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EDITORIAL

Quick and easy assessment of sarcopenia in cirrhosis: Can ultrasound be the solution?

Francesca Campani, Tancredi Vincenzo Li Cavoli, Umberto Arena, Fabio Marra, Erica Nicola Lynch, Claudia Campani

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Abstract

Cirrhosis is frequently associated with sarcopenia, with reported rates of over 80% in patients with decompensated alcohol-related liver disease. Sarcopenia negatively impacts the prognosis of cirrhotic patients and affects the response to treatment of patients with hepatocellular carcinoma (HCC). For these reasons, identifying an easy-to-perform method to assess sarcopenia in is a key element in the optimization of care in this patient population. Assessment of muscle mass by computed tomography is considered the standard of care for the diagnosis of sarcopenia, but exposure to radiation and high costs limit its application in this setting, especially for repeated assessments. We believe that ultrasound, a cheap and harmless technique also used for HCC screening in cirrhotic patients, could have an expanding role in the diagnosis and follow-up of sarcopenia in these patients.

Key Words: Sarcopenia; Ultrasound; Cirrhosis; Hepatocellular carcinoma; Computed tomography

Core Tip: Cirrhosis is frequently associated with sarcopenia, which negatively impacts the prognosis of cirrhotic patients and affects the response to treatment of patients with hepatocellular carcinoma (HCC). For these reasons, identifying an easy-to-perform method to assess sarcopenia in is a key element in the optimization of care in this patient population. We believe that ultrasound, a cheap and harmless technique also used for HCC screening in cirrhotic patients, could have an expanding role in the diagnosis and follow-up of sarcopenia in these patients.

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INTRODUCTION

Cirrhosis is frequently associated with sarcopenia, with reported rates of over 80% in patients with decompensated, alcohol-related cirrhosis[1]. Various pathogenetic mechanisms contribute to muscle wasting in these patients, such as altered protein metabolism, resulting in reduced levels of circulating branched chain amino acids[2] and decreased protein synthesis, increased autophagy, proteolysis, and mitochondrial oxidative dysfunction in the skeletal muscle due to hyperammonemia[3,4]. Chronic systemic inflammation[5], reduction in circulating testosterone levels[6,7], and physical inactivity[8,9] are other factors contributing to sarcopenia in patients with advanced liver disease. Sarcopenia negatively affects the prognosis of cirrhotic patients and the response to treatment in patients with hepatocellular carcinoma (HCC). For these reasons, identifying an easy-to-perform method to assess sarcopenia is a key element in the optimization of care in this patient population. Assessment of muscle mass by computed tomography (CT) is considered the standard of care for the diagnosis of sarcopenia, but exposure to radiation and high costs limit its application in this setting, especially for repeated assessments. We believe that ultrasound (US), a cheap and harmless technique also used for HCC screening in cirrhotic patients, may have an expanding role in the diagnosis and follow-up of sarcopenia in these patients.

DEFINITION OF SARCOPENIA

Sarcopenia is a progressive and generalized skeletal muscle disorder mainly defined by two parameters: Muscle mass and muscle strength. Low muscle strength is the key characteristic of probable sarcopenia, whereas a diagnosis of sarcopenia can be confirmed only after detection of low muscle quantity and quality[10]. Moreover, reduced physical performance is indicative of severe sarcopenia[10], which is associated with an increased likelihood of adverse outcomes including falls, fractures, disability, and mortality[10]. Loss of skeletal muscle mass and function commonly occurring with advancing age is classified as primary sarcopenia, but many other factors can cause or contribute to the development of secondary sarcopenia[10]. Systemic diseases, especially those characterized by inflammatory processes, are one of the leading causes of secondary sarcopenia[11]. Physical inactivity and inadequate energy or protein intake are also involved in the development of sarcopenia[11].

Sarcopenia is also common in overweight and obese patients[11,12], where the loss of muscle mass and function can be favored by chronic low-grade inflammation, increased oxidative stress, insulin resistance, sedentary lifestyle, and a higher incidence of comorbid chronic diseases that may negatively impact muscle metabolism[13]. Several lines of evidence show that sarcopenic obesity represents a strong and independent risk factor for frailty, comorbidities, and mortality, especially among the elderly[14,15].

PREVALENCE AND ROLE OF SARCOPENIA ACROSS LIVER DISEASES

Sarcopenia in metabolic dysfunction-associated steatotic liver disease patients

Sarcopenia is closely associated with metabolic dysfunction-associated steatotic liver disease (MASLD), the most common cause of chronic liver disease in Western countries[16,17]. Patients with sarcopenic MASLD are generally older and more frequently female[18]. Sarcopenia has been suggested to increase the risk of progression of liver fibrosis, and therefore its early recognition may play an important role in preventing the development of cirrhosis[19-21]. Petta *et al*[22] showed that MASLD-sarcopenic patients have more severe liver fibrosis compared with those without. Moreover, the co-occurrence of MASLD and sarcopenia is associated with higher mortality, suggesting that sarcopenia may play a role in increasing the risk of cardiovascular diseases, metabolic disorders, and physical disability in this group of patients[23,24].

Sarcopenia and cirrhosis

Sarcopenia affects between 30% to 70% of cirrhotic patients[25], with higher rates reported in men[26,27]. The etiology of cirrhosis plays a relevant role in the development of sarcopenia. The highest prevalence of sarcopenia can be found in

patients with alcohol-associated cirrhosis, with a prevalence of over 80% in alcohol-related decompensated cirrhosis[1,28]. Alcohol consumption affects muscle mass leading to muscle autophagy, inhibition of proteasome activity and a decrease in insulin-like growth factor 1[29]. Sarcopenia can be both a cause and a consequence of complications of cirrhosis. Ascites may favor muscle loss through anorexia, reduced mobility, and frequent hospitalizations[30]. On the other hand, reduced muscle mass is an independent risk factor for hepatic encephalopathy[31,32] and is linked to an increased risk of decompensation[33].

In cirrhosis, sarcopenia also negatively impacts quality of life[34], increases the risk of infection[35], and prolongs the duration of hospitalizations[36]. Additionally, several studies show that a diagnosis of sarcopenia in cirrhotic patients is associated with an increased risk of falls, fractures, acute-on-chronic liver failure, and death[37-39]. Indeed, a recent systematic review and metanalysis of 22 studies including 6965 cirrhotic patients showed that the risk of death was 2.6 times higher in patients with sarcopenia[27]. Low muscle density has been shown to predict mortality even in patients with compensated cirrhosis[33,40], and sarcopenic obesity is associated with a higher incidence of sepsis-related death [41]. The presence of sarcopenia prior to liver transplantation can significantly increase the length of hospital and intensive care unit (ICU) stay[42,43] and worsens the overall prognosis of these patients[44].

Sarcopenia and HCC

Up to 30%-40% of HCC patients are affected by sarcopenia at the time of diagnosis, at least partially because of the pro-inflammatory state triggered by the altered tumor microenvironment[45]. As sarcopenia influences the response to surgical, locoregional, and systemic treatments, its timely recognition is essential. In patients who undergo liver resection or liver transplantation, tackling sarcopenia reduces sepsis-related complications and length of ICU stay, and decreases patient mortality[46]. In patients treated with thermal ablation, sarcopenia has been linked to a reduced overall survival (OS) and to a higher risk of HCC recurrence[47]. A worse prognosis and high rate of progression has been also described for HCC patients treated with transarterial chemoembolization[48].

Sarcopenia also appears to impact the response to systemic treatments. Scheiner *et al*[49] showed that sarcopenia is associated with worse OS (6.5 months *vs* 20.9 months), progression-free survival (5.8 months *vs* 8.3 months) and objective response rate (22% *vs* 39%) in patients treated with atezolizumab-bevacizumab. Sarcopenic patients treated with sorafenib were subject to a higher drug exposure and increased dose-limiting toxicities *vs* non-sarcopenic patients[50]. In patients treated with lenvatinib, Dong *et al*[51] showed that sarcopenia is an independent prognostic factor of a shorter OS. Sarcopenia might also predict drug toxicity and poor tolerance to lenvatinib[52]. Based on the above findings, an adequate evaluation and diagnosis of sarcopenia in patients with HCC is likely to improve their prognosis.

CURRENT METHODS FOR SARCOPENIA DIAGNOSIS

Although the diagnosis of sarcopenia involves both a functional and quantitative assessment of muscle mass, current research is mainly directed at finding an objective and reproducible method to measure muscle mass. CT imaging currently represents the gold standard to quantify skeletal muscle. Muscle mass is conventionally reported as skeletal mass index (SMI), calculated as the total skeletal muscle area at the level of L3 normalized for height[26]. SMI is the only parameter for which cut-off values for the diagnosis of sarcopenia have been validated, < 50 cm for men and < 39 cm for women[10,26,53]. Alternatively, the psoas muscle index at L3 has been identified as an alternative to SMI, although it shows low accuracy in cirrhotic patients[54]. However, CT scan is not an adequate method to serially follow the improvement or deterioration of muscle mass over time, because of high radiation exposure[55]. For this reason, body composition is assessed with CT scans only when these are performed for other reasons, as in the setting of HCC.

Dual-energy x-ray absorptiometry (DXA), magnetic resonance imaging (MRI), and bioelectrical impedance analysis (BIA) are currently available alternatives, albeit various limitations should be considered. DXA is a costly, radiation-dependent technique influenced by body mass index and fluid retention. MRI is highly accurate but expensive and with restricted availability in most settings. BIA is population and device-dependent and is also affected by fluid retention. When technology-based devices (BIA, DXA, MRI or CT) are not available or feasible, anthropometric measures could be used to quantify skeletal muscle mass, at the expense of test sensitivity and reproducibility[56].

THE ROLE OF US IN SARCOPENIA DIAGNOSIS

US is an accurate and reliable technique, with high reproducibility for the assessment of muscle size[57,58]. Furthermore, abdominal US is used to screen cirrhotic patients for HCC semiannually, in accordance with guidelines of the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases[59,60]. Therefore, the availability of US in virtually all cirrhotic patients, its non-invasiveness and independence of exposure to X-rays, make it an appealing tool for the initial diagnosis and follow-up of sarcopenia in cirrhosis[61], also in clinical studies.

The use of US in muscle assessment has been specifically explored in patients with cirrhosis. It must be noted that most studies included patients with a mild or moderate reduction in liver function (Child Pugh classes A and B) due to the high impact of ascites on the evaluation of psoas muscle by US[62-64]. Furthermore, HCC patients are generally excluded by these studies due to neoplastic cachexia which is considered a confounding factor.

The anatomical site that best represents total skeletal muscle mass has not yet been defined. The rectus femoris (RF) could be a possibility as it is exposed to an earlier age-related decline than other sites such as the biceps femoris[65]. Most

studies evaluating sarcopenia in cirrhotic patients through US used the measurement of large muscles in the upper and lower limbs because of their ease of identification and lesser susceptibility to fluid retention[63]. In fact, ascites can influence the sonic window, especially when examining the muscles of the abdominal wall or psoas[63]. The same issue can be encountered in patients with obesity, a condition that, due to the rising global prevalence, is going to be very frequent in patients with cirrhosis[63]. Another aspect that needs to be defined is the US parameter to be used in muscle mass assessment. Thickness and cross-sectional area of the muscle show similar results as those of DXA, CT, and MRI and may be used to confirm the presence of muscle mass depletion[66]. Echo intensity is a measure of muscle composition in terms of fatty infiltration and presence of fibrous tissue[67]. Indeed, US machines are increasingly equipped with software that could be useful in qualitative analysis of the muscle, defining its microvasculature or stiffness[68-70]. Two-dimensional shear wave elastography of the RF is another qualitative parameter proposed for the assessment of lean mass using US. The measurement of stiffness with this method was feasible in all patients and correlated with liver frailty index (LFI) in a study that involved 44 outpatients with cirrhosis. In addition, RF thickness inversely correlated with LFI [70].

Other key aspects that require standardization are the type of probe that should be employed, the anatomical sites of measurement, the patient's position during the examination, the probe direction and pressure exerted on the muscle, and the parameters that should be measured[68]. A linear probe with a frequency of 5-12 MHz is usually preferred, except for the psoas muscle, for which the use of a convex probe with a frequency of 3.5-5 MHz appears to be more adequate[63].

Despite the lack of standardization, there is growing evidence on the use of US to assess sarcopenia in cirrhotic patients. A recent review evaluating 17 studies assessed the role of US in the diagnosis of sarcopenia in older adults, and showed that US is accurate for the assessment of muscles size, especially when the evaluation is targeted at the quadriceps femoris[57]. In a prospective study including 159 cirrhotic outpatients, Tandon *et al*[71] demonstrated that the combination of body mass index and US-measured thigh muscle thickness was able to identify sarcopenic patients, in both genders, with the same efficacy as CT[71]. This implies an evident advantage in terms of increased screening feasibility and serial assessment to monitor the effectiveness of nutritional interventions[71]. Of note, even in the context of cirrhosis and obesity, the assessment of lean mass through US has been demonstrated to be well-correlated with SMI calculated from CT[72]. Similarly, when LFI or subjective global assessment were employed as references for the assessment of muscle function, a robust correlation with US measurements (*i.e.*, the antero-posterior diameter of the RF, rectus abdominis thickness) was found[70,73].

Besides demonstrating a strong correlation with the reference gold standard, the assessment of lean mass using US also correlates with various clinical outcomes. For example, rectus abdominis thickness predicts survival in a study that included a small group of cirrhotic patients, and both US-SMI and US-psoas to height ratio were significantly related to hospitalization in patients with decompensated liver cirrhosis[73,74].

CONCLUSION

Despite the above outlined limitations and the limited amount of data in large series, the wide availability of the instrument, its ease of application, and especially the possibility of repeated monitoring on the same patient makes US assessment of lean mass in patients with cirrhosis an attractive area of interest for future study.

FOOTNOTES

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EDITORIAL

Expanding indications for chronic hepatitis B treatment: Is it really desirable to treat everyone?

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Abstract

Chronic viral hepatitis causes an increased risk of progressive liver disease and hepatocellular carcinoma. On the wave of the World Health Organization's goal to reduce new cases and deaths from hepatitis B and C by 2030, there is an increasing call to expand the indications for treatment of chronic hepatitis B. Currently, the main goal of treatment is to achieve a functional cure due to the inability of current drugs to completely eradicate the virus. There are still many discrepancies between available guidelines in terms of eligibility for treatment as well as an uncertainty about the appropriate treatment duration. This editorial addresses key questions about the topic and whether indications for treatment should be expanded.

Key Words: Hepatitis B virus; Interferon; Nucleos(t)ide analogues; Functional cure; Children

Core Tip: There is a growing trend to expand the indications for the treatment of chronic hepatitis B. Starting from the concept that current therapies for chronic hepatitis B are unable to completely eradicate hepatitis B virus infection, this editorial critically analyzes the long-term efficacy of the available therapies and the rationale for an extension of current indications.

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INTRODUCTION

In 2016, the World Health Organization set the goal of reducing the global incidence of new cases of hepatitis B and C by 90% and deaths from these two viruses by 65% by 2030[1]. It is well known that patients with chronic viral hepatitis are at increased risk of progressive liver disease and hepatocellular carcinoma (HCC). Over the last few decades, different treatments [first based on interferons and then on nucleos(t)ides analogues (NAs)] have become available for chronic hepatitis B (CHB); the efficacy rates have been variable but none have achieved complete eradication of hepatitis B virus (HBV)[2]. As such, over the last decade the treatment of choice has become long-term administration of NAs with a high barrier to resistance[3].

Currently, the main indications for CHB treatment in adults and children are cirrhosis or active hepatitis. According to available guidelines, the decision to initiate treatment is based on a combined evaluation of HBV-DNA serum levels, alanine aminotransferase concentrations, hepatitis B e antigen status, stage of liver disease, a family history of HCC, and concomitance of HIV infection or other liver diseases[4]. However, there are discrepancies in terms of eligibility for treatment, ranging from conservative (see the European Association for the Study of the Liver guidelines) to interventionist positions (see the American Association of the Study of Liver Diseases and Asian Pacific Association for the Study of the Liver guidelines)[5-7]. Although available treatments are unable to completely eradicate HBV infection, there is a growing trend to broaden the indications for treatment in order to reduce the rates of progression to cirrhosis and HCC and to increase long-term survival.

These hot-topic questions were the subject of a review by Broquetas *et al*[2] and a Letter to the Editor by Bao *et al*[8] recently published in the *World Journal of Gastroenterology*. In particular, Bao *et al*[8] proclaimed the urgent need to extend treatment criteria to improve both the cost-effectiveness and survival of patients with CHB[8].

SHOULD THE INDICATIONS FOR HBV TREATMENT BE EXPANDED?

While there is no doubt about the ability of antiviral therapy in chronic hepatitis C to permanently eradicate the virus, it is equally certain that current antiviral therapies for CHB do not achieve lasting virological eradication in most cases. Since HBV infection is incurable due to the persistence of covalently closed circular DNA in hepatocytes, integration of HBV-DNA into host cell genomes, and HBV-induced defective innate and cellular immune responses, the real advisable goal of therapy has become functional cure (loss of hepatitis B surface antigen and undetectable HBV-DNA in serum)[3]. This limited goal rather than complete eradication of the infection is indicative of the current dissatisfaction with available treatments and the desire to reset therapeutic strategies[9].

In 2022, representatives from academia, industry, regulatory agencies, and patient advocacy groups came together to reach a consensus on CHB treatment endpoints, to update the primary and alternative endpoints, and to revise the functional cure definition (from undetected levels of HBV-DNA in 2019 to levels lower than the lower limit of quantification in 2022)[10]. This indicates the limited effectiveness of the current therapies. These elements must be carefully weighed before considering a possible expansion of the indications for CHB treatment.

Furthermore, unlike chronic hepatitis C where the treatment with new antivirals has a defined duration, the length of therapy for CHB is still a matter of debate. Most people who start hepatitis B treatment must continue it for life to maintain the block of viral replication thus subjecting patients with the high costs of long-term therapy. Indeed, virological relapse is common upon withdrawal of treatment, and the risk of hepatic decompensation after withdrawal is real[11].

The relationships between levels of viral replication and the determination of liver damage are very intriguing in hepatitis B. In fact, patients, such as vertically infected children who present the highest levels of viremia, usually have no signs of liver damage (the so-called immunotolerance phase). In contrast, liver damage often occurs in phases in which viral replication declines and the organism recognizes the virus as non-self[2]. Despite this paradigm that is exhibited in the background of all available guidelines on the topic, the idea that the control of viral replication translates into a positive impact on the reduction of inflammation and liver fibrosis is increasingly strengthened[5-7]. However, the benefit of the treatments used is often based on surrogate parameters rather than mortality/survival percentages. In addition, if there had been a clear benefit in treated patients compared to untreated ones, the indications for therapy would have rapidly expanded in the same way as what happened for hepatitis C.

Much of the reasoning from Bao *et al*[8] to support the expansion of treatment indications comes from a modeling and economic impact analysis that demonstrated that expanding the treatment criteria could reduce HBV-related mortality rates and improve cost-effectiveness[12,13]. As already mentioned, there are studies that have demonstrated an advantage of the treatment, but other positions cannot be ignored. CHB patients included in therapeutic trials are heterogeneous for a series of parameters such as patient age, duration of infection, disease phase, geographical origin, genetic background, virological characteristics, disease severity, and comorbidities, all of which influence the evolution of the disease and complicate the interpretation of results regarding the effectiveness of treatments[9].

Furthermore, the tendency to mainly publish studies with favorable results should not be overlooked[14]. As for the favorable repercussion of treatment on the risk of HCC, there is substantial agreement on the positive impact of antiviral treatment, but controversies and open questions remain[15]. In addition, expanding treatment would also mean treating all children with CHB. Would this imply long-term therapy for these young patients with a long life expectancy? At what cost? It should not be ignored that studies with long observation periods of treated children compared to untreated children have not highlighted major differences in terms of complications and mortality over a period of 24-29 years[16, 17]. The other pediatric studies that demonstrated an advantage of the treatment focused heavily on obtaining laboratory

objectives rather than the risk of complications from cirrhosis and HCC and duration of survival[18,19]. Thus, as often happens, we run the risk of applying evidence carried out in adulthood to children and therefore medicalizing a group of subjects who may not have significant complications in the long term.

CONCLUSION

It would be desirable to define whether the time has already come to expand the therapeutic indications of antivirals with their current cost/effectiveness ratio or whether it is better to wait for new integrated therapeutic strategies that also include immunomodulators aimed at restoring immune functions depleted in CHB patients.

FOOTNOTES

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EDITORIAL

Surgical cystogastrostomy: Is it still worthwhile?

Kin Pan Au, Kenneth Siu Ho Chok

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Abstract

The article by Ker *et al* explores the treatment of peripancreatic fluid collection (PFC). The use of percutaneous drainage, endoscopy, and surgery for managing PFC are discussed. Percutaneous drainage is noted for its low risk profile, while endoscopic cystogastrostomy is more effective due to the wider orifice of the metallic stent. Surgical cystogastrostomy is a definitive treatment with a reduced need for reintervention, especially for cases with extensive collections and significant necrosis. The choice of treatment modality should be tailored to individual patient characteristics and disease factors, considering the expertise available.

Key Words: Endoscopic cystgastrostomy; Surgical cystgastrostomy; Pancreatitis; Pancreatic necrosis; Peripancreatic collection

Core Tip: Treatment options of peripancreatic fluid collection (PFC) include percutaneous drainage, endoscopy, and surgery. Percutaneous drainage is noted for its low risk profile, while endoscopic cystogastrostomy is more effective due to the wider orifice of the metallic stent. Surgical cystogastrostomy is a definitive treatment with a reduced need for reintervention, especially for cases with extensive collections and significant necrosis. The choice of treatment modality should be tailored to individual patient characteristics and disease factors, considering the expertise available.

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INTRODUCTION

Ker *et al*[1] provides valuable insights into the treatment of peripancreatic fluid collection (PFC). The author suggested that percutaneous, endoscopic and surgical drainage offer various treatment options for patients with PFC based on their conditions. We appreciate the author for initiating this important discussion. In our practice, we utilize percutaneous drainage, endoscopy, and surgery for the management of PFC, which relies on our experience in patient selection for these procedures.

When deciding between different procedures for the treatment of PFC, it is crucial to understand the unique characteristics of each approach. Percutaneous drainage is considered to have the lowest risk profile and can be performed under local anaesthesia. However, the external catheter used for percutaneous drainage has the narrowest drainage bore of these drainage techniques. Drain tract dilation and repeated retroperitoneal endoscopic necrosectomy are often required as a result of the small bore. Additionally, percutaneous drainage leads to the formation of a pancreatic fistula, resulting in the need for prolonged catheter drainage. On the other hand, endoscopic cystogastrostomy confers greater risk due to gastric puncture. There is a potential for intraperitoneal leakage and peritonitis, although this risk is reduced after allowing for the encapsulation to develop for more than 4 wk. Despite these risks, endoscopic cystogastrostomy is generally more effective than percutaneous drainage, given the wider orifice of the self-expanding metallic stent (SEMS) (2 cm). This procedure can typically be performed under sedation, avoiding the need for general anaesthesia. However, in cases where the collection contains a significant amount of solid debris, further endoscopic necrosectomy procedures may be required to prevent stent blockage and ensure effective drainage. Finally, surgical cystogastrostomy has the largest orifice, and allows a complete necrosectomy to be performed in the same procedure. This approach offers a more definitive treatment option with a reduced likelihood of reintervention. While laparoscopic techniques have been described, they are primarily utilized for pseudocysts rather than for wall-off necrosis (WON)[2]. Surgery requires general anaesthesia and represents the highest level of invasiveness among the discussed procedures.

The Atlanta classification divided PFCs into 4 categories (Table 1)[3]. It is first divided into acute (< 4 wk) or chronic (≥ 4 wk) collection. Acute collection is subdivided into acute PFC (APFC) if it contains mainly fluid, and acute necrotic collection (ANC) if it is predominantly necrotic. APFC usually requires no drainage. Treatment for infected ANC patients has evolved, emphasizing a shift towards minimally invasive interventions following the landmark study by van Santvoort *et al*[4] advocating for a step-up approach. Percutaneous drainage is preferred over endoscopic drainage because encapsulation may not be well formed and there is a risk of leakage[5].

Chronic collections are classified as pseudocysts, which contain mainly pancreatic juice, or WON if there is large amount of solid debris. Nevertheless, pseudocysts may become infected and contain thick pus and debris, and there is always a clinical spectrum between the two. Endoscopic ultrasound (EUS) often reveals many solid contents in pseudocysts diagnosed *via* computed tomography. For these collections, there is also a growing inclination towards minimally invasive treatments, particularly with the expanding use of EUS. The patients with chronic collection are usually less ill than those with infected ANC with systemic inflammatory response syndrome and organ dysfunction, which potentially make them better candidates for general anesthesia and surgical intervention. From our perspective, the ideal candidate for endoscopic drainage is a pure pseudocyst with minimal solid content. This approach minimizes the risk of pancreatic fistula and is associated with a reduced hospital stay[6]. The lumen created by a SEMS is sufficient for effective fluid drainage and has a low chance of requiring reintervention.

For patients with WON, percutaneous drainage may require repeated interventions, such as dilatation and retroperitoneal endoscopic necrosectomy. EUS-guided cystogastrostomy may be performed but may not be effective when there is considerable necrotic debris, which can lead to stent blockage and persistent infection. Multicentre trials have shown that endoscopic necrosectomy for WON is associated with high morbidity (25%-30%) and mortality (5%-10%)[7,8]. A WON case requires a median number of 3 procedures to be sufficiently treated. A meta-analysis comparing endoscopic and surgical drainage for pseudocysts and wall off necrosis demonstrated that the surgical approach had higher clinical success rates and lower re-intervention rates[9]. The difference is more pronounced in patients with significant parenchymal necrosis[10]. Therefore, it is essential to carefully consider the extent of pancreatic parenchymal necrosis when choosing the drainage method. Failed endoscopic therapy can increase the complexity and risks associated with subsequent surgical treatments[11], highlighting the importance of selecting the most appropriate initial approach based on the individual patient's condition.

Ultimately, while EUS-guided cystogastrostomy may be effective for pseudocysts with minimal necrotic debris, infected pseudocysts and wall off necrosis with significant solid components may be better suited for direct surgical intervention, especially in patients who are deemed fit for surgery and have extensive collections. Additionally, the availability of expertise in radiology, endoscopy, and surgery will influence the choice of treatment modality.

Table 1 Type of peripancreatic fluid collection by Atlanta classification

Type of Collection	Time (weeks)	Necrosis
APFC	< 4	No
ANC	< 4	Yes
Pseudocyst	> 4	No
WON	> 4	Yes

APFC: Acute peripancreatic fluid collection; ANC: Acute necrotic collection; WON: Wall-off necrosis.

CONCLUSION

In conclusion, the management of PFC should be tailored to specific patient and disease characteristics, taking into account factors such as the timing of intervention, the degree of pancreatic necrosis, and the expertise available in different modalities.

FOOTNOTES

Author contributions: Chok KSH initiated the idea of writing up the Editorial; Au KP and Chok KSH contributed to the manuscript writing equally; Chok KSH critically revised the final paper.

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EDITORIAL

Evaluation of urea breath test as a diagnostic tool for *Helicobacter pylori* infection in adult dyspeptic patients

Zeinab Nabil Ahmed Said, Asmaa Mohamed El-Nasser

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Abstract

In this editorial, we discuss the article in the *World Journal of Gastroenterology*. The article conducts a meta-analysis of the diagnostic accuracy of the urea breath test (UBT), a non-invasive method for detecting *Helicobacter pylori* (*H. pylori*) infection in humans. It is based on radionuclide-labeled urea. Various methods, both invasive and non-invasive, are available for diagnosing *H. pylori* infection, including endoscopy with biopsy, serology for immunoglobulin titers, stool antigen analysis, and UBT. Several guidelines recommend UBTs as the primary choice for diagnosing *H. pylori* infection and for reexamining after eradication therapy. It is used to be the first choice non-invasive test due to their high accuracy, specificity, rapid results, and simplicity. Moreover, its performance remains unaffected by the distribution of *H. pylori* in the stomach, allowing a high flow of patients to be tested. Despite its widespread use, the performance characteristics of UBT have been inconsistently described and remain incompletely defined. There are two UBTs available with Food and Drug Administration approval: The ^{13}C and ^{14}C tests. Both tests are affordable and can provide real-time results. Physicians may prefer the ^{13}C test because it is non-radioactive, compared to ^{14}C which uses a radioactive isotope, especially in young children and pregnant women. Although there was heterogeneity among the studies regarding the diagnostic accuracy of both UBTs, ^{13}C-UBT consistently outperforms the ^{14}C-UBT. This makes the ^{13}C-UBT the preferred diagnostic approach. Furthermore, the provided findings of the meta-analysis emphasize the significance of precise considerations when choosing urea dosage, assessment timing, and measurement techniques for both the ^{13}C-UBT and ^{14}C-UBT, to enhance diagnostic precision.

Key Words: *Helicobacter pylori*; Urea breath test; Diagnosis; Diagnostic test accuracy; Meta-analysis

Core Tip: This editorial comments on the article published in the *World Journal of Gastroenterology*, where it demonstrates that ^{13}C-UBT is an accurate test procedure to detect *Helicobacter pylori* infection. It is a safe and simple test for the patient, providing clear positive or negative test results for the clinician in the majority of cases, making it the preferred non-invasive test in clinical settings. Furthermore, the provided article highlights the importance of accurate and careful choosing of urea dosage, timing of assessment, as well as techniques of measurement for ^{13}C-UBT and ^{14}C-UBT, thereby improving diagnostic accuracy.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is a spiral-shaped Gram-negative, non-spore-forming bacterium that is microaerophilic and requires complex enriched growth media for its cultivation[1]. The bacterium typically colonizes the epithelium lining of the human stomach, particularly the gastric antrum. *H. pylori* are characterized by producing a powerful urease enzyme that hydrolyzes urea acquired in the diet to produce ammonia and carbon dioxide. This enzymatic process neutralizes gastric acidity and raises periplasmic pH to alkaline mediators, resulting in peptic ulcer (PU), gastritis, gastric adenocarcinoma, and low-grade B mucosa-associated lymphoma[1-4]. It is reported that about 50% of the world's population is infected with *H. pylori*. However, there are significant differences in the prevalence, incidence, age distribution, and outcomes of infection between developing and developed countries[2,5,6].

Diagnosis of patients infected with *H. pylori* can be achieved through non-invasive tests including serology, urea breath test (UBT) and stool antigen detection[7]. Alternatively, invasive techniques utilizing endoscopic gastric biopsy for histopathology and microbial identification tests including rapid urease test (RUT), bacterial culture and biochemical reactions can also be employed[3,8], as show in Figure 1 and Table 1[9-11]. The recommended protocol to identify *H. pylori* infection is a combination of RUT or microbiological culture with a histopathological examination of two different sites following having an endoscopic biopsy[12].

UBT can play a useful role in diagnosing dyspeptic patients with specific criteria, such as those with any associated comorbidity that increase the risk of gastric endoscopy, intolerance to gastric endoscopy, diagnosed or doubtful cases of gastric atrophy[13]. Stool antigen tests are alternative non-invasive assays for detection of active of *H. pylori* infection. The proper selection of diagnostic method is based on several factors including cost, laboratory infrastructure, and the accompanied administration of medical treatment such as antibiotics or proton pump inhibitors, which may affect the test results. It was well known that serum antibody test results are variable geographically among population and may remain positive for an extended period after eradication of *H. pylori*, which limits their clinical value in confirming or ruling out current *H. pylori* infection[11].

