Transient Elastography Identifies the Risk of Esophageal Varices and Bleeding in Patients With Hepatitis B Virus–Related Liver Cirrhosis

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Abstract: This study aimed to analyze the diagnostic accuracy of liver stiffness for predicting esophageal variceal grading and the risk of esophageal variceal bleeding (EVB) in cases of cirrhosis. Hematological and biochemical parameters were measured and transient elastography was performed in 88 patients with hepatitis B–related cirrhosis undergoing endoscopy for esophageal varices. Esophageal varices grade was highly correlated with liver stiffness measurement (LSM) and the liver stiffness spleen diameter-to-platelet score in cirrhosis. Compared with those from endoscopy, the LSM and the liver stiffness spleen diameter-to-platelet score for the absence of esophageal varices were as follows: area under the receiver operating characteristic curve (AUROC), 0.894/0.926; sensitivity, 0.836/0.818; and specificity, 0.875/1.000, respectively. The AUROC and the sensitivity and specificity of LSM and the liver stiffness spleen diameter-to-platelet score for predicting grade III esophageal varices were 0.954 and 0.901, respectively. The AUROCs of LSM and the liver stiffness spleen diameter-to-platelet score for discriminating grades II and III from grade I or the absence of esophageal varices were 0.958 and 0.941, respectively. We also found that EVB was closely associated with LSM and spleen diameter. The AUROC, sensitivity, and specificity were 0.855/0.819, 0.857/0.875, and 0.747/0.780, respectively. Meanwhile, LSM and spleen diameter were 2 independent factors for predicting EVB. These data suggest that LSM and the liver stiffness spleen diameter-to-platelet score could accurately rule out cirrhosis without esophageal varices and differentiate high- and low-risk patients. Furthermore, LSM and spleen diameter had excellent abilities to predict EVB.

Key Words: liver stiffness, hematological and biochemical parameters, esophageal variceal grading, esophageal variceal bleeding

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Reducing the high mortality from hepatitis B virus (HBV)–related cirrhosis in China[1] remains a top priority. Esophageal varices are the most commonly occurring severe complication of HBV-associated cirrhosis with portal hypertension.[2] With disease progression, esophageal varices become a major cause of morbidity and mortality because of the risk of hemorrhage[2]; therefore, early evaluation of high-risk esophageal varices is pivotal in reducing the morbidity and mortality rates among patients with cirrhosis.

The hepatic venous pressure gradient is considered an excellent predictor of portal hypertension severity and variceal presence, size, and bleeding.[3] Endoscopy is the best diagnostic test for varices in cases of liver cirrhosis,[4] and its use is recommended by current guidelines to identify esophageal varices in all cirrhotic patients.[5] However, both hepatic venous pressure gradient and endoscopy are invasive; some patients may also be less likely to undergo them because of their high cost and unpleasantness.[6] Consequently, identifying noninvasive methods of assessing esophageal varices severity and bleeding risk is essential.

As a novel noninvasive assessment method, transient elastography has become highly useful because of its accuracy, simplicity, and rapid results.[7–9] In particular, transient elastography can accurately predict liver cirrhosis.[10] Moreover, recent studies have suggested that transient elastography combined with platelet count could distinguish the absence of esophageal varices.[11] The Baveno VI criteria proposed that cirrhotic patients with a liver stiffness measurement (LSM) of less than 20 kPa and a platelet count of greater than 150,000/μL can avoid screening endoscopy; Maurice et al[12] further conformed these criteria. In addition, recent studies reported that LSM in patients with liver cirrhosis can predict the presence of large esophageal varices.[13,14] Although these data suggested that LSM may play key roles in assessing the progression of liver cirrhosis[15] and the presence of large esophageal varices,[14,16] whether LSM, the liver stiffness spleen diameter-to-platelet score, the platelet count/spleen diameter ratio, and spleen diameter could predict esophageal varices degree and the risk of variceal bleeding as well as which parameters were most valuable remain poorly understood.

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Considering the need to identify patients with high-risk esophageal varices but not esophageal variceal bleeding (EVB), an optimized surveillance and prophylaxis plan with risk stratification is urgently required. Here, we aimed to investigate the diagnostic accuracy of LSM conducted by transient elastography as well as other related parameters for evaluating esophageal varices grade and bleeding risk in cases of HBV-related cirrhosis.

