojejunostomy is a modification of the BII procedure with the BB anastomosis. Third, all the extracted data were cross-checked, and subgroup analysis was performed according to the type of the included studies to improve the credibility of our results. However, several limitations were also present in this study. First, most of the included studies were conducted in tertiary centers, and the recruited patients were carefully selected and had relatively low morbidity and low body mass index, which might result in a limited generalization of these findings. Second, the included studies are mostly observational ones, thus, with a potential selection bias. Third, the included RCTs have a certain bias in the implementation of blinding. This is inevitable because the surgeon cannot perform the procedure without knowing the assigned procedure. Therefore, a large sample size and a rigorously designed RCT are needed to confirm our results. Finally, all the LDG procedures were performed in China, probably because the incidence of GC is higher in East Asia than in most Western countries and distal tumors are more common in Eastern countries[2,49]. Nonetheless, our study provides clinical evidence for surgeons in deciding the optimal reconstruction technique for their patients. Moreover, our hope is that this topic can attract the attention of surgeons in more countries.

CONCLUSION

URY anastomosis is a safe and effective technique after LDG, and it is better than BB in terms of early postoperative recovery, postoperative gastric juice pH close to normal, and low incidence of reflux gastritis; thus, it can be recommended for gastrointestinal reconstruction after LDG. However, a rigorous RCT design and larger sample size cohorts (including long-term follow-up data) are still necessary to confirm our conclusions.

ARTICLE HIGHLIGHTS

Research background

Gastric cancer (GC) patients have a poor prognosis and high mortality. The efficacy and safety of uncut Roux-en-Y (URY) anastomosis after laparoscopic distal gastrectomy (LDG) are still controversial.

Research motivation

The URY gastrojejunostomy reduces these complications by blocking the entry of bile and pancreatic juice into the residual stomach and preserves the impulse originating from the duodenum, while BII combined Braun (BB) anastomosis reduces the postoperative biliary reflux without Roux-Y stasis syndrome. Therefore, the purpose of this study was to compare the efficacy and safety of laparoscopic URY with BB anastomosis in patients with GC who underwent radical distal gastrectomy.

Research objectives

The purpose of this study was to perform a systematic review and meta-analysis to evaluate the application value of URY anastomosis in LDG.

Research methods

PubMed, Embase, Web of science, Cochrane Library, Chinese National Knowledge Infrastructure, Wanfang, Chinese Biomedical Database, and VIP Database for Chinese Technical Periodicals (VIP) were used to search relevant studies published from January 1994 to August 18, 2021. The following databases were also used in our search: Clinicaltrials.gov (https://clinicaltrials.gov), Data Archiving and Networked Services, the World Health Organization International Clinical Trials Registry Platform Search Portal (https://www.who.int/clinical-trials-registry-platform/the-ictrp-search-portal), and the reference lists of articles and relevant conference proceedings in August 2021. In addition, we conducted a relevant search by Reference Citation Analysis (RCA) (https://www.referencecitationanalysis.com). We cited high-quality references using its results analysis functionality. The methodological quality of the eligible randomized clinical trials (RCTs) was evaluated using the Cochrane Risk of Bias Tool, and

the non-RCTs were evaluated using the Newcastle-Ottawa scale. Statistical analyses were performed using Review Manager (Version 5.4).

Research results

Eight studies involving 704 patients were included in this meta-analysis. The incidence of reflux gastritis [odds ratio = 0.07, 95% confidence interval (CI): 0.03-0.19, $P < 0.00001$) was significantly lower in the URY group than in the BB group. The pH of the postoperative gastric fluid was lower in the URY group than in the BB group at 1 d [mean difference (MD) = -2.03, 95%CI: (-2.73)-(-1.32), $P < 0.00001$] and 3 d [MD = -2.03, 95%CI: (-2.57)-(-2.03), $P < 0.00001$] after the operation. However, no significant difference in all the intraoperative outcomes was found between the two groups.

Research conclusions

This work demonstrated that URY is superior to BB in patients with GC when the postoperative outcome is considered. Therefore, this evidence supports the recommendation of URY gastrojejunostomy for gastrointestinal reconstruction after LDG.

Research perspectives

Several limitations were present in this study. First, most of the included studies were conducted in tertiary centers, and the recruited patients were carefully selected and had relatively low morbidity and low body mass index, which might result in a limited generalization of these findings. Second, the included studies are mostly observational ones, thus, with a potential selection bias. Third, the included RCTs has a certain bias in the implementation of blinding. This is inevitable because the surgeon cannot perform the procedure without knowing the assigned procedure. Therefore, a large sample size and a rigorously designed RCTs are needed for confirming our results. Finally, all the LDG procedures were performed in China, probably because the incidence of GC is higher in East Asia than in most Western countries and distal tumors are more common in Eastern countries. Moreover, our hope is that this topic can attract the attention of surgeons in more countries.

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FOOTNOTES

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CASE REPORT

Intestinal perforation with abdominal abscess caused by extramedullary plasmacytoma of small intestine: A case report and literature review

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Abstract

BACKGROUND

Extramedullary plasmacytoma (EMP) of the gastrointestinal tract is an extremely rare disease. Clinical manifestations of EMPs are varied and depend on the location and progression of the tumor.

CASE SUMMARY

Here, we firstly report a case of intestinal perforation with abdominal abscess caused by EMP of the small intestine in a 55-year-old female patient. The patient received emergency surgery immediately after the necessary preoperative procedures. During the operation, EMP was found to have caused the perforation of the small intestine and the formation of multiple abscesses in the abdominal cavity. Partial resection of the small intestine with peritoneal irrigation and drainage was performed. EMP was finally confirmed by postoperative histopathology and laboratory tests. Additionally, we performed a literature review of gastrointestinal EMP to obtain a deeper understanding of this disease.

CONCLUSION

EMP of the small intestine may have spontaneous perforation, which requires emergency surgery. Surgical resection can obtain good therapeutic effects.

Key Words: Extramedullary plasmacytoma; Perforation; Small intestine; Gastrointestinal tract; Treatment; Case report

Core Tip: Extramedullary plasmacytoma (EMP) of the gastrointestinal tract is an extremely rare disease, accounting for only 7% of all EMPs. Clinical manifestations of EMPs are varied and depend on the location and progression of the tumor. Here, we firstly report a case of intestinal perforation with abdominal abscess caused by EMP of the small intestine in a 55-year-old female patient. Additionally, we discussed the diagnosis and treatment of gastrointestinal EMP after a review of the literature worldwide to provide an overview of this disease.

