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ORIGINAL ARTICLE

High reproducibility of spleen stiffness measurement by vibration-controlled transient elastography with a spleen-dedicated module

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Abstract

Spleen stiffness measurement (SSM) by vibration-controlled transient elastography (VCTE) is a noninvasive technique for estimating portal hypertension in patients with chronic liver disease (CLD), with its reproducibility yet to be established and its feasibility still unknown beyond CLD. We have studied 420 participants from two tertiary referral centers for liver diseases (Novara, Milan): 297 patients with CLD (32% with cirrhosis) of different etiology (Group A), 63 Philadelphia-negative myeloproliferative neoplasms (Group B), and 60 heathy volunteers (Group C). All underwent SSM by VCTE with a spleen-dedicated module (SSM@100 Hz) and liver stiffness measurement (LSM), blindly performed by 2 different operators. In total, 1680 VCTE examinations for SSM were performed (1000 in Novara, 680 in Milan), with an overall 3.2% failure rate. Median SSM was 26.5 kPa (interquartile range [IQR] 20.0–42.3) in Group A, 26.3 kPa (IQR 22.3–33.6) in Group B, and 16.1 kPa (IQR 14.6–18.7) in Group C. In Group A, the median LSM was 6.8 kPa (IQR 4.9–11.3) in Novara and 8.3 kPa (IQR 7.1–10.8) in Milan, the proportion of patients with cirrhosis being 34% in Novara and 31% in Milan. The Group A interobserver agreement ICC was 0.90 (0.88–0.92), significantly lower in the absence of splenomegaly (ICC 0.87 vs. 0.91) and in absence of cirrhosis (ICC 0.84 vs. 0.90); overweight slightly, but not significantly reduced the interobserveragreement. The intra-observer agreement ICC ranged from 0.91 to 0.96 for the four operators. The Group B interobserver agreement ICC was 0.90 (0.83–0.94). In conclusion, SSM measured by the new spleen-dedicated VCTE module is a feasible, reliable, and highly reproducible tool in patients with CLD and hematological disorders, and in healthy volunteers.

INTRODUCTION

Vibration-controlled transient elastography (VCTE) is a widely used method to measure in vivo the stiffness of soft tissues, expressed in kiloPascal (kPa).[1] It has been used primarily in patients with chronic liver disease (CLD) to estimate noninvasively the extent of hepatic fibrosis and damage severity.[1] Liver stiffness measurement (LSM) has been proven to be a valuable clinical tool with high reproducibility.[2]

Spleen stiffness measurement (SSM) has been more recently introduced. SSM advocates the claim that this technique may complement LSM to provide noninvasive estimates of the presence and severity of portal hypertension, as well as of the risk of portal hypertension–associated complications.[3-7] A recent study by Wang et al. outlined the high degree of certainty with which SSM can exclude the presence of esophageal varices in patients with hepatitis B virus (HBV)–related cirrhosis,[8] whereas according to Marasco et al., SSM appears to predict hepatocellular carcinoma recurrence after resection.[9] Furthermore, according to the recent European Association Study of the Liver 2021 update of the Clinical Practice Guidelines on noninvasive tests for evaluation of liver disease severity and prognosis,[10] SSM can be used as an additional tool to refine the prediction of high-risk varices in compensated advanced CLD. Indeed, according to a panel of experts convened in the Baveno VII Consensus Conference,[10] two SSM cutoff values (<21 kPa and >50 kPa) may respectively be applied for the rule-out and rule-in of clinically significant portal hypertension in compensated advanced chronic liver disease due to viral hepatitis. The usefulness of SSM may not be limited to CLD, as SSM has shown to correlate with bone marrow fibrosis in patients with myeloproliferative neoplasms (MPNs) for whom the SSM value may represent a predictor of disease severity.[2,11-13]

Unfortunately, until now, most reports on SSM assessment by VCTE have been conducted with a FibroScan appliance not equipped with a spleen-dedicated module. This is arguably a problem, because the spleen is stiffer than the liver and the use of the VCTE liver examination module on the spleen possibly leads to SSM overestimation.[14,15] To overcome these limitations, a VCTE spleen-dedicated module (SSM@100 Hz) has recently been developed and shown to have higher accuracy than the liver-dedicated module (LSM@50 Hz).[15] However, the cutoff values to be applied using the spleen-dedicated module (SSM@100 Hz) need validating by *ad hoc* prospective studies,[16] which are still unavailable to the best of our knowledge.