MATERIALS AND METHODS

Patients

One hundred fifty-eight patients with HBV-related cirrhosis treated between September 2014 and December 2015 at Union Hospital, our University of Science and Technology, were screened for possible enrollment in this study. Of them, 70 were excluded by the exclusion criteria (Fig. 1); the remaining 88 were included in the statistical analysis. Each had been administered oral antiviral drugs for at least 6 months and underwent a systematic biochemical examination and endoscopy for detecting esophageal varices presence and severity and LSM with a FibroTouch (HISK MED, Wuxi, China), a new-generation transient elastography based on a 2-dimensional image-guided system to ensure precise orientation. The time interval between endoscopy and the transient elastography evaluation was less than 3 months. Cirrhosis was diagnosed based on history, clinical, laboratory, and ultrasonography findings.

The exclusion criteria were as follows: any cause of portal hypertension other than HBV; body mass index (BMI) greater than 35 kg/m^2; ascites, which may drastically influence LSM accuracy; an invalid liver stiffness value; a history of variceal bleeding or upper gastrointestinal tract bleeding; a history of β-blocker therapy or variceal ligation; positive for antibodies to human immunodeficiency virus or for hepatitis C virus; excessive alcohol consumption or drug abuse; and hepatocellular carcinoma at enrollment or history of it. Using our exclusion criteria, the remaining 88 patients were included in the final analysis. The clinical and biochemical information was reviewed. All patients signed a written informed consent form after being informed of the possible complications of the diagnostic procedures. The present study conformed with the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the institutional review board of our institution.

Endoscopy

All patients underwent upper gastrointestinal endoscopy performed by professional and experienced endoscopists at our endoscopy center with the aim of evaluating esophageal varices presence and severity. Eesophageal varices were divided into 4 categories: esophageal varices 0, no vein above the esophageal mucosal surface; grade I, veins are small and minimally elevated above the mucosal surface; grade II, tortuous varices accounting for less than one third of the esophageal lumen; and grade III, large varices occupying more than one third of the esophageal lumen.[6] High-risk esophageal varices were regarded as grade II/III or grade I esophageal varices with red signs or decompensated cirrhosis.[6]

Abdominal Ultrasonography and LSM

All patients underwent an abdominal ultrasonographic examination performed by 1 of 5 independent professional and experienced sonographers with more than 15 years of experience who were blinded to the patients' clinical details. The spleen bipolar diameter was the largest longitudinal dimension at the hilum of the spleen during deep inspiration on the monitor.[15] Spleen diameter was the mean value of 3 measurements.

After the upper abdominal ultrasonographic examinations, transient elastography was subsequently measured using Fibrotouch (Wuxi Hisky Medical Technologies Co, Ltd) by an experienced technician who had performed more than 10,000 examinations according to the previous technique and examination procedure.[17] In this study, LSM success was defined as an interquartile range/LSM of 0.3 or less, up to 10 validated measurements, and a success rate of 60% or higher.[18]

Clinical and Laboratory Parameters

Clinical and laboratory parameters including sex, age, BMI, and Child-Pugh grade were measured in all patients. Biochemical laboratory parameters included alanine aminotransferase, aspartate aminotransferase, total bilirubin, direct bilirubin, albumin, globulin, alkaline phosphatase, and γ-glutamyl transpeptidase levels; platelet count; red blood cell count; hemoglobin level; prothrombin time; and the international normalized ratio. Spleen diameter was measured using upper abdomen ultrasonographic examination. Noninvasive algorithms, including

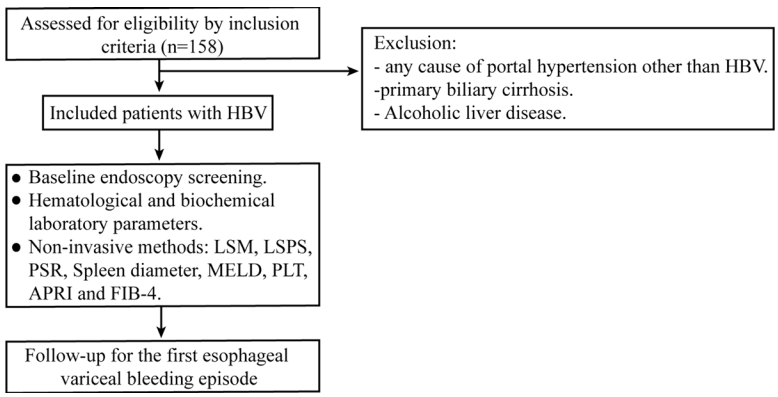

FIGURE 1. Diagram for selection of patients. APRI, AST-to-Platelet ratio index; FIB-4, Fibrosis 4; LSPS, the liver stiffness spleen diameter-to-platelet score; PLT, platelet; PSR, platelet count/spleen diameter ratio.

