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ORIGINAL ARTICLE

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A novel spleen-dedicated stiffness measurement by FibroScan® improves the screening of high-risk oesophageal varices

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Abstract

Background & Aims: Several non-invasive tests (NITs) have been developed to diagnose oesophageal varices (EV), including the recent Baveno VI criteria to rule out high-risk varices (HRV). Spleen stiffness measurement (SSM) with the standard FibroScan® (SSM@50Hz) has been evaluated. However, the EV grading could be underestimated because of a ceiling threshold (75 kPa) of the SSM@50Hz. The aims were to evaluate SSM by a novel spleen-dedicated FibroScan® (SSM@100Hz) for EV diagnosis compared with SSM@50Hz, other validated NITs and Baveno VI criteria.

Methods: This prospective multicentre study consecutively enrolled patients with chronic liver disease; blood data, endoscopy, liver stiffness measurement (LSM), SSM@50Hz and SSM@100Hz were collected.

Results: Two hundred and sixty patients met inclusion criteria. SSM@100Hz success rate was significantly higher than that of SSM@50Hz (92.5% vs 76.0%, $P < .001$). SSM@100Hz accuracy for the presence of EV (AUC = 0.728) and HRV (AUC = 0.756) was higher than in other NITs. SSM@100Hz AUC for large EV (0.782) was higher than SSM@50Hz (0.720, $P = .027$). AUC for HRV with SSM@100Hz (0.780) was higher than with LSM (0.615, $P < .001$). The spared endoscopy rate of Baveno VI criteria (8.1%) was significantly increased by the combination to SSM@50Hz (26.5%) or SSM@100Hz (38.9%, $P < .001$ vs others). The missed HRV rate was, respectively, 0% and 4.7% for combinations.

Conclusions: SSM@100Hz is a new performant non-invasive marker for EV and HRV providing a higher accuracy than SSM@50Hz and other NITs. The combination of Baveno VI criteria and SSM@100Hz significantly increased the spared endoscopy

Abbreviations: ALT, alanine aminotransferase; APRI, AST to platelets ratio index; AST, aspartate aminotransferase; AUC, area under receiving operator characteristics curve; BMI, body mass index; CI, confidence interval at 95%; CLD, chronic liver disease; CSPH, clinically significant portal hypertension; EGD, oesophagogastroduodenoscopy; EV, oesophageal varices; Fib-4, Fibrosis-4 score; GGT, gamma-glutamyltransferase; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HRV, high-bleeding risk varices; HVPG, hepatic venous pressure gradient; INR, international normalized ratio; IQR, interquartile range; kPa, kiloPascals; LSM, liver stiffness measurement; LSPS, LSM-spleen diameter to platelet ratio score; MELD, model for End-Stage Liver Disease; NSBB, non-selective beta-blockers; OR, odds ratio; PH, portal hypertension; PSR, platelet count/spleen ratio; SSM, spleen stiffness measurement; SSM@100Hz, SSM with the novel spleen-dedicated VCTE examination; SSM@50Hz, SSM with the standard liver dedicated VCTE examination; VCTE, vibration-controlled transient elastography

rate compared to Baveno VI criteria alone or combined with SSM@50Hz. Clinical trial number: NCT02180113.

KEYWORDS
Baveno VI criteria, liver stiffness measurement, portal hypertension, spleen stiffness measurement

1 | INTRODUCTION

Variceal bleeding represents one of the most severe and life-threatening complications in chronic liver disease (CLD).[1] The prevalence of oesophageal varices (EV) among cirrhotic patients is about 50%-60%.[1] The incidence of variceal bleeding is approximately 5% to 15% yearly, and variceal re-bleeding rate is 30% to 40% within the first 6 weeks.[1] Despite the clinical progress, the 6-week mortality associated with variceal bleeding is still in the order of 10 to 20%.[1] Oesophagogastroduodenoscopy (EGD) is the reference diagnostic tool for detecting and grading EV and for the recognition of indicators of at high-bleeding risk EV (HRV).[2] However, EGD is an invasive method with constraints and may lead to complications.[3] In addition, it is an expensive method and its use is limited to specialized clinical setting.

In the last decade, several authors tried to assess the presence and severity of portal hypertension (PH) by using non-invasive methods, among which liver stiffness measurement (LSM) proved to have a primary role.[4,5] Along these lines, the recent 2015 Baveno VI consensus workshop [6] highlighted the diagnostic accuracy of LSM in defining the presence of clinically significant PH (CSPH), EV and HRV. In particular, patients with LSM < 20 kPa (assessed by vibration-controlled transient elastography, VCTE) and a platelet count >150 G/L were considered very unlikely to have HRV (<5%), and EGD could be safely avoided. Nevertheless, LSM has a poor correlation with portal pressure and its complications when hepatic venous pressure gradient (HVPG) is >10 mm Hg.[7] Once this critical threshold is reached, portal-systemic collaterals develop and extrahepatic factors contribute to increase HVPG.[8] Hence, at this stage, LSM might underestimate the PH severity and the risk of variceal bleeding.

Recently, spleen stiffness measurement (SSM)[9-12] has also been proposed as a non-invasive marker for the prediction of CSPH and EV. It has been postulated that SSM could overcome some of the limitations of LSM.[9,12] Several authors found a good correlation between SSM by standard VCTE (SSM@50Hz) and PH degree, EV and the natural history of cirrhotic patients.[9,10,12]

However, the spleen is stiffer than the liver and the use of the current VCTE examination dedicated to the liver on the spleen leads to overestimation of the SSM.[13] To overcome those limitations, a novel spleen-dedicated examination (SSM@100Hz) based on VCTE has recently been developed[13] and found to have a better accuracy in detecting EV and large EV.

The aim of the present study was to evaluate new SSM@100Hz as a surrogate non-invasive marker for the presence of EV, large EV and HRV in patients with CLD. Secondary objectives were (a) to compare the EV prediction by this new SSM@100Hz with the SSM@50Hz and other non-invasive tests (NITs), (b) to evaluate the correlation between SSMs and HVPG, and (c) to test whether SSM@100Hz might improve the Baveno VI criteria to better select patients for HRV screening by EGD.

