

# Multimodal Ultrasound Model Based on the Left Gastric Vein in B-Viral Cirrhosis: Noninvasive Prediction of Esophageal Varices

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**OBJECTIVES:** To establish and verify a simple noninvasive model based on the left gastric vein (LGV) to predict the grade of esophageal varices (EV) and high-risk EV (HEV), to facilitate clinical follow-up and timely treatment.

**METHODS:** We enrolled 320 patients with B-viral cirrhosis. All patients underwent endoscopy, laboratory tests, liver and spleen stiffness (SS), and ultrasonography. HEV were analyzed using the  $\chi^2$  test/*t* test and logistic regression in the univariate and multivariate analyses, respectively. EV grades were analyzed using the variance/rank-sum test and logistic regression. A prediction model was derived from the multivariate predictors.

**RESULTS:** In the training set, multivariate analysis showed that the independent factors of different EV grades were SS, LGV diameter, and platelet count (PLT). We developed the LGV diameter-SS to PLT ratio index (LSPI) and LGV diameter/PLT models without SS. The area under the receiver operating characteristic curve of the LSPI for diagnosis of small EV, medium EV, large EV, and HEV was 0.897, 0.899, 0.853, and 0.954, respectively, and that of the LGV/PLT was 0.882, 0.890, 0.837, and 0.942, respectively. For the diagnosis of HEV, the negative predictive value was 94.07% when LSPI < 19.8 and the positive predictive value was 91.49% when LSPI > 23.0. The negative predictive value was 95.92% when LGV/PLT < 5.15, and the positive predictive value was 86.27% when LGV/PLT > 7.40. The predicted values showed similar accuracy in the validation set.

**DISCUSSION:** Under appropriate conditions, the LSPI was an accurate method to detect the grade of EV and HEV. Alternatively, the LGV/PLT may also be useful in diagnosing the varices when condition limited.

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## INTRODUCTION

Cirrhosis is the advanced stage of various liver diseases, and hepatitis B infection is one of the common causes of the condition in China. Portal hypertension (PH) is the main consequence of cirrhosis and the cause of ascites, hepatic encephalopathy, and esophageal varices (EV) (1,2).

The presence of EV denotes clinically significant PH, which is a landmark in the course of cirrhosis associated with decompensation and a high mortality rate. Approximately 7%–8% patients with compensated cirrhosis develop new EV annually, and 10%–12% of small EV can progress to medium/large EV after 1–2 years (3). Mortality rates as high as 20% have been reported because of progression of EV to variceal hemorrhage (4), and

approximately 60% patients experience recurrence of bleeding within 1–2 years despite clinical treatment (5). In addition, the presence of EV might influence the outcomes of cirrhosis (6). Current guideline recommends endoscopy for all patients with cirrhosis; however, only 15%–25% of EV demonstrate a high risk of bleeding. Regular endoscopy for all patients would increase medical workload, as well as cause discomfort in asymptomatic patients. Furthermore, endoscopy is not a risk-free procedure. Therefore, an early, accurate, and repeatable noninvasive method is required for timely evaluation of EV.

Some guidelines recommend certain proposed novel noninvasive methods to predict EV (3,7). The left gastric vein (LGV) is directly related to the portal system and is a major vessel linked

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to EV anatomically and hemodynamically. It is difficult to identify the LGV because of limitations of early ultrasound instruments (8). However, advances in ultrasound technology have enabled detection of the LGV. Previous studies have reported that assessment of the LGV helped in diagnosis of high-risk EV (HEV) (9). Liver stiffness and spleen stiffness (LS and SS, respectively) have been researched widely; however, the parameter that is more closely related to EV remains unknown (10–13). Acoustic radiation force impulse (ARFI) imaging is a new method to assess tissue elasticity, which has demonstrated higher success rates than transient elastography.

To date, no research has attempted to establish a prediction model based on the LGV combined with other noninvasive tests to reflect the grade of EV. Follow-up of patients would be facilitated by rough evaluation of the EV grade, thereby enabling prediction of the bleeding risk. The purpose of this study was to generate and validate the usefulness of a simple prediction model based on the LGV.

## METHODS

### Patients

Patients were recruited from the China-Japan Union Hospital between September 2016 and September 2018. Our Institutional Ethics Committee approved the study protocol (2018062808), and written informed consent was obtained from all patients.

According to the Agenzia Italiana del Farmaco criteria, cirrhosis is diagnosed based on at least one of the following clinical characteristics: esophageal and/or gastric varices on endoscopy, platelet count (PLT)  $<100 \times 10^9/L$ , and/or ultrasound signs of cirrhosis (polycyclic margins of the liver and/or splenomegaly). Laboratory investigations were performed to determine hepatitis B virus (HBV) infection. The Child-Pugh score was used to indicate the functional class of cirrhosis. The exclusion criteria were patients with (i) cirrhosis due to other causes ( $n = 26$ ); (ii) right heart failure, myelodysplasia, hematological, or autoimmune disease ( $n = 5$ ); (iii) portal vein or splenic vein thrombosis ( $n = 7$ ), family history of thrombocytopenia, and liver cirrhosis with hepatocellular carcinoma ( $n = 12$ ); (iv) history of digestive tract hemorrhage ( $\leq 15$  days) ( $n = 8$ ); (v) history of PH treatment such as splenectomy, transjugular intrahepatic portosystemic shunt, partial splenic embolization, or endoscopic treatment ( $n = 45$ ); (vi) ARFI failure or unreliable measurement ( $n = 6$ ); and (vii) intolerance to endoscopy ( $n = 6$ ).

### Endoscopic evaluation of EV

Endoscopy was performed by an experienced clinician ( $>1,000$  examinations) using the OLYMPUS SEVLS LUCERA CV-260SL instrument. The EV were divided into 3 groups based on the UK guidelines (14): (i) collapse on inflation of the esophagus with air (grade I, small EV), (ii) varices between grades 1 and 3 (grade II, medium EV), and (iii) large varices that occlude the lumen (grade III, large EV). High-risk EV were considered if any one of the following endoscopic features was met: (i) beaded or tumor-like EV; (ii) red-colored EV; (iii) EV with clots; or (iv) EV with the maximal diameter  $>0.5$  cm (7).

