THERAPEUTIC ADVANCES in
Chronic Disease

Original Research

Spleen stiffness determined by spleen-dedicated device accurately predicted esophageal varices in cirrhosis patients

Ther Adv Chronic Dis

2023, Vol. 14: 1–13

DOI: 10.1177/20406223231206223

Jiqing Liu*, Hangfei Xu*, Weiyuan Liu*, Hongmei Zu, Huiguo Ding, Fankun Meng and Jing Zhang

Abstract

Background: The advantages of spleen stiffness in prediction of high-risk varices (HRV) in cirrhosis patients have been confirmed. Recently, a new device utilizing a 100 Hz probe dedicated to spleen stiffness measurement (SSM) was developed.

Objectives: To validate the clinical applicability of SSM@100 Hz in predicting HRV by comparing it with other non-invasive tests (NITs).

Design: A prospective cohort study.

Methods: A total of 171 cirrhosis patients who underwent esophagogastroduodenoscopy (EGD) examination were included in this study. SSM using a 100 Hz probe and liver stiffness measurement using a 50 Hz probe were performed. Additionally, 22 healthy controls underwent spleen stiffness evaluation using the 100 Hz probe.

Results: The failure rates of spleen stiffness examination in patients with cirrhosis and in healthy controls were 2.9% and 4.5%, respectively. The means of SSM values were 56.4 ± 21.6 and 13.8 ± 6.7 kPa in cirrhosis and controls. SSM increased proportionally with the severity of esophageal varices. The area under receiver operating characteristic (ROC) for spleen stiffness in predicting HRV was 0.881 (95% confidence interval 0.829–0.934), with a cutoff value of 43.4 kPa. The accuracy, false negative rate and EGD spare rate were 86.5%, 2.5% and 24.3%, respectively. For HRV prediction, SSM was comparable to expanded Baveno VI and VII and superior to other NITs. As to viral *versus* non-viral cirrhosis and compensated *versus* decompensated cirrhosis, the cut-off and performance of SSM were different.

Conclusion: SSM@100 Hz demonstrates high accuracy in predicting HRV with a low missed HRV rate. Our findings suggest that SSM@100 Hz can be used independently due to its simplicity and effectiveness. However, further studies are needed to determine appropriate cutoff values based on the cause of cirrhosis and liver function.

Trail Registration: ChiCTR2300070270.

Keywords: esophageal varices, non-invasive tests, portal hypertension, spleen stiffness measurement

Received: 22 March 2023; revised manuscript accepted: 19 September 2023.

Correspondence to:
Jing Zhang
Department of Hepatology, Beijing YouAn Hospital, Capital Medical University, No.8, Youanmenwai Street, Fengtai District, Beijing 100069, China
zjyouan@ccmu.edu.cn

Jiqing Liu
Beijing Youan Hospital, Capital Medical University, Beijing, China

The Fourth People's Hospital of Qinghai Province, Xining, Qinghai, China

Hangfei Xu
Beijing Youan Hospital, Capital Medical University, Beijing, China

Beijing Institute of Hepatology, Beijing Youan Hospital, Capital Medical University, Beijing, China

Weiyuan Liu
Huiguo Ding
Fankun Meng
Beijing Youan Hospital, Capital Medical University, Beijing, China

Hongmei Zu
The Fourth People's Hospital of Qinghai Province, Xining, Qinghai, China

*These authors contributed equally

Introduction

Esophageal varices (EV) and esophageal variceal bleeding are the main complications of cirrhosis and accounting for 10–15% of all causes of death.[1,2] The gold standard for diagnosis of EV is esophagogastroduodenoscopy (EGD). However, not all individuals with cirrhosis require EGD examination as only 50–60% may develop EV.[3] And EGD examination for patients could be uncomfortable and costly. Thus, a crucial challenge for physicians is to identify patients at high risk of developing varices (HRV) who truly require EGD.[4–6]

Accordingly, several non-invasive tests (NITs) have been developed to predict HRV and consequently spare patients form undergoing EGD examination, such as platelet count to spleen diameter ratio (PSR),[7] Liver stiffness-spleen diameter to platelet ratio score (LSPS),[8] etc. Amongst them, the most widely accepted criteria are Baveno criteria. Baveno VI criteria was defined as liver stiffness measurement (LSM) < 20 kPa and platelet count $> 150 \times 10^9$/L to rule out HRV.[9] The probability of presence of HRV was less than 5% in patients who met Baveno VI criteria. Owing to the EGD spare rate being only around 15–25% according to Baveno VI, expanded Baveno VI and Baveno VII were proposed in which cutoff of LSM and platelet count were regulated.[10,11] Consequently, the EGD spare rate was improved to about 30%.[4] However, the large 'grey zone' (LSM between 15 and 25 kPa) resulted in more than 40% of eligible patients.

In the last decade, spleen stiffness measurement (SSM) has been demonstrated to correlate more closely with portal hypertension (PH) and the severity of EV compared to LSM.[12–17] Given the accumulating evidence, Baveno VII consensus and the 2021 European Association for the Study of the Liver guidelines suggested that SSM should be added on to current diagnostic algorithms.[15]

SSM could be assessed by various techniques such as transient elastography (TE), acoustic radiation force impulse elastography and magnetic resonance elastography.[13,18] In most studies, SSM was evaluated by TE with a 50 Hz probe which is the same probe for LSM measurement.[19] The range of SSM@50 Hz falls between 5 and 75 kPa. Recently, a dedicated equipment for SSM had been developed which had a B type probe to locate spleen and a probe of 100 Hz to determine SSM. The upper limit of SSM@100 Hz was increased to 100 kPa. Limited studies have proved that SSM@100 Hz outperforms SSM@50 Hz in HRV prediction.[9,12,20] And most previous studies emphasized that SSM should be used in conjunction with other NITs. Herein we carried out a diagnostic study on SSM@100 Hz with the following objectives: ① further validate the performance; ② explore the optimal cutoff; ③ evaluate its feasibility for separate application.

Methods and patient selection

Patient selection and enrollment criteria

The present research was a single-center diagnostic study conducted from March 2022 to October 2022. Adult outpatients and inpatients with cirrhosis who underwent EGD were continuously enrolled in the study. Cirrhosis was diagnosed according to imaging and laboratory results. The following exclusion criteria were applied: previous splenectomy or splenic embolism; space-occupying lesion in spleen; previous EV bleeding; esophageal ligation or sclerotherapy; patients who were taking non-selective β blocker, transjugular intrahepatic portosystemic shunt or spleen-kidney shunt. Patients with cardiac dysfunction, tricuspid regurgitation, liver malignant tumors, or other tumors, as well as those with conditions that could affect LSM or SSM measurements (e.g. large hydrothorax or ascites, obesity, small spleen, etc.), were also excluded. Eventually, 171 cases were included (Supplemental Figure 1). Simultaneously, SSM of 22 healthy controls were determined to evaluate the normal range.