Key points

- A novel spleen-dedicated examination (SSM@100Hz) has recently been developed and found to have a better accuracy in detecting EV and large EV.
- A sequential algorithm to rule out HRV, starting with Baveno VI criteria and followed optionally by SSM@100Hz, allowed to spare more EGD compared to Baveno VI criteria alone or combined with standard SSM@50Hz.

2 | PATIENTS AND METHODS

2.1 | Study population

This is a multicentre European prospective study conducted in Bologna and Milan (Italy), Cluj (Romania), Angers, Bordeaux and Bondy (France) and London (United Kingdom); patients with CLD undergoing a VCTE examination and scheduled for EGD were prospectively and consecutively enrolled, according to the following criteria: Inclusion criteria were: CLD because of hepatitis virus C (HCV), hepatitis virus B (HBV) or alcoholic liver disease; 18-79 years old; health insurance; ultrasound (US) examination, blood examination and EGD performed within 6 months of VCTE examination. Exclusion criteria were: consuming illness (HIV infection, malignancy); pacemaker or heart defibrillator; pregnancy; obese patients (body mass index (BMI) ≥35 kg/m^2); ascites; previous endoscopic treatment of EV; serum aminotransferases ≥ 250 IU/L; ongoing non-selective β-blockers (NSBB) treatment at the time of the study; HCV or HBV treatment ongoing or ended within 2 months from inclusion, liver transplantation, acute alcoholic hepatitis, jaundice (defined by total serum bilirubin ≥ 50 μmol/L) and hepatocellular carcinoma. This study was conducted in compliance with the Declaration of Helsinki and approved by the local Ethics Committee of each centre and other national Competent Authority if required. This study

was initially approved by the Ethics Committee of S.Orsola-Malpighi Hospital in Bologna (Italy, coordinating centre). This study was also registered on ClinicalTrials.gov (NCT 02 180 113) in 2014. In 2015, the design of the study was modified before knowing the statistical results to account for the new definitions for compensated advanced CLD (cACLD) (defined as LSM ≥ 10 kPa) and HRV provided by the Baveno VI Consensus Conference.[6] All patients provided written informed consent before any inclusion procedure. A subgroup of 193 patients was previously reported for the development of the acquisition algorithm for SSM@100Hz.[13] This study follows the liverFibroSTARD statements[14]

2.2 | Study assessment

For each patient, the following demographic and clinical characteristics were recorded: age, gender, body weight, height and BMI. Blood variables (platelet count, INR, AST, ALT, total bilirubin, creatinine) were obtained from each local laboratory. A standard ultrasound examination was performed by an experienced sonographer blinded to the other exams to measure the longitudinal spleen length and the mean portal vein velocity. According to published formula, LSM-longitudinal spleen diameter to platelet ratio score (LSPS),[15] platelet count/longitudinal spleen diameter ratio (PSR),[16] Lok index,[17] Fib-4[18] and APRI[19] were calculated. In a single centre (Bologna), HVPG was also measured[20] and collected within 6 months from SSM and LSM. A standard EGD was performed by a senior or experienced operator blinded to the other exams. The endoscopic findings for EV were recorded as follows: grade of EV and presence of red signs. Patients were also categorized according to the Baveno VI criteria[21] and the recently published expanded Baveno VI criteria[22]

2.3 | Definitions

2.3.1 | Outcomes

The main outcomes were: EV, large EV and HRV. The HRV were defined as large EV (grade 2 or 3 EV ie diameter ≥ 5 mm[23]) or grade 1 EV with red signs according to Baveno VI consensus.[6]

The outcome measures were AUC for outcome diagnosis by NITs and HVPG, and two clinical descriptors for outcome diagnosis by algorithms as follows.

The spared EGD rate was calculated as the ratio between the number of patients with EGD that could be avoided, because of a low HRV risk according to the diagnostic test or algorithm, and the total number of patients.

The missed HRV rate was measured as the rate of patients with missed HRV either among the patients with HRV (privileged definition) or patients with spared EGD or all patients[24]

2.3.2 | Diagnostic tests

Success rate: a successful LSM or SSM was defined by at least 10 or 8,[13] respectively, single valid measures obtained in a patient. The success rate refers to the rate of patients with successful LSM in the whole population. The lack of success was called failure.

Reliability is defined as diagnostic test measures having better accuracy according to precise patient characteristics. Thus, reliable LSM (for successful LSM only) was defined as LSM < 7 kPa or LSM > 7.1 kPa with interquartile range (IQR) <30%.[25] As reliability criteria are not yet defined for SSM, the largest subgroup comprised patients with successful SSM and reliable LSM.

2.3.3 | Subpopulations

Four subpopulations were used according to the maximum of suitable stiffness results available in patients with available EGD: subpopulation A with successful SSM@100Hz, used for SSM@100Hz evaluation, from which two subpopulations were extracted; subpopulation B with successful SSM@50Hz used for comparison of SSM@100Hz with SSM@50Hz, and subpopulation C with successful and reliable LSM, used for comparison of SSM@100Hz and LSM. Finally, subpopulation D included patients with successful and reliable LSM, successful SSM@50Hz and available platelets, used for Baveno VI criteria evaluation.

