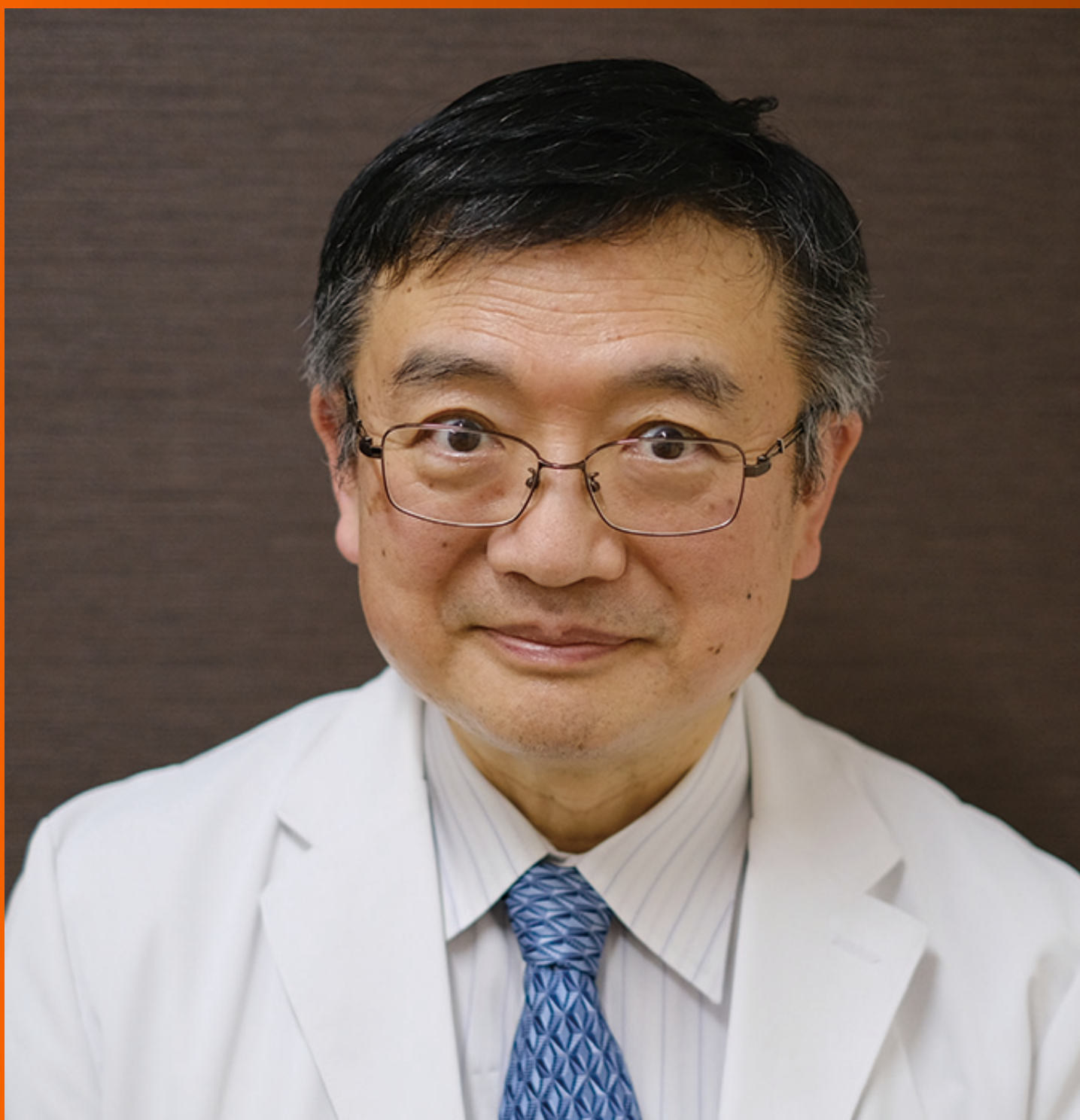


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## Retrospective Study

# Non-invasive model for predicting high-risk esophageal varices based on liver and spleen stiffness

Long-Bao Yang, Xin Gao, Hong Li, Xin-Xing Tantai, Fen-Rong Chen, Lei Dong, Xu-Sheng Dang, Zhong-Cao Wei, Chen-Yu Liu, Yan Wang

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## Abstract

### BACKGROUND

Acute bleeding due to esophageal varices (EVs) is a life-threatening complication in patients with cirrhosis. The diagnosis of EVs is mainly through upper gastrointestinal endoscopy, but the discomfort, contraindications and complications of gastrointestinal endoscopic screening reduce patient compliance. According to the bleeding risk of EVs, the Baveno VI consensus divides varices into high bleeding risk EVs (HEVs) and low bleeding risk EVs (LEVs). We sought to identify a non-invasive prediction model based on spleen stiffness measurement (SSM) and liver stiffness measurement (LSM) as an alternative to EVs screening.

### AIM

To develop a safe, simple and non-invasive model to predict HEVs in patients with viral cirrhosis and identify patients who can be exempted from upper gastrointestinal endoscopy.

### METHODS

Data from 200 patients with viral cirrhosis were included in this study, with 140 patients as the modelling group and 60 patients as the external validation group, and the EVs types of patients were determined by upper gastrointestinal endoscopy and the Baveno VI consensus. Those patients were divided into the HEVs group (66 patients) and the LEVs group (74 patients). The effect of each parameter on HEVs was analyzed by univariate and multivariate analyses, and a non-invasive prediction model was established. Finally, the discrimination ability,

calibration ability and clinical efficacy of the new model were verified in the modelling group and the external validation group.