The present study aimed at evaluating the reproducibility and applicability of SSM assessed by VCTE equipped with a spleen-dedicated module (SSM@100 Hz).

METHODS

This is a prospective multicenter study conducted at the tertiary referral centers for liver diseases at two Italian university hospitals: Internal Medicine Department, Azienda Ospedaliero-Universitaria Maggiore della Carità (Novara; Center 1) and Gastroenterology Department, Fondazione IRCCS Ca′ Granda Ospedale Maggiore Policlinico (Milan; Center 2). Overall, 297 patients with CLD of different etiology (187 in Novara, between September and October 2020, and 110 in Milan, between April and May 2021) were consecutively enrolled to undergo VCTE examination for SSM and LSM assessment.

The exclusion criteria were pregnancy, age < 18 years, presence of ascites, previous splenectomy, and lack of signed informed consent to the study.

In addition, 63 patients with Philadelphia-negative (Ph-) MPNs followed at the Hematology Department (Center 1) were included in the study.

For the purposes of the study, a control population was enrolled: 60 heathy volunteers (HV) with no previous history of liver or hematological disease and with alcohol intake within recommended limits were recruited at the Gastroenterology Department (Center 2).

For every included patient, the following data were collected: demographic and clinical data, including blood tests, previous liver histology if available, last abdominal ultrasound, and upper gastrointestinal endoscopy findings.

The study protocol was approved by the Ethics Committees, and all of the participants provided written consent before enrollment.

Cirrhosis was defined according to previous liver histology (when available), imaging (ultrasound or computed tomography or magnetic resonance imaging) compatible with cirrhosis, and clinical or laboratory data.[17] Splenomegaly was defined as spleen longitudinal diameter longer than 12.5 cm.

Vibration-controlled transient elastography

VCTE examinations for LSM and SSM were performed by means of the FibroScan 630 Expert machine (Echosens), equipped with liver (LSM@50 Hz) and spleen (SSM@100 Hz)–dedicated modules coupled with an ultrasound localization system for the spleen. Results were expressed in kPa. LSM and SSM were considered reliable only if at least 10 successful measurements were obtained; the success rate was at least 60%, and the interquartile range–to-median ratio (IQR/median) was ≤0.3. Failure of the examination was defined as absence of any valid measurement.[18]

LSM and SSM were performed by placing the patient in a supine position with the right and left arm,

respectively, in maximum abduction and by placing the transducer in the right and left intercostal spaces, respectively. For SSM, the tip of the probe transducer was placed in a previously ultrasound-targeted point in which the spleen parenchyma had been previously identified. VCTE examinations were performed by 2 experienced operators in Novara (C.R. and M.G.C.) and 2 in Milan (M.F. and A.S.). Each patient, who had been fasting for at least 3 hours, underwent four SSM assessments (2 by each of the investigators who were blinded to each other's results). LSM was assessed once by one of the operators in each center. All of the operators had undergone an earlier training period in which they had individually performed at least 300 VCTE examinations. The analysis of SSM reproducibility (in terms of both interobserver and intra-observer agreement) was based on the results of the four SSM assessments (two per operator). Subsequently, only the first SSM determination (whichever operator performed the examination) was used to assess the influence of different patient-related covariates on interobserver agreement and to build the Bland–Altman plot.

Statistical analysis

The continuous variables were presented as median and IQR. Intra-observer and interobserver agreement was analyzed using the intraclass correlation coefficient (ICC).[19] As SSM results are a continuous response variable, interrater and intrarater agreement between two or more raters was adequately measured by ICC. Using analysis of variance, ICC measures the SSM variability rates attributable to the patients. ICC values range from +1 (100% agreement; all of the variability being due to patient characteristics) to 21 (100% disagreement; all of the variability being due to the raters' performance). An ICC equal to 1 means that all SSM variability relates to patient variability (patient effect) and that there is no variability related to the raters (rater effect). As ICC decreases, the rater effect begins to prevail over patient effect. Interrater agreement was calculated as the agreement between the 2 investigators on their respective first SSM. Intrarater agreement was calculated as the agreement between the first and the second SSM evaluations. Agreement was classified as poor (ICC = 0.00 to 0.40), fair (ICC = 0.40 to 0.60), good (ICC = 0.60 to 0.80), or excellent (ICC > 0.80).[19,20] The effect on interobserver agreement of the body mass index (BMI, kg/m^2), splenomegaly, and severity of liver disease expressed as cirrhosis were also weight-assessed. For descriptive purposes, the Bland–Altman plot[21] was also prepared for reporting the means of the ratings of the two raters versus the differences of ratings for each patient. This plot allows the graphical inspection of interobserver agreement according to the echo time values; thus, it was used as a graphical tool to evaluate trends of disagreement across mean values of echo time.

