


Article

Spleen Thickness Plus Platelets Can Effectively and Safely Screen for High-Risk Varices in Cirrhosis Patients

Fengbin Zhang ^{1,2,†}, Yonghe Zhou ^{3,†}, Xin Li ³, Chunyan Wang ², Jie Liu ², Shuang Li ², Shuting Zhang ^{1,2}, Weiming Luo ⁴, Lili Zhao ^{2,*} and Jia Li ^{2,*} 

¹ Clinical School of the Second People's Hospital, Tianjin Medical University, Tianjin 300070, China; fb15525119825@163.com (F.Z.); meshuting@163.com (S.Z.)

² Department of Gastroenterology and Hepatology, Tianjin Second People's Hospital, Tianjin 300192, China; water4645@sina.com (C.W.); liujie_0802@163.com (J.L.); ronnie112233@163.com (S.L.)

³ Department of Ultrasonography, Tianjin Second People's Hospital, Tianjin 300192, China; zhoutonghe@pku.org.cn (Y.Z.); hp-5555@163.com (X.L.)

⁴ Department of Toxicology and Sanitary Chemistry, School of Public Health, Tianjin Medical University, Tianjin 300070, China; luoweiming@tmu.edu.cn

* Correspondence: ZhLL_stone2013@tmu.edu.cn (L.Z.); 18622663700@163.com (J.L.)

† These authors contributed equally to this work.

Abstract: Currently, most primary hospitals cannot routinely perform liver stiffness measurements (LSMs) and spleen stiffness measurements (SSMs), which are recommended by guidelines to exclude high-risk varices (HRVs). We tried to find more convenient indicators for HRV screening. We enrolled 213 cirrhosis patients as the training cohort (TC) and 65 primary biliary cirrhosis patients as the validation cohort (VC). We included indicators such as SSM by two-dimensional shear wave elastography, LSM by transient elastography, and other imaging and laboratory tests. Variable analysis revealed SSM, platelets (PLT), and spleen thickness (ST) as independent risk indicators for HRV. In TC, ST+PLT ($ST < 42.2$ mm and $PLT > 113.5 \times 10^9/L$) could avoid 35.7% of the esophagogastroduodenoscopies (EGDs), with a 2.4% missed HRV rate. Although the proportion of EGDs spared by ST+PLT was less than SSM+PLT ($SSM < 29.89$ kPa + $PLT > 113.5 \times 10^9/L$) (35.7% vs. 44.1%), it was higher than that of the Baveno VI criteria (B6) (35.7% vs. 28.2%). We did not validate SSM+PLT in VC considering our aims. ST+PLT safely spared 24.6% of EGDs in VC, identical to B6. Conclusions: The ability of ST+PLT to exclude HRVs was superior to B6 but slightly inferior to SSM+PLT. When SSM cannot be routinely performed, ST+PLT provides an extra option for patients to exclude HRVs as a more convenient model.

Keywords: spleen thickness; liver stiffness measurement; spleen stiffness measurement; 2D-SWE; primary biliary cirrhosis; high-risk varices



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1. Introduction

Portal hypertension (PH) is a common clinical syndrome characterized by an elevated hepatic vein pressure gradient (pressure difference between the portal vein and hepatic veins). Based on the location of the etiology, PH can be categorized into pre-hepatic, intra-hepatic, and post-hepatic types [1]. The most prevalent in clinical settings is intra-hepatic PH, which arises from cirrhosis, and gastroesophageal varices (GEVs) are the direct result. Acute bleeding of GEVs represents the most severe complication caused by PH. The six-week mortality rate in cirrhosis patients is considered a primary indicator for evaluating the efficacy of acute bleeding therapy, which ranges from 15% to 25% [2]. Research indicates that varices resulting from PH are reversible [3]. Hence, early detection of high-risk varices (HRVs) is critical for lifestyle and clinical interventions that ultimately improve patients' quality of life and survival rates.

Esophagogastroduodenoscopy (EGD), known as the gold standard for diagnosing GEVs, is still recommended in guidelines. For patients with decompensated cirrhosis and HRVs, EGD should be performed annually or every six months, depending on their condition [4]. However, due to its high cost, discomfort, and invasive nature, the clinical application of EGD is restricted. In recent years, non-invasive assessment methods for HRVs have been gradually maturing. According to the Baveno VII criteria, patients with cirrhosis who do not meet the criteria of a liver stiffness measurement (LSM) ≤ 20 kPa and platelets (PLT) $\geq 150 \times 10^9$ /L can further avoid EGD screening based on a spleen stiffness measurement (SSM) ≤ 40 kPa [4]. The validation by Wang et al. demonstrated that these criteria are relatively safe and efficient [5]. However, in clinical practice, most HRV screenings are conducted in primary hospitals, where routine LSM and SSM monitoring may not be available. As a result, many experts have explored and studied more indicators associated with PH that are easier to monitor, such as albumin (ALB), spleen thickness (ST), spleen diameter (SD), portal vein diameter (PVD), and spleen vein diameter (SVD) [6–11].

This study aims to obtain more easily measurable indicators and validate their abilities to exclude HRVs. Simultaneously, we will analyze these indicators in comparison with LSMs and SSMs.

2. Materials and Methods

2.1. Patients

We retrospectively collected relevant clinical data from all patients admitted to Tianjin Second People's Hospital from September 2020 to April 2023 who obtained LSMs and SSMs to form the training cohort (TC). Additionally, we enrolled all patients diagnosed with primary biliary cholangitis (PBC) from January 2016 to April 2023 as the validation cohort (VC). All PBC patients in the VC were also clinically diagnosed with cirrhosis.

Inclusion criteria: (1) Age ≥ 18 years; (2) SSM was obtained by two-dimensional shear wave elastography (2D-SWE) in the TC, and LSM was obtained by transient elastography (TE) in all patients; (3) patients with data records (EGD, imaging, and laboratory tests) that were updated within three months of our study; and (4) patients diagnosed with compensated and decompensated cirrhosis (limited to those with ascites or hepatic encephalopathy as decompensation symptoms) were confirmed based on clinical symptoms, laboratory tests, and imaging examinations [12,13].

Exclusion criteria: (1) Decompensated patients with a history of varix bleeding; (2) splenectomy or congenital absence of the spleen; (3) splenic lesions due to hematological disorders; (4) portal vein or splenic vein thrombosis; (5) benign or malignant spleen tumors; (6) patients who have received transjugular intrahepatic portosystemic shunt (TIPS) surgery; (7) non-cirrhotic PH; (8) use of non-selective β -blockers in the last two weeks; (9) patients with liver cancer; (10) liver transplantation; and (11) patients with missing data.

The ethics committee approved all these studies. Moreover, informed consent materials were available for all examinations.