Current guidelines recommend the use of UBT as a noninvasive test for diagnosing *H. pylori* infection and demonstrate eradication after treatment[14,15]. These recommendations are primarily documented by many researchers that demonstrate UBT sensitivity of 90%–96% and specificity of 88%–98%; in addition to its cost effectiveness and acceptance by patients compared to the invasive gold standard endoscopy[16,17]. Moreover, on comparison with other non-invasive tests, such as stool antigen test and serology, UBT exhibits the highest accuracy[17,18]. The UBT is particularly appropriate for all healthcare settings where endoscopy is not strictly indicated and for assessing the effectiveness of eradication therapy[19].

The ^{13}C and ^{14}C tests are two versions of the UBTs approved by the Food and Drug Administration. Both tests are cost-effective and provide real-time availability results[20]. Doctors like the use of ^{13}C-UBT test since it is non-radioactive when compared to ^{14}C-UBT. However, the latter uses a relatively low radiation dose (approximately 1 microCi) of a radioactive isotope. Despite this, ^{14}C-UBT demonstrates a high degree of diagnostic accuracy[21].

Labeling urea with the ^{13}C non-radioactive isotope is preferable as the test can be used frequently on the same patient and can be applied safely to children and pregnant females. Meanwhile, the UBT that uses ^{14}C as a diagnostic test for *H. pylori* is still not approved by most health care authorities, as it is associated with a dose of radiation that might be hazardous. Thus, its use is contraindicated in some situations such as pregnancy and in young age groups[22,23]. The provided meta-analysis results also revealed high UBT performance, as well as high discrimination ability between patients and healthy individuals. However, the quality of this evidence is not strong enough due to heterogeneity that is explained by various factors such as using different reference standards, timing between capsule intake and test performance, or variation in the quality of the methodology of the included studies[24].

Beside the non-invasiveness of UBT, the test provides a comprehensive evaluation that is not dependent on the possible errors which may occur during sampling of gastric endoscopic biopsy because of the *H. pylori* patchy distribution[9]. Moreover, the biopsy-based tests largely depend on the skills and experience of the pathologist, with studies confirming internal observer variability[10,25]. On the other hand, results of UBT test can be impaired by the intake of *H. pylori* eradication medication, including antibiotics, proton pumps inhibitors, or bismuth. Additionally, it needs special CO_2 tracing equipment, as well as infrastructure to deal with radioactive materials in the case of ^{14}C-UBT. Consequently,

Table 1 Comparative assessment of different techniques for diagnosis of *Helicobacter pylori* Infection

Criteria	Invasive tests	Non-invasive tests
Technique	Endoscopy	UBT, stool antigen, serology
Sample	Biopsy	UB, stool, serum
Sampling error	++	Variable
Accuracy	The gold standard	Variable
Skill and experience	++	Easily applicable
Time of results	Short	Longer (variable)
Cost	++	+
Contraindications	May not be suitable for all patients	Suitable for most patients
Equipment and infrastructure	+++	++
Availability	Available in specialized settings	Widely available in various healthcare settings
Patient discomfort	++	Minimum
Post-treatment monitoring	+	+++

UB: Urea breath; UBT: Urea breath test.

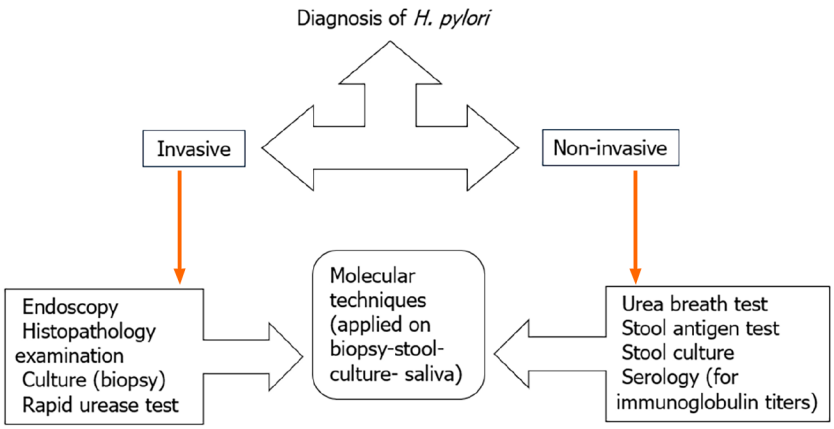

Figure 1 Invasive and non-invasive *Helicobacter pylori* diagnostic tools. *H. pylori: Helicobacter pylori.*

it is considered an expensive test.

Although the UBT is well known for its high diagnostic accuracy in detection of *H. pylori* infection in dyspeptic patients, caution should always be taken in interpreting the test results due to significant limitations related to unexplained heterogeneity documented in several studies and assigned to various factors. For instance, the mouth normal flora urease enzyme activity may impair the UBT results; this can be avoided by advising each patient to wash his mouth before being tested[24]. The use of a nasogastric tube can be a solution. It is of note that both time of having the reading results following the meal intake and the cut-off value were not clarified in a lot of the recruited studies[11]. The nature of the radioactive isotopic meal and patients' individual variations as age, gender, and anthropometric measures may also contribute to variability within and between different studies[26]. These factors may endorse the diversity persistence even after UBT type adjustment (^{13}C *vs* ^{14}C) and method of measurement (infrared spectrometry *vs* radioisotope mass spectrometry). The recommendations for using UBT include precise considerations on adjusting dose of urea, timing of assessment, and measurement techniques for the ^{13}C-UBT and ^{14}C-UBT, so improving diagnostic accuracy.

H. PYLORI DIAGNOSTIC TOOLS

Based on the availability of various diagnostic techniques, including invasive and non-invasive tests with different proportion of sensitivity and specificity for detection of *H. pylori* infection, the choice of one or more tests will depend on clinical conditions, clinical experience, cost-effectiveness, as well as sensitivity and specificity[27]. The diagnostic tests, as shown in Figure 1, are divided into two approaches: Invasive tests (upper endoscopy, histopathology, bacterial culture,

Table 2 ^{13}C-urea breath test & ^{14}C-urea breath test performance

Test type	^{14}C-UBT		^{13}C-UBT	
	Optimal sensitivity	Optimal specificity	Optimal sensitivity	Optimal specificity
Urea dose	99.21% with 5 μCi	93.43% with 5 μCi	98.85% with 25 mg	99.13% with 25 mg
Time of assessment after urea administration	98.39% (15 min)	98.71% (15 min)	98.87% (20 min)	98.14% (20 min)
Assessment technique	-98.79% (liquid scintillation counting); -95.40% (solid scintillation UBT)	-87.24% (liquid scintillation counting); -97.46% (solid scintillation UBT)	98.99% (ICOS)	98.55% (ICOS)
Overall accuracy, %	96.15	89.84	96.60	96.93
Safety	Not permitted		Used several times on the same patient and safe for children and pregnant females	

ICOS: Integrated cavity output spectrometry; UBT: Urea breath test.

and molecular techniques) and non-invasive tests (urea breath test, stool antigens, serological, and molecular tests) for diagnosing *H. pylori* infection[28]. UBT is considered as the gold standard non-invasive test for diagnosing *H. pylori* that shows high accuracy, sensitivity and specificity. It is of note that UBT has been used for nearly thirty years and remains the most accurate and most common non-invasive assay for diagnosing *H. pylori* infection[11]. The provided meta-analysis determines the UBT diagnostic accuracy for detecting *H. pylori* infection in adult dyspeptic patients and evaluates various variables related to the test accuracy, such as urea dose, assessment timing and selection of measurement technique for both ^{13}C UBT & ^{14}C UBT.

^{13}C-UBT PERFORMANCE: DOSE OF UREA, TIMING OF ASSESSMENT, AND CHOICE OF MEASUREMENT TECHNIQUE

The provided results in the current meta-analysis highlighted the crucial importance of adjusting the appropriate dose of urea when performing the ^{13}C-UBT for diagnosing *H. pylori* infection. The dose of twenty-five mg urea shows the highest sensitivity and specificity (98.85% & 99.13%) respectively[13]. As regards the timing of the assessment following urea administration, the results of the current meta-analysis revealed that the maximum sensitivity and specificity, both above 98%, are reached at 20-min following urea intake. The selection of assessment technique is also critical for accuracy of the test. Integrated Cavity Output Spectrometry (ICOS) is the most precise assessment test, with nearly equal sensitivity of and a specificity of (98.99% & 98.55%) respectively. However, it is of note that ICOS was assessed in one study only[29].

^{14}C-UBT PERFORMANCE: UREA DOSE, TIMING OF ASSESSMENT, AND CHOICE OF MEASUREMENT TECHNIQUE

Results indicate that the dose of urea used in the ^{14}C-UBT can also affect accuracy of the test. Particularly, five μCi dose of urea was evaluated in four studies and showed a sensitivity and a specificity of (99.21% & 93.43%) respectively. As regards the time for measurement after ingestion of the urea meal, conducting tests 15 min post urea intake constantly showed the highest sensitivity and specificity (98.39% & 98.71%) respectively. This shows that the 15-min time point is optimal for augmenting the test precision[30]. In terms of assessment techniques, the meta-analysis revealed differences in sensitivity and specificity. Liquid scintillation counting showed the highest sensitivity (98.79%) but at the expense of specificity (87.24%). On the other hand, Solid Scintillation UBT (scintillation counting) demonstrated higher specificity (97.46%) on expense of sensitivity (95.40%).

The trade-off between sensitivity and specificity must be put in mind in clinical setting, when selecting the assessment technique[31]. For instance, liquid scintillation counting is the recommended method when high sensitivity is essential to bypass missing true results, while solid scintillation counting could be a better selection, when high specificity is crucial to minimize false positives.

The meta-analysis showed that both ^{13}C-UBT and ^{14}C-UBT revealed high area under the curve values near 1.00, confirming their high precision and endorsing any of them as reliable diagnostic technique in clinical setting. However, the outperformance diagnostic accuracy of ^{13}C-UBT over ^{14}C-UBT is demonstrated by higher sensitivity, specificity, likelihood ratios, and area under the curve Table 2. ^{13}C-UBT's Diagnostic odd ratio (DOR) significantly outperforms that of ^{14}C-UBT (DOR), making it the preferred diagnostic tool for dyspeptic individuals with *H. pylori* infection[32].

CONCLUSION

The authors conducted a thorough and comprehensive evaluation of the UBT, demonstrating a profound understanding of its diagnostic capabilities for *H. pylori*. The research reflects a rigorous methodology, highlighting the authors' commitment to scientific excellence in evaluating the accuracy and advantages of UBT in diagnosing *H. pylori*. The efforts of the authors are particularly appreciated for bridging the gap between research and clinical practice, providing valuable insights that can directly impact patient care and management. The study significantly contributes to the medical knowledge by advancing our understanding of UBT as a diagnostic tool, and potentially influencing future guidelines and protocols. The authors' acknowledgment of the limitations of their meta-analysis demonstrates intellectual honesty and contributes to the overall reliability of their research, guiding future investigations in this field. The collective efforts of the authors have a meaningful impact on advancing diagnostic approaches for *H. pylori*, highlighting their dedication to advancing medical science and improving healthcare outcomes.

FOOTNOTES

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EDITORIAL

Chronic active and atrophic gastritis as significant contributing factor to the development of gastric cystica profunda

Veronika Papp, Pál Miheller

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Abstract

Gastric cystica profunda (GCP) is an uncommon but underestimated gastric lesion. Its precancerous potential determines its significance. In addition to previous mucosa injury due to operations, biopsy or polypectomy, chronic active and atrophic gastritis may also lead to the development of GCPs. By carefully examining the stomach and taking biopsy samples from the susceptible regions, the stage of atrophy can be determined. Chronic atrophic gastritis is a risk factor for cancer evolvement and it can also contribute to GCPs formation. GCPs frequently occur close to early gastric cancers (EGCs) or EGC can arise from the cystic glands. Endoscopic resection is an effective and minimally invasive treatment in GCP.

Key Words: Gastric cystica profunda; Chronic active gastritis; Atrophic gastritis; Operative Link for Gastritis Assessment staging; Early gastric cancer; Endoscopic resection

Core Tip: Gastric cystica profunda (GCP) is a premalignant lesion developing on basis of ischemia. Chronic active or atrophic gastritis are considered to be a significant etiological factors in the development of GCPs and carry a risk for cancer formation. GCPs, with or without early gastric cancer, can be removed effectively by endoscopic resection.

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INTRODUCTION

In this editorial we comment on the article by Geng *et al*[1] published in the recent issue of the *World Journal of Gastroenterology*.

Gastric cystica profunda (GCP) is a rare gastric lesion characterized by poor clinical symptoms and mostly unremarkable endoscopic features. Therefore, the incidence of a polypoid cystic ectasia of the gastric glands is underestimated [2]. It's pathomechanism remains obscure. A prior stomach operations, biopsy, or polypectomy can cause the development of GCP. In contrast, mucosa damage or ischaemia are factors that commonly manifest in chronic active and atrophic gastritis. Carcinoma cascade is well known since the last decade, intestinal metaplasia occurs following the loss of normal glandular tissue[3]. *Helicobacter pylori* (*H. pylori*) is frequently the cause of chronic inflammatory processes. Identification of high-risk individuals for chronic gastritis, appropriate diagnostic interventions and follow-up are critical to the prevention of invasive cancer.

It is yet not well understood how early stomach cancer development is related to GCP. The migration of stomach glands into the submucosa occurs when the muscularis mucosa is disrupted. GCP and gastric adenocarcinoma can occur simultaneously with recurrent erosion and regeneration of the mucosa if no surgical intervention was performed previously. This suggests that GCP is both a paracancerous lesion and a precancerous lesion based on the progression from dysplasia to invasive carcinoma. Mitomi *et al*[4] reported a case in which atypical or dysplastic epithelium in the deeper part of GCP was seen adjacent to carcinoma. In a Korean report on 39 GCP cases 16 were associated with early gastric carcinoma, 9 with adenoma and 3 with advanced adenocarcinoma[5]. If cancer cells are detected in GCPs, this may be because the submucosa provides an easier path for cancer cells to move through[6]. Data from Itami *et al*[6] suggest that gastric cancer (GC) has a tendency to arise in association with, linked to, above or near the GCPs, not growing from them. Xu *et al*[2] revealed dysplasia or intramucosal carcinoma in 50% of reported GCP cases; these were found in the glands overlying GCPs. Moreover, Kaizaki *et al*[7] described that EBV infection presenting together with chronic inflammation, may facilitate the development of GCPs and therefore GC. GCP may also be paracancerous or premalignant lesion. Alternatively, it might be the result of a field-effect damaging the stomach mucosa, which can result in cancer[6].

Endoscopic procedures play not only a role in adequate diagnosis of chronic inflammation, atrophy, or intestinal metaplasia, are also useful for differentiating submucosal lesions. Conventional white-light endoscopy, the most common endoscopic feature, is nonspecific in GCPs. Endoscopic ultrasonography is highly helpful in detecting the shape, size, and echoic patterns of GCP, but a definitive diagnosis should be established by histologic examination with numerous biopsy samplings to map the extent of the lesions. If GCP is discovered, according to standard protocols, endoscopic resection (ER; endoscopic mucosa resection or endoscopic submucosa dissection) depending on size, shape and location can be performed with *en bloc* and complete resection of the lesion[2]. According to data of the current article of Geng *et al*[1], ER might serve as an effective and minimally invasive treatment for GCP with or without early GCs (EGC).

CLINICAL IMPLICATION

A pathological examination is required for the diagnosis of chronic gastritis, therefore several appropriate biopsy samples are needed. Normal gastric mucosa contains only small numbers of scattered mononuclear inflammatory cells, increased infiltration of the lamina propria with mononuclear leukocytes suggest chronic inflammation while polymorphonuclear neutrophils indicate acute inflammation. Most often, they have an infectious etiology; gastritis is most commonly caused by *H. pylori*. The severity of inflammation depends on the H. pylori strain[3]. In order to standardize the pathological diagnosis, the updated Sydney System's recommendations are adhered to. The Operative Link for Gastritis Assessment (OLGA) and Operative Link for Gastritis Intestinal Metaplasia Assessment (OLGIM) stages allow for the identification of high-risk individuals with chronic gastritis who need special attention[8].

Active chronic inflammation can persist as non-atrophic chronic gastritis (no gland loss), or progress to multifocal atrophic gastritis, which is the initial significant step in the precancerous cascade followed by dysplasia and invasive carcinoma[3]. A different extent and topographical distribution of atrophy is associated with different cancer risk. Multiple biopsy samples should be used to map the mucosa, and the oxyntic and antral mucosa need to be examined as well. The earliest onset of atrophic–metaplastic transformation is located on the incisura angularis. The OLGA proposal recommends at least five biopsy samples from the following locations: The greater and lesser curvatures of the distal antrum, the lesser curvature at the incisura angularis and the anterior and posterior walls of the proximal corpus. The OLGA stage means the combination of the overall "antrum score" with the overall "corpus score". The goal of this staging system is to help physicians to find high-risk patients for malignancy, develop a follow-up protocol and tailor a clinical or endoscopic management[9].

In a prospective study from Zhou *et al*[10], 71 patients with early GC and 156 patients with non-EGC underwent endoscopic examination and systematic biopsy. Logistic regression modeling showed significant correlations between EGC and moderate-to-severe EGA (Japanese endoscopic gastric atrophy classification) and OLGA stages III-IV, but no significant correlation between EGC and OLGIM stages[10].

Chronic inflammation due to atrophy and ischaemia are suggested to play a role in the development of GCPs, as repeated erosion and regeneration causes aberration of the gastric glands. GCP may be a risk factor for multiple GC.

CONCLUSION

According to the fact that GCPs may also be paramalignant or precancerous lesions, as was previously mentioned, its detection carries significance to prevent the precancerous cascade and invasive gastric formation, as well as identifying high risk patients for GC. Particularly in mucosal and submucosal types, the OLGA method could be used for screening. If GCP is discovered ER might serve as an effective and minimally invasive treatment even in cases when EGC exist. A prospective study is needed for better understanding the pathophysiology and to estimate incidence of GCP as well as coincidence with chronic active and atrophic gastritis. Although there are not enough data, the OLGA method may be used to screen GCPs, especially in mucosal and submucosal forms.

FOOTNOTES

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MINIREVIEWS

Contrast-enhanced guided endoscopic ultrasound procedures

Marcel Ioan Gheorghiu, Andrada Seicean, Cristina Pojoga, Claudia Hagiu, Radu Seicean, Zeno Sparchez

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Abstract

Contrast-enhanced endoscopic ultrasound (CH-EUS) can overcome the limitations of endoscopic ultrasound-guided acquisition by identifying microvessels inside inhomogeneous tumours and improving the characterization of these tumours. Despite the initial enthusiasm that oriented needle sampling under CH-EUS guidance could provide better diagnostic yield in pancreatic solid lesions, further studies did not confirm the supplementary values in cases of tissue acquisition guided by CH-EUS. This review details the knowledge based on the available data on contrast-guided procedures. The indications for CH-EUS tissue acquisition include isoechoic EUS lesions with poor visible delineation where CH-EUS can differentiate the lesion vascularisation from the surrounding parenchyma and also the mural nodules within biliopancreatic cystic lesions, which occur in select cases. Additionally, the roles of CH-EUS-guided therapy in patients whose pancreatic fluid collections or bile ducts that have an echogenic content have indications for drainage, and patients who have nonvisualized vessels that need to be highlighted *via* Doppler EUS are presented. Another indication is represented if there is a need for an immediate assessment of the post-radiofrequency ablation of pancreatic neuroendocrine tumours, in which case CH-EUS can be used to reveal the incomplete tumour destruction.

Key Words: Endosonography; Contrast-enhanced endoscopic ultrasound; Tissue acquisition; Fine needle aspiration; Fine needle biopsy; Drainage; Pancreatic fluid collections; Biopsy; Pancreas

Core Tip: Contrast-enhanced endoscopic ultrasound may be better at identifying the targeted area in lesions by avoiding necrosis and vessels and improving the delineation of lesion margins. Guided fine-needle aspiration or fine-needle biopsy is simple and safe, but its benefit is limited to isoenhanced lesions or those with important surrounding fibrosis. These guided endoscopic ultrasound techniques can also be useful for guiding drainage in patients who have very echogenic content of pancreatic fluid collections or bile ducts.

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INTRODUCTION

Endoscopic ultrasound (EUS) has been developed as a valuable diagnostic technique for different intra-abdominal conditions, especially for tissue acquisition for the confirmation of oncologic diseases. A meta-analysis comprising 18 randomized controlled studies and 2718 patients with solid masses showed that the diagnostic accuracy of EUS-fine needle aspiration (EUS-FNA) was 67%-100%, the diagnostic accuracy of EUS-fine needle biopsy (EUS-FNB) was 69-100% and there was an advantage of using EUS-FNB needles [risk ratio: 0.94, 95% confidence interval (95%CI): 0.92-0.97; P = 0.0002][1]. Limited sample adequacy leads to false negative results, caused by technical difficulty due to the needle positioning (*e.g.*, head/uncinate processus lesions) or intrinsic fibrosis of solid pancreatic masses[2]. Additionally, the presence of avascular areas inside pancreatic solid lesions was associated with a 72.9% sampling sensitivity, as compared to a 94.3% sampling sensitivity in lesions without avascular areas[3].

To improve and overcome the limitations of grayscale images, harmonic contrastenhanced EUS (CH-EUS) has become a promising imaging modality for visualizing microvessels inside targeted lesions for diagnostic or therapeutic purposes by using contrast microbubbles to enhance the low flow of capillary vascular network signals.

More than ten years ago, a study that combined EUS-FNA with CH-EUS guidance reported a sensitivity of 100% for diagnosing malignancies, and a hypoenhanced pattern was considered to indicate malignancy when there were false-negative FNA results[4]. In a subsequent study on 100 pancreatic solid lesions, CH-EUS helped to identify the target for EUS-FNA in the subgroup of mixed enhancement patterns (26% of adenocarcinoma cases) by targeting the hypoenhanced area, which led to a very good sensitivity of 95%[5].

Guiding CH-EUS-FNA was developed as an advanced medical procedure for improving the characterization of the margins and internal components of solid and cystic lesions and subsequently for improving the diagnostic accuracy.

Another rare application of CH-EUS is during the drainage of pancreatic fluid collections or bile ducts because it allows for better visualization of the structures that are to be crossed during puncture, but related data in the literature are scarce.

METHODOLOGY

We performed a systematic search of the English literature published in the PubMed, Embase and Cochrane Library databases using the following keywords: "Contrastenhanced endoscopic ultrasound", "contrast enhancement", "contrastenhanced endosonography", "biopsy", "fine needle aspiration", "fine needle biopsy", "interventional EUS", "radiofrequency ablation", "pancreatic cancer", "pancreatic fluid collection", "drainage", "walled-off necrosis", "biliary drainage", "gallbladder drainage", "radiofrequency ablation", and "tumour ablation". All the authors participated in the search and selection of relevant studies.

SOLID PANCREATIC LESIONS

According to recent guidelines, CH-EUS is recommended for the characterization of pancreatic solid lesions[6-10], especially inhomogeneous lesions[6]. The hypoenhanced pattern had a sensitivity of 93% and a specificity of 80% for the diagnosis of pancreatic adenocarcinoma[11]. In contrast, the hyperenhanced pattern was described in cases of benign lesions such as autoimmune pancreatitis, mass forming chronic pancreatitis or an intrapancreatic accessory spleen or in cases of neuroendocrine tumours or pancreatic metastases[12-16]. The presence of the hyperenhanced pattern had a sensitivity of 78.9% and a specificity of 98.0% for its ability to predict neuroendocrine tumours[4]. A hypoenhanced or heterogeneous aspect of neuroendocrine tumours is an indicator of a poor prognosis[15] and aggressiveness[17].

An improvement in the sensitivity and specificity of up to 94% was obtained using an artificial neural network model [18,19]. Moreover, the use of time-intensity curve analysis improved the conventional EUS diagnosis rate by using qualitative analysis (OR = 6) or quantitative analysis (OR = 10): Low peak enhancement and low in-slope in adenocarcinomas; high peak enhancement and normal in-slope in neuroendocrine tumours; and normal peak enhancement and low in-slope in cases of mass forming chronic pancreatitis[20]. Postprocessing analysis of the CHEUS timeintensity curve revealed that the contrast uptake ratio (representing the uptake of the mass *vs* the normal parenchyma) was significantly lower in adenocarcinoma than in mass-forming chronic pancreatitis, with a cut-off value of 0.17[21].

Technical points

As the poorer contrast enhancement areas contained a greater number of necrotic and fibrotic cells[5,15,22], vessels should be avoided while using the contrast EUS for fine needle aspirate guidance in solid pancreatic lesions (Figure 1A and B) and nonenhanced regions, as they could represent an area of haemorrhage or necrosis.

While placing the needle, the areas with contrast uptake (the most hypoenhanced areas in hypoenhanced lesions or the most contrast-enhanced regions in hyper/isoenhanced lesions) should be targeted[12,23].

The large vessels are visible with contrast enhancement, so they are easily avoided, but the needle visibility could be impaired in cases where there is a deep lesion located away from the EUS probe.

Literature data

There are nine studies on CH-EUS-FNA, seven of which have shown that compared with conventional EUS-FNA, CH-EUS-FNA has no statistical benefit (Table 1).

The first randomized controlled study used parallel small groups with twenty patients each and used up to five passes, and they compared Sonazoid contrastenhanced EUS to conventional EUS-guided FNA using 22 G and 25 G needles. The only significant difference was a higher diagnosis rate of the first pass with the use of contrast EUS (60% *vs* 25%), but the final diagnosis rate was similar in both groups[24]. Additionally, 25 G needles were used only in the conventional EUS-FNA group, but perhaps this did not influence the outcome, as the noninferiority of using 25 G needles as compared to 22 G needles for FNA has been demonstrated in a meta-analysis[25].

A second randomized controlled study involving parallel groups, which included 120 patients in the contrast EUS group (80% using first-generation EUS-FNB) and 120 patients in the conventional group, used needles of different sizes and up to five passes. In that study, no difference was revealed when contrast agent was used for guiding tissue acquisition (85.8% *vs* 88.3%)[26]. Neither the use of EUS-FNB needles nor the use of larger needles showed any difference in the multivariate analysis or in improving the diagnosis, although these needles are associated with a higher diagnostic yield[26]. The diagnostic accuracy of first-generation EUS-FNB was shown to be similar to that of EUSFNA[27,28], so the results of this study again reflect the same efficiency of EUS-guided tissue sampling, with and without contrast.

The third randomized controlled study included 148 patients who underwent crossover randomization; each patient had one EUS-FNA pass with contrast enhancement guidance and one EUS-FNA pass without contrast guidance. The diagnostic accuracy for each pass was 89.2% *vs* 88.5%, and the false-negative rate was similar for hypoenhanced or hyperenhanced lesions, for different mass locations and for masses of different sizes[29]. That study included 34 patients with chronic pancreatitis features and who had a pancreatic mass suspected to be malignant. The diagnostic rate of malignancy in this group was 85% for the CH-EUS-FNA passes compared to 79.4% for the EUS-FNA passes, which were lower rates than that for patients without chronic pancreatitis features (90.4% compared to 88.6%, respectively), but the difference was not significant[29].

Only one prospective study, including 93 patients, reported advantages in the use of CH-EUS-FNA using 22 G needles; however, that study reported a lower sensitivity than that reported in the literature (76.5% in the CH-EUS-FNA group *vs* 58.8% in the conventional EUS-FNA group), perhaps related to the limitations of only using two FNA passes only and the operator's experience (300 EUS-FNA procedures)[30].

A preliminary meta-analysis that included only six studies (among which two were retrospective) and 701 patients reported superiority for CH-EUS-FNA[31], but subsequent studies[23,26,32] did not confirm this conclusion.

The results concerning the use of newer EUS-FNB needles were published recently. A retrospective study using Sonazoid contrast agent and second-generation EUSFNB needles achieved 91.7% accuracy in 48 patients with CH-EUS-FNB and 90.6% accuracy in 85 patients with conventional EUS-FNB; however, there was a lower number of passes in the CH-EUS-FNB group (2.21 ± 0.68 compared to 3.64 ± 1.20)[32]. There have been no prospective studies that have compared the time needed for each type of procedure (with and without contrast), but an additional 3 to 5 min are suggested for the preparation and observation of contrast agents[23,33], but the lower the number of passes might compensate for this needed time[32]. Another randomized controlled trial compared the fanning technique *vs* contrast-enhanced guidance for EUSFNB sampling and reported no differences in the sensitivity or accuracy (98% *vs* 100%). However, that study was monocentric, used up to five passes, and yielded false positive results; additionally, 24.6% of the samples were nondiagnostic on histology, which is unusual with the use of FNB needles[23].

Overall, based on the literature results, there is no demonstrable advantage with the use of routine CH-EUS tissue acquisition over conventional EUS tissue acquisition. Perhaps further research on chronic pancreatitis patients will show that the use of CH-EUS-FNB has advantages, especially when a differential diagnosis of a pancreatic mass is required or when it is used in patients with recent acute pancreatitis and suspicion of a pancreatic tumour.

Another potential field for CH-EUS tissue acquisition could be extravascular migratory metastasis (Figure 1C and D), which were identified by EUS-FNA as a perivascular soft-tissue cuff in 28% of 223 patients and changed the management of 29 patients[34].

Table 1 Studies comparing contrast-enhanced endoscopic ultrasound-guided fine needle aspiration versus conventional endoscopic ultrasound-guided fine needle aspiration

Ref.	Study design	No. of pts CH-EUS/ EUS	Needle size (G), type	Contrast agent	Sensitivity (%), CH-EUS-FNA/B *vs* no CH-EUS-FNA/B	*P* value	Other findings
Hou *et al*[71], 2015	R	58/105	22, FNA	Sonovue	81.6 *vs* 70.8	NS	
Sugimoto *et al* [24], 2015	RCT	20/20	22, 25, FNA	Sonazoid	90.0 *vs* 85.0	NS	Adequate for the 1st pass only
Seicean *et al* [12], 2017	P	51	22, FNA	Sonovue	82.9 *vs* 73.2	NS	
Facciorusso *et al* [72], 2020	R	103/103	22, FNA	Sonovue	87.6 *vs* 80.0	NS	
Seicean *et al* [29], 2020	RCT	148	22, FBA	Sonovue	87.6 *vs* 85.5	NS	
Cho *et al*[26], 2021	RCT	120/120	19-25, FNA, FNB	Sonovue	85.8 *vs* 88.3	NS	Procore in 80%
Itonaga *et al* [30], 2020	P	93	22, FNA	Sonazoid	84.9 *vs* 68.8	0.003	Better adequacy in homogenous lesions and heterogenous lesions with non-enhancement areas
Lai *et al*[32], 2022	R	48/85	22, FNB	Sonazoid	91.0 *vs* 90.0	NS	2.2 *vs* 3.6 passes
Kuo *et al*[23], 2023	RCT	59/59	22, FNB	Sonazoid	100.0 *vs* 100.0	NS	A nodule < 4 cm and a sample length > 1 cm improved the rate of diagnosis

R: Retrospective; RCT: Randomized controlled trial; P: Prospective; CH-EUS-FNA/B: Contrast-enhanced endoscopic ultrasound fine-needle aspiration/biopsy; EUS: Endoscopic ultrasound; NS: Not significant; FNA: Fine needle aspiration; FNB: Fine needle biopsy.