To measure the diagnostic accuracy of SSM in the presence of esophageal varices (of any size), the area under the receiver operating characteristic curve (AUROC) was assessed. The diagnostic estimates were given as sensitivity, specificity, and corresponding positive and negative likelihood ratio (LR+ and LR−).

RESULTS

Patients

CLD (Group A)

A total of 297 patients with CLD were included (187 in Novara and 110 in Milan). The main demographic, clinical, laboratory, and elastographic characteristics are summarized in Table 1, which reports overall and grouped-by-center data.

In the patients with CLD from Novara, there were 119 females (64%); the patients' median age was 63 years (IQR 53–71). CLD etiology was related to different causes: 21% viral hepatitis, 5% alcohol, 6% metabolic, 56% autoimmune/cholestatic, 5% after liver transplant, and 7% other. Splenomegaly was present in 49 cases (26%), and 64 patients (34%) had cirrhosis.

In the patients with CLD from Milan there were 43 females (39%), and the patients' median age was 54 years. CLD etiology was related to different causes: 15% viral hepatitis, 21% iron overload, 18% metabolic, 9% autoimmune/cholestatic, 7% after liver transplant, 10% alcohol, and 20% other. Splenomegaly was present in 43 cases (39%), and 34 patients (31%) had cirrhosis.

With regard to treatment in the overall CLD group, 23 of the 26 patients with hepatitis C virus had obtained sustained virological response, and all of the 29 patients with HBV were on viral suppression with antiviral treatment. All of the 114 patients with autoimmune or cholestatic disease were on immunosuppressive treatment or standard treatment with ursodeoxycholic acid and/or obeticholic acid. The 23 patients with primary iron overload were all on an iron-depleting maintenance regimen. All of the patients with metabolic disease were on a low-calorie diet, and 40% of them performed regular physical exercise toward weight loss, 21% of them reaching a weight loss of at least 20% of the basal weight. Patients with diabetes were

TABLE 1 Clinical features of 297 patients with CLD (Group A). Continuous variables are presented as median (interquartile range); dichotomous variables are presented as numbers (%)

Features	Patients with CLD overall (n = 297)	Patients with CLD Novara (n = 187)	Patients with CLD Milan (n = 110)
Female gender, n	162 (54)	119 (64%)	43 (39%)
Age, years	57 [49.1–59.9]	63 [53–71]	54 [37–64]
BMI, kg/m^2	25 [25.0–28.3]	25.3 [22.7–28.7]	24.1 [22.2–27.4]
Etiology of CLD			
HBV	29 (11%)	16 (9%)	13 (9%)
HCV	26 (9%)	23 (12%)	3 (6%)
NAFLD	31 (10%)	11 (6%)	20 (18%)
Alcohol	20 (6%)	9 (5%)	11 (10%)
AIH	66 (22%)	59 (32%)	7 (6%)
PBC	48 (16%)	45 (24%)	3 (3%)
Liver transplant	18 (6%)	10 (5%)	8 (7%)
Genetic hemochromatosis	23 (8%)	0 (0%)	23 (21%)
Other	36 (12%)	14 (7%)	22 (20%)
Cirrhosis, n	98 (33%)	64 (34%)	34 (31%)
Splenomegaly, n	93 (31%)	49 (26%)	44 (40%)
Spleen longitudinal diameter, cm	11.6 [11.6–14]	11.5 [10.1–13.9]	11.8 [10–14.3]
Endoscopic signs of portal hypertension, n	47 (16%)	28 (15%)	19 (17%)
HCC, n	9 (3%)	2 (1%)	7 (6%)
VCTE examination			
LSM, kPa	7.3 [4.9–12.9]	6.8 [4.9–11.3]	8.3 [7.1–10.8]
SSM, kPa	26.5 [20.0–42.3]	24.9 [20.6–36.1]	29.1 [16.7–34.5]
Blood tests			
AST, UI/L	29 [29–45]	25 [19–36]	37 [37–54]
ALT, UI/L	29 [29–43]	23 [18–32]	37 [37–47]
GGT, UI/L	32 [32–67]	30 [16–78]	34 [34–66]
ALP, UI/L	117 [117–190]	147 [93–201]	94 [76–94]
Total bilirubin, mg/dl	0.8 [0.8–1.1]	0.7 [0.5–1.1]	0.8 [0.8–1.1]
Albumin, g/dl	4.2 [4.2–4.5]	4.3 [4–4.6]	4.0 [4.0–4.73]
INR	1.01 [1.01–1.12]	1.0 [0.98–1.12]	1.0 [1.0–1.1]
Platelets, ×10^9/L	194 [134–194]	206 [147–241]	171 [171–221]