2.2. Laboratory Tests

The laboratory data we collected encompassed PLT, ALB, creatinine (CR), alanine aminotransferase (ALT), aspartate transaminase (AST), total bilirubin (TBIL), prothrombin time (PT), and international normalized ratio (INR).

2.3. EGD Assessment

For this study, EGD was conducted using Olympus CV-260SL equipment (Olympus Medical Imaging, Osaka, Japan). The findings were recorded following guidelines, mainly including the location, size, and presence of red signs in varices [14]. HRVs were defined as medium-to-large diameter varices (≥ 5 mm) or varices of any size with a red sign [4,15]. Patients undergoing endoscopic ligation or sclerotherapy were also considered to have HRVs [2].

2.4. LSM and SSM

SSMs were performed using an Aixplorer ultrasound system (Supersonic Imagine SA, Aix-en-Provence, France) in the TC. LSMs were performed using a FibroScan502 (Echosens, Paris, France) in all patients. Patients were required to be fasting before the examinations. For LSMs, the patient lay supine on the bed with the right arm extended to expose the liver region fully. For SSMs, the patient was in a right lateral position on the bed with the left arm extended to expose the spleen region fully. The physicians were unaware of the patients' other clinical data. The units of the LSMs and SSMs are kilopascals (kPa). Each LSM or SSM value was the median of ten measurements. The results were considered valid if the interquartile range/median $\leq 30\%$ for the ten measurements. Patients with ascites performed abdominocentesis before undergoing LSMs and SSMs (no or trace ascites on ultrasound).

2.5. Abdominal Ultrasound Assessment

Abdominal ultrasonography was conducted using a Toshiba SSH-140A Doppler ultrasound (Toshiba Medical Systems, Tokyo, Japan). Patients fasted and rested for at least ten minutes before the examination. During the examination, the patient was lying supine on the bed with arms raised, fully exposing the abdomen. We measured the SD, ST, PVD, and SVD as candidate indicators.

2.6. Statistical Analysis

We used the R language (version 4.2.2, 2022) for the statistical analyses. Continuous variables are expressed as median (interquartile range, IQR); categorical variables are expressed as number (proportions). The Mann–Whitney U test was utilized to compare samples of continuous variables, while the chi-square test was employed for categorical variable comparisons. The stepwise logistic regression was applied for multivariable screening. We plotted the receiver operating characteristic curve (ROC) for each indicator and calculated the area under the curve (AUC) to evaluate the diagnostic accuracy of each model. The maximum Youden index determined the optimal cutoff value. Comparisons of paired AUCs were performed using the DeLong test. The primary outcomes of interest for evaluating indicators and models were the proportion of spared EGDs and the missed HRV rate. Other statistical indicators to evaluate the diagnostic value included sensitivity (Sen), specificity (Spe), positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR), negative likelihood ratio (NLR), and accuracy (ACU). The simplified model derived from the TC was validated in the VC. *P* values less than 0.05 were considered significant.

Calculation formulas: (1) Proportion of spared EGDs = patients eligible for non-invasive models/total patients; (2) missed HRV rate = patients who fit the non-invasive models but had HRVs/total patients with HRVs.

3. Results

3.1. Patients Characteristics

The details of the participant selection are shown in Figure 1. The 213 eligible participants were enrolled in the TC, with 41 (19.2%) having HRVs. A total of 65 participants were enrolled in the VC, with 28 (43.1%) having HRVs. Table 1 presents the essential characteristics of the participants. In the TC, the median age of the participants was 53 years (IQR, 42–60), with 81 females (38.0%). In the VC, the median age of the participants was 59 years (IQR, 52–66), with 57 females (87.7%). The most common etiology of cirrhosis in the TC was hepatitis B virus (70.9%, HBV), while all patients had PBC in the VC. In the TC, 43 patients with ascites as decompensation manifestation were included, while the VC included 17 individuals.

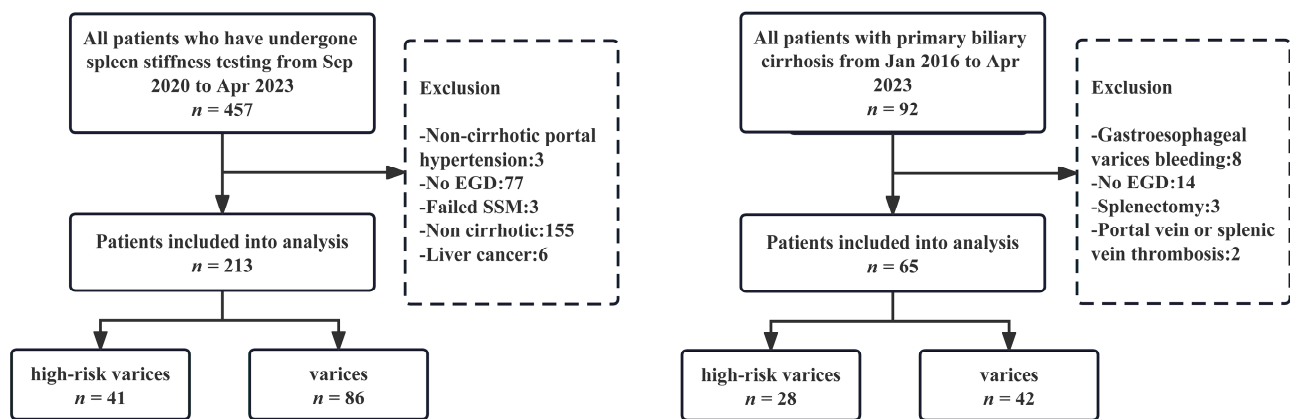


Figure 1. Flow chart for participant selection in training cohort (left) and validation cohort (right). EGD: esophagogastroduodenoscopy; SSM: spleen stiffness measurement.

Table 1. General characteristics in training cohort and validation cohort.

	TC (n = 213)	VC (n = 65)
Age, years	53 [42, 60]	59 [52, 66]
Women, n (%)	81 [38.0]	57 [87.7]
Etiology, n (%)	-	-
HBV	151 [70.9]	-
HCV	25 [11.7]	-
Alcoholic	3 [1.4]	-
PBC	7 [3.3]	65 [100]
AIH	9 [4.2]	-
Other	18 [8.5]	-
Starting treatment	170 [79.8]	-
LSM, kPa	14.7 [10.3, 23.5]	16.7 [13.10, 24.6]
SSM, kPa	26.4 [21.3, 37.3]	-
PLT, $\times 10^9/L$	122 [77, 170]	116 [83, 169]
Spleen thickness, mm	42.90 [36.9, 49.6]	48.0 [40.0, 52.2]
Spleen diameter, mm	120.5 [113.5.2, 139.1]	-
Portal vein diameter, mm	12.1 [11.1, 13.0]	-
Spleen vein diameter, mm	6.4 [5.3, 7.8]	-
ALT, U/L	40.0 [20.8, 85.2]	-
AST, U/L	38.5 [23.9, 78.0]	-
ALB, g/L	41.3 [35.8, 44.8]	-
TBIL, $\mu\text{mol/L}$	18.8 [14.6, 27.4]	-
CR, $\mu\text{mol/L}$	61.1 [52.3, 70.6]	-
INR	1.1 [1.0, 1.1]	-
PT, s	12.1 [11.2, 13.2]	-
Varices, n (%)	86 [40.4]	42 [64.6]
HRVs, n (%)	41 [19.2]	28 [43.1]
Child Pugh score	-	-
A	164 [77.0]	48 [73.8]
B	49 [23.0]	17 [26.2]
C	0 [0]	0 [0]
Decompensation, n (%)	43 [20.2]	18 [27.7]
Ascites	43 [100]	17 [94.4]
Hepatic encephalopathy	0 [0]	1 [0.6]