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INTRODUCTION

Plasmacytoma is a malignant tumor that originates from bone marrow hematopoietic tissue. It is characterized by an imbalance in the monoclonal proliferation of plasma cells. Extramedullary plasmacytoma (EMP) refers to a localized monoclonal plasma cell proliferation that occurs in soft tissues without bone marrow involvement. It is a rare type of malignant monoclonal plasma cell lesion, accounting for approximately 2%-3% of all plasmacytomas[1,2]. Plasmacytoma primarily occurs in the upper respiratory tract but is rarely found in the gastrointestinal tract. Gastrointestinal EMP only accounts for approximately 7% of all EMPs[3]. EMP is found in all parts of the gastrointestinal tract, including the small intestine[4-7]. Clinical manifestations of gastrointestinal EMPs vary with the location and progression of the tumor and lack specificity. Common clinical manifestations include abdominal pain, abdominal discomfort, changes in bowel habits, gastrointestinal bleeding and intestinal obstruction[8-12]. However, there are no reports of spontaneous perforation and abdominal abscess caused by EMP of the small intestine. Reports on EMP of the small intestine are mostly single case reports, and most of the patients underwent routine surgery[7,13]. It is rare to find this disease during an emergency surgery. In this paper, we firstly present a case of intestinal perforation with abdominal abscess caused by EMP of the small intestine and review the relevant literature from PubMed.

CASE PRESENTATION

Chief complaints

A 55-year-old female was admitted to the Department of Emergency of our hospital with sudden abdominal pain and abdominal distension.

History of present illness

The patient's symptoms started 3 d prior and were accompanied by nausea and vomiting without gas or defecation. Since onset, the patient had a loss of appetite, limited diet, poor sleep and decreased urination. No significant change in body weight was noted.

History of past illness

The patient's previous medical history was not remarkable. She and her family had no history of multiple myeloma (MM) or other gastrointestinal diseases.

Personal and family history

The patient has no personal and family history.

Physical examination

During physical examination, the patient had a normal heart rate and mild hypotension. The patient's abdomen was slightly distended, and the abdominal tenderness was more severe in the left upper abdomen accompanied by rebound pain and muscle tension.

Laboratory examinations

Laboratory tests showed the following: White blood cells 10.5 × 10^{-9}/L, neutrocyte (NE) 9.63 × 10^{-9}/L, NE% 91.7%, hemoglobin 108 g/L, and platelet 330 × 10^{-9}/L. Liver and kidney function were normal.

Imaging examinations

Enhanced computed tomography (CT) showed that the small intestinal lumen in the upper left abdomen was dilated with gas and fluid accumulation, and showed multiple fluid-gas level changes were noted. The intestinal wall was edematous and thickened, and the density of the surrounding fat interspace had increased. Small air bubbles were scattered under the left diaphragm, and multiple encapsulated effusions were observed between the small intestines. These imaging findings suggested local perforation and multiple abscesses in the abdominal cavity (Figure 1).

FINAL DIAGNOSIS

Microscopic analysis showed that the pathological specimen displayed a large number of neoplastic plasma cells with inflammatory cell infiltration (Figure 2A). These plasma cells were positive for CD38 (+), CD138 (+), kappa (+), lambda (week+), CD79a (week+), and MUM1 (+) and negative for creatine kinase (-), CD117 (-), Dog-1 (-), S-100 (-), B cell lymphoma-2 (-), beta-catenin (-), CD56 (-), immunoglobulin G4 (-) and Pax-5 (-) with a Ki-67 proliferative index of 10% (Figures 2B-F). The final pathological specimens were highly suspicious of plasmacytoma. Postoperative laboratory tests showed that the bone marrow cytology was normal and no abnormal monoclonal plasma cells were detected in the flow cytometric analysis. Urine free light chain and serum immunofixation electrophoresis were also normal. Lytic lesions were not found on X-rays. Therefore, the final diagnosis of this patient was primary EMP of the small intestine.

TREATMENT

Considering that the patient may have a perforation of the digestive tract, we performed emergency surgery. During the operation, we found that the small intestinal serosa 100 cm away from the Treitz ligament had a dark-red polyp-like protrusion with a perforation approximately 0.5 cm in diameter at the top. The local intestinal wall was hyperemic, edematous and thickened, and the surface of the surrounding small intestine and lateral peritoneum was covered with many purulent masses (Figure 3). Several abscesses were observed between the left paracolic groove and small intestine and filled with a yellow, turbid fluid. After the abscesses were removed, the abdominal cavity was flushed with a large amount of warm normal saline. Then, a segment of the jejunum 33 cm in length was resected, and a primary side-to-end anastomosis of the small intestine was performed. The lumen of the intestinal tube 6 cm from the nearest end resection margin was narrow with a diameter of approximately 1.5 cm. The serosal surface was similar to a polypoid with a size of approximately 2 cm × 1 cm × 1 cm.

OUTCOME AND FOLLOW-UP

The patient had a good postoperative recovery with no complications, and she was discharged smoothly from the hospital one week after her surgery. As of August 1, 2021, she has been regularly followed up for 2 years at an outpatient clinic, and there have been no signs of recurrence or metastasis.

DISCUSSION

Primary plasmacytoma of the small intestine is rare in clinical practice. Here, we firstly report a case of intestinal perforation with abdominal abscess caused by EMP of the small intestine in a 55-year-old female. The diagnosis is based on a pathologically confirmed small intestinal mass with clonal growth of plasma cells, normal bone marrow histological examination, and normal serum monoclonal immunoglobulin levels[14]. EMP can be divided into two types: Primary and secondary. EMP can also present as a secondary tumor of another plasma cell neoplasm, such as MM[15]. MM must be excluded before the diagnosis of primary EMP[16]. The case we reported had no positive laboratory or imaging findings of MM, which met the diagnostic criteria of primary EMP. In this paper, we performed a review of the well-documented primary gastrointestinal EMP cases in the last 20 years and presented these results in table form[4-7,11,17-45] (Table 1). These results show that gastrointestinal EMP is common in patients over the age of 50 years, and the incidence rate is higher in men compared with women (2:1). The clinical manifestations of gastrointestinal EMPs vary with the location of the tumor and lack specificity. In the early stage, this disease is often asymptomatic, and patients often seek medical treatment because of pain or discomfort caused by local tumor compression. Other clinical manifestations include gastrointestinal bleeding or obstruction, changes in bowel habits, *etc*. In our case, the patient presented with sudden abdominal pain and abdominal distension, which may have been caused by intestinal

