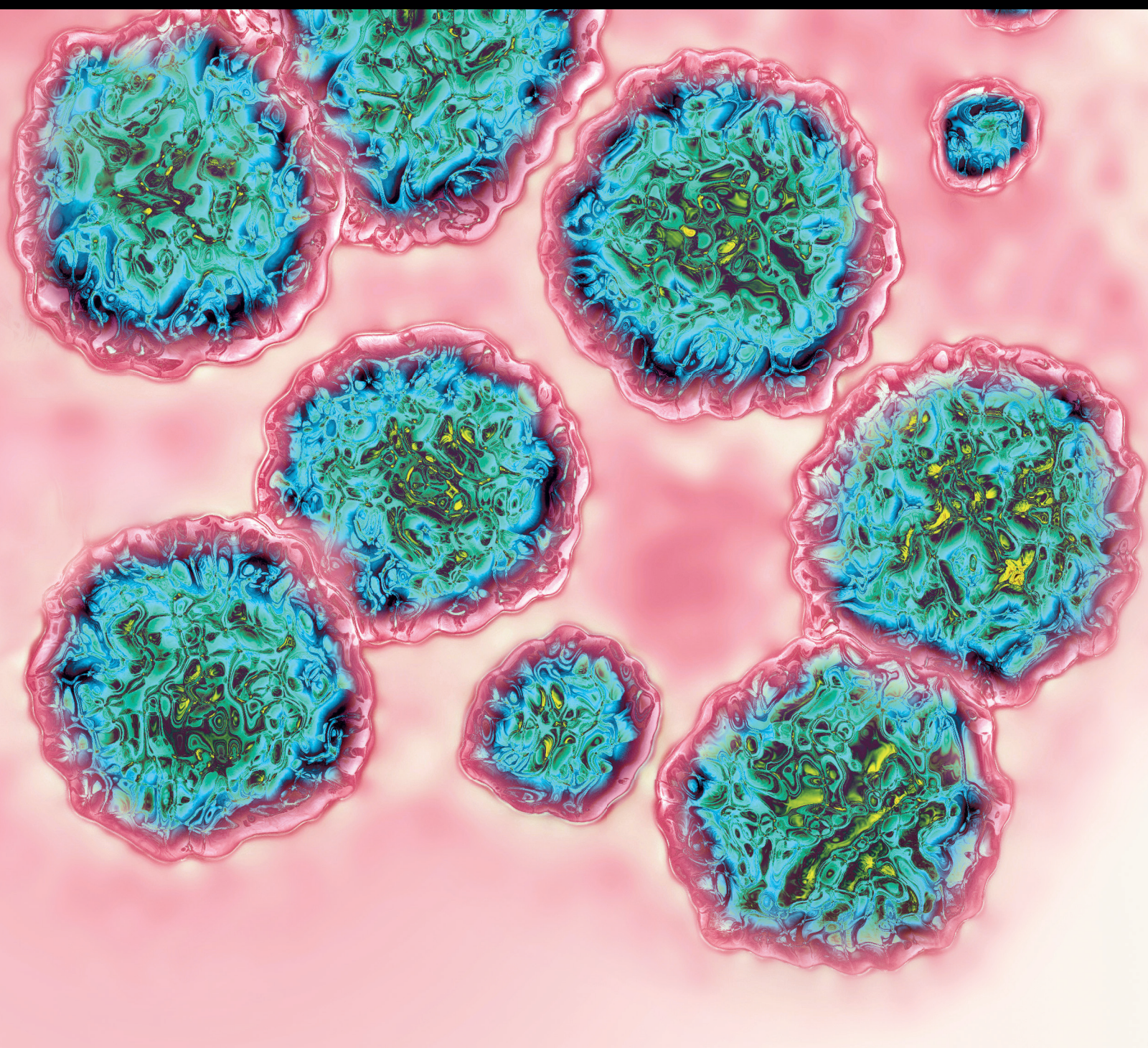
Canadian Journal of Gastroenterology and Hepatology

Portal Hypertension

Lead Guest Editor: Mingyu Sun
Guest Editors: Xingshun Qi, Fernando G. Romeiro, and Andrea Mancuso



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Editorial Board

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Editorial

Portal Hypertension

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A major cause of morbidity and mortality in cirrhosis is the development of variceal bleeding, a direct consequence of portal hypertension. Portal hypertension occurs when hepatic venous pressure gradient (HVPG) is above 5 mmHg, but the main complications are clinically expressed when it exceeds 10 mmHg. Ascites, gastroesophageal variceal bleeding, hepatorenal syndrome, and hepatic encephalopathy are life-threatening conditions related to portal hypertension. In some countries, the economic burden caused by liver diseases and portal hypertension complications is higher than that of chronic kidney disease and type 2 diabetes combined. Most cases of portal hypertension in the Western world are attributed to liver cirrhosis (90% of patients). Structural changes such as depots of fibrous tissue, microthrombi, collapse of the liver parenchyma, and vascular alterations account for approximately 70% of the hepatic vascular resistance observed in portal hypertension due to cirrhosis.

This special issue aims to bring innovative articles on this matter, given to the readers an integrative point of view about the hot topics on diagnostic and treatment of portal hypertension complications. The articles received by the journal were carefully selected, thus offering a high-quality collection.

A study by H. Li et al. explored the association between the pathological damage of mitochondrial ultrastructure according to the Flameng classification system and risk of hepatic encephalopathy in patients treated with transjugular intrahepatic portosystemic shunt. The investigators provided invaluable data from the transjugular liver biopsy procedures. Based on the histological and clinical data, the investigators reported interesting findings that more severe damage to mitochondrial ultrastructure was significantly associated with a higher risk of hepatic encephalopathy after transjugular intrahepatic portosystemic shunt. Additionally, they found that the severity of damage to mitochondrial ultrastructure positively correlated with the venous ammonia level. These findings would be useful to deeply understand the mechanisms of developing hepatic encephalopathy after transjugular intrahepatic portosystemic shunt and to establish the preventive strategy in future.

The noninvasive serological scoring system has become a research hotspot in predicting hepatic fibrosis. F. Zhang et al. contributed their research paper "Predictive Value of a Noninvasive Serological Hepatic Fibrosis Scoring System in Cirrhosis Combined with Oesophageal Varices". They retrospectively analysed cirrhosis patients with or without oesophageal varices, aiming to evaluate the predictive value of the four following scoring systems in cirrhosis combined with oesophageal varices: aspartate and platelet ratio index (APRI), aspartate aminotransferase-alanine aminotransferase ratio (AAR), FIB-4, and S index. A total of 153 patients with cirrhosis were categorized into groups with or without oesophageal varices. AAR harbored a poor predictive value for oesophageal varices, APRI can be used as a reference index for the prediction of severe oesophageal varices, and the S index harbored potential value in predicting the degree of progression of cirrhosis.

X. Qi et al. review paper "Transient Elastography for Significant Liver Fibrosis and Cirrhosis in Chronic Hepatitis B" performed the meta-analysis describing diagnostic accuracy

of transient elastography (TE) for predicting CHB-related fibrosis. Hierarchical summary receiver operating curves model and the bivariate random efforts model were applied to generate summary receiver operating characteristic curves and pooled estimates of sensitivity and specificity. TE is of great value in the detection of patients with CHB-related cirrhosis but has a suboptimal accuracy in the detection of significant fibrosis.

D. Kara et al. presented a paper on portal hypertensive polyposis in advanced liver cirrhosis aiming to identify relevant endoscopic findings in patients with advanced cirrhosis and consecutive portal hypertension. This retrospective study on liver transplant candidates undergoing 1,045 upper endoscopies found that portal hypertensive gastric and duodenal polyps were frequently observed and were significantly associated with thrombocytopenia, Child-Pugh score, MELD, and previous rubber band ligation. These polyps often recurred after polypectomy; however, no malignant transformation occurred during observation. The most common endoscopic finding was esophageal varices, observed in more than 90% of patients. The authors concluded that portal hypertensive polyposis is common in patients with advanced cirrhosis and these polyps are generally benign.

X. Luo et al. prepared a paper on the "Short-Term Outcome of Patients with Cirrhosis and Concurrent Portal Cavernoma Presenting with Acute Variceal Bleeding" in which they compared short-term outcomes after acute variceal bleeding (AVB) in cirrhotics with and without portal cavernoma, finding that the 5-day treatment failure rate was higher in the cavernoma group than in the control group (32.1% versus 12.5%). The 6-week mortality rate did not differ significantly between the cavernoma and control group (25% versus 12.5%). Multivariable Cox proportional hazard regression analyses revealed that 5-day treatment failure independently predicted 6-week mortality.

In another interesting paper written by Tseng et al., the authors present their own experience facing severe adverse events after endoscopic cyanoacrylate injection. The authors also made a review on this issue, looking for findings that could be associated with an increased risk in this procedure, thus providing a further insight into the study. Since cyanoacrylate injection is the first line therapy for variceal bleeding from gastric varices, the readers have the chance of knowing the authors' experience. For instance, they have used some pre- and posttreatment medications and their protocol applies the sandwich technique injection of lauromacrogol and cyanoacrylate. Furthermore, the article has detailed information on the patient's conditions before the procedure, including some findings that are lacking in prior studies. It is a remarkable advantage of this paper, presenting some hints on how to predict severe adverse effects after cyanoacrylate injection.

Conflicts of Interest

As the guest editorial team, we all have no conflicts of interest to declare.

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Research Article

Predictive Value of a Noninvasive Serological Hepatic Fibrosis Scoring System in Cirrhosis Combined with Oesophageal Varices

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Objective. In recent years, the noninvasive serological scoring system has become a research hotspot in predicting hepatic fibrosis and has achieved good results. However, it has rarely been applied to the prediction of oesophageal varices. The aim of the study was to evaluate the predictive value of the four following scoring systems in cirrhosis combined with oesophageal varices: aspartate and platelet ratio index (APRI), aspartate aminotransferase-alanine aminotransferase ratio (AAR), FIB-4, and S index. *Methods*. A total of 153 patients with cirrhosis were categorized into groups with or without oesophageal varices. In addition, cirrhosis patients with oesophageal varices were further divided into mild, moderate, and severe grades. The rank sum test was used to compare the significant differences of APRI, AAR, FIB-4, and S index between the two groups of cirrhosis patients with or without oesophageal varices. A ROC curve was generated to compare the area under the curve of the three groups and to obtain the corresponding optimal prediction value. Moreover, multivariate logistic regression analysis was employed to assess the predictive factors for cirrhosis combined with oesophageal varices. *Results*. 44 patients had no oesophageal varices and 108 patients had oesophageal varices. Of the 108 patients with oesophageal varices, 43 were mild, 32 were moderate, and 33 were severe. The rank sum test indicated that the APRI, FIB-4, and S index were statistically significant between two groups ($P < 0.05$), while no significant difference was detected in terms of AAR between the two groups ($P > 0.05$). In addition, all four scoring systems were statistically significant between nonoesophageal varices group and severe oesophageal varices group ($P < 0.05$). In the ROC curve of oesophageal varices, the AUC values of APRI, FIB-4, and S index for predicting oesophageal varices were 0.681, 0642, and 0.673, respectively. However, in the ROC curve of severe oesophageal varices, the AUC values of APRI, AAR, FIB-4, and S index were 0.729, 0.648, 0.673, and 0.695, respectively. Multivariate logistic regression analysis indicated that APRI and FIB-4 were predictors of disease progression ($P < 0.05$). *Conclusion*. AAR harboured a poor predictive value for oesophageal varices, APRI can be used as a reference index for the prediction of severe oesophageal varices, and the S index harboured potential value in predicting the degree of progression of cirrhosis.

1. Introduction

Liver cirrhosis, a common chronic liver disease, is caused by long-term or repeated damage to liver tissue due to one or more causes, leading to diffuse degeneration and necrosis of hepatocytes, regenerative nodules, and fibrous tissue hyperplasia. Portal hypertension is observed in the advanced stage of cirrhosis. When the portal vein pressure increases to a certain degree, oesophageal varices can occur, while, in severe cases, oesophageal variceal bleeding will emerge, which is the most common and severe complication of cirrhosis and cirrhotic portal hypertension, as well as the most common cause of death for cirrhosis [1]. In the 1990s, the mortality rate after the onset of oesophageal variceal bleeding was as high as 50% [2]. With the development and advancements of medical technology and equipment, along with a further understanding of the disease, the mortality rate has decreased; however, new statistics indicate that the 6-week mortality rate is still as high as 20% [3]. Digestive endoscopy is considered the gold standard for the screening and diagnosis of oesophageal varices [4]. However, as an invasive examination, there are potential risks, such

Table 1: Grading method of oesophageal varices [8].

Grade)	EV morphology (F)	EV red-color sign (RC)
mild (G1)	EV Straight or slightly tortuous (F1)	no
moderate (G2)	EV Straight or slightly tortuous (F1)	yes
	EV Swelling and distortion like snake (F2)	no
severe (G3)	EV Swelling and distortion like snake (F2)	yes
	EV Bead-like, nodular or tumor-like (F3)	yes/no

as bleeding and anaesthesia accidents during operation, and repeated monitoring can introduce more pain, leading to poor compliance, which makes it difficult to conduct clinical observations on patients with oesophageal varices. In recent years, the exploration of noninvasive methods for predicting oesophageal varices has become a research focus, aiming to selectively assess patients with a relatively high risk of oesophageal varices to further effectively monitor the degree of varices, to administer selective interventions, and to reduce the pain and burden of patients to some extent. Recently, the application noninvasive serological examinations in the prediction and diagnosis of the degree of hepatic fibrosis has become a hotspot. Among them, the classic ones, including APRI and FIB-4 scores, have been recommended by the World Health Organization (WHO) guidelines for assessing hepatic fibrosis [5]. In addition, it has also been shown that AAR is 0.8 in healthy individuals, and AAR > 1 indicates the presence of cirrhosis. Chinese scholars have established an S index in the analysis of risk factors for hepatic fibrosis in chronic hepatitis B virus (HBV), which harbours a higher accuracy in the assessment of hepatic fibrosis in HBV [6]. The above four scoring methods are simple and easy to obtain in clinical practice. However, few studies have applied it in the prediction of cirrhosis and oesophageal varices. Hence, in this study, we aimed to explore and compare the predictive value of the APRI, AAR, FIB-4, and S index scoring systems in oesophageal varices.

2. Subjects and Methods

2.1. Subject. We retrospectively analysed patients with cirrhosis who were admitted to the Affiliated Hospital of Xuzhou Medical University from January 2010 to September 2017. The inclusion criteria were as follows: ① all patients met the diagnostic criteria for cirrhosis in the Guidelines for Chronic Hepatitis B Prevention and Treatment (2015 Update) by the Chinese Medical Association, 2015 Edition) [7] (gastroscopy and serum biochemical examination were performed after admission). The exclusion criteria were as follows: ① a history of hepatic carcinoma; ② prior hepatic operation and splenectomy; ③ prior transjugular intrahepatic portosystemic shunt; ④ prior sclerotherapy or ligation for oesophageal varices; ⑤ the existence of other factors that might affect the platelet count and spleen size; ⑥ patients with severe heart, lung, and kidney disease; ⑦ patients who have used drugs that inhibit or promote bone marrow haematopoiesis or that decrease portal vein pressure and albumin in the last six months; ⑧ the emergence of upper gastrointestinal bleeding during previous and current admission.

2.2. Methods. We recorded the age of the patients and the levels of AST, ALT, albumin, and PLT in peripheral blood. In addition, patients were divided into slight, moderate, and severe groups according to the morphology of oesophageal varices (EV) and the severity of haemorrhage under gastroscopy (shown in Table 1).

2.3. Calculation. APRI = (AST/upper limit of normal)×100/PLT ($10^{\wedge}9$/L); AAR = AST/ALT; FIB-4 = (year of age × AST)/(PLT × the square root of ALT); S index: 1000∗GGT/(PLT∗ albumin^2).

2.4. Statistical Analysis. SPSS22.0 statistical software was used for all data processing and analysis. The chi-square test was used for enumeration data, the median (quartile) was used for nonnormally distributed measurement data, and the rank sum test was employed for comparisons between groups. $P < 0.05$ represented statistical significance. The combination with or without oesophageal varices in cirrhosis was taken as the demarcation point, and the diagnostic criteria of gastroesophageal varices under gastroscopy were considered the gold standard to investigate whether the four scoring systems of APRI, AAR, FIB-4, and S index were statistically significant between cirrhosis without oesophageal varices and cirrhosis with oesophageal varices. Whether cirrhosis was combined with oesophageal varices or with severe oesophageal varices or not was taken as two demarcation points. The ROC curve was generated, followed by the use of the AUC value to evaluate the predictive accuracy of three scores in cirrhosis combined with oesophageal varices or severe oesophageal varices. The optimal demarcation point was detected, which corresponded to the maximum value by adding sensitivity and specificity on the ROC curve. AUC values > 0.7 indicated clinical value, AUC values of 0.8-0.9 suggested relatively good clinical value, and AUC values > 0.9 indicated very good clinical value. Nonconditional multivariate logistic regression analysis was performed on multiple sets of data. A $P < 0.05$ was considered to represent statistical significance.

3. Results

3.1. General State. A total of 153 patients with cirrhosis who met the requirements were collected (shown in Table 2). Of them, there were 109 patients with HBV cirrhosis, 11 patients with hepatitis C virus (HCV) cirrhosis, 10 patients with alcoholic cirrhosis, 10 patients with autoimmune cirrhosis, and 13 patients with other causes (drug-induced cirrhosis, mixed cirrhosis, and cryptogenic cirrhosis). There were

Table 2: General state of the 153 patients with cirrhosis.

General information	no	mild	moderate	severe
Number of cases	44	43	32	33
Mean age	51.0±12.6	48.8±12.7	52.9±11.3	47.5±9.3
Male (cases)	25	31	19	24
Female (cases)	19	12	13	9
APRI	1.0 (0.6,3.5)	1.7 (1.1,2.9)	2.2 (1.4,4.9)	2.7 (1.9,4.2)
AAR	1.1 (0.8,1.2)	1.0 (0.8,1.4)	1.1 (0.9,1.4)	1.2 (0.9,1.4)
FIB-4	102. (55.5,562.7)	196.3 (104.9,392.2)	324.3 (165.9,708.1)	244.0 (153.3,518.1)
S index	0.3 (0.1,1.0)	0.7 (0.2,1.3)	0.9 (0.4,1.9)	0.8 (0.4,1.9)

44 cirrhosis patients without oesophageal varices (nonoesophageal varices group), 43 with mild oesophageal varices (mild group), 31 with moderate oesophageal varices (moderate group), and 32 patients with severe oesophageal varices (severe group). There was no significant difference in age or gender between patients in each group (all $P > 0.05$).

3.2. APRI, AAR, FIB-4, and S Index. Due to the nonnormal distribution of the data, median (M) and quartile range (Q) were used. The group and data of each group are shown in Table 2.

3.3. Comparison of the Nonoesophageal Varices Group and Oesophageal Varices Group. APRI: 1.0 (0.6-3.5) versus 2.2 (1.5-3.8); AAR: 1.1 (0.8-1.2) versus 1.1 (0.9-1.4); FIB-4: 102.6 (55.5-562.7) versus 247.8 (130.2-529.4); S index: 0.3 (0.1-1.0) versus 0.8 (0.4-1.8). The rank sum test was used to compare the nonoesophageal varices group and oesophageal varices group, which revealed that APRI scoring system statistically significant ($P < 0.001$), and the P values of AAR, FIB-4, and S index were 0.078, 0.006, and 0.001; in other words, all three scoring systems were statistically significant (all $P < 0.05$).

3.4. Comparison of the Nonoesophageal Varices Group and Severe Oesophageal Varices Group. APRI: 1.0 (0.6-3.5) versus 2.7 (1.9- 4.2); AAR: 1.1 (0.8-1.2) versus 1.2 (0.9-1.4); FIB-4: 102.6 (55.5-562.7) versus 244.0 (153.3-518.1); S index: 0.3 (0.1-1.0) versus 0.8 (0.4,1.9). The rank sum test was used to compare the nonoesophageal varices group and severe oesophageal varices group, which revealed P values of 0.001, 0.026, 0.009, and 0.003, respectively; in other words, all four scoring systems were statistically significant (all $P < 0.05$).

3.5. Predictive Value of APRI, FIB-4, and S Index in Oesophageal Varices (Shown in Figure 1). ROC curve analysis showed that the AUC values of APRI, FIB-4, and S index in predicting oesophageal varices were 0.681, 0.642, and 0.673, respectively (shown in Table 3). The optimal demarcation point of blood APRI in predicting cirrhosis combined with oesophageal varices was 1.29, and the corresponding sensitivity and specificity were 0.815 and 0.600, respectively. The optimal demarcation point of FIB-4 in predicting cirrhosis combined with oesophageal varices was 103.7, with a corresponding sensitivity and specificity of 0.843 and 0.511, respectively. The optimal demarcation point of the S index in predicting cirrhosis combined with oesophageal varices was 0.23, with a corresponding sensitivity and specificity of 0.861 and 0.467, respectively.

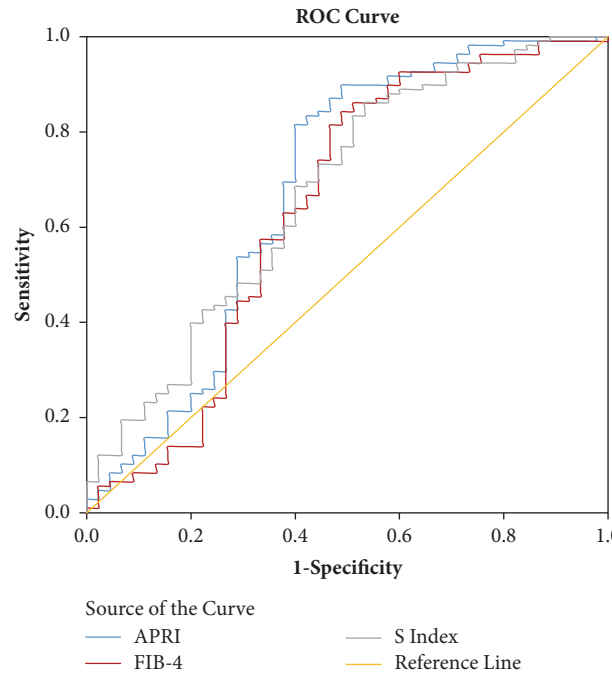

Figure 1: Receiver operating characteristic curve of APRI, FIB-4, and S index in diagnosis of cirrhosis combined with oesophageal varices. APRI: aspartate aminotransferase and platelet ratio; FIB-4: fibrosis index based on factor-4.