the platelet count/spleen diameter ratio, Fibrosis 4 score (age [years] × aspartate aminotransferase [IU/L]/platelet count [10^9/L] × square root of alanine aminotransferase [IU/L]), aspartate-to-platelet ratio index (APRI = [(AST level/ULN)/platelet count (10^9/L)] × 100), the liver stiffness spleen diameter-to-platelet score (liver stiffness × spleen size/platelets), and model for end-stage liver disease (MELD) score were calculated based on the related reports.[7–12]

Statistical Analysis

The χ^2 test was used to analyze categorical data, whereas Student *t* test was used to analyze continuous data. One-way analysis of variance was used to compare the mean values of 3 or more groups. The diagnostic performances of LSM, spleen diameter, the platelet count/spleen diameter ratio, and the liver stiffness spleen diameter-to-platelet score were assessed using receiving operating characteristic (ROC) curves to evaluate esophageal varices presence and severity and predict EVB. The trapezoidal rule was applied to calculate the area under the ROC curve (AUROC). The DeLong test was used to compare AUROCs among the different groups. A multiple logistic regression analysis was used to identify risk factors associated with EVB, including LSM, spleen diameter, the liver stiffness spleen diameter-to-platelet score, and the platelet count/spleen diameter ratio. For the multiple logistic regression analysis, variables maintained in the final model were selected using the stepwise selection method.

Cutoff values obtained from ROC curves could be used to compute sensitivity and specificity. Those cutoff values maximizing sensitivity and specificity were considered optimal cutoff values. Confidence intervals of 95% calculated for each predictive test were used to compare AUROCs. The results are reported as frequencies and percentage for categorical variables, mean ± SD for normally distributed continuous variables, and median and interquartile range for nonnormally distributed continuous variables. Statistical analyses were performed using SPSS version 20 (SPSS Inc, Chicago, IL). A probability level (*P*) of 0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

The baseline characteristics of the 88 included patients are shown in Table 1. The average age was 49.5 years, and male sex was predominant (n = 66; 75%). The mean BMI was 23.43 kg/m^2. Moreover, most cases were Child-Pugh A (81.82%), whereas 16 (18.18%) were Child-Pugh B. The spleen diameter and mean LSM values were 142.91 mm and 24.14 kPa, respectively.

Table 2 shows a summary comparison of the characteristics of patients with or without esophageal varices. Varices were present in 81.82% of cases (n = 72). Compared with patients without varices, patients with esophageal varices had a statistically higher alkaline phosphatase, larger spleen diameter, lower hemoglobin levels, and lower platelet count/spleen diameter ratio. Liver stiffness measurement and the liver stiffness spleen diameter-to-platelet score values were significantly elevated in patients with esophageal varices than in those without. There were no significant intergroup differences in the other indexes.

TABLE 1. Baseline Characteristics of Entire Population

Items	Hepatitis B–Related Cirrhosis (n = 88)
Sex, male/female	66/22
Age, y	49.55 ± 10.20
BMI, kg/m^2	23.43 ± 4.17
Child-Pugh	
A	72 (81.82%)
B	16 (18.18%)
ALT, U/L	42.67 ± 47.38
AST, U/L	42.69 ± 30.32
TBIL, μmol/L	23.02 ± 15.73
DBIL, μmol/L	10.71 ± 7.96
ALB, g/L	38.07 ± 6.11
GLB, g/L	29.03 ± 6.06
ALP, U/L	101.19 ± 46.62
γ-GT, U/L	55.67 ± 61.16
Red blood cell, T/L	3.98 ± 0.83
Hemoglobin, g/L	122.65 ± 25.82
Platelet, ×10^9/L	116.99 ± 96.06
PT, s	15.54 ± 1.89
INR	1.26 ± 0.20
Spleen diameter, mm	142.91 ± 34.22
PSR	707.02 ± 513.79
LSPS	6.10 ± 6.56
LSM, kPa	24.14 ± 15.39
FIB-4	4.69 ± 4.27
APRI	1.37 ± 1.16
MELD	6.73 ± 3.89

ALB, albumin; ALP, alkaline phosphatase; ALT, aminotransferase; AST, aspartate aminotransferase; DBIL, direct bilirubin; FIB-4, Fibrosis 4; γ-GT, γ-glutamyltranspeptidase; GLB, globulin; INR, international normalized ratio; LSPS, liver stiffness × spleen diameter/platelet count ratio score; PSR, platelet count/spleen diameter ratio; PT, prothrombin time; TBIL, total bilirubin.