## RESULTS

Univariate and multivariate analyses showed that SSM and LSM were associated with the occurrence of HEVs in patients with viral cirrhosis. On this basis, logistic regression analysis was used to construct a prediction model:  $\text{Ln} [P/(1-P)] = -8.184 - 0.228 \times \text{SSM} + 0.642 \times \text{LSM}$ . The area under the curve of the new model was 0.965. When the cut-off value was 0.27, the sensitivity, specificity, positive predictive value and negative predictive value of the model for predicting HEVs were 100.00%, 82.43%, 83.52%, and 100%, respectively. Compared with the four prediction models of liver stiffness-spleen diameter to platelet ratio score, variceal risk index, aspartate aminotransferase to alanine aminotransferase ratio, and Baveno VI, the established model can better predict HEVs in patients with viral cirrhosis.

## CONCLUSION

Based on the SSM and LSM measured by transient elastography, we established a non-invasive prediction model for HEVs. The new model is reliable in predicting HEVs and can be used as an alternative to routine upper gastrointestinal endoscopy screening, which is helpful for clinical decision making.

**Key Words:** Cirrhosis; High-risk esophageal varices; Non-invasive prediction model; Spleen stiffness measurement; Liver stiffness measurement; Upper gastrointestinal endoscopy

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**Core Tip:** The non-invasive prediction model for predicting high risk esophageal varices (HEVs) in patients with viral cirrhosis was successfully established based on the spleen stiffness measurement and liver stiffness measurement. It is a novel model that has not been reported. The model was shown to be better than previous prediction models. The new model is reliable in predicting HEVs and can be used as an alternative to routine upper gastrointestinal endoscopy screening, which is helpful for clinical decision making.

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## INTRODUCTION

Liver cirrhosis is the end stage of chronic liver disease. When hepatic venous pressure gradient (HVPG)  $\geq 10$  mmHg is defined as clinically significant portal hypertension (CSPH), the patients who meet this criteria may suffer from complications such as esophageal variceal bleeding, ascites, hepatic encephalopathy, and jaundice due to portal hypertension and liver insufficiency[1,2]. Rupture of esophageal varices (EVs) is a common and life-threatening complication in patients with liver cirrhosis. The incidence of EVs bleeding is approximately 5%-15% per year, the re-bleeding rate within 6 wk after EVs rupture bleeding is 30% to 40%, and the mortality rate is 15%-25%[3-5]. The severity of liver cirrhosis, the size of EVs and the presence or absence of the red sign (RS) are related indicators of EVs bleeding [6]. For routine assessment of the above indicators, the Baveno VI consensus recommends that patients with cirrhosis need to undergo regular screening upper gastrointestinal endoscopy so that appropriate preventive treatment can be administered to prevent variceal bleeding events[7]. To date, HPVG and upper gastrointestinal endoscopy are considered the gold standards for the assessment of PH and EVs, respectively[6]. However, the prevalence of varicose veins requiring treatment (VNT), as defined by the Baveno VI guidelines, is very low in Compensated advanced chronic liver disease (cACLD) patients who are detected at an early stage[8]. HPVG and EGD are invasive procedures and expensive, and the patient compliance associated with them is poor[9,10]. Therefore, in clinical practice, it is necessary to develop a safe, non-invasive and patient-acceptable prediction model that can not only prevent frequent HPVG or gastrointestinal endoscopy examinations but also better predict HEVs in patients with viral cirrhosis. With the development of transient elastography (TE), studies have shown that liver stiffness

(LS) and spleen stiffness (SS) detected by TE are associated with liver fibrosis, significant portal hypertension, and EVs. SS is increased in patients with viral hepatitis, and SS is positively correlated with HVPG, which has good predictive performance for CSPH and EVs in patients with cACLD[11-13].

At present, in addition to ultrasound, CT, MRI, and other imaging methods, there are also several common prediction models[14,15]. The LS-spleen diameter to platelet (PLT) ratio score (LSPS), variceal risk index (VRI), aspartate aminotransferase (AST) to alanine aminotransferase (ALT) ratio (AAR) and Baveno VI model have all achieved good clinical effects in predicting HEVs[16-19]. In addition, the Baveno VI consensus states that LS measurement (LSM) combined with PLT helps to exclude HEVs[8, 19,20]. To initially predict HEVs in patients with viral cirrhosis, the aim of this study is to establish a non-invasive prediction model that can predict HEVs based on SS measurement (SSM) and LSM and to evaluate the accuracy of the new model in identifying HEVs in patients with viral cirrhosis who can be exempted from upper gastrointestinal endoscopy.

## MATERIALS AND METHODS

### *Patients and study design*

The study was authorized by the Ethics Committee of the Second Affiliated Hospital of Xi'an Jiaotong University (Xi'an, Shaanxi Province, China). As a retrospective study; therefore, the Ethics Committee waived the informed consent. This study retrospectively analyzed the data of patients with viral cirrhosis who were admitted to the Second Affiliated Hospital of Xi'an Jiaotong University and underwent upper abdominal computed tomography (CT) examination from March 2020 to November 2022. The inclusion criteria were: (1) Age > 18 years old; (2) patients with hepatitis B and hepatitis C cirrhosis; (3) patients who underwent endoscopy, upper abdominal CT, and laboratory examinations with complete results; and (4) the interval between two examinations was not more than 3 mo. Exclusion criteria: (1) Other liver injury factors, such as alcoholic liver disease, autoimmunity, metabolic liver disease, occult liver cirrhosis, *etc*; (2) suspicious liver tumor; (3) history of liver resection, liver transplantation or splenectomy; (4) frequent use of proton pump inhibitors; (5) other diseases that may impact the haemodynamics of the splenic vein or portal vein, such as cavernous degeneration, thrombosis, embolism; (6) cirrhotic patients with moderate or massive ascites; (7) previous treatment of portal hypertension, such as splenectomy, transjugular intrahepatic portosystemic shunt, endoscopic therapy, and nonselective  $\beta$ -blocker therapy; (8) diseases may affect the liver or spleen size, such as cysts, leukaemia, thrombocytopenic purpura, haemolytic anaemia, multiple myeloma, *etc*; (9) patients with a history of esophageal bleeding undergoing endoscopic or surgical treatment; (10) severe malnutrition or weight loss; (11) unreliable LSM: Quartile range/median > 0.3, success rate < 60%, or the number of effective measurements < 10; or (12) other conditions affecting LSM, such as body mass index > 35 kg/m<sup>2</sup>.