Abbreviations: AIH, autoimmune hepatitis; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; GGT, gamma-glutamyltransferase; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; INR, international normalized ratio; LSM, liver stiffness measurement; NAFLD, nonalcoholic fatty liver disease; PBC, primary biliary cirrhosis; SSM, spleen stiffness measurement; VCTE, vibration-controlled transient elastography.

on antidiabetic treatment (85%) and/or on low-glycemic diet (15%). All patients with esophageal varices were under prophylactic nonselective beta-blockers according to the Baveno VI guidelines.[22]

Philadelphia-negative MPNs (Group B)

Among the 63 patients with Ph- MPNs (9 polycythemia vera, 32 essential thrombocythemia, and 22 myelofibrosis), 47% were females, and the median age was 72 years (IQR 58–80); 44% of the patients showed splenomegaly. The main clinical features are summarized in Table 2.

Healthy volunteers (Group C)

Sixty healthy volunteers (median age 40 years, IQR 27–60.5) underwent VCTE for SSM and LSM. None of the healthy volunteers showed abnormal spleen size (Table 2).

VCTE

A total number of 1680 VCTE examinations for SSM were performed (1000 in Novara, 680 in Milan) with an overall 3.2% failure rate (3.5% in Novara, 2.8% in Milan). The examination failure was mostly (9 of 11

cases in CLD and 2 of 2 cases in patients with MPNs) due to obesity (BMI > 30 kg/m^2).

CLD (Group A)

For the patients with CLD from Novara, the median LSM and SSM were 6.8 kPa (IQR 4.9–11.3) and 24.9 kPa (20.6–36.1), respectively; for the patients with CLD from Milan, the median LSM and SSM were 8.3 kPa (IQR 7.1–10.8) and 29.2 (IQR 16.7–34.5), respectively.

In the whole Group A, the median LSM was 7.3 kPa (IQR 4.9–12.9), median SSM was 26.5 kPa (IQR 20.0–42.3), and the failure rate for SSM was 4.2%. SSM was significantly correlated with LSM (r = 0.67), spleen longitudinal diameter (r = 0.58), presence of cirrhosis (r = 0.54), and BMI (r = 0.24) ($p < 0.0001$ for all comparisons).

TABLE 2 Clinical features of 63 patients with Philadelphia-negative myeloproliferative neoplasms (Ph- MPNs; Group B) and 60 heathy volunteers (HV; Group C). Continuous variables are presented as median [interquartile range]; dichotomous variables are presented as numbers (%)

Features	Ph- MPN (n = 63)	HV (n = 60)
Age, years	72 [58–80]	40 [27–60]
Female gender, n	30 (47%)	45 (75%)
BMI, kg/m^2	28.4 [23.3–30.3]	21.6 [20–23.2]
Spleen longitudinal diameter, cm	15.6 [12.5–18.5]	9.8 [9–10.8]
Splenomegaly, n	28 (44%)	0 (0%)
VCTE		
LSM, kPa	5.7 [4.5–7.2]	4.3 [3.3–5.5]
SSM, kPa	26.3 [22.3–33.6]	16.1 [14.6–18.7]
Blood tests		
Platelets, ×10^9/L	331 [221–456]	–
White blood cells, ×10^9/L	6.5 [4.8–9.2]	–

PH- MPNs (Group B)

Among the patients with Ph- MPNs, the median LSM was 5.7 kPa (IQR 4.5–7.2) and median SSM was 26.3 kPa (IQR 22.3–33.6). SSM significantly correlated with LSM (r = 0.38, p = 0.002) and spleen longitudinal diameter (r = 0.39, p = 0.04), but not with BMI and age. Failure rate for SSM examination was 3.1%.

HVs (Group C)

In the 60 HVs, the median SSM was 16.1 kPa (IQR 14.6–18.7) and LSM was 4.3 kPa (IQR 3.3–5.5). Failure rate was 1.6%.

Reproducibility of SSM

Table 3 summarizes the characteristics of VCTE for each operator of the two centers, including the quality criteria of examination (IQR/SSM and success rate). The median time for every VCTE examination for SSM was 50 s (IQR 35–80).