Continuous variables are expressed as median (interquartile range); categorical variables are expressed as number (proportion). “-” indicates that no results were obtained. TC: training cohort, VC: validation cohort, HBV: hepatitis B virus, HCV: hepatitis C virus, PBC: primary biliary cholangitis, AIH: autoimmune hepatitis, LSM: liver stiffness measurement, SSM: spleen stiffness measurement, PLT: platelets, ALT: alanine aminotransferase, AST: aspartate transaminase, ALB: albumin, TBIL: total bilirubin, CR: creatinine, INR: international normalized ratio, PT: prothrombin time, HRVs: high-risk varices.

3.2. Variable Screening in TC

Firstly, we conducted a univariate analysis for all variables and included those with a statistical difference ($p < 0.05$) between the HRV and non-HRV groups in the multivariate analysis. According to Table 2, LSM, SSM, PLT, ST, SD, PVD, SVD, ALT, INR, and PT significantly differed between the two groups. The multivariate analysis revealed that SSM, PLT, and ST were independent risk indicators for the development of HRVs ($p < 0.001$, $p = 0.001$, $p = 0.011$). Based on the ROC, the optimal cutoff values for SSM, PLT, and ST were 29.89 kPa, $113.5 \times 10^9/L$, and 42.2 mm, respectively.

Table 2. Variable analysis in the training cohort for predicting high-risk varices.

Variable	Univariate Analysis			Multivariate Analysis	
	Non-HRV ($n = 172$)	HRV ($n = 41$)	p	OR, 95% CI	p
Age, years	52.00 [42.00, 59.00]	54.00 [44.00, 65.00]	0.072	-	-
LSM, kPa	13.25 [9.25, 21.83]	21.30 [14.10, 30.80]	<0.001	-	-
SSM, kPa	24.05 [20.20, 31.96]	40.20 [33.70, 46.90]	<0.001	1.092, 1.047–1.146	<0.001
PLT, $\times 10^9/L$	141.00 [93.75, 179.50]	66.00 [48.00, 85.00]	<0.001	0.980, 0.966–0.991	0.001
ST, mm	41.55 [35.48, 47.08]	51.40 [43.00, 57.90]	<0.001	1.042, 1.007–1.076	0.011
SD, mm	117.45 [104.02, 128.90]	140.00 [128.40, 159.10]	<0.001	-	-
PVD, mm	12.00 [11.00, 12.72]	12.60 [11.80, 13.50]	0.003	-	-
SVD, mm	6.00 [5.07, 7.50]	8.10 [6.90, 9.30]	<0.001	-	-
ALB, g/L	41.35 [36.98, 44.87]	41.00 [34.20, 44.20]	0.335	-	-
ALT, U/L	41.05 [23.60, 100.80]	33.00 [16.00, 52.00]	0.020	-	-
AST, U/L	38.25 [23.82, 79.15]	40.00 [24.00, 56.20]	0.483	-	-
TBIL, $\mu\text{mol/L}$	18.05 [13.97, 28.23]	22.00 [18.20, 26.90]	0.040	-	-
CR, $\mu\text{mol/L}$	61.95 [52.90, 70.08]	60.00 [50.10, 73.00]	0.812	-	-
INR	1.00 [1.00, 1.10]	1.10 [1.00, 1.20]	<0.001	-	-
PT, s	11.90 [11.00, 12.80]	13.10 [12.00, 13.90]	<0.001	-	-

Continuous variables are expressed as median (interquartile range); categorical variables are expressed as number (proportion). “-” indicates that no results were obtained. HRVs: high-risk varices, OR: odds ratio, CI: confidence interval, LSM: liver stiffness measurement, SSM: spleen stiffness measurement, PLT: platelets, ST: spleen thickness, SD: spleen diameter, PVD: portal vein diameter, SVD: spleen vein diameter, ALT: alanine aminotransferase, AST: aspartate transaminase, ALB: albumin, TBIL: total bilirubin, CR: creatinine, INR: international normalized ratio, PT: prothrombin time.

3.3. Model Performance in TC

The AUCs for LSM, SSM, PLT, and ST were 0.694 (95% confidence interval, 95% CI: 0.617–0.771), 0.868 (95% CI: 0.817–0.918), 0.852 (95% CI: 0.795–0.909), and 0.782 (95% CI: 0.707–0.856), respectively (Figure 2). SSM and PLT exhibited the most favorable AUCs, followed by ST, while LSM performed the least effectively (Table 3). When using single indicators as models (SSM < 29.89 kPa, PLT > $113.5 \times 10^9/L$, ST < 42.2 mm), the proportions of spared EGDs were 58.2%, 54.2%, and 45.5%, respectively. However, the missed HRV rates in each model were 7.3% (3/41), 9.8% (4/41), and 9.8% (4/41), respectively (Table 4). The missed HRV rates were higher when single-indicator models were used.

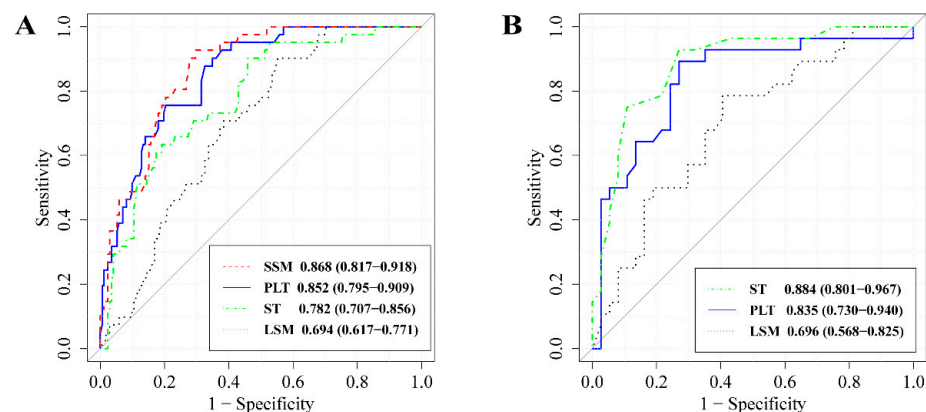


Figure 2. Cont.