A total of 140 patients who met the inclusion criteria were selected as the modelling group. According to the results of upper gastrointestinal endoscopy and the Baveno VI criteria, the patients were divided into the HEVs group and the LEVs group; 66 patients were HEVs patients, and 74 patients were LEVs patients. In addition, 60 patients who met the inclusion criteria were used as the validation group. The patient's data were collected when the model was established, and the data collection procedure and the model application did not interfere with each other.

### *Definition of EVs*

Patients with liver cirrhosis were graded and scored using the Child-Pugh scoring system[21]. According to Baveno VI criteria, HEVs were defined as EVs with a diameter  $\geq$  5 mm, EVs with a diameter  $\leq$  5 mm and a positive RS, EVs in patients with Child grade C, and EVs that did not meet these criteria were LEVs with a low risk of bleeding[22,23].

### *CT scan-based liver and spleen volume measurement*

The CT examinations were conducted by a multislice spiral CT scanner (GE 128-slice spiral CT scanner; Linux Medical System, United States) with a 5 mm reconstructed layer thickness, and the time interval was 5 s.

Actual liver volume measured by CT (CTLV), actual spleen volume measured by CT (CTSV), portal vein diameter (PVD) and spleen long diameter (SLD) were simultaneously measured by experienced radiologists who did not know the basic information of the patients. CTLV and CTSV were obtained by manually tracing the surface area of the liver and spleen at each level and multiplying by the layer thickness. The entire measurement process requires active avoidance of large blood vessels, gallbladder, and fissure. The SLD was defined as the length of the superior pole to the inferior line of the spleen at the plane of maximum surface area. The PVD needs to be measured at the midpoint between the portal vein bifurcation site and the vein confluence site[24].

### Laboratory examination

For each patient, data on age, sex, height, weight, medical history, medication use, the presence or absence of ascites, and Child-Pugh score were collected. The white blood cell count, red blood cell count, PLT, ALT, AST, total bilirubin (TBil), alkaline phosphatase (ALP), glutamine transferase (GGT), albumin (ALB), total cholesterol (TCHO), prothrombin time (PT), international prothrombin ratio (INR), and prothrombin activity (PTA) of all patients included in the study were collected. The blood test was tested by an XN-9000 analyser (Xisen Meikang Medical Electronics Co. Ltd., Shanghai, China), and the coagulation function was tested by a Sysmex CO-CS-1500 system (SYSMEX Co., Ltd, Kobe, Japan) and the liver function test was performed using a Cobas 8000 analyser (Roche Diagnostics, Mannheim, Germany).

### Liver and SS measurements by TE

LSM and SSM were measured in all patients using FibroScan (Echosens, Paris, France) and FibroTouch (Hai's Medical Technology Center, Beijing, China). The LSM was assessed by a trained and experienced operator after at least 4 h of fasting, and the SSM was performed on the same day as the LSM assessment. All measurements were obtained by experienced operators who had performed at least 300 tests in patients with chronic liver disease. The TE results of the patients were collected retrospectively, and the obtained results were expressed in kilopascals (kPa). The interquartile range (IQR) was defined as the intrinsic variation index between the 25<sup>th</sup> and 75<sup>th</sup> percentiles of the LS results containing 50% of the valid measurements. Therefore, LSM and SSM values were considered to be reliable when at least 10 valid measurements were obtained and the results were reliable, with an overall success rate of more than 60% and IQR/median  $\leq 0.3$ [25,26].

### Upper gastrointestinal endoscopy

Upper gastrointestinal endoscopy was performed by an endoscopic operator who was experienced in the assessment of patients with cirrhosis (with a minimum of 500 endoscopic procedures). Endoscopic examinations were performed to determine whether the patients had EVs, and if so, the EVs were graded according to the location (L), shape and size (F), colour (C), and presence or absence of RS of the lesion.

### Non-invasive score of EVs

The non-invasive prediction models we choose to compare were as shown blow: LSPS = [LSM (KPa)  $\times$  SLD (cm)]/PLT ( $\times 10^9$ /L)[16]; VRI =  $-4.364 + 0.538 \times \text{SLD} - 0.049 \times \text{PLT} - 0.044 \times \text{LSM} + 0.001 \times (\text{LSM} \times \text{PLT})$ [17]; AAR = AST/ALT[18] and the Baveno VI criteria proposed by the consensus conference. The Baveno VI criteria were defined as LSM < 20 kPa and platelet count >  $150 \times 10^9$ /L. The extended Baveno VI criteria were defined as LSM < 25 kPa and platelet count >  $110 \times 10^9$ /L[8,27]. The results of upper gastrointestinal endoscopy were used as the gold standard. The receiver operating characteristic (ROC) curves of LSPS, VRI, AAR and Baveno VI were drawn, and the area under the ROC curve (AUC), sensitivity, specificity and Youden index were calculated to evaluate the performance of the new model and the previous four models in identifying HEVs. The point with the largest sum of sensitivity and specificity was selected as the best cut-off value for the diagnosis of HEVs.

### EVs saluation of new prediction models

The discrimination ability of the new model was assessed by the ROC curves in the modelling group and the external validation group. The Z test was used to evaluate differences in ROC curves. If there was no significant difference in the ROC between the two groups and AUC > 0.7, the model was considered to have good discrimination ability. The calibration ability of the prediction model was evaluated by the Hosmer-Lemeshow test and the two sets of calibration scatter plots. Decision curve analysis (DCA) was performed to evaluate the clinical efficacy of the new model.