Data collection

Patient data were recorded from electronic medical record system, including demography data, medical history, the cause of cirrhosis, liver function, coagulation function, routine blood test, etc. LSM was examined by FibroScan®502 (Echosens, Paris, France) with a 50 Hz probe. LSM used the same technical background and examination procedure was performed as previously described.[21] All LSM were conducted within 6 months before or after EGD examination. The operators of SSM and gastroscopy are unaware of each other's results.

SSM was determined by FibroScan®630 (Echosens) with a probe of 100 Hz. An experienced ultrasound operator (Weiyuan Liu) with more than 10 years of experience performed the SSMs. SSMs were conducted within 2 weeks before or after EGD examination. The patients were in supine position with their left arm in maximum abduction with the transducer placed in the left intercostal space, usually on the posterior axillary line. The median value of 10 successful acquisitions was kept as representative of SSM. The same quality threshold was used as LSM determination [interquartile range (IQR)/medium $\leqslant 30\%$, success rate $\geqslant 60\%$].

Definitions

EGD and EV diagnosis were performed by experienced physicians. Grading of EV was diagnosed according to Baveno VI criteria[22]: grade 1, varices were flattened by insufflation; grade 2, varices were non-confluent and protruding in the lumen despite insufflation; and grade 3, confluent varices were not flattened by insufflation. HRV was defined as grade 1 with red sign or grade 2 or 3. The other type of EV was defined as LRV.[22]

Baveno criteria were used to identify patients who need not be screened for EV by EGD. Baveno VI criteria: LSM $<$ 20 kPa and platelet count $>$ 150×10^9/L.[22] Expanded Baveno VI criteria: LSM $<$ 25 kPa and platelet count $>$ 110×10^9/L.[23] Baveno VII criteria: either conforming to the Baveno VI criteria or not up to Baveno VI criteria (LSM $\geqslant$ 20 kPa or platelet count $\leqslant$ 150×10^9/L) but SSM $\leqslant$ 40 kPa.[11,15]

Liver stiffness to spleen/platelet ($\times 10^9$) score (LSPS) was calculated as: LSM (kPa) $\times$ spleen diameter (cm)/platelet count ($\times 10^9$).[24] PSR was calculated as: platelet count ($\times 10^9$)/spleen diameter (cm).[7] Spleen stiffness-spleen diameter-to-platelet ratio risk score (SSPS) = SSM (kPa) $\times$ spleen diameter (cm)/platelet count ($\times 10^9$). Aspartate aminotransferase (AST) to platelets ratio index (APRI) = AST (U/L)/platelet count ($\times 10^9$).[25]

Sample-size calculation and statistical analysis

The sample size was calculated to estimate 90% of sensitivity based on a meta-analysis about detection of EV[26] with relative error of 10% and the power of 95%. Therefore, the number of patients required is at least 158.

Clinical characteristics of subjects were compared between the HRV and LRV group, also viral and non-viral cirrhosis group. Descriptive values were expressed as mean $\pm$ standard deviation (SD) or medians and IQR, depending on the underlying distribution of the data. The Student *t*-test or Mann–Whitney–Wilcoxon test was used to assess continuous variables according to value distribution. Frequencies and percentages were used to summarize categorical variables and data were compared by using Pearson's Chi-square or Fisher's exact tests when appropriate. The χ^2 test was also used if indicated. All comparison tests between the two groups were 2-tailed with a 95% confidence interval (CI). Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+) and negative likelihood ratio (LR−) were calculated as per the cut-offs recommended by Baveno VI criteria,[22] expanded Baveno VI criteria[23] and Baveno VII.[15] Diagnostic performances of other conventional NITs were compared using the receiver operating characteristic (ROC) curve, sensitivity, specificity, PPV, and NPV. All statistical analyses were performed by R software version 4.2.0 and GraphPad Prism Version 9.3.1. A p value $<$ 0.05 was considered statistically significant and p values are shown as $*p < 0.05$, $**p < 0.01$, and $***p < 0.001$.

Results

SSM determination

Totally, SSM was observed for 171 cirrhosis patients and 5 patients failed (2.9%) due to small spleen size, hydrothorax or obesity. The mean SSM was 56.4 $\pm$ 21.6 kPa, ranging from 13.2 to 100.0 kPa. Among the 22 healthy controls, 1 case (4.5%) was excluded due to a small spleen size. The mean SSM was 13.8 $\pm$ 6.7 kPa, ranging from 3.4 to 24.8 kPa.

Clinical characteristics of patients

In the cohort, the main causes of cirrhosis were chronic hepatitis B (80, 46.8%) and alcohol use disorders (38, 22.2%). Compensated cirrhosis accounted for 25.1% of cases. Patients without EV, with grade 1, grade 2 and grade 3 were 24 (14%), 37 (21.6%), 34 (19.8%) and 76 (44%) cases, respectively. HRV accounted for 64.3% (110 cases) and the others were LRV. As shown in Table 1, when compared to LRV group, HRV groups had lower white blood cell, platelet count, alanine aminotransferase (ALT), and albumin. Meanwhile, they had higher international standardized ratio (INR), SSM, LSM, spleen diameter and thickness, portal vein and spleen vein diameter. The other NITs, including PSR, APRI, LSPS and SSPS of HRV group were all significantly higher than LRV group (Table 1 and Figure 1). As depicted in Figure 2, the SSM, LSM, LSPS, and SSPS showed a parallel increase from the G0 to G3 groups, except for APRI.

Table 1. Demographic and clinical characteristics of patients.