3.6. Predictive Value of APRI, AAR, FIB-4, and S Index in Severe Oesophageal Varices (Shown in Figure 2). ROC curve analysis showed that the AUC values of APRI, AAR, FIB-4, and S index in predicting severe oesophageal varices were 0.729, 0.648, 0.673, and 0.695, respectively (shown in Table 4). The optimal demarcation point of blood APRI in predicting cirrhosis combined with oesophageal varices was 1.4, with the corresponding sensitivity and specificity being 0.939 and 0.600, respectively. The optimal demarcation point of AAR in predicting cirrhosis combined with oesophageal varices was 1.3, with a corresponding sensitivity and specificity of 0.394 and 0.933, respectively. The optimal demarcation point of FIB-4 in predicting cirrhosis combined with oesophageal varices was 113.4, with a corresponding

Table 3: The predictive value of noninvasive serological hepatic fibrosis scoring system in cirrhosis combined with oesophageal varices.

indicator	AUC	Cut-off	sensitivity	specificity	PPV	NPV
APRI	0.681	1.29	0.815	0.600	0.832	0.578
FIB-4	0.642	103.7	0.843	0.511	0.805	0.564
S index	0.673	0.23	0.861	0.467	0.793	0.613

APRI: aspartate aminotransferase and platelet ratio; FIB-4: fibrosis index based on factor-4; AUC: area under the curve; PPV: positive predictive value; NPV: negative predictive value.

Table 4: The predictive value of noninvasive serological hepatic fibrosis scoring system in cirrhosis combined with severe oesophageal varices.

indicator	AUC	Cut-off	sensitivity	specificity	PPV	NPV
APRI	0.729	1.4	0.939	0.600	0.640	0.963
AAR	0.648	1.3	0.394	0.933	0.667	0.661
FIB-4	0.673	113.4	0.939	0.533	0.588	0.885
S index	0.695	0.27	0.861	0.467	0.545	0.864

APRI: aspartate aminotransferase and platelet ratio; FIB-4: fibrosis index based on factor-4; AUC: area under the curve; PPV: positive predictive value; NPV: negative predictive value.

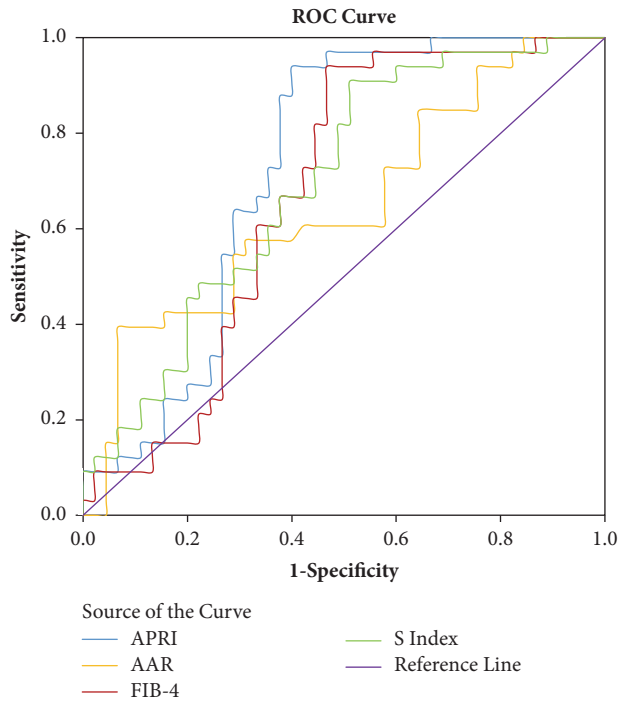

Figure 2: Receiver operating characteristic curve of APRI, AAR, FIB-4, and S index in diagnosis of cirrhosis combined with severe oesophageal varices. APRI: aspartate aminotransferase and platelet ratio; FIB-4: fibrosis index based on factor-4; AAR: aspartate aminotransferase-alanine aminotransferase ratio.

sensitivity and specificity of 0.939 and 0.533, respectively. The optimal demarcation point of the S index in predicting cirrhosis combined with oesophageal varices was 0.27, with a corresponding sensitivity and specificity of 0.861 and 0.467, respectively.

3.7. Nonconditional Multivariate Logistic Regression Analysis of APRI, FIB-4, and S Index for Oesophageal Varices. According to whether cirrhosis was combined with oesophageal varices, which was a two-class response variable, nonconditional logistic regression analysis was used to construct a predictive model for the three values. The introduction criterion was $P < 0.05$, and the elimination criterion was $P > 0.10$. As a result, APRI and FIB-4 could be used as an independent predictive model for cirrhosis combined with oesophageal varices (shown in Table 5).

3.8. Nonconditional Multivariate Logistic Regression Analysis of APRI, AAR, FIB-4, and S Index for Severe Oesophageal Varices. According to whether cirrhosis was combined with severe oesophageal varices, which was a two-class response variable, nonconditional logistic regression analysis was used to construct a predictive model for the four values. The introduction criterion was $P < 0.05$, and the elimination criterion was $P > 0.10$. Consistently, APRI and FIB-4 could be used as independent predictive models for cirrhosis combined with severe oesophageal varices (shown in Table 6).

4. Discussion

Oesophageal variceal bleeding is the most lethal complication of cirrhotic portal hypertension. However, in most cirrhosis patients, no obvious clinical manifestations are present, even at decompensation period. This is especially true of oesophagogastric varices, which is difficult to detect if gastroscopy is not performed. Gastroscopy and portal vein pressure testing harbour a relatively good predictive value for the degree of oesophagogastric varices, but they are invasive procedures that are not easily tolerated by patients due to the pain. In addition, their safety is relatively low; hence, their clinical application is limited [3, 9]. In recent years, the noninvasive prediction of oesophagogastric varices has become a hotspot of research. In consideration of the emergence of portal hypertension due to the progression of hepatic fibrosis, noninvasive biochemical markers of hepatic fibrosis have been used to predict the incidence rate of oesophageal varices in patients with cirrhosis [10]. The noninvasive serological hepatic fibrosis score has the advantages of accurate data,

Table 5: Logistic regression analysis of APRI, FIB-4, and S index in prediction of cirrhosis combined with oesophageal varices.

	B	S.E.	Wald	df	Sig.	Exp(B)
APRI	.731	.264	7.647	1	.006	2.077
FIB-4	-.002	.001	8.961	1	.003	.998
S Index	.280	.205	1.855	1	.173	1.323
constant	-.187	.350	.286	1	.593	.829

Table 6: Logistic regression analysis of APRI, AAR, FIB-4, and S index in prediction of cirrhosis combined with oesophageal varices.

	B	S.E.	Wald	df	Sig.	Exp(B)
APRI	2.833	.762	13.814	1	.000	16.990
AAR	.016	.937	.000	1	.986	1.017
FIB-4	-.012	.003	12.302	1	.000	.988
S Index	.173	.148	1.375	1	.241	1.189
constant	-2.967	1.117	7.057	1	.008	.051

good repeatability, and little effect on patients, which can avoid sampling errors and interpretation errors of imaging examinations; however, its evaluation effect is not clear yet.

Cheung et al. [11] demonstrated that glutamic-oxaloacetic transaminase/glutamic-pyruvic transaminase and AAR index > 1 generally indicate the occurrence of cirrhosis. Iwata et al. [12] reported that AAR is associated with the severity of oesophageal varices. In this study, there was no significant difference in the AAR index between cirrhosis without oesophageal varices and cirrhosis combined with oesophageal varices. In the prediction of severe oesophageal varices, the AUC value of AAR was the lowest of the four scores. Hence, we demonstrate that the AAR index harboured limited predictive value for oesophageal varices.

The APRI index and FIB-4 are two classic scores and harbour good diagnostic efficiency for cirrhosis [13–15]. In this study, the AUC value of APRI for oesophageal varices and severe oesophageal varices was higher than those of the other three indexes. Notably, the AUC in the prediction of severe oesophageal varices was > 0.7 (AUC = 0.729) and the negative predictive value (NPV) was 0.963. In severe oesophageal varices, an APRI value < 1.4 was only detected in two patients, accounting for 6% of the severe oesophageal varices. Therefore, APRI > 1.4 can be used as a reference indicator for the early intervention of severe oesophageal varices. Although the FIB-4 index was found to be an independent predictor of oesophageal varices in an unconditional logistic regression analysis, the AUC value was less than 0.7; hence, FIB-4 failed to harbour a clinical diagnostic value.

The S index was proposed by Chinese scholars. In this study, the AUC value of the S index was higher than that of the FIB-4 index. However, the S index was not detected as an independent predictor of oesophageal varices by the unconditional logistic regression analysis (all $P > 0.01$). The calculation formula was 1 000×GGT/(PLT×albumin^2). Of the albumin, GGT, and PLT established by this model, PLT and albumin have been confirmed to be associated with the severity of cirrhosis [6, 16]. GGT mainly originated from liver and is generated by the mitochondria of hepatocytes, confined to the cytoplasm and intrahepatic bile duct epithelium. However, GGT levels can be significantly elevated in the cases of fatty liver, alcoholic liver disease, and biliary system diseases [17, 18]. In this study, patients with alcoholic liver disease and autoimmune liver disease were included, which may have a certain impact on the experimental results. Additionally, ALT and AST are associated with the degree of liver damage. Intriguingly, GGT was replaced with ALT and AST in the formula of 1000×ALT/(PLT×albumin^2) and 1000×AST/(PLT×albumin^2), which revealed that the AUC value of predicting oesophageal varices was 0.681 and 0.663, respectively, and that the AUC value of predicting severe oesophageal varices was 0.718 and 0.701, respectively. All the AUC values were greater than 0.7. However, it was not considered as an independent risk factor for oesophageal varices by further unconditional logistic regression analysis. Therefore, whether the formula can be applied to the diagnosis and evaluation of the degree of fibrosis and hepatic lesions remains unknown.

Thus, in the four scoring systems, the AAR score harboured a poor diagnostic efficiency for oesophageal varices, while APRI scores have clinical value for the prediction of severe oesophageal varices. APRI>1.4 may be used as a reference index for early intervention in severe oesophageal varices. The S index cannot effectively predict the degree of oesophageal varices, which is possibly affected by the aetiology of cirrhosis. However, we demonstrated that the modified formula after replacing AST and ALT with GGT can be used as a potential predictive formula to assess the degree of cirrhosis progression.

Data Availability

The datasets used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Research Article

Portal Hypertensive Polyposis in Advanced Liver Cirrhosis: The Unknown Entity?

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Background. Portal hypertension is a serious complication of liver cirrhosis. *Objective*. To identify relevant endoscopic findings in patients with advanced cirrhosis and consecutive portal hypertension. *Methods*. This was a retrospective study of liver transplant candidates who underwent upper gastrointestinal endoscopy between April 2011 and November 2015. *Results*. A total of 1,045 upper endoscopies were analyzed. Portal hypertensive gastric and duodenal polyps were frequently observed and were associated with thrombocytopenia ($p = 0.040$; OR: 2.4, 95% CI 1.04–5.50), Child-Pugh score > 6 ($p = 0.033$; OR: 2.3, 95% CI 1.07–4.92), Model for End Stage Liver Disease score > 16 ($p = 0.030$; OR: 4.1, 95% CI 1.14–15.00), and previous rubber band ligation ($p < 0.001$; OR = 5.2, 95% CI 2.5–10.7). These polyps often recurred after polypectomy; however, no malignant transformation occurred during the observational time until October 2017. The most common endoscopic finding was esophageal varices, observed in more than 90% of patients. *Conclusion*. Portal hypertensive polyposis is common in patients with advanced cirrhosis. Our data suggest that these polyps have benign characteristics.

1. Introduction

Portal hypertension is a common consequence and major complication of cirrhosis [1]. Portal hypertension is defined by an elevated portal pressure gradient caused by increased resistance to portal blood flow due to architectural changes in the cirrhotic liver, contraction of intrahepatic components as a result of decreased intrahepatic nitric oxide production, and increased splanchnic blood flow [1, 2]. Portal hypertension is a syndrome that involves several organ systems, leading to the formation of portosystemic collaterals, esophageal and gastric varices, gastropathy, enteropathy, colopathy, and splenomegaly with consecutive blood abnormalities including thrombocytopenia caused by hypersplenism [1].

In cirrhotic patients, endoscopy not only is used to detect esophageal varices but can also detect further gastrointestinal complications of portal hypertension such as portal hypertensive gastropathy or gastric varices. There have also been a few recent reports of polyposis related to portal hypertension [3–15]. The clinical relevance of this so-called portal hypertensive polyposis (PHP) remains unclear.

The present study was performed at a tertiary center and aimed to identify pathological findings during upper gastrointestinal endoscopy in patients with advanced cirrhosis who were under consideration for liver transplantation (LT) or who were already on the waiting list for LT in general and to explore the clinical characteristics of PHP in these patients.

2. Patients and Methods

This was an investigator-initiated, single center, retrospective analysis. All patients with cirrhosis who were under the care of the Department for Transplant Medicine at the University Hospital of Muenster and who underwent upper gastrointestinal endoscopy between April 2011 and November 2015 were considered for inclusion in this study. Inclusion criteria

Table 1: Demographic data and clinical and laboratory characteristics.

	n = 407
Age [years], median (range)	60 (21–88)
Females/males, n (%)	127 (31.2%)/280 (68.8%)
Ethanol (active or past substantial consumption)	111 (27.3%)
Hepatitis C	77 (18.9%)
Non-alcoholic fatty liver disease	63 (15.4%)
Cryptogenic	40 (9.8%)
Hepatitis B	23 (5.7%)
Primary sclerosing cholangitis	21 (5.2%)
Autoimmune hepatitis	15 (3.7%)
Hemochromatosis	9 (2.2%)
Wilson's disease	7 (1.7%)
Primary biliary cirrhosis	5 (1.2%)
Miscellaneous	36 (8.8%)
Splenomegaly	328 (82.8%)
Ascites	228 (56.4%)
Encephalopathy	118 (29.0%)
I–II	103 (25.3% of all patients)
III–IV	15 (3.7% of all patients)
Thrombocyte count	101 (18–630) thousand/μl
International normalized ratio	1.3 (0.86–4.80)
Creatinine	1 (0.10–16.60) mg/dL
Albumin	3.3 (0.20–4.80) g/dL
Bilirubin	3.9 (0.2–40.1) mg/dL
Child-Pugh score	
≤ 6	142 (34.9%)
> 6	265 (65.1%)
Child-Pugh class	
A	142 (34.9%)
B	158 (38.8%)
C	107 (26.3%)
Model for End Stage Liver Disease score, mean ± SD/ median (range)	15.2 ± 7.3/ 13 (6–40)
Portal vein thrombosis	35 (8.6%)
Hepatocellular carcinoma	78 (19.2%)
Beta-blocker	299 (73.5%)
Proton-pump inhibitor	378 (92.9%)

were the presence of liver cirrhosis, patient age 18 years or above, and available patient data. Patients' clinical and demographic data were collected from electronic healthcare files. All patients were regularly followed up at our outpatient clinic until October 2017. This study was approved by the Ethics Committee of the University Hospital of Muenster on April 28, 2016, and was carried out in accordance with the standards in the Declaration of Helsinki. Written informed consent was given by all patients prior to intervention.

2.1. Statistical Analysis. Statistical analysis was performed using IBM SPSS® Statistics 24 for Windows (IBM Corporation, Somers, NY, USA). Data are presented in both absolute and relative frequencies. Continuous variables with normal distribution are expressed as the mean ± standard deviation, whereas variables that do not follow normal distribution are shown as the median and maximal range.

Stepwise variable selection using univariable binary logistic regression analysis was performed to explore potential single risk factors for endoscopic findings. All variables that reached a significance level of $p \leq 0.1$ were included in the multivariable binary logistic regression analysis to identify independent risk factors for the endoscopic finding being investigated.

3. Results

3.1. Study Population and Clinical Data. A total of 1,045 upper endoscopies performed in 407 cirrhotic patients were eligible for statistical analysis. The demographic data and clinical and laboratory characteristics of these patients are summarized in Table 1. Most of the patients were male. Mean patient age was 59 ± 11.2 years. The most common Child-Pugh category was B, followed by A and then C.

Table 2: Endoscopic findings.

Gastroscopy	n = 407
Esophageal varices	373 (91.6%)
Grade I	145 (38.9%)
Grade II	137 (36.7%)
Grade III	91 (24.4%)
Barrett's esophagus	28 (6,9%)
Gastric varices	40 (9.8%)
Portal hypertensive gastropathy	373 (91.6%)
Gastric polyps	38 (9.5%)
Histopathology of endoscopically obtained biopsies (n = 36)	
Hyperplastic	29 (80.6%)
Foveolar hyperplasia	3 (8.3%)
Tubular adenoma	1 (2.8%)
Inflammatory	3 (8.3%)
Helicobacter pylori	23 (10.5%) (n = 219)*
Duodenal polyps	32 (7.9%)
Histopathology of endoscopically obtained biopsies (n = 22)	
Hyperplastic	10 (45.5%)
Tubular adenoma	2 (9.1%)
Inflammatory	1 (4.5%)
Brunner glands	4 (18.2%)
Lipoma	2 (9.1%)
Endocrine tumor	2 (9.1%)
LGIEN	1 (4.5%)
Colonoscopy	n = 363
Colon polyps	135 (37.2%)
Histopathology of endoscopically obtained biopsies (n = 113)	
Hyperplastic	34 (30.1%)
Hyperplastic and LGIEN	16 (14.2%)
LGIEN	55 (48.7%)
Sessile adenoma	2 (1.8%)
Adenocarcinoma	4 (3.5%)
Leiomyoma	2 (1.8%)

*Only tested in 219 patients.
LGIEN = low grade intraepithelial neoplasia.

3.2. Endoscopic Findings. The endoscopic findings are summarized in Table 2. Esophageal varices were present in most patients. Grade I and II varices were present in 35.6% and 33.6% of cases, respectively, while grade III varices were found in 22.4% of patients. Gastric varices were found in approximately 10% of patients. Portal hypertensive gastropathy was as prevalent as esophageal varices and was observed in about 90% of patients. *Helicobacter pylori* was detected in 23 of the 219 patients (11%) in whom a biopsy was performed. Gastric polyps were present in about 10% of patients; these polyps mainly had the histologic characteristics of hyperplastic polyps, with foveolar hyperplasia and markedly proliferating, ectatic capillaries in the lamina propria. These portal hypertensive polyps were the most commonly found gastric polyps on biopsy and comprised more than 80% of all detected polyps. Adenomas were very rare (2.8%). Duodenal polyps were present in 8% of patients; these were also mostly hyperplastic. However, hyperplastic polyps were less frequent in the duodenum than in the stomach. Tubular adenoma and endocrine tumors were seen in two patients, with one patient showing a low-grade intraepithelial neoplasia.

An additional colonoscopy was performed in 363 of the 407 included patients. A total of 135 patients (37.2%) had evident colon polyps, of which 113 polyps were endoscopically removed. Of these 113 removed colon polyps, 71 (62.8%) were adenoma with low-grade intraepithelial neoplasia, 34 (30.1%) were hyperplastic, two (1.8%) were sessile adenoma, four (3.5%) were adenocarcinoma, and two (1.8%) were leiomyoma (Table 2).

3.3. Portal Hypertensive Gastric Polyposis. More than one polypoid lesion was present in the stomach in 79% of PHP cases. A total of 19 polypectomies were performed in 16 patients. There was no bleeding or perforation observed in

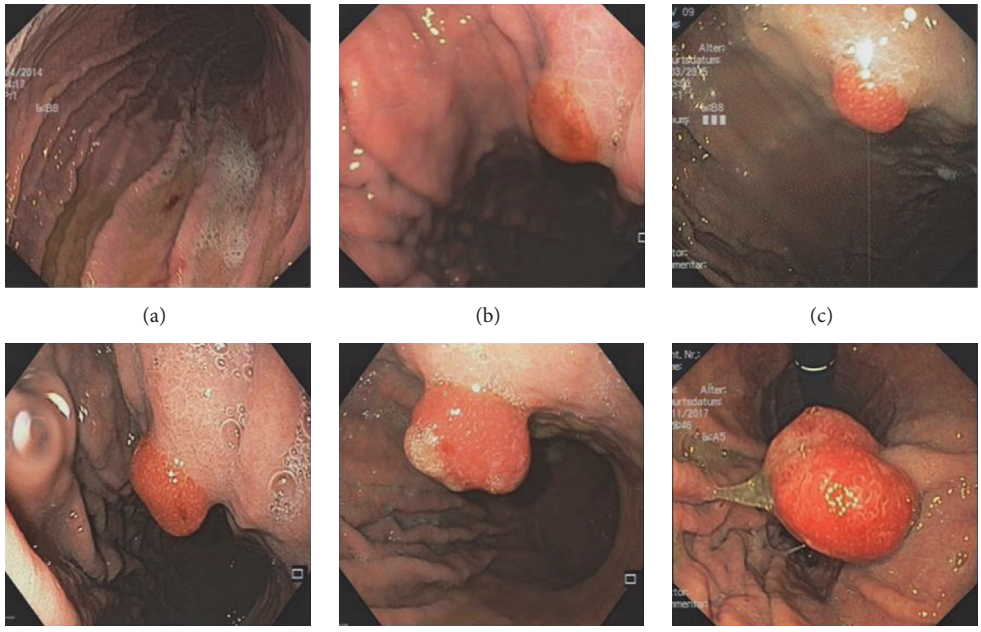


Figure 1: Chronological evolution of a portal hypertensive polyp in one patient after rubber band ligation of esophageal varices between 2014 and 2017 (a-f).

any of the cases. Of the resected portal hypertensive polyps, 15 polyps (79%) recurred after polypectomy and were detectable in subsequent endoscopies. Notably, 55% of hyperplastic polyps with typical signs of PHP first arose or progressed following rubber band ligation (Figure 1).