2.4 | Liver and spleen stiffness measurement

LSM and SSM@50Hz procedure was performed as previously reported.[26] The technical characteristics of the SSM@100Hz examination are detailed elsewhere [13]

2.5 | Statistical analysis

Continuous variables were reported as median [Q1-Q3] and categorical variables were reported as proportion (percentage). For group comparisons of categorical and continuous variables, Kruskal-Wallis test and Wilcoxon's test were used, as appropriate. To compare categorical variables, Chi square test (unpaired samples) and McNemar's test (paired samples) were used as appropriate. Spearman's rank test was used for correlations among continuous variables. To evaluate the variables associated with the failure of SSM@100Hz and SSM@50Hz, a multivariate logistic regression was used: *P* values and odds ratio (OR) were reported. In order to measure the accuracy of the different NITs for EV, large EV or HRV presence, area under the receiver operator characteristic curve (AUC) was assessed. Paired Delong's test was used for the AUC comparison. In algorithm construction, a combined model was constructed for ruling-out HRV using first Baveno VI criteria and, consecutively, SSM using a cut-off for ruling-out HRV calculated with sensitivity at 95% in remaining patients, that is, at high-risk for HRV according to Baveno VI criteria. As various methods are currently used in the literature to calculate the rate of patients with HRV left without EGD (missed HRV), we calculated this rate with all the three following calculations: the numerator is always the number of missed HRV and the denominator can be the total number of HRV,[27] or the number of spared endoscopy[28] or the total number of patients.[28] According to the results of

a recent study[24], we privilege the first calculation. We selected for our study patients with a large spectrum of liver disease severity; therefore, in order to evaluate the impact of liver disease severity on test performance, we also applied the sequential model Baveno VI criteria and SSM@100Hz in two subgroups of subpopulation D defined by median MELD score. All statistical analyses were performed using Microsoft R Open 3.4.2, for Windows.

3 | RESULTS

3.1 | Patient characteristics

During the study period from September 2011 to January 2017, 403 patients with CLD were enrolled; 28 were excluded for protocol deviation. Among the remaining 375 enrolled patients, 91 (24.3%) patients did not undergo EGD within 6 months of SSM; among the remaining 284 patients, SSM@100Hz fully failed (no valid measurement) in 11 patients (2.9%) and did not reach the success criterion in further 13 patients (3.5%). A total of 260 patients were thus included in the core subpopulation A (Figure 1). The bioclinical characteristics of these 260 patients are presented in Table 1.

3.2 | SSM descriptors

3.2.1 | SSM@100Hz

Successful SSM@100Hz was obtained in 347 patients out of 375 (92.5%). A multivariate logistic regression found the following independent predictors of SSM@100Hz failure: longitudinal spleen diameter (P = .016, OR: 0.733 [0.569-0.944]) and a higher BMI (P = .050, OR: 1.136 [1.000-1.290]). Among the 260 patients with EGD within 6 months of successful SSM@100Hz (subpopulation A), patients with EV had a median SSM@100Hz of 55.2 kPa [40.9-72.3] which was significantly higher (P < .001) than that of patients without EV (39.7 kPa [27.6-49.6]). Among patients with EV, SSM@100Hz values of grade 2 EV (61.4 kPa [49.2-78.5]) were significantly higher (P < .001) than in grade 1 (48.5 kPa [38.3-65.7]) but not significantly different (P = .328) from grade 3 (78.3 kPa [68.2-88.0]) as shown in Figure 2A. The AUC of SSM@100Hz for EV presence was 0.728 (95% CI: 0.665-0.791) and for large EV (grade ≥ 2) was 0.767 (0.700-0.834). SSM@100Hz in the 69 patients with HRV (65.0 kPa [51.6-80.1]) was significantly higher than in those without HRV (43.0 kPa [33.9-57.9], P < .001). The AUC of SSM@100Hz for HRV presence was 0.756 (0.691-0.821).

3.2.2 | SSM@50Hz

SSM@50Hz was successful in 285 out of 375 patients (76.0%) which was significantly lower than the success rate of SSM@100Hz (92.5%, P < .001). A multivariate logistic regression found the following independent predictors of SSM@50Hz failure: a smaller longitudinal spleen diameter (P < .001, OR: 0.764) and a smaller mean portal vein velocity (P = .010, OR: 0.946). Out of the 260 patients with EGD within 6 months of successful SSM@100Hz (subpopulation A), 222 patients also had a successful SSM@50Hz. In this subpopulation B, SSM@50Hz was significantly higher (P < .001) in patients with EV (65.9 kPa [48.0-75.0]) than in patients without EV (50.0 kPa [32.4-67.5]). In patients with EV, SSM@50Hz values were not significantly different between adjacent EV grades (Figure 2B). The AUC of SSM@50Hz was 0.672 (0.598-0.746) for EV presence, 0.720 (0.639-0.802) for large EV (grade ≥ 2) and 0.737 (0.665-0.809) for HRV presence.

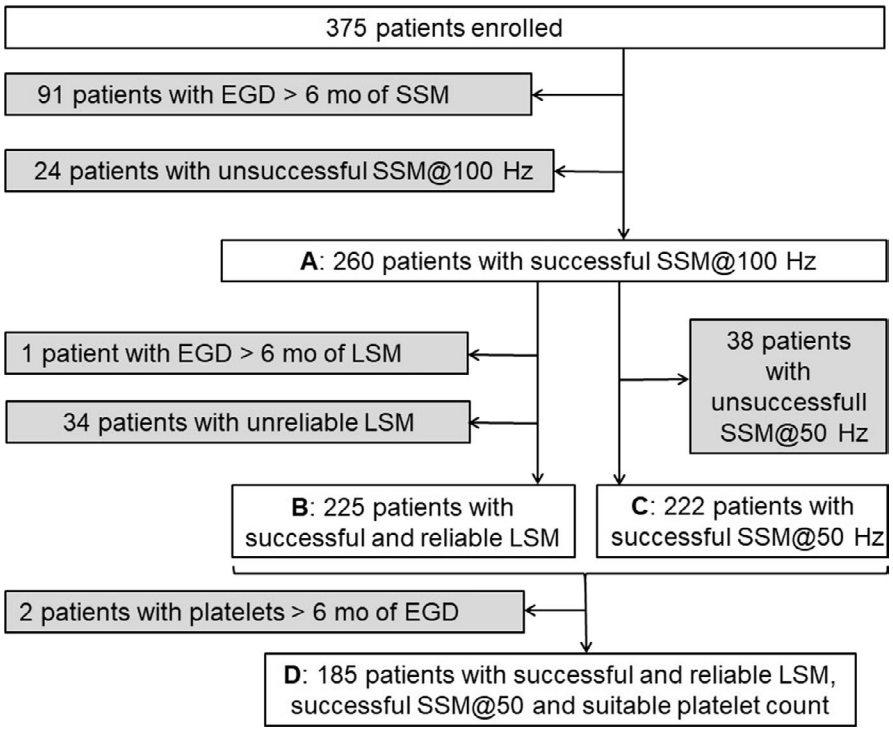

FIGURE 1 Study flow chart. EGD, oesophagogastroduodenoscopy; LSM, liver stiffness measurement; SSM@100Hz, new spleen stiffness measurement with transient elastography; SSM@50Hz, standard spleen stiffness measurement with transient elastography