Characteristics	Total (*n* = 171)	LRV (*n* = 61, 35.7%)	HRV (*n* = 110, 64.3%)	*p* Value
Male (%)	110 (64.3)	43 (70.5)	67 (60.9)	0.277
Age (year)	58.0 (48.0, 64.0)	57.0 (45.0, 62.0)	58.0 (49.0, 64.0)	0.215
Etiology, *n* (%)				0.255
Hepatitis B, *n* (%)	80 (46.8)	35 (57.4)	45 (40.9)	
Hepatitis C, *n* (%)	15 (8.8)	5 (8.2)	10 (9.1)	
Alcoholic, *n* (%)	38 (22.2)	10 (16.4)	28 (25.5)	
NAFLD, *n* (%)	7 (4.1)	1 (1.6)	6 (5.5)	
AIH, *n* (%)	15 (8.8)	5 (8.2)	10 (9.1)	
PBC, *n* (%)	8 (4.7)	4 (6.6)	4 (3.6)	
Others, *n* (%)	8 (4.7)	1 (1.6)	7 (6.4)	
White blood cell (10^9/L)	3.6 (2.8, 5.0)	4.2 (3.4, 5.6)	3.2 (2.5, 4.5)	<0.001
Platelets (10^9/L)	72.0 (52.5, 107.0)	99.0 (70.0, 166.0)	61.0 (44.0, 88.0)	<0.001
Alanine aminotransferase (U/L)	26.0 (17.0, 36.5)	27.0 (20.0, 47.0)	23.0 (16.0, 35.0)	0.030
Aspartate aminotransferase (U/L)	39.0 (28.0, 62.5)	40.0 (29.0, 70.0)	37.5 (28.0, 59.0)	0.311
Bilirubin (μmol/L)	32.6 (19.9, 57.7)	31.3 (18.3, 64.2)	34.3 (21.6, 54.4)	0.854
Albumin (g/L)	33.5 (29.5, 38.3)	37.4 (30.8, 43.3)	32.3 (29.1, 35.8)	<0.001
Creatinine (μmol/L)	60.0 (50.0, 76.5)	61.0 (53.0, 75.0)	59.5 (49.0, 78.0)	0.668
INR	1.3 (1.2, 1.5)	1.2 (1.1, 1.4)	1.3 (1.2, 1.5)	<0.001
MELD score	10.8 (7.8, 14.9)	9.2 (7.4, 15.3)	11.2 (8.2, 14.1)	0.350
Child-Pugh score	7.0 (6.0, 9.0)	6.0 (5.0, 8.0)	8 (7.0, 10.0)	<0.001
Compensated cirrhosis, *n* (%)	43 (25.2)	35 (57.4)	8 (7. 3)	<0.001
Esophageal varices				<0.001
G0/G1/G2/G3 (*n*)	24/37/34/76	24/36/1/0	0/1/33/76	
Red color sign, *n* (%)	67 (39.2)	0 (0)	67 (61.0)	<0.001
Gastric varices, *n* (%)	70 (40.9)	1 (1.6)	69 (62.7)	<0.001
Portal vein diameter (mm)	12.0 (11.0, 13.0)	12.0 (11.0, 13.0)	13.0 (12.0, 13.0)	0.012
Splenic vein diameter (mm)	9.0 (8.0, 11.0)	8.0 (7.0, 10.0)	9.5 (8.0, 11.0)	0.001
Spleen diameter (mm)	144.5 ± 31.3	128.5 ± 31.7	153.4 ± 27.4	<0.001

(Continued)

Table 1. (Continued)

Characteristics	Total ($n = 171$)	LRV ($n = 61$, 35.7%)	HRV ($n = 110$, 64.3%)	p Value
Splenic thickness (mm)	48.0 (41.5, 54.0)	42.0 (36.0, 50.0)	51.0 (44.0, 56.0)	<0.001
SSM (kPa)	54.7 (43.8, 71.5)	36.5 (26.2, 49.1)	62.2 (53.1, 78.5)	<0.001
LSM (kPa)	27.6 (15.3, 45.0)	18.7 (9.9, 35.8)	32.2 (17.8, 47.7)	<0.001
PSR	0.5 (0.3, 0.8)	0.8 (0.5, 1.6)	0.4 (0.3, 0.6)	<0.001
APRI	0.6 (0.3, 1.0)	0.6 (0.2, 0.9)	0.7 (0.4, 1.1)	0.013
LSPS	53.7 (24.5, 111.3)	22.0 (6.8, 57.1)	72.8 (42.5, 131.3)	<0.001
SSPS	120.2 (57.3, 190.1)	45.5 (18.9, 94.6)	166.7 (111.2, 224.0)	<0.001

Data expressed as mean ± SD or median values with interquartile range.
AIH, autoimmune hepatitis; APRI, AST/platelets ratio index; AST, Aspartate aminotransferase; HRV, high risk varices; INR, international normalized ratio; LRV, low risk varices; LSM, liver stiffness measurement; LSPS, liver stiffness-spleen diameter to platelet ratio score; MELD, model of end-stage liver disease; NAFLD, non-alcoholic fatty liver disease; PBC, primary biliary cirrhosis; PSR, platelet count/spleen diameter ratio; SSM, spleen stiffness measurement; SSPS, spleen stiffness-spleen diameter-to-platelet ratio risk score.

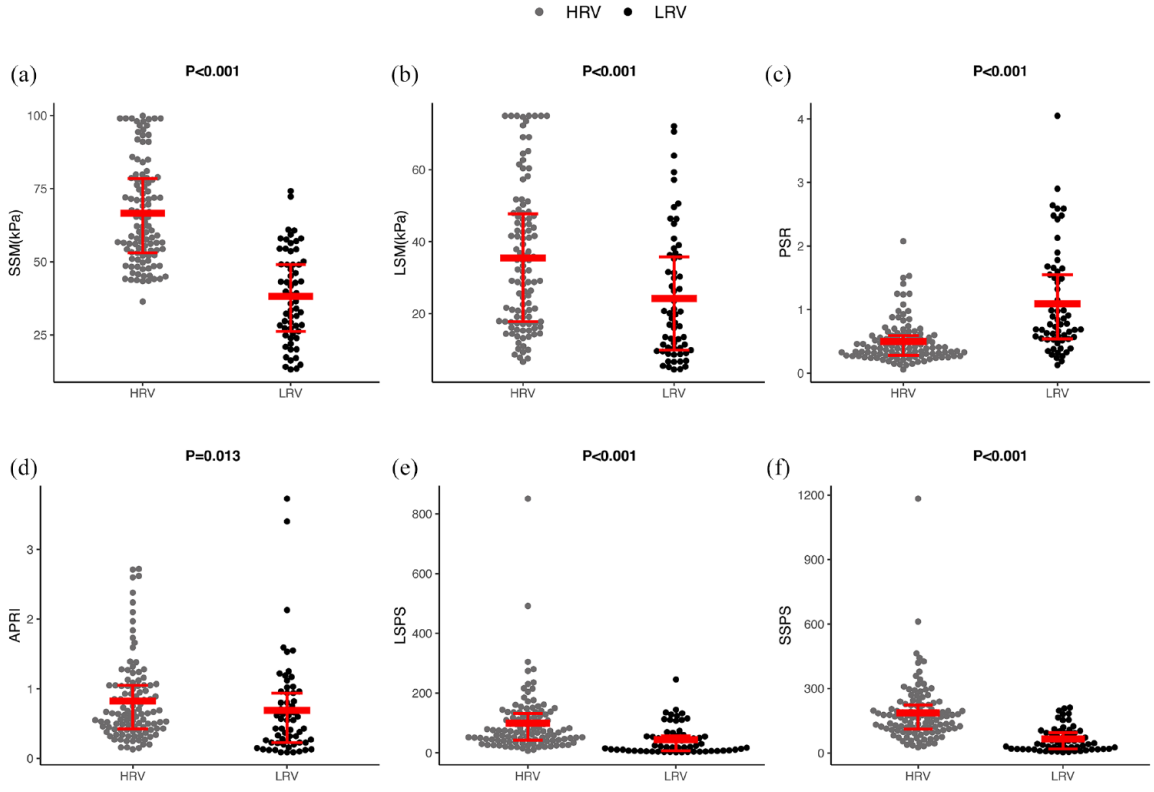

Figure 1. Comparison of SSM and other NITs between high-risk varices and low risk varices groups. (a) SSM. (b) LSM. (c) PSR. (d) APRI. (e) LSPS. (f) SSPS.
APRI, AST/platelets ratio index; AST, aspartate aminotransferase; HRV, high risk varices; LRV, low risk varices; LSM, liver stiffness measurement; LSPS, liver stiffness-spleen diameter to platelet ratio score; NIT, non-invasive test; PSR, platelet count/spleen diameter ratio; SSM, spleen stiffness measurement; SSPS, spleen stiffness-spleen diameter-to-platelet ratio risk score.