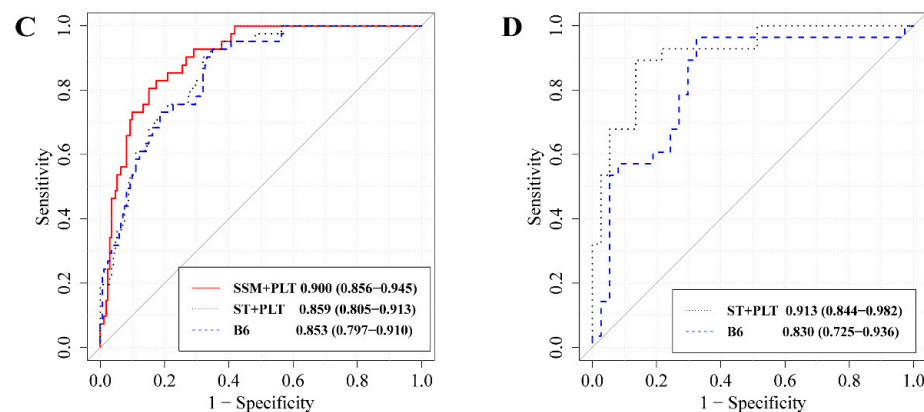


Figure 2. The receiver operating characteristic curves of different models for predicting high-risk varices in training cohort (A,C) and validation cohort (B,D). The areas under the curves (95% confidence interval) are labeled in the figures. LSM: liver stiffness measurement, SSM: spleen stiffness measurement, PLT: platelets, ST: spleen thickness, SSM+PLT: SSM and PLT combined model, ST+PLT: ST and PLT combined model, B6: LSM and PLT combined model (Baveno VI criteria).

Table 3. Delong test in the training cohort and validation cohort.

Comparison of Paired AUCs	Cohort	<i>p</i>
PLT vs. SSM	TC	0.627
PLT vs. ST	TC	0.100
PLT vs. LSM	TC	<0.001
SSM vs. ST	TC	0.063
SSM vs. LSM	TC	<0.001
ST vs. LSM	TC	0.088
ST+PLT vs. SSM+PLT	TC	0.024
ST+PLT vs. B6	TC	0.475
B6 vs. SSM+PLT	TC	0.009
ST vs. PLT	VC	0.462
ST vs. LSM	VC	0.005
PLT vs. LSM	VC	0.090
ST+PLT vs. B6	VC	0.027

p value greater than 0.05 indicates that there is no statistically significant difference in the predictive performance of the two indicators. TC: training cohort, VC: validation cohort, AUC: the area under receiver operating characteristics curve, LSM: liver stiffness measurement, SSM: spleen stiffness measurement, PLT: platelets, ST: spleen thickness, SSM+PLT: SSM and PLT combined model, ST+PLT: ST and PLT combined model, B6: LSM and PLT combined model (Baveno VI criteria).

Table 4. Main results of different models for excluding high-risk varices in study populations.

Model	Cutoff	TC		VC	
		Spared EGD %	Missed HRV %	Spared EGD %	Missed HRV %
SSM	<29.89 kPa	58.2 (124/213)	7.3 (3/41)	-	-
PLT	>113.5 × 10 ⁹ /L	54.5 (116/213)	9.8 (4/41)	-	-
ST	<42.20 mm	45.5 (97/213)	9.8 (4/41)	-	-
ST+PLT	-	35.7 (76/213)	2.4 (1/41)	24.6 (16/65)	0 (0/28)
SSM+PLT	-	44.1 (94/213)	2.4 (1/41)	-	-
B6	-	28.2 (60/213)	0 (0/41)	24.6 (16/65)	0 (0/28)

“-” indicates that no results were obtained. ST+PLT: ST < 42.2 mm + PLT > 113.5 × 10⁹/L. SSM+PLT: SSM < 29.89 kPa + PLT > 113.5 × 10⁹/L. B6: LSM < 20 kPa + PLT > 150 × 10⁹/L. TC: training cohort, VC: validation cohort, LSM: liver stiffness measurement, SSM: spleen stiffness measurement, PLT: platelets, ST: spleen thickness, HRVs: high-risk varices, EGD: esophagogastroduodenoscopy, SSM+PLT: SSM and PLT combined model, ST+PLT: ST and PLT combined model, B6: LSM and PLT combined model (Baveno VI criteria).

According to the Baveno VII criteria, we combined LSM, SSM, and ST with PLT to reduce the missed HRV rate. ST+PLT (<42.2 mm + >113.5 × 10⁹/L) spared 35.7% of EGDs,

with a 2.4% missed HRV rate, 97.6% Sen, 43.6% Spe, 98.7% NPV, and 0.06 NLR. ST+PLT could correctly classify 54% of patients with HRVs (Tables 4 and 5). The Baveno VI criteria (LSM <20 kPa + PLT >150 × 10⁹/L, B6) spared 28.2% of EGDs, with a 0% missed HRV rate, 100% Sen, 34.9% Spe, 100% NPV, and 0 NLR (Tables 4 and 5). SSM+PLT (<29.89 kPa + >113.5 × 10⁹/L) spared 44.1% of EGDs, with a 2.4% missed HRV rate, 97.6% Sen, 54.1% Spe, 98.9% NPV, and 0.05 NLR (Tables 4 and 5).

Table 5. Diagnostic efficacy of different models for excluding high-risk varices in study populations.

Model	Cohort	Cutoff	Sen (%)	Spe (%)	PPV (%)	NPV (%)	ACU (%)	PLR	NLR
SSM	TC	<29.89 kPa	92.7	70.3	42.7	97.6	74.6	3.13	0.10
PLT	TC	>113.5 × 10 ⁹ /L	90.2	65.1	38.1	96.6	70.0	2.59	0.15
ST	TC	<42.2 mm	90.2	54.1	31.9	95.9	61.0	1.96	0.18
ST+PLT	TC	-	97.6	43.6	29.2	98.7	54.0	1.73	0.06
B6	TC	-	100	34.9	26.8	100	47.4	1.54	0
SSM+PLT	TC	-	97.6	54.1	33.6	98.9	62.4	2.12	0.05
B6	VC	-	100	43.2	57.1	100	67.7	1.76	0
ST+PLT	VC	-	100	43.2	57.1	100	67.7	1.76	0

The cutoff values represented by “-” are all explained in the footer. ST+PLT: ST < 42.2mm + PLT > 113.5 × 10⁹/L. SSM+PLT: SSM < 29.89 kPa + PLT > 113.5 × 10⁹/L. B6: LSM < 20 kPa + PLT > 150 × 10⁹/L. TC: training cohort, VC: validation cohort, LSM: liver stiffness measurement, SSM: spleen stiffness measurement, PLT: platelets, ST: spleen thickness, HRVs: high-risk varices, EGD: esophagogastroduodenoscopy, SSM+PLT: SSM and PLT combined model, ST+PLT: ST and PLT combined model, B6: LSM and PLT combined model (Baveno VI criteria), Sen: sensitivity, Spe: specificity, PPV: positive predictive value, NPV: negative predictive value, PLR: positive likelihood ratio, NLR: negative likelihood ratio, ACU: accuracy.