TABLE 1 Demographics and clinical data of patients enrolled (subpopulation A)

Characteristics	N	Median [Q1-Q3] or n (%)
Male	260	169 (65)
Female	260	91 (35)
Age (y)	260	59 [51-68]
BMI (kg/m^2)	260	26.0 [23.7-28.6]
ALT (IU/L)	251	51 [29-88]
AST (IU/L)	242	56 [36-93]
Platelets (G/L)	254	101 [77-142]
Grade of EV		
G0	260	95 (36.5)
G1		111 (42.7)
G2		42 (16.2)
G3		12 (4.6)
Cherry spots	260	29 (11.2)
Red wale marks	260	42 (16.2)
Presence of HRV	260	69 (26.5)
Spleen longitudinal length (cm)	260	13.6 [11.9-15.5]
Aetiology		
HCV	260	155 (59.6)
HBV		19 (7.3)
Alcohol		79 (30.4)
Others		7 (2.7)
MELD score	204	9.2 [7.9-11.7]
LSM (kPa)[a]	225	23.4 [15.4-35.3]
SSM@100Hz (kPa)[b]	260	48.0 [36.6-66.1]
SSM@50Hz (kPa)[b]	222	60.0 [41.3-74.6]
HVPG (mm Hg)	102	13 [11-15]

Note: Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; EV: oesophageal varices, HRV: high-bleeding risk oesophageal varices; HBV, hepatitis B virus; HCV, hepatitis C virus; HVPG, hepatic venous pressure gradient; IQR, interquartile range; KPa, kilopascal; LSM, liver stiffness measurement; MELD, model for end-stage liver disease; SSM, spleen stiffness measurement.

[a]In patients with reliable LSM.

[b]In patients with successful SSM.

3.2.3 | SSM comparison

SSM@50Hz and SSM@100Hz were highly correlated (Spearman's r = 0.820, $P < .001$). AUCs of SSM@100Hz and SSM@50Hz were not significantly different for EV presence ($P = .113$) and HRV presence ($P = .105$) as shown in Table 2. However, for the presence of large EV (grade ≥ 2), the AUC of SSM@100Hz (0.782 [0.709-0.855]) was significantly higher ($P = .027$) than the AUC of SSM@50Hz (0.720 [0.639-0.802]).

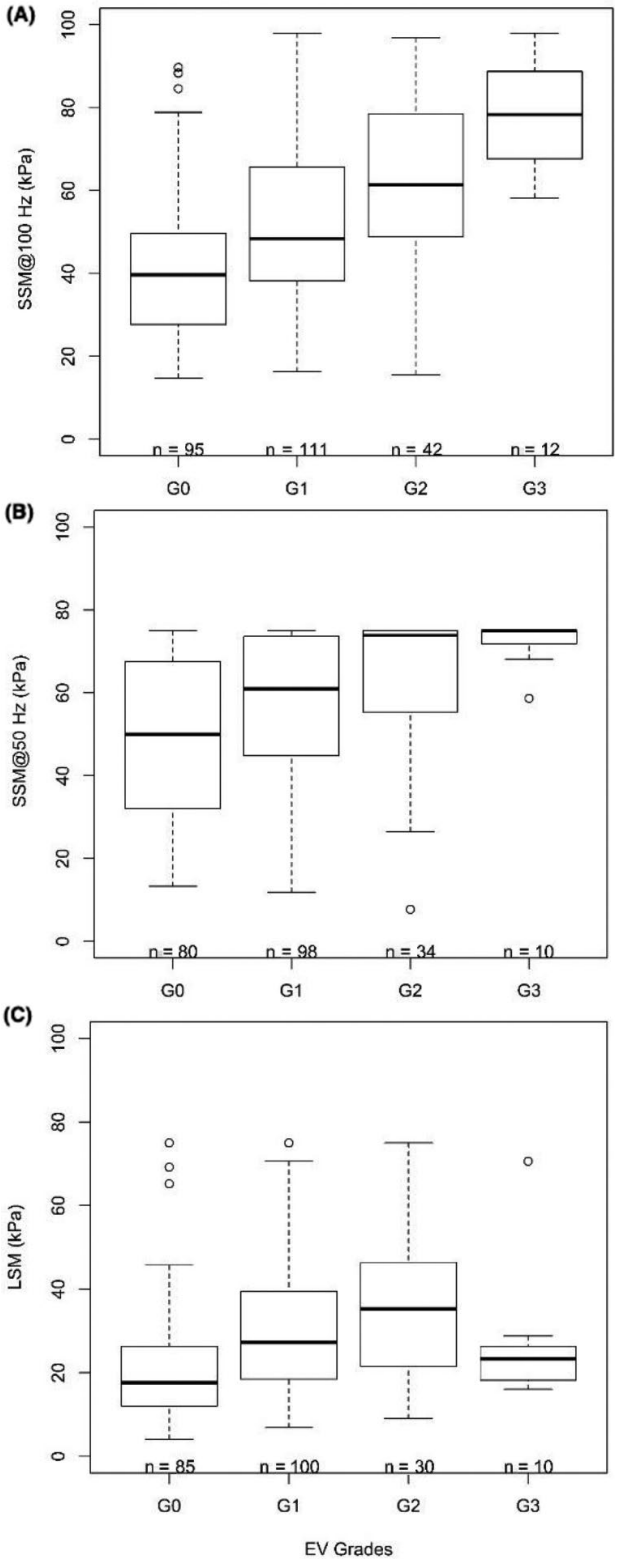

FIGURE 2 Box plots of (A) SSM@100Hz (n = 260); (B) SSM@50Hz (n = 222) and (C) LSM (n = 225) versus oesophageal varices grade assessed by EGD. EGD, oesophagogastroduodenoscopy; LSM, liver stiffness measurement; SSM@100Hz, new spleen stiffness measurement with transient elastography; SSM@50Hz, standard spleen stiffness measurement with transient elastography