### Statistical analysis

SPSS 26.0 and R software (IBM SPSS, Chicago, IL, United States) were used for statistical analysis. Data are presented as the mean  $\pm$  SD. The chi-square test was used to compare the measurement data between the HEVs group and the LEVs group. The Mann-Whitney *U* test was used for univariate analysis of continuous variable measurement data, and WALD backwards regression analysis was used for multivariate analysis. SPSS 26.0 software was used to draw the ROC curve and calculate the AUC to evaluate the diagnostic performance of the model. The maximum corresponding point of the Youden index was selected as the best cut-off value, and a positive prediction result was defined as equal to or greater than the best cut-off value. The best discrimination probability threshold, sensitivity, specificity and predictive value were calculated, and the diagnostic accuracy was compared. The higher the Youden index (1% or 100%), the more effective the correlation. Hosmer-Lemeshow test results, calibration charts and DCA were obtained using R software. All statistical tests were two-sided, with an alpha value of 0.05 and a statistical significance threshold of  $P < 0.05$ .

## RESULTS

### **Baseline characteristics of the patients**

Tables 1 and 2 List the baseline characteristics of the modelling group and the external validation group, respectively. In the LEVs group, the mean age was 50.88 years  $\pm$  11.6 years, 43 (58.1%) were male, and 61 (82.4%) had hepatitis B. The age of the HEVs patients was 55.36 years  $\pm$  11.1 years old, 37 (56.1%) were male, and 53 (80.3%) had hepatitis B. In the modelling group, there was a significant difference in age between the HEVs group and the LEVs group ( $P < 0.05$ ) but no significant difference in sex or hepatitis type ( $P > 0.05$ ), and the two groups were comparable. In the external validation group, there was no significant difference in sex, age or hepatitis type ( $P > 0.05$ ).

### **Univariate analysis of HEVs**

T tests and non-parametric rank sum tests were used for the univariate analysis. The summarized results are shown in Table 3. There were significant differences in SSM, PLT, LSM, ALT, AST, GGT, SLD, PT, INR, PTA, PVD, CTLV, and CTSV between the HEVs group and the LEVs group ( $P < 0.05$ ). There were no significant differences in ALP, TBil, and TCHO between the two groups ( $P > 0.05$ ).

### **Multivariate analysis of HEVs**

The parameters shown in Table 3 with statistically significant differences between the HEVs and LEVs groups were analyzed by multivariate analysis using backwards WALD regression analysis. As shown in Table 4, the SSM and LSM between the HEVs group and LEVs group were significantly different ( $P < 0.05$ ). There were no significant differences in PLT, ALT, AST, GGT, SLD, PT, INR, PTA, PVD, CTLV, and CTSV ( $P > 0.05$ ).

### **Establishment of a non-invasive prediction model**

Based on the results of the multivariate analysis, the parameters with no statistically significant difference between the two groups were excluded, and the parameters with statistically significant differences, including SSM and LSM, were used to establish a non-invasive prediction model. The logistic regression analysis showed that SSM and LSM were independent factors affecting the occurrence of HEVs and were statistically significant ( $P < 0.05$ ). As shown in Table 5, the model was as follows:  $\text{Ln}[P/(1-P)] = -8.184 - 0.228 \times \text{SSM} + 0.642 \times \text{LSM}$ . HEVs in patients with viral cirrhosis were negatively correlated with SSM and positively correlated with LSM.

### **Comparison of non-invasive prediction models**

The new model was compared with other models reported to predict EVs in patients with liver cirrhosis, namely, the LSPS, VRI, AAR, and Baveno VI models. The sensitivity, specificity and AUC of the new model based on the SSM and LSM and LSPS, VRI, AAR and Baveno VI models were calculated. The cut-off value of the model was defined as the maximum value of the sum of the specificity and sensitivity. Patients were considered to have HEVs when the P value calculated by the established formula was greater than the cut-off value. As shown in Figure 1A and Table 6, the AUC of this model was 0.965, while the AUCs of LSPS, VRI, AAR and Baveno VI were 0.835, 0.744, 0.641, and 0.675, respectively. The AUC  $> 0.7$  indicated the good discrimination power of the model. The higher the AUC is, the better the discriminative power of the model, so the new model has good discriminative power.

### **Diagnostic accuracy of non-invasive tests for predicting HEVs**

The accuracy, positive predictive value and negative predictive value of LSPS, VRI, ARR, Baveno VI, and the new model of 140 patients in the modelling group were calculated according to the calculation formula. As shown in Table 7, the non-invasive prediction model shown in this study had an accuracy of 89.30% and a positive predictive value of 83.52%. The accuracy and positive predictive values suggest the likelihood that the new model can correctly diagnose HEVs, with higher values indicating a more correct diagnosis.

### **Discriminating ability edicting HEVs**

Evaluation of the ability of the non-invasive model was performed by drawing the ROC curve of the established new model in the external validation group and using the Z test to compare the AUC curve between the modelling group and the external validation group and to evaluate the discriminative power of the new model. The AUC of the new model for predicting HEVs in the modelling group was 0.965, which was higher than that of the LSPS, VRI, AAR, and Baveno VI models. The AUC of the new model in the external validation group was 1. The Z test result was 0.896, and the  $P$  value was 0.37, indicating that there was no significant difference between the modelling group and the external validation group. The ROC curve of the external validation group is shown in Figure 1B.