### Ultrasound examination

Ultrasound was performed after 8–12 hours of strict fasting. The ultrasound doctor was blinded to the results of the endoscopy. Conventional ultrasound and ARFI imaging were performed

using the Siemens Acuson S2000 system. The oblique diameter of the right lobe of the liver, spleen thickness, and spleen diameter (SD) were measured, and the degree of ascites was defined based on recent guidelines (15). The portal vein system was observed, and the collateral vessels were determined as described in the literature (13). Successful detection of the LGV was defined as identification of the vein on the B-mode image (8). The average of 3 valid measurements was considered, and the LGV flow volume (mL/min) was calculated as  $\pi \times (\text{diameter}/2)^2 \times 60 \times \text{velocity}$ . LS and SS were measured by ARFI (m/s). Each parameter was repeatedly measured 10 times, and the average was calculated. Failure of ARFI imaging was defined as absence of valid shots, and unreliable measurements were defined as a median interquartile range greater than 30% or success rate less than 60%.

### Statistical analyses

Statistical analyses were performed using SPSS 20.0 for Windows (SPSS, Chicago, IL) and MedCalc Software.

The data are expressed as  $\bar{X} \pm S$ . The analysis of the variance/rank-sum test was used for comparison among multiple groups. The  $\chi^2$  test/ $t$  test was used for comparison between 2 groups. Considering the endoscopy results as the gold standard, multivariate logistic regression analysis included variables of the univariate logistic regression analysis with  $P < 0.05$ . Accordingly, independent factors that could affect the occurrence of EV were screened. To avoid the effects of collinearity, Child-Pugh classification, LGV flow, LGV shunt index, among others were not included in the multivariate analysis because they contain composite parameters. The Spearman correlation coefficient was used to analyze the relationship between the model/independent factor and EV grade. The receiver operating characteristic (ROC) curve was used to analyze the clinical value and was expressed as the area under the ROC curve (AUROC). The DeLong test was used to compare between the AUROCs. The ROC curve was used to calculate the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).  $P < 0.05$  was considered statistically significant.

## RESULTS

### Characteristics of patients in the training and validation sets

The characteristics of patients in the training and validation sets are shown in Table 1. A total of 435 patients were enrolled, and 115 were excluded based on the previously described criteria. Among the 179 patients in the training set (mean age, 52.66 years; 121 men), 126 patients had EV (small, medium, and large EV,  $n = 42$  each), and 59 had HEV. One hundred patients were graded as Child-Pugh class A (55.9%), 59 as class B (32.9%), and 20 as class C (11.2%).

There were no significant differences in the basic characteristics between patients in the training and validation sets.

### Predictors of the EV grade in the training set

Table 2 shows the parameters with different grades of EV in the training set. First, univariate analysis was performed to evaluate variables related to the grade of EV, which were then entered into a stepwise logistic regression model. Finally, the LGV diameter ( $P < 0.001$ , odds ratio [OR] 4.196, 95% confidence interval [CI] 2.737–6.432), SS ( $P = 0.048$ , OR 3.122, 95% CI 1.026–9.501), and PLT ( $P = 0.037$ , OR 0.990, 95% CI 0.981–1.000) were identified as independent predictors of the grade of EV.

**Table 1.** Baseline patient characteristics of the training and validation sets and comparisons between the 2 groups

Variable	Training set (n = 179)	Validation set (n = 141)	P value
Basic information			
Age (yr)	52.66 ± 12.30	54.85 ± 9.83	0.085
Sex (male)	121 (67.6%)	72 (65.2%)	0.721
BMI (kg/m <sup>2</sup> )	23.20 ± 2.80	21.78 ± 1.88	<0.001
Child-Pugh classification (A/B/C)	100/59/20	65/57/19	0.222
Ultrasound measurement			
RL	11.16 ± 1.55	11.38 ± 1.50	0.202
LD	6.51 ± 1.42	6.72 ± 1.48	0.020
LT	6.34 ± 1.06	6.70 ± 1.74	0.185
Portal vein diameter (cm)	1.33 ± 0.23	1.34 ± 0.18	0.526
Portal vein velocity (cm/s)	14.27 ± 3.61	14.33 ± 2.21	0.864
Spleen thickness	4.46 ± 0.99	4.41 ± 0.94	0.635
Spleen diameter	12.37 ± 2.89	12.40 ± 2.88	0.921
Spleen vein diameter (cm)	0.98 ± 0.24	1.00 ± 0.21	0.589
Spleen vein velocity (cm/s)	16.80 ± 4.31	15.98 ± 2.91	0.053
LGV diameter (mm)	4.87 ± 1.67	4.98 ± 1.57	0.561
LGV velocity (cm/s)	11.09 ± 2.37	11.33 ± 1.34	0.288
Blood test			
AST (IU/L)	56.53 ± 89.63	57.42 ± 39.54	0.913
ALT (IU/L)	49.08 ± 103.36	43.76 ± 34.52	0.558
ALP (IU/L)	111.23 ± 61.36	116.94 ± 62.59	0.413
GGT (IU/L)	90.38 ± 162.37	81.02 ± 111.18	0.559
LAP (U/L)	40.94 ± 17.62	42.96 ± 17.55	0.309
GLDH (U/L)	13.05 ± 23.87	16.18 ± 32.67	0.323
LDH (IU/L)	228.15 ± 125.14	262.79 ± 180.46	0.044
T-bil (μmol/L)	26.32 ± 30.74	25.71 ± 20.98	0.842
TBA (μmol/L)	15.85 ± 19.90	26.75 ± 53.41	0.013
ALB (g/L)	37.41 ± 7.15	36.36 ± 7.91	0.216
PT (s)	14.52 ± 2.76	14.36 ± 2.83	0.612
PLT (10 <sup>9</sup> /L)	121.81 ± 81.66	121.26 ± 58.38	0.947
EV, n (%)			0.951
None	53 (29.6%)	43 (30.5%)	
Small	42 (23.5%)	32 (22.7%)	
Medium	42 (23.5%)	36 (25.5%)	
Large	42 (23.5%)	30 (21.3%)	
High-risk EV	59 (34.1%)	44 (31.2%)	
Liver stiffness (m/s)	2.04 ± 0.54	2.07 ± 0.34	0.534
Spleen stiffness (m/s)	2.82 ± 0.47	2.91 ± 0.33	0.065

ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; EV, esophageal varices; GGT, γ-glutamyl transferase; GLDH, glutamine dehydrogenase; LAP, leucine aminopeptidase; LD, left lobe of liver diameter; LDH, lactate dehydrogenase; LGV, left gastric vein; LT, left lobe of liver thickness; PT, prothrombin time; PLT, platelet count; RL, right lobe of liver oblique diameter; T-bil, total bilirubin; TBA, total bile acid.