These data indicated that alkaline phosphatase, spleen diameter, the platelet count/spleen diameter ratio, LSM, and the liver stiffness spleen diameter-to-platelet score might be useful for distinguishing cirrhosis patients with esophageal varices from those without.

Esophageal Varices Degree Is Closely Associated With Spleen Diameter, the Platelet Count/Spleen Diameter Ratio, the Liver Stiffness Spleen Diameter-to-Platelet Score, and LSM Alterations

Because spleen diameter, the platelet count/spleen diameter ratio, the liver stiffness spleen diameter-to-platelet score, and LSM were associated with esophageal varices (Table 2), we further analyzed their correlations. Spleen diameter, the platelet count/spleen diameter ratio, the liver stiffness spleen diameter-to-platelet score, and LSM among patients without esophageal varices and those with different grades were significantly different (Table 3). Patients with more severe varices had a statistically larger spleen diameter, lower platelet count/spleen diameter ratio, higher liver stiffness spleen diameter-to-platelet score, and higher LSM levels than did those without or with moderate varices ($P < 0.001$; Table 3).

TABLE 2. Comparison of Characteristics Between HBV Related Liver Cirrhosis Patients With and Without Esophageal Varices

Items	Esophageal Varices		P
	Absent (n = 16)	Present (n = 72)	
Sex, male/female	10/6	56/16	0.191
Age, y	50.94 ± 8.09	49.25 ± 10.63	0.551
BMI, kg/m^2	24.74 ± 3.91	23.14 ± 4.20	0.166
Child-Pugh			0.880
A	13 (81.25%)	59 (81.94%)	
B	3 (18.75)	13 (18.06%)	
ALT, U/L	40.18 ± 48.09	43.22 ± 47.54	0.818
AST, U/L	43.75 ± 45.36	42.45 ± 26.36	0.878
TBIL, μmol/L	27.86 ± 26.79	21.96 ± 12.11	0.175
DBIL, μmol/L	12.60 ± 14.06	10.29 ± 5.94	0.297
ALB, g/L	40.57 ± 5.24	37.52 ± 6.19	0.071
GLB, g/L	29.63 ± 4.03	28.90 ± 6.44	0.667
ALP, U/L	77.63 ± 25.04	106.36 ± 48.74	0.025
γ-GT, U/L	47.06 ± 52.73	57.56 ± 63.02	0.537
Red blood cell, T/L	4.07 ± 1.28	3.97 ± 0.73	0.683
Hemoglobin, g/L	138.14 ± 17.76	119.68 ± 26.15	0.013
Platelet, $\times 10^9$/L	128.57 ± 48.18	114.77 ± 102.82	0.625
PT, s	15.15 ± 2.38	15.61 ± 1.80	0.446
INR	1.23 ± 0.25	1.27 ± 0.19	0.518
Spleen diameter, mm	111.79 ± 15.38	152.82 ± 32.63	0.000
PSR	1206.67 ± 508.10	570.75 ± 427.71	0.000
LSPS	1.01 ± 0.66	7.49 ± 6.77	0.002
LSM, kPa	10.25 ± 4.43	27.19 ± 16.27	0.000
FIB-4	3.46 ± 3.06	4.92 ± 4.45	0.244
APRI	1.14 ± 1.40	1.41 ± 1.11	0.420
MELD	6.03 ± 5.30	6.85 ± 3.64	0.520

ALB, albumin; ALP, alkaline phosphatase; ALT, aminotransferase; AST, aspartate aminotransferase; DBIL, direct bilirubin; FIB-4, Fibrosis 4; GLB, globulin; γ-GT, γ-glutamyltranspeptidase; INR, international normalized ratio; LSPS, liver stiffness × spleen diameter/platelet count ratio score; PSR, platelet count/spleen diameter ratio; PT, prothrombin time; TBIL, total bilirubin.