Moreover, the AUCs of SSM+PLT, ST+PLT, and B6 were 0.900 (95% CI: 0.856–0.945), 0.859 (95% CI: 0.805–0.913), and 0.853 (95% CI: 0.797–0.910), all of which had improved over the single-indicator model (Figure 2). SSM+ PLT achieved the highest AUC, with B6 and ST+PLT following closely (Table 3). For further details on the diagnostic values of the models, please refer to Table 5.

3.4. Models Performance in VC

The AUCs for LSM, PLT, and ST were 0.696 (95% CI: 0.568–0.825), 0.835 (95% CI: 0.730–0.940), and 0.884 (95% CI: 0.801–0.967), respectively (Figure 2). Both B6 and ST+PLT avoided EGD in 24.6% of cases, with a 0% missed HRV rate, 100% Sen, 43.2% Spe, 100% NPV, and 0 NLR (Tables 4 and 5). According to Figure 2, the AUCs for ST+PLT and B6 were 0.913 (95% CI: 0.844–0.982) and 0.830 (95% CI: 0.725–0.936). ST surpassed LSM in diagnostic accuracy for HRVs ($p = 0.005$), and ST+PLT exhibited a similar superiority over B6 in AUC ($p = 0.027$, Table 3). For further details on the B6 and the ST+PLT diagnostic values, please refer to Table 5.

4. Discussion

In our study, the prevalence of HRVs in the TC was 19.2% (41/213), including 12.9% (22/170) in patients with compensated cirrhosis. According to previous studies, the prevalence of HRVs in patients with compensated cirrhosis was about 10–20% [16,17], highlighting the necessity for screening for HRVs in this population. All the decompensated patients we included had ascites or hepatic encephalopathy as the symptom of decompensation. We did not find relevant studies on the prevalence of HRVs in decompensated patients, but the TC showed a 44.2% rate (19/43). Ascites have been reported to be the most common first symptom of decompensation in cirrhosis patients, with an annual incidence of 5–10% [18,19]. In addition, only some decompensated patients are willing to undergo EGD, so non-invasive screening is also necessary in this population.

In the TC, from an array of candidate indicators, we found that SSMs, PLT, and ST were most significantly associated with the occurrence of HRVs. Moreover, we concluded that single-indicator models, while sparing a more significant number of EGDs, had higher missed HRV rates (according to the Baveno VII criteria, a missed HRV rate exceeding 5% was considered unsafe for this model). However, the combined models could exclude HRVs well, with all Sen values greater than 95%, all NLR values less than 0.1, all NPVs greater than 95%, and all missed HRV rates less than 5%. Similar to our findings, past research has indicated that PLT is more effective when combined with other non-invasive indicators [4,15,20,21].

Compared with SSMs and LSMs, ST and PLT are indicators that are more readily monitored and accessible in the clinic. Therefore, we recommend the ST+PLT model to exclude HRVs, and its results are promising. In the TC, ST+PLT was superior to B6 but slightly inferior to SSM+PLT. To date, the majority of hospitals do not perform SSMs, and the cutoff value is not standardized. LSMs have been more widely used, making the cutoff value more mature. Therefore, in the VC, we only compared ST+PLT with B6. Several studies have demonstrated that B6 could exclude HRVs equally well in patients with PBC with a low missed rate (<5%) [22,23]. Although ST+PLT safely spared the same proportion of EGDs as B6 in the VC, its AUC was superior to B6. In conclusion, the diagnostic efficacy of ST+PLT is superior to B6 for excluding HRVs.

In our study, the AUCs for ST in predicting HRVs were 0.782 in the TC and 0.884 in the VC. Liang et al. concluded that ST was the crucial factor in identifying HRVs, and its AUCs in the two cohorts were 0.808 (95% CI: 0.760–0.857) and 0.858 (95% CI: 0.816–0.894), similar to our results [8]. The AUC for SSM by 2D-SWE was 0.868 in the TC. A meta-analysis by Liu et al. indicated that the AUC for SSMs by 2D-SWE was 0.88 (95% CI: 0.85–0.91) [24], which was close to our results. The AUCs for LSMs in TC and VC were 0.694 and 0.696, respectively. The meta-analysis by Manatsathit et al. showed that the AUC for LSMs in predicting HRVs was 0.830 [25], which differed significantly from our results. We analyzed the possible reasons for this situation as differences in etiology and severity of liver disease in the enrolled population. In Liang et al.'s study, the AUC for LSMs was 0.655 (95% CI: 0.594–0.716) in the mixed etiology cohort and 0.811 (95% CI: 0.764–0.852) in the cohort of HBV patients with sustained virologic responses [8]. Karagiannakis et al., who including patients with a mixed etiology and varying severities of liver disease, reported an AUC of 0.628 for LSMs [26]. The above analysis suggests a significant variation in the prediction of HRVs by LSMs when the etiology and degree of treatment are unclear. In contrast, ST and SSMs are not limited by these elements. Because the splenic vein is a branch of the portal vein, the spleen becomes congested, enlarged, and stiff when PH occurs. The degree of splenomegaly and stiffness is directly related to the severity of PH [27]. After excluding hematologic disorders, most cases of splenomegaly are attributable to PH [28]. In summary, ST and SSMs are more widely used in clinical practice than LSMs.

Furthermore, we determined a new cutoff value for SSMs by 2D-SWE (Aixplorer ultrasound system) of 29.89 kPa. There are several advantages offered by 2D-SWE [1,29–31] including (1) no ceiling effect measured; (2) the inclusion of B-mode imaging allows for precise selection of the imaging region, avoiding large blood vessels and nodules; and (3) it is less affected by factors such as abdominal fat, ascites, and cholestasis, resulting in a higher success rate. Like our results, Cassinotto et al. found that the cutoff for SSMs was 25.6 kPa, with a 0.75 (95% CI, 0.67–0.82) AUC and 90% NPV [32], among 237 patients with compensated cirrhosis. Karagiannakis et al., who enrolled 64 cirrhosis patients, reported that an SSM < 33.7 kPa had an AUC of 0.792 for excluding HRVs, allowing 40.6% of patients to avoid EGDs with a 3.1% missed HRV rate [26]. Since each machine has specific cutoff values, standardizing them requires further efforts. Recently, a new spleen-dedicated probe by TE (SSM@100Hz) has appeared. Several studies have demonstrated the high applicability and reproducibility of the SSM@100Hz compared to the conventional 50 Hz probe [33–35]. Gaspar et al. concluded that a cutoff value of 53.25 kPa regarding spleen stiffness combined with LSMs and PLT could spare 78.3% of EGDs, with 100% Sen and

72.6% Spe [35]. However, SSM@100Hz is currently available only with an M-type probe, which is less applicable for obese patients [33]. In the future, we will perform a comparative study of 2D-SWE and TE-SSM@100Hz.