The AUROC of the LGV diameter for different EV grades was 0.900 (small, 95% CI 0.838–0.963), 0.759 (medium, 95% CI 0.652–0.866), and 0.814 (large, 95% CI 0.715–0.912). Similarly, the values for SS were 0.715 (small, 95% CI 0.613–0.818), 0.630

(medium, 95% CI 0.509–0.752), and 0.663 (large, 95% CI 0.546–0.780). AUROCs for the PLT were 0.811 (small, 95% CI 0.724–0.898), 0.611 (medium, 95% CI 0.489–0.732), and 0.789 (large, 95% CI 0.691–0.886).

**Table 2.** Comparisons and uni/multivariate analysis of varices according to different grades of EV in the training set

Variable	NEV group (n = 53)	Small EV (n = 42)	Medium EV (n = 42)	Large EV (n = 42)	Univariate analysis P value	Multivariate analysis	
						OR (95% CI)	P value
Basic information							
Age (yr)	46.94 ± 14.23	54.05 ± 11.38	54.36 ± 10.52	56.79 ± 9.75	<0.001	0.986 (0.954–1.019)	0.412
Sex (male/female)	29/24	35/7	35/7	29/13	0.228		
BMI (kg/m <sup>2</sup> )	23.65 ± 2.75	23.44 ± 2.95	22.71 ± 2.89	22.90 ± 2.61	0.111		
Child-Pugh classification (A/B/C)	42/11/0	33/8/1	19/15/8	6/25/11	<0.001		
Ultrasound measurement							
RL	11.02 ± 1.47	11.62 ± 1.53	10.94 ± 1.54	11.09 ± 1.65	0.804		
LD	6.31 ± 1.12	6.44 ± 1.01	6.47 ± 1.61	6.30 ± 1.40	0.794		
LT	6.45 ± 1.43	6.81 ± 1.22	6.31 ± 0.89	6.28 ± 1.21	0.491		
Portal vein diameter (cm)	1.16 ± 0.21	1.33 ± 0.21	1.39 ± 0.19	1.45 ± 0.22	<0.001	6.480 (1.017–41.299)	0.051
Portal vein velocity (cm/s)	15.59 ± 3.18	14.05 ± 3.64	14.37 ± 3.48	12.73 ± 3.69	<0.001	0.962 (0.866–1.068)	0.483
Spleen thickness	3.94 ± 0.65	4.11 ± 0.71	4.63 ± 0.95	5.29 ± 1.03	<0.001	0.647 (0.357–1.174)	0.161
Spleen diameter	10.29 ± 1.66	11.99 ± 2.19	12.70 ± 2.75	15.05 ± 2.69	<0.001	1.164 (0.935–1.449)	0.183
Spleen vein diameter (cm)	0.84 ± 0.19	0.94 ± 0.15	1.01 ± 0.18	1.19 ± 0.26	<0.001	1.673 (0.200–13.996)	0.630
Spleen vein velocity (cm/s)	15.05 ± 2.97	17.39 ± 4.08	14.53 ± 2.99	14.43 ± 3.26	0.350		
LGV diameter (mm)	3.38 ± 0.73	4.48 ± 0.55	5.13 ± 1.04	6.87 ± 1.72	<0.001	4.196 (2.737–6.432)	<0.001
LGV velocity (cm/s)	10.02 ± 1.85	10.46 ± 1.95	11.93 ± 2.18	12.21 ± 2.77	<0.001	1.172 (0.983–1.398)	0.077
Liver stiffness (m/s)	1.68 ± 0.39	2.05 ± 0.48	2.25 ± 0.57	2.29 ± 0.47	<0.001	1.001 (0.421–2.381)	0.998
Spleen stiffness (m/s)	2.47 ± 0.42	2.81 ± 0.35	2.94 ± 0.37	3.17 ± 0.41	<0.001	3.122 (1.026–9.501)	0.048
Blood test							
AST	30.78 ± 17.70	84.91 ± 197.90	67.17 ± 51.86	49.93 ± 34.83	0.051		
ALT	28.29 ± 30.12	85.71 ± 197.70	53.21 ± 53.84	34.54 ± 31.62	0.102		
ALP (IU/L)	95.87 ± 34.26	113.12 ± 46.97	135.34 ± 99.52	104.58 ± 42.38	0.269		
GGT (IU/L)	49.85 ± 51.94	138.44 ± 167.75	113.98 ± 249.52	69.8 ± 123.07	0.609		
LAP (U/L)	36.81 ± 13.94	46.94 ± 18.67	42.70 ± 20.53	38.37 ± 14.21	0.732		
GLDH (U/L)	7.12 ± 3.53	20.98 ± 40.70	16.57 ± 24.92	9.08 ± 4.35	0.742		
LDH (IU/L)	193.49 ± 47.04	219.02 ± 56.59	252.25 ± 151.47	256.92 ± 189.62	0.656		
T-bil (μmol/L)	15.70 ± 5.21	26.59 ± 28.60	38.02 ± 52.78	27.73 ± 13.25	0.344		
TBA (μmol/L)	7.12 ± 6.73	21.00 ± 27.97	18.75 ± 18.13	18.73 ± 20.30	0.013	0.986 (0.968–1.004)	0.139
ALB (g/L)	40.99 ± 6.38	39.46 ± 5.03	34.92 ± 7.68	33.10 ± 6.40	<0.001	0.942 (0.870–1.020)	0.149
PT (s)	13.35 ± 2.28	13.62 ± 1.72	14.53 ± 2.31	16.88 ± 3.14	<0.001	1.068 (0.903–1.264)	0.446
PLT (10 <sup>9</sup> /L)	151.53 ± 100.99	111.24 ± 43.50	99.62 ± 52.82	66.59 ± 36.19	<0.001	0.990 (0.981–1.000)	0.037

CI, confidence interval; EV, esophageal varices; LGV, left gastric vein; OR, odds ratio; PLT, platelet count.