TABLE 4. Comparison of Characteristics Between HBV-Related Liver Cirrhosis Patients With and Without Variceal Bleeding

Items	Variceal Bleeding		P
	Absent (n = 74)	Present (n = 14)	
Sex, male/female	53/21	13/1	0.186
Age, y	48.76 ± 10.06	53.79 ± 10.25	0.091
BMI, kg/m^2	23.49 ± 4.45	23.08 ± 2.29	0.738
Child-Pugh			0.575
A	60 (80%)	12 (85.71%)	
B	14 (18.67%)	2 (14.29%)	
C	1 (1.33%)	0 (0)	
ALT, U/L	44.48 ± 51.25	33.00 ± 10.96	0.408
AST, U/L	43.13 ± 32.37	40.29 ± 15.89	0.749
TBIL, μmol/L	23.60 ± 16.33	19.90 ± 12.02	0.422
DBIL, μmol/L	10.86 ± 8.19	9.9 ± 6.75	0.681
ALB, g/L	38.74 ± 6.10	34.46 ± 4.98	0.015
GLB, g/L	29.10 ± 5.79	28.63 ± 7.60	0.789
ALP, U/L	99.85 ± 48.50	108.36 ± 35.46	0.534
γ-GT, U/L	55.59 ± 63.61	56.14 ± 47.80	0.975
Red blood cell, T/L	4.09 ± 0.85	3.43 ± 0.43	0.006
Hemoglobin, g/L	127.64 ± 24.73	96.64 ± 12.51	0.000
Platelet, $\times 10^9$/L	121.27 ± 101.76	94.64 ± 55.25	0.345
PT, s	15.45 ± 1.91	15.95 ± 1.80	0.385
INR	1.25 ± 0.20	1.31 ± 0.19	0.351
Spleen diameter, mm	137.56 ± 32.01	176.38 ± 29.64	0.002
PSR	741.99 ± 526.36	497.19 ± 393.96	0.215
LSPS	5.37 ± 6.54	10.47 ± 5.04	0.041
LSM, kPa	21.13 ± 13.28	40.29 ± 16.33	0.000
FIB-4	4.56 ± 4.25	5.33 ± 4.47	0.542
APRI	1.36 ± 1.20	1.38 ± 0.96	0.974
MELD	6.56 ± 3.88	7.53 ± 4.00	0.419

ALB, albumin; ALP, alkaline phosphatase; ALT, aminotransferase; AST, aspartate aminotransferase; DBIL, direct bilirubin; FIB-4, Fibrosis 4; GLB, globulin; γ-GT, γ-glutamyltranspeptidase; INR, international normalized ratio; LSPS, liver stiffness × spleen diameter/platelet count ratio score; PSR, platelet count/spleen diameter ratio; PT, prothrombin time; TBIL, total bilirubin.

The Liver Stiffness Spleen Diameter-to-Platelet Score and LSM Values Are Closely Related to Esophageal Varices Bleeding in Cirrhosis

The characteristics of cirrhosis patients with and without variceal bleeding are shown in Table 4. Patients with EVB had significantly lower albumin levels, lower red blood cell count, and decreased hemoglobin levels. In addition, spleen diameter values were larger in patients with EVB than in those without EVB. In addition, the liver stiffness spleen diameter-to-platelet score and LSM values were drastically higher in patients with variceal bleeding than those without, suggesting the role of the liver stiffness spleen diameter-to-platelet score and LSM in predicting EVB. No significant differences were observed in Fibrosis 4, APRI, or MELD.

TABLE 3. Comparison of Mean Values of Spleen Diameter, PSR, LSPS, and LSM According to the Degree of Esophageal Varices

Items	Esophageal Varices				P
	Absent (n = 16)	F1 (n = 20)	F2 (n = 25)	F3 (n = 27)	
Spleen diameter, mm	111.79 ± 15.38	140.79 ± 26.93	148.57 ± 33.93	167.06 ± 32.51	0.000
PSR	1206.67 ± 508.10	805.57 ± 580.91	414.64 ± 207.30	501.88 ± 339.78	0.000
LSPS	1.01 ± 0.66	2.93 ± 2.67	6.71 ± 3.99	12.16 ± 8.25	0.000
LSM, kPa	10.25 ± 4.43	12.54 ± 4.19	23.55 ± 5.56	40.91 ± 14.67	0.000

LSPS, liver stiffness × spleen diameter/platelet count ratio score; PSR, platelet count/spleen diameter ratio.