Table 1 Well documented case reports of primary gastrointestinal extramedullary plasmacytoma

Ref.	Age	Gender	Location	Presentation	Operative	Non-operative	Outcome
Katodritou *et al* [17], 2008	68	Male	Stomach	Upper-gastrointestinal bleeding	None	Bortezomib, dexamethasone	No recurrence 13 mo after diagnosis
Park *et al*[18], 2009	50	Female	Stomach	None	Endoscopic submucosal dissection	None	No recurrence during 12 mo follow-up
Krishnamoorthy *et al*[19], 2010	57	Male	Stomach	Upper-gastrointestinal bleeding	Gastrectomy	None	N/A
Park *et al*[20], 2014	70	Male	Stomach	Indigestion	Endoscopic submucosal resection	Oral thalidomide therapy	No recurrence during 24 mo follow-up
Zhao *et al*[21], 2014	79	Male	Stomach	Epigastric pain	Surgical resection	None	No recurrence during 8 mo follow-up
Fukuhara *et al* [22], 2016	36	Male	Stomach	Dyspnoea, fatigue	Total gastrectomy, lymphadenectomy	Chemotherapy and autologous peripheral blood stem-cell transplantation	No recurrence during 18 mo follow-up
Kang *et al*[23], 2016	78	Female	Stomach	Epigastric pain	Refused	High-dose dexamethasone	Completely regressed and remission was maintained for over 1 yr
Takahashi *et al* [24], 2016	64	Female	Stomach	Loss of appetite and reduced body weight	Surgical resection	None	No recurrence during 36 mo follow-up
Oliveira *et al*[25], 2017	61	Male	Stomach	Upper gastrointestinal bleeding	Endoscopic polypectomy	None	No recurrence during 6 yr follow-up
Ding *et al*[6], 2019	65	Male	Stomach	Epigastric discomfort and mass	Distal gastrectomy	None	No recurrence during 3 mo follow-up
Weidenbaum *et al* [26], 2022	83	Female	Stomach	None	None	Radiation therapy, chemotherapy	N/A
Carneiro *et al*[27], 2009	72	Male	Duodenum	Epigastric pain, vomiting and weight loss	Resection of the fourth part of the duodenum and proximal segment of jejunum	None	No recurrence after 12 mo follow-up
Ammar *et al*[28], 2010	69	Female	Duodenum	Fatigue, melaena	Percutaneous transhepatic biliary drainage	Extra-corporeal radiotherapy	N/A
Yoshida *et al*[29], 2004	70	Female	Ileum	High fever, bowel obstruction	Combined resection of the terminal ileum and ascending colon	Chemotherapy	Died of cachexia 4 mo after surgery
Moriyama *et al* [30], 2006	73	Female	Ileum	Abdominal pain	Local resection of the tumor	None	No recurrence after 28 mo follow-up
Gabriel *et al*[31], 2014	62	Male	Ileocecum	Melena	Right hemicolectomy	None	N/A
Zhang *et al*[32], 2017	63	Female	Ileocecum	Episodic pain around the umbilicus	Right hemicolectomy surgery	None	N/A
Hanawa *et al*[7], 2019	63	Male	Ileocecum	Abdominal distention and weight loss	Surgically removed stenotic lesion of small intestine	Anti-Crohn's disease	No recurrence during 36 mo follow-up
Evans *et al*[5], 2020	35	Male	Appendix	Upper abdominal pain	Appendectomy	None	Alive without evidence of disease
Doki *et al*[33], 2008	64	Male	Ascending colon	Aggravated pain in the right lower abdomen	Surgical resection	Chemotherapy (recurrence)	Recurrence 4 mo after surgery. Dead after 12 mo
Zhu *et al*[11], 2017	67	Female	Ascending colon	Abdominal pain, and reduced gas and stool passage	Refused	Chemotherapy	Died of agranulo-cytosis and sepsis
Han *et al*[34], 2014	49	Male	Transverse	Periumbilical	Extended laparoscopic left	None	No recurrence during

			colon	abdominal pain	hemicolectomy		36 mo follow-up
Lee *et al*[35], 2013	45	Male	Descending colon	Lower abdominal pain, diarrhoea, weight loss	Laparoscopic extended left hemicolectomy with lymph node dissection	None	No recurrence during 36 mo follow-up
Zihni *et al*[36], 2014	54	Male	Descending colon	Abdominal pain	Left hemicolectomy, small bowel resection	None	Died on the thirty-fifth post-operative day due to sepsis
Lattuneddu *et al* [37], 2004	86	Male	Sigmoid colon	Abdominal pain, rectal bleeding and asthenia	Segmental resection of the left colon, with a complementary colecystectomy	None	No recurrence during 6 mo follow-up
Jones *et al*[38], 2008	65	Male	Sigmoid colon	Dysuria, constant left lower quadrant abdominal pain	Sigmoid colon resection	None	N/A
	57	Male	Sigmoid colon	Fatigue, hematochezia	Hartmann resection of the sigmoid colon	None	Died on day 19 after surgery
Mjoli *et al*[39], 2016	42	Male	Sigmoid colon	Rectal bleeding	Sigmoid colectomy	None	No recurrence during 3 mo follow-up
Kitamura *et al* [40], 2018	77	Female	Sigmoid colon	Lower abdominal pain, nausea	Resection of the sigmoid colon, artificial anus	None	No recurrence during 14 mo follow-up
Gupta *et al*[41], 2007	42	Male	Colon (multiple sites)	Diarrhea, progressive weight loss and malaise	Subtotal colectomy	Adjuvant chemotherapy (melphalan, prednisolone)	No recurrence during 17 mo follow-up
Nakagawa *et al* [42], 2011	84	Female	Cecum, rectum	None	Endoscopic mucosal resection	None	N/A
Gohil *et al*[43], 2015	55	Male	Rectum	Perianal pain, altered bowel habits	Surgical resection	Adjuvant radiotherapy	No recurrence during 17 mo follow-up
Bhangoo *et al*[44], 2021	82	Male	Rectosigmoid colon	Rectal bleeding and obstruction	Open sigmoid low anterior resection	Radiotherapy	N/A
Lin *et al*[4], 2021	80	Male	Rectum	Change of his bowel habit and inhibited defecation	Radical resection of the mass by laparoscope	None	N/A
Antunes *et al*[45], 2010	61	Male	Anal canal	Abdominal discomfort, tenesmus, perineal pain	None	Radiotherapy	No recurrence during 24 mo follow-up

perforation. CT images usually show an infiltrating mass with clear boundaries. When the mass is large, a liquefied necrotic area may appear in the center. However, until now, there has been no description of the specific imaging characteristics of EMP[46]. Therefore, the role of imaging examinations in differentiating gastrointestinal EMP from other neoplastic diseases is limited. EMP may be occasionally misdiagnosed as cancer[47], stromal tumors or inflammatory bowel disease[41]. Hence, the accurate diagnosis of gastrointestinal EMP still depends on histopathological results. For gastrointestinal EMP, endoscopic biopsy is a convenient and practical diagnostic method.