We further analyzed the relationship among AUROC and the grade of EV and found that the severity significantly correlated with widening of the LGV diameter ( $r = 0.794$ ,  $P < 0.001$ ), increase in SS ( $r = 0.573$ ,  $P < 0.001$ ), and a reduction in the PLT ( $r = -0.689$ ,  $P < 0.001$ ).

#### Predictors of HEV in the training set

Table 3 shows the parameters of patients with HEV in the training set. The method of analysis was as described above. The LGV diameter, SS, and PLT were confirmed as independent predictors of HEV.

**Table 3.** Comparisons and uni/multivariate analysis of variables according to presence of high-risk EV in the training set

Variable	Patient without HEV (n = 120)	Patient with HEV (n = 59)	Univariate analysis (P value)	Multivariate analysis	
				OR (95% CI)	P value
Basic information					
Age (yr)	50.76 ± 12.89	56.53 ± 10.03	0.004	0.956 (0.875–1.044)	0.314
Sex (male/female)	39/81	19/40	0.968		
BMI (kg/m <sup>2</sup> )	23.25 ± 2.80	23.12 ± 2.83	0.983		
Child-Pugh classification (A/B/C)	89/26/5	11/33/15	<0.001		
Ultrasound measurement					
RL	11.13 ± 1.54	11.22 ± 1.59	0.716		
LD	6.52 ± 1.40	6.35 ± 1.11	0.983		
LT	6.33 ± 1.04	6.35 ± 1.12	0.914		
Portal vein diameter (cm)	1.27 ± 0.23	1.44 ± 0.20	<0.001	0.716 (0.013–41.017)	0.872
Portal vein velocity (cm/s)	14.86 ± 3.35	13.07 ± 3.85	0.002	1.001 (0.817–1.226)	0.994
Spleen thickness	4.08 ± 0.69	5.22 ± 1.07	<0.001	1.711 (0.444–6.589)	0.435
Spleen diameter	11.25 ± 2.06	14.64 ± 3.02	<0.001	0.923 (0.582–1.463)	0.733
Spleen vein diameter (cm)	0.91 ± 0.19	1.15 ± 0.24	<0.001	2.529 (0.021–297.595)	0.703
Spleen vein velocity (cm/s)	14.82 ± 3.10	14.32 ± 3.20	0.316		
LGV diameter (mm)	4.02 ± 0.90	6.59 ± 1.56	<0.001	13.649 (3.873–48.108)	<0.001
LGV velocity (cm/s)	10.59 ± 2.13	12.10 ± 2.54	<0.001	1.131 (0.776–1.648)	0.521
Liver stiffness (m/s)	1.90 ± 0.51	2.33 ± 0.47	<0.001	0.463 (0.074–2.892)	0.410
Spleen stiffness (m/s)	2.66 ± 0.42	3.16 ± 0.37	<0.001	10.412 (0.907–119.544)	0.060
Blood test					
AST	54.30 ± 103.88	61.07 ± 49.84	0.642		
ALT	50.94 ± 121.74	45.28 ± 48.55	0.734		
ALP (IU/L)	105.70 ± 39.52	122.48 ± 90.32	0.109		
GGT (IU/L)	84.11 ± 122.46	103.48 ± 223.37	0.469		
LAP (U/L)	40.39 ± 16.07	42.05 ± 20.53	0.553		
GLDH (U/L)	14.00 ± 27.89	11.11 ± 12.09	0.464		
LDH (IU/L)	214.51 ± 77.40	255.83 ± 186.03	0.056		
T-bil (μmol/L)	22.49 ± 25.53	34.10 ± 38.36	0.047	1.006 (0.975–1.039)	0.696
TBA (μmol/L)	13.58 ± 19.49	20.40 ± 20.12	0.042	0.977 (0.931–1.025)	0.346
ALB (g/L)	39.35 ± 6.69	33.30 ± 6.43	<0.001	1.081 (0.955–1.222)	0.217
PT (s)	13.66 ± 2.18	16.28 ± 2.99	<0.001	0.905 (0.752–1.089)	0.290
PLT (10 <sup>9</sup> /L)	146.10 ± 86.41	70.37 ± 33.68	<0.001	0.970 (0.943–0.998)	0.036

CI, confidence interval; EV, esophageal varices; HEV, high-risk esophageal varices; LGV, left gastric vein; OR, odds ratio; PLT, platelet count.

The AUROCs were 0.942 (95% CI 0.896–0.971) for the LGV diameter, 0.826 (95% CI 0.763–0.879) for SS, and 0.873 (95% CI 0.816–0.918) for PLT.