### **EVs saluation of the calibration ability of the new model**

The Hosmer-Lemeshow test was used to calculate the  $\chi^2$  value of the modelling group and the external

**Table 1 Comparison of general characteristics in the modelling group**

Parameter	Patients with LEVs, <i>n</i> = 74	Patients with HEVs, <i>n</i> = 66	<i>T</i> value/ $\chi^2$ value	<i>P</i> value
Age in yr	50.88 ± 11.60	55.36 ± 11.10	-2.333	0.021
Male (%)	43 (58.1%)	37 (56.1%)	0.060	0.807
Etiology, HBV/HCV	61/13	53/13	0.105	0.746

*P* < 0.05 is considered statistically significant. HEVs: High-risk esophageal varices; LEVs: Low-risk esophageal varices; HBV: Hepatitis B virus; HCV: Hepatitis C virus.

**Table 2 Comparison of general characteristics in the external validation group**

Parameter	Patients with LEVs, <i>n</i> = 28	Patients with HEVs, <i>n</i> = 32	<i>T</i> value/ $\chi^2$ value	<i>P</i> value
Age in yr	52.54 ± 13.70	54.97 ± 10.40	-0.780	0.438
Male (%)	15 (53.6%)	14 (43.8%)	0.577	0.448
Etiology, HBV/HCV	25/3	30/2	0.024	0.876

*P* < 0.05 is considered statistically significant. HEVs: High-risk esophageal varices; LEVs: Low-risk esophageal varices; HBV: Hepatitis B virus; HCV: Hepatitis C virus.

**Table 3 Univariate analysis of parameters of patients with high-risk esophageal varices and low-risk esophageal varices**

Parameter	Patients with LEVs, <i>n</i> = 74	Patients with HEVs, <i>n</i> = 66	<i>t</i> / <i>Z</i>	<i>P</i> value
SSM, KPa	22.70 ± 6.00	19.06 ± 4.90	3.880	< 0.001
PLT, × 10 <sup>9</sup> /L	108.55 ± 68.10	62.53 ± 29.00	5.096	< 0.001
LSM, KPa	14.90 ± 5.10	24.83 ± 4.30	-12.354	< 0.001
ALT, IU/L	37.50 (26.00, 49.50)	23.00 (16.00, 35.00)	-4.278	< 0.001
AST, IU/L	43.00 (31.75, 69.00)	34.50 (27.75, 45.25)	-2.796	0.005
ALP, IU/L	108.00 (81.25, 137.25)	93.50 (78.00, 128.75)	-1.012	0.311
GGT, IU/L	60.50 (28.00, 114.00)	33.00 (19.75, 58.75)	-3.609	< 0.001
SLD, mm	13.58 ± 3.10	15.10 ± 3.30	-2.806	0.006
TBIL, μmol/L	22.63 (16.01, 34.96)	27.80 (18.05, 39.65)	-0.960	0.337
ALB, g/dL	37.16 ± 8.30	36.02 ± 5.80	0.935	0.351
TCHO, mmol/L	3.57 ± 1.40	3.18 ± 0.90	1.981	0.050
PT, s	12.45 ± 2.20	13.34 ± 2.50	-2.284	0.024
INR	1.13 ± 0.20	1.21 ± 0.20	-2.175	0.031
PTA, %	82.15 ± 20.80	75.09 ± 16.10	2.228	0.028
PVD, mm	12.20 ± 1.90	13.64 ± 2.30	-4.024	< 0.001
CTLV, cm <sup>3</sup>	1031.88 ± 361.20	920.85 ± 241.50	2.111	0.037
CTSV, cm <sup>3</sup>	558.11 ± 338.70	808.25 ± 409.90	-3.951	< 0.001

*P* < 0.05 is considered statistically significant. HEVs: High-risk esophageal varices; LEVs: Low-risk esophageal varices; SSM: Spleen stiffness measurement; LSM: Liver stiffness measurement; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; GGT: Glutamine transferase; SLD: Spleen long diameter; TBIL: Total bilirubin; ALB: Albumin; TCHO: Total cholesterol; PT: Prothrombin time; INR: International prothrombin ratio; PTA: Prothrombin activity; PVD: Portal vein diameter; CTLV: Actual liver volume measured by computed tomography; CTSV: Actual spleen volume measured by computed tomography.

**Table 4 Multivariate analysis of parameters of patients with high-risk esophageal varices and low-risk esophageal varices**

Parameter	Patients with LEVs, <i>n</i> = 74	Patients with HEVs, <i>n</i> = 66	<i>t/Z</i>	<i>P</i> value
SSM, KPa	22.70 ± 6.00	19.06 ± 4.90	3.880	0.009
PLT, × 10 <sup>9</sup> /L	108.55 ± 68.10	62.53 ± 29.00	5.096	0.606
LSM, KPa	14.90 ± 5.10	24.83 ± 4.30	-12.354	< 0.001
ALT, IU/L	37.50 (26.00, 49.50)	23.00 (16.00, 35.00)	-4.278	0.669
AST, IU/L	43.00 (31.75, 69.00)	34.50 (27.75, 45.25)	-2.796	0.125
	60.50 (28.00, 114.00)	33.00 (19.75, 58.75)	-3.609	0.790
SLD, mm	13.58 ± 3.10	15.10 ± 3.30	-2.806	0.952
PT, s	12.45 ± 2.20	13.34 ± 2.50	-2.284	0.883
INR	1.13 ± 0.20	1.21 ± 0.20	-2.175	0.777
PTA, %	82.15 ± 20.80	75.09 ± 16.10	2.228	0.920
PVD, mm	12.20 ± 1.90	13.64 ± 2.30	-4.024	0.220
CTLV, cm <sup>3</sup>	1031.88 ± 361.10	920.85 ± 241.50	2.111	0.892
CTSV, cm <sup>3</sup>	558.11 ± 338.70	808.25 ± 409.90	-3.951	0.713

*P* < 0.05 is considered statistically significant. HEVs: High-risk esophageal varices; LEVs: Low-risk esophageal varices; SSM: Spleen stiffness measurement; LSM: Liver stiffness measurement; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; SLD: Spleen long diameter; PT: Prothrombin time; INR: International prothrombin ratio; PTA: Prothrombin activity; PVD: Portal vein diameter; CTLV: Actual liver volume measured by computed tomography; CTSV: Actual spleen volume measured by computed tomography.