TABLE 5. Optimal Cutoff Values of LSM, Spleen Diameter, PSR, and LSPS According to the Degree and Hemorrhage of Esophageal Varices

Method	Varices Grade	AUROC (95% CI)	Cutoff Value	Sensitivity	Specificity	*P*
LSM	≥GI	0.894 (0.822–0.966)	12.63	0.836	0.875	<0.0001
	≥GII	0.958 (0.916–0.999)	19.80	0.870	0.971	<0.0001
	GIII	0.954 (0.912–0.995)	23.85	0.928	0.836	<0.0001
	Varices bleeding	0.855 (0.774–0.936)	26.27	0.857	0.747	<0.0001
Spleen diameter	≥GI	0.873 (0.781–0.964)	130.0	0.773	0.851	<0.0001
	≥GII	0.762 (0.639–0.884)	146.5	0.600	0.786	<0.001
	GIII	0.767 (0.629–0.905)	152.5	0.688	0.738	0.002
	Varices bleeding	0.819 (0.663–0.975)	156.5	0.875	0.780	0.004
PSR	≥GI	0.833 (0.710–0.957)	1035	0.863	0.750	<0.001
	≥GII	0.776 (0.646–0.905)	553.9	0.733	0.731	<0.001
	GIII	0.644 (0.491–0.797)	368.8	0.500	0.750	0.095
	Varices bleeding	0.630 (0.443–0.818)	339.5	0.625	0.750	0.242
LSPS	≥GI	0.926 (0.859–0.993)	2.375	0.818	1.000	<0.0001
	≥GII	0.941 (0.878–1.00)	3.544	0.900	0.885	<0.0001
	GIII	0.901 (0.820–0.996)	6.934	0.875	0.875	<0.0001
	Varices bleeding	0.818 (0.672–0.963)	8.496	0.750	0.854	0.004

LSPS, liver stiffness × spleen diameter/platelet count ratio score; PSR, platelet count/spleen diameter ratio.

The Liver Stiffness Spleen Diameter-to-Platelet Score Can Predict Cirrhosis With or Without Esophageal Varices and Differentiate High-Risk From Low-Risk EVB

Tables 2 and 3 show that LSM, spleen diameter, the platelet count/spleen diameter ratio, and the liver stiffness spleen diameter-to-platelet score are highly associated with varices grade and EVB; therefore, we further investigated the diagnostic value of evaluating varices and EVB (Table 5). The AUROC values of LSM, spleen diameter, the platelet count/spleen diameter ratio, and the liver stiffness spleen diameter-to-platelet score for detecting varices (GI–III) were 0.894, 0.873, 0.833, and 0.926, respectively. The AUROC values of LSM, spleen diameter, the platelet count/spleen diameter ratio, and the liver stiffness spleen diameter-to-platelet score for discriminating GII–III from GI varices or the absence of varices were 0.958, 0.762, 0.776, and 0.941, respectively. For predicting GIII varices, the AUROC values of LSM, spleen diameter, the platelet count/spleen diameter ratio, and the liver stiffness spleen diameter-to-platelet score were 0.954, 0.767, 0.644, and 0.901, respectively (Table 5). Liver stiffness measurement had a statistically larger AUROC (0.855) for predicting EVB than the other indexes (Table 5). These findings implied that the 4 indexes had potential diagnostic performance for varices and EVB.

Therefore, we then assessed the optimal cutoff values for evaluating varices and EVB (Fig. 3). The optimal cutoff value of LSM for detecting varices (GI–III) was 12.63 kPa (Fig. 3), with a sensitivity and a specificity of 83.6% and 87.5%, respectively (Fig. 2A). The best cutoff value of LSM for predicting the presence of GII–III varices was 19.8 kPa (Fig. 3), with a sensitivity and a specificity of 87.0% and 97.1% (Fig. 2B), respectively. The optimal cutoff value of LSM for distinguishing GIII varices was 23.85 kPa (Fig. 3); the sensitivity and specificity were 92.8% and 83.6% (Fig. 2C), respectively. The prime cutoff value of LSM for detecting EVB was 26.27 kPa (Fig. 3); the sensitivity and specificity were 85.7% and 74.7%, respectively (Fig. 2D). Spleen diameter, the platelet count/spleen diameter ratio, and the liver stiffness spleen diameter-to-platelet score values are shown in Table 5 and Figure 2. According to these results, we found that LSM and the liver stiffness spleen diameter-to-platelet score were better able than spleen diameter and the platelet count/spleen diameter ratio to distinguish patients with varices from those with cirrhosis and those with GIII varices from those with cirrhosis. Furthermore, LSM and spleen diameter have advantages over the other indexes for predicting EVB.