Given the rarity of gastrointestinal EMP, unified treatment guidelines for this disease are not available. At present, complete surgical resection is a good choice for the treatment of gastrointestinal EMP. Several studies have reported that patients with gastrointestinal EMP can be completely cured after surgical resection of tumors[21,24,34,40]. Most of the patients underwent routine surgery. However, the EMP patient we reported with perforation of the small intestine required emergency surgery. In addition to perforation of small intestinal EMPs, perforation of colon EMPs can also occur. Kitamura *et al*[40] reported one case of EMP in the sigmoid colon with perforation. The patient underwent emergency surgery without postoperative adjuvant chemotherapy with no recurrence after 14 mo of regular follow-up. In recent years, endoscopic treatments, such as endoscopic mucosal resection or endoscopic submucosal dissection, have become increasingly popular in gastrointestinal EMP surgery and have obtained a good therapeutic effect[18,20,25]. Due to the high sensitivity of primary EMP to radiotherapy, local radiotherapy is also an effective treatment method[45,48]. At present, many hospitals use radiotherapy as an adjuvant treatment for patients with gastrointestinal EMP after surgery to prevent local recurrence or metastasis. Moreover, radiotherapy can also represent an additional therapeutic option for cases with incomplete resection, lymph node involvement or recurrence. There are also some results suggesting that EMP is well controlled with a dose of 40 Gy or more[49]. In cases that are small, well-defined, or postexcision with positive margins, 40 Gy is acceptable[50]. Currently, most studies in this area are retrospective, and more prospective randomized controlled studies are needed to verify these results.

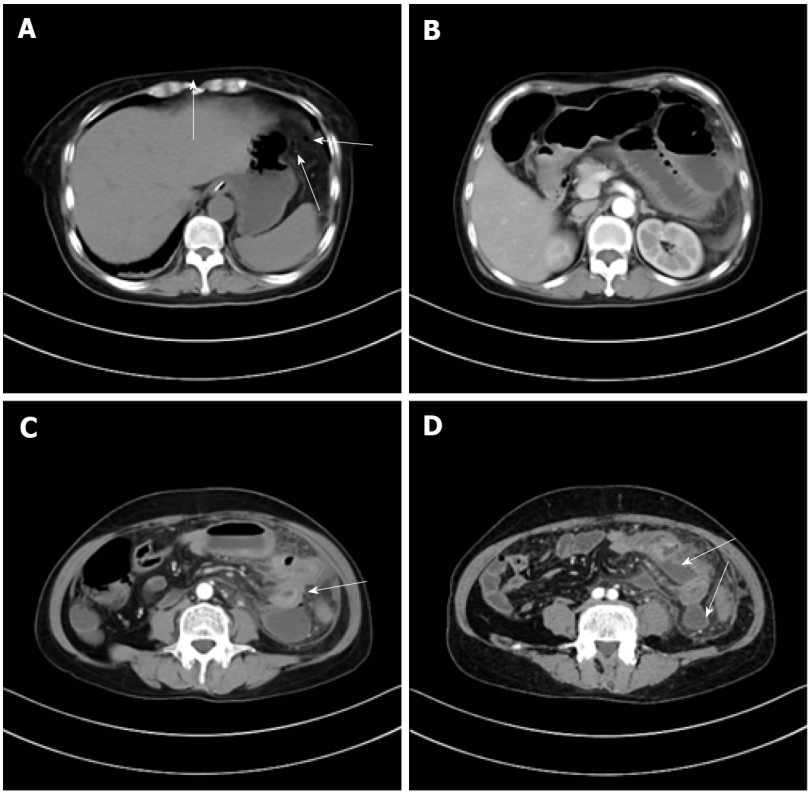

Figure 1 Preoperative computed tomography scan findings. A: There are small air bubbles scattered under the left diaphragm (indicated by white arrow); B: The small intestinal lumen in the upper left abdomen is dilated with gas and fluid accumulation, showing multiple fluid-gas level changes; C: The intestinal wall presents edematous thickening (indicated by white arrow), and the density of local mesentery increases; D: Multiple abscesses can be seen between the intestinal lumen (indicated by white arrow).

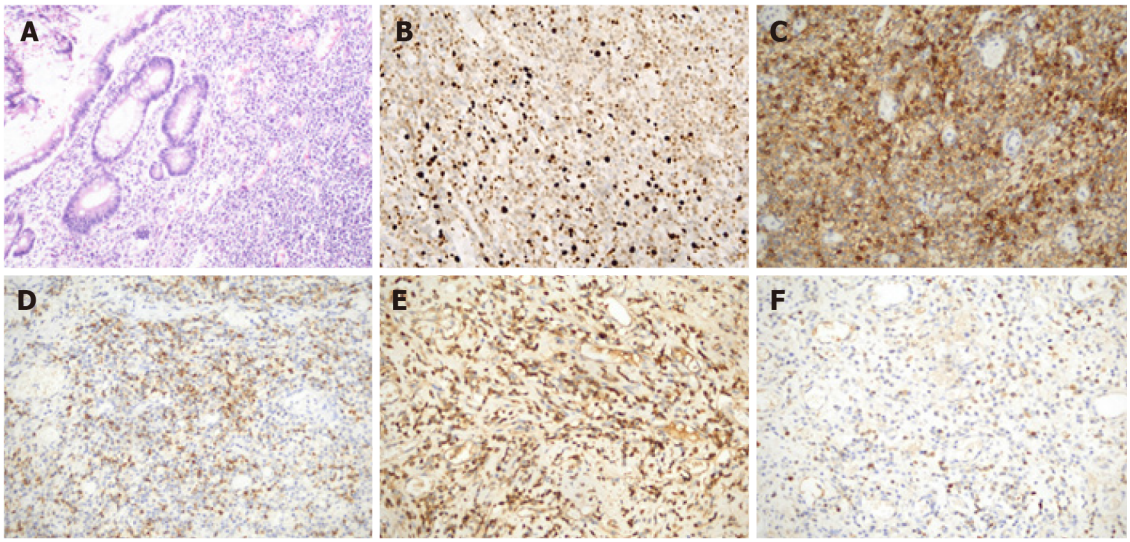

Figure 2 Histopathological examination of extramedullary plasmacytoma of small intestine. Microscopic view of the resected extramedullary plasmacytoma originating from small intestine. A: Hematoxylin and eosin staining, magnification × 100; B: Ki67, magnification × 200; C: CD38, magnification × 200; D: CD138, magnification × 200; E: Kappa, magnification × 200; F: Lambda, magnification × 200.