TABLE 2 AUC (CI 95%) of SSM@100Hz for EV presence, large EV and HRV presence compared to SSM@50Hz, LSM, HVPG, and other non-invasive tests (subpopulation A)

		EV			Large EV			HRV		
Comparator	N	Comparator	SSM@100Hz[a]	*P*-value[b]	Comparator	SSM@100Hz[a]	*P*-value[b]	Comparator	SSM@100Hz[a]	*P*-value[b]
SSM@50Hz	222	0.672 (0.598-0.746)	0.709 (0.639-0.779)	0.113	0.720 (0.639-0.802)	0.782 (0.709-0.855)	0.027	0.737 (0.665-0.809)	0.778 (0.709-0.846)	0.105
LSM	225	0.712 (0.642-0.782)	0.742 (0.676-0.808)	0.424	0.618 (0.527-0.709)	0.811 (0.749-0.872)	<0.001	0.615 (0.532-0.697)	0.780 (0.714-0.846)	<0.001
LSPS	191	0.718 (0.640-0.795)	0.749 (0.678-0.821)	0.435	0.654 (0.562-0.746)	0.784 (0.714-0.854)	0.010	0.637 (0.549-0.724)	0.760 (0.685-0.834)	0.007
Lok index	198	0.687 (0.606-0.769)	0.736 (0.663-0.810)	0.273	0.723 (0.648-0.799)	0.743 (0.667-0.819)	0.686	0.704 (0.625-0.784)	0.721 (0.644-0.799)	0.732
PSR	219	0.299 (0.223-0.375)	0.731 (0.661-0.800)	<0.001	0.285 (0.210-0.361)	0.755 (0.684-0.825)	<0.001	0.323 (0.245-0.401)	0.737 (0.666-0.808)	<0.001
Fib-4	236	0.598 (0.516-0.679)	0.713 (0.645-0.782)	0.009	0.623 (0.547-0.700)	0.764 (0.694-0.833)	0.005	0.609 (0.534-0.684)	0.743 (0.673-0.813)	0.005
APRI	235	0.549 (0.465-0.632)	0.712 (0.643-0.780)	<0.001	0.588 (0.507-0.669)	0.767 (0.697-0.836)	<0.001	0.555 (0.476-0.633)	0.746 (0.676-0.816)	<0.001
HVPG	102	0.760 (0.663-0.857)	0.761 (0.667-0.855)	0.979	0.764 (0.652-0.877)	0.822 (0.740-0.905)	0.343	0.749 (0.643-0.854)	0.835 (0.757-0.913)	0.109

Abbreviations: APRI, AST to platelets ratio index; AUC, area under receiving operator characteristics curve; CI, confidence interval; EV, oesophageal varices; Fib-4, Fibrosis-4 score; HRV, high-bleeding risk oesophageal varices; HVPG, hepatic venous pressure gradient; IQR, interquartile range; LSM, liver stiffness measurement; LSPS, LSM-spleen diameter to platelet ratio score; N, number; PSR, platelet count/spleen ratio; SSM@100Hz, SSM with the novel spleen-dedicated VCTE examination; SSM@50Hz, SSM with the standard liver dedicated VCTE examination.

[a]The result is variable since corresponding to the maximum size of the group with comparator available.

[b]Delong's test.

3.3 | SSM comparison with LSM and other NITs

Out of the 260 cases with EGD, within 6 months of successful SSM@100Hz (subpopulation A), 225 patients had also a reliable LSM. Among patients with EV, LSM was not significantly different between adjacent EV grades (Figure 2C). The AUCs for the presence of EV and HRV were compared between SSM@100Hz, LSM and other NITs in Table 2 and detailed in Data S1.

3.4 | Combination with Baveno VI criteria

The comparison of the performances of the different methods to identify patients for whom EGD can be safely avoided (low risk for HRV) was conducted on the 185 patients with EGD within 6 months of successful SSM@100Hz or SSM@50Hz and reliable LSM and of platelet count. In this subpopulation D, applying Baveno VI criteria, 15 out of 185 patients (8.1%) were classified at low risk for HRV (Table 3). Among them, none had HRV so that the missed HRV rate was 0% (regardless of the way to calculate it). In the remaining 170 patients identified as at high-risk for HRV (using the Baveno VI criteria alone), we investigated if the consecutive use of SSM would help to safely spare more EGD. Indeed, SSM@100Hz and SSM@50Hz when tested alone with a cut-off for the detection of 95% of HRV allowed to spare more EGD when compared to Baveno VI criteria alone ($P < .001$). To do so, we identified, in this high HRV risk group, the cut-off for the detection of 95% of HRV (ie 95% sensitivity) at 40.1 kPa for SSM@50Hz and 41.3 kPa for SSM@100Hz. Table 3 compares the rate of spared EGD and of missed HRV. The sequential combination of SSM@100Hz to Baveno VI criteria spared further 30.8% of unneeded EGDs; thus, the total spared EGD rate was 38.9%. The missed HRV rate was 4.7% (using the total number of HRV as the denominator, ie the calculation based on sensitivity). No difference in spared EGD was found comparing SSM@100Hz alone with the combination Baveno VI criteria + SSM@100Hz (37.8% Vs 38.9%, $P = .480$). When the combination of Baveno VI criteria and SSM@50Hz was considered, a greater number of EGD were spared than with Baveno VI alone (26.5% vs 8.1%, $P < .001$) but it was significantly lower than with the combination of Baveno VI criteria and SSM@100Hz (26.5% vs 38.9%, $P < .001$). Figure 3 therefore proposes a new sequential diagnostic algorithm for the detection of patients at high-risk of HRV. The superiority of the combined model Baveno VI + SSM@100Hz was highlighted also when dichotomizing the subpopulation D for the severity of liver disease according to the median MELD score (Table S1). Additionally, we applied expanded Baveno VI criteria for trying to spare more EGD (Table S2), but the missed HRV rate of those criteria alone was too high (12.6%) precluding to determine a useful combination with SSM@100Hz.