#### Novel formula for prediction of HEV and grade of EV

We devised a new formula, the LGV diameter-SS to PLT ratio index (LSPI), including the LGV diameters and SS (OR > 1 each) as the numerator, and PLT (OR < 1) as the denominator to amplify the effect of each factor during the progression of EV.

$$\text{LSPI} = \frac{\text{LGV diameters (mm)} \times \text{SS (m/s)}}{\text{PLT} (\times 10^9/\text{L})}$$

Simultaneously, we also considered that measurement of SS might not be possible in some areas. To achieve comprehensive clinical outcomes, we removed the ARFI data and reanalyzed the remaining data. The LGV diameters (OR = 4.375 > 1, *P* < 0.001) and PLT (OR = 0.989 < 1, *P* = 0.016) were the independent factors for the analysis to derive the formula:

**Table 4.** The correlation coefficients between independent factors/formula and EV grade in the training set

	Correlation coefficients ( <i>r</i> )	<i>P</i> value
Spleen stiffness	0.573	<0.001
PLT	-0.689	<0.001
LGV diameter	0.794	<0.001
AAR	0.250	<0.001
APRI	0.589	<0.001
SD/PLT	0.704	<0.001
ASPS	0.727	<0.001
LSPI	0.816	<0.001
LGV/PLT	0.798	<0.001

AAR, aspartate aminotransferase/alanine aminotransferase ratio; APRI, AST-to-platelet ratio index; ASPS, acoustic radiation force impulse-spleen diameter to platelet ratio score; EV, esophageal varices; LGV, left gastric vein; LSPI, LGV diameter-SS to PLT ratio index; PLT, platelet count; SD, spleen diameter.

$$\text{LGV/PLT} = \frac{\text{LGV diameters (mm)}}{\text{PLT} (\times 10^9/\text{L})}$$

Correlation between the grade of EV with the LSPI ( $r = 0.816$ ,  $P < 0.001$ ) and the LGV/PLT ( $r = 0.798$ ,  $P < 0.001$ ) was higher than the individual factors (Table 4).

#### Diagnostic accuracy of the noninvasive methods in determining the EV grade and HEV

Table 5 shows the diagnostic accuracy of the noninvasive methods in the training and validation sets.

In the training set, for the small EV group, the AUROCs of both the LSPI and LGV/PLT were significantly higher than the

individual factors SS ( $P = 0.0003$ ,  $P = 0.0031$ , respectively) and PLT (both  $P = 0.0004$ ). The AUROCs of the LGV diameter, LSPI, and LGV/PLT were not statistically different. The AUROCs of the LSPI and LGV/PLT in the medium EV group were significantly higher than the individual factors; the LSPI and LGV/PLT have no statistical difference. There was no significant difference between the formulas and individual factors in the large EV group, which could be due to the accompanying spleen hyperactivity, making the PLT and SS highly predictable, but unstable. The LGV/PLT cutoff values to predict small, medium, and large EV were 3.04, 4.57, and 6.35, respectively, whereas those of the LSPI were 9.0, 10.8, and 19.9, respectively. The LSPI and LGV/PLT values in the validation group also showed excellent diagnostic efficacy. The AUROCs of the LSPI for small, medium, and large EV were 0.999, 0.954, and 0.985, respectively, and for the LGV/PLT, AUROCs were 0.997, 0.952, and 0.985, respectively.

The AUROCs of the LGV diameter, SS, PLT, LSPI, and LGV/PLT for predicting HEV in the training set were 0.942, 0.826, 0.873, 0.954, and 0.942, respectively. The LGV diameter and the formulas showed satisfactory diagnostic efficacy, and the LSPI was significantly superior to the former parameters ( $P < 0.05$ ). For further verification, we compared the formulas proposed in our study with previous formulas, aspartate aminotransferase/alanine aminotransferase ratio (0.640, 95% CI 0.565–0.710), aspartate aminotransferase-to-platelet ratio index [APRI] (0.784, 95% CI 0.716–0.842), ARFI-SD to platelet ratio score (ASPS) (0.891, 95% CI 0.836–0.933), and SD/PLT (0.882, 95% CI 0.825–0.925), and found that our formulas were superior ( $P < 0.05$ ). The same results were obtained in the validation group.

#### Determination and verification of the cutoff value for detection of HEV

Table 6 shows the sensitivity, specificity, NPV, and PPV of the cutoff values obtained from the ROC curves, for prediction of HEV in the training set. Two cutoff values of the LGV/PLT were chosen to predict HEV. LGV/PLT values  $< 5.15$  indicated that patients

**Table 5.** Formula and independent factor for predicting EV grade and HEV in the training set and the validation set

Training set				
	Prediction of small EV AUROC (95% CI)	Prediction of medium EV AUROC (95% CI)	Prediction of large EV AUROC (95% CI)	Prediction of high-risk EV AUROC (95% CI)
Spleen stiffness	0.715 (0.613–0.818)	0.630 (0.509–0.752)	0.663 (0.546–0.780)	0.826 (0.761–0.891)
Platelets counts	0.811 (0.724–0.898)	0.611 (0.489–0.732)	0.789 (0.691–0.886)	0.873 (0.817–0.929)
LGV diameter	0.900 (0.838–0.963)	0.759 (0.652–0.866)	0.814 (0.715–0.912)	0.942 (0.901–0.982)
LSPI	0.897 (0.832–0.962)	0.899 (0.845–0.939)	0.853 (0.772–0.933)	0.954 (0.926–0.983)
LGV/PLT	0.882 (0.813–0.951)	0.890 (0.834–0.932)	0.837 (0.751–0.923)	0.942 (0.909–0.974)
Validation set				
	Prediction of small EV AUROC (95% CI)	Prediction of medium EV AUROC (95% CI)	Prediction of large EV AUROC (95% CI)	Prediction of high-risk EV AUROC (95% CI)
Spleen stiffness	0.996 (0.989–1.000)	0.707 (0.576–0.837)	0.838 (0.738–0.938)	0.881 (0.825–0.937)
Platelets counts	0.967 (0.926–1.000)	0.660 (0.530–0.790)	0.879 (0.795–0.963)	0.908 (0.859–0.957)
LGV diameter	0.991 (0.972–1.000)	0.930 (0.860–1.000)	0.986 (0.966–1.000)	0.943 (0.909–0.977)
LSPI	0.999 (0.997–1.000)	0.954 (0.925–0.983)	0.985 (0.964–1.000)	0.946 (0.910–0.982)
LGV/PLT	0.997 (0.991–1.000)	0.952 (0.922–0.981)	0.985 (0.963–1.000)	0.944 (0.907–0.981)

AUROC, area under the receiver operating characteristic curve; CI, confidence interval; EV, esophageal varices; HEV, high-risk esophageal varices; LGV, left gastric vein; LSPI, LGV diameter-SS to PLT ratio index; PLT, platelet count.