During a mean follow-up of 44.6 ± 14.7 months, none of the polyps degenerated into malignant carcinoma. No episodes of spontaneous bleeding related to portal hypertensive polyps were observed during the time of the study. All polyps were localized in the distal part of the stomach (antrum and prepyloric region). Using multivariable binary regression analysis, thrombocytopenia (defined as platelet count $< 130 \times 10^3/\mu l$) was shown to be an independent risk factor of PHP (p = 0.040; OR = 2.4, 95% CI 1.04–5.50). The other independent predictors of the occurrence of PHP were Child-Pugh score > 6 (p = 0.033; OR = 2.3, 95% CI 1.07–4.92), MELD score > 16 (p = 0.030; OR = 4.1, 95% CI 1.14–15.00), and previous rubber band ligation (p < 0.001; OR = 5.2, 95% CI 2.5–10.7) (Figures 2 and 3).

In multivariable analysis, male sex (p = 0.01; OR 1.9, 95% CI 1.2-3.2), evidence of duodenal polyps (p = 0.02; OR 2.5, 95% CI 1.4-5.3), and HCC (p = 0.04; OR 1.8, 95% CI 1.0-3.1) were found to be significantly associated with colonic polyps.

Statistical analysis showed no association between proton-pump inhibitors and PHP (p = 0.680; OR = 0.946). However, it should be pointed out that the majority of patients received PPI. Therefore, the analysis regarding the role of PPIs may be limited by this fact.

Binary regression analysis showed no association between beta-blockers and PHP (p = 0.460; OR = 0.968)

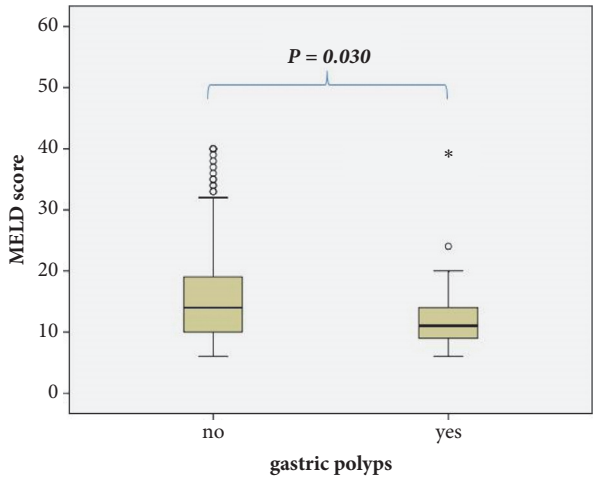


Figure 2: Distribution of gastric polyps with regard to MELD score. Higher MELD score was associated with the presence of hypertensive polyposis of the stomach, suggesting a higher prevalence of gastric polyps in advanced cirrhosis. MELD: Model for End Stage Liver Disease.

4. Discussion

To the best of our knowledge, the present study is the largest study investigating upper gastrointestinal endoscopy findings in LT candidates with advanced cirrhosis. The present study identified a very high prevalence (> 90%) of esophageal varices and portal hypertensive gastropathy. Previous studies have estimated the prevalence of esophageal varices at the

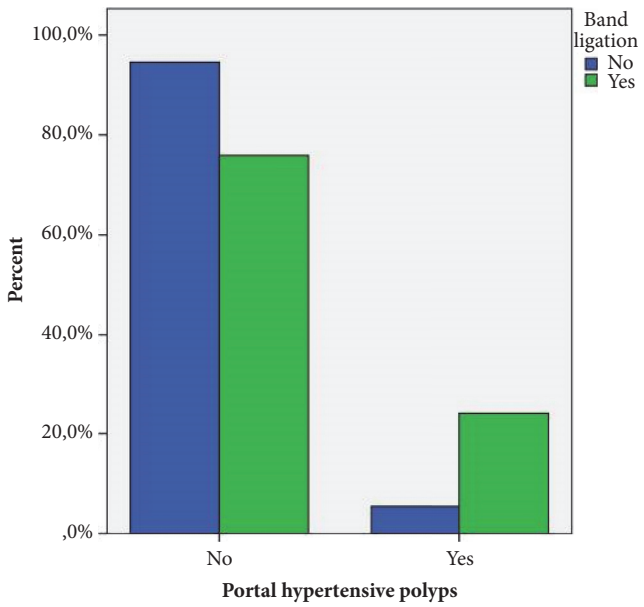


Figure 3: Bar chart showing the distribution of portal hypertensive polyposis with regard to rubber band ligation.

time of diagnosis of liver cirrhosis as about 35% in patients with compensated cirrhosis and 60% in patients with decompensated cirrhosis [1], while portal hypertensive gastropathy is reportedly seen in 11–80% of cirrhotic patients [1, 16–18]. Our patients underwent endoscopy at the time of referral to a tertiary center, which probably explains the greater frequencies of varices and portal hypertensive gastropathy. One study on LT candidates undergoing screening endoscopy reported incidences of varices and portal hypertensive gastropathy of 73% and 62%, respectively [17]. The higher prevalence of these findings in our study may be explained by the presence of more advanced disease in our cohort (Child-class C in 26% in our study versus 17% in the study by Zaman et al. [17]). The prevalence of both portal hypertensive gastropathy and variceal progression is strongly correlated with the increasing severity of cirrhosis [1, 17, 18]. The higher prevalence of these complications in our study may also partly be explained by the extensive experience of our endoscopists in endoscopic examination of patients with cirrhosis, as our center is highly specialized in this field, allowing the detection of early endoscopic alterations. The detection of grade I varices in nearly 40% of cases may be consistent with this assumption.

In our study, splenomegaly (83%) and ascites (56%) were also highly prevalent findings. This is consistent with another study on LT candidates [19].

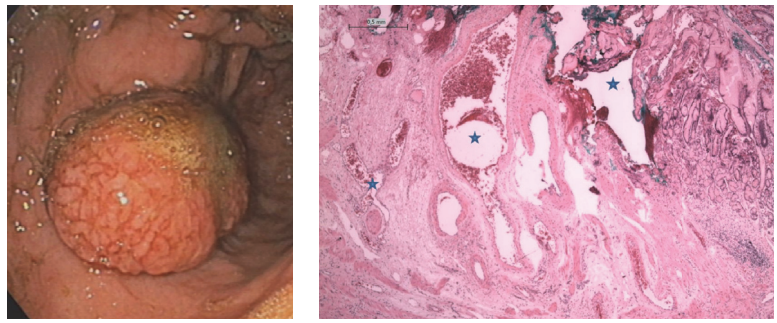
4.1. Portal Hypertensive Polyposis. Apart from the expected cirrhosis-related pathologies such as esophagogastric varices and portal hypertensive gastropathy, there was a noticeable high prevalence of gastroduodenal polyposis observed in our patients. The prevalence of gastroduodenal polyps in the general population reportedly ranges from 0.5% to 6.35% [3, 4]. In contrast, gastroduodenal polyps were far more frequent in our study; almost 10% of patients had gastric polyps, and 8% had duodenal polyps.

Gastric and duodenal hypertension has been associated with the presence of portal hypertensive polyps, but this has mostly been reported in case reports and a few small case series [5–10, 12–15]. In our study, we comprehensively evaluated the clinical appearance of PHP. These polyps are typically localized in the stomach; however, they can be found all through the intestine [8, 11, 14]. Macroscopically, portal hypertensive polyps cannot be distinguished from normal hyperplastic polyps but frequently present with small ulcerations [7, 9]. Even histologically, there are similarities between hyperplastic and portal hypertensive polyps [6]. There are still no clear diagnostic criteria for portal hypertensive polyps [11]. However, typical features of portal hypertensive polyps reportedly include foveolar hyperplasia of the epithelium as well as proliferating, ectatic capillaries in the lamina propria; this indicates their portal hypertensive nature and distinguishes them from inflammatory polyps (Figure 4) [3, 7, 8, 11, 14].

In our cohort, polyps were pathologically classified as "hyperplastic" in the majority of cases, even though they showed the abovementioned histological criteria of portal hypertensive polyps. One notable characteristic of these polyps in our study was that they almost always occurred in multiples. Other studies including cirrhotic patients have reported a PHP frequency of 0.9–1.3% [6, 8, 11]. As portal hypertensive polyps are still relatively unknown by both endoscopists and pathologists, they may be considerably underdiagnosed. The pathogenic mechanism of PHP remains unknown, but increased congestion caused by increased portal pressure may play an important role in inducing proliferation and angiogenesis. Some observations suggest that these polyps may respond to the treatment of portal hypertension [8–10]. Therefore, the presence of these portal hypertensive polyps may have been particularly high in the present study due to the advanced stage of cirrhosis in our cohort. Accordingly, the independent risk factors for PHP were identified as thrombocytopenia (platelet count $< 130 \times 10^3/\mu$l), Child-Pugh score > 6, and MELD score > 16. Of note, the strongest risk factor for the development of these polyps was previous rubber band ligation. This may be because band ligation of the esophageal varices leads to increased formation of portosystemic shunts, including the gastric wall. This hypothesis is also consistent with the histological finding of proliferating ectatic vessels in the gastric mucosa and strongly supports our hypothesis of an evident proliferation stimulus of the increased portal blood flow on the gastric mucosa.

PHP is still poorly understood, and little is known about the risks and benefits of endoscopic resection. Although endoscopic resection was performed in all cases without complications in our study, the necessity of polypectomy should be critically considered, as portal hypertensive polyps frequently recurred and not one malignant transformation was observed during follow-up of 44.6 ± 14.7 months.

In our study, the incidence of colon polyps and the frequency of adenoma within these polyps were similar to those reported in another cohort of LT candidates (37% versus 42% for colon polyps and 54.1% versus 53.6% for adenoma within colon polyps) [20]. In contrast to the polyps



(a) (b)

Figure 4: Images of hypertensive polyps. (a) Macroscopic aspect of a portal hypertensive antral polyp. (b) Histological image of a hypertensive gastric polyp showing proliferating ectatic vessels (starlets).

found in the upper gastrointestinal tract, adenomas are the most common detected entity of colon polyps. As this entity represents a preliminary stage of adenocarcinoma, colon polyps should always be resected and studied histopathologically to assess their potential for malignant transformation. Subsequent endoscopic surveillance of colonic polyps depends on number, size, and histopathology of polyps, as well as the prevalence of hereditary conditions [21]. The Paris classification of gastrointestinal lesions can be used to classify colon lesions into polypoid, nonpolypoid, and depressed or excavated, where the latter is more likely to show high-grade dysplasia or malignancy (the Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon).

Some data indicate a positive association between higher levels of sex hormones in men and the development of colorectal carcinoma, while estradiol seems to have protective effects [22]. Given the adenoma-carcinoma-sequence, these findings may give an explanation for the higher rate of colon polyps in men in our patient cohort.

The higher prevalence of colon neoplasia in patients with the evidence of incidental duodenal polyps emphasizes the recommendation for colonoscopy in patients with sporadic duodenal neoplasia that has been stated in former studies [23, 24].

One interesting finding of our study was the positive association between HCC and the prevalence of colon polyps. This fact may be explained by the results of several studies indicating a higher rate of colorectal polyps in patients with liver cirrhosis, while liver cirrhosis is also the main risk factor of HCC [20, 25].

5. Conclusions

PHP is a common finding in patients with advanced liver cirrhosis, which until now may have been underestimated by both endoscopists and pathologists. These PHP lesions are typically localized in the antrum of the stomach, are mostly multiple, and show typical microscopic findings. Portal hypertension seems to play a crucial role in the pathogenesis of PHP, as these lesions are mostly seen in advanced cirrhosis, frequently after rubber ligation of preexistent esophageal varices. There is currently no evidence of these polyps having malignant potential. In our opinion and based on these findings, both polypectomy and endoscopic surveillance are dispensable in case of PHP.

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Authors' Contributions

Miriam Maschmeier and Iyad Kabar contributed equally to this work.

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Clinical Study

Pathological Features of Mitochondrial Ultrastructure Predict Susceptibility to Post-TIPS Hepatic Encephalopathy

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Background. Post-TIPS hepatic encephalopathy (PSE) is a complex process involving numerous risk factors; the root cause is unclear, but an elevation of blood ammonia due to portosystemic shunt and metabolic disorders in hepatocytes has been proposed as an important risk factor. *Aims.* The aim of this study was to investigate the impact of pathological features of mitochondrial ultrastructure on PSE via transjugular liver biopsy at TIPS implantation. *Methods*. We evaluated the pathological damage of mitochondrial ultrastructure on recruited patients by the Flameng classification system. A score ≤2 (no or low damage) was defined as group A, and a score >2 (high damage level) was defined as group B; routine follow-up was required at 1 and 2 years; the incidence of PSE and multiple clinical data were recorded. *Results.* A total of 78 cases in group A and 42 in group B completed the study. The incidence of PSE after 1 and 2 years in group B (35.7% and 45.2%, respectively) was significantly higher than that in group A (16.7% and 24.4%, respectively); the 1- and 2-year OR (95% CI) were 2.778 (1.166-6.615) and 2.565 (1.155-5.696), respectively, for groups A and B. Importantly, group B had worse incidence of PSE than group A [P=0.014, hazard ratio (95%CI): 2.172 (1.190-4.678)]. *Conclusion*. Aggressive damage to mitochondrial ultrastructure in liver shunt predicts susceptibility to PSE. The registration number is NCT02540382.

1. Introduction

Transjugular intrahepatic portosystemic shunt (TIPS) is an effective and safe approach for treating esophageal gastric varices bleeding, refractory ascites, and other related complications mainly due to liver cirrhosis and portal vein hypertension. TIPS is currently widely used in clinical practice [1–3]. In addition, problems with the rate of shunt restenosis have decreased dramatically because of the use of covered stents [4–6]; however, another challenge still exists, which is a relatively high (15~48%) incidence of postoperative hepatic encephalopathy [1, 7, 8]. Post-TIPS hepatic encephalopathy (PSE) significantly reduces the curative rate of TIPS, quality of postoperative life, and overall survival of patients [3, 9]. Presently, PSE remains a major challenge in clinical practice.

PSE is a complex process that involves numerous factors interacting with one another, which may be related to patient age, stent diameter, preoperative liver function, preoperative and postoperative portal vein blood flow direction, pressure, sarcopenia, and the presence of preoperative hepatic encephalopathy [10–12]. Moreover, Silvia Nardelli et al. performed a prospective study that indicated sarcopenia as a risk factor independently associated with development of PSE, which may be related to the reduction of the capacity of ammonia removal[13]. Elevation of blood ammonia due to portosystemic shunt has been proposed as a risk factor, mainly because toxic ingredients in portal vein blood can openly access the systemic circulation directly after the shunt without being first detoxified by the liver, thus promoting the development of hepatic encephalopathy [14–16]. In fact, increased systemic blood ammonia partially enters the liver through the hepatic artery [17, 18]. In addition, hepatic hemodynamic changes after TIPS aggravate metabolic disorders [15, 19, 20]. Therefore, systemic blood ammonia at varying levels after TIPS may be related to the degree of blood ammonia metabolic disorders that occur in hepatic

cellular mitochondria. However, whether the occurrence of PSE results from ammonia metabolic disorders due to mitochondrial damage and whether the pathological features of mitochondrial ultrastructure can be used as a biomarker to assess mitochondrial function remain unknown [21–24]. In the current study, transjugular liver biopsy was obtained during positioning of the TIPS, and a transmission electron microscope was used to observe the pathological features of mitochondrial ultrastructure to fill in knowledge gaps. A semiquantitative scoring method was adopted to evaluate mitochondrial damage according to the Flameng classification system. The relationship between the pathological features of mitochondria ultrastructure and the incidence of PSE was explored in 150 patients recruited from January 2012 to December 2013.

2. Materials and Methods

2.1. Patient Selection. In total, 150 patients who underwent TIPS at Beijing Shijitan Hospital from January 2012 to December 2013 were recruited. The inclusion criteria were confirmed diagnosis of posthepatic cirrhosis portal hypertension; scheduled for elective TIPS; transjugular liver biopsy obtained during positioning of the TIPS successfully; and shunt channel with a diameter of 8 mm. The exclusion criteria were aged <18 or >70 years; combined with malignant liver tumor; liver tissue not conforming with the requirements (the size of liver tissue is $< 0.4\times0.4$ cm^2); and hepatic encephalopathy before TIPS.

2.2. Methods. Transjugular liver biopsy was obtained during positioning of the TIPS and a transmission electron microscope was adopted to identify the pathological features of mitochondrial ultrastructure; thus, patients were prospectively divided into subgroups according to the level of mitochondrial damage for follow-up observation.

2.2.1. TIPS and Obtaining Liver Tissue from Preshunt Channel. Local disinfection and anesthesia were performed at the selected piercing site, and then jugular vein puncture was conducted. A liver access set (RUPS-100; Cook, USA) was delivered into the hepatic vein or hepatic inferior vena cava, the left and right trunk of the portal vein or portal vein bifurcation were punctured, and the liver access set was then placed in the portal vein. A pigtail catheter was used for portography and measurement of portal venous pressure. The leading end of the ultra-smooth ultra-long hard guide wire was placed in the superior mesenteric vein or splenic vein. The sheath of the liver access set was withdrawn into the preshunt channel in the liver parenchyma, and biopsy forceps (Minimally Invasive Medical Technology Co., LTD, Nanjing, China) were inserted through the sheath to obtain liver tissue of the preshunt channel in the liver parenchyma (the size range of each obtained liver tissue sample ranged from 0.4×0.4 cm^2 to 0.8×0.8 cm^2, and recollection of tissue was required for samples of a smaller size) (Figure 1-A1). A balloon was introduced along the guide wire to dilate the shunt, and then a covered stent (Bard Fluency) with a diameter of 8 mm was implanted (Figures 1-A2 and 1-A3), followed by stent dilation (Figure 1-A4), measurement of portal venous pressure, and portography.

2.2.2. Postoperative Routine Observation and Treatment. All patients were asked to stay in bed for 24 hours after the operation; pressure dressing and sand bag pressing were applied to the piercing site area, and the vital signs of each patient were monitored in real time. Prophylactic antibiotics were employed. Subcutaneous injection of low molecular weight heparin (5000 IU, Bid) was performed from the second day after the operation and lasted for at least 5 days; then treatment was switched to an oral intake of warfarin for at least half a year (2.5-5.0 mg, Qd). The dose of warfarin was adjusted based on coagulation function every 15 days to ensure an INR between 2 and 3. Oral administration of branched chain amino acids (3 g, Tid) and lactulose (15-30 ml, Bid or Tid) was performed routinely to prevent hepatic encephalopathy. A liver protection strategy was also taken (bicyclol tablets, 25 mg, Tid).

2.2.3. Observing Pathological Features of Mitochondrial Ultrastructure on Transmission Electron Microscopy (TEM). Liver tissue obtained during TIPS was directly transferred into 3% glutaraldehyde, fixed with 1% osmium tetroxide, dehydrated in ethanol solution, infiltrated in a mixed solution of Epon-812 agar and acetone, embedded overnight, and then polymerized in pure Epon-812 agar. The polymerized blocks were stained by toluidine blue, embedded, and sectioned with LKB-V ultramicrotome successively. Subsequently, the pathological features of mitochondrial ultrastructure were observed in the samples, and photos were taken by transmission electron microscopy (TEM, HITACHIH-600). Five fields were randomly selected in the electron microscopy images of each specimen, and then at least 20 mitochondria were randomly selected in each field to obtain a semiquantitative score of mitochondria according to the Flameng classification system [25]. Mitochondria were graded with scores of 0-4 according to the degree of damage, with a higher score representing a higher degree of damage. The damage of each mitochondrion and the average score for all mitochondria were evaluated independently by at least two investigators to avoid bias (Figure 2).

2.2.4. Recording Multiple Preoperative and Intraoperative Clinical Characteristics of Patients. Preoperative baseline data included age, gender, CTP, MELD score, AST, ALT, and venous blood ammonia level. Intraoperative data included portal pressure gradient (PPG) before and after shunt and PPG reduction.

2.2.5. Cohort Formation. On the basis of semiquantitative scores, liver tissue obtained from the shunts was evaluated according to the Flameng classification system. Accordingly, patients were divided into 2 groups: a score ≤2 (no or low level of damage) was defined as group A, whereas a score >2 (higher level of damage) was defined as group B. All cases were followed up for up to 2 years.

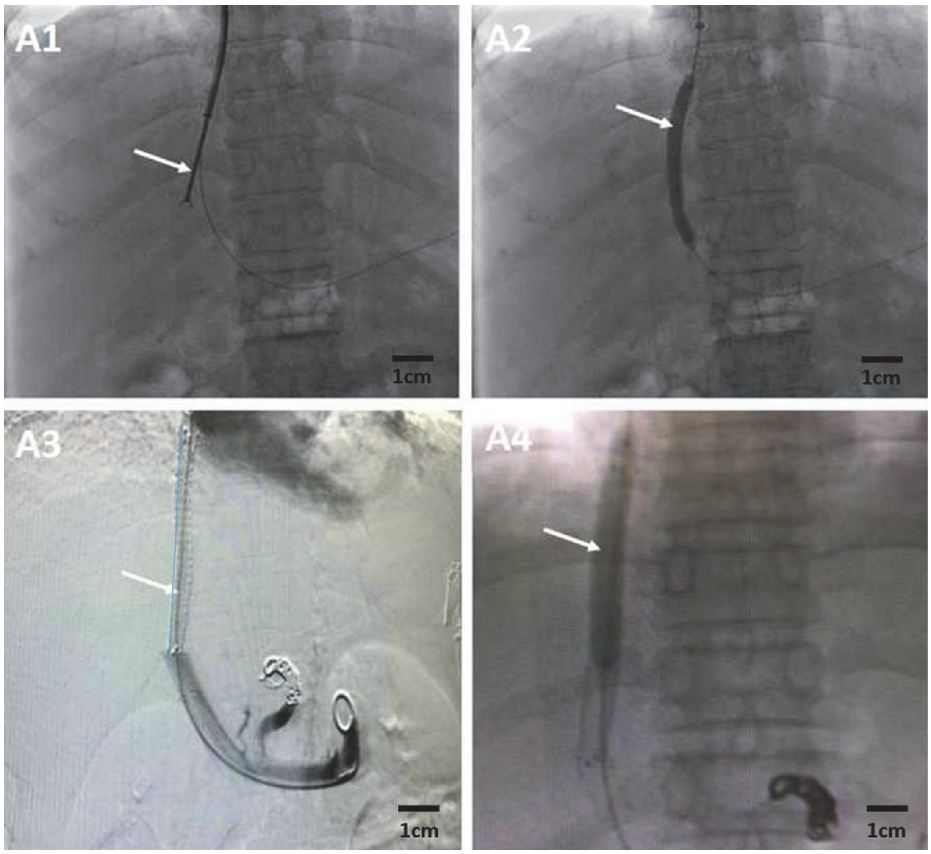

Figure 1: Procedure for obtaining liver tissue of preshunt channel. A1: A RUPS-100 liver access set was delivered into the portal vein. Liver tissue of the shunt was obtained before balloon dilation (white arrow). A2: Balloon dilation of the shunt (white arrow). A3: Stent was implanted among the inferior vena cava, hepatic vein, preshunt channel, and portal vein to establish a shunt (white arrow). A4: Balloon dilation of the stent (white arrow).