PANCREATIC CYSTS

Pancreatic cysts are mostly incidental findings, and there has been an increasing frequency of pancreatic cysts in recent years mainly because of improvements in the resolution of imaging methods. CH-EUS has limited yield for the characterization and differential diagnosis of pancreatic cystic lesions, but CH-EUS is recommended for the identification of mural nodules[6] because the contrast agent can highlight fine vascularisation while discharging nonenhanced mucin plugs[6,35,36].

A meta-analysis reported that the size of the mural nodule after contrast enhancement had a considerable effect on predicting malignancy, while another group reported a sensitivity of 97% and a specificity of 90% for the discrimination of malignant mural nodules[37,38]. Previous studies have shown that malignancy is present in 70%-100% of patients with mural nodules[35,39,40]. A size greater than 5 mm represents an absolute indication for surgery according to the European and Fukuoka guidelines[41,42], while the American guidelines recommend resection of cysts with mural nodules, regardless of their size[43].

Only one prospective study assessed the role of CH-EUS-FNA in cases of mural nodules within cysts. Among the 21 patients suspected of having mural nodules, only 13 had arterial enhancement, and only 10 (76.9%) had high dysplasia or carcinoma. The remaining patients had low or moderate dysplasia; the authors showed that not all the mural nodules were malignant; therefore, close follow-up is needed, regardless of the lesion size[44] (Figure 1E and F).

HEPATOBILIARY LESIONS

CH-EUS has been recommended for the guidance of tissue acquisition of liver masses in which a previous attempt had been negative[6]. CH-EUS allows the differentiation of millimetric lesions not visible *via* conventional imaging, and a longer follow-up into the late washout phase, over 240 s, is required for this purpose. Oh *et al*[45] published a retrospective series including 28 patients who underwent tissue acquisition after CH-EUS for confirmation. Metastases had typical non or hypo-enhancement behaviour; moreover, half of the neuroendocrine tumours presented early enhancement with early washout, while only 40% of the hepatocellular carcinomas presented hyperenhancement with delayed washout. The diagnostic value of CH-EUS-FNA was 86.7%[45], which is similar to other data from the literature that showed an 86.3% accuracy by using the same type of needle[46].

EUS tissue acquisition of suspected extrahepatic cholangiocarcinoma is indicated in selected cases of undetermined biliary strictures, unresectable tumours or metastatic masses forming cholangiocarcinomas[47-49]. A meta-analysis of 6 studies including 497 patients with extrahepatic biliary tumours and who underwent EUS-FNA revealed a diagnostic

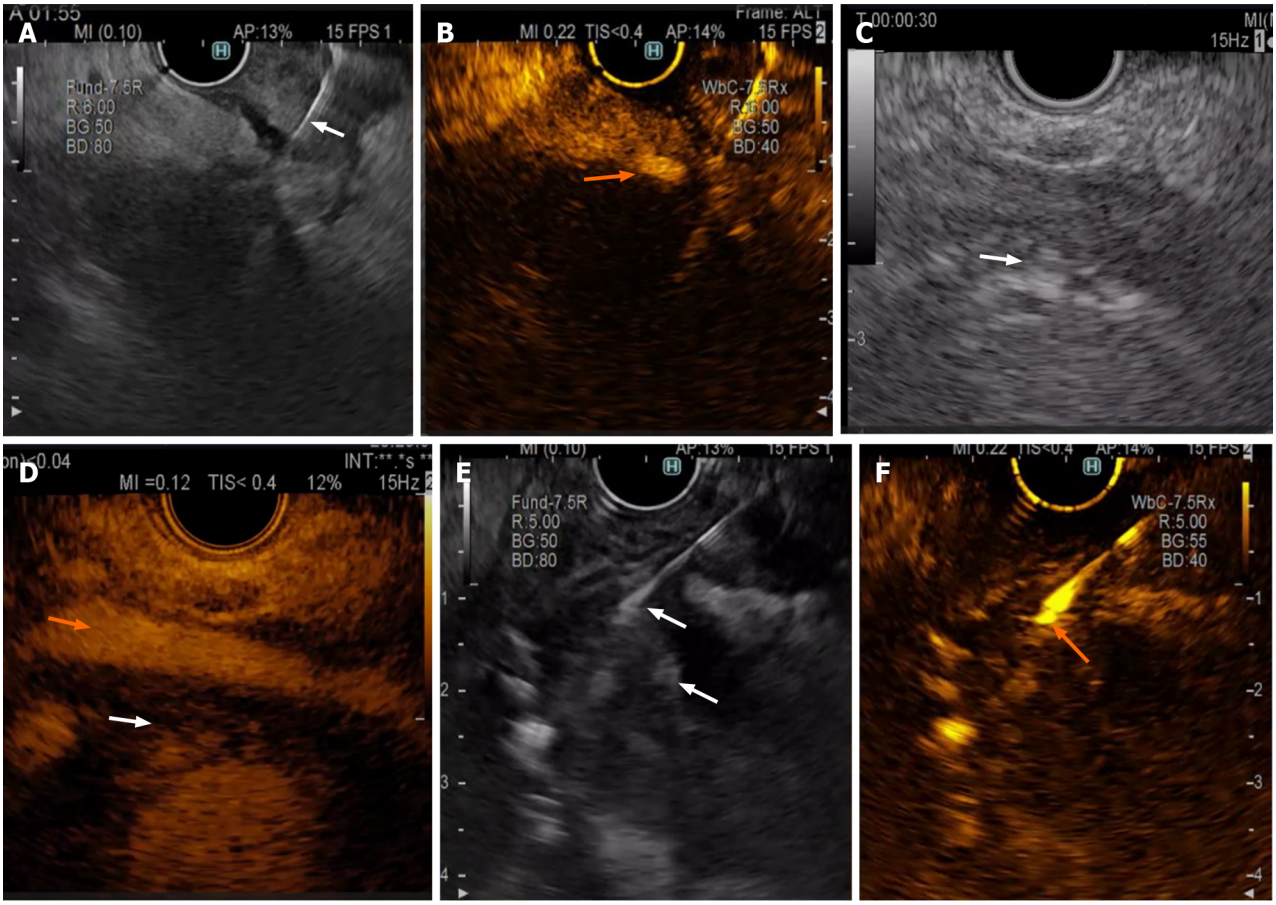

Figure 1 Contrast-enhanced endoscopic ultrasound. A and B: Contrast-enhanced endoscopic ultrasound (CE-EUS)-guided fine needle aspiration (FNA). CE-EUS-guided FNA (white arrow) of a pancreatic mass suggestive of adenocarcinoma. A large vessel near the gut wall is more visible during contrast enhancement (orange arrow); C and D: CE-EUS view of perivascular tumour infiltration. CE-EUS view of perivascular tumour infiltration (superior mesenteric artery, orange arrow) as a hypoenhanced rim (white arrow, both images) around the artery in a patient with pancreatic head adenocarcinoma; E and F: Contrast enhanced endoscopic ultrasound-guided FNA from a hyperenhanced mural nodule inside a branch-duct intraductal papillary mucinous neoplasm (IPMN). CHEUSFNA was performed on a hyperenhanced mural nodule inside a branchduct IPMN, revealing carcinoma cells. On the left, a conventional endoscopic ultrasound image of an IPMN with multiple hyperechoic nodules in the wall (white arrows) is shown. On the right, only one of the nodules was hyperenhanced by the contrast agent, so endoscopic ultrasound-guided FNA sampling was performed.

sensitivity of 76% and an accuracy of 94.5% for EUS-FNA[49]. However, the role that contrast-enhanced EUS-guided tissue acquisition played in improving the analysis of these lesions has not yet been identified.

GASTROINTESTINAL LESIONS

The CH-EUS features suggestive of lymph node malignancy include heterogeneous hyperenhancement and fast washout [50], but the actual guidelines do not recommend routinely performing this technique in addition to EUS tissue acquisition for differentiating between malignant and benign lymph nodes[6]. In a cohort of 37 subjects with oesophageal cancer, the use of CH-EUS identified suspected lymph nodes that were not identified by conventional EUS and increased the rate of malignancy detection from 45% to 86%[51]. However, no studies on guiding CH-EUS tissue acquisition in lymph nodes or subepithelial lesions have been published.

THERAPEUTIC EUS

The utility of intracavitary contrast transabdominal ultrasound for assessing drainage quality, such as in cases of stent dislodgements, the need for additional therapeutic procedures or the presence of communications with the surrounding structures, has been demonstrated by previous experience[52]. Additionally, complications such as fistulas associated with the biliary system, blood vessels, small or large intestine or to the peritoneal cavity were noted[53]. However, the daily usefulness of intracavity contrast in EUS-guided therapeutic procedures is less known.

CH-EUS PANCREATIC FLUID COLLECTIONS DRAINAGE

The use of CH-EUS before endoscopic drainage was proposed for a better evaluation of the wall, which is less visible on standard EUS, especially when the content is thick (blood or pus)[54-56]. In such situations, CH-EUS shows the collection wall as an unenhanced structure and the vessels within the wall as hyperenhanced structures, and CH-EUS allows safe needle puncture as the first step of drainage[52]. The presence of vessels crossing the fluid collection area is also important because their visualization might change the drainage strategy (*e.g.*, choosing plastic stents instead of lumen-apposing metal stents). Additionally, the interposition of the vascularized parenchyma between the gut wall and the fluid collection can be identified during CH-EUS. Moreover, CH-EUS can reveal necrosis as unenhanced areas and can differentiate the vascularized tissue within cystic pancreatic lesions to avoid a mis diagnosis and allow for the drainage of such lesions. However, large studies on its use during drainage are lacking.

CH-EUS BILIARY DRAINAGE

The aim in the use of CEH-EUS to guide biliary drainage is to obtain better detection of a poorly visible intrahepatic bile duct due to echogenic, concentrated bile or intrabilliary neoplastic material[57]. The use of CH-EUS has been reported for only seven patients, and it allowed for clarifying the borders of the intrahepatic (3 patients) and extrahepatic (4 patients) bile ducts before planning EUS drainage[58-62].

EUS gallbladder drainage is contraindicated in cases of gangrenous cholecystitis with special transabdominal ultrasound features (decreased focal wall perfusion on colour Doppler, irregular mucosal outline, gallbladder wall thickening and delamination, gas within the gallbladder, absence of gallstones, and large pericholecystic collections) or computed tomography scan features (gas in the wall or lumen, intraluminal membranes, an irregular or absent wall)[63-66]. Its identification (disruptive layered structure, focal hypoenhanced gallbladder wall) could represent a potential application for CH-EUS prior to gallbladder drainage[60,62,63]. To our knowledge, no specific study in this area has been published.

The evaluation of residual stones in the common bile duct after endoscopic retrograde cholangio-pancreatography by the injection of a contrast agent through a nasobiliary tube was reported in 6 patients and confirmed by EUS cholangiography[67], but its usefulness remains anecdotical.

CH-EUS-GUIDING RADIOFREQUENCY ABLATION

Contrast enhancement allows for real-time visualization of the perfusion of the target nodule in parallel with that of the normal parenchyma, similar to what occurs in hepatic conditions treated by ultrasoundguided procedures. Choi *et al*[68] evaluated the dynamics of perfusion of solid intraabdominal nodules 5-7 d after radiofrequency ablation and reported incomplete ablation in 12 of 19 patients. At the 1-year followup, a complete response was reported in 68.4% of patients, with a median of 2 sessions[68]. Similar to the use of CH-EUS after ablation of liver masses, its immediate use after ablative procedures might reveal incomplete ablations and prevent 3-6 months of waiting until a CT scan evaluation[69,70].

CONCLUSION

CH-EUS tissue acquisition is a promising advanced EUS technique that can improve the diagnosis in selected patients by differentiating tumoral vascularisation from the surrounding parenchyma, thus improving the histological results. Additionally, this technique reveals vessels that are not visible *via* colour Doppler EUS, and allows the identification of structures with thick content to be targeted for drainage while avoiding the puncture of these vessels. Additionally, CH-EUS assessment allows for timely evaluation of any tissue destruction after ablative procedures.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Study

Efficacy and safety of targeted therapy plus immunotherapy combined with hepatic artery infusion chemotherapy (FOLFOX) for unresectable hepatocarcinoma

Zhi-Peng Lin, Xiao-Long Hu, Du Chen, Da-Bei Huang, Xu-Gong Zou, Hai Zhong, Sheng-Xiang Xu, Yuan Chen, Xiao-Qun Li, Jian Zhang

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Abstract

BACKGROUND

The advent of cutting-edge systemic therapies has driven advances in the treatment of hepatocellular carcinoma (HCC), and therapeutic strategies with multiple modes of delivery have been shown to be more efficacious than monotherapy. However, the mechanisms underlying this innovative treatment modality have not been elucidated.

AIM

To evaluate the clinical efficacy of targeted therapy plus immunotherapy combined with hepatic arterial infusion chemotherapy (HAIC) of FOLFOX in patients with unresectable HCC.

METHODS

We enrolled 53 patients with unresectable HCC who received a combination of targeted therapy, immunotherapy, and HAIC of FOLFOX between December 2020 and June 2021 and assessed the efficacy and safety of the treatment regimen.

RESULTS

The objective response rate was 60.4% (32/53), complete response was 24.5% (13/53), partial response was 35.9% (19/53), and stable disease was 39.6% (21/53). The median duration of response and median progression-free survival were 9.1 and 13.9 months, respectively. The surgical conversion rate was 34.0% (18/53), and 1-year overall survival was 83.0% without critical complicating diseases or adverse events (AEs).

CONCLUSION
The regimen of HAIC of FOLFOX, targeted therapy, and immunotherapy was curative for patients with unresectable HCC, with no serious AEs and a high rate of surgical conversion.

Key Words: Hepatocellular carcinoma; Hepatic arterial infusion chemotherapy; Targeted therapy; Immunotherapy; Adverse events

Core Tip: The therapeutic strategy of combining multiple modes of drug delivery for the treatment of hepatocellular carcinoma (HCC) has been shown to be more efficacious than single treatment modality, but the underlying mechanism of action has not been clarified. In this study, we observed the clinical efficacy of targeted therapy plus immunotherapy combined with FOLFOX hepatic artery infusion chemotherapy in the treatment of unresectable HCC, which provides a clinical basis for the clinical application of the combination of therapy in HCC.

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INTRODUCTION

Globally, the third most prevalent cause of cancer-related mortality and the sixth most frequently occurring cancer type is primary hepatocellular carcinoma (HCC)[1]. The first-line treatment options for early-stage HCC are surgical resection and liver transplantation[2,3]. Most patients with early-stage HCC do not have obvious symptoms, and many of them have already developed middle- or late-stage disease at the time of diagnosis. Additionally, since malignant vascular invasion is considered a contraindication to surgical treatment, only 5%-10% of patients with HCC are suitable candidates [4]. There are a variety of treatment methods for unresectable HCC, including interventional therapy, ablation therapy, antitumor targeted therapy, antitumor immunotherapy, radiation therapy, and radioactive seed implantation therapy. The efficacy of hepatic arterial infusion chemotherapy (HAIC) for advanced HCC with vascular invasion or multiple intrahepatic lesions is highly regarded in clinical practice. The Japan Society of Hepatology recommends HAIC as the first-line option for HCC with portal vein tumor thrombus (PVTT)[5]. HCC tumors receive a dual blood supply from the portal vein and hepatic artery (primarily from the hepatic artery). HAIC involves injecting chemotherapeutic drugs directly into the HCC tumor through the hepatic artery. Although HAIC increases the concentration of anticancer drugs in tumor cells, the incidence of side effects is reduced due to the localized distribution. Therefore, HAIC may have a stronger antitumor effect and a lower incidence of adverse events (AEs) compared with other chemotherapeutic methods. Although sorafenib plus HAIC of FOLFOX was reported to improve the objective response rate (ORR) in patients with HCC rather than sorafenib alone, the survival duration remained inadequate[6].

The advent of cutting-edge systemic therapy has led to rapid advances in HCC treatment. Strategies involving medications with various modes of administration have proved much more effective than monotherapy, even though the causes of the success of such innovative HCC remedies remain poorly clarified. A two-drug approach, including concurrent or successive therapy with personalized treatment and immunotherapy, is among those protocols currently being explored[7-9]. The aim of this study was to retrospectively evaluate the effect of a regimen of targeted therapy, immunotherapy, and HAIC of FOLFOX.

MATERIALS AND METHODS

Patient information

We enrolled patients with HCC who underwent HAIC of FOLFOX combined with antitumor targeted therapy plus immunotherapy at Zhongshan People's Hospital for HCC from December 2020 to June 2021. The inclusion criteria were as follows: (1) HCC diagnosed by ≥ 2 experienced physicians or pathologically diagnosed and no previous HCC treatment; (2) age 18-75 years old; (3) Child-Pugh class A or B; (4) Eastern Cooperative Oncology Group (ECOG) performance status grade 0 or 1; and (5) Barcelona Clinic Liver Cancer (BCLC) stage B or C. The exclusion criteria were: (1) White blood cell count < 2.0 × 10^9/L; (2) platelet count < 30 × 10^9/L; (3) serum total bilirubin > 51 μmol/L; (4) uncontrolled or systemic infection surrounding the lesion (excluding viral hepatitis); (5) severe liver, kidney, heart, or lung function insufficiency; (6) history of other malignant tumors; and (7) known history of human immunodeficiency virus infection.

This retrospective study was approved by the Ethics Committee of Zhongshan People's Hospital (approval No. 2022-029). All study participants or their legal guardians provided informed written consent prior to study enrollment.

Surgical methods: Hepatic artery catheterization

The patient was placed supine on the catheter bed, and the bilateral inguinal areas were disinfected. Then, the femoral artery (or radial artery or distal radial artery) was punctured under local anesthesia for the placement of an arterial sheath. The catheter was selectively inserted into the celiac artery and superior mesenteric artery, and angiography was used to observe the blood supply to the intrahepatic tumor. If the intrahepatic tumor was fed by a separate hepatic artery, the microcatheter was placed into the appropriate vascular target. If the intrahepatic tumor was fed by both hepatic arteries, the microcatheter was placed into the appropriate hepatic artery. In cases where the intrahepatic tumor was supplied by the left and right hepatic arteries and the gastroduodenal artery could not be avoided, the gastroduodenal artery underwent coil embolization before placing the microcatheter into the appropriate hepatic artery. Finally, the microcatheter was bandaged and fixed. FOLFOX chemotherapy was initiated upon return to the ward.

HAIC

The regimen for HAIC of FOLFOX included oxaliplatin (85 mg/m^2 intra-arterial infusion) for 2 h, followed by leucovorin (400 mg/m^2 intravenous infusion) combined with 5-fluorouracil (400 mg/m^2 intra-arterial infusion) for 1 h and then 2400 mg/m^2 for 23 h, repeated every 3 wk. If the tumor shrunk significantly after HAIC treatment, the chemotherapy perfusion dose was appropriately reduced.

Selection of antitumor targeted therapy drugs and immunotherapy drugs

Lenvatinib (Eisai Co., Ltd.), sorafenib (Bayer), sintilimab (Innovent Biologics Suzhou Co., Ltd.), camrelizumab (Suzhou Suncadia Biopharmaceuticals Co., Ltd.), atezolizumab (Roche), and bevacizumab (Roche) were administered within 1 wk after the first HAIC treatment. The dosages were as follows: Lenvatinib, 8 mg [body weight (BW) < 60 kg] or 12 mg (BW ≥ 60 kg), orally, daily; sorafenib, 0.4 g, orally, daily; bevacizumab, 15 mg/kg, intravenous drip, once every 3 wk; sintilimab and camrelizumab, 200 mg, intravenous drip, once every 3 wk; and atezolizumab, 1200 mg, intravenous drip, once every 3 wk. Each drug was suspended, re-used (including dose reduction), or permanently discontinued according to the level of the corresponding drug-related AEs that occurred during treatment.

Efficacy and safety evaluations

Each patient underwent enhanced magnetic resonance imaging or enhanced computed tomography of the upper abdomen; routine blood, liver function, and renal function tests; HCC index evaluations; and other examinations prior to HAIC. Curative effects included complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) and were assessed using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and modified RECIST (mRECIST)[10,11]. The ORR was calculated as the PR + CR, and the disease control rate (DCR) was calculated as the PR + CR + SD. The duration of response (DOR), surgical conversion rate, progression-free survival (PFS), 6-month and 12-month PFS, and safety were also determined.

Statistical methods

Statistical analysis was performed using SPSS 20.0 software. Data were shown as means ± SD or range. Survival data were presented using Kaplan-Meier curves.

RESULTS

Patient information

Of the 61 patients initially recruited, four withdrew after the first or second round of HAIC, and four showed poor compliance and did not come to our hospital for regular treatment on time (HAIC interval > 2 months). The final study cohort (n = 53) comprised 45 males and 8 females aged 51.6 (27.0-74.0) years. Of them, 45 (84.9%) had a history of hepatitis B, and 48 (90.1%) had a history of liver cirrhosis. The ECOG performance status was grade 0 in 26 (49.1%) and grade 1 in 27 (50.9%) cases, the BCLC stage was B in 27 (50.9%) and C in 26 (49.1%) cases, and there were 42 (79.2%) cases of Child-Pugh class A and 11 (20.8%) of Child-Pugh class B. Alpha-fetoprotein was elevated in 23 patients (43.4%) and was > 400 ng/mL in 30 (56.6%) patients. The tumor diameter was < 5 cm in 9 (16.9%), 5-10 cm in 18 (34.0%), and > 10 cm in 26 (46.7%) cases. The tumor capsule was complete in 28 (52.8%) and incomplete in 25 (47.2%) cases. Portal and/or hepatic vein tumor thrombus were present in 24 patients, including 5 cases each of PVTT in the second-order branches of the portal vein and the first-order branch of the portal vein, respectively, 11 cases of PVTT in the main trunk and/or a contralateral portal vein, and 6 cases of hepatic vein trunk tumor thrombus. Extrahepatic metastases were present in 12 patients (lung, 7; adrenal gland, 1; bone, 2; bone and lung, 2; and lymph nodes, 6; Table 1). The follow-up end date was June 30, 2022.

Targeted therapy, immunotherapy, and HAIC treatment

Patients received 4-6 rounds of HAIC (average, 4.5 rounds), and the time interval between each round was 28.6 d (median time interval, 27.0 d). The average doses were as follows: Oxaliplatin, 79.9 mg/m^2 (arterial infusion); leucovorin, 371.6 mg/m^2 (intravenous infusion); 5-fluorouracil, 375.5 mg/m^2 (intravenous infusion); and 5-fluorouracil, 2197.3 mg/m^2

Table 1 Basic patient information

Characteristics	Number	Proportion (%)
Gender		
Male	45	0.849
Female	8	0.151
Age (yr)		
< 50	22	0.415
≥ 50	31	0.585
HBsAg		
Positive	45	0.849
Negative	8	0.151
Liver cirrhosis		
Yes	48	0.901
No	5	0.099
ECOG grade		
0	26	0.491
1	27	0.509
Child-Pugh class		
A	42	0.792
B	11	0.208
BCLC stage		
B	27	0.509
C	26	0.491
Maximum tumor diameter (cm)		
< 5	9	0.169
5-10	18	0.340
> 10	26	0.491
Tumor capsule		
Complete	28	0.528
Incomplete	25	0.472
Alpha-fetoprotein (ng/mL)		
< 400 ng/mL	23	0.434
≥ 400 ng/mL	30	0.566
Number of tumors		
≤ 3	30	0.566
> 3	23	0.434
Vascular invasion		
Vp2	5	0.099
Vp3	5	0.099
Vp4	11	0.208
Vv2	6	0.113
Vv3	0	0.000
Extrahepatic metastases		

Yes	12	0.226
No	41	0.774
Lymph node metastases		
Yes	6	0.113
No	47	0.887

HBsAg: Hepatitis B surface antigen; ECOG: Eastern Cooperative Oncology Group; PVTT: Portal vein tumor thrombus; BCLC: Barcelona Clinic Liver Cancer; Vp2: PVTT in the second-order branches of the portal vein; Vp3: PVTT in the first-order branch of the portal vein; Vp4: PVTT in the main trunk and/or a contralateral portal vein; Vv2: Hepatic vein trunk tumor thrombus.

(arterial infusion).

The choice of targeted therapy drugs and immunotherapy drugs depended on the patient's wishes and their economic status. There were 18 patients who received sorafenib combined with camrelizumab (sorafenib: 800.0 mg/d, average 666.7 mg/d; camrelizumab: 200 mg every 3 wk, intravenous drip); 10 chose sorafenib combined with sintilimab (sorafenib: 800.0 mg/d, average 640.0 mg/d; sintilimab: 200 mg every 3 wk, intravenous drip); 13 chose lenvatinib combined with camrelizumab (lenvatinib: average 10.8 mg/d; camrelizumab: 200 mg every 3 wk, intravenous drip); 11 chose lenvatinib combined with sintilimab (lenvatinib: < 60 kg BW, 8.0 mg/d and > 60 kg BW, 12.0 mg/d, average 10.5 mg/d; sintilimab: 200 mg every 3 wk, intravenous drip); and 1 chose atezolizumab combined with bevacizumab (atezolizumab: 1200 mg every 3 wk, intravenous drip; bevacizumab, 1100 mg every 3 wk, intravenous drip).

Tumor treatment response

Assessment of the tumor treatment responses using mRECIST revealed that the number of cases of CR, PR, SD, and PD was 13 (24.5%), 19 (35.9%), 21 (39.6%), and 0 (0.0%), respectively, the ORR was 60.4%, and the DCR was 100.0%. Assessment according to RECIST v1.1 revealed that the number of cases of CR, PR, SD, and PD was 2 (3.8%), 23 (43.4%), 28 (52.8%), and 0 (0.0%), respectively, the ORR was 47.2%, and the DCR was 100.0% (Table 2).

AEs

AEs of different degrees were observed in all patients after receiving the combination therapy. Abdominal pain, nausea, vomiting, increased levels of transaminases, anorexia, fatigue, and diarrhea mainly occurred in the perioperative period of HAIC, and all patients recovered within a few days. No treatment-related grade 4 or 5 AEs were reported (Table 3).

Follow-up outcomes

The follow-up period was 14.1 (3.8-23.6) months. PFS at 6- and 12 months was 88.7% and 62.3%, respectively. The median DOR was 9.1 months [95% confidence interval (95%CI): 8.40-not estimable (NE)] and 10.7 months (95%CI: 10.26-NE) according to mRECIST and RECIST v1.1, respectively. The median PFS (mPFS) was 13.9 months (95%CI: 12.63-NE), the 1-year overall survival (OS) rate was 83.0%, and a median OS (mOS) was not reached (95%CI: NE-NE) (Figure 1). Eighteen patients (34.0%) met the criteria for surgical resection, and all underwent surgery (Figure 2).

DISCUSSION

HCC is a serious threat to human life and has a high rate of morbidity and mortality. Despite the wide use of a combined therapeutic approach to HCC in recent years, there are no reports of > 2 therapies working together. In this study, we explored the clinical efficacy of targeted therapy plus immunotherapy combined with HAIC in patients with unresectable HCC. We found that HAIC of FOLFOX, targeted therapy, and immunotherapy were effective for patients with unresectable HCC.

In 2018, there were approximately 841000 new cases of HCC worldwide and 781000 associated deaths, of which around 50% of newly reported cases and associated deaths occurred in China[12,13]. The main treatments in early-stage HCC are surgical resection, liver transplantation, and ablation. Transcatheter arterial chemoembolization is effective in middle-stage unresectable HCC with multiple nodules. However, systemic treatments, such as targeted therapy and immunotherapy, are ineffective for some patients with late-stage HCC, and their prognosis is often poor[14]. One of the important means of interventional therapy for HCC is HAIC, and excellent results have been achieved using HAIC of an oxaliplatin-based sequential FOLFOX regimen to treat advanced HCC, making HAIC a more preferred method[15].

HAIC is an interventional treatment method. HCC tumors often have a rich blood supply, with > 95% originating from the hepatic artery, which justifies the treatment of HCC through the hepatic artery[16]. The direct infusion of drugs into the arterial blood supply of the tumor overcomes the physiological barriers through which some intravenous chemotherapeutics are unable to pass, thereby significantly increasing the local drug concentration in the tumor and improving the curative effect. At the same time, the chemotherapeutic drugs circulate in the bloodstream throughout the entire body, playing a role in systemic chemotherapy. Compared with systemic chemotherapy, HAIC improves the local drug perfusion concentration and reduces the systemic toxic and side effects of chemotherapeutics, opening up a wide range of valuable clinical applications[17].

Table 2 Tumor treatment response assessment, *n* (%)

Variables	CR	PR	SD	PD	ORR	DCR
mRECIST	13 (24.5)	19 (35.9)	21 (39.6)	0 (0)	32 (60.4)	53 (100.0)
RECIST V1.1	2 (3.8)	23 (43.4)	28 (52.8)	0 (0)	25 (47.2)	53 (100.0)

CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease; ORR: Objective response rate; DCR: Disease control rate; mRECIST: Modified Response Evaluation Criteria in Solid Tumors.

Table 3 Patient treatment-related adverse events, *n* (%)

AEs	Any grade	Grade 1	Grade 2	Grade 3
Leukopenia	21 (39.62)	11 (20.75)	10 (18.87)	0
Thrombocytopenia	12 (22.64)	12 (22.64)	0 (0.00)	0
Rash	7 (13.21)	3 (5.66)	4 (7.55)	0
Itchy skin	5 (9.43)	5 (9.43)	0 (0.00)	0
Hand-foot syndrome	17 (32.08)	10 (18.87)	7 (13.21)	0
Increased serum ALT and AST levels	25 (47.17)	23 (43.40)	2 (3.77)	0
Increased serum bilirubin	8 (15.09)	6 (11.32)	2 (3.77)	0
Diarrhea	5 (9.43)	3 (5.66)	2 (3.77)	0
Nausea, vomiting	24 (45.28)	13 (24.53)	11 (20.75)	0
Proteinuria	10 (18.87)	4 (7.55)	6 (11.32)	0
Hypothyroidism	16 (30.19)	0 (0.00)	16 (30.19)	0
Gastrointestinal bleeding	5 (9.43)	0 (0.00)	1 (1.88)	4 (7.55)
Stomachache	17 (32.08)	10 (18.87)	7 (13.21)	0
Hair loss	4 (7.55)	4 (7.55)	0 (0.00)	0
Weight loss	9 (16.98)	9 (16.98)	0 (0.00)	0
Decreased appetite	25 (47.17)	23 (43.40)	2 (3.77)	0
Fatigue	19 (35.85)	19 (35.85)	0 (0.00)	0
Hypertension	24 (45.28)	2 (3.77)	22 (41.51)	0

HAIC has been used for HCC treatment for over 60 years, and the earliest date can be traced back to 1961. Some scholars used femoral artery puncture and catheterization or right gastroepiploic artery incision and catheterization to infuse HCC therapeutics[18]. In 1986, there were reports of epirubicin-based HAIC for HCC treatment, but the effect was poor[19]. Around 2000, the cisplatin-based HAIC regimen was used abroad, resulting in the ORR reaching 27.6%-40.5% [20]. Because HAIC has long been used to treat HCC, the arterial perfusion schemes, doses, and number of cycles vary across countries and regions, and their therapeutic effects also differ. However, due to a lack of high-level evidence-based medicine, its clinical application is limited. In 2013, the EACH trial proved the curative effect of FOLFOX chemotherapy for HCC[21]. In 2018, Chinese scholars demonstrated an effective rate of 79.6% for HAIC of FOLFOX[15], and in 2022, an oxaliplatin-based FOLFOX4 regimen of systemic chemotherapy and HAIC therapy became the recommended treatment for advanced HCC[22].