EMP is a low malignancy tumor with a good prognosis. Local recurrence or recurrence at other sites occurred in 7.5% and 10% of patients, respectively, and the 15-year survival rate was 78%[51]. Given that EMP may recur or progress to MM in some patients, regular long-term follow-up is recommended and necessary. Detailed medical records, physical examination, laboratory tests, including complete blood cell count, beta-2 microglobulin and immunoglobulin levels, renal function, and imaging

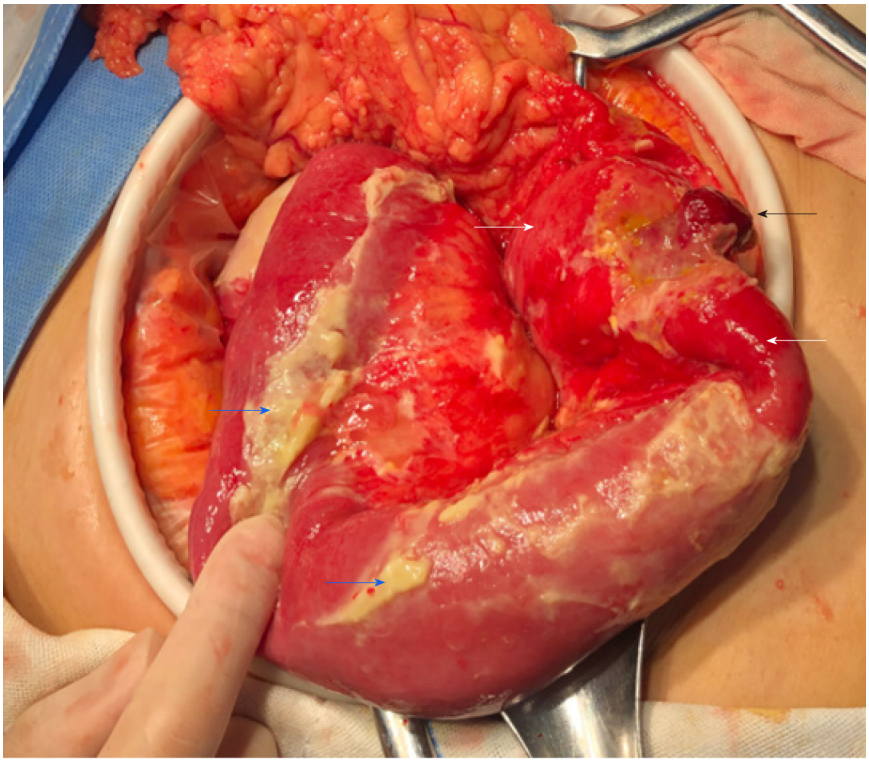

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Figure 3 Intra-operative findings. The small intestinal serosa has a dark red polyp-like protrusion (black arrow) with a perforation about 0.5 cm in diameter at the top. The local intestinal wall presents hyperemia, edema and thickening (white arrow). The surface of the surrounding small intestine is covered with a large amount of purulent material (blue arrow).

examination of the abdomen are required for patients during follow-up[52].

CONCLUSION

In conclusion, EMP of the small intestine is extremely rare and lacks specific clinical and imaging manifestations. EMP may be associated with spontaneous perforation, which requires emergency surgery. We firstly report a case of intestinal perforation caused by EMP of the small intestine. The diagnosis of EMP still depends on the histopathological results. Surgical resection and radiotherapy can obtain good therapeutic effects. The cooperation of a multidisciplinary team, including pathologists, hematologists, radiologists and surgeons, is needed to develop the best diagnostic and therapeutic plan for gastrointestinal EMP.

FOOTNOTES

Author contributions: Wang KW reviewed the literature and contributed to manuscript drafting; Xiao N was responsible for the collection and analysis of case data; and all authors issued final approval for the version to be submitted.

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CASE REPORT

Bowel intussusception caused by a percutaneously placed endoscopic gastrojejunostomy catheter: A case report

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Abstract

BACKGROUND

In adults, bowel intussusception is a rare diagnosis and is mostly due to an organic bowel disorder. In rare cases, this is a complication of a percutaneously placed endoscopic gastro (jejunostomy) catheter.

CASE SUMMARY

We describe a case of a 73-year-old patient with a history of myocardial infarction, chronic idiopathic constipation and Parkinson's disease. For the admission of his Parkinson's medication, a percutaneous endoscopic gastrostomy with jejunal extension (PEG-J) was placed. The patient presented three times at the emergency department of the hospital with intermittent abdominal pain with nausea and vomiting. There were no distinctive abnormalities from the physical and laboratory examinations. An abdominal computed tomography scan showed a small bowel intussusception. By push endoscopy, a jejunal bezoar at the tip of the PEG-J catheter was found to be the cause of small bowel intussusception. The intussusception was resolved after removing the bezoar during push enteroscopy.

CONCLUSION

Endoscopic treatment of bowel intussusception caused by PEG-J catheter bezoar.

Key Words: Bowel intussusception; Percutaneous endoscopic gastrojejunostomy; Bezoar; Percutaneous endoscopic gastrostomy; Case report

Core Tip: In patients with a proximal feeding catheter and complaints of acute or intermittent abdominal pain, intussusception must be considered. An abdominal computed tomography scan is recommended for additional investigation. If small bowel intussusception is present/suspected, we recommend first investigating the cause *via* gastroscopy/push enteroscopy and, if possible, treating it endoscopically immediately so that surgery can be prevented.

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INTRODUCTION

If normal oral intake of food or medication is insufficient or poorly tolerated for a longer period of time, an endoscopically placed percutaneous gastric tube (PEG) can be considered. PEG can be extended to the jejunum (PEG-J) or placed directly in the jejunum (PEJ). These procedures are considered to be safe [1-3]. Common complications of a PEG are a clogged or dislocated PEG catheter, pain at the insertion site, infection and peristomal leakage. Severe complications are rare, including bleeding, perforation, buried bumper syndrome, necrotizing fasciitis and metastatic spread[1,2]. In this case, we describe proximal intussusception of the small intestine as a rare complication of a PEG-J catheter.