2.2.6. Follow-Up. Routine follow-up was required for all patients before discharge and at 3 months, 6 months, 12 months, 18 months, and 24 months after TIPS. Medical history, physical examination, laboratory tests (e.g., routine blood, liver and kidney function, blood coagulation, and venous blood ammonia), abdominal CT/MRI, portal venous ultrasound, and endoscopy were conducted at each time point. In particular, venous blood ammonia level and incidence of PSE were recorded. PSE was assessed and graded on admission by a single investigator and confirmed by a senior investigator using the West Haven Criteria for grading of mental status[26].

2.3. Statistical Analysis. Statistical analysis was conducted using SPSS software (version 22.0). Quantitative data were described as the mean ± standard deviation (SD) and compared by independent sample t-test. Qualitative data were compared by χ^2 test or Fisher's exact test. Pearson correlation analysis was used to correlate two continuous variables. Hepatic encephalopathy cumulative risk was estimated using a Kaplan-Meier plot, and Log-rank (Mantel-Cox) test was used to calculate the hazard ratio. A p value of <0.05 was considered statistically significant.

2.4. Ethical Requirements and Informed Consent. This study had been approved by the Institutional Review Board (IRB) Committee in Beijing Shijitan Hospital, Capital Medical University. Informed consent was acquired from each participant before the operation. All procedures were conducted according to the guidelines approved by the Ethics Committee in Beijing Shijitan Hospital, Capital Medical University.

3. Results

3.1. Patient Population. A total of 133 patients met the inclusion criteria and were recruited from January 2012 to December 2013; however, 13 patients were excluded because of failure to meet the criteria during the operation or follow-up. Finally, 120 patients (78 cases in group A and 42 cases in group B) completed the study (Figure 3). No procedure-related deaths or serious complications (e.g., abdominal bleeding, hepatic failure, or distant embolism) occurred. Clinical symptoms improved to varying degrees.

3.2. Perioperative Patient Information. Perioperative clinical characteristics of the two groups were compared. No significant differences were observed in age, gender, Child-Pugh

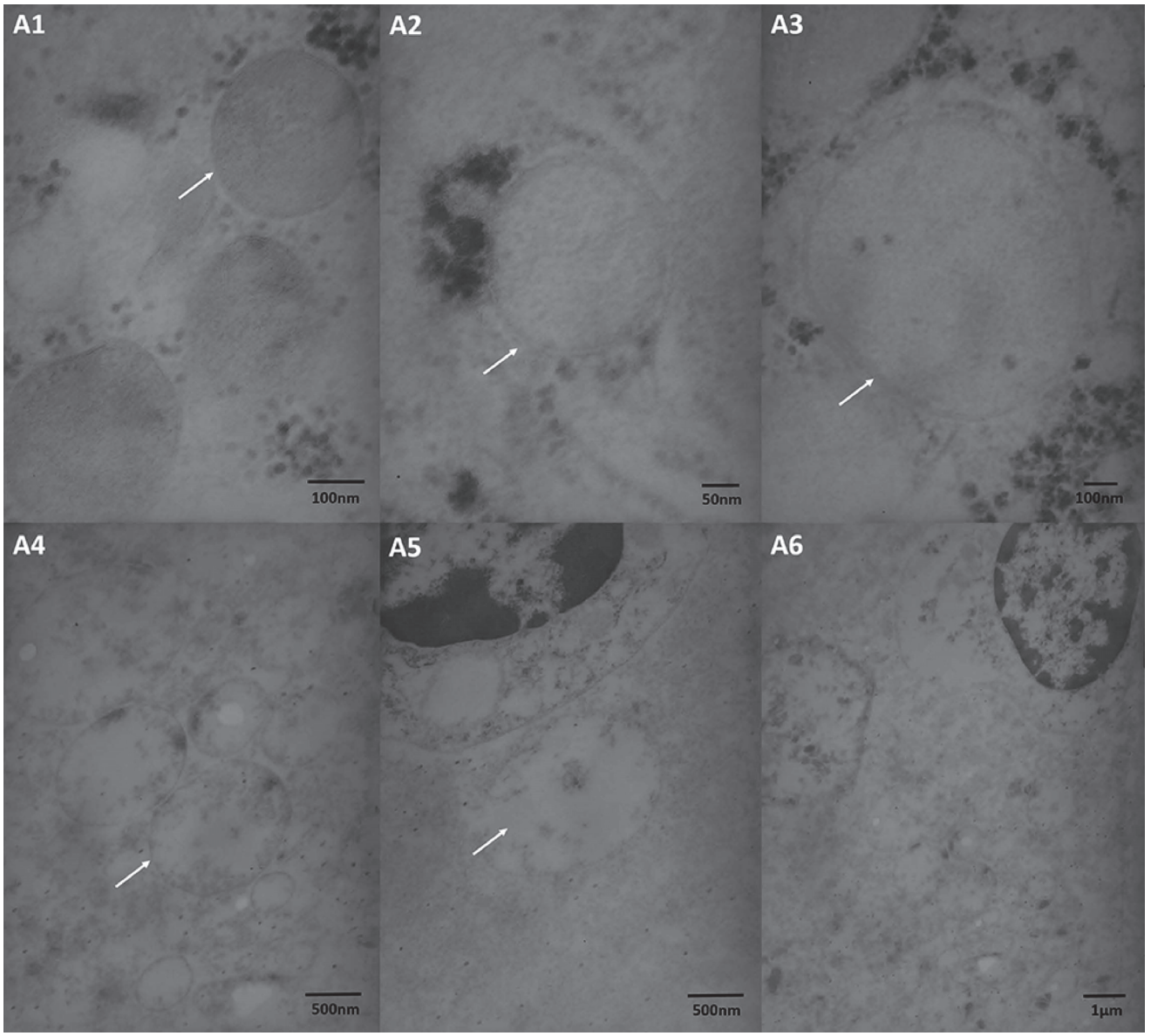

Figure 2: Mitochondrial ultrastructure at 5 different damage levels according to the Flameng classification system. A1: Level 0 (score 0) mitochondrial structure is normal and full of substrate particles (white arrow). A2: Level 1 (score 1) mitochondrial structure is essentially normal with a lack of substrate particles (white arrow). A3: Level 2 (score 2) mitochondria are markedly swollen with transparent substrate (white arrow). A4: Level 3 (score 3) mitochondrial crest is divided with transparent or thick substrate (white arrow). A5: Level 4 (score 4) mitochondria are vacuolated with divided crest, and substrate and membrane integrity have disappeared (white arrow). A6: microcellular ultrastructure vision obtained more mitochondrial structure.

stage, MELD score, AST, ALT, preoperative blood ammonia level, or PPG before or after shunt between the two groups (Table 1).

3.3. Relationship between Hepatic Encephalopathy and Mitochondrial Damage. The incidence of HE 1 year after TIPS was notably higher in group B (13/42, 35.7%) than in group A (15/78, 16.7%) with an OR (95% CI) of 2.778 (1.166-6.615). The incidence of HE 2 years after TIPS was significantly higher in group B (19/42, 45.2%) than in group A (19/78, 24.4%) with an OR (95% CI) of 2.565 (1.155-5.696) (Table 2), except for 1 case of group B for grade II, and the rest are grade I. In addition, univariate competing risk regression for time to PSE is reported in Table 3. At multivariate analysis, ammonia (HR 1.830, 95%CI 1.093-3.712, p=0.032) and mitochondrial damage level (HR 2.172, 95%CI 1.190-4.678, p=0.014) were independently associated with PSE development, which showed an induced risk of PSE in group B compared to that in group A (Figure 4).

3.4. Relationship between Postoperative Blood Ammonia Level and Mitochondrial Damage. For follow-up of up to 1 year

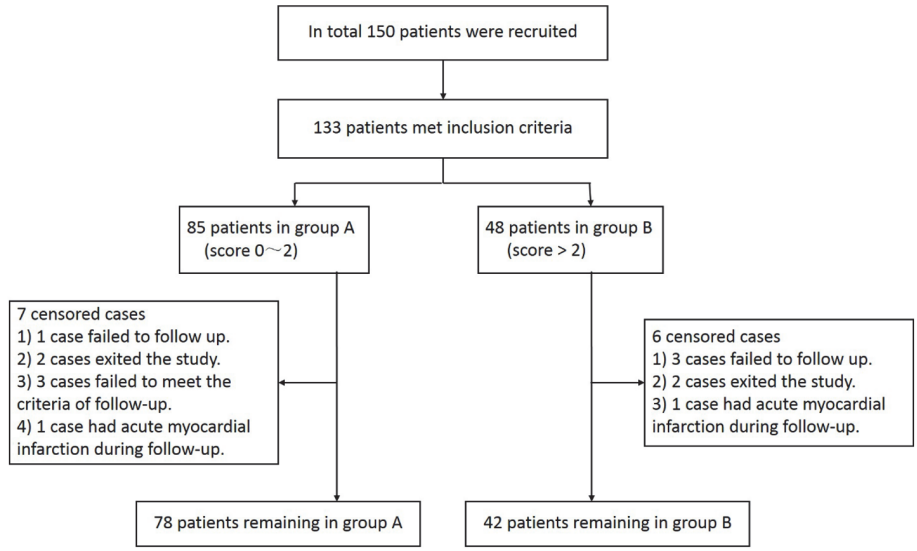

Figure 3: Flowchart of patient recruitment and selection.

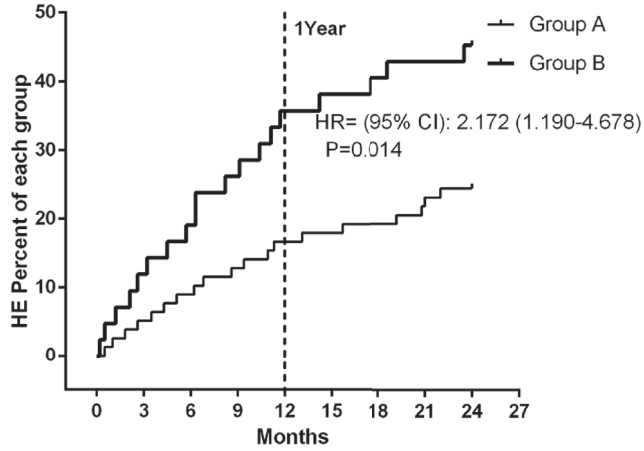

Figure 4: HE cumulative risk was estimated by Kaplan-Meier curves. Log-rank (Mantel-Cox) test was used to calculate the hazard ratio. Compared to group A, group B had a significantly increased risk of HE during the study ($p<0.05$).

(before discharge, 3 months, 6 months, and 12 months), the average venous blood ammonia level (μmol/L) in group A was significantly lower than that in group B (64.2±15.7 and 95.8±21.4, respectively). For follow-up of up to 2 years (before discharge, 3 months, 6 months, 12 months, 18 months, and 24 months), the average venous blood ammonia level (μmol/L) in group A was significantly lower than that in group B (53.4±16.5 and 83.3±18.9, respectively) (Table 4).

3.5. Relationship between Average Blood Ammonia Level and PSE. At 1-year follow-up, the average venous blood ammonia level of 28 patients with PSE was 110.8±18.7 μmol/L and that of 92 patients without PSE was significantly lower at 55.8±21.1 μmol/L ($P<0.005$). At 2-year follow-up, the average venous blood ammonia level of 38 patients with PSE was 99.4±20.9 μmol/L and that of 82 patients without PSE was significantly lower at 51.6±16.7 μmol/L ($P<0.013$) (Table 5), At multivariate analysis, ammonia (HR 1.830, 95%CI 1.093-3.712, p=0.032) was independently associated with PSE development.

3.6. Correlation between Average Ammonia Level and Flameng Classification Scores. Pearson correlation analysis demonstrated that the average postoperative venous blood ammonia level and mitochondrial Flameng classification scores were positively correlated. The correlation coefficients at 1 year and 2 years were r=0.574 (P=0.040) and r=0.531 (P=0.017), respectively.

4. Discussion

In cirrhosis, liver ischemia hypoxia, endotoxin, inflammatory reaction, and immune factors can cause mitochondrial or cytoplasmic damage [27–29]. Dysfunction of mitochondrial respiratory chain complex III causes damage to the electron

Table 1: Perioperative clinical characteristics of two groups.

Items	Group A	Group B	t/χ^2	P
Patient (n)	78	42		
Gender (M/F, n)	54/24	30/12	0.063	0.802
Age (mean ± SD, years)	54.2±8.18	52.9±9.13	0.775	0.440
CTP (n, %)			6.753	0.056
Stage A	39 (50.0)	25 (59.5)		
Stage B	24 (30.8)	13 (31.0)		
Stage C	15 (19.2)	4 (9.5)		
MELD score	7.04±3.21	8.23±4.83	1.250	0.214
ALT (U/L)	28.6±14.4	28.0±15.4	0.215	0.830
AST (U/L)	47.7±12.6	45.3±13.2	0.342	0.647
Ammonia (mean ± SD, μmol/L)	50.4±17.0	64.8±29.3	1.741	0.306
PPG (mean ± SD, mmHg)				
Before shunt	26.0±4.67	25.7±4.82	0.431	0.668
After shunt	15.1±4.31	15.2±4.10	0.030	0.976
PPG reduction (mean ± SD, mmHg)	10.9±2.60	10.5±2.51	0.841	0.402

ALT: alanine transaminase; AST: aspartate aminotransferase; CTP: Child-Pugh stage; MELD: model for end-stage liver disease; PPG: portal pressure gradient.

Table 2: Incidence of HE stratified by groups.

PSE incidence	Group A	Group B	OR (95% CI)	P
1-year (n, %)	13 (16.7)	15 (35.7)	2.778 (1.166-6.615)	0.019
2-year (n, %)	19 (24.4)	19 (45.2)	2.565 (1.155-5.696)	0.019

PSE: post-TIPS hepatic encephalopathy; OR: odds ratio.

transport chain, and then more reactive oxygen species (ROS) are generated as substrates. ROS induce mitochondrial lipid peroxidation reactions to produce malondialdehyde (MDA), which triggers mitochondrial membrane permeability transition by activating mitochondrial permeability transition pore (mPTP) and calcium dyshomeostasis and further undermines mitochondrial oxidative phosphorylation as a vicious circle [30–33], thus resulting in tricarboxylic acid cycle (TCA) disturbance. The urea cycle and TCA are correlated and interdependent. NH_3 entering liver cells requires the TCA to provide enough energy to activate and maintain a series of enzymatic reactions in mitochondria and the cytoplasm. Carbamoyl phosphate synthetase I (CPS-I) and ornithine carbamoyl transferase (OCT) are two of the most important enzymes in the urea cycle, and CPS-I is the rate-limiting enzyme. The levels of CPS-I and OCT can reflect mitochondrial enzymatic activity and urea cycle function in hepatocytes [34, 35]. The ability of mitochondria to transform blood ammonia can be weakened to varying degrees because of decreased levels of CPS-I when liver function is seriously damaged, leading to increased blood ammonia and hepatic encephalopathy [36, 37].

In addition, alterations in nutritional status are frequently associated with liver disease. Sarcopenia, a condition of loss of muscle mass, is associated with cirrhosis' complications, including HE. Nardelli S et al.[13] designed a study to investigate whether a decrease in muscle mass was independently associated with the occurrence of PSE. The results (sarcopenia HR, 31.3; 95% CI, 4.5–218.07; P<0.001) support the viewpoint that sarcopenia is risk factor for development of PSE; the rationale for this relationship derives from the possible involvement of muscle in ammonia metabolism and trafficking. This study suggests that sarcopenia should be considered in selecting the patients for TIPS therapy. Nutritional status should be evaluated in patients with sarcopenia before TIPS placement, which might reduce the incidence of PSE. Considering the results of this study, the indices of sarcopenia in the examined patients that should be incorporated into our study could be a possible bias of our work.

On the other hand, a prospective study [38] found that early decreasing ammonia obviously improved the survival rate and prognosis of patients with liver failure. It is speculated that decreasing the blood ammonia level effectively attenuates mitochondrial damage and promotes the functional recovery of hepatocellular detoxification, synthesis, and transformation. Meanwhile, elevated blood ammonia may cause a "secondary damage" to hepatocellular mitochondria as an alternative indicator. Yu et al. established a rat model with acute high blood ammonia attack and found that high blood ammonia aggravated liver failure through "secondary injury" [39, 40]. Presently, the underlying mechanism remains unclear. One possibility is that ammonia accumulated in hepatocytes is initially transported by regulating ammonia transport-related proteins AQP8 and RHCG in mitochondria, which impairs the structure and function of mitochondria via opening mPTP and the intrinsic apoptotic pathway, thus causing energy metabolic disorders and oxidative damage, which affect the urea cycle [41–43].

Table 3: Univariate competing risk regression for the relationship between clinical characteristics of the patients and time to PSE.

Items	PSE Present (n=38)	PSE Absent (n=82)	HR(95%CI)	*P*
Age (mean ± SD, years)	55.3±8.31	51.9±8.97	0.634(0.218-1.402)	NS
CTP Stage A/B/C (n.)	19/14/5	45/23/14	1.482(0.547-3.563)	NS
MELD score	8.07±3.96	7.36±4.13	0.744(0.156-1.215)	NS
Ammonia (mean ± SD, μmol/L)	51.6±16.7	99.4±20.9	1.997(1.163-3.563)	0.027
PPG reduction (mean ± SD, mmHg)	11.3±1.51	10.1±2.63	1.133(0.896-1.427)	NS
Mitochondrial damage(Group A/B)	19/19	23/59	2.561(1.615-3.873)	0.017

HR: hazard ratio.

Table 4: Postoperative average ammonia levels stratified by groups.

Index	Group A	Group B	*t*	*P*
1-year Ammonia (mean ± SD, μmol/L)	64.2±15.7	95.8±21.4	3.733	0.002
2-year Ammonia (mean ± SD, μmol/L)	53.4±16.5	83.3±18.9	3.279	0.003

Table 5: Average blood ammonia level and PSE.

PSE	Absent	Present	*t*	P^*
1-year Ammonia (mean ± SD, μmol/L)	110.8±18.7	55.8±21.1	3.216	0.005
2-year Ammonia (mean ± SD, μmol/L)	99.4±20.9	51.6±16.7	2.423	0.013

In our study, the incidence of PSE in group B was approximately doubled (2.14- and 1.85-fold at 1 and 2 years, respectively) compared to that in group A. As an independent risk factor, the average blood ammonia level of PSE cases was almost doubled compared to that of non-PSE cases at 1 year and 2 years. Our results support the viewpoint that elevated postoperative blood ammonia correlates with hepatic encephalopathy [44, 45].

Notably, postoperative average venous blood ammonia levels and mitochondrial Flameng classification scores were positively correlated at 1 year and 2 years. In addition, HE cumulative risk was significantly increased in group B, which had a higher level of mitochondrial damage. Our results indicate that mitochondrial damage predicts blood ammonia metabolic disorders and subsequently positively correlates with risks of PSE; elevated blood ammonia may serve as an important bridge.

5. Conclusion

In summary, the pathological features of mitochondrial ultrastructure in transjugular liver biopsy positively correlate with increased postoperative average blood ammonia and, more importantly, the development of PSE. Therefore, this approach could be important for helping evaluate the reserve of liver ammonia metabolism as demonstrated by mitochondrial damage, which is of great significance for forecasting and preventing HE. However, this preliminary research is limited to partial mitochondrial damage of liver shunt and funds; therefore, further in-depth investigations (such as studies including other metabolic derangement parameters, e.g., ROS, RCR, MAPR, and membrane potential) are required as is a larger sample size.

Abbreviations

ALT: Alanine transaminase
AST: Aspartate aminotransferase
CTP: Child-Pugh stage
CPS-I: Carbamoyl phosphate synthetase I
HR: Hazard ratio
MELD: Model for end-stage liver disease
MDA: Malondialdehyde
mPTP: Mitochondrial permeability transition pore
MAPR: Mitochondrial ATP production rate
OR: Odds ratio
OCT: Ornithine carbamoyl transferase
PSE: Post-TIPS hepatic encephalopathy
PPG: Portal pressure gradient
ROS: Reactive oxygen species
RCR: Respiratory control ratio
TIPS: Transjugular intrahepatic portosystemic shunt
TCA: Tricarboxylic acid cycle.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

Authors' Contributions

Fu-quan Liu and Xiao-qun Dong contributed to the study design and revisions. Hong-bin Li contributed to patient

management, data collection, and drafting of the manuscript. Zhen-dong Yue, Hong-wei Zhao, Lei Wang, and Zhen-hua Fan performed TIPS placement and biopsies. Fu-liang He contributed to patient management. All authors had access to study data and reviewed and approved the final manuscript.