**Table 6.** Diagnostic accuracy of LGV diameter, LGV/PLT, and LSPI for prediction of high-risk EV in the training set

LGV cutoff values	5.1 mm	5.6 mm
NPV (%)	93.69 (86.98–97.21)	87.97 (80.92–92.75)
PPV (%)	76.47 (64.35–85.56)	93.48 (81.07–98.30)
Sensitivity (%)	88.14 (76.46–94.70)	72.88 (59.51–83.26)
Specificity (%)	86.67 (78.96–91.95)	97.50 (92.32–99.35)
Interpretation	Absence of HEV	Presence of HEV
LGV/PLT cutoff values	5.15	7.40
NPV (%)	95.92 (89.28–98.68)	88.28 (81.11–93.07)
PPV (%)	67.90 (56.49–77.60)	86.27 (56.49–77.60)
Sensitivity (%)	93.22 (82.73–97.81)	74.58 (61.30–84.63)
Specificity (%)	78.33 (69.69–85.12)	94.17 (87.92–97.42)
Interpretation	Absence of HEV	Presence of HEV
LSPI cutoff values	19.8	23.0
NPV (%)	94.07 (87.72–97.38)	87.88 (81.78–92.70)
PPV (%)	85.25 (73.33–92.62)	91.49 (78.73–97.24)
Sensitivity (%)	88.14 (76.43–94.70)	72.88 (59.50–83.26)
Specificity (%)	92.50 (85.85–96.30)	96.67 (91.17–98.93)
Interpretation	Absence of HEV	Presence of HEV

EV, esophageal varices; HEV, high-risk esophageal varices; LGV, left gastric vein; LSPI, LGV diameter-SS to PLT ratio index; NPV, negative predictive value; PLT, platelet count; PPV, positive predictive value.

**Table 7.** Diagnostic accuracy of LGV diameter, LGV/PLT, and LSPI for prediction of high-risk EV in the validation set

LGV cutoff values	5.1 mm	5.6 mm
NPV (%)	91.01 (82.57–95.76)	85.32 (76.96–91.12)
PPV (%)	69.23 (54.74–80.88)	87.50 (70.07–95.92)
Sensitivity (%)	81.82 (66.76–91.29)	63.64 (47.74–77.17)
Specificity (%)	83.51 (74.29–89.99)	95.88 (89.18–98.67)
Interpretation	Absence of HEV	Presence of HEV
LGV/PLT cutoff values	5.15	7.40
NPV (%)	95.12 (87.31–98.43)	87.04 (78.88–92.48)
PPV (%)	67.80 (54.24–79.03)	90.91 (74.53–97.62)
Sensitivity (%)	90.81 (77.42–97.05)	68.18 (52.29–80.93)
Specificity (%)	80.41 (70.85–87.51)	96.91 (90.58–99.20)
Interpretation	Absence of HEV	Presence of HEV
LSPI cutoff values	19.8	23.0
NPV (%)	90.10 (82.13–94.89)	86.26 (78.00–91.84)
PPV (%)	85.00 (69.48–93.75)	90.63 (73.83–97.55)
Sensitivity (%)	77.29 (61.78–88.01)	65.91 (50.00–79.07)
Specificity (%)	93.81 (86.50–97.46)	96.91 (90.58–99.20)
Interpretation	Absence of HEV	Presence of HEV

EV, esophageal varices; HEV, high-risk esophageal varices; LGV, left gastric vein; LSPI, LGV diameter-SS to PLT ratio index; NPV, negative predictive value; PLT, platelet count; PPV, positive predictive value.

without HEV could be correctly excluded (95.92% NPV), and these low-risk patients could avoid endoscopy. Likewise, LGV/PLT values >7.4 indicated accuracy in the diagnosis of HEV (86.27% PPV), signifying the need for primary prophylaxis and endoscopy.

Similarly, 2 cutoff values of the LSPI were chosen to predict HEV. When the LSPI values were <19.8, 94.07% of the patients without HEV were accurately excluded. Likewise, when the values were >23.0, 91.49% of patients with HEV were diagnosed correctly.

We verified the above cutoff values in the validation set (Table 7), and the formulas showed excellent diagnostic capabilities. The AUROC of the LGV/PLT was 0.944 (95% CI 0.907–0.981) based on which 95.04% HEV could be diagnosed correctly. The LSPI was 0.946 (95% CI 0.910–0.982), and 90.78% of the patients were diagnosed correctly.

Based on the above analysis, we established a prediction system for EV in cirrhosis caused by HBV according to guidelines (2,4), as shown in Figure 1.

#### Hemodynamic assessment of the LGV to diagnose EV

The LGV is a major pathway that brings blood into the esophageal veins through the upper stomach (16); therefore, it plays an important role in predicting EV. The direction of the LGV flow should be hepatic under normal circumstances. The proportion of reverse direction flow increases with the grade of EV (normal vs small vs medium vs large, 15.1% vs 45.2% vs 73.8% vs 100%, respectively;  $P < 0.001$ ). Reverse direction flow in the HEV group (59/59, 100%) was significantly higher than in the non-HEV group (36/120 30%;  $P < 0.001$ ).

In the training set, the LGV diameter was 2.0–11.6 mm, flow velocity was 6.7–19.2 cm/s, and flow volume was 14.7–1,033.1 mL/min.