In this study, we included some biochemical indicators for the variable analysis. In the past, numerous experts have also designed algorithms using biochemical indicators to exclude varices or HRVs. Tan et al. validated the feasibility of the VariScreen (sequential algorithm consisting of LSM, INR, and PLT) [36]. Chen et al. concluded that an ALBI-PLT score of 2 could exclude HRVs safely (a ranked score consisting of ALB, TBIL, and PLT) [37]. In our results, the independent correlations with HRVs did not include other biochemical markers besides PLT, which was expected. Mechanistically, they mainly reflect the function of the liver and are not very relevant to PH. On the contrary, indicators related to the spleen (SSM, ST, PLT, etc.) are directly related to PH. In any case, multi-center and large sample studies on biochemical indicators are still needed.

Our article has three main features. On the one hand, we enrolled PBC patients as the VC to find a new non-invasive model to exclude HRVs for them, considering there were few relevant studies. Patanwala et al. proposed the NVP score for predicting varices in PBC patients but failed to carry out the clinical application due to the complicated calculations [38]. Although some studies had demonstrated that B6 could safely exclude HRVs in PBC patients [22,23], LSMs sometimes did not represent the degree of PH well due to the influence of cholestasis and presinusoidal elements [39–42]. Thus, ST+PLT offers a new option for PBC patients. On the other hand, regarding the missed HRV rate, we adopted a more rigorous calculation to avoid the impact caused by the prevalence of HRVs. Next, unlike most articles exploring easy models [8,43–45], ST+PLT does not require complex calculations, which makes it easier to apply in clinical practice.

Of course, our study had some limitations. First, our data came from a single center and were collected retrospectively, inevitably resulting in selection bias. Next, our sample size was relatively small due to rigorous screening, necessitating further validation with a larger dataset, which is also the direction of our future efforts.

5. Conclusions

ST demonstrated a favorable capacity in excluding HRVs and could replace LSMs, offering a new option for primary hospitals. Although a better non-invasive indicator, SSMs are not currently applicable to primary hospitals. At present, ST+PLT ($ST < 42.2\text{mm} + PLT > 113.5 \times 10^9/L$) could exempt a significant number of patients from EGD screening with a low missed HRV rate (<5%).

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Data Availability Statement: The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

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Abbreviations

PH	portal hypertension
GEVs	gastroesophageal varices
HRVs	high-risk varices
EGD	esophagogastroduodenoscopy
LSM	liver stiffness measurement
PLT	platelets
SSM	spleen stiffness measurement
ALB	albumin
ST	spleen thickness
SD	spleen diameter
PVD	portal vein diameter
SVD	spleen vein diameter
TC	training cohort
PBC	primary biliary cholangitis
VC	validation cohort
2D-SWE	two-dimensional shear wave elastography
TE	transient elastography
TIPS	transjugular intrahepatic portosystemic shunt
CR	creatinine
ALT	alanine aminotransferase
AST	aspartate transaminase
TBIL	total bilirubin
PT	prothrombin time
INR	international normalized ratio
kPa	kilopascals
IQR	interquartile range
ROC	receiver operating characteristic curve
AUC	area under the curve
Sen	sensitivity
Spe	specificity
PPV	positive predictive value
NPV	negative predictive value
PLR	positive likelihood ratio
NLR	negative likelihood ratio
ACU	accuracy
CI	confidence interval
B6	Baveno VI criteria

References

1. Berzigotti, A. Non-invasive evaluation of portal hypertension using ultrasound elastography. *J. Hepatol.* **2017**, *67*, 399–411. [[CrossRef](#)] [[PubMed](#)]
2. Garcia-Tsao, G.; Abraldes, J.G.; Berzigotti, A.; Bosch, J. Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases. *Hepatology* **2016**, *65*, 310–335. [[CrossRef](#)] [[PubMed](#)]
3. Alqahtani, S.A.; Jang, S. Pathophysiology and Management of Variceal Bleeding. *Drugs* **2021**, *81*, 647–667. [[CrossRef](#)] [[PubMed](#)]
4. de Franchis, R.; Bosch, J.; Garcia-Tsao, G.; Reiberger, T.; Ripoll, C.; Abraldes, J.G.; Albillos, A.; Baiges, A.; Bajaj, J.; Bañares, R.; et al. Baveno VII—Renewing consensus in portal hypertension. *J. Hepatol.* **2021**, *76*, 959–974. [[CrossRef](#)]
5. Wang, Q.; Zhao, H.; Deng, Y.; Zheng, H.; Xiang, H.; Nan, Y.; Hu, J.; Meng, Q.; Xu, X.; Fang, J.; et al. Validation of Baveno VII criteria for recompensation in entecavir-treated patients with hepatitis B-related decompensated cirrhosis. *J. Hepatol.* **2022**, *77*, 1564–1572. [[CrossRef](#)]
6. Tag-Adeen, M.; Alsenbesy, M.; Ghweil, A.A.; Elrazek, M.A.H.A.; Elgohary, E.A.; Sallam, M.M.; Ismael, A.; Nawara, A. Liver stiffness measurement and spleen diameter as predictors for the presence of esophageal varices in chronic hepatitis C patients. *Medicine* **2017**, *96*, e8621. [[CrossRef](#)]