**Table 5 Parameters used to establish the non-invasive prediction model**

Parameter	B	S.E.	Wald	<i>P</i>	Exp (B)	95%CI of exp (B)
SSM	-0.228	0.074	9.647	0.002	0.796	0.689-0.919
LSM	0.642	0.123	27.245	< 0.001	1.900	1.493-2.418
Constant	-8.184	2.300	12.659	< 0.001	0.000	-

SSM: Spleen stiffness measurement; LSM: Liver stiffness measurement; CI: Confidence interval.

**Table 6 Comparison of various parameters of each model**

	Area	SE	<i>P</i>	95%CI of exp (B)
LSPS	0.835	0.033	< 0.001	0.771-0.900
VRI	0.744	0.041	< 0.001	0.663-0.824
AAR	0.641	0.046	0.004	0.550-0.732
Baveno VI	0.675	0.045	< 0.001	0.586-0.764
The new model	0.965	0.015	< 0.001	0.936-0.995

LSPS: Liver stiffness-spleen diameter to platelet ratio score; VRI: Variceal risk index; AAR: Aspartate aminotransferase/alanine aminotransferase ratio; BavenoVI: Baveno VI criteria were defined as liver stiffness measurement < 20 kPa and platelet count > 150 × 10<sup>9</sup> /L; CI: Confidence interval.

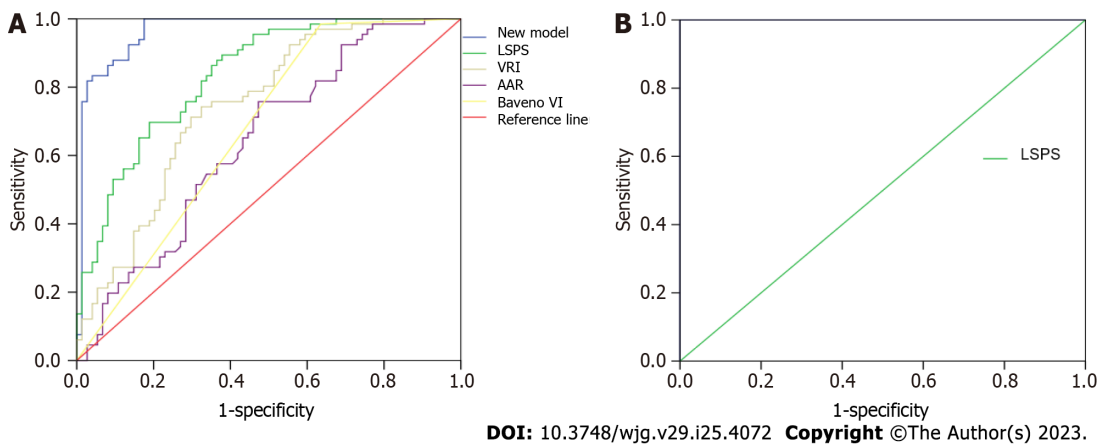
validation group to evaluate the calibration ability of the new model. The results showed that  $\chi^2$  was -10.39 in the modelling group and 0.03 in the external validation group. The *P* values were 0.999 and 1.000, respectively. Both the groups' *P* value were greater than 0.05, indicating that the model could predict HEVs accurately. The calibration scatter plots of the two groups were shown in Figure 2. As seen from the figure, all scatter points fluctuated around the baseline without significant deviation because the *P* values of both groups were greater than 0.05 and the difference between the groups was not statistically significant. The results showed that the HEVs patients who were predicted to have viral

**Table 7 Comparison of various parameters of each model**

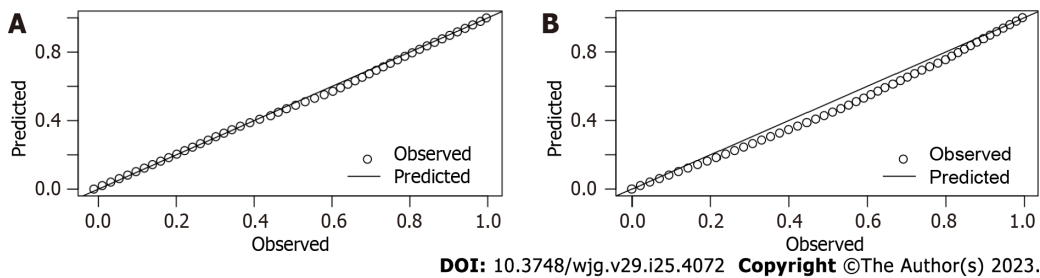
	Sensitivity	Specificity	Accuracy, %	Positive predictive value, %	Negative predictive value, %	Cutoff value
LSPS	89.39	62.16	74.30	67.78	86.81	3.12
VRI	74.24	67.57	69.30	67.09	74.66	0.03
AAR	75.76	52.70	57.90	58.78	70.95	1.27
Baveno VI <sup>1</sup>	98.48	36.49	65.70	57.99	96.42	-
The new model	100.00	82.43	89.30	83.52	100.00	0.27

<sup>1</sup>Baveno VI criteria were defined as liver stiffness measurement < 20 kPa and platelet count > 150 × 10<sup>9</sup> /L.

LSPS: Liver stiffness-spleen diameter to platelet ratio score; VRI: Variceal risk index; AAR: Aspartate aminotransferase/alanine aminotransferase ratio.



**Figure 1 Area under the curve of various models in predicting high-risk esophageal varices of patients.** A: Modelling group; B: External validation group. The area under the curve of the new model in predicting high-risk esophageal varices of patients was 0.965 in the modelling group, which was higher than that of liver stiffness-spleen diameter to platelet ratio score, variceal risk index, aspartate aminotransferase/alanine aminotransferase ratio and Baveno VI; and it was 1 in the external validation group. LSPS: Liver stiffness-spleen diameter to platelet ratio score; VRI: Variceal risk index; AAR: Aspartate aminotransferase/alanine aminotransferase ratio.