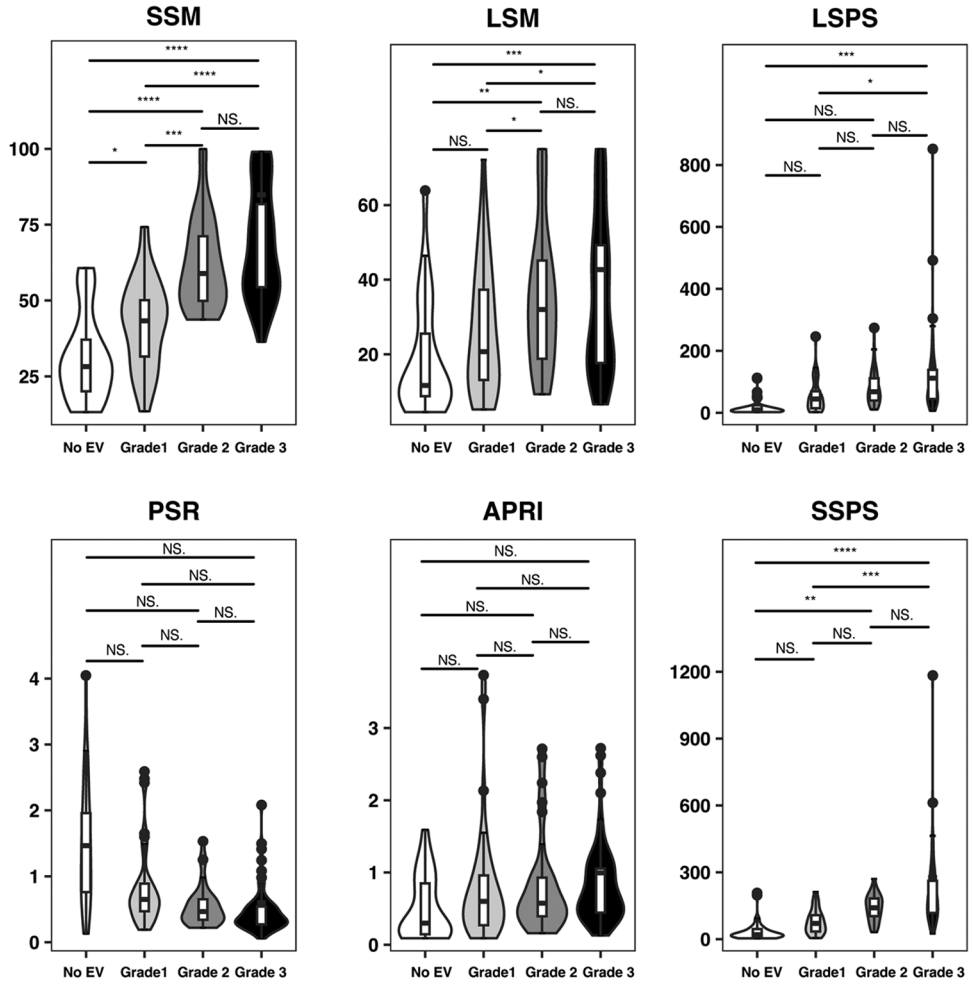

Figure 2. Comparison of SSM and other NITs among esophageal varices grades. (a) SSM. (b) LSM. (c) PSR. (d) APRI. (e) LSPS. (f) SSPS.
APRI, AST/platelets ratio index; AST, aspartate aminotransferase; HRV, high risk varices; LRV, low risk varices; LSM, liver stiffness measurement; LSPS, liver stiffness-spleen diameter to platelet ratio score; NIT, non-invasive test; PSR, platelet count/spleen diameter ratio; SSM, spleen stiffness measurement; SSPS, spleen stiffness-spleen diameter-to-platelet ratio risk score.
*$p < 0.05$. **$p < 0.01$. ***$p < 0.001$.

Comparison of SSM performance to other NITs in HRV prediction

The ROC of SSM, LSM, PSR, APRI, LSPS and SSPS for HRV prediction were 0.88 (95% CI 0.83–0.93), 0.68 (95% CI 0.60–0.77), 0.77 (95% CI 0.70–0.85), 0.61 (95% CI 0.52–0.71), 0.76 (95% CI 0.68–0.84) and 0.86 (95% CI 0.80–0.93), respectively (Figure 3). Both SSM and SSPS exhibited comparable ROC values, which were significantly higher than the ROC values of the other NITs. The cutoff of SSM was 43.4 kPa, and the SV, SP, PPV, NPV were 83.2%, 97.5%, 99.1% and 64.0%, respectively. The false negative rate and the diagnosis accuracy were 2.5% and 86.5%, respectively (Table 2).

Comparison of SSM performance to Baveno VI criteria and expanded Baveno VI criteria

Diagnosis accuracy of SSM (86.5%) was significantly higher than Baveno VI (72.5%, $p = 0.001$) and expanded Baveno VI (73.7%, $p = 0.003$). Besides, the accuracy rate was also significantly higher than combination SSM with Baveno VI (70.8%, $p < 0.001$) or combination with expanded Baveno VI (74.9%, $p = 0.006$). The misdiagnosis

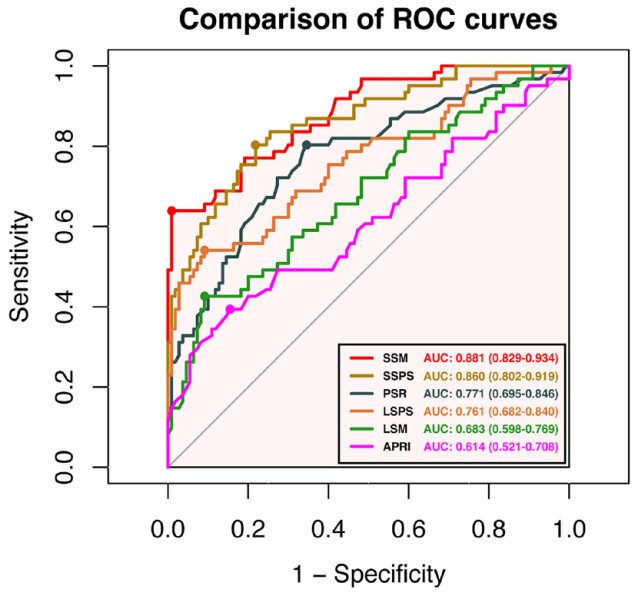

Figure 3. Diagnostic performance of SSM and other NITs for high-risk varices prediction.
APRI, AST/platelets ratio index; AST, aspartate aminotransferase; LSM, liver stiffness measurement; LSPS, liver stiffness-spleen diameter to platelet ratio score; NIT, non-invasive test; PSR, platelet count/spleen diameter ratio; SSM, spleen stiffness measurement; SSPS, spleen stiffness-spleen diameter-to-platelet ratio risk score.