7. Chen, R.; Deng, H.; Ding, X.; Xie, C.; Wang, W.; Shen, Q. Platelet Count to Spleen Diameter Ratio for the Diagnosis of Gastroesophageal Varices in Liver Cirrhosis: A Systematic Review and Meta-Analysis. *Gastroenterol. Res. Pr.* **2017**, *2017*, 7407506. [\[CrossRef\]](#)
8. Liang, X.-E.; Hu, X.-M.; Wang, H.-Y.; Dai, L.; Lin, X.-Y.; Chen, J.-J.; Chen, Y.-P.; Wen, B.; Jiang, R.-L. Ultrasonic spleen thickness-based indexes surpass Baveno VI criteria in high-risk gas-troesophageal varices detection. *Hepatol Int.* **2022**, *16*, 649–657. [\[CrossRef\]](#)
9. Calvaruso, V.; Cacciola, I.; Licata, A.; Madonia, S.; Benigno, R.; Petta, S.; Bronte, F.; Conte, E.; Malizia, G.; Bertino, G.; et al. Is Transient Elastography Needed for Noninvasive Assessment of High-Risk Varices? The REAL Experience. *Am. J. Gastroenterol.* **2019**, *114*, 1275–1282. [\[CrossRef\]](#)
10. Zhang, C.-X.; Xu, J.-M.; Li, J.-B.; Kong, D.-R.; Wang, L.; Xu, X.-Y.; Zhao, D.-M. Predict esophageal varices via routine trans-abdominal ultrasound: A design of classification analysis model. *J. Gastroenterol. Hepatol.* **2015**, *31*, 194–199. [\[CrossRef\]](#)
11. Gao, L.; Meng, F.; Cheng, J.; Li, H.; Han, J.; Zhang, W. Prediction of oesophageal varices in patients with primary biliary cirrhosis by non-invasive markers. *Arch. Med. Sci.* **2017**, *13*, 370–376. [\[CrossRef\]](#) [\[PubMed\]](#)
12. Xu, X.-Y.; Ding, H.-G.; Li, W.-G.; Xu, J.-H.; Han, Y.; Jia, J.-D.; Wei, L.; Duan, Z.-P.; Ling-Hu, E.-Q.; Zhuang, H. Chinese guidelines on the management of liver cirrhosis (abbreviated version). *World J. Gastroenterol.* **2020**, *26*, 7088–7103. [\[CrossRef\]](#)
13. Carey, E.J.; Ali, A.H.; Lindor, K.D. Primary biliary cirrhosis. *Lancet* **2015**, *386*, 1565–1575. [\[CrossRef\]](#) [\[PubMed\]](#)
14. Tajiri, T.; Yoshida, H.; Obara, K.; Onji, M.; Kage, M.; Kitano, S.; Kokudo, N.; Kokubu, S.; Sakaida, I.; Sata, M.; et al. General rules for recording endoscopic findings of esophagogastric varices (2nd edition). *Dig. Endosc.* **2009**, *22*, 1–9. [\[CrossRef\]](#)
15. de Franchis, R. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. *J. Hepatol.* **2015**, *63*, 743–752. [\[CrossRef\]](#) [\[PubMed\]](#)
16. Abraldes, J.G.; Bureau, C.; Stefanescu, H.; Augustin, S.; Ney, M.; Blasco, H.; Procopet, B.; Bosch, J.; Genesca, J.; Berzigotti, A.; et al. Noninvasive tools and risk of clinically significant portal hypertension and varices in compensated cirrhosis: The “Anticipate” study. *Hepatology* **2016**, *64*, 2173–2184. [\[CrossRef\]](#) [\[PubMed\]](#)
17. Zhao, L.; Wang, T.; Guo, C.; Zhou, L.; Han, P.; Wang, C.; Ma, Y.; Wang, J.; Gao, M.; Li, J. Modified and alternative Baveno VI criteria based on age for ruling out high-risk varices in patients with compensated cirrhosis. *Hepatol. Int.* **2022**, *16*, 936–943. [\[CrossRef\]](#) [\[PubMed\]](#)
18. Tonon, M.; Piano, S. Cirrhosis and Portal Hypertension: How Do We Deal with Ascites and Its Consequences. *Med. Clin. N. Am.* **2023**, *107*, 505–516. [\[CrossRef\]](#) [\[PubMed\]](#)
19. Balcar, L.; Tonon, M.; Semmler, G.; Calvino, V.; Hartl, L.; Incicco, S.; Jachs, M.; Bauer, D.; Hofer, B.S.; Gambino, C.G.; et al. Risk of further decompensation/mortality in patients with cirrhosis and ascites as the first single decompensation event. *JHEP Rep.* **2022**, *4*, 100513. [\[CrossRef\]](#)
20. Berzigotti, A.; Seijo, S.; Arena, U.; Abraldes, J.G.; Vizzutti, F.; García-Pagán, J.C.; Pinzani, M.; Bosch, J. Elastography, Spleen Size, and Platelet Count Identify Portal Hypertension in Patients With Compensated Cirrhosis. *Gastroenterology* **2013**, *144*, 102–111.e1. [\[CrossRef\]](#)
21. Ding, N.S.; Nguyen, T.; Iser, D.M.; Hong, T.; Flanagan, E.; Wong, A.; Luiz, L.; Tan, J.Y.C.; Fulforth, J.; Holmes, J.; et al. Liver stiffness plus platelet count can be used to exclude high-risk oesophageal varices. *Liver Int.* **2015**, *36*, 240–245. [\[CrossRef\]](#) [\[PubMed\]](#)
22. Moctezuma-Velazquez, C.; Saffioti, F.; Tasayco-Huaman, S.; Casu, S.; Mason, A.; Roccarina, D.; Vargas, V.; Nilsson, J.-E.; Tsochatzis, E.; Augustin, S.; et al. Non-Invasive Prediction of High-Risk Varices in Patients with Primary Biliary Cholangitis and Primary Sclerosing Cholangitis. *Am. J. Gastroenterol.* **2018**, *114*, 446–452. [\[CrossRef\]](#) [\[PubMed\]](#)
23. Corpechot, C. Noninvasive Evaluation of Fibrosis and Portal Hypertension in Primary Biliary Cholangitis. *Clin. Liver Dis.* **2022**, *26*, 681–689. [\[CrossRef\]](#) [\[PubMed\]](#)
24. Liu, Y.; Tan, H.-Y.; Zhang, X.-G.; Zhen, Y.-H.; Gao, F.; Lu, X.-F. Prediction of high-risk esophageal varices in patients with chronic liver disease with point and 2D shear wave elastography: A systematic review and meta-analysis. *Eur. Radiol.* **2022**, *32*, 4616–4627. [\[CrossRef\]](#) [\[PubMed\]](#)
25. Manatsathit, W.; Samant, H.; Kapur, S.; Ingviya, T.; Esmadi, M.; Wijarnpreecha, K.; McCashland, T. Accuracy of liver stiffness, spleen stiffness, and LS-spleen diameter to platelet ratio score in detection of esophageal varices: Systemic review and meta-analysis. *J. Gastroenterol. Hepatol.* **2018**, *33*, 1696–1706. [\[CrossRef\]](#) [\[PubMed\]](#)
26. Karagiannakis, D.S.; Voulgaris, T.; Koureta, E.; Chloupi, E.; Papatheodoridis, G.V.; Vlachogiannakos, J. Role of Spleen Stiffness Measurement by 2D-Shear Wave Elastography in Ruling Out the Presence of High-Risk Varices in Cirrhotic Patients. *Dig. Dis. Sci.* **2019**, *64*, 2653–2660. [\[CrossRef\]](#)
27. Okumura, H.; Aramaki, T.; Katsuta, Y. Pathophysiology and Epidemiology of Portal Hypertension. *Drugs* **1989**, *37*, 2–12. [\[CrossRef\]](#)
28. Pozo, A.L.; Godfrey, E.M.; Bowles, K.M. Splenomegaly: Investigation, diagnosis and management. *Blood Rev.* **2009**, *23*, 105–111. [\[CrossRef\]](#)
29. Friedrich-Rust, M.; Poynard, T.; Castera, L. Critical comparison of elastography methods to assess chronic liver disease. *Nat. Rev. Gastroenterol. Hepatol.* **2016**, *13*, 402–411. [\[CrossRef\]](#)