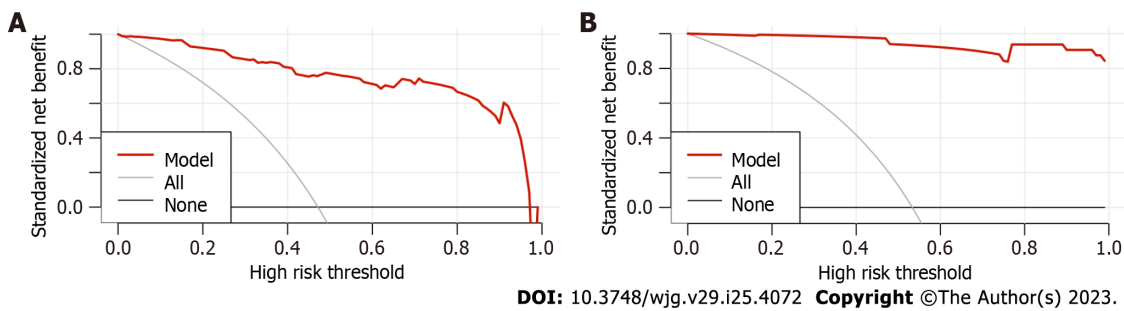


**Figure 2 Calibration scatter plot of data of patients.** A: Modelling group; B: External validation group. In predicting patients in the modelling group and external validation group, the scattered points fluctuated around the reference line without significant deviations.

cirrhosis by using the new model were in good agreement with the actual HEVs patients.

### EVs salvation of the clinical efficacy of the new model

DCA was plotted against the probability of actual HEVs occurrence by predicting the probability of the modelling group and the external validation group by the new model. The DCA of the two groups is shown in Figure 3. In the DSA curve, the two dashed lines represent the two extreme cases, and the black line indicates that the new model predicts there was no HEVs, and a net clinical benefit of zero. The other grey line with a negative slope indicates that the new model predicts HEVs in all patients with viral cirrhosis, and the net clinical benefit is a back-slope with a negative slope[28]. The red line is the new model's DCA. As the DCA curve shown, the red line was higher than the black and grey lines, indicating that when the new model was applied to the modelling group and the external validation group, both groups of patients could benefit, so the new model had certain clinical efficacy.



**Figure 3 Adjusted decision curve analysis of data of patients.** A: Modelling group; B: External validation group. The black line indicates that in extreme cases, the new model predicted that there were no high-risk esophageal varices in all patients with viral cirrhosis, and the clinical net benefit was 0. The gray curve indicates that in extreme cases, the new model predicts there are high-risk esophageal varices in all patients with viral cirrhosis, the clinical net benefit is the negative slope. The red line indicates that the new model has a clinical net benefit. The red line is higher than the black and gray lines, indicating that patients in the modelling group can benefit from the new model.

## DISCUSSION

Long-term chronic viral hepatitis can lead to liver cirrhosis and is associated with high morbidity and mortality; therefore, it is a public health concern that deserves attention[29-31]. EVs rupture and bleeding are common causes of death in patients with liver cirrhosis. Clinical guidelines recommend the use of upper gastrointestinal endoscopy in screening and periodic reexamination of patients with cirrhosis regardless of the disease cause[9]. According to the results of upper gastrointestinal endoscopy and the Baveno VI criteria, EVs were divided by the low bleeding risk EVs (LEVs) and the high bleeding risk EVs (HEVs). For patients with HEVs, early precession measures can significantly reduce the esophageal variceal bleeding risk[22,32]. However, the invasiveness of upper gastrointestinal endoscopy, the high price, and the risk of anaesthesia make the compliance of patients to upper gastrointestinal endoscopy very low[9,10]. Considering that many patients do not have EVs in the early stage of liver cirrhosis, there is a need for non-invasive, simple, and safe means to identify liver cirrhosis patients with HEVs. In addition to upper gastrointestinal endoscopy, a variety of imaging methods, such as ultrasound, CT, and MRI, can be used to predict HEVs. However, these three methods cannot visually observe EVs, and the accuracy of identifying HEVs is poor[33]. A number of non-invasive models have been developed to predict HEVs, and several studies have shown that the LSPS, VRI, AAR, and Baveno VI models have achieved good results in predicting HEVs. Measurement of LS and SS by TE (using FibroScan) is a fast, non-invasive, easy to perform and reproducible procedure for predicting the presence of clinically significant EVs and PH, so LS and SS were measured by TE in this study[34]. In this study, to ensure the homogeneity of aetiology, we included patients with cirrhosis and HBV/HCV infection. Our study showed that LSM and SSM were two independent variables associated with the presence of HEVs. The results of our study are similar to those of several studies. LSM is associated with PH, and LSM combined with other indicators can predict HEVs[35,36]. Splenomegaly is common in patients with chronic viral cirrhosis, and splenic blood flow enters the portal vein system through the splenic vein. Therefore, SSM can simultaneously reflect static resistance fibrosis of the liver (LSM can also reflect) and dynamically capture PH-related visceral hypoperfusion, changes in spleen results, changes in blood flow, and PH-induced splenic fibrosis[37].