3.5 | SSM comparison with HVPG

HVPG (available in 102 patients), which was significantly higher in patients with EV than in those without EV and different among EV grades ($P < .001$), was better correlated with SSM@100Hz values (Spearman's $r = 0.532$, $P < .001$) than SSM@50Hz (Figure 4).

TABLE 3 Comparison of diagnostic performance of Baveno VI, SSM@100Hz, SSM@50Hz, Baveno VI + SSM@100Hz and Baveno VI + SSM@50Hz for ruling out HRV. Subpopulation D including 185 patients

	Baveno VI	SSM@100Hz	*P*-value[a]	SSM@50Hz	*P*-value[a]	Baveno VI + SSM@100Hz[d]	*P*-value[a]	*P*-value[b]	Baveno VI + SSM@50Hz[e]	*P*-value[a]	*P*-value[c]
Spared endoscopy	15/185 8.1% (4.6%-13.0%)	70/185 37.8% (30.8%-45.2%)	<0.001	44/185 23.8% (17.8%-30.6%)	<0.001	72/185 38.9% (31.9%-46.3%)	<0.001	0.480	49/185 26.5% (0.3%-33.5%)	<0.001	<0.001
Missed HRV/ number of HRV	0/43 0% (0%-6.7%)	2/43 4.7% (0.6%-15.8%)	0.480	2/43 4.7% (0.6%-15.8%)	0.480	2/43 4.7% (0.6%-15.8%)	0.480	1.000	2/43 4.7% (0.6%-15.8%)	1.000	1.000
Missed HRV/ number of spared endoscopy	0/15 0% (0%-18.1%)	2/70 2.9% (0.3%-9.9%)	1.000	2/44 4.5% (0.6%-15.5%)	0.989	2/72 2.8% (0.3%-9.8%)	1.000	1.000	2/49 4.1% (0.5%-14.0%)	1.000	1.000
Missed HRV/all patients	0/185 0% (0%-1.6%)	2/185 1.1% (0.1%-3.9%)	0.480	2/185 1.1% (0.1%-3.9%)	0.480	2/185 1.1% (0.1%-3.9%)	0.480	1.000	2/185 1.1% (0.1%-3.9%)	1.000	1.000

[a]P-value of the proportion comparison with Baveno VI alone by McNemar's test (except for missed HRV among spared endoscopy: Chi square test).
[b]P-value of the proportion comparison with SSM@100Hz by McNemar's test (except for missed HRV among spared endoscopy: Chi square test).
[c]P-value of the proportion comparison with Baveno VI + SSM@100Hz by McNemar's test (except for missed HRV among spared endoscopy: Chi square test).
[d]The cut-off of 41.3 kPa was calculated in the subgroup of 170 of 185 patients with available SSM@100Hz and at high-risk for HRV according to Baveno VI by setting sensitivity of SSM@100Hz for HRV at 95%.
[e]The cut-off of 40.1 kPa was calculated in the subgroup of 170/185 patients with available SSM@50Hz and at high-risk for HRV according to Baveno VI by setting sensitivity of SSM@50Hz for HRV at 95%.

Additionally, we evaluated the accuracy of SSM@100Hz in detecting patients with CSPH (78 out of 102, 76.5%) finding a best cut-off of 34.15 kPa with an AUC of 0.811 (95% CI: 0.672; 0.950); furthermore, for detecting patients with HVPG ≥ 12 mm Hg the best cut-off was 44.95 kPa with an AUC of 0.782 (95% CI: 0.677; 0.887). The results of these comparisons are detailed in Table S3.

4 | DISCUSSION

In the last decade, LSM and SSM by the standard VCTE liver dedicated examination (SSM@50Hz) were proposed as accurate diagnostic tools for EV diagnosis.[9,11,12] The aims of the present study were the evaluation of a new spleen dedicated VCTE examination (SSM@100Hz) as surrogate non-invasive marker for the presence of HRV in patients with CLD and its comparison with other NITs to select patients for endoscopic screening of HRV. In addition, we compared the new SSM@100Hz with standard SSM@50Hz.

Firstly, SSM@100Hz showed a higher success rate than SSM@50Hz. Secondly, diagnostic accuracy of SSM@100Hz for EV, large EV and HRV presence was significantly higher than with most other NITs. Moreover, SSM@100Hz accuracy was significantly higher than SSM@50Hz for large EV (grade ≥ 2). Then, the combination of Baveno VI criteria and SSM@100Hz for the diagnosis of HRV allowed to almost triple the spared EGD rate, without missing more than 5% of HRV, compared to Baveno VI criteria alone. Finally, SSM@100Hz was more closely correlated to HVPG than SSM@50Hz.

Several studies identified SSM@50Hz as a good surrogate marker of PH [9,10] and a good non-invasive test for EV presence and grading.[9,29,30] In addition, for the evaluation of PH and EV grading, a better diagnostic accuracy for SSM compared to LSM has been demonstrated. This was attributed to the inability of LSM in evaluating the extrahepatic component of PH that is present for high degree of PH (HVPG> 10 mm Hg)[7]

In almost all the available studies done so far, SSM was performed with the same device used for LSM.[29] As the spleen is significantly stiffer than the liver, the use of the standard VCTE liver dedicated device (SSM@50Hz) leads to SSM overestimation.[13] Moreover, most patients with severe PH reached upper detection limit for tissue stiffness of VCTE by FibroScan®, which is set at 75 kPa, thus potentially limiting its accuracy [5,9,13] To overcome this limitation, one monocentric study[31] of patients with HCV-related liver disease, using VCTE with an algorithm for SSM, was performed by simply expanding the range of stiffness values up to 150 kPa and reported a good accuracy for large EV. Recently, a spleen adapted version of VCTE (SSM@100Hz) was developed and subsequently tested in a pivotal study,[13] finding a greater accuracy for EV presence than SSM@50Hz. Indeed, in addition to the wider range stiffness values (from 5 to 100 kPa), the use of a higher shear wave frequency (100 Hz) and adapted measurement depths (25 to 55 mm) reduced the sources of overestimation by SSM@50Hz[13]

In the present multicentric European study using the SSM@100Hz, the good diagnostic accuracy for EV presence was confirmed.