Targeted therapy and immunotherapy have been widely used in clinical practice and are the main treatment methods for advanced tumors. However, their efficacy as a single application is low and does not meet the clinical needs. Thus, a combination of targeted therapy and immunotherapy has been proposed in an effort to develop a more effective treatment method. The current understanding of tumor pathogenesis involves not only the study of tumor cells but also the study of various cells and cytokines within cancer tissues, termed the tumor microenvironment (TME)[23]. For the indefinite proliferation of tumor cells, the TME must be hypoxic, with a low pH and low nutrient levels. This induces the formation of proangiogenic factors and an immunosuppressive microenvironment[24,25]. The TME both increases and decreases immunosuppression, while targeted therapy inhibits the migration and distant metastasis of immune cells. Immunotherapy stimulates the body's immune system by affecting the target and enhancing the tumor suppression effect of immune cells.

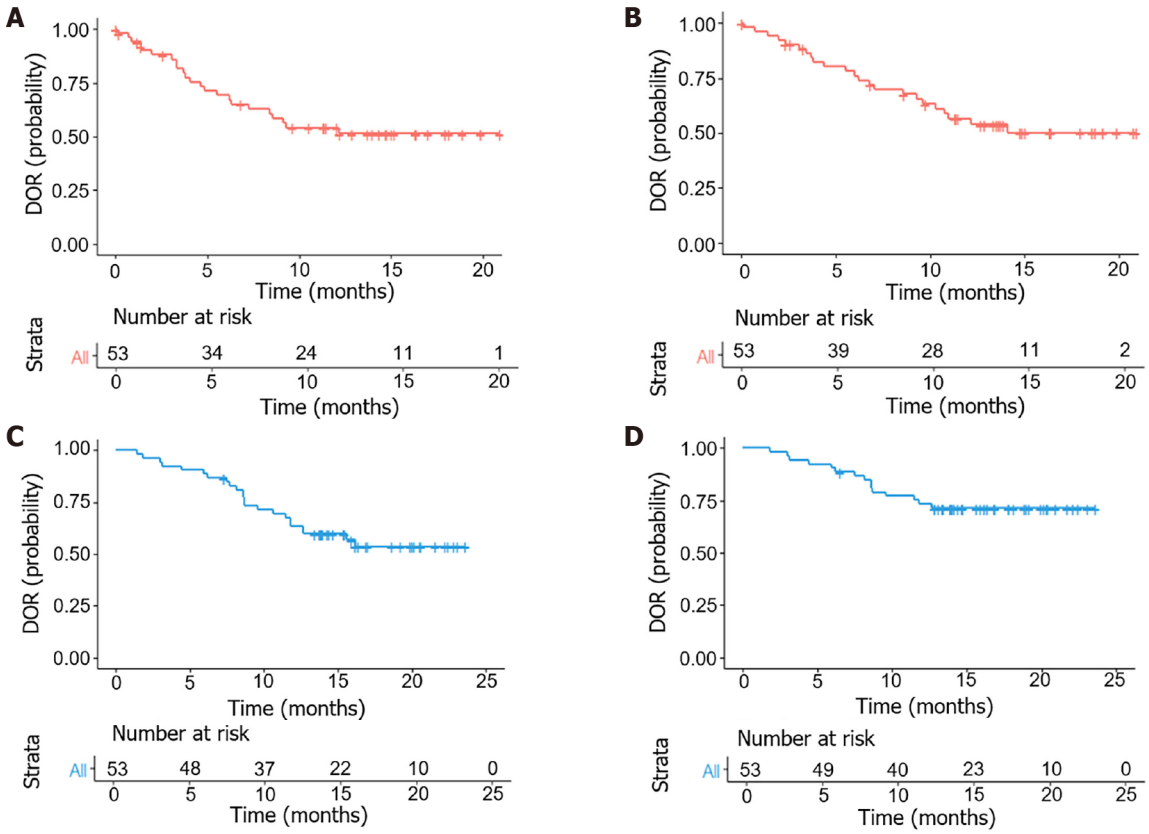

Figure 1 Prognostic outcomes of patients with hepatocellular carcinoma followed up within 25 months after treatment. A: Median duration of response (DOR) using modified Response Evaluation Criteria in Solid Tumors; B: Median DOR using RECIST v1.1; C: Median progression-free survival; D: Median overall survival.

Targeted therapy and immunotherapy have been widely used to treat unresectable HCC. Another option for patients with unresectable HCC is whole-body treatment. The phase III IMbrave150 clinical trial compared a regimen of atezolizumab and bevacizumab (n = 336) with that of sorafenib (n = 165) in 501 patients with advanced unresectable HCC[9]. The mOS in the combination regimen group was notably increased compared with the sorafenib regimen group (19.2 months *vs* 13.4 months, respectively), while in the 194 Chinese subgroups, the mOS and OS in the combination regimen group were 19.2 and 24 months, respectively, with the risk of death reduced by 47%. Most major guidelines prefer a regimen of atezolizumab and bevacizumab for late-stage HCC. The phase Ib KEYNOTE-524 clinical trial with a regimen of lenvatinib and pembrolizumab[26] reported the mOS and mPFS of 100 patients as 22 months and 9.3 months and the ORR and DCR as 46% and 88%, respectively. However, the OS and PFS of this regimen failed expectations. Study117, a phase Ib clinical study with a regimen of lenvatinib and nivolumab, demonstrated better results than a regimen of lenvatinib and pembrolizumab. For the 30 patients in the study, the CR was 10%, PR was 66.7%, ORR was 76.7%, and DCR was 96.7%[27]. A phase II/III clinical study compared a regimen of sintilimab and bevacizumab with that of sorafenib in 157 patients with unresectable or metastatic HCC[28]. Compared with the sorafenib regimen, the effect of the sintilimab and bevacizumab regimen was markedly better (mOS: NE *vs* 10.4 months), notably reduced the risk of mortality by 44%, and improved ORR by 20%. Targeted therapy and immunotherapy are also effective second-line treatments for unresectable HCC. A phase Ia/IIb clinical study with a regimen of apatinib and camrelizumab in advanced HCC[29] reported an mOS and mPFS of 3.4 and 9.3 months, respectively, an ORR of 46%, and a DCR of 88%.

The continuous exploration and progress of new treatment methods for advanced HCC has revealed that the effect brought about by a single treatment mode is inadequate. The upcoming therapies for progressed, incurable HCC are expected to increasingly integrate local and universal approaches. A prospective randomized controlled study suggested that a regimen of HAIC and sorafenib had better outcomes than that of sorafenib alone[6]. The OS of the combination regimen and sorafenib regimen was 13.37 months and 7.13 months, the PFS was 7.03 months and 2.60 months, and the ORR was 40.80% and 2.46%, respectively. Radical surgical resection was performed for 16 patients with the combined regimen and only 1 patient with the sorafenib regimen, and the success rate of surgical conversion was 12.8% and 0.8%, respectively. A single-center retrospective single-arm study reported the effect of HAIC of FOLFOX combined with targeted therapy and immunotherapy[30], in which the CR was 48.0%, PR was 48.0%, SD was 4.0%, and the ORR was as high as 96.0%. Furthermore, the median time to resolve was 50.5 d (95%CI: 31.02-64.00). Studies have shown that local therapy combined with systemic therapy has a better effect and a higher tumor remission rate.

Multiple treatment combinations can achieve surgical conversion in approximately 15%-20% of cases of unresectable HCC[31]. A potential multidisciplinary strategy for addressing severe HCC involves integrating HAIC-based locoregional treatment with selective treatment and immunotherapy[32]. Furthermore, a retrospective study with a regimen of

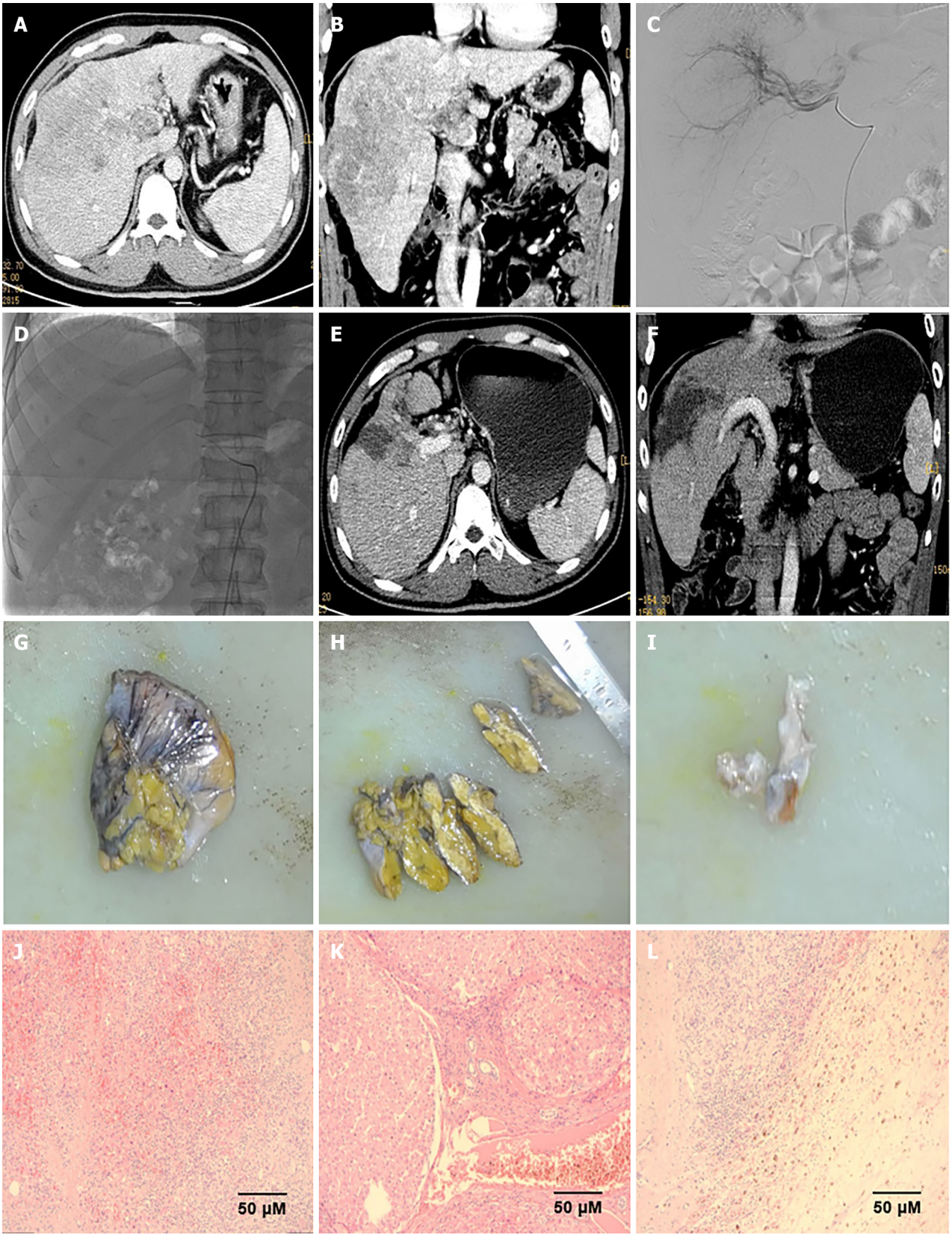

Figure 2 Imaging and pathological results of patients with hepatocellular carcinoma. A and B: Massive hepatocellular carcinoma in the right lobe of the liver and tumor thrombus formation in the main portal vein and right branch; C: Digital subtraction angiography showing a mass in the right lobe of the liver; D: Microcatheter insertion into the appropriate hepatic artery for FOLFOX chemotherapy; E and F: After four rounds of hepatic arterial infusion chemotherapy, enhanced computed tomography of the upper abdomen revealed that the intrahepatic lesions were significantly reduced, the portal vein was reopened, and the portal vein tumor thrombus was significantly reduced; G-I: Gross pathological specimens after surgery; J-L: The tumor was completely necrotic with no residual cancer tissue, indicating complete pathological remission.

HAIC and targeted therapy and immunotherapy showed that 15 of 25 (60.0%) patients underwent conversion to operable criteria; 1 refused surgery and the remaining 14 underwent surgical resection. Of them, 7 (28.0%) achieved pathological CR after resection, and the recurrence-free survival was 13.17 months[30]. A prospective, single-arm phase II clinical study on 30 patients with unresectable HCC treated with HAIC combined with sintilimab and bevacizumab biosimilar (IBI305) reported that R0 resections were achieved in all 14 (100.0%) patients who underwent surgical resection (2022 ASCO POSTER Abstract #4073). In this retrospective analysis, the surgical conversion rate did not achieve the above-mentioned results as expected. This might have been because a large proportion of the enrolled patients were BCLC grade C, the tumor burden was high, and there was a large number of patients with PVTT and extrahepatic metastases. Therefore, the surgical conversion rate was not significantly increased.

The common AEs of targeted therapy and immunotherapy combined with HAIC include decreased appetite, fatigue, leukopenia, thrombocytopenia, abdominal pain, nausea and vomiting, hypertension, diarrhea, liver function damage, and hand-foot syndrome, and effective relief occurs after medication. Patients undergoing curative-specific treatment most frequently experienced hypertension as an acute side effect[33,34], occurring in approximately 42% of patients receiving lenvatinib and 36% receiving combination therapy. Furthermore, the first side effect observed in patients with advanced HCC receiving combination therapy was hypertension[26]. Thus, it is recommended that blood pressure is monitored before combined treatment and antihypertensives be timely administered if blood pressure rises. If antihypertensive drugs are ineffective, the dosage of targeted drugs can be reduced or even terminated. In our study, the AEs in both groups were manageable, and no grade 4 or 5 AEs occurred.

The main limitation of our study is its single-center retrospective single-arm design, which leads to selection bias in treatment choice. Thus, higher-quality multicenter prospective studies are necessary to verify our findings. Second, the targeted therapy and immunotherapy drugs used by the patients in this study varied, and there were many different combinations. Third, patients had a large baseline range in terms of tumor stage and liver function, which may have affected clinical treatment effects and outcomes. Fourth, the follow-up period to assess OS was short (1 year), and a longer follow-up of OS is required. Fifth, the intervals between HAIC rounds were relatively long, which may have affected its efficacy.

CONCLUSION

Targeted therapy and immunotherapy combined with HAIC of FOLFOX is clinically effective for unresectable HCC, improves the surgical conversion rate, and has controllable AEs.

FOOTNOTES

Author contributions: Lin ZP and Zhang J conceived and designed the study; Lin ZP, Hu XL, Chen D, Huang DB, Zou XG, Zhong H, Xu SX, and Chen Y contributed to data collection and analysis; Lin ZP drafted the manuscript; Lin ZP, Li XQ, and Zhang J supervised data analysis and interpretation, revised the manuscript, and gave final approval for the version to be published; and all authors read and approved the final manuscript.

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

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

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Prospective Study

Transanal eco-Doppler evaluation after hemorrhoidal artery embolization

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Abstract

BACKGROUND

Hemorrhoidal artery embolization (Emborrhoid) is a novel method for the treatment of severe hemorrhoidal bleeding. Despite having a technical success rate of 93%-100%, the clinical success ranges between 63% and 94%, with a rebleeding rate of 13.6%.

AIM

To evaluate the effectiveness of this procedure in reducing hemorrhoidal flow and hemorrhoidal bleeding.

METHODS

This prospective observational pilot study was conducted at Division of General Surgery 1 and Tertiary Referral Pelvic Floor Center, Treviso Regional Hospital, Italy. In a 2 months period (February-March 2022), consecutive patients with hemorrhoidal bleeding scores (HBSs) ≥ 4, Goligher scores of II or III, failure of non-operative management, and a candidate for Emborrhoid were included. Endoanal ultrasound with eco-Doppler was performed preoperatively and 1 month after the procedure. The primary endpoint was to quantify the changes in arterial hemorrhoidal flow after treatment. The secondary endpoint was to evaluate the correlation between the flow changes and the HBS.

RESULTS

Eleven patients underwent Emborrhoid. The overall pretreatment mean systolic peak (MSP) was 14.66 cm/s. The highest MSP values were found in the anterior left lateral (17.82 cm/s at 1 o'clock and 15.88 cm/s at 3 o'clock) and in the posterior right lateral (14.62 cm/s at 7 o'clock and 16.71 cm/s at 9 o'clock) quadrants of the anal canal. After treatment, the overall MSP values were significantly reduced (P = 0.008) although the correlation between MSP and HBS changes was weak (P = 0.570). A statistical difference was found between distal embolization compared with proximal embolization (P = 0.047). However, the coil landing zone was not related to symptoms improvement (P = 1.000). A significant difference in MSP changes was also reported between patients with type 1 and type 2 superior rectal artery (SRA) anatomy (P = 0.040). No relationship between hemorrhoidal grades (P = 1.000), SRA anatomy (P = 1.000) and treatment outcomes was found.

CONCLUSION

The preliminary findings of this pilot study confirm that Emborrhoid was effective in reducing the arterial hemorrhoidal flow in hemorrhoidal disease. However, the correlation between the post-operative MSP and HBS changes was weak. Hemorrhoidal grade, SRA anatomy and type of embolization were not related to treatment outcomes.

Key Words: Hemorrhoidal artery embolization; Hemorrhoidal embolization; Hemorrhoidal vascularization; Transanal eco-Doppler; Transanal ultrasound

Core Tip: This was a prospective observational pilot study seeking to evaluate the changes in the arterial hemorrhoidal flow after hemorrhoidal artery embolization, and the correlation between the mean systolic peak and the hemorrhoidal bleeding score changes. Embolization was effective in reducing the arterial hemorrhoidal flow in hemorrhoidal disease, however the correlation between flow and symptoms was weak.

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INTRODUCTION

The main vascular hemorrhoidal supply is provided by the superior rectal artery (SRA), which splits into three to five distal branches[1,2]. Panneau *et al*[3] described three patterns of arterial hemorrhoidal vascularization: (1) Type 1 consists of one or more dominant SRAs without hypertrophy of the middle rectal artery (MRA); (2) Type 2 includes unilateral hypertrophy of the SRA and hypertrophy of the contralateral MRA; (3) Type 3 includes bilateral hypertrophy of the MRA without hypertrophy of the SRA. Schuurman *et al*[4] found that vascularization of the corpus cavernosum recti and distal rectum is provided almost exclusively by branches of the SRA, and that the distal distribution is not limited to sectorial o'clock positions. By using endoanal duplex color, Ratto *et al*[5] showed that the hemorrhoidal arteries lie in the perirectal fat outside the rectal walls at 6.5 cm and 4.0 cm over the anorectal junction (ARJ) where they are located in the right and left lateral and in the right and left posterolateral sectors. No hemorrhoidal arteries were found in the right and left anterolateral sectors. From 3 cm at the lowest 2 cm above the ARJ, arteries move toward the submucosa and distribute circumferentially in each quadrant[6].

Symptomatic hemorrhoids are associated to destructive changes in the supporting connective tissue with downward displacement of normal anal cushions and to abnormal arterial supply to the anal canal with hyperperfusion, dilation and distortion of the hemorrhoidal plexus[7-9]. The hemorrhoidal bleeding score (HBS; range 0-9) has been proposed to evaluate the severity of this symptom[10].

In patients with early stage hemorrhoidal disease, if non-operative treatment fails, minimally invasive techniques including rubber band ligation, injection sclerotherapy, infrared coagulation, cryosurgery, and laser are proposed[11]. In advanced stages, traditional hemorrhoidectomy, stapled mucoprolapsectomy or transanal hemorrhoidal dearterialization (THD) are used to treat both the prolapse and the bleeding[12].

Hemorrhoidal artery embolization (Emborrhoid) is a novel method for the treatment of severe bleeding. Through the catheterization of the femoral or radial arteries and a selective angiogram of the inferior mesenteric artery, embolic agents are used to occlude the SRA branches[13]. Despite a technical success rate up to 93%-100%, clinical success was reported in 63%-94% of cases with a rebleeding rate of 13.6%. It was shown that in 24% of cases, rebleeding was due to the presence of a significant MRA[14]. There are no data in the literature that evaluated the changes in the hemorrhoidal arterial flow after embolization.

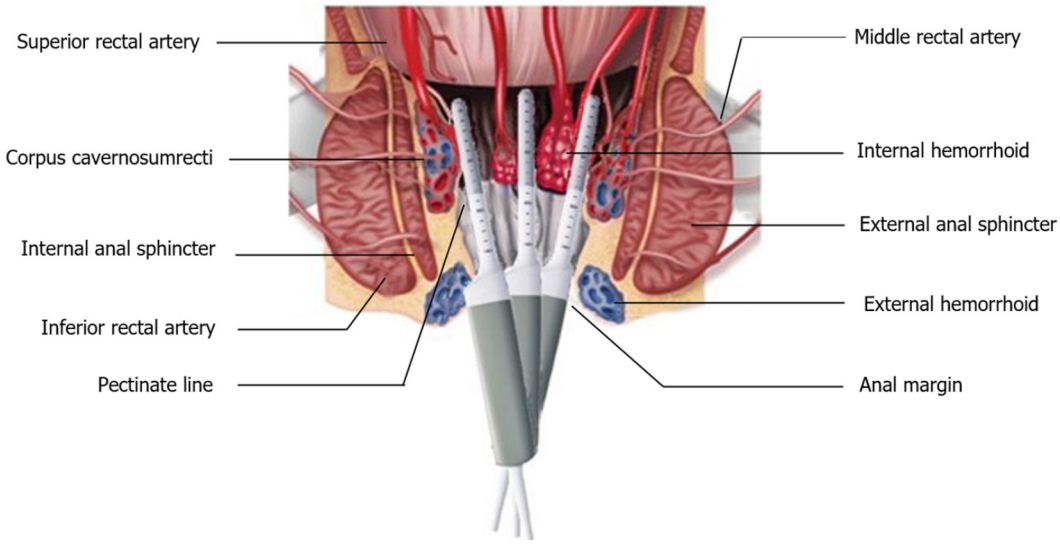

Figure 1 Schematic representation of endoanal ultrasound technique with the linear transducer positioned 2 cm above the anorectal junction.

The primary endpoint of this study was to quantify the reduction in the blood supply occurring after Emborrhoid by using transanal eco-Doppler. The secondary endpoint was to evaluate the correlation between the flow reduction and the hemorrhoidal bleeding.

MATERIALS AND METHODS

A prospective observational pilot study was conducted at the Division of General Surgery 1, Treviso Regional Hospital, Italy. In a 2-mo period (February-March 2022), consecutive patients who were candidates for hemorrhoidal artery embolization were included. The study was approved by the local Ethical Committee (No. 1286/CE Marca) and registered on clinicaltrials.gov (NCT05627999). All patients gave written informed consent.

Indications to the procedure were HBS ≥ 4, Goligher score II or III, more than 18 years of age, failure of non-operative management (lifestyle change, dietary modification, supplemental fibers, and over-the-counter treatment). Exclusion criteria were a Goligher score of IV, pregnancy, previous hemorrhoidal surgery, inflammatory bowel disease. Use of anticoagulants or anti-aggregants was not considered an exclusion criterion[15].

Patients underwent history and physical (proctological) examination and assessment of the Goligher and HBS scores by a single operator (RT) before and 1 mo after the procedure. Symptom improvement was defined a reduction of at least three points of the HBS score.

To measure the hemorrhoidal artery flow, transanal ultrasonography with eco-color Doppler was performed the same day of the procedure and at 1-mo follow-up at the Tertiary Referral Pelvic Floor Center, Treviso Regional Hospital, Italy by a single expert operator, who was blinded at the clinical findings. Data on SRA anatomy[3], type of embolization (distal or proximal) and the coil landing zone (distal *vs* proximal) were collected. Relationships between hemorrhoidal grade and treatment outcome, between changes in the mean arterial systolic peak (MSP) and the type of embolization (distal or proximal) and between the SRA anatomy[3], the coil landing zone (distal *vs* proximal) and treatment outcomes were analyzed. The correlation between changes in the MSP and the HBS score before and after treatment was also evaluated. Post-procedural complications were reported according to Clavien-Dindo classification[16].

Endoanal ultrasound

Ultrasound was performed by using a Flexfocus 5000 (BK Medical, Herlev, Denmark) with an endocavitary transducer (3DX14L4-9038, BK Medical), 16 mm diameter, frequency range 4-14 MHz, focal range 3-60 mm, linear array with 65 mm acoustic surface and automatic three-dimensional acquisition. Before examination, patients were administered two enemas to flush the rectum and were placed in the left lateral position. Close contact of the transducer with the rectal mucosa was maintained while carefully avoiding excessive pressure on the rectal wall to minimize artifacts due to arterial compression. The same care was taken to maintain the transducer perpendicular to the examined structures in order to have a perpendicular angle of intersection between the Doppler beam and the vessels. Angle correction was used to adjust the angulation of the ultrasound beam and standardize the calculations of the velocity flow.

According to Ratto *et al*[5], the hemorrhoidal arterial flow was assessed in the 1, 3, 5, 6, 7, 9, 11, and 12 o'clock positions 2 cm above the ARJ, localized by ultrasound at the proximal edge of the puborectalis sling (Figure 1). Pulsed wave Doppler was used to measure the peak systolic velocity (cm/s), corresponding to the tallest peak in the spectrum window (Figure 2). For each investigated sector, pictures graphically displaying the flow velocity over time were obtained for reviewing after the examination.

Table 1 Patient demographics and pre-treatment symptom severity

Patient	Age	Sex	Comorbidities	Anticoagulant therapy	Goligher score	Pre-treatment HBS
1	56	F	No comorbidities	No therapy	3	5
2	43	F	No comorbidities	No therapy	3	6
3	75	M	Atrial fibrillation	Warfarin	3	4
4	54	F	Hypothyroidism	No therapy	2	5
5	62	M	No comorbidities	No therapy	3	6
6	53	M	No comorbidities	No therapy	3	3
7	46	F	No comorbidities	No therapy	2	4
8	46	M	No comorbidities	No therapy	3	3
9	63	F	No comorbidities	No therapy	3	4
10	55	M	No comorbidities	No therapy	2	5
11	28	M	No comorbidities	No therapy	3	3

HBS: Hemorrhoidal bleeding score.

Emborrhoid technique

Embolization was performed as described by Vidal *et al*[1] under local anesthesia *via* the femoral or radial routes. No prophylactic antibiotic was given. The inferior mesenteric artery was catheterized using a 4 Fr Simmons catheter (Cordis Corp, Bridgewater, NJ, United States) and the SRAs were then catheterized with a microcatheter (Direxion HI-FLO; Boston Scientific, Marlborough, MA, United States) and a microwire (0.16-inch Fathom; Boston Scientific; Figure 3A-C). In distal embolization, each superior rectal branch was selectively embolized as distally as possible with 2–3 pushable coils, usually 3 mm in diameter (0.018 VortX; Boston Scientific). In proximal embolization, one or two coils, usually 4 mm in diameter (0.018 VortX; Boston Scientific) were deployed before the bifurcation into the main branch of the SRA. If a middle or inferior rectal artery anastomosis was observed on one or both sides of the hemorrhoidal plexus from the right or left internal iliac arteries, treatment was by selective catheterization of the distal branches of the SRA with a microcatheter and slow injection of a small amount of biocompatible, hydrophilic, non-resorbable microspheres (700 μm in diameter, acrylic polymer; Embosphere; Merit Medical, South Jordan, UT, United States) until the anastomosis was occluded. Then the distal branches of the SRA were embolized with pushable coils as previously described. Embolization was carried out until the angiographic endpoint of neither flow in the distal branches of the SRA or in the hemorrhoidal terminal branches (Figure 3D-F). At the end of the procedure, hemostasis of the femoral or radial arteries was achieved by manual compression. Patients were sent home the day after the procedure.

Statistical analysis

Descriptive data were analyzed using SPSS version 16 for Windows (SPSS Inc., Chicago, IL, United States). The results were reported as mean ± SD, median (range) and number (percentage) of patients. Overall and sectorial mean arterial systolic peaks were compared preoperatively and at 1-mo follow-up by using the Student *t*-test. Relationships between MSP changes, treatment outcomes and anatomical and technical details were analyzed by using the Student *t*-test and the chi-squared test. A P value of < 0.05 was considered statistically significant. The linear correlation between changes in MSP and changes in HBS was calculated using Pearson's correlation coefficient.

RESULTS

Eleven patients, consisting of five women and six men with median of age 52.6 (range 28-75) years and who are candidates for Emborrhoid, were included in the study. Patient demographics and pre-treatment symptom severity are shown in Table 1. Three patients (27.3%) had Goligher grade 2, and eight patients (72.7%) had Goligher grade 3 hemorrhoids. Median HBS was 4 (range 4-6). No major comorbidities were reported. In a patient on oral anticoagulant therapy for chronic atrial fibrillation, the therapy was discontinued and replaced with low molecular weight heparin for the procedure.

The overall pre-treatment MSP was 14.66 cm/s (SD ± 1.93). Sectorial analysis showed that the highest values were found in the anterior left lateral (17.82 cm/s at 1 o'clock, 15.88 cm/s at 3 o'clock positions) and in the posterior right lateral (14.62 cm/s at 7 o'clock and 16.71 cm/s at 9 o'clock positions) quadrants of the anal canal. The lowest values were registered at 5 o'clock (13.03 cm/s) and 11 o'clock (12.74 cm/s) positions (Table 2, Figure 4A-D).

The radial artery was catheterized in 7 patients and the femoral artery was catheterized in 4. Eight patients (72.7%) had type 1 SRA anatomy and three patients (27.3%) had type 2 SRA anatomy (Table 3). Embolization was performed distally in 8 patients (72.7%) and proximally in 3 patients (27.3%). In patients with type 2 SRA anatomy, the SRA/MRA

Table 2 Sectorial pre- and post-treatment systolic peaks

Patient	1 o'clock		3 o'clock		5 o'clock		6 o'clock		7 o'clock		9 o'clock		11 o'clock		12 o'clock	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	9.61	13.10	5.12	5.44	9.50	6.19	20.50	14.90	15.00	9.93	7.47	10.80	20.10	17.40	6.62	13.00
2	20.40	5.12	24.91	16.10	15.90	8.11	24.90	13.10	10.90	6.62	15.40	14.90	6.50	8.11	10.40	20.50
3	17.00	19.90	10.70	17.00	13.70	19.40	8.86	8.97	15.80	12.40	8.97	22.60	12.00	14.40	20.00	14.90
4	13.10	20.40	18.50	20.40	16.19	7.36	6.19	6.83	12.00	9.61	19.40	15.80	13.00	8.00	21.00	24.90
5	25.40	25.20	16.90	10.60	6.62	7.58	8.65	8.00	13.60	10.60	26.40	20.20	19.40	14.10	15.00	7.47
6	20.50	14.50	15.50	8.43	8.11	13.00	7.79	9.39	13.20	8.22	12.80	14.30	7.36	13.70	10.10	5.87
7	17.70	ND	16.40	ND	8.22	ND	8.86	ND	19.40	ND	13.80	ND	8.11	ND	8.65	ND
8	17.40	20.40	15.60	13.60	8.11	8.65	12.70	8.22	15.50	7.79	25.00	15.70	20.50	15.30	15.50	8.00
9	24.00	20.40	25.00	6.51	8.00	6.40	15.70	8.22	11.20	12.20	18.60	14.30	11.00	19.00	16.20	8.86
10	5.90	14.10	13.00	13.00	20.00	11.60	7.79	7.79	8.22	8.97	10.00	4.38	12.70	8.00	5.70	5.87
11	25.00	ND	13.10	ND	29.00	ND	25.00	ND	26.00	ND	26.00	ND	9.50	ND	15.20	ND
Mean	17.82	17.01	15.88	12.34	13.03	9.81	13.36	9.49	14.62	9.59	16.71	14.77	12.74	13.11	13.12	12.15

Systolic peak data are in cm/s. ND: Not defined.

anastomosis was also embolized (Table 3). The angiographic complete interruption of the blood flow in the distal branches of the SRA was achieved in all cases (technical success of the procedure 100%).