Table 2. Diagnostic performance for different NITs in prediction of high-risk varices in cirrhosis patients.

Parameter	Cutoff value	Sensitivity (%)	Specificity (%)	+LR	−LR	PPV (%)	NPV (%)	Missed diagnosis rate (%)	Misdiagnosis rate (%)	Diagnostic accuracy (%)	ROC	95% CI	p Value
SSM (kPa)	43.4	83.2	97.5	0.3	0.2	99.1	64.0	2.5	36.1	86.6	0.9	0.8–0.9	–
LSM (kPa)	13.6	74.1	72.2	0.3	0.4	90.9	42.6	27.8	57.4	73.7	0.7	0.6–0.8	<0.001[a]
PSR	0.5	85.7	56.3	0.2	0.3	65.5	80.3	43.7	19.7	70.8	0.8	0.7–0.8	0.013[b]
APRI	0.3	71.5	58.5	0.2	0.5	84.5	39.3	41.5	60.7	68.4	0.6	0.5–0.7	<0.001[c]
LSPS	24.5	78.1	76.7	0.3	0.3	90.9	54.1	23.3	45.9	77.8	0.8	0.7–0.8	0.005[d]
SSPS	105.0	87.8	67.1	0.3	0.2	78.2	80.3	32.9	19.7	79.0	0.9	0.8–0.9	0.5[e]

[a]Comparison of SSM and LSM.
[b]Comparison of SSM and PSR.
[c]Comparison of SSM and APRI.
[d]Comparison of SSM and LSPS.
[e]Comparison of SSM and SSPS.
APRI, AST/platelets ratio index; AST, aspartate aminotransferase; ROC, area under the receiver operating characteristic curve; 95% CI, confidence interval; LR, likelihood ratio; LSM, liver stiffness measurement; LSPS, liver stiffness-spleen diameter to platelet ratio score; NIT, non-invasive test; NPV, negative predictive value; PPV, positive predictive value; PSR, platelet count/spleen diameter ratio; SSM, spleen stiffness measurement; SSPS, spleen stiffness-spleen diameter-to-platelet ratio risk score.

rates of SSM, SSM combined with Baveno VI or SSM combined with expanded Baveno VI were 2.5%, 0% and 0% (both $p=1$). The EGD spared rate was significantly higher for SSM (23.4%) than Baveno VI (9.4%, $p<0.001$), SSM plus Baveno VI (6.4%, $p<0.001$) and SSM plus expanded Baveno VI (10.5%, $p=0.002$), but not for expanded Baveno VI (17.5%, $p=0.18$) (Table 3).

Table 3. Performance for NITs in prediction of high-risk varices in cirrhosis patients.

NITs	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Diagnostic accuracy (%)	P1	Missed HRV rate (%)	P2	EGDs spare rate (%)	P3	Misdiagnosis rate (%)	P4
SSM	83.2	97.5	99.1	64.0	86.5	–	2.5	–	23.4	–	36.1	–
Baveno VI criteria	99.1	24.6	70.3	93.8	72.5	0.001*	6.3	0.494*	9.4	<0.001*	75.4	<0.001*
Expanded Baveno VI criteria	93.6	37.7	73.0	76.7	73.7	0.003$	23.3	0.017$	17.5	0.18$	62.3	0.004$
Baveno VI criteria + SSM	100.0	18.0	68.8	100	70.8	<0.001‡	0	1‡	6.4	<0.001‡	82.0	<0.001‡
Expanded Baveno VI criteria + SSM	100.0	29.5	71.9	100	74.9	0.006§	0	1§	10.5	0.002§	70.5	<0.001§
Baveno VII criteria	98.2	62.3	82.4	95.0	85.4	0.765‖	5.0	1‖	23.4	1‖	37.7	0.851‖

*Comparison of Baveno VI criteria and SSM.
$Comparison of Expanded Baveno VI criteria and SSM.
‡Comparison of Baveno VI criteria + SSM and SSM.
§Comparison of Expanded Baveno VI criteria + SSM and SSM
‖Comparison of Baveno VII criteria.
EGD, esophagogastroduodenoscopy; HRV, high risk varices; NITs, non-invasive tests; NPV, negative predictive value; P1: comparison of diagnostic accuracy; P2: comparison of HRV missed/number of spared endoscopy; P3: comparison of EGDs spare rate (%); P4: Comparison of missed diagnosis rate; PPV, positive predictive value; SSM, spleen stiffness measurement.

Performance of Baveno VII algorithm

We substituted 43.4 for 40 kPa according to our study. In our cohort, Baveno VII algorithm avoided EGD examination of 40 patients (23.4%), including 16 patients (9.4%) who met Baveno VI criteria, and another 24 patients (14.0%) were further spared by SSM. At the same time, the missed diagnosis rate of HRV was 2.5%. Our results demonstrated that Baveno VII algorithm had the same performance with separate application of SSM@100 Hz. When 40 kPa was used as cutoff, the performance of SSM@100 was similar to 43.4 kPa (data not shown).

Performance of SSM according to cause of cirrhosis

As indicated in Baveno VII, performance of SSM was fully verified mainly in compensated advanced chronic liver disease due to viral hepatitis, not in non-viral etiologies. Herein we compared the difference of SSM @100 Hz in viral and non-viral cirrhosis group. As showed in Supplemental Table 1, viral cirrhosis patients were younger and had higher model of end-stage liver disease score in our study. The ROC of viral and non-viral cirrhosis were 0.92 (95% CI 0.86–0.97) and 0.82 (95% CI 0.70–0.93), respectively. The cut-offs were 50.4 and 43.4 kPa, respectively (Figure 4). And the ROC of SSM and SSPS were comparable, and both were higher than other NITs.

Performance of SSM in compensated and decompensated cirrhosis

Prediction of HRV was mainly used in compensated liver disease. But not all decompensated cirrhosis had HRV. In our cohort, there were 26 cases (20.3%) that did not have HRV in decompensated cirrhosis group. Hence, we evaluated whether SSM was useful in decompensated cirrhosis. As shown in Supplemental Figure 2, the ROC of SSM in compensated and decompensated cirrhosis were 0.95 (95% CI 0.89–1.0) and 0.78 (95% CI 0.69–0.88), respectively. The cut-offs of the two groups were 47.9 and 61.5 kPa, respectively. Similarly, SSM and SSPS have also shown better prediction efficiency than others NITs.