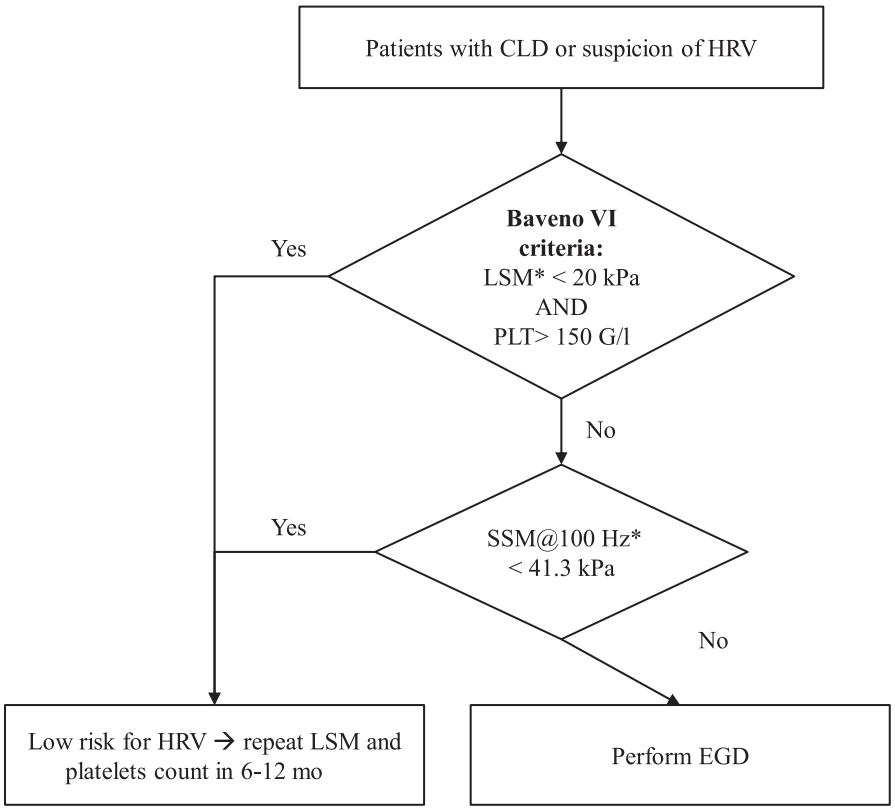

FIGURE 3 New algorithm combining Baveno VI and SSM@100Hz for ruling out patients at risk of HRV (* by VCTE). CLD, chronic liver disease; EGD, oesophagogastroduodenoscopy; HRV: high-bleeding risk oesophageal varices; LSM, liver stiffness measurement; PLT, platelet count; SSM@100Hz, new spleen stiffness measurement with transient elastography

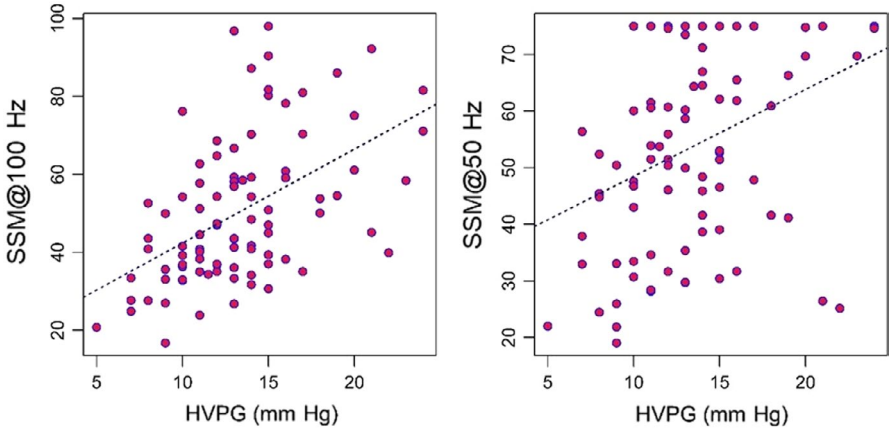

FIGURE 4 Correlation between HVPG and SSM@100Hz (r_s: 0.532) or SSM@50Hz (r_s: 0.363, P = .008). HVPG, hepatic venous pressure gradient; SSM@100Hz, new spleen stiffness measurement with transient elastography; SSM@50Hz, standard spleen stiffness measurement with transient elastography

Furthermore, regarding EV grading, we found SSM@50Hz values in agreement with those previously reported [11,32] but without significant differences between EV grades. SSM@100Hz showed a greater accuracy for EV grading than SSM@50Hz and thus, it had a significant higher diagnostic accuracy for large EV presence (grade ≥ 2) than SSM@50Hz. Moreover, our results confirm previous studies [9,31,33] that highlighted the greater diagnostic accuracy of SSM when compared to LSM, PSR, APRI test and LSPS, especially for large EV or HRV presence.