Four patients (36.4%) reported post-operative complications, including one patient C-D 1, two patients C-D 2 and one patient C-D 3b. Complications included acute urine retention, orchitis, radial artery thrombosis with deep brachial vein and superficial cephalic vein thrombosis. One patient reported severe hemorrhoidal bleeding requiring transfusions and an emergency excisional hemorrhoidectomy. In that case, it was not possible to perform the post-operative Doppler assessment.

After 1 mo, a follow-up evaluation was performed in 9 patients because 1 refused to repeat an endoanal ultrasound. All patients had persisting prolapse. Bleeding was absent or slight in 5 patients (55.5%, median HBS 1; Figure 4E and F) and persistent in 4 (44.5%, mean HBS 3.75; Figure 5A).

Overall post-treatment MSP was 12.29 cm/s (SD ± 2.68). The difference between pre- and post-treatment overall MSP was significant (P = 0.008) (Table 4, Figure 5B). Sectorial analyses showed that the MSP reduction was significant only at 7 o'clock (14.62 cm/s *vs* 9.59 cm/s; P = 0.008; Table 2). MSP was significantly reduced in patients treated by distal compared with proximal embolization [−2.52 cm/s (SD 1.70) *vs* 1.03 cm/s (SD 2.53); P = 0.047]. However, the coil landing zone was not associated with symptom improvement (P = 1.000). The difference in MSP change in patients with type 1 and type 2 SRA anatomy was significant [−2.54 cm/s (SD 1.68) *vs* 1.10 cm/s (SD 2.43); P = 0.040].

Table 3 Superior rectal artery classification, Emborrhoid treatment, and outcomes

Patient	SRA classification	Type of embolization	Pre-treatment MSP	Post-treatment MSP	Pre-treatment HBS	Post-treatment HBS
1	Type 1	Distal (particles and coils)	11.74	11.34	5	0
2	Type 1	Distal (particles and coils)	16.16	11.57	6	0
3	Type 2	Proximal (particles and coils; coils in SRA/MRA anastomosis)	13.38	16.20	4	4
4	Type 1	Proximal (particles and coils)	14.92	14.16	5	0
5	Type 1	Distal (particles and coils)	16.50	12.97	6	4
6	Type 2	Distal (particles and coils; particles and coils in SRA/MRA anastomosis)	11.92	10.93	3	0
7	Type 1	Distal (particles and coils)	12.64	ND	4	ND
8	Type 1	Distal (particles and coils)	16.29	12.21	3	0
9	Type 1	Distal (particles distally; one coil proximal)	16.21	11.99	4	4
10	Type 1	Distal (coils)	10.41	9.21	5	3
11	Type 2	Proximal (particles and coils; particles and coils in SRA/MRA anastomosis)	21.10	ND	3	ND

HBS: Hemorrhoidal bleeding score; MRA: Middle rectal artery; MSP: Mean systolic peak; ND: Not defined; SRA: Superior rectal artery.

Table 4 Overall pre- and post-treatment mean systolic peak

Position	Pre-treatment MSP	Post-treatment MSP	*P* value
1 o'clock	17.82	17.01	0.993
3 o'clock	15.88	12.34	0.158
5 o'clock	13.03	9.81	0.314
6 o'clock	13.36	9.49	0.077
7 o'clock	14.62	9.59	0.008
9 o'clock	16.71	14.77	0.604
11 o'clock	12.74	13.11	0.708
12 o'clock	13.12	12.15	0.592
Overall	14.66	12.29	0.008

Systolic peak data are in cm/s. MSP: Mean systolic peak.

In 5 patients (55.5%) with HBS reductions ≥ 3, no significant difference was found between pre- (14.20 cm/s) and post-treatment (12.04 cm/s) MSP values ($P = 0.07$). The same was reported in 4 patients (44.5%) who complained of persisting bleeding and who showed no significant difference between pre- (14.12 cm/s) and post-treatment (12.59 cm/s) MSP values ($P = 0.41$). No relationship was found between hemorrhoidal grade and treatment outcome ($P = 1.000$) or between SRA anatomy and treatment outcome ($P = 1.000$). Pearson's correlation analysis showed a weak positive correlation [rs (9) = 0.21, $P = 0.57$] between MSP and HBS changes, with a monotonic relationship, as assessed by visual inspection of the scatterplot (Figure 6).

DISCUSSION

Hemorrhoidal peak velocities were shown to be significantly different in a healthy control group and in patients with hemorrhoidal disease[17]. Doppler ultrasound-guided hemorrhoidal artery ligation (DHAL) and THD techniques have been proposed as minimally invasive modalities to treat hemorrhoidal bleeding by selective dearterialization[5,13]. A systematic review and meta-analysis showed an advantage of THD over traditional hemorrhoidectomy in terms of shorter operative time and reduced pain and complications[18]. However, this procedure is associated with a recurrence

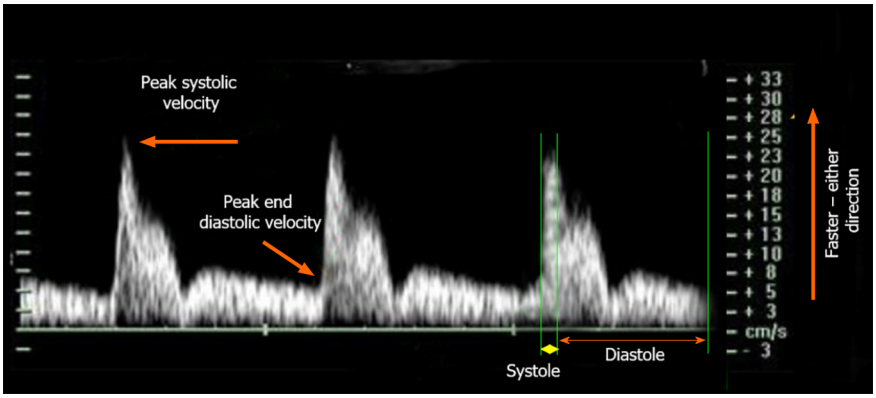

Figure 2 Characteristic of the waveform and measurement of the arterial systolic peak.

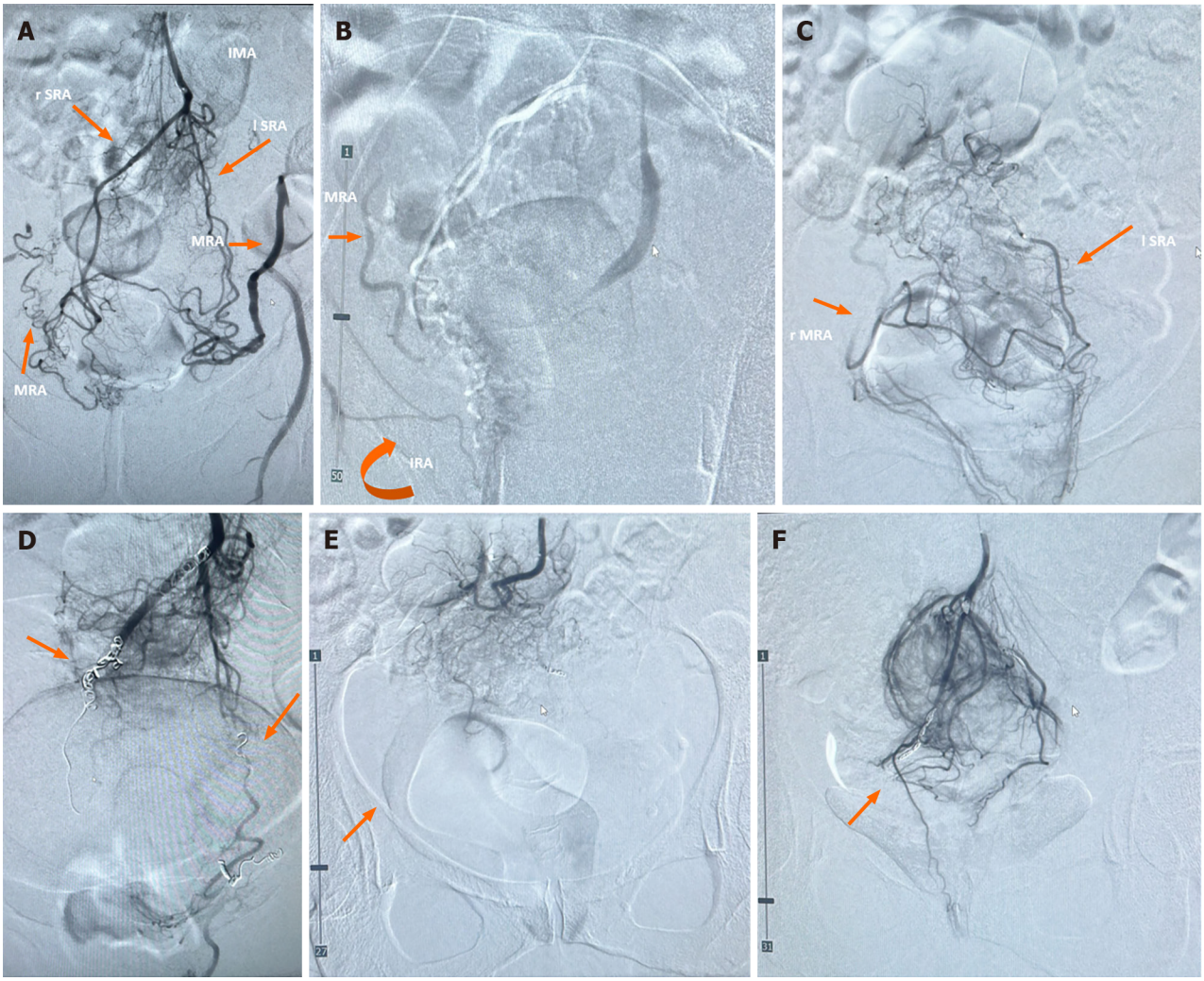

Figure 3 Pre-treatment and post-treatment angiography. A: Case 1, anastomosis between superior (SRA) and middle (MRA) rectal arteries, bilaterally; B: Case 5, anastomosis between right MRA and inferior (IRA) rectal arteries; C: Case 8, anastomosis between right MRA and left SRA; D: Case 1, embolization of the distal branches of the SRA (arrows) and occlusion of the anastomosis with MRA; E: Case 5, embolization of the distal branches of the SRA and occlusion of the anastomosis with IRA and MRA (arrow); F: Case 8, embolization of the distal branches of the SRA (arrow) and occlusion of the anastomosis between right MRA and left SRA. IMA: Inferior mesenteric artery.

rate up to 40%[18,19]. A systematic review of the literature showed an overall recurrence rate of 17.5% after DHAL[20]. These data are different from those of Ratto *et al*[5] who reported a correlation between technical success and clinical success of the THD procedure at a 1-year follow-up. These findings may be due to the peripheral hemorrhoidal artery ligation used in their study[6].

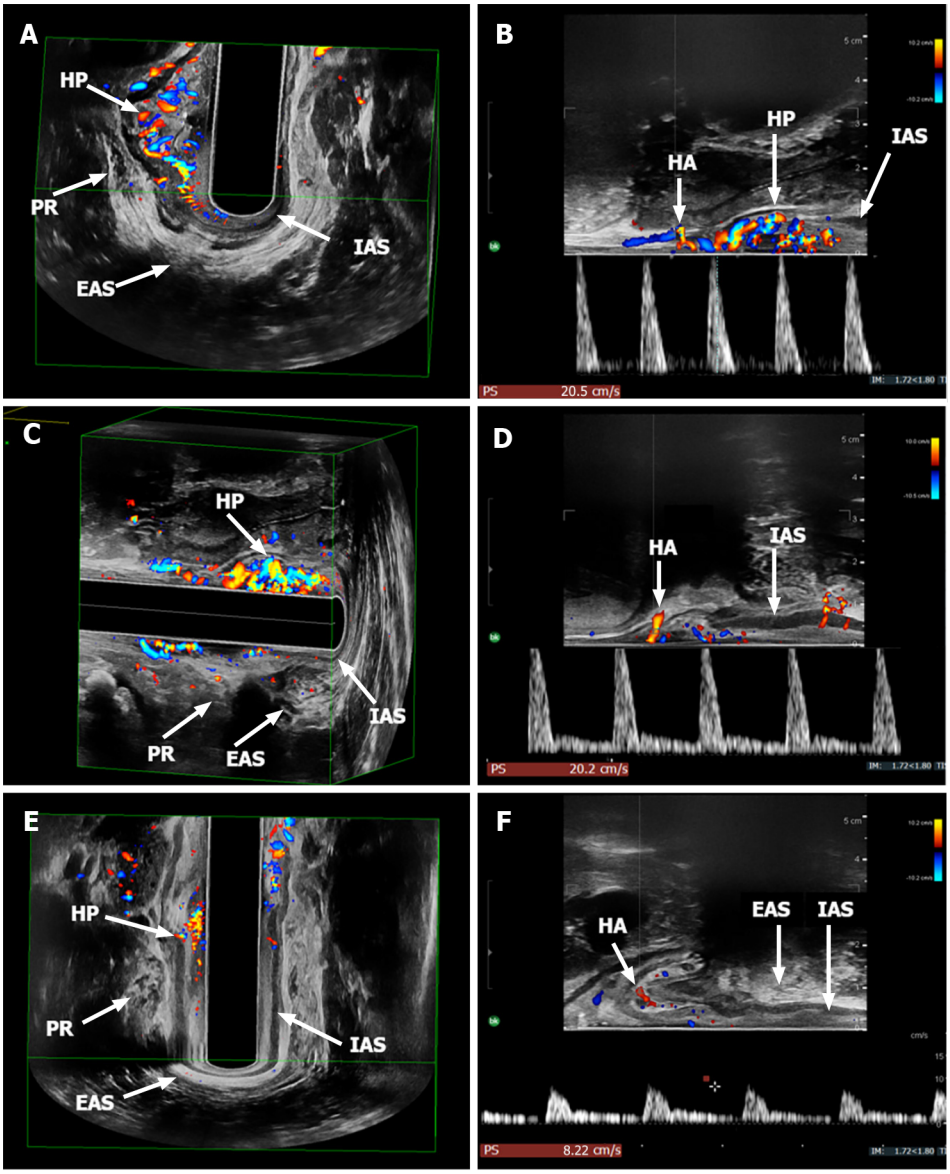

Figure 4 Endoanal ultrasound. A-D: Preoperative endoanal ultrasound performed by a linear endocavitary transducer (3DX14L4-9038, BK Medical, Herlev, Denmark). Three-dimensional ultrasound with color Doppler showing grade 3 hemorrhoidal plexus (HP) at 11 o'clock position (A); The mean hemorrhoidal artery (HA) systolic peak velocity was 20.5 cm/s (B); Three-dimensional ultrasound with color Doppler showing grade 3 HP at 1 o'clock position (C); and the mean HA systolic peak velocity was 20.2 cm/s (D); E and F: Endoanal ultrasound at 1-mo follow-up. Three-dimensional ultrasound with color Doppler showing the regression of HP at 11 o'clock position (E); and the reduction of the mean HA systolic peak velocity (8.22 cm/s) (F, same case of Figure A and B). EAS: External anal sphincter; IAS: Internal anal sphincter; PR: Puborectalis muscle.

Embolization with particles conceptually mirrors the DHAL and THD techniques[21]. Compared to those procedures, Emborrhoid has the advantage of identifying all the hemorrhoidal arterial branches to be occluded by arteriography, potentially improving therapeutic effectiveness[1]. This technique was initially performed in the 1990s in patients with disabling chronic rectal bleeding[22]. Currently, indications for the procedure include mild-to-severe hemorrhoidal bleeding, recurrence after hemorrhoidal surgery, coagulation disorders, and presence of high operative risk[13]. Embolization, avoiding anal manipulation, has also been proposed for patients with faucal incontinence and hemorrhoidal bleeding to avoid anal sphincter damages due to hemorrhoidectomy[23]. In the United Kingdom, Emborrhoid is still carried out only for research purposes as its advantage over the others techniques has not yet been demonstrated[21].

Ratto *et al*[5] analyzed the effects of THD on the hemodynamic parameters of the hemorrhoidal arteries, finding a significant reduction in MSP values (post treatment 10.3 cm/s *vs* pretreatment 18.7 cm/s). However, the analysis was limited to patients who reported resolution of the bleeding after treatment. These results are consistent with those of our pilot study showing that the overall MSP of hemorrhoidal arteries was significantly reduced after Emborrhoid. The present study demonstrated that distal embolization resulted in a greater reduction in MSP values compared with proximal embolization. Sectorial analysis revealed that the reduction was significant in the right posterolateral quadrant. Similar results were reported by Zakharchenko *et al*[21] who measured the hemorrhoidal blood flow by ultrasound. They demonstrated a drop in the flow from 109.0 mL/min/100 g ± 1.2 mL/min/100 g (SD) to 60.2 mL/min/100 g ± 4.4 mL/min/100 g (SD) ($P < 0.05$) the day after embolization, and unchanged at 1 mo of follow-up. Patient satisfaction was 94% in

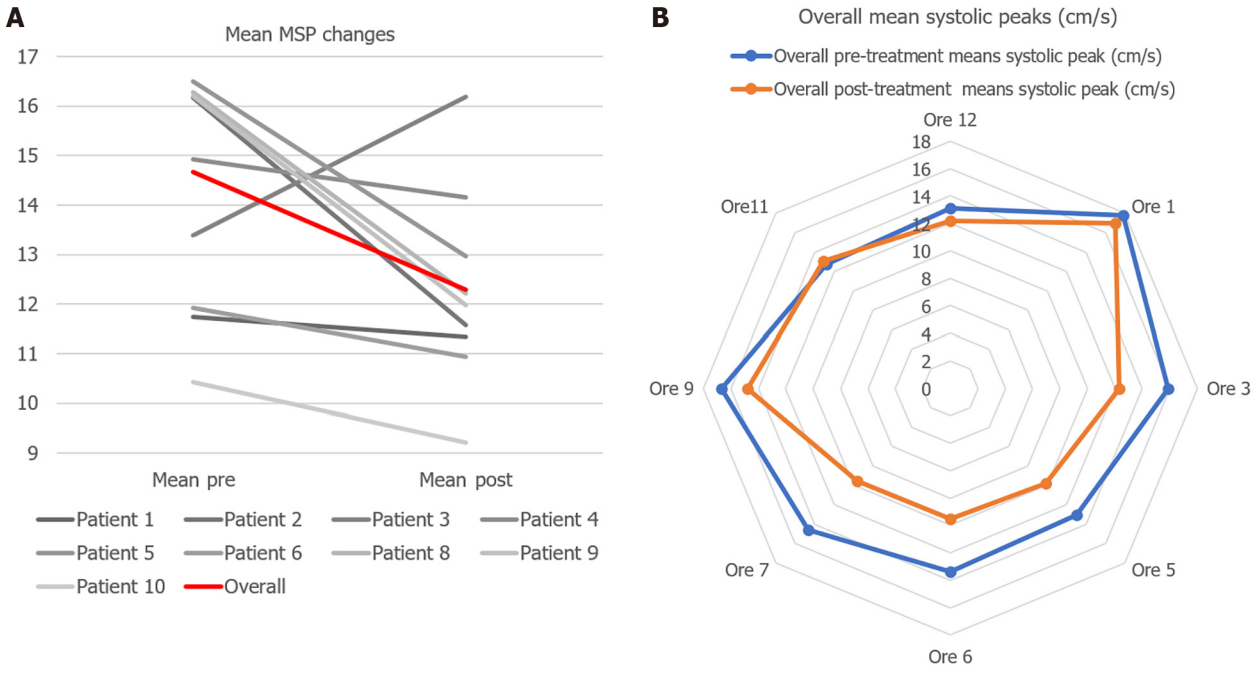

Figure 5 Mean systolic peak. A: Pre- and post-treatment mean systolic peak (MSP, cm/s) changes; B: Overall pre- and post-treatment MSP (cm/s).

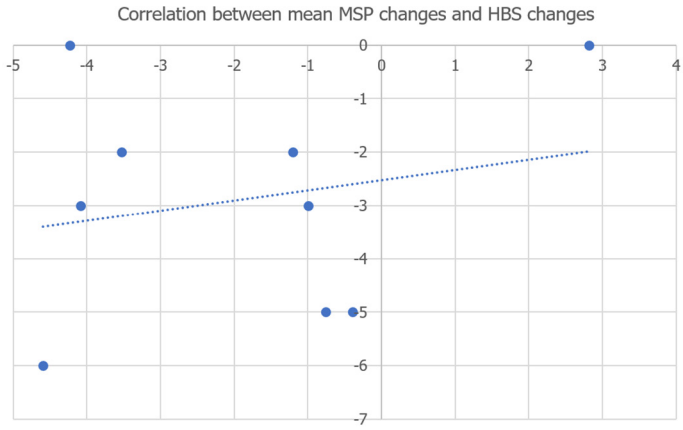

Figure 6 Scatterplot of the correlation between mean systolic peak and hemorrhoidal bleeding score change. HBS: Hemorrhoidal bleeding score; MSP: Mean systolic peak.

grade 1-2 and 83% in grade 3 hemorrhoids. These investigators used 0.3 mm diameter non-lysing synthetic polyvinyl alcohol particles and standard metallic coils. No data were provided on the correlation between flow and symptoms.

Our findings demonstrate that the benefit of Emborrhoid was not associated with the hemorrhoidal, probably due to the small size of the study cohort. However, in a previous study, we reported that Emborrhoid was more effective in grade 2 than in grade 3 hemorrhoids, with 84% *vs* 50% of symptoms resolution, respectively at the 6 mo follow-up[15].

Particles over coils or a combination of both, as in our patients, were not superior in terms of clinical success in a comparative study by Moussa *et al*[24] with a longer follow-up period.

Our study findings included a weak, nonsignificant correlation between post-operative MSP and HBS changes in both asymptomatic patients and in cases with persistent bleeding. Consequently, our results do not confirm the hypothesis that hypervascularization of the branches of the SRA and severity of hemorrhoidal bleeding are correlated. This data could explain why the technical success of the procedure, defined as the absence of the flow in the branches of SRA and absence of opacification of the terminal branches in the projection of the hemorrhoids, has been reported up to 93%-100%. On the other hand, the clinical success, assessed by using composite scores for symptoms evaluation, quality of life, and satisfaction, ranged between 63.0% and 94.0%, with 13.6% of rebleeding[14]. Vidal *et al*[13] treated 14 patients with embolization, reporting 100% technical success and 72% clinical success (mean follow-up, 192 d). These data are consistent with the results of our study, with 100.0% technical success, 55.5% clinical success, and persistent bleeding in 44.5% of cases (mean HBS: 3.75). The difference between the technical success reported at the end of the procedure and the clinical success at 1-mo of follow-up could be due to a revascularization of the branches of the SRA or the MRA.

The type of SRA anatomy is crucial to the effectiveness of MSP changes. We demonstrated greater flow reduction in patients with type 1 SRA anatomy compared with those with type 2. Accordingly, patients with persistent or recurrent bleeding and no significant hemorrhoidal flow reduction at the follow-up eco-Doppler assessment may receive a second or third embolization. However, as described by Vidal *et al*[13], clinical success after repeated sessions was still not achieved in 28% of cases.

Post-operative complications after SRA embolization included fever, persistent bleeding, hematoma at the site of the puncture, tenesmus, hemorrhoidal thrombosis and pain. Eberspacher *et al*[25] reported a case of rectal ischemia resulting in rectal stenosis treated with bowel dilation. In our study, post-operative complications occurred in 36.4% of cases. The radial artery access, proposed to reduce the need for post-operative bed rest and offer patients a prompt return to normal activities[13,26], was complicated by a radial artery thrombosis.

Limitations

Limitations of this study are the small sample-size and the short follow-up period. However, given the novelty of this technique, we decided to conduct a pilot study to preliminarily assess the effectiveness of the procedure. Our results in terms of moderate efficacy and weak correlation between symptoms and flow suggest a word of caution. In hemorrhoidal disease the increased arterial flow might not be the main cause of symptoms. Studies in a larger group of patients and with a longer follow-up are needed to draw definitive conclusion on long term effectiveness and recurrence rate.

CONCLUSION

The preliminary findings of this pilot study confirm that Emborrhoid was effective in reducing the arterial hemorrhoidal flow in hemorrhoidal disease. The MSP reduction was significant in type 1 SRA anatomy and in distal embolization. However, the correlation between post-operative changes in MSP values and HBS was weak and no relationship was found between hemorrhoidal grades, SRA anatomy, type of embolization, and treatment outcomes.

FOOTNOTES

Author contributions: Massani M and Santoro GA contributed equally to this paper; Tutino R and Santoro GA made substantial contributions to conception and design, data acquisition, data analysis and interpretation; Stecca T and Farneti F made substantial contributions to data acquisition; Massani M made substantial contributions to data analysis and interpretation; Tutino R and Santoro GA drafted the article and revised it critically for important intellectual content; Stecca T, Farneti F, and Massani M also revised it critically for important intellectual content; All the authors provided final approval of the version to be published.

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ORIGINAL ARTICLE

Prospective Study

Diagnostic and prognostic performances of GALAD score in staging and 1-year mortality of hepatocellular carcinoma: A prospective study

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Abstract

BACKGROUND

The GALAD score has improved early hepatocellular carcinoma (HCC) detection rate. The role of the GALAD score in staging and predicting tumor characteristics or clinical outcome of HCC remains of particular interest.

AIM

To determine the diagnostic/prognostic performances of the GALAD score at various phases of initial diagnosis, tumor features, and 1-year mortality of HCC and compare the performance of the GALAD score with those of other serum biomarkers.

METHODS

This prospective, diagnostic/prognostic study was conducted among patients with newly diagnosed HCC at the liver center of Vajira Hospital. Eligible patients had HCC staging allocation using the Barcelona Clinic Liver Cancer (BCLC) categorization. Demographics, HCC etiology, and HCC features were recorded. Biomarkers and the GALAD score were obtained at baseline. The performance of the GALAD score and biomarkers were prospectively assessed.

RESULTS

Exactly 115 individuals were diagnosed with HCC. The GALAD score increased with disease severity. Between BCLC-0/A and BCLC-B/C/D, the GALAD score

predicted HCC staging with an area under the curve (AUC) of 0.868 (95%CI: 0.80–0.93). For identifying the curative HCC, the AUC of GALAD score was significantly higher than that of Alpha-fetoprotein (AFP) (0.753) and Lens culinaris agglutinin-reactive fraction of AFP-L3 (0.706), and as good as that of Protein induced by vitamin K absence-II (PIVKA-II) (0.897). For detecting aggressive features, the GALAD score gave an AUC of 0.839 (95%CI: 0.75–0.92) and significantly outperformed compared to that of AFP (0.761) and AFP-L3 (0.697), with a trend of superiority to that of PIVKA-II (0.772). The performance to predict 1-year mortality of GALAD score (AUC: 0.711, 95%CI: 0.60–0.82) was better than that of AFP (0.541) and as good as that of PIVKA-II (0.736). The optimal cutoff value of GALAD score was ≥ 6.83, with a specificity of 72.63% for exhibiting substantial reduction in the 1-year mortality.

CONCLUSION

The GALAD model can diagnose HCC at the curative stage, including the characteristic of advanced disease, more than that by AFP and AFP-L3, but not PIVKA-II. The GALAD score can be used to predict the 1-year mortality of HCC.

Key Words: Alpha-fetoprotein; Barcelona clinic liver cancer; GALAD score; Hepatocellular carcinoma; Lens culinaris agglutinin-reactive fraction of alpha-fetoprotein; Protein induced by vitamin K absence-II

Core Tip: The GALAD score performance showed a benefit not only in the accuracy of curative hepatocellular carcinoma (HCC) staging but also in the characteristic of advanced disease. Incorporating the GALAD model may increase the opportunity for prognosis prioritization for patients with HCC to predict the 1-year mortality.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related mortality worldwide. In Thailand, it was the leading cause of cancer-related deaths among males and the third-highest cause among females[1]. Despite the rapid introduction of novel and efficient HCC treatments, screening for HCC using a combination of serum alpha-fetoprotein (AFP) and ultrasonography, slightly improved the early detection rate of HCC[2,3].

Due to the suboptimal improvements obtained from combining AFP with ultrasound, the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases recommended only biannual ultrasound for HCC surveillance[3-5]. Other biomarkers including AFP-L3, the Lens culinaris agglutinin-reactive fraction of AFP, which appears to be more specific for HCC[6,7]; and des-carboxy-prothrombin (DCP), a prothrombin precursor produced by HCC, have been investigated as potential tumor markers for HCC in several ethnic populations[8-10]. Additionally, AFP, AFP-L3, and DCP levels have been extensively studied in relation to prognosis[11-15]. According to a meta-analysis, combining these serum biomarkers may boost sensitivity and specificity compared to that from using each biomarker alone[16].

Previous research has presented a novel diagnostic algorithm, the GALAD score, which considers gender, age, AFP-L3, AFP, and DCP. This model shows enhanced early-stage HCC detection sensitivity[17-20]. As such, the role of the GALAD score in terms of tumor stage or clinical outcomes of HCC was intriguing. Thus, this study aimed to determine the diagnostic/prognostic performances of the GALAD score at various phases of the initial HCC diagnosis, tumor features, and 1-year mortality of patients with HCC and compare the performance of the GALAD score with that of individual serum biomarkers.

MATERIALS AND METHODS

Study design and study population

This prospective study was conducted at Faculty of Medicine Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand. Participants were required to be at least 18 years old and diagnosed with HCC for the first time between September 2021 and March 2022. Hepatitis B and C virus (HBV and HCV, respectively) infections were verified based on the presence of hepatitis B surface antigen and anti-HCV antibodies. Alcohol consumption was considered a cause of

HCC when there was a significant and documented history of alcohol abuse in the patient[21]. Metabolic-associated fatty liver disease (MAFLD) was diagnosed based on either an increase in liver ultrasound echogenicity or steatosis, as determined by a transient liver stiffness test in the presence of metabolic syndrome[22]. Cirrhosis was defined by: (1) Histology; (2) cirrhosis characteristics in imaging studies using ultrasound or computed tomography (CT) imaging (nodular configuration of the liver, dilated portal vein (PV), splenomegaly with or without ascites); or (3) transient elastography with a cut point of liver stiffness greater than 12.5 kPa. The predictive prognosis of cirrhosis was evaluated using both the Child-Pugh and Model for End-Stage Liver Disease scores. HCC was diagnosed based on: (1) Histology; or (2) presence of cirrhosis with the radiologic characteristics of HCC on a CT scan. In chronic HBV infection, HCC diagnosis is determined by the presence of both radiologic hallmarks and an AFP level > 200 ng/mL[23-25]. Patients with other primary liver malignancies, patients with liver metastases, and patients with HCC who did not complete the informed consent form were excluded. All individuals who receive a diagnosis of HCC will be eligible for standard treatment according to the Barcelona Clinic Liver Cancer (BCLC) guideline. Each individual provided informed consent prior to enrollment, after the researchers had thoroughly explained them the research topic. Participants' demographic information, including age, sex, body mass index, symptoms at initial presentation, HCC etiology, performance status, tumor burden and characteristics of advanced disease, was collected. The following biochemical data were collected: Total blood count, blood urea nitrogen, creatinine level, levels of electrolytes, coagulogram, liver function test, and viral markers.