Clinical significance of improving the upper limit of SSM

The upper limit of spleen stiffness was 100 kPa for SSM@100 Hz and 75 kPa of SSM@50 Hz. Therefore, we compared EV grade distribution in group with SSM between 43.4 and 75 kPa and in those with SSM higher than 75 kPa. In patients

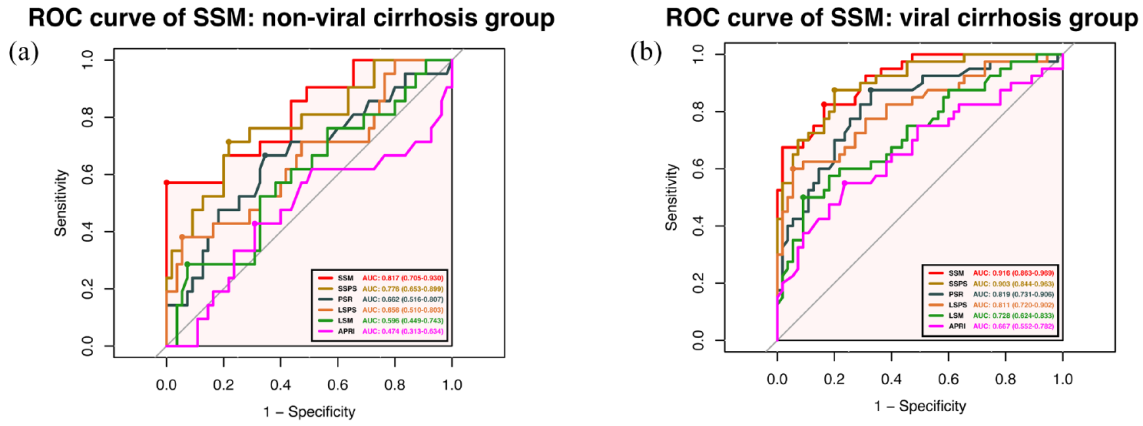

Figure 4. Diagnostic performance of spleen stiffness measurement and other non-invasive tests for high-risk varices prediction in viral (a) and non-viral (b) cirrhosis group.

with SSM ⩾ 75 kPa, they all had grade 3 EV. In those with 43.4 ⩽ SSM < 75 kPa, the proportion was 56.7% ($p < 0.001$). The result indicated that improvement of SSM detection range by new device favored the identification of patients with serious PH.

Discussion

Over the past decade, various NITs have been developed to predict HRV and avoid unnecessary EGD, and most of which included LSM.[24,26–31] Due to plenty of evidence that SSM was superior to LSM, a new device dedicated to SSM detection had been recently invented with enhanced performance. Nevertheless, the priority of the new device and the cutoff was not confirmed until now. In our study, we determined SSM@100 Hz in 171 cirrhosis patients and suggested that SSM ⩾ 43.4 kPa as a cutoff to predict HRV with ROC as high as 0.881. The rate of missed HRV cases was below 5%. SSM@100 Hz outperformed other NITs and was comparable to expanded Baveno VI criteria and Baveno VII indicating that SSM could be applied separately.

In our study, 171 cirrhosis patients were included. The demography feature of our cohort was similar to other studies on SSM@100 Hz. In our cohort, nearly half of the cirrhosis was caused by hepatitis B due to its high prevalence in China.[32] In addition, more patients with decompensated cirrhosis (74.8%) and HRV (64.3%) were included in our cohort. The proportion of HRV in compensated and decompensated cirrhosis were 18.6% and 79.6%. The decompensated cirrhosis and HRV percentage of Nagai *et al.*'s study[33] was 25.4% and 34.8%. The proportion of HRV was 26.5% in Stefanescu *et al.*'s study but the proportion of decompensated cirrhosis was not reported.[20] In our study, some patients had not undergone prior EGD examinations before being transferred to our hospital, resulting in a relatively higher severity of cirrhosis and HRV prevalence compared to other studies. Consequently, the spare rate of Baveno criteria were relatively low in our study, ranging from 6.4 to 17.5%. In our cohort, the HRV incidence in patients with decompensated cirrhosis and compensated cirrhosis was 79.4% and 18.6% respectively. The incidence of HRV is consistent with the reported epidemiological results (85% and 15%, respectively).[34] Given that approximately 20% of decompensated cirrhosis patients do not have HRV and may be predicted by NITs, and their management and prognosis depend on the presence/severity of other decompensating events, we suggest that decompensated cirrhosis patients could also be evaluated by NITs prior to EGD examination instead of screening all patients.

In recent years, several NITs have been developed to rule out LRV. As the best indicator of cirrhosis and PH in the past, LSM was included in most NITs. However, LSM does have certain limitations. Firstly, the cutoff values for diagnosing cirrhosis vary according to the underlying cause, whereas the cutoff for predicting HRV

remains the same. Second, LSM was significantly influenced by liver inflammatory, cholestasis or hepatic congestion,[35,36] thus the value of LSM should be analysed carefully. Third, LSM may not correlate with PH in certain situations, such as portal thrombosis, portosystemic shunting and NAFLD-related cirrhosis in which presents pre-sinusoidal component of PH[37,38]. Therefore, LSM was always used together with other indicators, such as platelet count, spleen thickness, etc.

Since 2012, Colecchia *et al.*[16] initially proposed that SSM may exhibit superiority over LSM in evaluating PH and the presence of EV. More than 100 studies confirmed the viewpoint. As concluded from a meta-analysis, compared to LSM, SSM correlated better with hepatic venous pressure gradient ($\gamma = 0.72$), better predicted clinically significant PH (ROC = 0.92) and severe PH (ROC = 0.87).[14] At the year 2018, Bastard *et al.*[39] published their first research on SSM@100 Hz determined by FibroScan®630. The new equipment had an ultrasound probe to locate spleen and a probe of 100 Hz to determine SSM within a range of 1.5–100 kPa. Although there were limited studies comparing the probe of 100 with 50 Hz, the benefits of probe 100 Hz has been proved, including high successful rate (92.5% *versus* 76.0%, $p < 0.001$), more accurate prediction of EV and HRV.[11,18,20,33,40]

To further verify the priority of SSM@100 Hz, we determined SSM in 22 healthy controls and 171 cirrhosis patients in the study. The mean SSM of the control group was 13.5 ± 6.7 kPa (3.4–24.8 kPa), similar to the findings of Rigamonti *et al.*[41] They determined 60 healthy controls and the SSM ranged from 14 to 18 kPa with a mean value of 16.1 kPa. In our study only 4.5% of healthy controls and 2.9% of cirrhosis patients failed to determine SSM. The failure rate was similar to Rigamonti *et al.*'s study (3.2%).[41] In conclusion, probe 100 Hz was more suitable to determine SSM than probe 50 Hz, which exhibited a failure rate ranging from 10 to 27%.

As observed in previous studies,[20,39,42,43] we again confirmed a notable correlation between SSM and EV stages. Most importantly, no other NITs were superior to SSM alone (ROC 0.881) in HRV prediction, including Baveno VI, expanded Baveno VI, Baveno VII, SSPS, etc. Even when combining the use of SSM with other NITs, such as Baveno VI and expanded Baveno VI, the performance was not improved. In Stefanescu's and Nagai's study, the ROC for HRV prediction were 0.756 and 0.941, respectively. We suggested that SSM could be used separately in HRV prediction in clinical practice. Amongst the various NITs, SSM was the only one which need not be calculated by formulas or be used in combination with other indicators.