30. Elkrif, L.; Rautou, P.-E.; Ronot, M.; Lambert, S.; Burgio, M.D.; Francoz, C.; Plessier, A.; Durand, F.; Valla, D.; Lebrech, D.; et al. Prospective Comparison of Spleen and Liver Stiffness by Using Shear-Wave and Transient Elastography for Detection of Portal Hypertension in Cirrhosis. *Radiology* **2015**, *275*, 589–598. [\[CrossRef\]](#)
31. Cui, X.-W.; Li, K.-N.; Yi, A.-J.; Wang, B.; Wei, Q.; Wu, G.-G.; Dietrich, C.F. Ultrasound elastography. *Endosc. Ultrasound* **2022**, *11*, 252–274. [\[CrossRef\]](#) [\[PubMed\]](#)
32. Cassinotto, C.; Charrie, A.; Mouries, A.; Lapuyade, B.; Hiriart, J.-B.; Vergniol, J.; Gaye, D.; Hocquelet, A.; Charbonnier, M.; Foucher, J.; et al. Liver and spleen elastography using supersonic shear imaging for the non-invasive diagnosis of cirrhosis severity and oesophageal varices. *Dig. Liver Dis.* **2015**, *47*, 695–701. [\[CrossRef\]](#)
33. Berzigotti, A. Bedside spleen stiffness measurement can be reliably performed in most cases: High applicability and reproducibility using a specific 100-Hz module on vibration-controlled transient elastography. *Hepatol Commun.* **2022**, *6*, 3001–3002. [\[CrossRef\]](#) [\[PubMed\]](#)
34. Rigamonti, C.; Cittone, M.G.; Manfredi, G.F.; Sorge, A.; Moia, R.; Patriarca, A.; Donato, M.F.; Gaidano, G.; Pirisi, M.; Fraquelli, M. High reproducibility of spleen stiffness measurement by vibration-controlled transient elastography with a spleen-dedicated module. *Hepatol. Commun.* **2022**, *6*, 3006–3014. [\[CrossRef\]](#)
35. Gaspar, R.; Silva, M.; Cardoso, P.; Goncalves, R.; Andrade, P.; Macedo, G. Spleen stiffness: A new tool to predict high-risk varices in cirrhotic patients. *J. Gastroenterol. Hepatol.* **2023**. [\[CrossRef\]](#) [\[PubMed\]](#)
36. Tan, M.; Zhang, W.; Zhou, H.; Liu, Y.; Lu, T.; Zhang, Y.; Li, C.; Yang, Y.; Wu, Y.; Hu, H.; et al. VariScreen secures the screening of high-risk varices in patients with hepatitis B virus-related cirrhosis beyond Baveno VI criteria. *Front. Physiol.* **2022**, *13*, 1006657. [\[CrossRef\]](#)
37. Chen, P.-H.; Hsieh, W.-Y.; Su, C.-W.; Hou, M.-C.; Wang, Y.-P.; Hsin, I.-F.; Yang, T.-C.; Liao, W.-C.; Lin, H.-C.; Lee, F.-Y.; et al. Combination of albumin-bilirubin grade and platelets to predict a compensated patient with hepatocellular carcinoma who does not require endoscopic screening for esophageal varices. *Gastrointest. Endosc.* **2018**, *88*, 230–239.e2. [\[CrossRef\]](#)
38. Patanwala, I.; McMeekin, P.; Walters, R.; Mells, G.; Alexander, G.; Newton, J.; Shah, H.; Coltescu, C.; Hirschfield, G.M.; Hudson, M.; et al. A validated clinical tool for the prediction of varices in PBC: The Newcastle Varices in PBC Score. *J. Hepatol.* **2013**, *59*, 327–335. [\[CrossRef\]](#)
39. Guo, H.; Liao, M.; Jin, J.; Zeng, J.; Li, S.; Schroeder, D.R.; Zheng, J.; Zheng, R.; Chen, S. How intrahepatic cholestasis affects liver stiffness in patients with chronic hepatitis B: A study of 1197 patients with liver biopsy. *Eur. Radiol.* **2019**, *30*, 1096–1104. [\[CrossRef\]](#)
40. Pfeifer, L.; Strobel, D.; Neurath, M.F.; Wildner, D. Liver stiffness assessed by acoustic radiation force impulse (ARFI) technology is considerably increased in patients with cholestasis. *Ultraschall Med.* **2014**, *35*, 364–367. [\[CrossRef\]](#)
41. Lebrech, D.; Sicot, C.; Degott, C.; Benhamou, J.-P. Portal Hypertension and Primary Biliary Cirrhosis. *Digestion* **1976**, *14*, 220–226. [\[CrossRef\]](#) [\[PubMed\]](#)
42. Huet, P.; Vincent, C.; Deslaurier, J.; Côté, J.; Matsutami, S.; Boileau, R.; Kerckvoorde, J.H. Portal Hypertension and Primary Biliary Cirrhosis: Effect of Long-Term Ursodeoxycholic Acid Treatment. *Gastroenterology* **2008**, *135*, 1552–1560. [\[CrossRef\]](#) [\[PubMed\]](#)
43. Kotwal, V.; Mbach, C.; Wang, Y.; Attar, B.; Randhawa, T.; Flores, E.; Robles, J.; Rosenstengle, C.; Demetria, M.; Adeyemi, O.; et al. A Novel Score to Predict Esophageal Varices in Patients with Compensated Advanced Chronic Liver Disease. *Dig. Dis. Sci.* **2020**, *66*, 2084–2091. [\[CrossRef\]](#) [\[PubMed\]](#)
44. Yan, Y.; Xing, X.; Wang, X.; Men, R.; Luo, X.; Yang, L. Development and Validation of an Easy-to-Use Risk Scoring System for Screening High-Risk Varices in Patients with HBV-Related Compensated Advanced Chronic Liver Disease. *Dig. Dis. Sci.* **2021**, *66*, 4518–4524. [\[CrossRef\]](#)
45. Liang, H.; Si, H.; Liu, M.; Yuan, L.; Ma, R.; Zhang, G.; Yang, J.; Mo, Z.; Zhao, Q. Non-Invasive Prediction Models for Esophageal Varices and Red Signs in Patients With Hepatitis B Virus-Related Liver Cirrhosis. *Front. Mol. Biosci.* **2022**, *9*, 930762. [\[CrossRef\]](#) [\[PubMed\]](#)

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