Individual blood samples (10 mL) for AFP, AFP-L3, and Protein induced by vitamin K absence- II (PIVKA-II) (stored at 20 °C) were measured using the μTASWako i30 fully automated immune analyzer (Fujifilm Wako Pure Chemical Corporation, Osaka, Japan)[26]. Microfluidic chips were analyzed using liquid-phase binding assays, followed by capillary electrophoresis and fluorescence detection. This machine had lower limited detections of 0.3 ng/mL for AFP and 5 mAU/mL for PIVKA-II for each biomarker. The percentage of AFP-L3 was measured when the AFP value was more than 0.3 ng/mL.

The GALAD score was computed as follows: Z = -10.08 + 0.09 × age + 1.67 × sex + 2.34 Log (AFP) + 0.04 × (AFP-L3) + 1.33 Log (DCP). The formula × 0.012 was used to convert the DCP (ng/mL) to the PIVKA-II value (mAU/mL)[27]. https://www.mayoclinic.org/medical-professionals/model-end-stage-liver-disease/GALAD is a web-based calculator. The definition of sex was 1 for males and 0 for females. The BCLC staging system was used to categorize tumor stages[28]. Participants who were eligible received conventional HCC treatment. Mortality was measured from the initial HCC diagnosis until death or at the end of follow-up at 1 year.

Sample size calculation

The sample size determined the number of participants for estimating accuracy index formula using the area under the curve (AUC)[29]:

$n = Z^2_{\alpha/2} V\,(\mathrm{AUC})/d^2$

Where n is the sample size for each group with disease/endpoint and non-disease/non-endpoint, $V_{(\mathrm{AUC})} = (0.0099 \times) \times (6a^2 + 16)$, $a = \varphi^{-1}_{(\mathrm{AUC})} \times 1.414$, and φ^{-1} is the inverse of standard cumulative normal distribution or Z_{AUC}.

The reference AUC values of GALAD score for calculating sample sizes for staging patients with HCC into each of the five stages of BCLC (0/A/B/C/D) and predicting other endpoints were not obtained from any research through our review. Therefore, we used the values from previous research that studied the GALAD performance to diagnose HCC. The reference AUC values were obtained from a systematic review and meta-analysis of the performance of GALAD score for diagnosing HCC in patients with chronic liver diseases, with an AUC of 0.86 for detecting early-stage HCC (BCLC 0/A)[20], and from a multicenter case-control study with an AUC of 0.933 for advanced HCC (BCLC B/C/D)[30]. The reference value used to calculate the sample size for 1-year mortality was obtained from a recent study with an AUC of 0.792[31]. $Z_{\alpha/2}$ is the Z-score corresponding to a normal distribution defined as 1.96 (α = 0.05) with 95% confidence; and the degree of precision of estimate being about 0.129[20], 0.14[30], and 0.1188[31] (d was set at 15% error of AUC) for statistical significance, with $V_{(\mathrm{AUC})}$ = 0.092483. Therefore, the required sample size obtained by inserting the formula[29] was 44 participants for detecting early-stage HCC, 18 participants for detecting advanced-stage HCC, and 68 participants for predicting 1-year mortality of patients with HCC.

Ethical approval

The institutional review board of the Faculty of Medicine at Vajira Hospital (COA 165/2564) authorized the study protocol, which was conducted in accordance with the ethical norms of the 1975 Declaration of Helsinki. All participants provided written informed consent prior to enrollment in the trial.

Statistical analysis

STATA version 13.0 (Stata Corporation, College Station, TX, United States) was used for statistical analyses. Pearson's chi-squared or Fisher's exact tests were used to assess comparable categorical data between HCC stages. A one-way analysis of variance (one-way ANOVA) or Kruskal–Wallis test was used to compare continuous variables. Statistical significance was set at P value < 0.05. The diagnostic and prognostic performance of GALAD score and biomarkers were estimated using the c-statistic, commonly referred to as the area under the receiver operating characteristic (ROC) curve analysis. The area under the ROC curve, sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratio, correctly classified of the GALAD score and each tumor marker for staging HCC, clinical features of the advanced disease, and 1-year mortality were obtained.

The diagnostic and prognostic performance of the GALAD score and other tumor markers were measured using the AUC that reflects the overall discriminative value of the test. The AUC ranged from 0 (at 0.5 representing "the probability

of a false and true diagnosis is both 50%" and such the test is no better than flipping a coin) to 1.0 (indicating excellent discrimination)[32]. Generally, an AUC of 0.75 is considered high enough for use in clinical practice. Therefore, the best cutoff point was the point closest-to- (0,1) corner in the ROC plane (Euclidean distance), that reached 100% sensitivity and 100% specificity. Hence, the cut-points for GALAD score and tumor markers were selected to optimize the values of both sensitivity and specificity based on the Euclidean distance[32,33]. The AUC of the GALAD score and each tumor marker were compared for very early stage (BCLC-0) and early stage (BCLC-A) HCC, curative HCC stage (BCLC-0 to A), and non-curative HCC stage (BCLC B to D), clinical features of poor prognosis, and 1-year mortality.

RESULTS

Tumor characteristics, biomarkers, GALAD score and staging of HCC

A total of 115 individuals were diagnosed with HCC, of which 98 (85.2%) were male. The most prevalent symptom was abdominal pain (38.3%), followed by gastrointestinal hemorrhage (10.4%). More than one-third (33.9%) of the patients had no symptoms. The most common cause of chronic hepatitis was hepatitis B (37.4%), followed by chronic hepatitis C (CHC) (12.2%), alcoholic hepatitis (14.8%), and MAFLD (7.8%). The remaining 27.8% of the patients were classified as having mixed etiologies. Eighty percent of the patients with HCC were diagnosed with cirrhosis. Child-Pugh scores A, B, and C were distributed as follows: 56.5%, 34.8%, and 8.7%, respectively. Most participants (68.1%) were in good physical condition. Sixty-four individuals (55.7%) had tumors > 5 cm in size. Fifty patients (43.5%) were diagnosed with a single lesion. The percentage of each stage (0, A, B, C, and D) according to the BCLC criteria was 11.3%, 23.47%, 31.3%, 13.3%, and 20%, respectively. Approximately 65.2% of the patients were in the non-curative stage. Characteristics of advanced-stage HCC (PV thrombosis, macrovascular invasion, and metastasis) were observed in 21.7%, 13.9%, and 8.0% of the cases, respectively. The median levels of AFP, AFP-L3 (%), and PIVKA-II at the time of HCC diagnosis were 38.9 ng/mL (5.4-3305), 7% (1-34.1), and 604 mAU/mL (54-21878), respectively. The median GALAD score for BCLC stages 0, A, B, C, and D were -2.27 (-3.9, 1.2), -0.62 (-1.81, 1.86), 4.15 (1.21, 8.81), 9.59 (6.17, 13.33), and 7.22 (3.7, 10.12), respectively (Table 1). There were no significant differences in median GALAD score and the various etiology of HCC (Supplementary Table 1).

Comparisons of the diagnostic performance between GALAD score and serum biomarkers

For very early stage (BCLC-0) and early stage (BCLC- A) of HCC: AUC for predicting very early stage HCC was non-significantly superior with GALAD score (0.6097, 95%CI: 0.40 to 0.82) compared to that using individual AFP (0.5655, 95%CI 0.36 to 0.77, P = 0.3721) and AFP-L3 (0.5128, 95%CI 0.32 to 0.70, P = 0.2992), and was comparable with that of PIVKA-II (0.7236, 95%CI 0.54 to 0.91, P = 0.1798). PIVKA-II showed a trend of higher AUC than that of AFP (P = 0.1100) and AFP-L3 (P = 0.0409; Table 2).

For curative HCC stage (BCLC- 0 to A) and non-curative HCC stage (BCLC B to D): The diagnostic performance of the GALAD score in curative HCC stage was more accurate than that in very early stage (0.6097 to 0.8677). For the prediction of BCLC stage 0 to A, AUC of the GALAD score (0.8677, 95%CI 0.80 to 0.93) was significantly higher than that of AFP (0.7525, 95%CI 0.67 to 0.84, P < 0.001) and AFP-L3 (0.7058, 95%CI 0.61 to 0.80, P < 0.001). The performance of the GALAD score was as good as PIVKA-II: AUC at 0.8970 (95%CI 0.84 to 0.95, P = 0.2353) to predict for curative stage of HCC. For predicting curative stage of HCC, the optimal cutoff value of the GALAD score was ≥ 2.65, with 74.67% sensitivity and 85.0% specificity (Table 2 and Figure 1A).

For characteristics of advanced diseases and patient's mortality: The characteristics of advanced diseases were composed of any one of the following: Macrovascular invasion, 13.9% (n = 16); PV thrombosis, 21.7% (n = 25); and extrahepatic metastasis, 8.7% (n = 10). For predicting aggressive feature of HCC, AUC of the GALAD score (0.8385, 95%CI 0.75 to 0.92) significantly outperformed that of AFP (0.7613, 95%CI 0.65 to 0.87, P = 0.0136) and AFP-L3 (0.6969, 95%CI 0.58 to 0.82, P = 0.0152); moreover, the AUC of the GALAD score showed a superior trend to that of PIVKA (0.7718, 95%CI 0.68 to 0.86, P = 0.0683). There was no significant difference in aggressive feature between PIVKA-II and AFP (P = 0.8476; Table 2 and Figure 1B).

After the diagnosis of HCC, standard therapy was commenced following the BCLC guidelines; however, after 1-year of follow-up, none of the 20 patients (17.39%) survived. Reasons for mortality included severe or terminal disease (12), HCC rupture (3), or sepsis (5). All non-survivors were in advanced or terminal stages, except one patient with BCLC stage B and ruptured HCC.

In terms of predicting the 1-year mortality, the GALAD score (0.7108, 95%CI 0.61–0.82) outperformed AFP (0.5405, 95%CI 0.39–0.69, P < 0.001), but was as good as PIVKA-II (0.7395, 95%CI 0.63–0.85, P = 0.5349). For predicting 1-year mortality of HCC, the optimal cutoff value of the GALAD score was ≥ 6.83, this cutoff value was within intermediate or advanced HCC stage, and gave 60.0% sensitivity and 72.63% specificity. The optimal cutoff value of PIVKA-II for patient's mortality was ≥ 2959 mAU/mL, which gave a slightly lower specificity (68.42%). Even though the GALAD score gave lower sensitivity, it gave higher specificity to predict 1-year mortality than that of PIVKA-II (Table 2 and Figure 1C).

DISCUSSION

The prevalence of HCC among all cancer diagnoses in the global population is increasing. Currently, ultrasonography with AFP is the recommended screening method for diagnosing HCC. Other biomarkers, including AFP, AFP-L3, and

Table 1 Patient characteristics and biomarkers, *n* (%)

	Total (*n* = 115)	Stage 0 (*n* = 13)	Stage A (*n* = 27)	Stage B (*n* = 36)	Stage C (*n* = 16)	Stage D (*n* = 23)	*P* value[a]
Age (mean ± SD)	60.83 ± 12.93	60.69 ± 11.64	61.07 ± 11.34	58.67 ± 15.03	62.00 ± 12.73	63.22 ± 12.48	0.754
Male	98 (85.2)	11 (84.6)	22 (81.5)	31 (86.1)	15 (93.8)	19 (82.6)	0.849
BMI (kg/m^2)	23.12 ± 3.5	24.31 ± 3.12	23.43 ± 2.74	23.06 ± 3.33	22.98 ± 5.06	22.26 ± 3.53	0.543
Symptom at first presentation							
Abdominal pain	44 (38.3)	1 (7.7)	7 (25.9)	16 (44.4)	10 (62.5)	10 (43.5)	0.02
Jaundice	7 (6.1)	1 (7.7)	0 (0)	1 (2.8)	1 (6.3)	4 (17.4)	0.106
Anemia	1 (0.9)	0 (0)	0 (0)	1 (2.8)	0 (0)	0 (0)	0.697
Ascites	9 (7.8)	2 (15.4)	1 (3.7)	1 (2.8)	2 (12.5)	3 (13)	0.368
Weight loss	7 (6.1)	0 (0)	0 (0)	5 (13.9)	0 (0)	2 (8.7)	0.102
Fever	1 (0.9)	1 (7.7)	0 (0)	0 (0)	0 (0)	0 (0)	0.095
Edema	4 (3.5)	0 (0)	1 (3.7)	0 (0)	2 (12.5)	1 (4.3)	0.223
Abdominal mass	3 (2.6)	0 (0)	0 (0)	3 (8.3)	0 (0)	0 (0)	0.154
GI bleeding	12 (10.4)	1 (7.7)	0 (0)	2 (5.6)	5 (31.3)	4 (17.4)	0.012
Asymptomatic	39 (33.9)	8 (61.5)	17 (63)	11 (30.6)	1 (6.3)	2 (8.7)	< 0.001
Etiology							
CHB	43 (37.4)	8 (61.5)	7 (25.9)	18 (50)	5 (31.3)	5 (21.7)	0.043
CHC	14 (12.2)	1 (7.7)	5 (18.5)	3 (8.3)	3 (18.8)	2 (8.7)	0.615
Alcohol	17 (14.8)	2 (15.4)	4 (14.8)	5 (13.9)	2 (12.5)	4 (17.4)	0.995
MAFLD	9 (7.8)	1 (7.7)	4 (14.8)	2 (5.6)	1 (6.3)	1 (4.3)	0.64
CHB with alcohol	20 (17.4)	0 (0)	4 (14.8)	4 (11.1)	5 (31.3)	7 (30.4)	0.069
CHC with alcohol	12 (10.4)	1 (7.7)	3 (11.1)	4 (11.1)	0 (0)	4 (17.4)	0.526
Cirrhosis	92 (80)	9 (69.2)	21 (77.8)	27 (75)	12 (75)	23 (100)	0.108
CTP-A/B/C (%)	56.5/34.8/8.7	88.9/11.1/0	81/19/0	70.4/29.6/0	50/50/0	8.7/56.5/34.8	< 0.001
MELD (mean ± SD)	10.31 ± 7.28	7.54 ± 7.24	8.78 ± 6.73	8.28 ± 6.33	10.5 ± 6.98	16.74 ± 6.17	< 0.001
Performance status							
0-1	79 (68.7)	12 (92.3)	26 (96.3)	36 (100)	4 (25)	1 (4.3)	< 0.001
2	2 (1.7)	0 (0)	1 (3.7)	0 (0)	0 (0)	1 (4.3)	0.613
3	15 (13)	0 (0)	0 (0)	0 (0)	10 (62.5)	5 (21.7)	< 0.001
4	19 (16.5)	1 (7.7)	0 (0)	0 (0)	2 (12.5)	16 (69.6)	< 0.001
Tumor size (cm)							
≤ 2	23 (20)	12 (92.3)	8 (29.6)	1 (2.8)	0 (0)	2 (8.7)	< 0.001
2.1-3	14 (12.2)	1 (7.7)	12 (44.4)	0 (0)	0 (0)	1 (4.3)	< 0.001
3.1-5	14 (12.2)	0 (0)	7 (25.9)	4 (11.1)	0 (0)	3 (13)	0.065
> 5	64 (55.7)	0 (0)	0 (0)	31 (86.1)	16 (100)	17 (73.9)	< 0.001
Tumor number							
1	50 (43.5)	13 (100)	14 (51.9)	17 (47.2)	2 (12.5)	4 (17.4)	< 0.001
2	35 (30.4)	0 (0)	10 (37)	8 (22.2)	10 (62.5)	7 (30.4)	
≥ 3	30 (26.1)	0 (0)	3 (11.1)	11 (30.6)	4 (25)	12 (52.2)	
Tumor characteristic							
Macrovascular	16 (13.9)	0 (0)	0 (0)	2 (5.6)	8 (50)	6 (26.1)	< 0.001

invasion							
PV thrombosis	25 (21.7)	0 (0)	0 (0)	1 (2.8)	11 (68.8)	13 (56.5)	< 0.001
Metastasis	10 (8.7)	0 (0)	0 (0)	0 (0)	6 (37.5)	4 (17.4)	< 0.001
Liver function test							
Albumin (mg/dL)	3.7	3.8	4.1	3.9	3.55	2.7	< 0.001
	(3.1, 4.2)	(3.7, 4.4)	(3.5, 4.3)	(3.45, 4.25)	(3.15, 3.7)	(2.3, 3.4)	
Total bilirubin (mg/dL)	1.04	0.91	0.69	0.86	1.35	3.44	< 0.001
	(0.63, 1.84)	(0.69, 1.12)	(0.56, 1.64)	(0.55, 1.5)	(1.17, 1.83)	(0.92, 5.19)	
AST (IU/L)	79 (47, 130)	34 (29, 67)	52 (36, 68)	79 (53, 116.5)	145 (94.5, 207.5)	141 (93, 479)	< 0.001
ALT (IU/L)	41 (24, 65)	24 (20, 43)	35 (20, 43)	53 (38, 71)	41 (20.5, 124)	48 (24, 97)	0.017
ALP (IU/L)	136 (92, 237)	86 (71, 108)	108 (79, 130)	143.5 (102, 271.5)	176 (152, 276.5)	201 (159, 314)	< 0.001
Biomarker (median, 25-75 quartile)							
AFP (ng/mL)	38.9	3.1	10	50	22146.3	79	< 0.001
	(5.4, 3305.3)	(1.7, 50)	(2.8, 61)	(13.2, 2482.65)	(190.55, 163697)	(17.2, 23475)	
AFP- L3 (%)	7	4.55	4.83	6.07	25.8	30.5	< 0.001
	(1, 34.1)	(0.5, 6.76)	(0.5, 8.1)	(0.9, 24.7)	(3.95, 63.9)	(8.16, 74.7)	
PIVKA II (mAU/mL)	604	26	55	7820	20188	4807	< 0.001
	(54, 21878)	(20,35)	(37, 220)	(139, 44019.5)	(761, 91915)	(581, 203031)	
GALAD score							
Median (range)	3.08	-2.27	-0.62	4.15	9.59	7.22	< 0.001
	(-0.56, 9.09)	(-3.9, 1.2)	(-1.81, 1.86)	(1.21, 8.81)	(6.17, 13.33)	(3.7, 10.12)	

[a]*P* value < 0.05 is statistically significant, ANOVA test, Kruskal–Wallis test, Chi-square test, or Fisher's exact test were used.
AFP: Alpha-fetoprotein; AFP-L3: Lens culinaris agglutinin-reactive fraction of alpha-fetoprotein; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; BMI: Body mass index; CTP: Child Turcotte Pugh; CHB: Chronic hepatitis B; CHC: Chronic hepatitis C; GI: Gastrointestinal; MAFLD: Metabolic associated fatty liver disease; MELD: Model for end stage liver disease; PIVKA II: Protein induced by vitamin K absence- II; PV: Portal vein.

PIVKA-II, have been shown to boost the diagnostic sensitivity for HCC[34-38]. The GALAD score was developed to enhance the utility of combining various markers derived from sex and age, which has been validated in non-alcoholic fatty liver disease[18,38].

Our investigation revealed a higher median GALAD score in CHC, which was consistent with data from the Chinese population, with the use of the GALAD score in CHC offering greater diagnostic power for HCC than for other etiologies [39]. In contrast to previous studies in which the GALAD utility was established for early HCC diagnosis[16,18], our study demonstrates the novel utility of the GALAD score for accurate HCC staging and prognosis. We emphasized that GALAD has multiple utilities, and it was demonstrated that GALAD has a high AUC for HCC at the curative stage. According to comparable patient's age for each HCC stage, the increase of the GALAD score in parallel with higher BCLC stage, with the exception of BCLC stage D, reflects liver decompensation itself but not tumor burden.

Serum prothrombin produced by the lack of PIVKA-II is an aberrant prothrombin caused by a deficiency of gamma-glutamyl carboxylase and vitamin K[40]. PIVKA-II is not only more specific than AFP, but a positive result also increases the likelihood of micro- and macrovascular invasion[41,42]. Owing to the distinct synthesis pathway, the benefits of PIVKA-II were complementary to those of AFP[43]. Enrollment in our curative-stage HCC study showed that PIVKA-II performed much better than AFP. Some nations have suggested using both biomarkers for the initial detection of HCC. The cause of HCC in majority of our patients was chronic hepatitis B (CHB), and our PIVKA-II identification of early CHB-related HCC was comparable to that of previous reports[44,45]. According to our data, using PIVKA-II was associated with poor performance in MAFLD-HCC enrollment, which is consistent with the results of a previous study [46]. However, because only a few MAFLD cases were analyzed, our findings may not be definitive. Regarding to the enrollment of substantial number of patients with BCLC stage 0 or A, this may be of interest for prospective clinical outcome prediction research.

The characteristics of advanced disease can be evaluated by utilizing both GALAD scores and PIVKA-II levels. In the present study, after 1-year of mortality monitoring, all non-survivors were in the intermediate and advanced stages of HCC, as established by disease staging and treatment. According to a recent systematic review and meta-analysis,

Table 2 Diagnostic performances of GALAD score and other biomarkers on Barcelona Clinic Liver Cancer staging, aggressive features, and prognostic performances for 1-year mortality of hepatocellular carcinoma

Scores	Barcelona Clinic Liver Cancer staging		Aggressive features[a,2]	1-year mortality[3]
	0 *vs* A[2]	0/A *vs* B/C/D[2]		
GALAD				
AUC (95%CI)	0.6097 (0.40–0.82)	0.8677 (0.80–0.93)	0.8385 (0.75–0.92)	0.7108 (0.60–0.82)
Cutoff values	≥ -1.95	≥ 2.65	≥ 7.22	≥ 6.83
Sensitivity/Specificity (%)	81.48/53.85	74.67/85.00	75.00/85.54	60.00/72.63
PPV/NPV (%)	78.57/58.33	90.32/64.15	66.67/89.87	31.58/89.61
Positive/Negative LR	1.77/0.34	4.98/0.30	5.19/0.29	2.19/0.55
Correctly classified (%)	72.50	78.26	82.61	70.43
PIVKA-II				
AUC (95%CI)	0.7236 (0.54–0.91)	0.8970 (0.84–0.95)	0.7718 (0.68–0.86)	0.7395 (0.63–0.85)
Cutoff values	≥ 37	≥ 354	≥ 581	≥ 2959
Sensitivity/Specificity (%)	77.78/76.92	81.33/92.50	93.75/63.86	75.00/68.42
PPV/NPV (%)	87.50/62.50	95.31/72.55	50.00/96.36	33.33/92.86
Positive/Negative LR	3.37/0.29	10.84/0.20	2.59/0.10	2.38/0.37
Correctly classified (%)	77.50	85.22	72.17	69.57
AFP				
AUC (95%CI)	0.5655 (0.36–0.77)	0.7525 (0.67–0.84)	0.7613 (0.65–0.87)	0.5405 (0.39–0.69)
Cutoff values	≥ 4.4	≥ 16	≥ 79	≥ 79
Sensitivity/Specificity (%)	74.07/53.85	74.67/60.00	75.00/71.08	50.00/60.00
PPV/NPV (%)	76.92/50.00	77.78/55.81	50.00/88.06	20.83/85.07
Positive/Negative LR	1.60/0.48	1.87/0.42	2.59/0.35	1.25/0.83
Correctly classified (%)	67.50	69.57	72.17	58.26
AFP-L3				
AUC (95%CI)	0.5128 (0.32–0.70)	0.7058 (0.61–0.80)	0.6969 (0.58–0.82)	0.7361 (0.61–0.86)
Cutoff values	≥ 4.83	≥ 7.4	≥ 12.3	≥ 14.5
Sensitivity/Specificity (%)	51.85/53.85	64.00/77.50	65.63/71.08	65.00/72.63
PPV/NPV (%)	70.00/35.00	84.21/53.45	46.67/84.29	33.33/90.79
Positive/Negative LR	1.12/0.89	2.84/0.46	2.27/0.48	2.38/0.48
Correctly classified (%)	52.50	68.70	69.57	71.30
Comparison of AUC				
GALAD and PIVKA-II	$P = 0.1798$	$P = 0.2353$	$P = 0.0683$	$P = 0.5349$
GALAD and AFP	$P = 0.3721$	$P < 0.001$[a]	$P = 0.0136$[a]	$P < 0.001$[a]
GALAD and AFP-L3	$P = 0.2992$	$P < 0.001$[a]	$P = 0.0152$[a]	$P = 0.6656$
PIVKA-II and AFP	$P = 0.1100$	$P < 0.001$[a]	$P = 0.8476$	$P = 0.0086$[a]
PIVKA-II and AFP-L3	$P = 0.0409$[a]	$P < 0.001$[a]	$P = 0.2801$	$P = 0.9610$

[a]*P* value < 0.05 is statistically significant.
[1]Macrovascular invasion or portal vein thrombosis or extrahepatic metastasis.
[2]Optimal cutoff points were determined to the point closest-to- (0,1) corner in the receiver operating characteristic plane (Euclidean distance).
[3]Cutoff values were adapted based on the Euclidean distance criteria to maximize specificity for predicting the 1-year mortality with acceptable sensitivity.
AFP: Alpha-fetoprotein; AFP-L3: Lens culinaris agglutinin-reactive fraction of alpha-fetoprotein; AUC: Area under the curve; LR: The likelihood ratio; NPV: Negative predictive value; PIVKA-II: Protein induced by vitamin K absence- II; PPV: Positive predictive value; ROC: Receiver operating

characteristic.

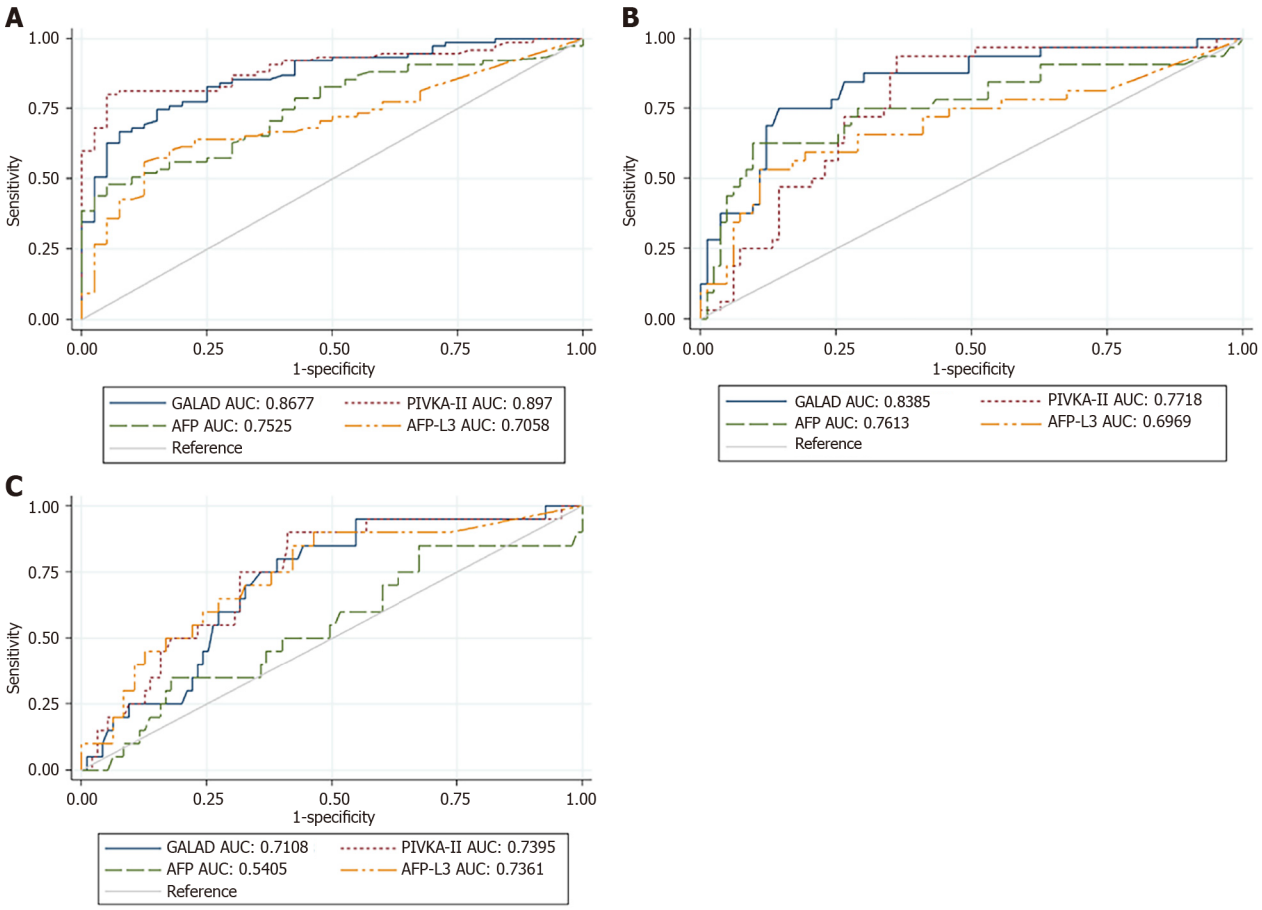

Figure 1 Receiver operating characteristic curves displaying the diagnostic performances of GALAD and other biomarkers. A: On staging curative hepatocellular carcinoma; B: On aggressive features of hepatocellular carcinoma; C: On 1-year mortality of hepatocellular carcinoma. AFP: Alpha-fetoprotein; AFP-L3: Lens culinaris agglutinin-reactive fraction of alpha-fetoprotein; AUC: Area under the curve; PIVKA II: Protein induced by vitamin K absence – II.

GALAD score was useful for diagnostic performance but not for prognosis of disease progression[20]. We highlight the updated significance of GALAD performance not only in the accuracy of curative HCC staging, but also in the characteristic of advanced diseases and predicting a decline in 1-year mortality. A combination of age and PIVKA-II in the GALAD model may offer an indirect method for determining the aggressiveness of malignancies[47]. It would be intriguing to incorporate the GALAD model in future research for increasing the staging accuracy and for the personalized prognosis of HCC. High pre-treatment serum AFP-L3% levels were also associated with a poor prognosis in our patients with HCC; however, we believe that high AFP-L3% levels may have considerable prognostic value for patients with HCC with low AFP concentrations.

This study had some limitations. Despite the ability to recruit participants based on our sample size calculations, the number of participants in each stage, particularly the initial stage, is very low. This could potentially impact the performance of the GALAD application. If more patients with HCC utilize the GALAD score, the overall advantage in proper disease staging and prognosis may become more apparent. Second, our clinical data was archived with short follow-up periods. The prognostic performance may increase with longer follow-up periods.

CONCLUSION

The GALAD model can enhance the diagnosis of HCC at the curative stage more than that by AFP and AFP-L3, but not PIVKA-II; moreover, it can also be used to predict the 1-year mortality in non-curative HCC.