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Review Article

Transient Elastography for Significant Liver Fibrosis and Cirrhosis in Chronic Hepatitis B: A Meta-Analysis

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Background. The hepatitis B virus infection is a global health issue and the stage of liver fibrosis affects the prognosis in patients with chronic hepatitis B (CHB). We performed the meta-analysis describing diagnostic accuracy of transient elastography (TE) for predicting CHB-related fibrosis. *Methods*. We performed an adequate literature search to identify studies that assessed the diagnostic accuracy of TE in CHB patients using biopsy as reference standard. Hierarchical summary receiver-operating curves model and the bivariate mixed-effects binary regression model were applied to generate summary receiver-operating characteristic curves and pooled estimates of sensitivity and specificity. *Results*. The area under the summary receiver-operating curve for significant fibrosis and cirrhosis was 0.86 (95% confidence interval (CI): 0.83–0.89) and 0.92 (95% CI: 0.90–0.94), respectively. The sensitivity, specificity, and diagnostic odds ratio of TE for significant fibrosis were 0.78 (95% CI: 0.73–0.81, $p < 0.01$; $I^2 = 85.59\%$), 0.81 (95% CI: 0.77–0.84, $p < 0.01$; $I^2 = 88.20\%$), and 14.44 (95% CI: 10.80–19.31, $p < 0.01$; $I^2 = 100\%$) and for cirrhosis were 0.84 (95% CI: 0.80–0.88, $p < 0.01$; $I^2 = 76.67\%$), 0.87 (95% CI: 0.84–0.90, $p < 0.01$; $I^2 = 90.89\%$), and 36.63 (95% CI: 25.38–52.87, $p < 0.01$; $I^2 = 100\%$), respectively. The optimal cut-off values of TE were 7.25 kPa for diagnosing significant fibrosis and 12.4 kPa for diagnosing cirrhosis, respectively. *Conclusion*. TE is of great value in the detection of patients with CHB-related cirrhosis but has a suboptimal accuracy in the detection of significant fibrosis.

1. Introduction

Chronic hepatitis B virus infection continues to be a major public health issue worldwide with the prevalence of 3.61% [1]. As well known, liver fibrosis, one of the main prognostic factors in chronic hepatitis B (CHB), was associated with the risk of developing cirrhosis and cirrhosis-related complications [2, 3]. Therefore, liver fibrosis stage plays one of the most important roles in diagnostic and prognostic assessments in patients with CHB.

Liver biopsy (LB), as invasive in nature with related risks, is the gold standard for fibrosis assessment. However, LB is associated with obvious patient discomfort and risk of complications ranging from pain to more serious events with hospitalization rate of 1.4–3.2% [4] and mortality varying from 0.0088 to 0.3% [5]. Besides, LB provides only a quite small part of the organ, and thus there is a risk that the small part might not be representative for the live fibrosis in the whole liver [6].

Noninvasive methods of assessing fibrosis and cirrhosis were urgently needed, and serologic tests and novel imaging techniques were recently developed [7, 8]. Most of these studied focused on whether noninvasive methods can accurately detect minimal (F0-1), significant (≥F2), or advanced (≥F3-4) fibrosis based on the METAVIR score [9]. Transient elastography (TE), also known as FibroScan, was

a device and a well-validated method with advantages of a short procedure time (<5 min), immediate results, and the ability to perform the test at the bedside or in an outpatient clinic [10]. Compared with blood tests, TE has a similar performance to predict significant fibrosis (SF) and higher accuracy to identify cirrhosis [11]. Measurement of liver fibrosis without biopsy is very tempting. In spite of the fact that recommendations suggested that noninvasive tests were still not ready to replace LB [12, 13], TE has become widely present in clinical practice. The accuracy of TE for detection of fibrosis has been assessed extensively in a variety of liver diseases [14–17]. However, it was reported that the presence of an IQR/M > 30% and liver stiffness median ≥7.1 kPa lead to a lower accuracy determined by the area under receiver-operating curve (AUROC) and these cases were considered "poorly reliable" [18]. Another study also indicated that there was a significant discrepancy in up to 20% of cases cirrhosis between different TE devices [19].

In the study, we performed an independent meta-analysis of the diagnostic accuracy of TE for predicting significant liver fibrosis (F2–4 versus F0-1) and cirrhosis (F4 versus F0–3) in CHB patients.

2. Methods

2.1. Literature Search Strategy. PubMed, Web of Science, and EMBASE database were searched to October 10, 2016, as well as Wanfang database and China National Knowledge Infrastructure. The search strategy was "FibroScan or transient elastography" in combination with "liver fibrosis assessment," "significant fibrosis or cirrhosis or advanced liver fibrosis," and "liver stiffness measurement." All eligible studies were retrieved and their reference lists were checked for additional relevant publications.

2.2. Inclusion Criteria. All diagnostic cross-sectional studies, cohort studies, and randomized studies that compared TE accuracy with biopsy in diagnosis fibrosis grade were eligible for inclusion. Studies that met all the following criteria were included: (i) studies which reported that all patients had undergone biopsy and TE; (ii) having enough data to create 2 × 2 table of test performance (with numbers of true and false positives and negatives); and (iii) studies which reported the method of definition of the fibrosis grade.

2.3. Exclusion Criteria. The exclusion criteria were as follows: (i) the patients belonging to the pediatric population, hepatitis C/hepatitis B virus coinfected patients, mixed chronic liver disease patients (but not CHB and nonalcoholic fatty liver disease), and liver/kidney transplant patients; (ii) studies that were clearly extensions of previously published cohorts; and (iii) studies unable to obtain sufficient data for statistical analysis.

2.4. Methodological Assessment. Methodological quality was assessed by the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool. QUADAS-2 was designed to assess the internal and external validity. Any differences between two authors were resolved with discussion between the two review authors and the third author was final arbiter.

2.5. Data Extraction and Management. As for each study, the following information was extracted: year of publication, study design, sample size, presence of HIV coinfection, the QUADAS-2 methodological items, prevalence of each fibrosis stage on biopsy, along with total prevalence of SF and cirrhosis, interval between biopsy and TE, size of biopsy sample, type of scoring system used for histology (METAVIR versus other), and AUROC. Two authors performed the data extraction independently. Disagreement was resolved with discussion between the two review authors, with a third author as final arbiter.

2.6. Statistical Analysis and Data Synthesis. Initial analysis was performed with the Review Manager (RevMan) 5.0. Stata 12.0 was used for meta-analysis of diagnostic accuracy studies, to compute the pooled sensitivity and specificity and to plot the summary receiver-operating characteristics curve (SROC) with summary point and corresponding 95% confidence interval (CI). Regression analysis was performed by Stata 12.0, with each time point providing another covariate to verify the influence of the chosen covariate on the accuracy estimates. We used hierarchical SROC model and the bivariate random efforts model to produce SROC and pooled estimates of sensitivity and specificity. We performed Fagan test to detect clinical significant by Stata 12.0. Heterogeneity was assessed with the inconsistency index (I^2) and I^2 values over 50% indicated substantial heterogeneity. Heterogeneity from threshold effect was explored by meta-disc 1.4.

3. Results

3.1. Search Results. 1238 articles were obtained and 188 were excluded for duplicates. 882 were excluded based on title and abstracts, and full-text copies of 106 studies were obtained and assessed for eligibility. Furthermore, 62 were excluded for inappropriate methodology, duplicate sample, pediatric population, or inability to obtain data for at least 2 × 2 table. Finally, a total of 44 articles comprising 45 studies were enrolled in the meta-analysis (Figure 1).

3.2. Characteristics of Included Studies. The overall prevalence of SF (F2–4) and cirrhosis (F4) ranged from 14.8% to 92.3% and from 1.1% to 69.2%, respectively. Reported AUROCs for SF diagnosis ranged from 0.614 to 0.98 (Table 1).

As shown in Table 1, only Miailhes et al. ($N = 59$) reported HIV coinfected patients [20]. In sixteen studies ($N = 2664$), LB was assessed with a histological score other than METAVIR [21–36]. In eight studies ($N = 1109$), mean length of biopsy sample was ≥20 mm [22, 34, 37–42]. Besides, in nineteen studies ($N = 1358$), data on time interval between biopsy and TE were not obtained [11, 21, 23, 25, 27, 28, 32–34, 39, 40, 42–47]. Three studies did not report cirrhosis (F4) [24, 35, 48]. Only four studies were retrospective [31, 48–50].

As presented in Figure 2, the results of methodological quality assessment based on the QUADAS-2 scale were depicted for all of the 44 eligible studies. The majority of the methodological concern lies within the index test, because TE in ten studies interpreted with knowledge of the results of the biopsy [24, 29, 33, 39, 46, 48, 51–54] and TE in one study

Table 1: Characteristics of the included studies.

Author	Study type	Year	HIV/HBV	METAVIR	Biopsy size	Biopsy to TE time (days)	Sample	Prevalence F2–F4	Prevalence F4	TE cut-off	AUROC
Cao et al.	Prospective	2014	NO	YES	>=15 mm and >=6 portal tracts	NA	162	0.61	0.12	7.3/17.5	NA/NA
Cardoso et al.	Retrospective	2011	NO	YES	>=15 mm and/or >=6 portal tracts	1	202	0.421	0.079	7.2/11	0.867/0.935
Castéra et al.	Prospective	2010	NO	YES	>=16 mm	NA	60	0.73	0.25	7.1/9.6	0.76/0.89
Chan et al.	Prospective	2009	NO	YES	>=15 mm and >=6 portal tracts	28	136	NA	0.25	NA/9	NA/0.93
Chen et al.	Retrospective	2011	NO	YES	>=15 mm	7	213	0.479	0.15	7.0/13.0	0.916/0.971
Chen et al.	Prospective	2012	NO	YES	>=15 mm and >=10 portal tracts	7	315	0.771	0.235	NA/10.4	NA/0.88
Cheng et al.	Prospective	2015	NO	YES	>=10 mm and >=8 portal tracts	1	459	0.61	0.152	7.2/18.2	0.82/0.87
Cheng et al.	Prospective	2014	NO	NO	>=15 mm and >=6 portal tracts	1	99	0.54	NA	8.15/NA	0.896/NA
Cho et al.	Prospective	2011	NO	YES	>=15 mm	1	121	0.727	0.074	7.8/14.0	0.849/0.867
Degos et al.	Prospective	2010	NO	YES	>=18 mm	1	284	0.415	0.102	5.2/12.9	0.78/0.90
Dong et al.	Prospective	2015	NO	NO	>=15 mm and >=6 portal tracts	NA	81	0.604	0.098	10.3/9.4	0.753/0.873

Table 1: Continued.

Author	Study type	Year	HIV/HBV	METAVIR	Biopsy size	Biopsy to TE time (days)	Sample	Prevalence F2–F4	Prevalence F4	TE cut-off	AUROC
Gaia et al.	Prospective	2011	NO	YES	>=20 mm	120	70	0.53	0.31	7.2/10.6	0.674/0.763
Goyal et al.	Prospective	2013	NO	YES	>=15 mm and >=6 portal tracts	38	357	0.792	0.059	6.0/11.0	0.84/0.93
Huang et al.	Prospective	2016	NO	NO	>=15 mm	NA	263	0.148	0.011	8/NA	0.911/NA
Jia et al.	Prospective	2015	NO	YES	>=10 mm and >=8 portal tracts	NA	469	0.612	0.122	7.3/10.7	0.82/0.90
Kim et al. 1	Prospective	2012	NO	NO	>=20 mm	1	194	0.845	0.387	8.8/14.1	0.873/0.910
Kim et al. 2	Prospective	2012	NO	YES	>=20 mm	1	170	0.712	0.276	8.0/14.0	0.937/0.963
Kim et al.	Prospective	2009	NO	YES	>=10 mm and >=10 portal tracts	1	91	NA	0.692	NA/10.3	NA/0.803
Kim et al. 1	Prospective	2009	NO	YES	>=6 portal tracts	1	130	0.923	0.515	NA/10.1	NA/0.840
Kim et al. 2	Prospective	2009	NO	YES	>=15 mm	NA	91	0.868	0.396	NA/NA	0.837/0.913
Kim et al. 3	Prospective	2012	NO	NO	>=15 mm	1	150	0.847	0.453	6.0/9.4	NA/NA
Lesmana et al.	Retrospective	2011	NO	YES	>=15 mm and >=5 portal tracts	1	117	0.624	NA	5.85/NA	0.614/NA
liu et al.	Prospective	2015	NO	NO	>=8 portal tracts	NA	115	0.53	0.15	8.50/11.75	0.838/0.914
Liu et al.	Prospective	2012	NO	NO	>=10 mm	NA	134	0.43	0.11	7.60/13.20	0.93/0.96
Marcellin et al.	Prospective	2009	NO	YES	>=6 portal tracts	1	173	0.503	0.081	7.2/11.0	0.81/0.93

Table 1: Continued.

Author	Study type	Year	HIV/HBV	METAVIR	Biopsy size	Biopsy to TE time (days)	Sample	Prevalence F2–F4	Prevalence F4	TE cut-off	AUROC
Meng et al.	Prospective	2015	NO	YES	>=12 mm and >=6 portal tracts	2	287	0.488	0.157	8.85/17.05	0.909/0.815
Meng et al.	Prospective	2016	NO	NO	>=15 mm	7	168	NA	0.15	15.1	0.927
Miailhes et al.	Prospective	2011	YES	YES	>=10 mm	3	59	0.61	0.203	5.9/9.4	0.85/0.96
Osakabe et al.	Prospective	2011	NO	YES	>=15 mm and >=8 portal tracts	30	51	0.882	0.275	7.1/16.0	0.844/0.93
Qin et al.	Prospective	2015	NO	NO	NA	1	152	0.68	0.07	8.2/13.1	0.752/0.973
Seo et al.	Retrospective	2015	NO	NO	>=15 mm	90	567	0.72	0.2	7.8/11.6	0.774/0.902
Sporea et al.	Prospective	2010	NO	YES	>=20 mm and >=8 portal tracts	NA	140	0.764	0.05	7/13.6	0.658/0.974
Stibbe et al.	Prospective	2011	NO	YES	>=20 mm	NA	48	0.458	0.104	7.0/14.0	NA/0.89
Trembling et al.	Prospective	2013	NO	YES	>=20 mm	1	182	0.626	0.198	NA/11.85	NA/O.95
Vigano et al.	Prospective	2011	NO	YES	>=20 mm	NA	125	0.53	0.16	6.2/13.1	NA/NA
Wang et al.	Prospective	2015	NO	NO	>=15 mm and >=6 portal tracts	NA	142	0.585	0.092	8.15/13.95	0.897/0.968
Wang et al.	Prospective	2014	NO	NO	>=15 mm	NA	80	0.7	0.1125	7.3/12.4	0.865/0.944
Wang et al.	Prospective	2016	NO	NO	NA	NA	127	0.76	0.24	NA/15.2	NA/0.805
Wong et al.	Prospective	2009	NO	YES	>=15 mm and >=6 portal tracts	NA	134	0.78	0.24	NA/13.4	NA/0.89
Wong et al. Tr-c	Prospective	2014	NO	YES	>=15 mm and >=6 portal tracts	NA	238	0.693	0.235	NA/10	NA/0.9

Table 1: Continued.

Author	Study type	Year	HIV/HBV	METAVIR	Biopsy size	Biopsy to TE time (days)	Sample	Prevalence F2–F4	Prevalence F4	TE cut-off	AUROC
Wong et al. Va-c	Prospective	2014	NO	YES	>=15 mm and >=6 portal tracts	NA	85	0.565	0.259	NA/10	NA/0.87
Zhang et al.	Prospective	2016	NO	NO	>=22 mm	7	180	0.72	0.18	7.5/10.6	0.813/0.799
Zhang et al.	Prospective	2016	NO	NO	>=15 mm	NA	124	0.54	NA	6.95	0.732
Zhang et al.	Prospective	2011	NO	NO	>=15 mm and >=6 portal tracts	NA	88	0.671	0.159	7.25/12.40	0.857/0/948
Zhu et al.	Prospective	2011	NO	YES	>=15 mm and >=6 portal tracts	1	175	NA	0.166	7.9/13.8	NA/0.98

AUROC, area under the receiver-operating curve; TE, transient elastography; HIV/HBV, hepatitis B and HIV-coinfected patients; METAVIR, liver biopsy assessed according to METAVIR or not; TE cut-off, TE cut-off used to predict; NA, data not available.

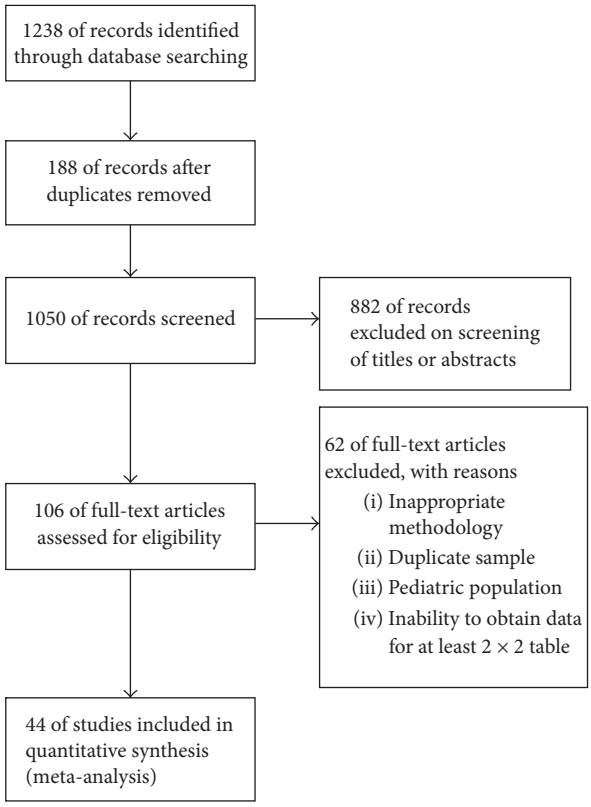

Figure 1: Flow diagram of study selection process.

was conducted with assistance by a time-motion ultrasound image [40]. Another possible issue was addressed in patient selection that participants might be enrolled consecutively with confirmed diagnosis in three studies [31, 50, 55]. Both of these concerns might be located in heterogeneity and sensitivity analyses.

3.3. Diagnosis of SF. We included 35 studies (N = 6,202) in the analysis for SF (F2–F4) [15–23, 25–27, 29–35, 37–40, 43, 56–59]. Summary representation of the overall analysis was presented in Figure 3(a) and Supplementary Figure 1. Sensitivity and specificity ranged from 51 to 97% and 38 to 100%, respectively (Supplementary Figure 1).

The area under SROC for SF was 0.86 (95% CI: 0.83–0.89) (Figure 3(a)). The meta-analysis summary estimate indicated pooled sensitivity of 0.78 (95% CI: 0.73–0.81, $p < 0.01$; I^2 = 85.59%), specificity of 0.81 (95% CI: 0.77–0.84, $p < 0.01$; I^2 = 88.20%) (Supplementary Figure 1(A)), positive likelihood ratio (LR+) of 4.01 (95% CI: 3.31–4.84, $p < 0.01$; I^2 = 86.27%), negative likelihood ratio (LR−) of 0.28 (95% CI: 0.23–0.33, $p < 0.01$; I^2 = 81.95%) (Supplementary Figure 1(B)), diagnostic score (DS) of 2.67 (95% CI: 2.38–2.96, $p < 0.01$; I^2 = 71.57%), and diagnostic odds ratio (DOR) of 14.44 (95% CI: 10.80–19.30, $p < 0.01$; I^2 = 100%) (Supplementary Figure 1(C)). However, it must be carefully considered as they were not pooled from studies with identical TE threshold. Overall, there was heterogeneity as graphically illustrated on the forest plot in Supplementary Figure 1. The cut-off value for SF (F2–4) ranged from 5.2 to 10.3 kPa with a mean value of 8.6 kPa and a median of 7.25 kPa.

As shown in Figure 3(b) and Table 2, in the analysis of LB-related factors with an impact on accuracy, there was no significant difference (joint p = 0.47 for classification criteria; joint p = 0.29 for interval time; joint p = 0.77 for average sample size). 26 studies conducted in Asian presented a better both pooled sensitivity (0.78, 95% CI: 0.73–0.82) and specificity (0.83, 95% CI: 0.79–0.87) than in Caucasian (joint p = 0.03).

As presented in Figure 3(c), it was indicated that posttest probability of LR+ increased to 86% and LR− decreased to 29% after TE was performed based on Fagan test.

3.4. Diagnosis of Cirrhosis. 41 studies were included in the cirrhotic analysis with a total of 7,205 patients, as four studies did not have any cases of liver cirrhosis (METAVIR F4) [21, 24, 35, 48]. The overall prevalence of METAVIR F4 and the AUROCs in the included studies ranged from 5% to 69.2% and from 0.80 to 0.98 (Table 1), respectively.

Summary representation of the overall analysis was shown in Figure 4(a). The area under the SROC for liver cirrhosis was 0.92 (95% CI: 0.90–0.94). Sensitivity ranged from 49% to 100%, much more widely than specificity which ranged from 62% to 99% (Supplementary Figure 2). The meta-analysis summary estimate covered the pooled sensitivity of 0.84 (95% CI: 0.80–0.88, $p < 0.01$; I^2 = 76.67%), specificity of 0.87 (95% CI: 0.84–0.90, $p < 0.01$; I^2 = 90.89%) (Supplementary Figure 2(A)), LR+ of 6.66 (95% CI: 5.34–8.31, $p < 0.01$; I^2 = 84.77%), LR− of 0.18 (95% CI: 0.14–0.23, $p < 0.01$; I^2 = 80.80%) (Supplementary Figure 2(B)), DS of 3.60 (95% CI: 3.23–3.97, $p < 0.01$; I^2 = 66.54%), and DOR of 36.63 (95% CI: 25.38–52.87, $p < 0.01$; I^2 = 100%), respectively (Supplementary Figure 2(C)). Again, these measures must be carefully considered without identical TE thresholds. The cut-off value for cirrhosis ranged from 9 kPa to 18.2 kPa with both a mean value and a median of 12.4 kPa.

As shown in Figure 4(b) and Table 3, although summary sensitivity was lower and summary specificity was higher in studies with METAVIR score (sensitivity: 0.82, 95% CI: 0.77–0.87; specificity: 0.88, 95% CI: 0.85–0.91), TE performed on the next day of LB (sensitivity: 0.79, 95% CI: 0.71–0.86; specificity: 0.88, 95% CI: 0.84–0.93), and average sample length $\geqslant$ 20 mm (sensitivity: 0.79, 95% CI: 0.69–0.89; specificity: 0.88, 95% CI: 0.83–0.94), respectively, no statistical significance was detected (joint p = 0.17 for classification criteria; joint p = 0.21 for interval time; joint p = 0.47 for average sample size). Besides, pooled sensitivity and specificity were without significant difference (joint p = 0.12) between Caucasian (sensitivity: 0.78, 95% CI: 0.67–0.88; specificity: 0.91, 95% CI: 0.86–0.95) and Asian (sensitivity: 0.86, 95% CI: 0.81–0.90; specificity: 0.86, 95% CI: 0.83–0.89).