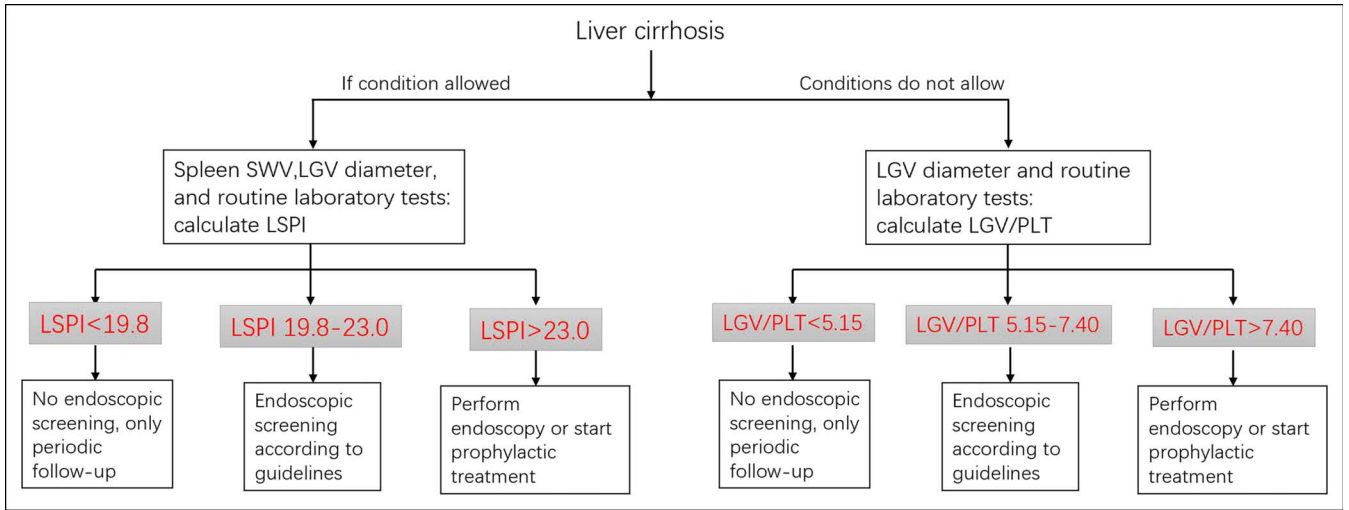
The diameter, flow velocity, and flow volume of the LGV increased with the grade of EV and were significantly higher in the HEV group. The AUROCs of the LGV diameter of small EV, medium EV, large EV, and HEV were 0.900, 0.759, 0.814, and 0.942, respectively. The LGV flow volume also showed good diagnostic efficacy, while the flow velocity was relatively poor (Table 8). There was no statistical difference between the LGV diameter and flow volume ( $P = 0.7477$ ) in the diagnosis of HEV, and the flow velocity was lower than the 2 values ( $P < 0.001$ ). Moreover, calculation of LGV flow volume is cumbersome; therefore, we focused on the LGV diameter.

Table 6 shows the sensitivity, specificity, NPV, and PPV of the LGV diameter in the training group.

The LGV diameter was satisfactory for the diagnosis of HEV and is worthy of further study. Two cutoff values were chosen to predict the HEV. When the LGV diameter was <5.1 and >5.6 mm, 93.69% and 93.48% of the patients were correctly excluded and diagnosed with HEV, respectively.

#### DISCUSSION

HBV infection is one of the common causes of cirrhosis in China. Approximately 200 million people worldwide have HBV infection, and approximately 1.2 million people die annually because of cirrhosis and associated complications (17). EV bleeding is one of the main causes of death. Current guidelines recommended screening all patients with cirrhosis by endoscopy (3,14); however, this may be hampered by lack of compliance especially because of the need for periodic repetition. Moreover, endoscopy is an invasive, expensive, and uncomfortable



**Figure 1.** Prediction and management system of esophageal varices in patients with cirrhosis.

procedure and is not risk-free. Therefore, it is imperative to establish an economic, convenient, and noninvasive prediction system for EV.

Although several studies have been conducted on noninvasive tests to predict EV, our research has many advantages. First, we have focused on the LGV and are the first to combine it with other noninvasive tests.

**Table 8.** The diagnostic ability of LGV hemodynamics to identify EV

	Value	P value	AUROC (95% CI)	Cutoff value	Sensitivity (%)	Specificity (%)
LGV flow direction (forward/bidirectional/reverse)						
None	42/8/3	<0.001				
Small EV	11/12/19					
Medium EV	5/6/31					
Large EV	0/0/42					
Non-HEV	58/26/36	<0.001				
HEV	0/0/59					
LGV diameter (mm)						
None	3.38 ± 0.73	<0.001				
Small EV	4.48 ± 0.55		0.900 (0.838–0.963)	4 mm	78.57	90.57
Medium EV	5.13 ± 1.04		0.759 (0.652–0.866)	5 mm	59.52	83.33
Large EV	6.87 ± 1.72		0.814 (0.715–0.912)	6.5 mm	61.90	97.62
Non-HEV	4.02 ± 0.90	<0.001				
HEV	6.59 ± 1.56		0.942 (0.896–0.971)	5.3 mm	83.05	94.17
LGV velocity (cm/s)						
None	10.02 ± 1.85	<0.001				
Small EV	10.46 ± 1.95		0.583 (0.463–0.704)	10.2 cm/s	59.52	66.04
Medium EV	11.93 ± 2.18		0.580 (0.571–0.799)	11.4 cm/s	59.52	73.81
Large EV	12.21 ± 2.77		0.524 (0.398–0.649)	14.9 cm/s	19.05	95.24
Non-HEV	10.59 ± 2.13	<0.001				
HEV	12.10 ± 2.54		0.682 (0.609–0.750)	11.1 cm/s	67.8	65.83
LGV flow volume (mL/min)						
None	57.0 ± 32.4	<0.001				
Small EV	100.3 ± 30.6		0.881 (0.813–0.949)	67.1	88.10	75.47
Medium EV	155.9 ± 71.9		0.800 (0.700–0.899)	140.1	61.90	90.48
Large EV	295.1 ± 189.7		0.793 (0.694–0.892)	195.2	69.05	88.10
Non-HEV	86.3 ± 44.2	<0.001				
HEV	268.2 ± 170.4		0.938 (0.892–0.969)	154.0	83.05	93.33

AUROC, area under the receiver operating characteristic curve; CI, confidence interval; EV, esophageal varices; HEV, high-risk esophageal varices; LGV, left gastric vein.