Independent Factors for Predicting EVB

Multiple logistic regression analyses were performed to evaluate the connection between explanatory variables and variceal hemorrhage (Table 6). Liver stiffness measurement was positively correlated with the presence of EVB (odds ratio, 1.093; $P = 0.030$), and spleen diameter was significantly linked with variceal hemorrhage (odds ratio, 1.051; $P = 0.021$). However, hemoglobin level, red blood cell count, albumin level, the liver stiffness spleen diameter-to-platelet score, and the platelet count/spleen diameter ratio were not independent factors of variceal hemorrhage.

DISCUSSION

Here, we showed that LSM and the liver stiffness spleen diameter-to-platelet score are able to differentiate cirrhosis patients without varices from those with varices and distinguish between cirrhosis patients with GIII varices and those without GIII varices. Furthermore, LSM and spleen diameter had excellent abilities to predict EVB.

Hepatitis B virus–related cirrhosis has caused high mortality rates worldwide, especially in China. Esophageal variceal bleeding is considered one of the most serious complications of liver cirrhosis.[2] Hepatic venous pressure gradient and endoscopy are considered reliable methods for estimating the risk of

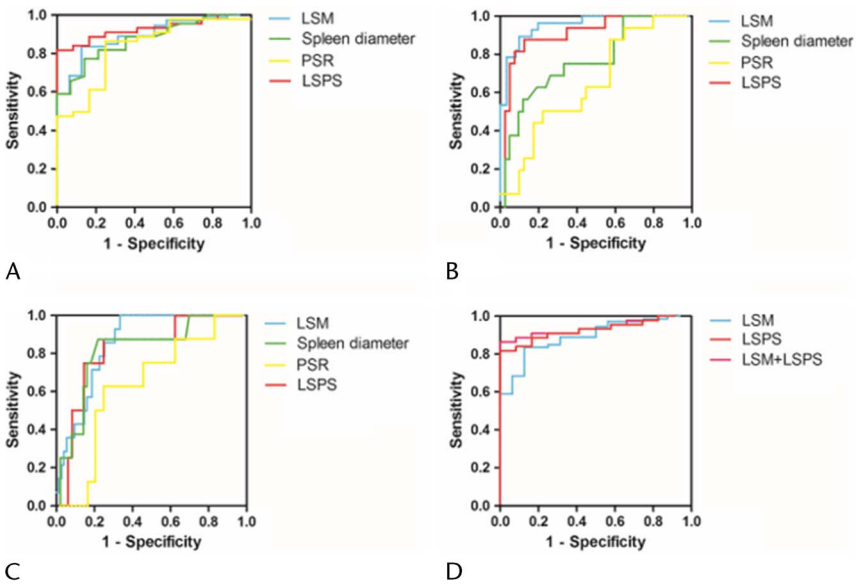

FIGURE 2. Comparative AUROC for predicting the presence, grade, severity, and bleeding of esophageal varices. Analyses of the liver stiffness spleen diameter-to-platelet score (LSPS), platelet count/spleen diameter ratio (PSR), spleen diameter (SD), LSM, and LSM + LSPS in predicting the presence (A), grade (B), severity (C), and bleeding (D) of esophageal varices.

varices and bleeding to determine whether prophylactic treatment is necessary.[3–5] However, considering the relatively low prevalence and unpleasant experience associated with high-risk varices in cirrhotic patients, some noninvasive and accurate procedures for diagnosing high-risk varices are urgently required to partially replace invasive hepatic venous pressure gradient and endoscopy.