CASE PRESENTATION

Chief complaints

The patient was a 73-year-old man who visited the emergency care centre on three occasions in three weeks with intermittent epigastric and lower thoracic pain accompanied by nausea and vomiting.

History of present illness

At the first two presentations, no clear leads were found in anamnesis, physical examination or exploratory additional examinations. No abnormalities were found on point-of-care ultrasound of the abdominal wall or abdomen. Additionally, no anomaly of the PEG-J catheter was found. There were no signs of myocardial ischaemia, as indicated by a normal electrocardiogram (ECG) and troponins. Gastroscopy showed candida oesophagitis, for which fluconazole was prescribed. Due to chronic constipation, laxatives were also started. During the last presentation, the stool pattern had improved, and defecation was daily and of normal consistency.

History of past illness

The patient had a history of myocardial infarction, chronic idiopathic constipation and Parkinson's disease. PEG-J (AbbVie PEG 15 Fr; J extension 9 Fr) was placed 1.5 years ago for the administration of Parkinson medication (levodopa/carbidopa).

Personal and family history

The patient has no personal and family history.

Physical examination

On physical examination, the patient was damp and sweaty, with normal vitals: Heart rate (67/min), blood pressure (141/80 mmHg) and temperature (36.6 °C). Auscultation of the heart and lungs showed a regular heart rhythm without murmur and clear lung sounds. During abdominal examination, sparse, normal-sounding peristalsis was heard. Palpation gave severe pressure pain in the upper left abdomen and in the epigastrio, without rebound pain. No rigidity or guarding was observed. The insertion of the PEG catheter appeared normal without redness, bleeding or hard subcutaneous swelling. PEG-J was open and well situated against the abdominal wall and easy to submerge and reapply.

Laboratory examinations

The laboratory examinations showed (normal values in parentheses) mildly elevated C-reactive protein of 39 mg/L (< 5), normal lipase of 14 U/L (< 60) and a stable troponin-T of 16 ng/L compared to three days prior (< 14). Renal and liver function were normal. Remarkably, an elevated creatine kinase of 366

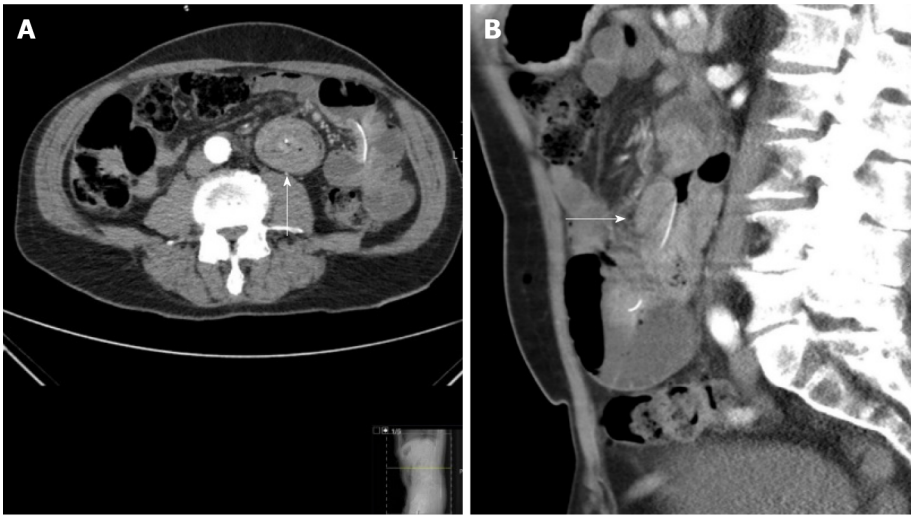

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Figure 1 Abdominal computed tomography scan with intravenous contrast in the arterial and portal venous phases of a 73-year-old man with intussusception at the duodenojejunal junction. A: The transverse section shows a 'target sign'; B: The sagittal section shows a 'sausage sign'.

U/L (< 200) and a mildly elevated lactate of 2.2 mmol/L (0.5-1.6) were detected. The ECG showed a sinus rhythm of 68/min, with no ST-T abnormalities.

Imaging examinations

In the differential diagnosis of peptic/duodenal ulcer disease, cholecystitis, perforation, constipation due to bowel mobility problems in Parkinson's disease, intestinal ischaemia and a complication of PEG-J were considered. Due to these considerations, abdominal computed tomography (CT) scans were performed with intravenous contrast in the arterial and portal venous phases (Figure 1), which showed intussusception at the duodenojejunal junction. There was no evident leadpoint for intussusception, and the intestinal loops proximal to intussusception were not dilated.

FINAL DIAGNOSIS

Small bowel intussusception.

TREATMENT

Proximal push enteroscopy was performed on suspicion of an intussusception possibly caused by PEG-J, a malignant or benign tumor. The button of the PEG was not situated against the stomach wall, and there was traction at the jejunum extension (Figure 2A). A lumen-filling bezoar, *i.e.*, a stony mass, was found in the small intestine at the distal part of the jejunum extension. The bezoar was reduced endoscopically, after which the jejunal extension luxated and returned to the stomach with the remnant of the bezoar (Figure 2B). The jejunum extension was replaced, and the patient was discharged in good condition.

OUTCOME AND FOLLOW-UP

On the first outpatient revision, the patient had no complaints.

DISCUSSION

Bowel intussusception, in which a part of the intestine slides into the next part of the intestine ("telescoping"), is rare in adults. In adults, 1%-5% of intestinal obstructions are caused by intussusception. Most cases (90%) are due to an organic condition, such as inflammatory bowel disease, postoperative adhesions, (Meckel's) diverticula, polyps or carcinoma. An iatrogenic factor is sometimes

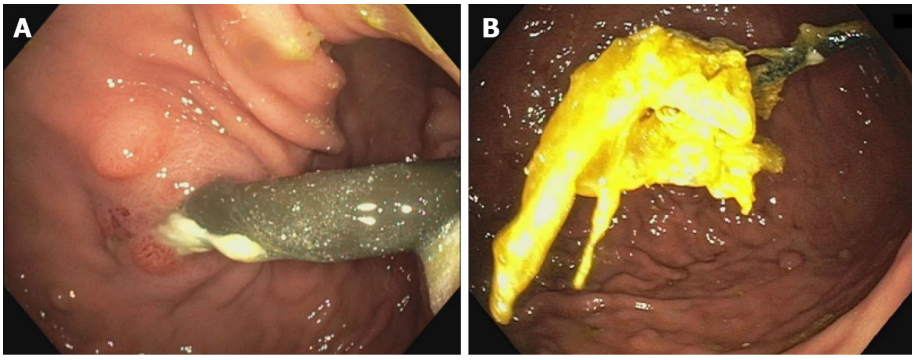

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Figure 2 Push enteroscopy: In a 73-year-old man with intussusception. A: Showing a view of the stomach. Due to traction at the jejunal extension, the button of the percutaneous endoscopic gastrostomy catheter was not situated against the stomach wall; B: Showing the luxated jejunum extension with remnant bezoar after endoscopic reduction.

the cause of intussusception, such as after bariatric surgery or in the presence of intestinal feeding probes[4].