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FOOTNOTES

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META-ANALYSIS

Minocycline in the eradication of *Helicobacter pylori* infection: A systematic review and meta-analysis

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Abstract

BACKGROUND

Difficulty in obtaining tetracycline, increased adverse reactions, and relatively complicated medication methods have limited the clinical application of the classic bismuth quadruple therapy. Therefore, the search for new alternative drugs has become one of the research hotspots. In recent years, minocycline, as a semisynthetic tetracycline, has demonstrated good potential for eradicating *Helicobacter pylori* (*H. pylori*) infection, but the systematic evaluation of its role remains lacking.

AIM

To explore the efficacy, safety, and compliance of minocycline in eradicating *H. pylori* infection.

METHODS

We comprehensively retrieved the electronic databases of PubMed, Embase, Web of Science, China National Knowledge Infrastructure, SinoMed, and Wanfang database as of October 30, 2023, and finally included 22 research reports on *H. pylori* eradication with minocycline-containing regimens as per the inclusion and exclusion criteria. The eradication rates of *H. pylori* were calculated using a fixed or a random effect model, and the heterogeneity and publication bias of the studies were measured.

RESULTS

The single-arm meta-analysis revealed that the minocycline-containing regimens achieved good overall *H. pylori* eradication rates, reaching 82.3% [95% confidence

interval (CI): 79.7%-85.1%] in the intention-to-treat analysis and 90.0% (95%CI: 87.7%-92.4%) in the per-protocol analysis. The overall safety and compliance of the minocycline-containing regimens were good, demonstrating an overall incidence of adverse reactions of 36.5% (95%CI: 31.5%-42.2%). Further by traditional meta-analysis, the results showed that the minocycline-containing regimens were not statistically different from other commonly used eradication regimens in eradication rate and incidence of adverse effects. Most of the adverse reactions were mild to moderate and well-tolerated, and dizziness was relatively prominent in the minocycline-containing regimens (16%).

CONCLUSION

The minocycline-containing regimens demonstrated good efficacy, safety, and compliance in *H. pylori* eradication. Minocycline has good potential to replace tetracycline for eradicating *H. pylori* infection.

Key Words: *Helicobacter pylori*; Minocycline; Eradication; Safety; Resistance

Core Tip: Regarding the utilization of minocycline in the eradication therapy of *Helicobacter pylori* (*H. pylori*) infection, there is a lack of literature summarizing the potential and role of minocycline in the eradication of *H. pylori* infection. This is the first comprehensive account of the role, efficacy, and current state of research on minocycline in the eradication therapy of *H. pylori* infection by traditional meta-analysis as well as single-arm meta-analysis methods. We have summarized this minocycline in terms of bactericidal mechanism, pharmacodynamics, pharmacokinetics, drug resistance, eradication efficacy, safety and compliance.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) infection and its related diseases (gastric cancer, peptic ulcer, chronic atrophic gastritis/intestinal metaplasia, dyspepsia, *etc.*) are crucial global health issues. In clinics, many patients require eradication therapy for *H. pylori* infection for its effective prevention and treatment[1,2]. *H. pylori* infection eradication has become more and more difficult with the increasing resistance to antibiotics, such as clarithromycin, levofloxacin, *etc*[3,4]. The global consensuses of experts in diagnosing and treating *H. pylori* infection generally recommends the classic bismuth quadruple therapy (BQT) for eradication, *i.e.,* proton pump inhibitor, tetracycline, full-dose metronidazole, and bismuth[1,5-8]. However, this regimen demonstrated a high incidence of adverse reactions and relatively complex usage. Tetracycline is difficult to clinically obtain in many countries and regions, which has greatly limited the clinical application of BQT[9,10]. The use of other drugs to replace tetracycline to effectively eradicate *H. pylori* infection has become one of the hot research directions in this field.

Minocycline, as a semi-synthetic tetracycline[11,12], has been currently prominently used in clinical treatment of diseases such as acne, sexually transmitted diseases, and special respiratory infections. Compared with tetracycline, minocycline has demonstrated better bactericidal activity on other bacteria[13]. In 2002, scholars attempted to use the minocycline-containing regimen for eradicating *H. pylori* infection[14]. Since then, basic and clinical studies have successively investigated the efficacy, safety, compliance, and drug resistance of different minocycline-containing regimens in treatment-naive or retreated patients with *H. pylori* infection[11,12]. In general, these studies have demonstrated that minocycline demonstrated good potential and effect in eradicating *H. pylori* infection and is a very promising alternative in cases where tetracycline is difficult to obtain. Herein, we conducted a review and meta-analysis of the minocycline-containing regimens to comprehensively explore their role, effect, and research status in eradicating *H. pylori* infection.

MATERIALS AND METHODS

Bactericidal mechanism of minocycline

Chlortetracycline, the first tetracycline compound, was introduced in the 1950s. Shortly thereafter, Duggar *et al*[15] analyzed the mutant of chlortetracycline in *Staphylococcus aureus* and revealed demeclocycline, a precursor, which was further reduced and transformed into minocycline. Minocycline is a tetracycline derivative with a similar mechanism of

action to that of tetracycline. It enters the bacteria mainly through the outer membrane protein channel and specifically binds to A site of the 30S subunit aminoacyl group of bacterial ribosomes, thereby blocking the aminoacyl-tRNA binding at this site, preventing peptide chain extension and bacterial protein synthesis, and playing the bactericidal role[16] (Figure 1). The affinity between minocycline and ribosome is 20 times higher and the *in vitro* translational suppression efficiency is 2-7 times higher than that of tetracycline. Therefore, minocycline demonstrated better and more potent bactericidal effects[17,18]. Minocycline contains a broad antimicrobial spectrum covering Gram-positive cocci, Gram-negative bacilli, and cocci, as well as atypical pathogens[16].

Pharmacodynamics and pharmacokinetics of minocycline

Minocycline has a longer serum half-life than tetracycline of up to 12-18 h and can reach the peak plasma concentration within 2-3 h after oral administration. Minocycline is only taken once or twice daily and is not taken as frequently as tetracycline, which helps improve treatment compliance[12,19]. Compared with tetracycline, minocycline is not susceptible to food impact and has a high absorption rate, which is conducive to obtaining better bioavailability[19]. Minocycline demonstrated better lipid solubility and tissue permeability than other tetracyclines, which are beneficial to improving drug distribution and concentration in tissues[20]. Minocycline is almost completely absorbed in the duodenum and jejunum (95%-100%), widely distributed in body fluids, bile, and tissues, and mainly excreted through feces (20%-34%) and kidneys (5%-15%)[19].

Drug resistance of minocycline

In 2009, Horiki *et al*[21] discussed the antibiotic resistance rate of the *H. pylori* strain (n = 3521) in an investigation in Japan from 1996 to 2008, and they revealed a very low primary drug resistance rate of minocycline [0.06% (2/3, 521)]. Five studies from China, including drug resistance testing, clinical cohort, and randomized controlled trials (RCTs), discussed the drug resistance of minocycline in the Chinese mainland. The results indicated a low drug resistance rate of minocycline (approximately 0.7%-8.2%), which was similar to that of tetracycline in the same period[11,22-25]. A study in Japan evaluated the antibacterial activity, *i.e.,* the minimum inhibitory concentration (MIC) of minocycline against clarithromycin-resistant *H. pylori* strain, and revealed MIC50 and MIC90 of 0.5 μg/mL, which were similar to those of tetracycline (1 μg/mL), indicating that minocycline, similar to tetracycline, had significantly sensitive antibacterial activity against *H. pylori* strain[21]. Further, Murakami *et al*[26] concluded similar results. The in-depth study of antibiotic resistance revealed that tetracycline resistance mutation has been discovered in the stem-loop of the 31st helix of 16S rRNA of *H. pylori* strain, with the triple mutation A965U/G966U/A967C, conferring high-level resistance against tetracycline as well as an increased MIC for minocycline[27].

Methods

We conducted a comprehensive literature retrieval and meta-analysis, which was described in detail below, to explore the eradication rates, adverse reaction incidences, and minocycline-containing regimens compliance.

Literature retrieval: PRISMA statement guidelines were followed for conducting and reporting the meta-analysis data. We have conducted a comprehensive and systematic retrieval in PubMed, Web of Science, EMBASE, China National Knowledge Infrastructure, SinoMed and Wanfang database. The retrieval cut-off date was October 30, 2023. The retrieval keywords included (Minocycline) AND (Helicobacter pylori OR Helicobacter nemestrinae OR Campylobacter pylori OR Campylobacter pylori subsp. pylori OR Campylobacter pyloridis OR *H. pylori* OR Hp) AND (Eradication OR Therapeutics OR Therapeutic OR Therapy * OR Treatment * OR Eradicate * OR Regimen *).

Literature inclusion criteria were minocycline contained in *H. pylori* infection eradication regimen; adult patients over 18 years old; specific information of eradication regimens obtained, including drug types, dosages, frequencies, and treatment durations; reported numbers of successful and unsuccessful eradication in patients. Literature exclusion criteria were treatment duration of < 7 d; repeated studies; and loss to follow-up rate of > 20%.

First, preliminary screening was conducted on the included articles by titles, abstracts, and keywords. The remaining study reports passing the preliminary screening were then subjected to further review as per inclusion and exclusion criteria. Finally, the full text was thoroughly and carefully reviewed. We did not limit the minimum sample size in the analysis to reduce the bias. Figure 2 shows the process for article retrieval, screening, and inclusion.

Literature quality evaluation: Both authors (Zhou K and Li CL) used the Cochrane bias risk tool to assess bias risk in a single study across five domains, *i.e.,* selection bias, performance bias, detection bias, reporting bias, and other biases. Any disagreements were resolved through discussions with the expert (Song ZQ). The standard answers included: (1) Yes, indicating a high bias risk; (2) No, indicating a low bias risk; and (3) Unclear, indicating an uncertain bias risk.

Data extraction: All retrieved studies were loaded into the Endnote X9, which is a reference management software. Two authors (Zhou K and Li CL) extracted and recorded the following study data in pre-designed information extraction tables, including author, publication year, study country, study type, patient type, drug dose and frequency, sample size, treatment course, eradication rate, compliance, safety, and drug resistance rate. The two authors extracted the data independently and cross-checked them. Pre-extraction was performed before formal data extraction to assess the rationality of the data extraction table design and the consistent degree of understanding of the same issue. The two authors first communicated and resolved disagreements that arose during the extraction process. If disagreements persist, consensus is reached through discussions with the expert (Song ZQ).

Data analysis: The meta package of the R program (version 4.2.2) was used for the combined analysis of the single-arm

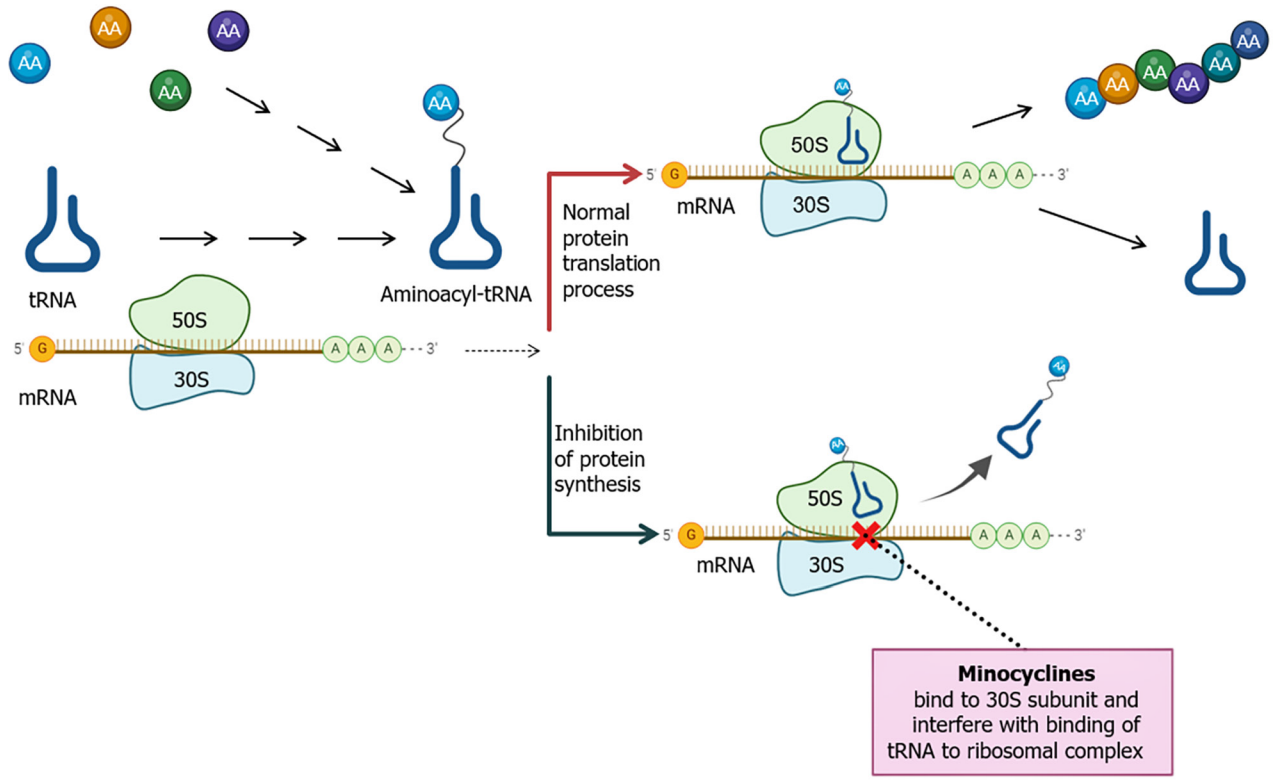

Figure 1 Scheme of the minocyclines' mechanism of action. Amino acids and tRNAs are linked together by aminoacyl-tRNA synthetase to produce specific Aminoacyl-tRNAs. ribosomes on the ribosomal complex then read the code along the 5'-3' direction of the mRNAs while linking various aminoacyl-tRNA-transported amino acids according to the instructions of the mRNA coding sequences for the process of protein synthesis. When minocycline enters into bacteria, it specifically binds to the A site of bacterial ribosomal 30S subunit aminoacyl group, thus blocking the aminoacyl-tRNA binding at this site, preventing peptide chain elongation and bacterial protein synthesis, and exerting bactericidal effects. AA: Amino acids.

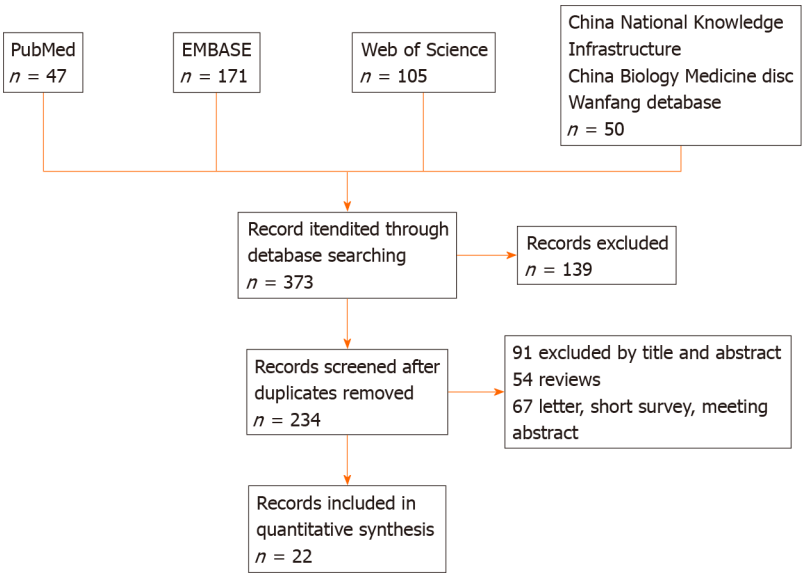

Figure 2 Literature identification process.

eradication rates. The heterogeneity was investigated using I^2. I^2 of > 50% is considered a heterogeneity, and the random effect model was adopted to assess the effect size of included studies; otherwise, the fixed effect model was utilized. A relatively large heterogeneity was observed in the single-arm eradication rates. Therefore, the eradication rates in intention-to-treat (ITT) and per-protocol (PP) analyses and the corresponding 95% confidence interval (CI) were respectively summarized by the random effect model. Funnel plot, Egger's test, and Begg's test were used to evaluate the publication bias, and publication bias was considered if P values were < 0.05. Sensitivity analysis was conducted by assessing the stability of the results by deleting each study in turn.

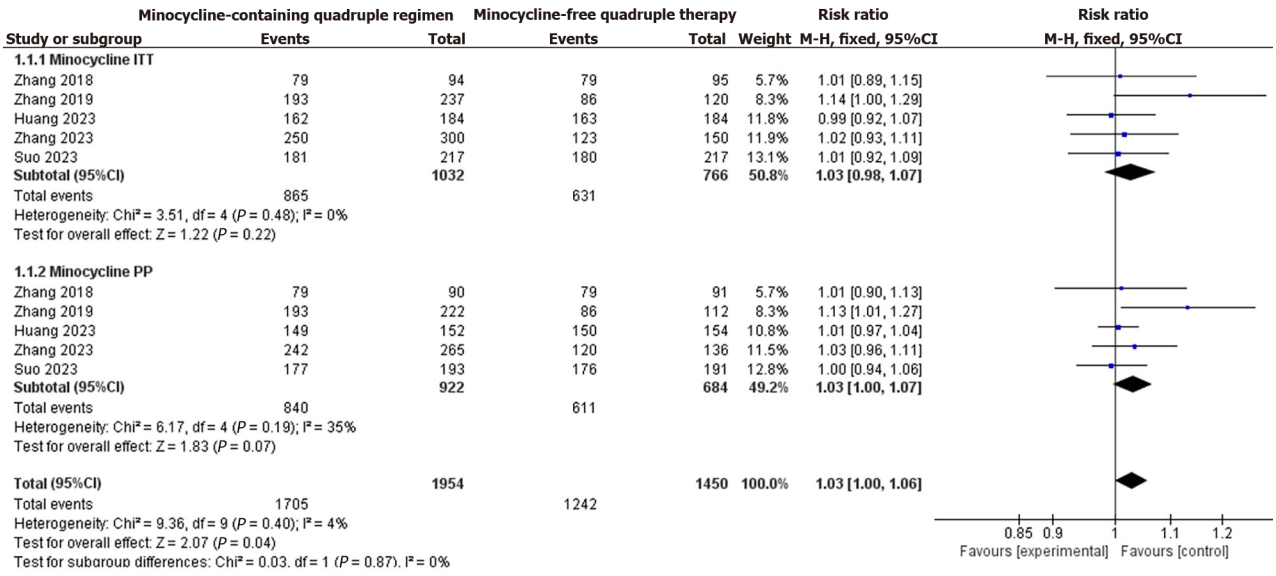

Figure 3 Forest plots comparing eradication rates for intention-to-treat and per-protocol analyses of quadruple regimens with and without minocycline. CI: Confidence interval.

RESULTS

Basic information of included studies

Table 1 shows the specific information of the included studies (n = 22)[11,12,23-26,28-43]. A total of 36 minocycline-containing treatment groups were found in 22 studies, including 19 treatment-naive and 17 retreatment groups. Regarding the eradication regimen type, 5 treatment groups in 2 studies received triplet minocycline-containing regimens, 30 treatment groups in 21 studies received quadruplet minocycline-containing regimens, and 1 treatment group received quadruple therapy combined with probiotics. Of the included studies, 20 originated from China, 1 from Japan, and 1 from Italy. Regarding treatment course, 4 treatment groups (n = 177) in 2 studies adopted a 7-d course, 7 treatment groups (n = 332) in 5 studies adopted a 10-d course, and 16 studies (n = 2588) adopted a 14-d course. Regarding study design type, 1 study used a randomized grouping approach in treatment-naive patients, and patients in the salvage treatment group were assigned to different treatment regimen subgroups according to metronidazole-resistance status. Among the remaining 21 studies, 11 were RCTs and 10 were cohort studies.

Pooled analysis of eradication rates and incidences of adverse reactions

Regarding antibiotic combinations in the minocycline-containing eradication regimens, nitroimidazole antibiotics (metronidazole, tinidazole, or ornidazole) were combined in 14 treatment groups from 12 studies[12,23-26,28,32,36-40], amoxicillin was combined in 17 treatment groups from 11 studies[11,26,29-31,33,34,36,41-43], and faropenem, levofloxacin, cefuroxime, furazolidone, and rifabutin were respectively combined in 1 treatment group[25,26,28,35,37]. Overall eradication rates of minocycline-containing eradication regimens were 82.3% (95%CI: 79.7%-85.1%, I^2 = 70%, P < 0.01) in ITT analysis and 90.0% (95%CI: 87.7%-92.4%, I^2 = 80%, P < 0.01) in PP analysis. The included studies demonstrated a high degree of heterogeneity. The pooled analysis included the overall eradication rates of the minocycline-containing regimens, the combination regimen of minocycline-containing and nitroimidazole antibiotics, the combination regimen of minocycline-containing and amoxicillin, the eradication rates in treatment-naive patients, and the eradication rates in retreated patients. Table 2 shows the results (see the appendix for details of the corresponding forest plots). Additionally, the overall incidence of adverse reactions in minocycline-containing eradication regimens was 36.5% (95%CI: 31.5%-42.2%)[9,11,12,23-25,31-33,36-38] (Supplementary Figures 1-10).

Comparative analysis of eradication rates

Comparison of efficacy of quadruplet eradication regimens with and without minocycline: The analysis included five RCTs that adopted minocycline-containing quadruple regimens[23-25,32,36]. Combinations of antibiotics in the minocycline-containing groups included metronidazole (n = 5), amoxicillin (n = 1), and cefuroxime (n = 1) and that in the control group included a tetracycline with metronidazole (n = 2), amoxicillin with clarithromycin (n = 2), and cefuroxime with metronidazole (n = 1). The figure shows no obvious heterogeneity in the ITT analysis using the fixed effect model (χ^2 = 3.51, P = 0.48, I^2 = 0), and the eradication efficacy between the quadruple regimens with and without minocycline was not statistically significantly different [risk ratio (RR) = 1.03, 95%CI: 0.98-1.07, P = 0.22]. The PP analysis revealed similar results to the ITT analysis. The two groups demonstrated no significant heterogeneity (χ^2 = 6.17, P = 0.19, I^2 = 35%) and no statistically significant difference in efficacy (RR = 1.03, 95%CI: 1.00-1.07, P = 0.07). ITT and PP analyses revealed the eradication rates of quadruple regimens with and without minocycline of 83.8% *vs* 82.4% and 91.1% *vs* 89.3%, respectively (Figure 3).

Table 1 Characteristics of included studies

Ref.	Country	Study type	Patient type	Regimen	Sample size	Duration (d)	Eradication rate (ITT analysis)	Eradication rate (PP analysis)	Compliance	Adverse effects rate	Resistance rate
Murakami *et al*[26], 2006	Japan	RCT	1st	R 20 mg bid + CLA 200 mg bid + AMX 750 mg bid	40	7	82.5% (33/40)	84.6% (33/39)			
				R 20 mg bid + MIN 100 mg bid + AMX 750 mg bid	39	7	38.5% (15/39)	40.5% (15/37)			
		Cohort study	2nd	R 20 mg bid + MIN 100 mg bid + MTZ 250 mg bid	67	7	85.1% (57/67)				
				R 20 mg bid + MIN 100 mg bid + FAR 600 mg bid	21	7	9.5% (2/21)				
Ierardi *et al*[28], 2014	Italy	RCT	≥ 2nd	R 20 mg bid + RIF 150 mg bid + MIN 100 mg bid + B 120 mg tid	27	10	77.8% (21/27)	84.0% (21/25)			
				R 20 mg bid + MIN 100 mg bid + TNZ 500 mg bid + B 120 mg tid	27	10	51.9% (14/27)	51.9% (14/27)			
Zhang *et al*[29], 2015	China	RCT	≥ 2nd	R 10 mg bid + MIN 100 mg bid + AMX 1000 mg bid + B 220 mg bid	63	10	84.1% (53/63)	88.3% (53/60)	95.2% (60/63)	23.8% (15/63)	
				Tailored therapy (triple treatment)	62	10	75.8% (47/62)	79.7% (47/59)	96.8% (60/62)	33.9% (21/62)	
Song *et al* [11], 2016	China	Cohort study	1st	R 10 mg bid + MIN 100 mg bid + AMX 1000 mg bid + B 220 mg bid	160	14	87.5% (140/160)	92.6% (137/148)	94.7% (213/225)	24.0% (54/225)	6.9% (4/58)
			2nd	R 10 mg bid + MIN 100 mg bid +AMX 1000 mg bid + B 220 mg bid	70	14	82.9% (58/70)	89.1% (57/64)	23.8% (15/63)		8.7% (2/23)
Song *et al* [12], 2016	China	Cohort study	1st	E 20 mg bid + MIN 100 mg bid + MTZ 400 mg qid + B 110 mg qid	152	14	85.5% (130/152)	92.6% (137/148)	91.3% (136/149)	35.6% (53/149)	
			2nd	E 20 mg bid + MIN 100 mg bid + MTZ 400 mg qid + B 110 mg qid	64	14	82.8% (53/64)	89.5% (51/57)	90.5% (57/63)	36.5% (23/63)	
Zhou[30], 2017	China	RCT	≥ 2nd	AMLZ 20 mg bid + MIN 100 mg bid + AMX 1000 mg bid	50	7	80.00% (40/50)				
				AMLZ 20 mg bid + MIN 100mg bid + AMX 1000 mg bid	50	10	82.00% (41/50)				
				AMLZ 20 mg bid + MIN 100 mg	50	10	84.00% (42/50)				

				bid + AMX 1000 mg bid + B 220 mg bid						
				AMLZ 20 mg bid + CLA 500 mg bid + AMX 1000 mg bid + B 220 mg bid	50	10	52.00% (26/50)			
Zhang *et al*[31], 2017	China	Cohort study	≥ 2nd	R 10 mg bid + MIN 100 mg bid + AMX 1000 mg bid + B 220 mg bid	180	14	79.4% (143/180)	84.1% (143/170)	≥ 90%	31.1% (56/180)
Zhang *et al*[32], 2018	China	RCT	1st	R 10 mg bid + MIN 100 mg bid + MTZ 400 mg tid + B 220 mg bid	94	14	84.0% (79/94)	87.8% (79/90)	≥ 90%	40.4% (38/94)
				R 10 mg bid + CLA 500 mg bid + AMX 1000 mg bid + B 220 mg bid	95	14	83.2% (79/95)	86.8% (79/91)	≥ 90%	41.1% (39/95)
Pu *et al* [33], 2018	China	Cohort study	1st	R 10 mg bid + MIN 100 mg bid + AMX 1000 mg bid + B 220 mg bid	130	14	83.9% (109/130)	94.8% (109/115)	96.2% (125/130)	41.5% (54/130)
			2nd	R 10 mg bid + MIN 100 mg bid + AMX 1000 mg bid + B 220 mg bid	96	14	86.5% (83/96)	96.5% (83/86)	97.9% (94/96)	44.8% (43/96)
Xu *et al* [34], 2019	China	Cohort study	1st	R 20mg bid + MIN 100mg bid + AMX 1000mg bid + B 300 mg bid	52	14	88.5% (46/52)	93.6% (44/47)	≥ 90%	
			2nd	R 20mg bid + MIN 100mg bid + AMX 1000mg bid + B 300mg bid	28	14	82.1% (23/28)	95.7% (22/23)	≥ 80%	
Li *et al* [35], 2019	China	RCT	≥ 2nd	E 20mg bid + RIF 150mg bid + FUR 100mg tid	74	10	82.4% (61/74)	91.0% (61/67)	90.5% (67/74)	
				E 20mg bid + MIN 100mg bid + FUR 100mg tid + B 110mg qid	72	10	84.7% (61/72)	93.8% (61/65)	90.3% (65/72)	
Zhang *et al*[36], 2019	China	RCT	1st	R 10mg bid + MIN 100mg bid + AMX 1000mg bid + B 220mg bid	119	14	85.7% (102/119)	89.5% (102/114)	96.6% (115/119)	30% (36/120)
				R 10mg bid + MIN 100mg bid + MTZ 400mg tid + B 220mg bid	118	14	77.1% (91/118)	84.3% (91/108)	94.9% (112/118)	37.5% (45/120)
				R 10mg bid + CLA 500mg bid + AMX 1000mg bid + B 220 mg bid	1020	14	71.7% (86/120)	76.8% (86/112)	95.8% (115/120)	40.0% (48/120)
Zhang *et al*[37], 2022	China	RCT	1st	R 10mg bid + MIN 100mg bid + MTZ 400mg tid + B 220mg	76	14	80.3% (61/76)	83.6% (61/73)	≥ 90%	47.4% (36/76)

				bid							
				R 10mg bid + MIN 100mg bid + LEV 500mg qd + B 220mg bid	74	14	89.2% (66/74)	90.4% (66/73)	≥ 90%	33.8% (25/74)	
Zhang *et al*[38], 2021	China	Cohort study	1st	R 10mg bid + MIN 100mg bid + MTZ 400mg tid + B 220mg bid	175	14	72.0% (126/175)	86.3% (126/146)	≥ 90%	50.9% (89/175)	
Huang *et al*[39], 2021	China	Cohort study	1st	E 20mg bid + MIN 100mg bid + ONZ 500mg bid + B 220mg bid	50	14	96.0% (48/50)		≥ 90%		
				E 20mg bid + MIN 100mg bid + ONZ 500mg bid + B 220mg bid + Bifidobacterium Lactobacillus trifecta 2000mg bid	51	14	92.2% (47/51)				
Cui *et al* [40], 2022	China	Cohort study	1st	R 10mg bid + MIN 100mg bid + MTZ 400mg tid + B 220mg bid	28	14	71.4% (20/28)	87.0% (20/23)			
Li *et al* [41], 2022	China	RCT	1st	E 20mg bid + CLA 500mg bid +AMX 1000mg bid + B 200mg bid	91	10	80.2% (73/91)	89.0% (73/82)		6.7% (9/134)	
				E 20mg bid + MIN 100mg bid + AMX 1000mg bid + B 200mg bid	43	10	81.4% (35/43)	87.5% (35/40)			
				E 20mg bid + FUR 100mg bid + AMX 1000mg bid + B 200mg bid	67	10	85.1% (57/67)	90.5% (57/63)		7.5% (5/67)	
Guo *et al* [42], 2023	China	Cohort study	1st	E 20mg bid + MIN 100mg bid + AMX 750mg tid + B 200mg tid	25	14	84.0% (21/25)		≥ 90%		
			≥ 2nd	E 20mg bid + MIN 100mg bid + AMX 750mg tid + B 200mg tid	65	14	86.2% (56/65)				
Hao *et al* [43], 2022	China	Cohort study	≥ 2nd	R 10mg bid + MIN 100mg bid + AMX 1000mg bid + B 300mg bid	80	14	78.8% (63/80)				
Suo *et al* [23], 2023	China	RCT	1st	E 20mg bid + MIN 100mg bid + MTZ 400mg qid + B 110mg qid	217	14	83.4% (181/217)	91.7% (177/193)	90.7% (195/215)	34.9% (75/215)	6.3% (4/63)
				E 20mg bid + TET 500mg qid + MTZ 400mg qid + B 110mg qid	217	14	83.0% (180/217)	92.2% (176/191)	89.7% (192/214)	41.1% (88/214)	7.0% (5/71)
Zhang *et al*[25], 2023	China	RCT	1st	E 20mg bid + MIN 100mg bid + MTZ 400mg qid + B 220mg	150	14	84.0% (126/150)	91.7% (122/133)	90.5% (134/148)	35.1% (52/148)	7% (3/43)

				bid						
				E 20mg bid + MIN 100mg bid + CEF 500mg bid + B 220mg bid	150	14	82.7% (124/150)	90.9% (120/132)	91.8% (134/146)	22.6% (33/146)	8.5% (4/47)
				E 20mg bid + CEF 500mg bid + MTZ 400mg qid + B 220mg bid	150	14	82.0% (123/150)	88.2% (120/136)	91.9% (137/149)	28.9% (43/149)	9.1% (4/44)
Huang *et al*[24], 2023	China	RCT	≥ 2 nd	E 20mg bid + MIN 100mg bid + MTZ 400mg qid + B 220mg bid	184	14	88.0% (162/184)	98.0% (149/152)	88% (162/184)	55.4% (102/184)	0.7% (1/145)
				E 20mg bid + TET 500mg qid + MTZ 400mg qid + B 220mg bid	184	14	88.6% (163/184)	97.4% (150/154)	88.6% (163/184)	53.3% (98/184)	0.7% (1/143)

RCT: Randomized controlled trial; ITT: Intention-to-treat; PP: Per-protocol; R: Rabeprazole; CLA: Clarithromycin; AMX: Amoxicillin; MIN: Minocycline; MTZ: Metronidazole; FAR: Faropenem; RIF: Rifabutin; B: Bismuth; TNZ: Tinidazole; E: Esomeprazole; AMLZ: Omeprazole; FUR: Furazolidone; LEV: Levofloxacin; ONZ: Ornidazole; TET: Tetracycline; CEF: Cefuroxime.