In addition, based on Fagan test, it was illustrated that posttest probability of LR+ and LR− rose and declined to 59% and 4%, respectively (Figure 4(c)).

3.5. Publication Bias. The results of publication bias analysis were performed with Stata in Supplementary Figure 3. No

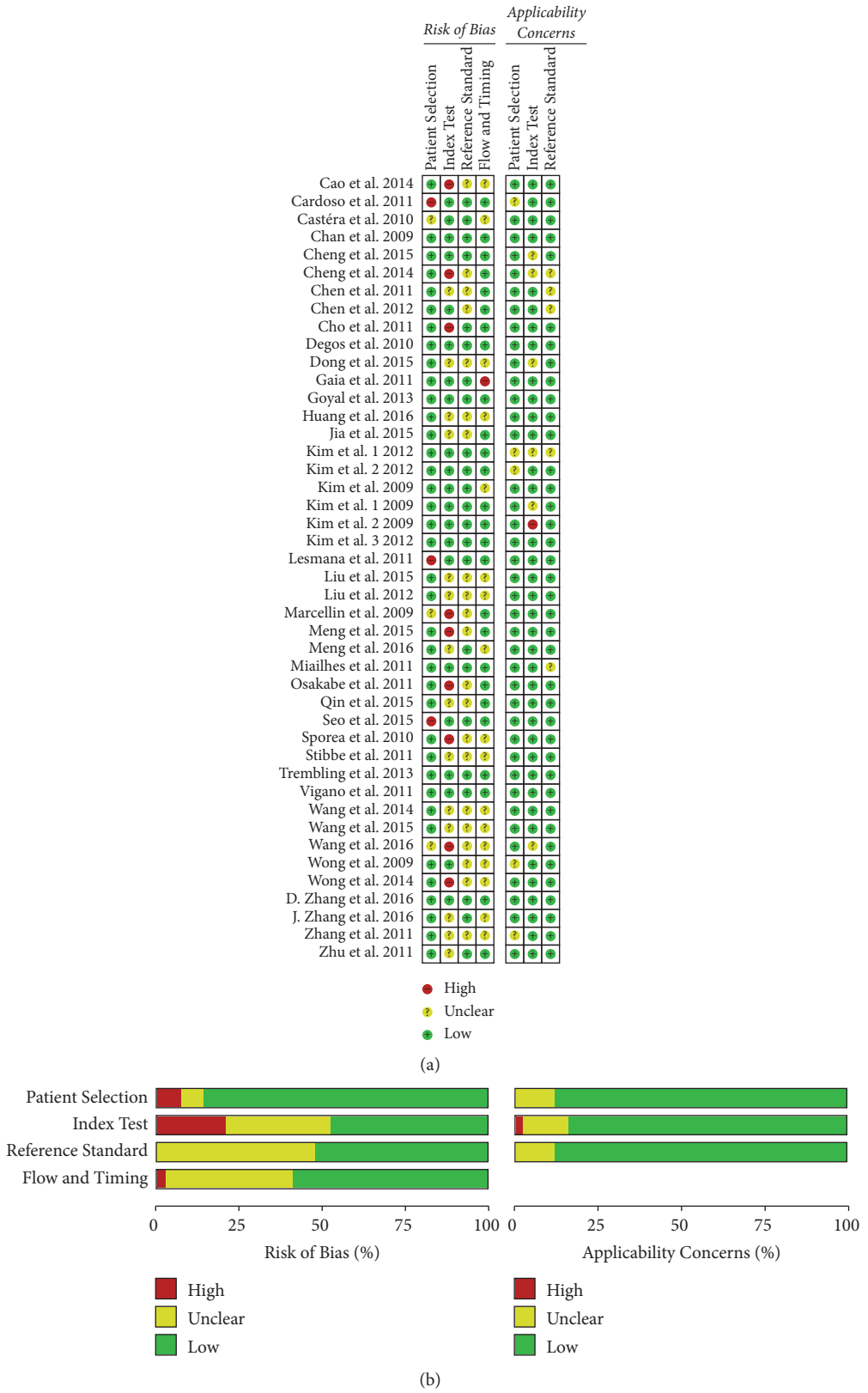

Figure 2: Summary of methodological quality of 44 studies according to Quality Assessment of Diagnostic Studies-2 (QUDAS-2) tool. (a) Overall and (b) study-level of bias.

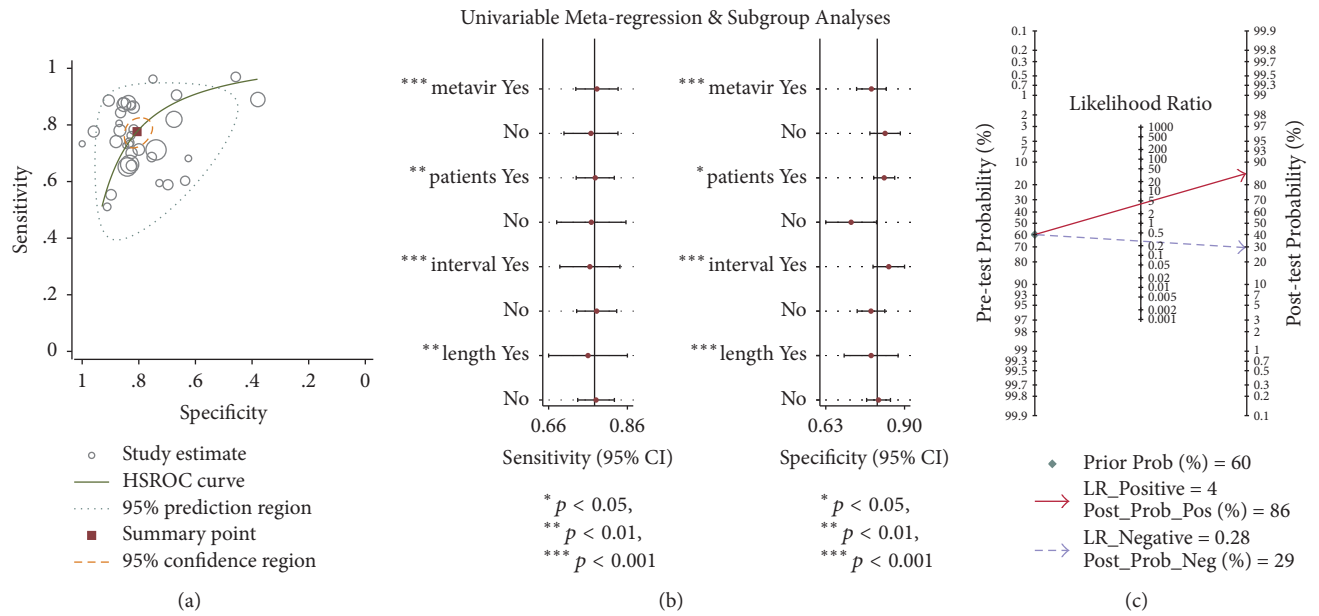

Figure 3: Meta-analysis of 32 studies that assessed the diagnosis accuracy of significant fibrosis based on transient elastography. (a) A summary receiver-operating characteristic (SROC) plot of transient elastography for detection of significant liver fibrosis (METAVIR F2–F4). (b) Regression analysis of studies whether reported with METAVIR score on the next day of biopsy or with sample size ≥ 20 cm for significant liver fibrosis. (c) Detection of clinical significance for significant liver fibrosis (METAVIR F2–F4) based on Fagan test. Heterogeneity was generated if $p < 0.01$ in sensitivity or specificity separately. However, joint p value was generated synthesisly for analysis of both sensitivity and specificity.

Table 2: Results of meta-regression for significant fibrosis.

Covariate	Number	Pooled sensitivity	p value	Pooled specificity	p value	Joint p value
Classification criteria						
METAVIR score	21	0.78 (0.75–0.83)	<0.01	0.79 (0.73–0.84)	<0.01	0.47
Non-METAVIR score	14	0.77 (0.70–0.83)		0.83 (0.78–0.89)		
Interval time						
On the next day of liver biopsy	11	0.76 (0.69–0.84)	<0.01	0.85 (0.79–0.90)	<0.01	0.29
More than one day after liver biopsy	24	0.78 (0.73–0.83)		0.78 (0.74–0.83)		
Average sample size						
⩾20 mm	7	0.76 (0.66–0.86)	<0.01	0.79 (0.69–0.88)	<0.01	0.77
Not ⩾ 20 mm	28	0.78 (0.74–0.82)		0.81 (0.77–0.85)		
Region						
Asian	26	0.78 (0.73–0.82)	<0.01	0.83 (0.79–0.87)	0.04	0.03
Caucasian	9	0.77 (0.68–0.85)		0.72 (0.63–0.80)		

significant publication bias was detected according to Deeks figures for SF ($p = 0.26$). However, there was bias among 41 studies enrolled in analysis of TE for cirrhosis ($p = 0.02$), which might result from the positive results of all 41 studies.

4. Discussion

TE can provide a reliable detection of liver fibrosis in patients with CHB and thus has been recommended by the American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL) [60, 61]. This meta-analysis was conducted in a total of 7,808 CHB patients to summarize the diagnostic accuracy of TE for CHB-related SF, with optimal statistical method SROC. In addition, regression analysis was carried out to further explore sources of heterogeneity.

In our study, TE performed well in both SF (F2–4) and cirrhosis (F4) with pooled sensitivity of 78% and 84%, summary specificity of 81% and 87%, DOR of 14.44 and 36.63, LR+ of 4.01 and 6.66, LR− of 0.28 and 0.18, respectively. Study by Li et al. [62] with hierarchical SROC model was also performed in CHB patients, with summary sensitivity and specificity for SF (F2–4) and cirrhosis (F4) of 80% and 86%, 82%, and 88%, however, without DOR, LR+ and LR−. Interestingly, the pooled specificity for diagnosis SF (F2–4) and cirrhosis (F4) in both studies were higher than

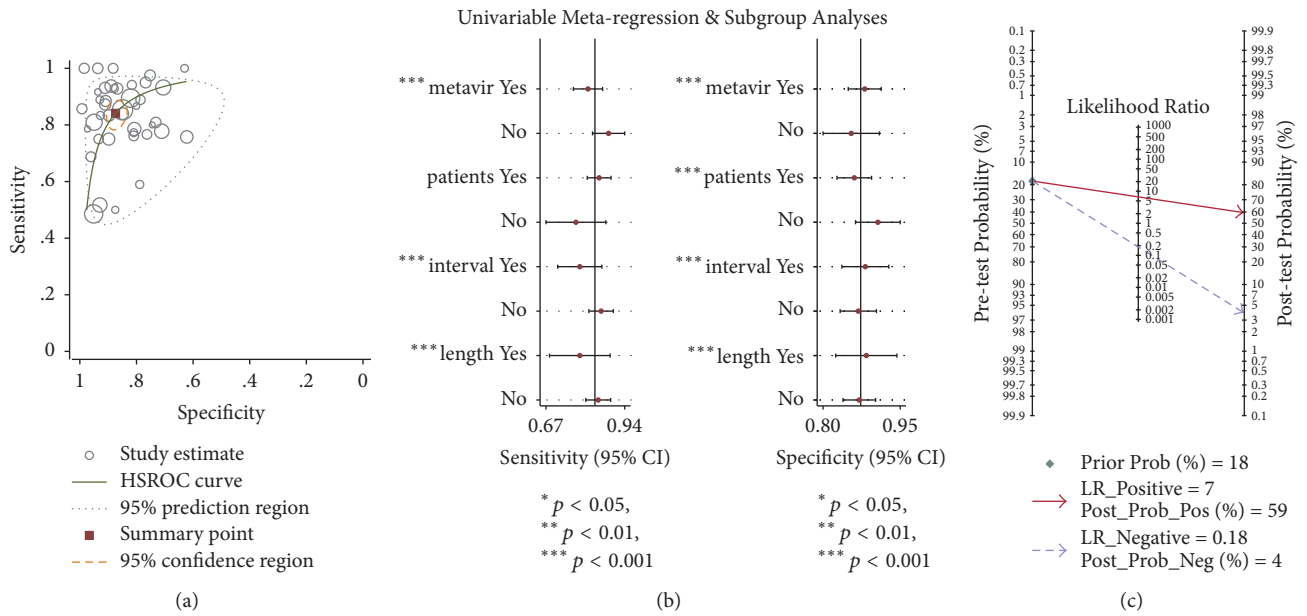

Figure 4: Meta-analysis of 37 studies that assessed the diagnosis accuracy of cirrhosis based on transient elastography. (a) A summary receiver-operating characteristic (SROC) plot of transient elastography for detection of cirrhosis (METAVIR F4). (b) Regression analysis of studies whether reported with METAVIR score on the next day of biopsy or with sample size ≥ 20 cm for cirrhosis. (c) Detection of clinical significance for cirrhosis (METAVIR F4) based on Fagan test.

Table 3: Results of meta-regression for cirrhosis.

Covariate	Number	Pooled sensitivity	p value	Pooled specificity	p value	Joint p value
Classification criteria						
METAVIR score	28	0.82 (0.77–0.87)	<0.01	0.88 (0.85–0.91)	<0.01	0.17
Non-METAVIR score	13	0.89 (0.83–0.94)		0.86 (0.80–0.91)		
Interval time						
On the next day of liver biopsy	13	0.79 (0.71–0.86)	<0.01	0.88 (0.84–0.93)	<0.01	0.21
More than one day after liver biopsy	28	0.86 (0.82–0.90)		0.87 (0.83–0.90)		
Average sample size						
⩾20 mm	8	0.79 (0.69–0.89)	<0.01	0.88 (0.83–0.94)	<0.01	0.47
Not ⩾ 20 mm	33	0.85 (0.81–0.89)		0.87 (0.84–0.90)		
Region						
Asian	31	0.86 (0.81–0.90)	<0.01	0.86 (0.83–0.89)	<0.01	0.12
Caucasian	10	0.78 (0.67–0.88)		0.91 (0.86–0.95)		

summary sensitivity, which suggested that the currently cut-off values of TE performed better in excluding diseases rather than confirming diseases. Furthermore, the areas under the SROC were 0.86 for SF (F2–4) and 0.92 for cirrhosis (F4), respectively, which indicated that TE was performed well in staging fibrosis in CHB patients. In addition, TE performed better for cirrhosis than SF with a higher value of AUC, sensitivity, specificity, DOR, LR+, and a lower value of LR−. Although the diagnostic accuracy was higher for cirrhosis, TE could also increase the diagnostic accuracy for SF based on Fagan test with increased LR+ and decreased LR−.

The higher TE values were used to confirm diagnosis, while the lower one was used to exclude the false positive diagnosis. However, if the TE value located between the values for rule in and rule out, biopsy was then recommended. Based on the descriptive statistics of enrolled studies, the cut-off values for diagnosing SF (F2–4) and cirrhosis (F4) ranged from 5.2 to 10.3 kPa and 9 to 18.2 kPa, respectively. The optimal cut-off values of TE in CHB patients in our study were 7.25 kPa for SF (F2–4) and 12.4 kPa for cirrhosis (F4). In the previous meta-analysis by Li et al., the weighted mean cut-off values of TE were comparable with 7.2 kPa for SF (F2-4) and 12.2 kPa for cirrhosis (F4) [62]. However, since there was no optimal statistical method to pool different cut-off values in individual studies, the optimal cut-off values in our meta-analysis were simply summarized as median, which could eliminate the impact resulting from the maximum and

minimum values that was better than the mean value in previous study [62].

Elevated ALT levels might affect the predictive accuracy of TE [16, 24, 45, 50, 55, 56]; however, the study by Cardoso et al. reported that the use of TE cut-off values adjusted to ALT level did not improve the performance of liver stiffness in CHB patients [49]. Although elevated ALT might be the most important confounder on liver stiffness measurement, the synthesis analysis of ALT elevation could not be conducted due to insufficient data. Therefore, it would be beneficial if more clinical studies focused on the correlation between ALT elevation and TE in CHB patients.

One of the main limitations in this meta-analysis was the significant heterogeneity of the included studies. Spearman correlation coefficient for SF and cirrhosis were 0.055 (p = 0.755) and 0.057 (p = 0.723), and no threshold effect was presented. Therefore, regression analysis was carried out. Besides, TE value could be applied as diagnosis criteria for both SF and cirrhosis in Asian. However, for Caucasian, it was noted that TE was valid to diagnosis of cirrhosis, while it was less precise for SF. Unfortunately, the regression analysis was not conducted owing to the small size of HIV- and non-HIV-coinfected patients. It should be noted that the overlapped cut-off values from included studies might also result in the heterogeneity.

In conclusion, TE is of great value for detection CHB-related cirrhosis, however, with a suboptimal performance in detection of SF. Further studies should focus on the TE cut-off value and the effect of ALT elevation in patients with CHB.

Abbreviations

CHB:	Chronic hepatitis B
CI:	Confidence interval
DOR:	Diagnostic odds ratio
LB:	Liver biopsy
LR:	Likelihood ratio
QUADAS-2:	Quality Assessment of Diagnostic Accuracy Studies-2
SF:	Significant fibrosis
SROC:	Summary receiver-operating curves
TE:	Transient elastography
AUROC:	Area under receiver-operating curve.

Conflicts of Interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patients received or pending, or royalties.

Authors' Contributions

Xiaolong Qi, Weidong Wang, Jing Wang, and CHESS Study Group contributed to study concepts and design; Min An and Tongwei Wu performed literature search; Min An and Jing Wang conducted data extraction; Min An, Tongwei Wu, Deke Jiang, Mengyun Peng, and Chunqing Zhang performed data analysis: Tongwei Wu, Weidong Wang, Chunqing Zhang, and CHESS Study Group were responsible for manuscript preparation and revision. All authors and CHESS Study Group have participated sufficiently in the study and approved the final version. Xiaolong Qi, Min An, and Tongwei Wu contributed equally to this work.

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Supplementary Materials

Supplementary Figure 1: meta-analysis of 32 studies that assessed the diagnosis accuracy of significant fibrosis (METAVIR F2–F4) based on transient elastography. A Forest plot of (A) sensitivity and specificity, (B) positive and negative likelihood ratio, and (C) diagnostic score (DS) and diagnostic odds ratio (DOR) for significant liver fibrosis (METAVIR F2–F4). Supplementary Figure 2: meta-analysis of 37 studies that assessed the diagnosis accuracy of cirrhosis (METAVIR F4) based on transient elastography. A Forest plot of (A) sensitivity and specificity, (B) positive and negative likelihood ratio, and (C) DS and DOR for cirrhosis (METAVIR F4). Supplementary Figure 3: Deeks' Funnel Plot Asymmetry Test for (A) significant fibrosis (METAVIR F2–F4) and (B) cirrhosis (METAVIR F4). *(Supplementary Materials)*

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Research Article

Thromboembolic Events Secondary to Endoscopic Cyanoacrylate Injection: Can We Foresee Any Red Flags?

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Background. Gastric varices (GV) are associated with high morbidity and mortality in patients with portal hypertension. Endoscopic cyanoacrylate injection is the first-line recommended therapy for GV obliteration. This study aims to explore the reason behind related adverse events and better prevent its occurrence. *Methods*. A retrospective case series study was conducted from January 1, 2013, to December 31, 2016, to identify patients who experienced severe adverse events secondary to endoscopic cyanoacrylate injection. A literature review of similar cases was performed on two medical databases, Medline and Embase. *Results*. A total of 652 patients underwent cyanoacrylate injection at our center within the study duration. Five cases of severe adverse events related to the use of tissue adhesives were identified. Detailed clinical presentation, patient treatment, and outcomes were reviewed and analyzed. Twenty-seven similar cases were identified based on the literature review providing further insight into the study. *Conclusion*. Although rare in incidence, systemic embolism associated with cyanoacrylate injection is often fatal or debilitating. This report may raise awareness in treatment protocol, including the necessity of preoperative angiographic studies, to avoid similar adverse events in clinical practice.

1. Introduction

Variceal hemorrhage is a fatal presentation of portal hypertension, commonly seen in patients with decompensated cirrhosis. Current treatment protocol for gastroesophageal varices includes primary prophylaxis, management of acute bleeding, and secondary prophylaxis [1]. According to the Baveno VI consensus, a combination of nonselective beta blockers (NSBB) and endoscopic variceal ligation (EVL) for esophageal varices and cyanoacrylate injection for gastric varices are recommended as first-line therapy [2]. Compared to esophageal varices, gastric varices are lower in prevalence but are associated with a higher risk of hemorrhage and mortality [3]. The use of *N*-butyl-2-cyanoacrylate (NB2-CYA) for gastric variceal obliteration was first reported in 1986 and is currently well recognized as first-line therapy with a high hemostasis rate [4–6]. Large cohort studies have demonstrated the safety and efficacy of cyanoacrylate injection; however others have highlighted individual adverse events [7–9]. Occurrence of systemic embolization is often associated with patient morbidity and mortality. We hereby report a series of adverse events associated with cyanoacrylate injection for the treatment of gastric varices.

2. Methods

A retrospective case series study was conducted at a tertiary hospital. The hospital database was reviewed; approval was granted by the hospital's institutional review board (IRB). All patients who underwent endoscopic procedure had

Table 1: Summary of patient characteristics, preoperative management, endoscopic findings, and subsequent treatment.

Patient	Cause of PH	Child-Pugh Class	Acute bleed	Preoperative drug	Endoscopic findings	Endoscopic treatment	Volume of cyanoacrylate
(1) 57 y/F	PBC	A	No	None	F0/IGV 1	NBCA	3.5 ml
(2) 74 y/M	Alcohol	A	No	None	F2/GOV2	NBCA + EIS	3 ml
(3) 50 y/M	HCV	A	No	None	F3/GOV2	NBCA + EBL	3.5 ml
(4) 51 y/M	HBV	B	Yes	Aminomethylbenzoic acid 0.4 g Etamsylate 2 g Carbazochrome 80 mg Hemocoagulase 1 IU Somatostatin 6 mg	F3/GOV2	NBCA + EBL	2.5 ml
(5) 52 y/F	PBC	B	Yes	Carbazochrome 80 mg Hemocoagulase 1 IU Somatostatin 6 mg	F3/GOV2	NBCA + EBL	1 ml

signed informed consent acknowledging the purpose and risk associated with the intervention. We included (1) patients with gastric varices with or without concurrent esophageal varices treated with injection of N-butyl-cyanoacrylate and (2) patients who experienced severe adverse events (SAE) associated with cyanoacrylate injection within 48 hours of the endoscopic procedure. SAE was defined as occurrence of death, life-threatening disability, or permanent deficit, resulting in a prolonged hospital stay.