In our study, the HRV missing rate was 2.5% when SSM cutoff was set as 43.4 kPa. The missing rates of Baveno VI and expanded Baveno VI were 6.3% and 23.3%, respectively. The rates of sparing unnecessary EGD were 23.4%, 9.4% and 17.5% when evaluated by SSM, Baveno VI and expanded Baveno VI. The results aligned with the Stefanescu *et al.*'s study.[20] The HRV missing rate was 4.7% by SSM and 0 by Baveno VI. EGD spare rates of SSM and Baveno VI criteria were 37.8% and 8.1%. In Zhang's study, addition of SSM@100 Hz improved EGD spared rate from 42.7% by Baveno VI to 75.4%.[11] No spare rate of SSM@100 Hz alone was reported. Our results indicated that SSM alone was better than other NITs with low missing rate and high EGD spare rate in HRV prediction.

As recommended by the Baveno VII criteria, further investigation is needed to determine the cutoff for SSM@100 Hz. In Stefanescu *et al.*'s[20] and Nagai *et al.*'s study,[33] the cutoff of SSM@100 Hz were 41.3 kPa (cirrhosis caused by HBV, HCV, and alcohol use disorder) and 43.8 kPa (cirrhosis caused by HCV, HBV, alcohol use disorder, NAFLD, and others), respectively. In Zhang *et al.*'s study[11] on HBV related cirrhosis, they used the same cutoff of 40 kPa for SSM@50 Hz and SSM@100 Hz. In our whole cohort, the performance of cutoff 40 and 43.4 kPa were the same. When the cohort was divided into viral and non-viral cirrhosis, the cutoff of HRV prediction were 43.4 and 50.4 kPa, respectively. The most accepted explanation was that NAFLD presented pre-sinusoid PH which led to higher and earlier onset of PH. But in our cohort, NAFLD only accounted for 4.1%. Therefore, the cutoff of different causes of cirrhosis needed further investigation and explanation. We also found that cutoff for compensated (47.9 kPa) and decompensated cirrhosis (67.5 kPa) was different. The results demonstrated that SSM was also applicable for decompensated cirrhosis, but the cutoff was much higher. Due to the relatively small sample

size of our cohort, it was premature to recommend these cutoffs to clinical use. Our results indicated that we should pay attention to confounding factors when conducting SSM.

Although the upper limit of SSM@100 Hz has been increased to 100 kPa, its clinical significance remains unclear. In our study, 34 patients (19.9%) with SSM higher than 75 kPa were all with grade 3 EV indicating that those patients with higher PH and higher risk of recent bleeding may need more active EGD examination or treatment. In our cohort, only one patient's SSM reached 100 kPa. In Naga's study of SSM@50 Hz,[33] there were 10 out of 123 patients (8.1%) who reached the ceiling threshold of 75 Hz. Together with the advantages mentioned above, we suggested that SSM should be determined by new equipment.

Limitations

First, the study was performed in a single center, which may limit the generalizability of the findings; second, the efficiency and cut-off were not validated in an external cohort; third, we didn't compare probe 50 and 100 Hz at the same time; fourth, there may be some subjectivity in staging grade of EV. We used the most widely used criteria in clinical practice (the Baveno VI consensus criteria).[22] What's more, the severity of our endoscopic varicose veins is diagnosed by experienced endoscopists. Therefore, we are confident that these results could more accurately reflect the level of bleeding risk.

Conclusion

In conclusion, compared to other non-invasive indicators, SSM@100 Hz demonstrates higher accuracy and a lower rate of missed HRV prediction, without the need to combine with other indicators. Meanwhile, the cutoffs need further study according to cause of cirrhosis and liver function. In our study, SSM@100 Hz was confirmed to be a reliable NIT for predicting HRV, with higher accuracy and a low rate of missed HRV. Similar to previous studies, we suggested the cutoff could be set at about 40 kPa. SSM@100 Hz demonstrated additional benefit that SSM between 75 and 100 kPa identified patients' grade 3 EV who had highest bleeding risk.

Declarations

Ethics approval and consent to participate

The study was in accordance with the ethical guidelines of the 2013 Declaration of Helsinki and approved by the Ethical Committee of Beijing Youan Hospital (Approval number: LL-2022-024-K). All patients provided written informed consent to have their data used (anonymously) for research purposes.

Consent for publication

Not applicable.

Author contributions

Jiqing Liu: Data curation; Methodology; Resources; Writing – original draft.

Hangfei Xu: Data curation; Methodology; Software; Writing – original draft.

Weiyuan Liu: Data curation; Methodology; Software.

Hongmei Zu: Investigation; Writing – review & editing.

Huiguo Ding: Funding acquisition; Investigation; Supervision; Writing – review & editing.

Fankun Meng: Funding acquisition; Supervision; Visualization; Writing – review & editing.

Jing Zhang: Funding acquisition; Methodology; Supervision; Writing – original draft; Writing – review & editing.

Acknowledgements

None.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article: This research received no specific grant from any funding agency in the public, commercial, or not for-profit sectors.

Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

Supplemental material for this article is available online.

ORCID iD
Jing Zhang https://orcid.org/0009-0004-4961-1942

Supplemental material
Supplemental material for this article is available online.