In the past, several authors tried to assess the performance of NITs for HRV with good results [30,34,35]; in particular, a recent meta-analysis stated the superiority of SSM@50Hz compared to LSM for HRV presence.[11] Our findings are in contrast with a previous report[36] which found a greater diagnostic accuracy of LSPS than SSM@50Hz for HRV presence. The difference with the present study could be explained by the use of SSM@100Hz[13]

The Baveno VI consensus conference[6] proposed new criteria for ruling-out the presence of HRV by the combination of LSM by VCTE and platelet count and, since then, several papers [27,35,37-42] provided validation of those Baveno VI criteria. The limitation of the Baveno VI criteria[6] is the low rate of spared EGDs (15%-25%).[37,38] To date, one recent meta-analysis,[43] merging 15 studies, documented that Baveno VI criteria for ruling out HRV were satisfied in 10%-40% of patients and the rate of missed HRV among HRV varied from 0% to 9% with a pooled estimate rate at 4.0%. Another review, merging 13 studies, reported

9.6% of HRV prevalence, 2.1% of missed HRV rate (recalculated in ref. [24]) and 20.6% of spared EGD.[44] Different calculations were used for missed HRV rate in the different studies. In our opinion, the missed HRV rate should be obtained using the number of patients with HRV as denominator because it corresponds to the test sensitivity which is the standard in test construction.[45] In the present study, the spared EGD rate by the Baveno VI criteria (8.1%) were into the range of reported studies[43,44] with a 0% missed HRV rate. The low rate of spared EGD in our population may be because of more severe CLD which resulted in a higher prevalence of large EV (20.8%) and HRV (26.5%). In our study, CLD, instead of cACLD as recommended by Baveno VI,[6] was an inclusion criterion since the study protocol was finalized in 2011 (before 2015 Baveno VI workshop). However, cACLD (defined by LSM ≥ 10 kPa) was observed in 92.4% of our patients. This is also the reason why large EV, instead of HRV, was initially an outcome in the study protocol.

Moreover, since SSM@100Hz was the most accurate NIT for HRV presence, we tried to combine it with the Baveno VI criteria, in order to spare more unneeded EGDs. Using SSM@100Hz, with a cut-off ≤ 41.3 kPa, in addition to Baveno VI criteria, the spared EGD rate was significantly increased to 38.9%, while the missed HRV rate was < 5% in accordance with the Baveno VI recommendation. A similar rate of spared EGD was reached using SSM@100Hz alone in all patients, thus the use of the sequential algorithm Baveno VI + SSM@100Hz proposed (Figure 3) could be debated; however, we support the sequential algorithm as it is clinically simpler. Thus, SSM@100Hz use is restricted to patients at high-risk according to Baveno VI criteria.

A possible explanation for SSM@100Hz greater performance in ruling out HRV when compared to Baveno VI criteria alone, which includes LSM, could be because of the fact that LSM is known to have a lower correlation with high degree of PH, if compared to SSM.[7,9] Indeed, the correlation between LSM and PH is lost when HVPG> 10 mm Hg.[7] On the other hand, the HVPG correlation was good with SSM@50Hz, as previously demonstrated,[9] and significantly higher with SSM@100Hz in the present study. Thus, SSM, especially SSM@100Hz, can better reflect PH severity or its complications than LSM[9] and, consequently, than Baveno VI criteria. In addition, according to our results, we confirmed the high accuracy of SSM@100Hz for detecting CSPH. Furthermore, SSM@100Hz overcomes the potential technical limitations of SSM@50Hz. In addition, the failure rate of SSM@100Hz (7.5%) was lower than the rates of SSM@50Hz (24.0%) and literature.[1,5] Thus, the higher success rate of SSM@100Hz improve its spared EGD rate compared to SSM@50Hz also when we performed an intention to diagnose analysis (P < .05), as reported in Data S2. This good success rate could be attributable to the new dedicated VCTE examination for the spleen; indeed, the use of a 100 Hz frequency appeared to be a good compromise between a sufficiently low shear wave length and a good tissue penetration tissue.[13] The only factors associated with SSM@100Hz failure were a smaller spleen longitudinal diameter and a higher BMI, the same as those reported[9,12] for SSM@50Hz.

The main limitation of the present exploratory study is the lack of a validation population. However, prospective studies in the field of non-invasive diagnosis of HRV are very rare; this characteristic, as well as the limitations because of the innovation of this device, precluded other methodological aspects such as validation population. Another limitation is the high rate of missing EGD (24.3%) data. Patients were enrolled at VCTE examination and scheduled for an EGD in the next 6 months; however, several patients did not show up or refused to undergo the EGD after the enrolment, especially when they already had done one in the past 6-12 months. Furthermore, HCV infection was prevalent in our population since the study protocol was designed in a pre-DAA era and HCV was the most prevalent cause of CLD in Italy and Romania.[46] Moreover, we excluded NAFLD and obese patients since we aimed to perform this pivotal study in best standardized conditions. Indeed, a validation in population with NASH will need a separate study given the specific cut-offs of elastography in NAFLD. Furthermore, a high failure rate of LSM was expected with M probe in these patients and XL probe was not considered in this study.

On the other hand, this study has several strengths. Firstly, to our knowledge, this is the first fully prospective study devoted on Baveno VI criteria since previous studies had retrospective recruitment and/or design. Secondly, this was a multicentre study of tertiary centres including a large number of patients. Thirdly, one can argue that patients were not selected as cACLD but as CLD. This difference provided the advantage of a prevalence of HRV sufficiently high (26.5%). Indeed, eight out 13 previous studies had a HRV prevalence < 10% and the mean HRV prevalence was 9.6%.[44] This precluded to evaluate performance of Baveno VI criteria in adequate methodological conditions. Therefore, the HRV prevalence should be > 10%.[24] Moreover, as patient selection according to severity of the underlying liver disease is concerned, we applied our Baveno VI and SSM@100Hz model considering two groups defined by the median MELD score in the subpopulation D (Data S1); accordingly, we found in both groups that the combination with SSM@100Hz significantly improved the rate of EGD spared compared to Baveno VI criteria (P < .001). Additionally, when we considered expanded Baveno VI criteria to spare more EGD, we observed a too high rate of missed HRV (12.6%). This precluded a combination to SSM@100Hz.

In conclusion, the new SSM@100Hz has a greater accuracy for the HRV presence than other NITs. A sequential algorithm to rule out HRV, starting with Baveno VI criteria and followed optionally by SSM@100Hz, allowed to spare more EGD compared to Baveno VI criteria alone or combined with standard SSM@50Hz, while keeping missed HRV rate < 5%.

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CONFLICT OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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