All endoscopic procedures were commenced after an overnight fast. First, a routine endoscopy exam was performed to assess the extent of gastroesophageal varices that were classified according to Sarin's classification. Concurrent esophageal varices were graded according to the Japanese Society of Portal Hypertension [10]. Each patient received individualized therapy as deemed fit by the operator. Gastric varices were uniformly treated via the sandwich technique, which starts with an injection of lauromacrogol (Tianyu Pharmaceutical, Zhejiang, China), followed by N-butyl cyanoacrylate (Beijing Suncon Medical Adhesive, Beijing, China), and then finished with flush of lauromacrogol [11]. The number of injection sites and volume of lauromacrogol and cyanoacrylate used directly correlated with the size of the varix. Multiple injection sites were chosen in attempt to obliterate the varix or varices in one session. Volume of lauromacrogol used ranged from 2 to 10 ml, while that of cyanoacrylate ranged from 0.5 to 2 ml, per injection site. Concurrent esophageal varices were treated with either endoscopic band ligation (EBL) or endoscopic sclerotherapy injection (EIS) determined by the operator.

Patients were hospitalized for postoperative observations for 24–48 hours. Any occurrence of severe adverse events (SAE), as previously defined, was recorded. Treatment and patient response secondary to the adverse events were documented. Patient follow-ups were accomplished via telephone interviews or out-patient services to determine survival or further complications.

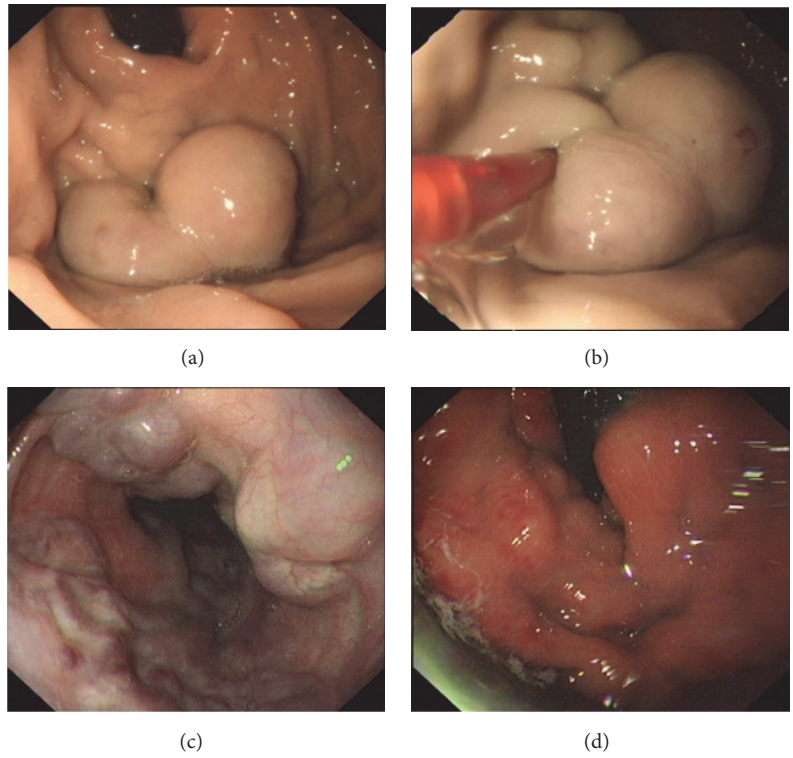
A literature review of case reports on adverse events related to cyanoacrylate injection was also conducted, specifically, occurrence of embolic or infarction events. Detailed search strategy of Medline (R), from 1946 to present with daily updates, and Embase, from 1974 to March 20, 2017, is provided in the Appendix.

3. Results

A thorough review of the inpatient and endoscopy database was carried out from January 1, 2013, to December 31, 2016. A total of 652 patients who underwent N-butyl-cyanoacrylate (NBCA) injection as secondary prophylaxis for gastric variceal hemorrhage were identified. Based on the a priori established inclusion criteria, the detailed hospital record and treatment protocol of 5 patients were reviewed for the purpose of this study. Three of the five patients were male, ranging from 50 to 74 years. The cause of cirrhosis was PBC in the two female patients, while the remaining were due to HBV, HCV, or alcohol, respectively. Three patients were classified as Child-Pugh Class A, while the remainder were Child-Pugh Class B. Two of the five patients were admitted to our hospital due to an episode of acute variceal hemorrhage, while others had either achieved hemodynamic stability or were admitted for a follow-up endoscopic examination. Prior to the procedure, two patients (patients (4) and (5)) received a combination of hemostatic agents and somatostatin. None of the patients had concurrent HCC or hepatic encephalopathy. Detailed patient characteristics are summarized in Table 1.

Based on the findings of the routine endoscopy, one patient had IGV Type 1, one had GOV Type 1, while three had GOV Type 2 (Figure 1). All gastric varices were treated with the sandwich technique injection of lauromacrogol and cyanoacrylate. The total volume of cyanoacrylate used ranged from 1.0 to 3.5 ml (average 2.7 ml), without exceeding 1.5 ml per injection site. Patients with concurrent esophageal varices were treated with either endoscopic band ligation (EBL) or endoscopic injection sclerotherapy (EIS).

One female patient (patient (1)) suffered from cardiac arrest during the procedure. The bedside echocardiogram revealed an enlarged right ventricle and right atrium, widened vena cava, and shrunken left ventricle. Despite aggressive measures including drug and equipment resuscitation, the patient did not survive. Patient (2) experienced fever, severe abdominal pain, and rebound tenderness after the



(a) (b) (c) (d)

Figure 1: Endoscopic findings of gastroesophageal varices (IGV Type 1 and F3/GOV Type 2) with red wale sign.

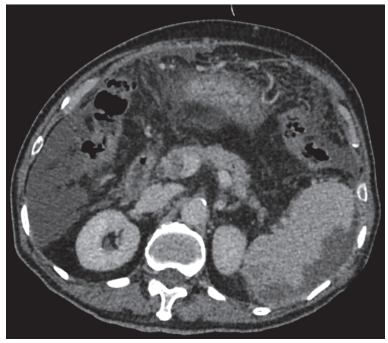


Figure 2: Large area splenic infarct based on CT angiography of the portal venous system.

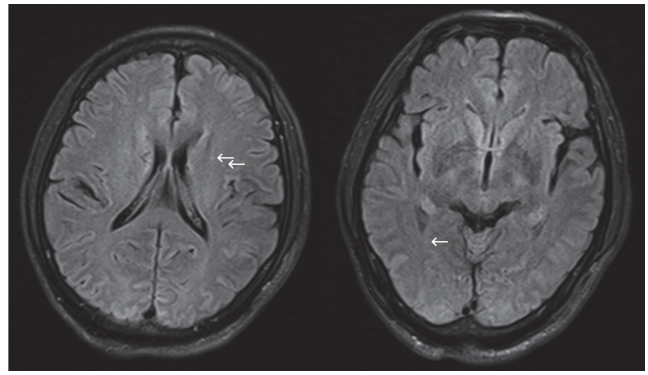


Figure 3: Diffuse hyperdense signals (←) on the cerebral MRI, indicative of acute cerebral infarction.

endoscopic procedure due to a large area splenic infarct (Figure 2), confirmed via CTA of the portal venous system. Two patients (patients (3) and (5)) became lethargic and confused and experienced loss of consciousness following endotherapy. Based on clinical symptoms and cerebral MRI findings, both were diagnosed with acute cerebral infarction (Figure 3). The last patient (patient (4)) experienced pain around the umbilical region with a low-grade fever (37.9°C) after the procedure. A subsequent abdominal CT and intestinal mesenteric CTA revealed intraluminal filling defects consistent with acute mesenteric ischemia (Figure 4). Detailed postoperative findings are listed in Table 2.

All patients received hemostatic medication after the endoscopic procedure as part of the standard protocol at our

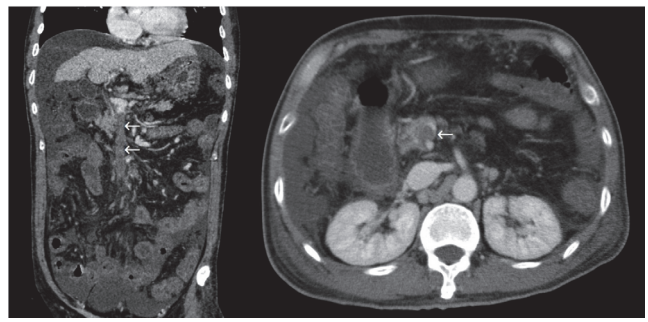


Figure 4: Intraluminal filling defect along the mesenteric vein and edema of the bowel wall (←).

Table 2: Postoperative events including subsequent severe adverse event (SAE), patient outcome, and probable cause.

Patient	Postoperative drug use	Adverse event	Treatment	Hospital stay	Outcome	Probable cause
(1)	None	Acute pulmonary embolism	BCLS	1 day	Death	Large spontaneous gastrorenal and splenorenal shunt
(2)	Carbazochrome 80 mg Vitamin K1 10 mg Somatostatin 6 mg	Acute splenic infarction	Dalteparin 5000 IU Antibiotics (meropenem + vancomycin)	64 days	Survival	Regurgitation of tissue adhesive through the portovenous system or probable AVM
(3)	Carbazochrome 80 mg Somatostatin 3 mg Hemocoagulase 2 U	Acute cerebral infarction	Dalteparin 5000 IU Edaravone Mannitol Dexamethasone	13 days	Survival	Spontaneous portorenal shunt
(4)	Hemocoagulase 1 IU Somatostatin 6 mg	Acute superior mesenteric infarction	LMWH 4000 IU Simethicone p.o.	9 days	Death	Regurgitation of tissue adhesive through the portovenous system or probable AVM
(5)	Hemocoagulase 1 IU Somatostatin 6 mg	Acute cerebral infarction	LMWH 4000 IU Citicoline GM-1 Dexamethasone	42 days	Survival	Spontaneous portoazygous shunt

hospital to prevent postoperative hemorrhage (Table 2). Once the patient developed signs of systemic embolization, all hemostatic agents were suspended. All patients were treated with a subcutaneous injection of low-molecular weight heparin (LMWH). Three of the four patients responded well to therapy and were subsequently discharged. Follow-up interviews confirmed survival in all three patients. However, one patient (patient (4)) developed a recurrent GI bleed, presented as melena, after 5 days of anticoagulation treatment. The patient also developed hepatic encephalopathy and deteriorated rapidly. Extraordinary life sustaining measures were refused and the patient died 9 days after the initial procedure. The overall rebleeding rate was 20% and mortality rate was 40% in the five patients who experienced SAE after cyanoacrylate injection. Of the three patients who survived (60%), only 2 received follow-up endoscopy examination. Complete variceal obliteration was observed in one patient (50%), while the other patient had recurrent gastroesophageal varices (GOV Type 2) treated with consolidation EBL plus cyanoacrylate injection.

A retrospective review of the radiological studies was conducted in attempt to identify a potential explanation for the occurrence of an embolic event. Three of the 5 patients had evident spontaneous portosystemic shunts upon review of imaging studies, including one case of portorenal shunt (patient (3), cerebral infarction), one case of portoazygous shunt (patient (5), cerebral infarction), and one case of concurrent portorenal and portosystemic shunt (patient (1), pulmonary embolism). The remaining cases of mesenteric and splenic infarction had no prominent vascular anomaly.

In order to further identify similar reports of adverse events in present literature, a detailed search of Medline (R), from 1946 to present with daily updates, and Embase, from 1974 to March 20, 2017, was conducted (the Appendix). A total of 43 and 119 reports were retrieved from each database, respectively. Forty-two duplicates were removed and a thorough review of title and abstract of 120 articles was performed. Ninety-seven reports were further eliminated due to irrelevance and finally 24 articles, along with 4 case reports identified from other sources, were included for the purpose of this literature review.

Of the 27 studies included, majority of reported adverse events were pulmonary embolism, 12/27 (44.44%), and splenic infarction, 9/27 (33.33%), while others include cases of portal vein, renal vein embolism, sclerosant extravasation, myocardial infarction, diaphragmatic embolism, cerebral infarction, right atrium emboli, esophageal variceal embolism, and subsequent septicemia or DIC. Several adverse events were attributed to cardiac abnormalities such as patent foramen ovale, prompting right-to-left shunt. Other hypotheses include volume and speed of injection or intravariceal pressure, resulting in regurgitation through the portovenous system. Interestingly, many authors presumed the presence of spontaneous portovenous shunt, such as gastrosplenorenal shunt or anomalous arteriovenous shunts, as a culprit for distant embolization. However, none of the reports provided radiological or morphological evidence of the vasculature anomaly. The results of the literature review were summarized in Table 3.

4. Discussion

Gastric varices are associated with a high morbidity and mortality rate in patients with portal hypertension. The current recommendation for first-line treatment is endoscopic injection of tissue adhesives. Obliteration can be achieved in one session, but sometimes repeat sessions are required [39]. Although cyanoacrylate injection has proven to be safe and effective, several reports on related adverse events have also

Table 3: Summary of adverse events related to cyanoacrylate injection found in current literature.

Study	Year	Country	Patient	Glue mixture (ratio), volume	Adverse event	Treatment	Outcome	Probable cause
Shim et al. [12]	1996	S. Korea	59 y/M	(0.5 : 0.8) 7 ml + 2 ml	Portal and splenic vein thrombosis	NA	NA	Large volume injection
Battaglia et al. [13]	2000	Italy	65 y/F	(1 : 1) 6 ml	Intraparenchymal subcapsular hematoma of the spleen	Splenectomy	Survival	Resin occluded branches of splenic vascularization or embolized intraparenchymal vessels and had been eliminated by macrophage action
Türler et al. [14]	2001	Germany	18 y/M	(1 : 1) 5 ml + 2 ml	Pulmonary embolism and left renal vein; recurrent left kidney abscess (5 months)	Thrombectomy and ventilation support; operative and CT-guided drainage (kidney abscess)	Survival	Spontaneous splenorenal shunt
Tan et al. [15]	2002	Malaysia	53 y/M	(0.5 : 0.7) 6 ml +1 ml	Pulmonary and splenic infarction	Supportive treatment and antibiotics	Survival	Collateral portosystemic circulation and presumable anomalous arteriovenous pulmonary shunts
Cheng et al. [16]	2004	Taiwan	65 y/F	(1 : 1) 3 ml	Sclerosant extravasation	Antibiotics and supportive treatment	Survival	High intravariceal pressure and large volume or high injection speed of tissue adhesive
Rickman et al. [17]	2004	USA	55 y/M	(1 : 1) 4 ml + 2 ml	Pulmonary emboli, splenic infarction	Oxygen support	Survival	NA
Kok et al. [18]	2004	S. Africa	24 y/F	(1 : 1) 2 ml + (1 : 2) 5 ml	Pulmonary infarction and septicemia	TIPS surgery	Death	Collateral vessels, size of varices, volume of injection, dilution of lipiodol
Upadhyay et al. [19]	2005	Oman	65 y/M	(1.5 : 2.1)	Inferior wall myocardial infarction and cortical blindness	Percutaneous occlusion of PFO followed by TIPS surgery	Survival	Patent foramen ovale
Alexander et al. [20]	2006	Australia	52 y/M	(1 : 3) 4 ml + 2 ml	Pulmonary embolism	Prednisolone and supportive treatment	Survival	Large volume injection
Liu et al. [21]	2006	Taiwan	42 y/M	(1 : 1) 2 ml	Splenic vein thrombosis	Antibiotics and supportive treatment	Survival	Volume of injection
Martins Santos et al. [22]	2007	Brazil	53 y/M	(1 : 1) 1 ml	Splenic infarction	Antibiotics and supportive treatment	Death	Arteriovenous shunt (probable)
Yu et al. [23]	2007	Taiwan	57 y/M	(1 : 0.7) 1.7 ml	Diaphragmatic embolism	Supportive treatment with narcotic analgesic and short course of terlipressin	Survival	Portophrenic shunt (probable)

Table 3: Continued.

Study	Year	Country	Patient	Glue mixture (ratio), volume	Adverse event	Treatment	Outcome	Probable cause
Chang et al. [24]	2008	Taiwan	53 y/M	(1 : 1) 2 ml	Pyogenic Portal venous thrombosis	Antibiotics	Death	Direct injection or regurgitation of tissue adhesive along the short gastric vein and splenic vein into the portal vein
Marion-Audibert et al. [25]	2008	France	77 y	(1 : 1) 1.5 ml	Pulmonary embolism	BCLS protocol	Death	Portosystemic vascular shunt (gastrosplenorenal shunt) (reconstruction with animal model)
Abdullah et al. [26]	2009	Malaysia	40 y/M	(1 : 1) 3 ml	Cerebral infarction	NA	Survival	Patent foramen ovale
Park et al. [27]	2010	S. Korea	34 y/M	NA	Right atrium emboli extended from inferior vena cava	NA	Survival	Gastrorenal shunt
Chen et al. [28]	2011	Taiwan	57 y/F	(1 : 1) 4 ml + 6 ml	Esophageal variceal embolism	Cyanoacrylate hemostasis	Survival	NA
Kazi et al. [29]	2012	Australia	44 y/F	(1 : 1) 4 ml	Pulmonary emboli and pulmonary infarct, resulting in DIC	Blood transfusion to correct coagulopathy	Survival	NA
Miyakoda et al. [30]	2012	Japan	76 y/F	(1 : 0.5) 1.5 ml + (1 : 0.5) 3.5 ml	Right atrium emboli	Heparin	Death	NA
Chan et al. [31]	2012	Malaysia	44 y/F	(0.5 : 0.8) 1.3 ml	Splenic infarction	Conservative treatment (analgesics, antihistamine, and antiemetic)	Survival	NA
Singer et al. [32]	2012	USA	75 y/M	(1 : 1) 3 ml	Pulmonary infarction	Empiric antibiotics and supportive care	Survival	NA
Mourin et al. [33]	2012	France	69 y/M	NA	Pulmonary infarction	Anticoagulant treatment + pneumonectomy	Death	Presumed portosystemic vascular shunts
Köksal et al. [34]	2013	Turkey	33 y/F	(1 : 1) 2 ml	Splenic infarction	Supportive treatment	Survival	Retrograde embolization through the splenic vein
Myung et al. [35]	2013	S. Korea	55 y/F	(1 : 1) 2 ml	Splenic infarction and cerebral infarction	NA	Survival	Patent foramen ovale
Nawrot et al. [36]	2014	Poland	54 y/F	(0.5 : 0.8) 12 ml	Pulmonary embolism with septicemia	Antibiotics	Survival	Large spontaneous splenorenal shunt
Chew et al. [37]	2014	UK	34 y/M	(1 : 1) 4 ml	Pulmonary emboli	Intravenous diuretics, empiric antibiotics	Survival	NA
Burke et al. [38]	2017	Australia	25 y/F	1 ml + 3 ml	Pulmonary emboli	BCLA protocol	Death	Presumed collateral circulation

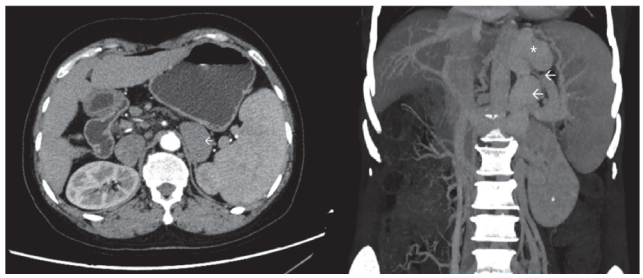


Figure 5: Spontaneous portosystemic shunt in the patient with IGV Type 1, presenting as portorenal and portosystemic shunt (←). The coronal view shows gastric varices (∗) connected to both the left renal and splenic vein through as large torturous, dilated venous shunt (←).

been documented [7]. Seewald et al. have emphasized the importance of a standardized technique, which can minimize the risk of embolization and local complications but also decrease variceal recurrence or rebleeding by effectively obliterating vessel tributaries. The recommended mixture proportion of N-butyl-2-cyanoacrylate to lipiodol is 0.5 ml : 0.8 ml, and injection of over 1 ml glue mixture may increase the risk of embolization [8, 40]. Researchers have also explored alternative treatments for gastric varices obliteration, minimizing or eliminating the use of tissue adhesives. Tan et al. conducted a randomized control trial comparing the efficacy of gastric variceal band ligation versus cyanoacrylate injection [41]. Meanwhile, Romero-Castro et al. reported fewer complications with endoscopic ultrasound-guided coil injection compared to that of traditional cyanoacrylate injection [42].

We report five cases of adverse events that occurred after the endoscopic injection of cyanoacrylate for the treatment of gastric varices. All cases involved the formation of systemic embolus, including cerebral vascular infarction, mesenteric infarction, splenic infarction, and pulmonary embolism. A retrospective review of radiological studies revealed presence of spontaneous portosystemic shunt (SPSS) in 3 patients with distant systemic emboli, including one case of portorenal shunt, one case of portoazygous shunt, and one case of concurrent portorenal and portosplenic shunt (Figure 5). Based on the clinical presentation and radiological findings, three cases can be ascertained as glue emboli, including the case of pulmonary embolism and two cases of cerebral infarction. The formation of spontaneous portosystemic shunts (SPSS) may serve as a shortcut for acute glue embolization, which calls into question the necessity of angiographic studies prior to endoscopic intervention and whether patients with diverging shunts should be tackled with a different therapeutic approach [43]. Our center has previously performed BRTO assisted cyanoacrylate injection for patients with large gastrorenal shunt or splenorenal shunt (data reported elsewhere). This procedure prevents the occurrence of systemic glue emboli for patients with evident portosystemic shunt; however, it is poorly tolerated by patients. BRTO assisted cyanoacrylate injection requires the patient to lay in a supine position with only local anesthesia and an angiography of the portosystemic system is performed via femoral access. After the portosystemic shunt is located a balloon is deployed and secured, while the endoscopist performs the subsequent cyanoacrylate injection.