The use of PEG catheters is increasing in popularity because it is considered to be a safe method for the administration of nutrition and medication[1]. Severe complications of a PEG-J catheter are rare, and few case reports have described intussusception after the placement of PEG catheters (PEG/PEG-J/PEJ)[5-8]. Only one similar case has been described in the literature, in which a bezoar was attached to the distal end of a jejunum extension of a PEG[5]. The most likely mechanism causing intussusception in our case was the formation of a bezoar at the jejunum extension and the migration of this bezoar distally through the small intestine by intestinal peristalsis. This served as a lead point, causing intussusception.

Symptoms of intussusception in adults are often nonspecific and can be both acute or chronic. The most common symptom is abdominal pain. Other complaints include nausea, vomiting, gastrointestinal bleeding, abdominal distension and constipation[4,9]. Other PEG complications that can cause similar nonspecific symptoms include, *i.e.*, malpositioning of the PEG, gastric/bowel perforation, or migration of the PEG catheter balloon into the pylorus or duodenum[1,10,11].

If a complication of PEG is suspected, a CT scan should be considered to differentiate between the complications of PEG. In adults, a CT abdomen is preferred in the diagnosis of intussusception because of its 90%-100% accuracy. A "target sign", "sausage sign" or oedematous wall thickening will be observed. Comparatively, ultrasounds have an accuracy of 50%-60%, while X-rays are not sensitive[9,12]. As intussusception in adults is often caused by organic abnormalities, surgery is the most common intervention[12].

Our case illustrates that PEG can be complicated by proximal intussusception of the small intestine. Our advice is to perform imaging for intussusception when a patient with a PEG catheter has acute or intermittent abdominal pain. In addition, when intussusception is diagnosed, a patient should first undergo endoscopic exploration while being treated, if possible, to avoid more invasive surgical treatment.

CONCLUSION

Intussusception is a rare complication of a PEG catheter, with nonspecific clinical presentation. In patients with a PEG catheter complaining of acute or chronic abdominal pain with nausea, vomiting or obstipation, intussusception should be considered. The most accurate diagnostic tool is a CT scan. In cases of intussusception of the small intestine, we recommend immediately exploring and if possible, treating the intussusception endoscopically, to prevent surgical intervention.

FOOTNOTES

Author contributions: All authors were involved in the care of the patient; Winters MW and Kramer S reviewed the literature and contributed to the manuscript drafting; van Putten PG, Mazairac AH and Jutte EH revised the manuscript for important intellectual content; and all authors issued final approval for the version to be submitted.

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LETTER TO THE EDITOR

Important role of acute care surgery during pandemic time

Ming Yang, Chun-Ye Zhang

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Abstract

Pandemic impacts acute care surgery for diseases, such as gallbladder disease and acute appendicitis. At the early stage of coronavirus disease 2019 (COVID-19) pandemic, the case number of patients needing surgery decreased in hospitals from different countries. This decline was associated with the stay-home order and fear of getting COVID-19 infection. However, recent reports show that the case number for acute surgery returns to the normal level, which is comparable to that before the beginning of the pandemic. In addition, a variety of diseases show more severe than the cases before the pandemic, which might be caused by factors such as lack of regular follow-up and screening diagnosis and infection of viruses.

Key Words: Pandemic impact; Acute care surgery; Outcome; Disease pattern and severity

Core Tip: The coronavirus disease 2019 (COVID-19) pandemic impacts the number of cases and disease patterns that required acute care surgery. At the early stage of pandemic COVID-19, the case number of patients for surgery care decreased in hospitals from different countries. The decline was associated with the stay-home order and fear of COVID-19 infection. However, recent reports show that the case number for acute surgery returns to the normal level, which is comparable to that before the beginning of the pandemic. COVID-19 pandemic increases the severity of diseases, such as gallbladder disease and acute appendicitis. This change may be caused by factors including lack of regular follow-up and screening diagnosis and infection of viruses.

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TO THE EDITOR

We read with great interest an observational study recently published by Farber *et al*[1], which investigated the impact of the coronavirus disease 2019 (COVID-19) pandemic on acute care surgery for gallbladder disease and acute appendicitis. This study showed that comparing clinical cases in COVID-19 pandemic time from March to June in 2020 with that in the same period in 2019 at a single tertiary academic medical center in Northern California, more patients with gallbladder disease showed acute and severe cholecystitis, and patients with appendicitis showed more severe situation with a perforated appendix[1].

The COVID-19 pandemic is caused by the infection of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[2], which poses a big challenge to all healthcare systems. During the early COVID-19 pandemic outbreak, the number of cases in patients who needed surgical care is significantly decreased in many hospitals. For example, the total surgical activity performed at Innsbruck Medical University Hospital in Austria was dramatically decreased, including elective, acute, and oncological surgeries[3]. Another study also showed during March 29 to April 25 in 2020, the number of emergency department (ED) visits in the Northeast part of the United States was lower compared to that in 2019[4]. However, a study located in the northern part of Kentucky showed that the number of trauma incidences was comparable, whereas the pattern of trauma to the ED changed, with more cases such as burns and fewer cases of falls[5]. Furthermore, the pandemic also decreased the academic training research activities in Nigeria[6]. The decline of cases is associated with the stay-at-home policy, social distance requirement, and the fear of getting SARS-CoV-2 infection. However, the reduced number caused by the early lockdown turns back to a normal level at the third lockdown time in 2021 at some institutions[7].