Table 2 Pooled eradication rates

	Overall eradication rate % (95%CI)		Eradication rate for first-treatment patients % (95%CI)		Eradication rate for retreatment patients % (95%CI)	
	Intention-to-treat analysis	Per-protocol analysis	Intention-to-treat analysis	Per-protocol analysis	Intention-to-treat analysis	Per-protocol analysis
Minocycline-containing regimen	82.3% (79.7%-85.1%)	90.0% (87.7%-92.4%)	83.6% (80.6%-86.7%)	90.5% (88.7%-92.3%)	82.3% (79.5%-85.2%)	90.8% (86.4%-95.4%)
Minocycline-containing combination regimen with nitroimidazole antibiotics	82.1% (77.9%-86.5%)	89.5% (86.0%-93.0%)	82.4% (77.9%-87.0%)	89.4% (86.9%-91.9%)	85.4% (81.0%-90.0%)	80.2% (56.8%-100.0%)
Minocycline-containing combination regimen with amoxicillin	83.8% (81.9%-85.9%)	89.9% (86.3%-93.6%)	85.9% (83.0%-89.0%)	92.7% (90.4%-95.1%)	82.7% (80.0%-85.5%)	90.9% (85.9%-96.1%)

CI: Confidence interval.

Comparison of eradication efficacy between quadruple regimens with or without minocycline and nitroimidazole antibiotics: The analysis included five RCTs that adopted minocycline-containing quadruple regimens with nitroimidazole antibiotics[23-25,32,36]. The combination of antibiotics in the control groups included tetracycline and metronidazole (n = 2), amoxicillin and clarithromycin (n = 2), cefuroxime and metronidazole (n = 1), minocycline and amoxicillin (n = 1), and minocycline and cefuroxime (n = 1). ITT analysis using a fixed effect model indicated no obvious heterogeneity (χ^2 = 0.36, P = 0.99, I^2 = 0) or statistically significant difference in the eradication efficacy between quadruple regimens with or without minocycline and nitroimidazole antibiotics (RR = 1.00, 95%CI: 0.96-1.05, P = 0.91). The PP analysis revealed similar results to those of the ITT analysis. The two groups demonstrated no obvious heterogeneity (χ^2 = 0.44, P = 0.98, I^2 = 0) and no statistically significant difference in efficacy (RR = 1.01, 95%CI: 0.98-1.04, P = 0.56). ITT and PP analyses revealed that the eradication rates of quadruple regimens with or without minocycline and nitroimidazole antibiotics were 83.7% *vs* 82.8% and 91.4% *vs* 89.6%, respectively (Figure 4).

Safety and compliance

The overall incidences of adverse reactions to minocycline-containing eradication regimens in the five studies were 22.6%-55.4%[23-25,32,36]. Most of the adverse reactions, mainly including inappetence, asthenia, abdominal discomfort, abdominal pain, diarrhea, headache, dizziness, nausea, vomiting, dysgeusia, rash, *etc.*, were mild to moderate and well-tolerated. Figure 5A shows no statistically significant difference in the incidences of adverse reactions between the quadruple regimens with and without minocycline (RR = 0.94, 95%CI: 0.84-1.06, I^2 = 0, P = 0.63). Among them, 16% of patients treated with the minocycline-containing eradication regimens developed dizziness symptoms. Further comparative analysis (Figure 5B) revealed that significantly more patients adopting eradication regimens with minocycline developed dizziness than those adopting eradication regimens without minocycline (23.4% *vs* 10.4%, P < 0.001). Additionally, minocycline-containing eradication regimens demonstrated better compliance (≥ 90%) in treatment-

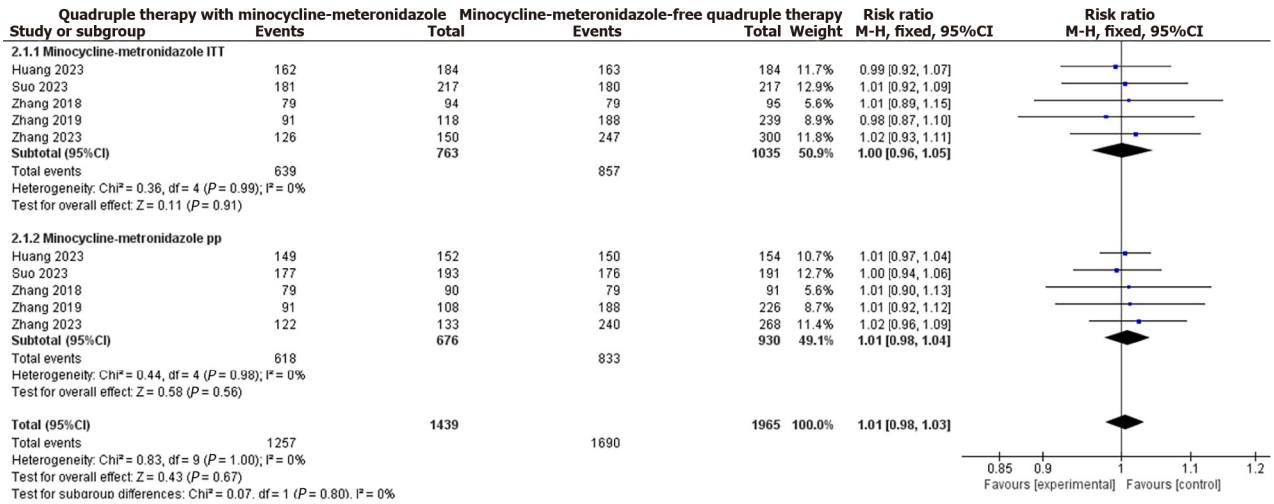

Figure 4 Forest plots comparing eradication rates for intention-to-treat and per-protocol analyses of quadruple regimens with and without minocycline-metronidazole. CI: Confidence interval.

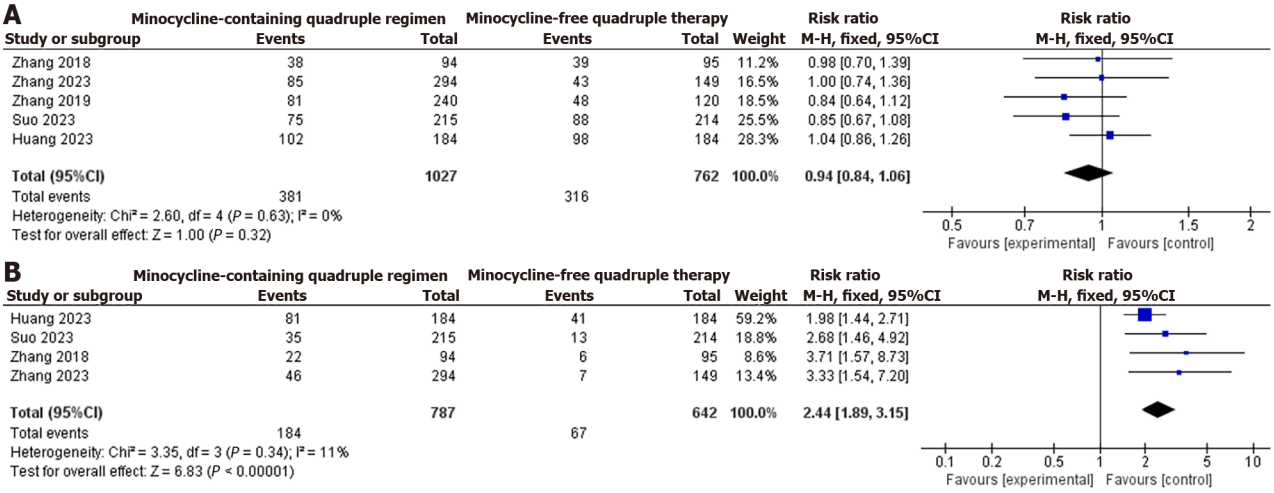

Figure 5 Comparison of the incidence of adverse reactions of quadruple therapy and dizziness in quadruple therapy with and without minocycline. A: Comparison of the incidence of adverse reactions of quadruple therapy with and without minocycline; B: Comparison of the incidence of dizziness in quadruple therapy with and without minocycline. CI: Confidence interval.

naive and retreated patients.

Publication bias analysis

Funnel plots of all included studies were plotted through ITT and PP analyses[11,12,23-26,28-43]. The funnel plots were all asymmetric, and the *P* values of Begg's test and Egger's test were < 0.05, indicating a risk of publication bias. Sensitivity analysis was conducted on the comprehensive results of the included studies by deleting each study in turn. The results were stable and the combination results fluctuated within a small range (Figures 6 and 7). We used the Cochrane Bias Risk Tool to evaluate the risk of bias in the study[23-25,32,36] and revealed that these five RCTs were mostly low risk in terms of selection, follow-up, and reporting biases, while high and unclear risks in terms of performance, measurement, and other biases (the bias risk plot was detailed in the Supplementary Figure 11).

DISCUSSION

The classic BQT has been recommended for eradicating *H. pylori* infection by many expert consensuses or guidelines globally. However, the difficulty in obtaining tetracycline clinically in many countries and regions has greatly limited its wide application[5-10]. In recent years, studies focused on the use of minocycline to replace tetracycline for eradicating *H. pylori* infection. The preliminary results have indicated good eradication efficacy, safety, and compliance. This has offered more drug options for clinical treatment and has become one of the hot spots and concerns in the current research[11,12,23]. Compared with tetracycline, minocycline has unique characteristics and advantages for eradicating *H. pylori*

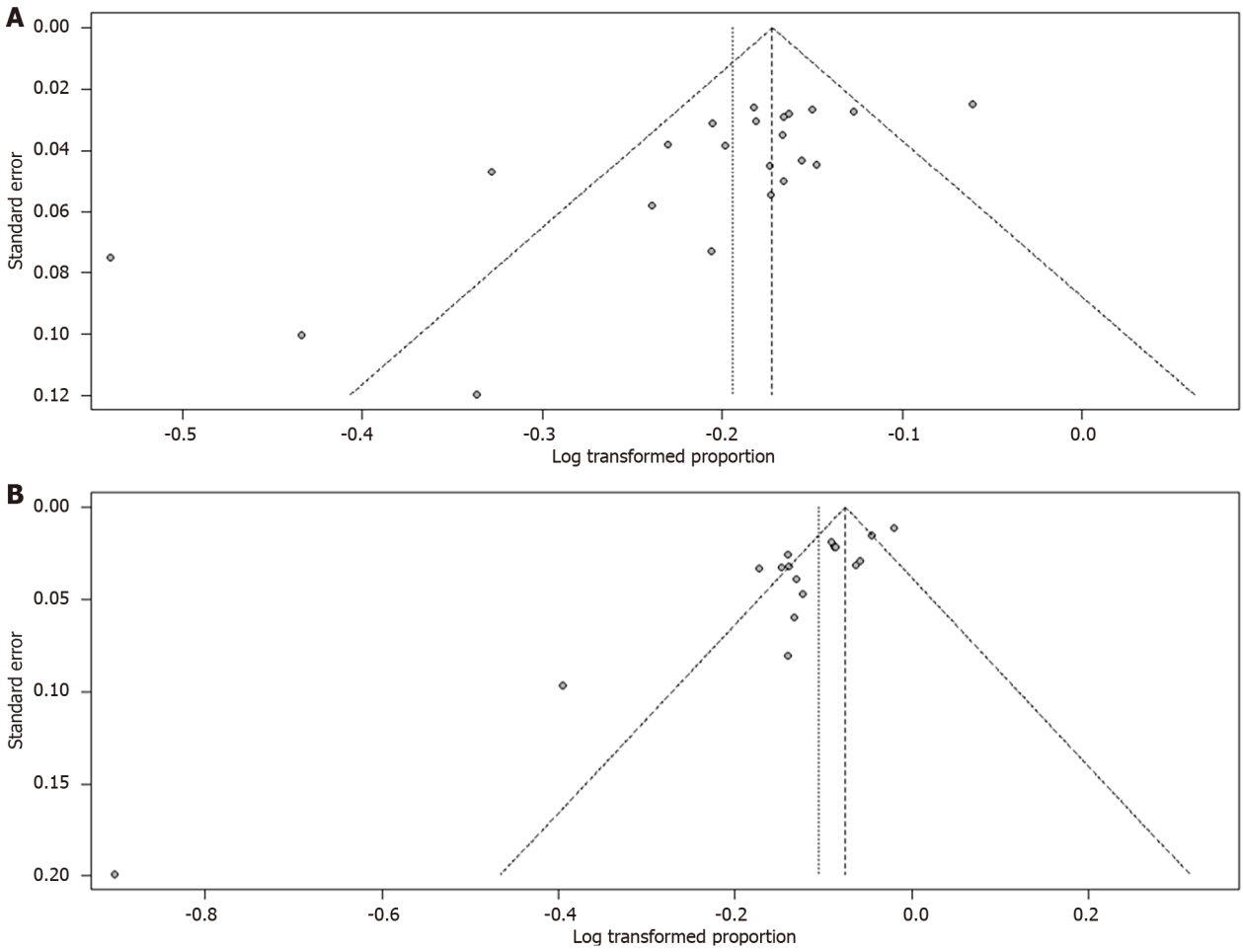

Figure 6 Funnel plots of all included studies through intention-to-treat and per-protocol analyses. A: Intention-to-treat analyses; B: Per-protocol analyses.

infection. In particular, longer half-life and dosing once or twice a day are conducive to improving the compliance of patients. Higher absorption rates, better lipid solubility, and fewer interactions with food are conducive to better bioavailability. Furthermore, minocycline demonstrated better clinical availability, bactericidal effects, and safety in studies on other bacteria[12,16,19,20].

Currently, the minocycline-containing eradication regimens are mostly in the form of a quadruple drug combination, *i.e.*, a combination of gastric acid inhibitor, bismuth agent, minocycline, and another antibiotic. We revealed through single-arm meta-analysis that the minocycline-containing regimen demonstrated good overall eradication effects, reaching an eradication rate of 82.3% (95%CI: 79.7%-85.1%) in the ITT analysis and 90.0% (95%CI: 87.7%-92.4%) in the PP analysis. The nitroimidazole combination was the most common among the antibiotic combinations, followed by the amoxicillin combination. Further, the combination with other antibiotics was relatively few. All antibiotic combinations have demonstrated good eradication efficacy. Moreover, the minocycline-containing regimens exhibited satisfactory eradication efficacy in both treatment-naive and retreated patients[12,23-26,28,30,32,36-40]. Furthermore, we compared the eradication efficacy difference between the minocycline-containing regimens and other eradication regimens through meta-analysis. The results revealed that minocycline-containing regimens or regimens containing minocycline and metronidazole were not statistically different from other commonly used eradication regimens (including the classic BQT) [23-25,32,36]. These analyses have strongly indicated that minocycline could be applied to eradicate *H. pylori* infection and used as a good alternative, especially when tetracycline is difficult to obtain.

The pooled analysis results revealed a relatively good overall safety of the minocycline-containing regimens, with an adverse reaction rate of 36.5% (95%CI: 31.5%-42.2%). Although the incidence of adverse reactions is relatively high in numerical terms, the results of this meta-analysis showed that minocycline-containing regimens were similar to other commonly used eradication regimens in terms of safety (P = 0.63). In addition, the RCT conducted by Suo *et al*[23] showed no significant difference in the incidence of adverse reactions between minocycline-containing regimen and classic BQT (combination of tetracycline and metronidazole) regimen (34% *vs* 41.1%, P = 0.18). Common adverse reactions were mild to moderate, and intolerable cases were rare. The types of adverse reactions were similar with other regimens [23-25,32,36]. However, patients who received the minocycline-containing regimens were more likely to experience dizziness (RR = 2.44, 95%CI: 1.89-3.15, P = 0.34), which might be associated with the reversible vestibular response of minocycline. Tinnitus, ataxia, nausea, vomiting, *etc.*, may accompany such a response[36]. Minocycline demonstrated strong lipophilicity and is more likely than other tetracyclines to pass through the blood-brain barrier, thereby causing

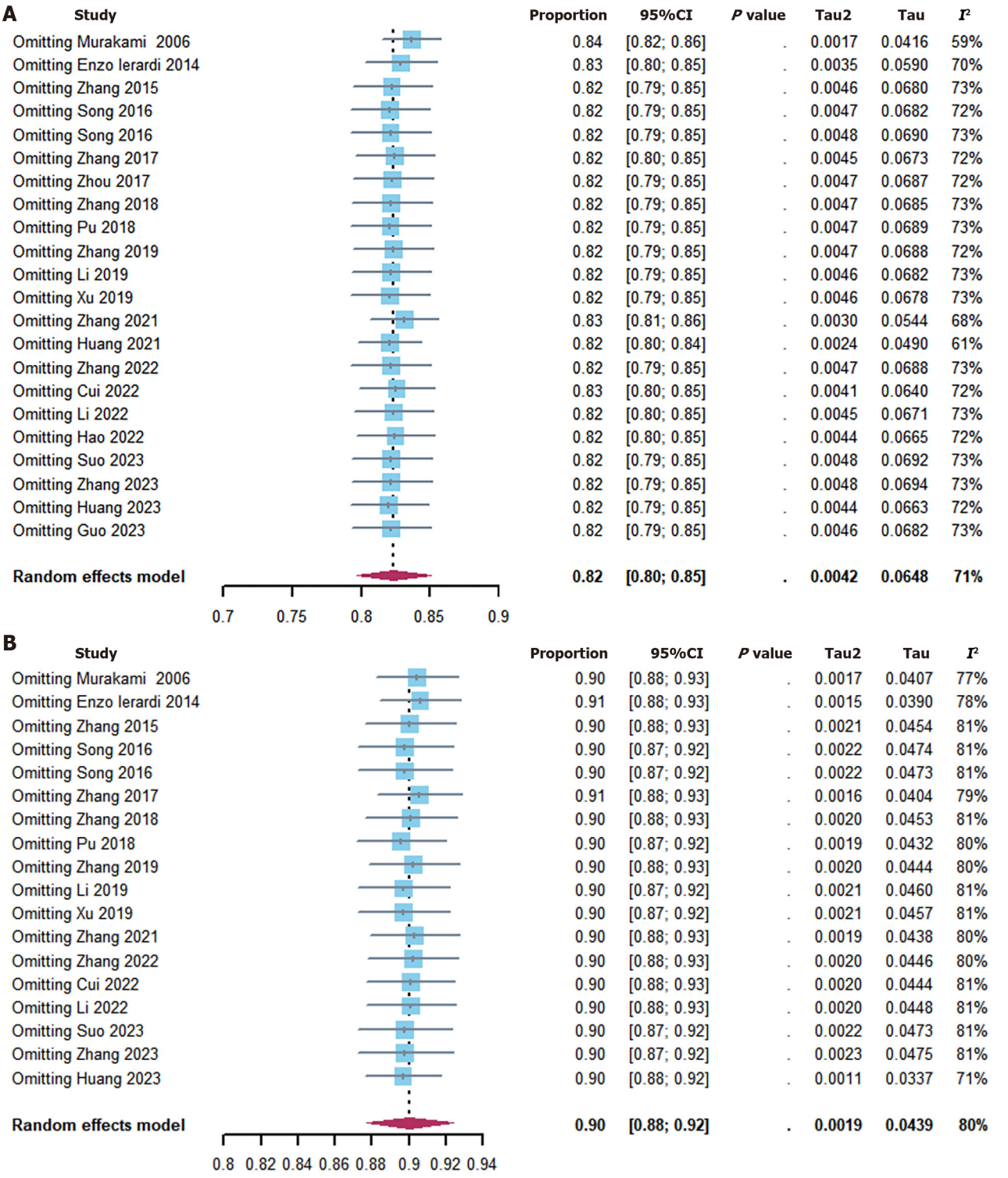

Figure 7 Sensitivity analysis of all included studies by sequentially removing each study with intention-to-treat and per-protocol analyses. A: Intention-to-treat analyses; B: Per-protocol analyses. CI: Confidence interval.

instability of the γ-aminobutyric supervisory acid loop in the cerebellar arch and resulting in vestibular dysfunction[44, 45]. This adverse reaction often occurs during initial administration and most patients recover 24-48 h after drug discontinuation[36]. Additionally, minocycline-containing regimens demonstrated good overall compliance (mostly > 90%), which was similar to other commonly used regimens.

As a relatively new drug for eradicating *H. pylori*, related pooled analyses that involve minocycline are currently lacking. We conducted a comprehensive and systematic analysis of the existing relevant literature through comprehensive literature retrieval and the use of standardized and systematic analytical methods. Both the single-arm meta-analysis method was used to summarize the eradication rate, and the traditional meta-analysis method was utilized to compare the efficacy with other commonly used regimens. This study has offered convenience and a good reference to a comprehensive understanding of the bactericidal mechanism, drug metabolism characteristics, eradication efficacy,

safety, compliance, use, and research of minocycline, and has also enhanced the rational drug selection for treating *H. pylori* infection. The recent meta-analysis on minocycline published by Gao *et al*[46] compared the efficacy and incidence of adverse reactions of the minocycline-containing quadruple regimen using the same traditional analytical methods, but two studies were repeatedly compared, which increased the weight of the article and might lead to biased results. Additionally, we further compared the efficacy of the combination of minocycline and nitroimidazole antibiotics and comprehensively summarized the efficacy and incidence of adverse reactions of minocycline in eradicating *H. pylori* infection through a single-arm meta-analysis that included more relevant research reports, thereby making the results more objective and accurate.

However, this study had certain limitations. At present, studies on minocycline-containing eradication regimens are lacking, and the countries and regions involved remain relatively small (20 studies originated from China, 1 from Japan, and 1 from Italy). The eradication regimens involved in the studies were relatively scattered, the study results had obvious heterogeneity, and the overall quality of the study design was low. These factors might affect the reliability of the obtained results. Large-sample, multi-center, RCTs from more countries and regions are warranted in the future to further determine its eradication efficacy, safety, *etc.*

CONCLUSION

Therefore, this comprehensive and systematic meta-analysis has demonstrated the satisfactory efficacy, safety, and compliance of minocycline-containing regimens in eradicating *H. pylori* infection. Compared with tetracycline, minocycline demonstrated low drug resistance and unique drug metabolism characteristics and advantages, but a few patients may experience dizziness due to vestibular dysfunction. Minocycline can be applied to clinical practice as a drug for eradicating *H. pylori* infection and used as an alternative, especially when tetracycline is difficult to obtain, but more research is needed to further confirm its effect.

FOOTNOTES

Author contributions: Zhou K and Song ZQ contributed to the research design; Zhou K was involved in the literature screening, quality assessment, and manuscript writing; Zhou K, Zhang H, and Tian XL participated to the statistical analysis; Li LC, Zhou LY, Tian XL, and Song ZQ edited the manuscript; Li CL contributed to literature mining; Li CL, Suo BJ, Zhang YX, Ren XL, Wang YX, Mi CM, and Ma LL were involved in the data analysis; Song ZQ contributed to the research concepts and funding acquisition; and all authors have read and approved the final manuscript. Zhou K and Li CL contributed equally to this work as co-first authors. The reasons are the following. First, the research was performed as a collaborative effort, and the designation of co-first authors authorship accurately reflects the distribution of responsibilities and burdens associated with the time and effort required to complete the study and the resultant paper. Second, co-first authors contributed efforts of equal substance throughout the research process. Song ZQ and Tian XL contributed equally to this work as co-corresponding authors. The reasons are the following. First, they played a key role in coordinating the research team. Second, they made a great contribution to the original innovation of the article. In summary, we believe that designating Zhou K and Li CL as co-first authors, Song ZQ and Tian XL as co-corresponding authors is fitting for our manuscript as it accurately reflects our team's collaborative spirit, equal contributions, and diversity.

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LETTER TO THE EDITOR

Targeting therapy for hepatocellular carcinoma by delivering microRNAs as exosomal cargo

Takeshi Suda

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Peer-review model: Single blind

Peer-review report's classification
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Novelty: Grade B
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Abstract

Exosomes, the smallest extracellular vesicles, have gained significant attention as key mediators in intercellular communication, influencing both physiological and pathological processes, particularly in cancer progression. A recent review article by Wang *et al* was published in a timely manner to stimulate future research and facilitate practical developments for targeted treatment of hepatocellular carcinoma using exosomes, with a focus on the origin from which exosomes derive. If information about the mechanisms for delivering exosomes to specific cells is incorporated, the concept of targeted therapy for hepatocellular carcinoma using exosomes could be more comprehensively understood.

Key Words: Exosomal delivery; Therapeutic targets; MicroRNAs; Hepatocellular carcinoma

Core Tip: Wang *et al* thoroughly explored the functions and biomedical significance of exosomal microRNAs transferred by both parenchymal and nonparenchymal cells in the framework of potential therapeutic targets for hepatocellular carcinoma. This review aimed to do more than just summarize the role of microRNAs in hepatocarcinogenesis. It also sought to illuminate the process of cellular communication using exosomal microRNA cargo. Therefore, it would be beneficial for the review to include information on how this cargo is delivered to target cells.

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TO THE EDITOR

We have read the original review article titled 'Function and biomedical implications of exosomal microRNAs delivered by parenchymal and nonparenchymal cells in hepatocellular carcinoma' by Wang *et al*[1], published in the October issue of *World Journal of Gastroenterology*. We would like to extend our congratulations to the authors for this informative article and offer some suggestions.

Following an introduction to exosomes regarding their formation, composition, and function, this review briefly summarizes the crucial role of microRNAs in hepatocarcinogenesis. Subsequently, the direct and indirect effects of various microRNAs carried by exosomes on hepatocellular carcinoma cells, such as hepatic stellate cells, cancer-associated fibroblasts, adipocytes, vascular endothelial cells, and immune cells of different types, are systematically categorized based on their origin. Finally, the authors list potential therapeutic applications of microRNA delivery through exosomes.

Most of this review is dedicated to listing examples of microRNAs involved in the development and progression of hepatocellular carcinoma. This review effectively illustrates which types of cells deliver specific microRNAs to communicate with hepatocellular carcinoma cells. In the concluding discussion, the authors explore the potential applications of microRNAs in the treatment of hepatocellular carcinoma using exosomes; however, there is no information provided on how the released exosomes will reach their target cells.

While exosomes theoretically have the ability to be delivered to various cell types, targeted delivery to specific cell types has been observed and achieved through the engineering of specific exosomes. Lima *et al*[2] reported that cytokines in tumor interstitial fluid bind to cancer exosomes and determine their biodistribution based on cytokine receptor expression. Liang *et al*[3] summarized the current knowledge of exosome engineering through genetic and chemical methods for targeted drug delivery.

The current review proposes targeted therapy for hepatocellular carcinoma using exosomal delivery of microRNAs. Understanding the specific exosome delivery mechanisms would significantly advance the development of more precise and effective therapies for hepatocellular carcinoma.

FOOTNOTES

Author contributions: Suda T read the review article by Wang *et al* and wrote this entire letter to the editor.

Conflict-of-interest statement: The author declares he has no conflicts of interest in relation to this letter.

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LETTER TO THE EDITOR

Metabolic dysfunction-associated fatty liver disease and low muscle strength: A comment

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Abstract

The diagnosis of non-alcoholic fatty liver disease (NAFLD) and metabolic dysfunction-associated fatty liver disease only on the basis of laboratory parameter score such as Hepatic Steatosis Index which includes liver enzymes, gender, basal metabolic index, and presence of diabetic mellitus is not sufficient to exclude other causes of deranged liver enzymes especially medications and autoimmune related liver diseases. As the guideline suggests ultrasound is the preferred first-line diagnostic procedure for imaging of NAFLD, as it provides additional diagnostic information and the combination of biomarkers/scores and transient elastography might confer additional diagnostic accuracy and evident from previous similar studies too.

Key Words: Non-alcoholic fatty liver disease; Metabolic dysfunction associated fatty liver disease; Low muscle strength; Hepatic Steatosis Index; Letter to the editor

Core Tip: Combining imaging modalities along with laboratory parameter-based scores increases the diagnostic yield of non-alcoholic fatty liver disease, and helps in the exclusion of the other secondary causes.

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TO THE EDITOR

We found the article by Lee *et al*[1] compelling as the article addressed an important aspect of metabolic dysfunction-associated fatty liver disease (MAFLD), which has emerged as an emerging pandemic and a major public health issue worldwide, particularly in Asian countries[1-4]. In this study, the author emphasized the significant yet underexplored link between muscle strength and MAFLD.

However, in the current study, the diagnosis of MAFLD was based on the "Hepatic Steatosis Index" (HSI), a score consisting of non-invasive laboratory parameters. While the HSI demonstrated the highest sensitivity and specificity at 93% and 92%, respectively, there is still a possibility of missing approximately 7%-8% of patients (equivalent to 1400 patients) with MAFLD in the context of this study[5].

Moreover, HSI is calculated as HIS = 8 × [alanine aminotransferase (ALT)/aspartate aminotransferase (AST) ratio] + basal metabolic index (+ 2, if female; + 2, if diabetes mellitus). According to this formula deranged liver enzymes (AST and ALT) due to any concomitant cause can result in false positive results when other causes were not ruled out especially medication and autoimmune-related liver injuries which were not excluded in this study.

Furthermore, the European Association Society for Liver Diseases guideline suggests ultrasound as the preferred first-line diagnostic procedure for imaging of MAFLD, as it provides additional diagnostic information. However, the combination of biomarkers/scores with transient elastography might confer additional diagnostic accuracy[6].

In a similar European study about the association between fatty liver disease and low muscle mass by Rigor *et al*[7], the ultrasound abdomen was used to screen patients with fatty liver disease. Additionally, another recent Korean population-based study by Seo *et al*[8] also measured hepatic steatosis based on Fibro scan.

In our opinion, using imaging modalities such as ultrasound abdomen or fibroscan along with laboratory parameter-based scores could have not only increased diagnostic yield but also helped in the exclusion of the other secondary causes.

FOOTNOTES

Author contributions: Karim MM and Butt AS designed research and performed research (literature review); Karim MM wrote the letter; Butt AS revised the letter.

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

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