The remaining cases of mesenteric infarction and splenic infarct remain controversial and cannot be ascertained as the presence of SPSS. A plausible explanation could be due to the injection of cyanoacrylate into the arterial system, which in some cases is located adjacent to the varix or is connected via an arteriovenous malformation. Glue emboli of the splenic artery may result in a large area splenic infarct as seen in patient (2). Another explanation is the regurgitation of tissue adhesives through the portovenous system, potentially due to high speed or volume injection or high intravariceal pressure. Patients with end-stage cirrhosis are also prone to clot formation, especially in the portal venous system [44]. The use of various hemostatic agents combined with a decrease in blood flow velocity, exacerbated by a stress event (endotherapy), may also be a probable explanation for an acute thrombus formation. Unlike other studies, our center employs lauromacrogol instead of lipiodol as a diluting agent for cyanoacrylate via sandwich technique [11]. Therefore, glue embolization is difficult to differentiate from a thrombus formation on imaging studies.

Antithrombotic treatment with LMWH is a fairly standard treatment protocol. However, in cases with recent interventional procedure or hemorrhagic episode, the use of LMWH can be precarious [45]. Development of a rebleed in such patients can be just as fatal as the adverse event itself. Anticoagulants are effective in the treatment of blood thrombus; however, the effect on glue emboli or improvement of patient outcome remains questionable.

The detailed literature review provided some further insights based on case reports of embolic events experienced after cyanoacrylate injection. Many authors theorized the presence of spontaneous portosystemic shunt as a probable explanation for embolization of tissue adhesives. However, no radiological or morphological evidence of vasculature malformation was provided. In our study, we meticulously reviewed the radiological imaging of all 5 patients and were able to identify the presence of spontaneous portosystemic shunt in 3/5 (60%) subjects.

Overall, the use of cyanoacrylate for gastric variceal obliteration is widely accepted with promising results. The safety of tissue adhesive injection is often guaranteed when endoscopist abides by the standardized sandwich technique [8, 40]. However, the necessity of preoperative imaging of the portovenous system should also be considered to identify patients with spontaneous portosystemic shunt (SPSS). In such cases, the risk of traditional endoscopic glue injection should be thoroughly vetted, or alternative treatment measures such as coil injection, TIPS, BRTO, or surgical therapy should be referred to. Utility of pre- and postoperative hemostatic agents should also be carefully considered to achieve a desirable hemostatic balance. Adverse events associated with tissue adhesives are often fatal and debilitating for patients; any red flags before endoscopic therapy should

Table 4

Number	Searches	Medline results	Embase results	Search type
(1)	(esophag* or esophag* gastr* or gastr* esophag* or gastr* oesophag* or gastroesophag* or gastrooesophag* or oesophag* or oesophag* gastr* or gastr*).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	169513	268529	Advanced
(2)	1 and (varic* or varix).mp.	14601	21427	Advanced
(3)	exp esophageal varices/	12569	17997	Advanced
(4)	exp gastric varices/	12569	2864	Advanced
(5)	(3) or (4)	12569	19501	Advanced
(6)	(2) or (5)	14601	22623	Advanced
(7)	(cyanoacrylate or n-butyl-2-cyanoacrylate or NBCA or NB2CYA or NB2-CYA or tissue adhesive or tissue glue or glue).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	13485	26245	Advanced
(8)	(infarct* or embol* or advers* event* or severe advers* event* or complicat*).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1649685	3380532	Advanced
(9)	(7) and (8)	4356	10406	Advanced
(10)	(endoscop* therap* or endoscop* treat* or endoscop* inject*).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	8912	21219	Advanced
(11)	(9) and (10)	186	657	Advanced
(12)	(case or case report* or case serie* or report*).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	4746115	6342357	Advanced
(13)	(6) and (11) and (12)	43	119	Advanced

Exp, explode.

be well recognized by physicians, prompting well-rounded consideration to effectively avoid the occurrence of adverse events.

Appendix

Detailed Search Strategy

The search strategy used was Ovid Medline (R), from 1946 to present with daily updates, and Embase, from 1974 to March 20, 2017(see Table 4).

Ethical Approval

All procedures followed were in accordance with the ethical standards of the responsible committee of human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Consent

Informed consent was obtained from all patients for being included in the study.

Disclosure

The abstract of this manuscript has been presented at China 17th Congress of Gastroenterology, Xi'an, China, September 14–16, 2017. This article does not contain any studies with animal subjects.

Conflicts of Interest

Yujen Tseng, Lili Ma, Tiancheng Luo, Xiaoqing Zeng, Yichao Wei, Ling Li, Pengju Xu, and Shiyao Chen declare that they have no conflicts of interest. All procedures followed were in accordance with the ethical standards of the responsible

committee of human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Authors' Contributions

Yujen Tseng and Lili Ma contributed equally to the manuscript and share first authorship.

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Research Article

Short-Term Outcome of Patients with Cirrhosis and Concurrent Portal Cavernoma Presenting with Acute Variceal Bleeding

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Background and Aim. The outcome of cirrhotic patients with main portal vein occlusion and portal cavernoma after the first episode of acute variceal bleeding (AVB) is unknown. We compared short-term outcomes after AVB in cirrhotic patients with and without portal cavernoma. *Methods.* Between January 2009 and September 2014, 28 patients with cirrhosis and portal cavernoma presenting with the first occurrence of AVB and 56 age-, sex-, and Child-Pugh score-matched cirrhotic patients without portal cavernoma were included. The primary endpoints were 5-day treatment failure and 6-week mortality. *Results.* The 5-day treatment failure rate was higher in the cavernoma group than in the control group (32.1% versus 12.5%; $p = 0.031$). The 6-week mortality rate did not differ between the cavernoma and control group (25% versus 12.5%, $p = 0.137$). Multivariable Cox proportional hazard regression analyses revealed that 5-day treatment failure (HR = 1.223, 95% CI = 1.082 to 1.384; $p = 0.001$) independently predicted 6-week mortality. *Conclusions.* Cirrhotic patients with AVB and portal cavernoma have worse short-term prognosis than patients without portal cavernoma. The 5-day treatment failure was an independent risk factor for 6-week mortality in patients with cirrhosis and portal cavernoma.

1. Introduction

Acute variceal bleeding (AVB) remains one of the most dangerous complications of portal hypertension and is associated with significant morbidity and mortality in patients with cirrhosis [1]. Despite the advances in AVB management, 6-week mortality still remains high and is related to the severity of the underlying cirrhosis, hepatic venous pressure gradient (HVPG), and the presence of portal vein thrombosis [1–5].

With the increased frequency of liver imaging modalities, portal vein thrombosis (PVT) is increasingly identified in the setting of liver cirrhosis. The estimated prevalence of PVT in these patients varies from 5 to 26% [6, 7]. The chronic PVT may result in main portal vein occlusion and cavernous transformation, while the obstructed portal vein is replaced by a network of hepatopetal vessels [8]. The presence of portal cavernoma negatively affects the prognosis of these patients because of the resultant further increases in portal hypertension, with an increased risk of variceal bleeding, and, furthermore, the extension of PVT may increase the risk of perioperative morbidity and mortality or exclude patients from liver transplantation [9, 10].

The effect of main portal vein occlusion and cavernous transformation on the short-term outcomes of patients with cirrhosis and AVB has not been previously described. The aim of the present study was to evaluate the short-term outcomes of patients with cirrhosis and concurrent main portal vein occlusion and portal cavernoma admitted due to the first episode of AVB in a retrospective matched study.

2. Materials and Methods

2.1. Study Cohort. This retrospective cohort study included consecutive patients with cirrhosis, admitted to West China Hospital (a 4800-bed tertiary medical center in China) from January 2009 to September 2014, with the first episode of AVB and portal cavernoma. Liver cirrhosis was diagnosed by liver biopsy and/or clinical and imaging findings. For each identified patient, 2 patients with cirrhosis and the first

episode of AVB without the presence of PVT, admitted during the same period, were matched for age, sex, and Child-Pugh score. Patients with hepatocellular carcinoma were excluded. This study was approved by the Institutional Review Board of West China Hospital.

2.2. Treatments. Vasoactive drugs (somatostatin) were administered to every patient as soon as possible after gastrointestinal bleeding and before endoscopic examination. Endoscopic treatment was performed in patients diagnosed with bleeding from gastroesophageal varices on endoscopy. Endoscopic variceal banding and endoscopic glue injection were used as the primary therapies for bleeding from esophageal or gastric varices, respectively.

2.3. Data Collection and Definition. Complete baseline data were collected through electronic medical records. These data included demographic information, etiology of liver cirrhosis, and basic laboratory information including regular blood tests, hepatic and renal function tests, prothrombin time, international normalized ratio (INR), Child-Pugh score and Model for End-Stage Liver Diseases (MELD) scores, imaging findings on color Doppler ultrasound, contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI), and information about the treatments, including endoscopic therapy, surgery, and use of β-blockers.

The diagnosis of portal cavernoma was based on contrast-enhanced CT or MRI, in which the main portal vein was completely obstructed and replaced by fibrous tissue with the development of a hepatopetal network of periportal collateral veins. The time frame for an acute bleeding episode was 120 h (5 days). Five-day treatment failure was defined as uncontrolled index variceal bleeding, rebleeding, or death within 5 days. In particular, we defined the control of active variceal bleeding as a lack of hematemesis; the hemoglobin (Hb) level was stable without requiring blood transfusions or hemodynamic stability for 24 h after drug therapy and endoscopic treatment. Early rebleeding was defined by any of the following events, whichever occurred first: fresh hematemesis or NG aspiration of 100 ml of fresh blood 2 h after the start of vasoactive drugs alone or in combination with endoscopic therapy; development of hypovolemic shock; or a 3 g decrease in Hb (9% drop of Ht) within any 24 h period if no transfusion is administered [11].

2.4. Statistical Analysis. Quantitative variables were expressed as the mean ± standard deviation, and Student's t-test was performed to assess the difference between variables. Qualitative variables were expressed as frequencies and were analyzed using Pearson's $\chi 2$ test or Fisher's exact test. The cumulative incidence of 6-week mortality rate was estimated using the Kaplan–Meier method and compared using the log-rank test. Independent predictors with a p value < 0.05 in univariate analysis were included in the multivariate analyses. Multivariate analyses were performed using Cox regression analysis. Individual variables already included in the Child-Pugh score or MELD score were not considered separately. The risks estimated from the Cox regression models were expressed as hazard ratios (HRs) with their respective 95% confidence intervals (CIs). A two-tailed p value of <0.05 was considered statistically significant. Statistical analysis was performed using SPSS for windows (version 19.0; SPSS, Chicago, IL).

3. Results

3.1. Characteristics of the Cohorts. Twenty-eight patients with cirrhosis and concurrent portal cavernoma presenting with the first episode of AVB were admitted in our hospital during the period of the study. Fifty-six age-, sex-, and Child-Pugh score-matched patients with cirrhosis who experienced the first incident of AVB without PVT were selected from the overall population of patients during the same time period. Overall, a total of 84 patients were enrolled in the study.

The clinical and laboratory characteristics of the cohort are summarized in Table 1. The most common etiology for liver cirrhosis was Hepatitis B Virus infection (60%) followed by alcoholic liver disease (13%). The mean Child-Pugh and MELD score at the time of hospital admission were 8.1 ± 1.9 and 15.8 ± 5.4, respectively. Bleeding originated from esophageal varices in 22 patients (78.6%), from gastric varices in 2 patients (7.1%), and from unknown site in 4 (14.3%) in the cavernoma group. Source of bleeding was esophageal varices in 40 patients (71.4%), gastric varices in 10 patients (17.9%), and unknown in 6 (10.7%) in the control group. These two groups had comparable clinical and laboratory data, except for the higher platelet level, more incidences of ascites and previous splenectomy in the cavernoma group.

3.2. 5-Day Treatment Failure. Table 2 shows the main outcomes of the cohort of patients. Failure to control the index-bleeding episode occurred in 5 cases in the cavernoma group and in 3 cases in the control group. The frequency of index bleeding was not controlled successfully by initial therapy and did not differ significantly between the cavernoma group and the control group (17.9% versus 5.4%, $p = 0.066$). In the cavernoma group, 2 patients were treated with balloon tamponade as a rescue therapy. One patient died of massive bleeding before further intervention could be performed, and 2 patients received pharmacological therapy alone. All 3 patients in the control group underwent transjugular intrahepatic portosystemic shunt (TIPS) as a salvage therapy.

Of the 67 patients in whom index bleeding was controlled successfully without rescue therapy, 6 (9.0%) patients rebled from varices within the first 5 days of their hospital admission. However, the rate of recurrent variceal bleeding did not differ significantly between these two groups (14.3% versus 3.6%, $p = 0.072$). Five patients (3 in the cavernoma group and 2 in the control group) died within the 5-day treatment period.

Ultimately, 5-day treatment failure occurred in 9 out of 28 patients (32.1%) in the cavernoma group and in 7 out of 56 patients (12.5%) in the control group. The rate of 5-day treatment failure was higher in the cavernoma group compared with the control group ($p = 0.031$). Among all of the subjects, no significant independent predictor of 5-day

Table 1: Demographics and clinical characteristics at admission.

Characteristic	The cavernoma group ($n = 28$)	The control group ($n = 56$)	p value
Age, years	53.1 ± 11.9	53.3 ± 11.8	0.487
Sex, male, %	19/9	38/18	1
Cause of liver disease, n			0.580
Chronic HBV infection	19	31	
Chronic HCV infection	0	2	
Alcohol	3	9	
others	6	14	
Hemoglobin, g/L	79.6 ± 23.9	73.2 ± 23.5	0.242
Platelet, 1000/mm3	121.7 ± 101.9	84.7 ± 57.1	0.036
WBC	5.3 ± 3.1	9.1 ± 11.3	0.091
Creatinine, μmol/L	70.0 ± 20.4	76.4 ± 20.9	0.962
ALT, IU/L	30.3 ± 19.7	41.0 ± 56.2	0.330
AST, IU/L	48.6 ± 30.3	57.2 ± 92.9	0.633
Bilirubin, μmol/L	35.9 ± 38.3	26.1 ± 22.9	0.149
Albumin, g/L	29.7 ± 7.0	30.5 ± 5.8	0.554
INR	1.3 ± 0.4	1.4 ± 0.4	0.455
Ascites, n (%)	24 (85.7%)	33 (58.9%)	0.013
Encephalopathy, n (%)	1 (3.6%)	1 (1.7%)	0.613
Child-Pugh grade, n (%)			0.447
A	4	14	
B	18	34	
C	6	8	
Child score	7.36 ± 2.14	7.96 ± 1.76	0.439
MELD score	15.43 ± 5.3	16.46 ± 5.4	0.851
Heart rate, beats/min	84 ± 13	83 ± 15	0.983
Systolic blood pressure, mmHg	109 ± 20	112 ± 18	0.530
Infection, n (%)	7 (25%)	12 (20.7%)	0.712
Splenectomy, n (%)	10 (35.7%)	9 (15.5%)	0.043

Abbreviations. HBV, hepatitis B virus; HCV, hepatitis C virus; WBC, white blood cell; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table 2: Summary of efficacy measurements during the 5-day period.

	The cavernoma group ($n = 28$)	The control group ($n = 56$)	p value
5-day treatment failure, n (%)	9 (32.1%)	7 (12.5%)	0.031
Failure to control acute bleeding, n (%)	5 (17.9%)	3 (5.4%)	0.066
Early rebleeding in 5 days, n (%)	4 (14.3%)	2 (3.6%)	0.072
5-day mortality, n (%)	3 (10.7%)	2 (3.6%)	0.192

treatment failure was identified using univariate regression and Cox proportional hazard modeling.

3.3. 6-Week Mortality. The overall 6-week mortality after AVB was 16.7% ($n = 14$) in the entire series, with 35.7% ($n = 5$) occurring within five days. The cumulative mortality rate did not differ between the cavernoma and control group (25% versus 12.5%, $p = 0.137$, Figure 1). Causes of death were uncontrolled or reported as relapsing bleeding ($n = 7$), liver failure ($n = 5$), sepsis ($n = 1$), and unknown ($n = 1$). The multivariable Cox proportional hazard regression analysis identified 5-day treatment failure (HR = 1.223, 95% CI = 1.082 to 1.384; $p = 0.001$) as the only independent predictor of 6-week mortality.

4. Discussion

Hemorrhage from gastroesophageal varices represents one of the most feared complications in the natural history of cirrhosis and is associated with significant morbidity and mortality [1, 3]. Our study was specifically designed to assess the short-term outcomes of cirrhotic patients with concurrent main portal vein occlusion and portal cavernoma presenting with the first episode of AVB. We found that the presence of portal cavernoma was associated with worse 5-day treatment failure in these patients.

The results of our study confirmed that PVT increased the risk of 5-day treatment failure in patients with AVB [2, 12]. In 2003, D'Amico and de Franchis evaluated the short-term

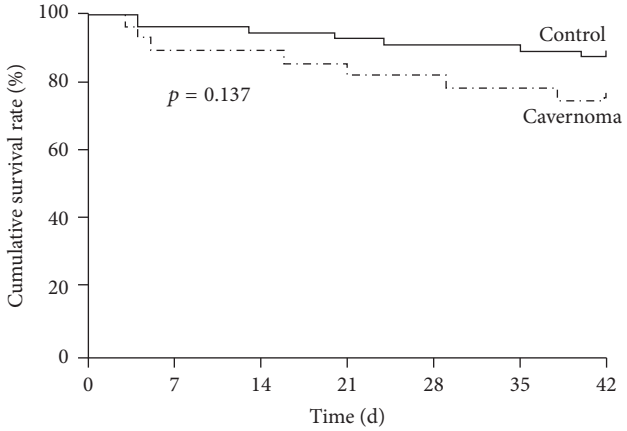

Figure 1: Kaplan–Meier estimates of 6-week survival in cirrhotic patients with portal cavernoma and active variceal bleeding.

outcomes and risk factors of 185 patients with liver cirrhosis and AVB retrospectively. They reported that the presence of PVT was an independent predictor for 5-day failure (for any sources of bleeding: OR = 3.19, 95% CI: 1.53–6.67, p = 0.002; for variceal bleeding: OR = 3.06, 95% CI: 1.39–6.68, p = 0.005) [2]. Another Italian study performed in 2012 enrolled 185 patients of whom 32 patients (17.3%) had PVT and demonstrated that the presence of PVT was associated with negative short-term outcomes [12]. This finding was potentially attributed to the higher portal venous pressure due to main portal vein occlusion, which makes the patients more susceptible to both initial medical/endoscopic therapy failure and early rebleeding. However, liver perfusion was decreased to a great extent, and further hepatic decompensation may occur.

TIPS used to be considered as a rescue treatment when bleeding was not controlled by less invasive endoscopic treatment and/or pharmacological therapy [3]. However, there is growing evidence for the support of early TIPS within 72 h (ideally < 24 h) in selected patients at a high risk of treatment failure [e.g., HVPG ≥ 20 mmHg, Child-Pugh C < 14 points, or Child-Pugh B with active bleeding] [13, 14]. All 3 patients who failed the initial therapy in the control group underwent TIPS as a rescue treatment and survived. In contrast, none of the patients in the cavernoma group could benefit from early placement of TIPS due to the complete obstruction of the main portal vein and lack of larger portal-portal collateral vein. The limitations of the treatment options demonstrated negative effects on the outcomes of the patient.

Currently, the effect of PVT on the prognosis of cirrhosis is debatable [7]. Luca et al., in their series of 42 patients with cirrhosis and partial PVT, revealed that liver function at diagnosis was the only independent predictor of survival and hepatic decompensation, instead of progression or regression of PVT [15]. Similarly, Maruyama and his colleagues found that the incidence of variceal bleeding did not differ statistically between patients with PVT compared to patients without PVT, as well as the survival rate [16]. Finally, a very recent prospective study, performed by Nery et al., enrolled 1,243 adults (863 Child A patients and 380 Child B patients) with cirrhosis but without PVT [17]. They found that the 5-year cumulative incidence of PVT was 10.7%, and PVT was mostly partial and varied overtime. In addition, there was no relationship between the development of PVT and the progression of liver disease, which was consistent with the findings obtained in previous reports [17].

Importantly, whether PVT affects the treatment effect and patients' survival in cirrhosis is associated with the degree and extension of PVT, as well as the severity of the underlying liver disease. In a study by Luca et al., which included 42 patients with cirrhosis and PVT, only 9 patients (21.4%) had grade 4 (≥76% of vessel lumen) thrombosis, 5 (11.9%) patients had large esophageal varices, and 12 (28.6%) patients experienced gastroesophageal variceal bleeding [15]. Over the 11-year study period, PVT developed in 28% (42/150) of patients with cirrhosis, and 11 patients (26.2%) suffered from complete portal vein obstruction [16]. Furthermore, 183 out of 1243 patients (16.3%) had grade ≥2 esophageal varices in a study by Nery et al. [17]. In the present series, all patients in the cavernoma group were admitted due to AVB. Unlike previous reports with a relatively high rate of spontaneous thrombosis improvement (45–47.5%), the possibility of spontaneous recanalization of the occluded main portal vein is very low [15, 16]. In addition, the mean MELD score (15.8) of our cohorts appeared to be higher than previous reports (12.1 from Luca, 10.2 in patients without PVT, and 10.6 in patients with PVT from Maruyama, resp.).

To the best of our knowledge, this is the first study to focus on the effect of portal cavernoma on the short-term outcomes of patients with cirrhosis and the first episode of AVB. The optimal management of AVB in patients with cirrhosis and portal cavernoma was difficult to establish due to the scarcity of the clinical trial data. This group of patients is usually excluded from clinical trials, and bleeding is particularly difficult to control because TIPS is often not applicable.

The major limitation of our study is the relatively small sample size and its retrospective design; therefore, bias may exist. The definition of portal cavernoma varied between different studies. Only patients with complete occluded main portal vein and the presence of portal-portal collateral vessels were included in the present study which influenced the number of patients for analysis greatly. We are aware that a prospective, large sample size trial may provide more convincing evidence on this subject. Unfortunately, only 28 patients with cirrhosis and portal cavernoma who presented with the first episode of AVB were identified during the study period in our hospital, which is one of the largest single-site hospitals in the world.

In conclusion, our data indicate that portal cavernoma in cirrhotic patients suffering from the first episode of AVB is associated with higher 5-day treatment failure. However, 6-week mortality did not significantly differ between the cavernoma and control groups. Long-term outcomes of patients with cirrhosis and portal cavernoma need further evaluation.

Conflicts of Interest

The authors disclose no conflicts of interest.

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