In this study, we constructed a non-invasive prediction model including LSM and SSM. The AUC of the new model was 0.965, the accuracy was 89.30%, which was better than that of the LSPS, VRI, AAR, and Baveno VI models, and the new model showed good diagnostic performance. When the optimal cut-off value was 0.27, the sensitivity and negative predictive value (NPV) of the new model in the modelling group were both 100%, and due to the Baveno VI criteria and other models, the new model could best identify non-HEVs patients so that these patients could be spared from undergoing upper gastrointestinal endoscopy. Morishita *et al*[38] used a similar approach in 135 patients with HCV-related cirrhosis to predict the presence of HEVs in patients with viral cirrhosis using a single indicator of LSM, and their results showed that the AUC of LSM for predicting the presence of HEVs was 0.868. The sensitivity, specificity, positive predictive value and negative predictive value were 81%, 82%, 69%, and 89%, respectively[38]. Similarly, in another study, Stefanescu *et al*[5] used a single-indicator SSM to assess the presence of HEVs, selecting an SSM@50 Hz with a 95% sensitivity for the best cut-off value [5]. Moreover, many studies have shown that when the HVPG value is  $\geq 12$  mmHg, LSM alone cannot reliably diagnose or exclude the risk grade of varices because of the poor correlation of extrahepatic factors. However, SSM can evaluate the severity of PH, the presence of EVs and the risk of bleeding but cannot predict the grade of EVs[39]. Therefore, this study developed and validated whether a non-invasive prediction model based on the combination of SSM and LSM indicators can be used as a useful tool to assess the severity of EVs and the risk of upper gastrointestinal bleeding (UGIB). These results of our study suggest that in the majority of patients with viral cirrhosis evaluated, the new model can

accurately exclude patients with HEVs, thereby allowing these patients to avoid endoscopy or prophylactic therapy. Furthermore, the higher NPV and sensitivity, regardless of the cirrhosis severity, suggest that use of the new model may be more cost-effective, as endoscopic screening of patients with both compensated and decompensated cirrhosis proved to be cost-effective[40]. In addition, a second independent dataset was used to externally validate the clinical utility of the new model, and the results showed that the new model had high discrimination power. In addition, DCA was cited to illustrate the clinical benefit of the new model, and both the modelling group and the external validation group could benefit from the new model. In addition, the included indicators in the new model can be obtained by TE and B-ultrasound, which are non-invasive, inexpensive, do not require radiation, are highly feasible in clinical practice, and are easy to popularize in clinical work.

Generally speaking, we have successfully developed a non-invasive prediction model using LSM and SSM indicators to predict the presence of HEVs in patients with viral cirrhosis, which has not been reported in the literature. Compared with other models LSPS, VRI, AAR, and Baveno VI, the new model has a good diagnostic performance, a high discrimination ability, calibration ability and a clinical application value. In addition, we enrolled patients with viral cirrhosis, which provided good consistency while minimizing bias in the results. However, this retrospective study has limitations. First, the sample size of this study is relatively small, and more data need to be collected for evaluation. Second, the patients in this study were all Chinese, and it is unclear whether this model can be applied in other ethnic groups. Additionally, because the patients in this study were all patients with viral cirrhosis and because changes in liver and spleen volume can vary with cirrhosis from different causes, it is unclear whether the new model can be applied to cirrhosis from other causes.

In conclusion, the new model based on SSM and LSM indicators,  $\ln [P/(1-P)] = -8.184 - 0.228 \times \text{SSM} + 0.642 \times \text{LSM}$ , can effectively rule out the presence of HEVs in patients with viral cirrhosis, and this model needs to be further verified in prospective trials. This model helps physicians recognize the presence of HEVs in patients with viral cirrhosis, make more informed decisions, and provide appropriate preventive treatment.

## CONCLUSION

The new model can effectively rule out the presence of HEVs in patients with viral cirrhosis and can be used as an alternative to routine upper gastrointestinal endoscopy screening.

## ARTICLE HIGHLIGHTS

### Research background

Acute bleeding due to esophageal varices (EVs) is a life-threatening complication in patients with cirrhosis. The diagnosis of EVs is mainly through upper gastrointestinal endoscopy, but the discomfort, contraindications and complications of gastrointestinal endoscopic screening reduce patient compliance.

### Research motivation

To develop a safe, simple and non-invasive model to predict high risk EVs (HEVs) in patients with viral cirrhosis and identify patients who can be exempted from upper gastrointestinal endoscopy.

### Research objectives

To establish a non-invasive prediction model based on spleen stiffness measurement (SSM) and liver stiffness measurement (LSM) as an alternative to EVs screening.

### Research methods

Two hundred Chinese adults, from March 2020 to November 2022, were included at the Second Affiliated Hospital of Xi'an Jiaotong University. Required data were collected by the medical records, and the EVs types of patients were determined by upper gastrointestinal endoscopy and the Baveno VI consensus. The effect of each parameter on HEVs was analyzed by univariate and multivariate analyses, and a non-invasive prediction model was established, and then the effect of each parameter on HEVs was analyzed by univariate and multivariate analyses, and a non-invasive prediction model was established.

### Research results

After univariate and multivariate analyses, SSM and LSM were used to establish a prediction model. The new non-invasive model was better than other four models to predict HEVs in patients with viral cirrhosis.

## Research conclusions

The new model is reliable in predicting HEVs and can be used as an alternative to routine upper gastrointestinal endoscopy screening, which is helpful for clinical decision making.

## Research perspectives

In the future, we will try to apply the new model to predict HEVs in patients with viral cirrhosis.

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## FOOTNOTES

**Author contributions:** Yang LB and Gao X contributed equally to this work; Li H, Dong L, and Dang XS designed the research study; Liu CY and Gao X performed the research; Tantai XX and Wei ZC contributed new reagents and analytic tools; Yang LB, Wang Y, and Chen FR analyzed the data and wrote the manuscript; and all authors have read and approve the final manuscript.

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**Institutional review board statement:** The study was reviewed and approved by the Ethics Committee of the Second Affiliated Hospital of Xi'an Jiaotong University (approval No. 2017-445).

**Informed consent statement:** This study is a retrospective study; thus, the ethics committee has exempted the informed consent of the patients.

**Conflict-of-interest statement:** There was no any interests conflicts.

**Data sharing statement:** No additional data are available.

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