Farber *et al*[1] also found that the 30-d re-presentation rate in patients with appendicitis was dramatically increased in 2020 than before[1]. Another study showed that the length of hospital stay increased for trauma patients with COVID-19 infection[8]. In addition, the case pattern and severity of cases are changed during pandemic time. Ajayi *et al*[9] showed that during the second wave of COVID-19 infection, three times more patients with trauma that was caused mainly by fall and traffic accidents were diagnosed with COVID-19 infection, and two times more patients who required surgical operation, but the mortality was decreased compared to the first wave of the pandemic[9]. In contrast, a study in Brazil showed that elective neurosurgical surgery decreased more than emergency surgery, but the mortality rate was increased even though the overall hospitalization was decreased[10].

Although the overall case number for acute care surgery may not be significantly impacted during the pandemic, the severity and pattern of diseases required emergency care may change. Lack of earlier diagnosis and screening for disease and routine follow-up may be the major reason that causes the severity of disease during the pandemic period[11]. Moreover, one study reported that an acute care surgery division is able to manage the intensive care for COVID-19 patients independent of surgical procedures[12].

In conclusion, infection of COVID-19 for patients with trauma or other surgical procedure can increase the risk of morbidity and mortality. A good management procedure and pre-operative COVID-19 testing for patients waiting for surgery care could provide favorable outcomes. With their expertise and experience, surgeons can aid the hospital to provide proper procedures to prevent the potential co-infection of COVID-19 for patients with non-surgical and surgical treatments.

FOOTNOTES

Author contributions: Yang M and Zhang CY collected data, wrote, finalized the letter, and contributed equally.

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

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LETTER TO THE EDITOR

Advances and effectiveness of the immunotherapy after liver transplantation

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Abstract

Transplant recipients usually have increased chances of graft rejection and graft *vs* host disease, requiring chronic immunosuppressive therapy. Nonetheless, long-term immunosuppression risks malignancies such as skin cancer, lymphoma, and Kaposi sarcoma. However, there are very few studies that included solid organ transplant recipients while studying the efficacy of immunotherapy. "Immuno-therapy after liver transplantation: Where are we now?" is a study, where the authors described the mechanism of action and outcomes of immune checkpoint inhibitors specific to liver transplant recipients. The authors reported the graft rejection rates and the factors contributing to the rejection in the liver transplant recipients.

Key Words: Immunotherapy; Hepatocellular carcinoma; Immune checkpoint inhibitors; Liver transplantation; Solid organ transplant; Graft rejection

Core Tip: There is an increased risk of cancer among transplant recipients receiving chronic immunosuppression. Immunotherapy has a beneficiary effect over immunosuppressors in reducing the overall cancer risk. However, there are very few studies that included solid organ transplant recipients while studying the efficacy of immunotherapy. "Immunotherapy after liver transplantation: Where are we now?" is a study, where the authors described the mechanism of action and outcomes of immune checkpoint inhibitors specific to liver transplant recipients.

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TO THE EDITOR

Au *et al*[1] studied the consequences of immunotherapy in patients who underwent liver transplantation (LT) for hepatocellular carcinoma (HCC). We are writing to thank the authors after reading their article conscientiously. Many trials were conducted in the literature studying the efficacy of immunotherapy. However, they excluded organ transplant recipients due to the higher risk of fatal graft rejection.

Transplant recipients usually have increased chances of graft rejection and graft *vs* host disease (GVHD), requiring chronic immunosuppressive therapy. Nonetheless, long-term immunosuppression risks malignancies such as skin cancer, lymphoma, and Kaposi sarcoma. These malignancies constitute the second most common cause of death in organ transplant recipients[2]. Immunotherapy is a breakthrough in managing transplant recipients and acts through interruption of the cancer-immunity cycle. Immune checkpoints, cytotoxic T-lymphocyte antigen 4 (CTLA-4), and programmed cell death 1 (PD-1) are physiologically responsible for preventing effector T cell overactivation.

Immunotherapy includes antibodies against CTLA-4 and PD-1, thereby upregulating the T-cell immune response to the cancer antigen[3]. Although the host immunity against tumor antigens is restored, on the other hand, T-cell stimulation is one of the significant components of graft rejection. The overall rejection rates following immunotherapy are 29%-54% and 25%, respectively, in patients who underwent solid organ transplantation and LT[4-6]. Kidney (40%) is associated with higher rates of graft rejection than liver (35%) and heart (20%)[3]. Au *et al*[1] studied that the graft rejection rates were seen in 32% of patients who specifically underwent an LT. The rejection rates among individuals who received immunotherapy within 2.9 years of transplant were increased compared to 5.3 years of transplant. They also noticed a higher mortality rate of 56% among graft rejected patients.

Compared with CTLA-4 inhibitors, PD-1 inhibitors are associated with higher rates of graft rejection and graft loss in LT recipients[7,8]. Kittai *et al*[9] reported graft rejection in 4 of 8 patients treated with anti-PD-1, whereas no rejections were detected in patients receiving anti-CTLA-4 therapy. Programmed death-ligand 1 (PD-L1) expression on the graft lymphocytes aids as a marker of rejection after immunotherapy[2]. Tacrolimus-based or combination agents (corticosteroids, antimetabolites, calcineurin inhibitors, and mechanistic target of rapamycin inhibitors) immunosuppression is shown to reduce graft rejection and improve the response to immunotherapy[2]. A 10%-20% of post-transplant patients encounter recurrence of HCC[10]. In such cases, immunotherapy is effective only in 11% of patients.

A higher dose of immunotherapy medication, a shorter interval between LT and immunotherapy initiation, expression of PD-L1 on the graft lymphocytes, and a previous GVHD history are positively related with the risk of and response to graft rejection[4]. Studies on patient characteristics such as gender, age, pathological type of primary tumor, donor type, type, and duration of ischemia during LT and post-operative hepatitis virus status of the patient are necessary to learn the factors associated with favorable outcomes after immunotherapy. Proper patient selection is quintessential to preventing lethal graft rejection. Hence, a close collaboration among oncologists and transplant specialists is encouraged when handling patients who require immunotherapy. However, prospective studies focusing on: (1) Although the PD-1 pathway is dominant in establishing immune tolerance, whether anti-PD-1 and anti-CTLA-4 antibodies are associated with graft rejection[9]; (2) The treatment of immunotherapy related graft rejection; and (3) Its efficacy is there any difference in treatment modality between immunotherapy related graft rejection and isolated graft rejection, are required beforehand to recommend immune checkpoint inhibitors in transplant recipients.

FOOTNOTES

Author contributions: Vulasala SSR, Onteddu NK, Kumar SP, Lall C, Bhosale P, and Virarkar MK have equal contributions to this article.

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