The usefulness of the LSM value as a predictor of cirrhosis and esophageal varices has been already demonstrated in several studies.[11,12,15,16] The results of these studies suggested that LSM in cirrhosis could predict the presence of large esophageal varices.[17–19] Our results also showed that varices grade was highly correlated with LSM in patients with HBV-related cirrhosis. Here, we found a more profound role of the liver stiffness spleen diameter-to-platelet score for evaluating varices. Specifically, we confirmed that the liver stiffness spleen diameter-to-platelet score was a good parameter, with AUC values of 0.926, 0.941, and 0.901 for diagnosing grade I, grade II, and grade III, respectively. Note that the diagnostic specificity of the liver stiffness spleen diameter-to-platelet score for identifying cirrhosis without varices was 1.000, meaning that it can accurately rule out patients without varices. Although the use of the spleen diameter value, platelet count, and the platelet count/spleen diameter ratio for predicting varices has been reported in some studies,[20,21] our results showed that both LSM and the liver stiffness spleen diameter-to-platelet score had a higher diagnostic accuracy for distinguishing cirrhosis without varices from that with varices and low-risk from high-risk varices. Although the number of patients without varices was low (16 vs 72), the population stratified according to the degree of varices was also comparable (cirrhosis without varices vs F1/F2/F3 = 16 vs 20/25/27), suggesting that our results were largely unaffected. The reason for the low mean LSM in the no-varices subgroup (10.25 ± 4.43) may be that most patients came from an outpatient service and received antiviral treatment as stated in a recent report.[22] However, LSM shows different cutoff values for varices in different reports.[19,23,24] This may be attributed to differences in demographics and patient characteristics, varices etiologies, and machine types.

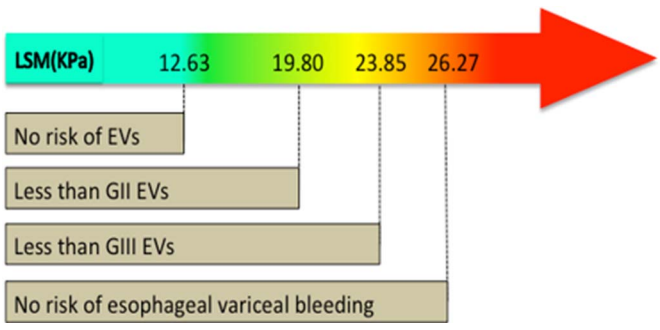

FIGURE 3. Usefulness of LSMs in clinical practice (cutoff values with negative predictive value of >90%).

Liver stiffness measurement and spleen diameter have reportedly been used to identify patients with high-risk varices.[25] Our study also showed that LSM and spleen diameter are significantly higher in patients with EVB than in those without EVB. Similar to previous studies,[22,26] we also reported that the liver stiffness spleen diameter-to-platelet score might be useful for predicting EVB among cirrhotic patients. Based on these results, the diagnostic values of LSM, spleen diameter, and the liver stiffness spleen diameter-to-platelet score were better than that of PSR. Furthermore, LSM and spleen diameter but not the liver stiffness spleen diameter-to-platelet score are independent risk factors associated with EVB on multiple logistic regression analysis. Therefore, we thought that LSM and spleen diameter had excellent abilities to predict the presence of EVB.

Our study has several limitations. First, because we selected only cirrhosis patients with a single etiology (HBV infection),

TABLE 6. Multiple Logistic Regression Analysis of Factors Associated With Esophageal Varices Hemorrhage

Variable	Estimate	SE	Wald-type χ^2 Statistic	*P*	OR	95% CI
Hemoglobin	−0.51	0.43	1.410	0.235	0.950	0.873–1.034
RBC	0.674	1.462	0.196	0.658	1.910	0.109–33.564
ALB	−0.083	0.114	0.529	0.467	0.921	0.737–1.150
LSM	0.089	0.041	4.724	0.030	1.093	1.009–1.185
Spleen diameter	0.049	0.021	5.353	0.021	1.051	1.008–1.095
LSPS	−0.121	0.103	1.387	0.239	0.886	0.723–1.084
PSR	0.001	0.002	0.125	0.724	1.0001	0.997–1.004

ALB, albumin; LSPS, liver stiffness × spleen diameter/platelet count ratio score; PSR, platelet count/spleen diameter ratio; RBC, red blood cell.

the population was small. Second, we used only our population to set our cutoff values, and our findings were not tested in a validation cohort. Further studies are required to determine cutoff values and offer stronger clinical significance.

In summary, our findings indicated that LSM and the liver stiffness spleen diameter-to-platelet score have higher diagnostic value for predicting esophageal varices size. Liver stiffness measurement and spleen diameter had excellent ability to predict the presence of EVB. Because our study was a small-scale study, further validation in a large-scale and long-term study is warranted for physicians to evaluate the value of these indexes in patients with different clinical backgrounds.

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