References

1. Simonetto DA, Liu M and Kamath PS. Portal hypertension and related complications: diagnosis and management. *Mayo Clin Proc* 2019; 94: 714–726.
2. Hernández-Gea V, Berbel C, Baiges A, *et al*. Acute variceal bleeding: risk stratification and management (including TIPS). *Hepatol Int* 2018; 12: 81–90.
3. Jakab SS and Garcia-Tsao G. Evaluation and management of esophageal and gastric varices in patients with cirrhosis. *Clin Liver Dis* 2020; 24: 335–350.
4. Colecchia A, Ravaioli F, Marasco G, *et al*. A combined model based on spleen stiffness measurement and Baveno VI criteria to rule out high-risk varices in advanced chronic liver disease. *J Hepatol* 2018; 69: 308–317.
5. Flemming JA, Saxena V, Shen H, *et al*. Facility- and patient-level factors associated with esophageal variceal screening in the USA. *Dig Dis Sci* 2016; 61: 62–69.
6. Berzigotti A, Bosch J and Boyer TD. Use of noninvasive markers of portal hypertension and timing of screening endoscopy for gastroesophageal varices in patients with chronic liver disease. *Hepatology* 2014; 59: 729–731.
7. Giannini E, Botta F, Borro P, *et al*. Platelet count/spleen diameter ratio: proposal and validation of a non-invasive parameter to predict the presence of oesophageal varices in patients with liver cirrhosis. *Gut* 2003; 52: 1200–1205.
8. Kim BK, Han KH, Park JY, *et al*. A liver stiffness measurement-based, noninvasive prediction model for high-risk esophageal varices in B-viral liver cirrhosis. *Am J Gastroenterol* 2010; 105: 1382–1390.
9. Wang H, Wen B, Chang X, *et al*. Baveno VI criteria and spleen stiffness measurement rule out high-risk varices in virally suppressed HBV-related cirrhosis. *J Hepatol* 2021; 74: 584–592.
10. Dajti E, Ravaioli F, Marasco G, *et al*. A combined Baveno VII and spleen stiffness algorithm to improve the noninvasive diagnosis of clinically significant portal hypertension in patients with compensated advanced chronic liver disease. *Am J Gastroenterol* 2022; 117: 1825–1833.
11. Zhang X, Song J, Zhang Y, *et al*. Baveno VII algorithm outperformed other models in ruling out high-risk varices in individuals with HBV-related cirrhosis. *J Hepatol* 2023; 78: 574–583.
12. Reiberger T. The value of liver and spleen stiffness for evaluation of portal hypertension in compensated cirrhosis. *Hepatol Commun* 2022; 6: 950–964.
13. Danielsen KV, Hove JD, Nabilou P, *et al*. Using MR elastography to assess portal hypertension and response to beta-blockers in patients with cirrhosis. *Liver Int* 2021; 41: 2149–2158.
14. Song J, Huang J, Huang H, *et al*. Performance of spleen stiffness measurement in prediction of clinical significant portal hypertension: a meta-analysis. *Clin Res Hepatol Gastroenterol* 2018; 42: 216–226.
15. de Franchis R, Bosch J, Garcia-Tsao G, *et al*. Baveno VII - renewing consensus in portal hypertension. *J Hepatol* 2022; 76: 959–974.
16. Colecchia A, Montrone L, Scaioli E, *et al*. Measurement of spleen stiffness to evaluate portal hypertension and the presence of esophageal varices in patients with HCV-related cirrhosis. *Gastroenterology* 2012; 143: 646–654.
17. Roccarina D, Rosselli M, Genesca J, *et al*. Elastography methods for the non-invasive assessment of portal hypertension. *Expert Rev Gastroenterol Hepatol* 2018; 12: 155–164.
18. Ma X, Wang L, Wu H, *et al*. Spleen stiffness is superior to liver stiffness for predicting esophageal varices in chronic liver disease: a meta-analysis. *PLoS One* 2016; 11: e0165786.
19. Colecchia A, Marasco G, Taddia M, *et al*. Liver and spleen stiffness and other noninvasive methods to assess portal hypertension in cirrhotic patients: a review of the literature. *Eur J Gastroenterol Hepatol* 2015; 27: 992–1001.
20. Stefanescu H, Marasco G, Calès P, *et al*. A novel spleen-dedicated stiffness measurement by FibroScan® improves the screening of high-risk oesophageal varices. *Liver Int* 2020; 40: 175–185.
21. Ziol M, Handra-Luca A, Kettaneh A, *et al*. Noninvasive assessment of liver fibrosis by measurement of stiffness in patients with chronic hepatitis C. *Hepatology* 2005; 41: 48–54.

22. 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.
23. Augustin S, Pons M, Maurice JB, *et al.* Expanding the Baveno VI criteria for the screening of varices in patients with compensated advanced chronic liver disease. *Hepatology* 2017; 66: 1980–1988.
24. Shibata S, Umemura T, Yamazaki T, *et al.* Liver stiffness-spleen size-to-platelet ratio risk score identifies esophageal varices in Japanese patients with chronic hepatitis C. *Hepatol Res* 2016; 46: 884–889.
25. Cho YS, Lim S, Kim Y, *et al.* Spleen stiffness-spleen size-to-platelet ratio risk score as noninvasive predictors of esophageal varices in patients with hepatitis B virus-related cirrhosis. *Medicine* 2022; 101: e29389.
26. Berzigotti A. Non-invasive evaluation of portal hypertension using ultrasound elastography. *J Hepatol* 2017; 67: 399–411.
27. Llop E, Lopez M, de la Revilla J, *et al.* Validation of noninvasive methods to predict the presence of gastroesophageal varices in a cohort of patients with compensated advanced chronic liver disease. *J Gastroenterol Hepatol* 2017; 32: 1867–1872.
28. Wong GLH, Kwok R, Hui AJ, *et al.* A new screening strategy for varices by liver and spleen stiffness measurement (LSSM) in cirrhotic patients: a randomized trial. *Liver Int* 2018; 38: 636–644.
29. Abe H, Midorikawa Y, Matsumoto N, *et al.* Prediction of esophageal varices by liver and spleen MR elastography. *Eur Radiol* 2019; 29: 6611–6619.
30. Berger A, Ravaioli F, Farcau O, *et al.* Including ratio of platelets to liver stiffness improves accuracy of screening for esophageal varices that require treatment. *Clin Gastroenterol Hepatol* 2021; 19: 777–787.e17.
31. Ding NS, Nguyen T, Iser DM, *et al.* Liver stiffness plus platelet count can be used to exclude high-risk oesophageal varices. *Liver Int* 2016; 36: 240–245.
32. Liu Z, Jiang Y, Yuan H, *et al.* The trends in incidence of primary liver cancer caused by specific etiologies: results from the Global Burden of Disease Study 2016 and implications for liver cancer prevention. *J Hepatol* 2019; 70: 674–683.
33. Nagai K, Ogawa Y, Kobayashi T, *et al.* Gastroesophageal varices evaluation using spleen-dedicated stiffness measurement by vibration-controlled transient elastography. *JGH Open* 2022; 6: 11–19.
34. Jakab SS and Garcia-Tsao G. Screening and surveillance of varices in patients with cirrhosis. *Clin Gastroenterol Hepatol* 2019; 17: 26–29.
35. European Association for Study of Liver and Asociacion Latinoamericana para el Estudio del Higado. EASL-ALEH clinical practice guidelines: non-invasive tests for evaluation of liver disease severity and prognosis. *J Hepatol* 2015; 63: 237–264.
36. Yoo JJ, Seo YS, Kim YS, *et al.* The influence of histologic inflammation on the improvement of liver stiffness values over 1 and 3 years. *J Clin Med* 2019; 8: 2065.
37. Baffy G and Bosch J. Overlooked subclinical portal hypertension in non-cirrhotic NAFLD: is it real and how to measure it? *J Hepatol* 2022; 76: 458–463.
38. Vizzutti F, Arena U, Romanelli RG, *et al.* Liver stiffness measurement predicts severe portal hypertension in patients with HCV-related cirrhosis. *Hepatology* 2007; 45: 1290–1297.
39. Bastard C, Miette V, Calès P, *et al.* A novel FibroScan examination dedicated to spleen stiffness measurement. *Ultrasound Med Biol* 2018; 44: 1616–1626.
40. 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.
41. Rigamonti C, Cittone MG, Manfredi GF, *et al.* High reproducibility of spleen stiffness measurement by vibration-controlled transient elastography with a spleen-dedicated module. *Hepatol Commun* 2022; 6: 3006–3014.
42. Sharma P, Kirnake V, Tyagi P, *et al.* Spleen stiffness in patients with cirrhosis in predicting esophageal varices. *Am J Gastroenterol* 2013; 108: 1101–1107.
43. Calvaruso V, Bronte F, Conte E, *et al.* Modified spleen stiffness measurement by transient elastography is associated with presence of large oesophageal varices in patients with compensated hepatitis C virus cirrhosis. *J Viral Hepat* 2013; 20: 867–874.