A study reported that the LGV gradually widened under CT with an increase in portal pressure (18). Zhang et al. (19) proposed that presence of lower esophageal Doppler signal, LGV hepatic venous blood flow, and paraumbilical vein recanalization could be considered HEV; however, the sensitivity was low. The LGV diameter has been considered valuable in predicting HEV (9,20). However, no research has focused on the relationship between the LGV and grade of EV. Our research not only predicted the grade of EV, but also HEV, that provided a general idea of the stage of the varices. Second, we combined multimodal ultrasound with laboratory investigations to achieve more stable and accurate diagnosis. LS and SS have been confirmed as promising indicators to predict EV in some studies; however, their diagnostic efficacy remains controversial. The Baveno VI Consensus (2015) reported that patients with an LS value  $<20$  kPa and PLT  $>150,000$  had a very low risk of treatment-requiring varices and could avoid screening endoscopy (7). This was verified by other studies (21,22); however, the endoscopy avoidance rate was not satisfactory (23). Salzl et al. (24) reported that LS was closely related to EV; however, other studies reported that antiviral therapy decreased LS (25). Recent studies reported that SS was more closely related to PH than LS (10,11,26,27). A recent study (28) suggested that SS might be predictive of liver decompensation; however, other researchers disputed the view (12,29). In addition, recent studies showed that LS and SS jointly predicted EV and were more effective than the Baveno VI standard. These parameters reduced the need for endoscopy in nearly 50% of the patients and had high applicability (30,31). In our study, SS demonstrated higher diagnostic ability. Third, to enhance clinical applicability, we proposed the LSPI and LGV/PLT formulas, both of which demonstrated excellent diagnostic capability. These enabled prediction of HEV and the grade of EV, which facilitated rough assessment of the stage. Thus, by follow-up of the patients based on the guidelines, adverse reactions caused by premature use of drugs can be avoided (32).

SS reflected the grade of EV more effectively than LS, which may be attributed to direct reflection of the dynamic state of blood flow by SS (10). LS cannot reflect this aspect (33), and long-term antiviral treatment has been reported to affect LS (25). Thrombocytopenia may be due to hypersplenism caused by PH and an impaired immune system (34–36). Calvaruso et al. (37) reported that PLT was superior to LS in predicting large EV; however, both showed low AUROCs. The study reported that these noninvasive tests did not accurately detect small EV. However, in our study, PLT in cirrhosis patients without EV was high, which could be due to active treatment after the initial diagnosis. Further research is required to validate this assumption.

Presently, there are limited studies on the LGV, and the efficacy of the vein in predicting HEV is unclear (9,20). Our study provided information on this parameter and demonstrated that the diagnostic ability of the LGV diameter was significantly higher than the SS and PLT. Hemodynamics of the LGV also plays an important role in predicting EV. Reverse blood flow may be seen in the LGV with an increase in the portal pressure. Previous studies reported that the LGV flow velocity was related to HEV (9). In our study, although the velocity increased with an increase in the grade of EV, the diagnostic efficacy was low. Furthermore, we defined the cutoff value of the LGV diameter to predict HEV. This parameter could roughly estimate the EV grade and risk in the absence of laboratory results.

Both LSPI and LGV/PLT demonstrated excellent diagnostic accuracy in predicting EV, showing superiority to other noninvasive tests (13,38–41). The formulas were more prominent in small and medium EV, which compensated for the deficiencies of existing research. In the training set, diagnostic efficacy of the LSPI was significantly better than the LGV/PLT (AUROC 0.954 vs 0.942); therefore, we believe that the

LSPI is more stable than the LGV/PLT. Hence, the LSPI would be ideal in suitable conditions; however, if measurement of SS was not possible, the LGV/PLT would be a good choice. Based on these results, it may be considered that the simple, noninvasive, and accurate system proposed in this study could predict the EV grade, diagnose HEV, and aid in patient follow-up and clinical decision-making.

This study has some limitations. First, we focused on patients with cirrhosis due to HBV alone. We aim to assess the applicability of the formulas in other forms of cirrhosis in future studies. Second, we did not conduct long-term follow-up to determine the incidence of bleeding events. Moreover, we did not exclude patients undergoing treatment that led to high PLT in the non-EV group. Finally, similar to the estimation of pulmonary artery pressure by echocardiography in liver transplant candidates (42,43), an accurate and safe method to noninvasively estimate portal pressure is important. We aim to conduct studies on this aspect.

In summary, we proposed the LSPI and LGV/PLT formulas, which showed excellent accuracy in diagnosis of the grade of EV and HEV. These results might lead to avoidance of unnecessary endoscopy. We hope that other studies will evaluate the reproducibility of the formulas for clinical application.

## CONFLICTS OF INTEREST

**Guarantor of the article:** Xinzhi Xu, MS.

**Specific author contributions:** X.X.: collecting and interpreting data, drafting the manuscript. Y.J.: interpreting data, conducting the study.

## Study Highlights

### WHAT IS KNOWN

- ✓ Guidelines recommended screening all patients with cirrhosis by endoscopy.
- ✓ Most patients with cirrhosis do not have varices or have varices that do not require therapy.
- ✓ Many noninvasive methods have been proposed to predict HEV. However, their accuracy requires further analysis.
- ✓ Research has chiefly focused on predicting HEV but not on the EV grade.

### WHAT IS NEW HERE

- ✓ Two novel LGV-based formulas, the LSPI and LGV/PLT, in which LSPI includes the LGV diameter, SS, and PLT and the LGV/PLT includes the LGV diameter and PLT. Both showed excellent diagnostic accuracy in predicting the grade of EV and HEV.
- ✓ LGV/PLT values  $<5.15$  facilitated exclusion of 95.92% of the patients without HEV. LGV/PLT values  $>7.40$  enabled correct diagnosis of 86.27% patients with HEV.
- ✓ LSPI values  $<19.8$  resulted in an NPV of 94.07%. A PPV of 91.49% was achieved at LSPI values  $>23.0$ .
- ✓ The LSPI and LGV/PLT could be reliable noninvasive tools to predict HEV and EV grade.
- ✓ The LGV diameter could also be a promising tool to evaluate the EV grade and HEV.

### TRANSLATIONAL IMPACT

- ✓ The simple formula based on LGV is more beneficial to clinically non-invasive and accurate diagnosis of esophageal varices in patients with liver cirrhosis and tracking at any time for timely intervention.

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**Potential competing interests:** None to report.

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