The overall interobserver agreement ICC was 0.90 (95% confidence interval [CI] 0.87–0.92) in Novara and 0.91 (95% CI 0.87–0.94) in Milan. The Bland–Altman plot (Figure 1) showed no systematic overestimation or underestimation between the two raters (mean difference 0.5), without any trend of difference across

TABLE 3 Characteristics of VCTE examinations for SSM stratified for operators and examination. Continuous variables are presented as median [interquartile range]; dichotomous variables are presented as numbers (%)

	Operator 1 examination 1	Operator 1 examination 2	Operator 2 examination 1	Operator 2 examination 2
Novara				
SSM, kPa	24.2 [19.1–38.2]	25.0 [18.8–35.3]	23.9 [19.8–35.9]	23.8 [19.2–33.6]
IQR/SSM, %	17 [11–24]	15 [11–21]	16 [11–23]	17 [11–22]
Success rate, %	87 [73–100]	90 [76–100]	90 [77–100]	92 [79–100]
Examination time, s	60 [40–120]	45 [35–77]	60 [40–100]	40 [30–60]
Failure, n	8 (3.2%)	11 (4.4%)	9 (3.6%)	8 (3.2%)
Milan				
SSM, kPa	29.2 [21.4–45.2]	30.7 [20.1–47.3]	30.7 [20–47.3]	31.4 21.2–47.8[]
IQR/SSM, %	16 [13–21]	14 [10–21]	17 [11–24]	18 [10–22]
Success rate, %	81 [50–100]	89 [61–100]	87 [75–100]	91 [77–100]
Examination time, s	57 [42–110]	56 [35–78]	58 [40–100]	61 [43–70]
Failure, n	6 (3.5%)	4 (2.3%)	5 (2.9%)	3 (1.8%)

Abbreviation: IQR, interquartile range.

the mean ratings. Only 12 patients scored outside the agreement limits. The intra-observer agreement ICCs of the Novara operators were 0.93 (95% CI 0.91–0.95) for one and 0.96 (95% CI 0.95–0.97) for the other. The intra-observer agreement ICCs of the Milan operators were 0.91 (95% CI 0.87–0.93) for one and 0.94 (95% CI 0.91–0.96) for the other.

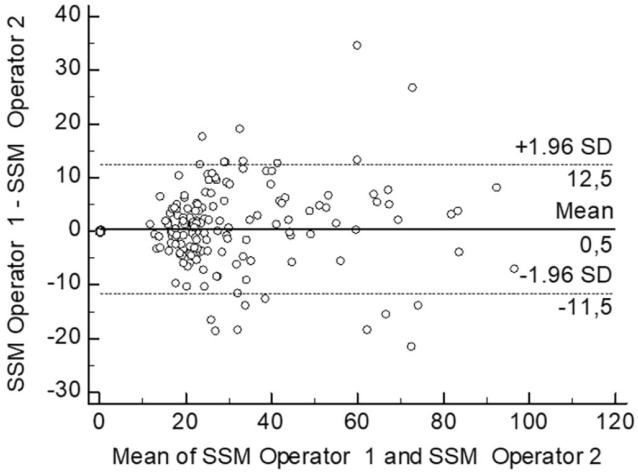

FIGURE 1 Bland-Altmann plot. The solid line represents the mean of the difference of ratings by the two operators. The dotted lines define the limits of agreement, mean of the difference (2 SD)

Group A

In the patients with CLD, the overall interobserver agreement ICC was 0.90 (0.88–0.92). Figure 2 shows the interobserver and intra-observer variability in the patients with CLD from Novara and Milan. As indicated in Table 4, the factors significantly associated with reduced interobserver agreement were absence of splenomegaly (ICC 0.91 in presence of splenomegaly vs. 0.87 in absence of splenomegaly) and absence of cirrhosis (ICC 0.90 in presence of cirrhosis vs. 0.84 in absence of cirrhosis). Overweight slightly, but not significantly, reduced interobserver agreement (ICC 0.91 in presence of BMI ≤ 24.9 kg/m^2 vs. 0.88 in patients with BMI > 24.9 kg/m^2).

We found no statistically significant differences in interobserver agreement based on the presence or absence of signs of portal hypertension and on CLD etiology. In particular, ICC was 0.96 in the presence of portal hypertension versus 0.93 in the absence of portal hypertension.

As to interobserver agreement, the ICC values according to the different etiologies are summarized in Table S1.

Group B

In the patients with MPNs, interobserver agreement ICC was 0.90 (0.83–0.94). As shown in Table 4,

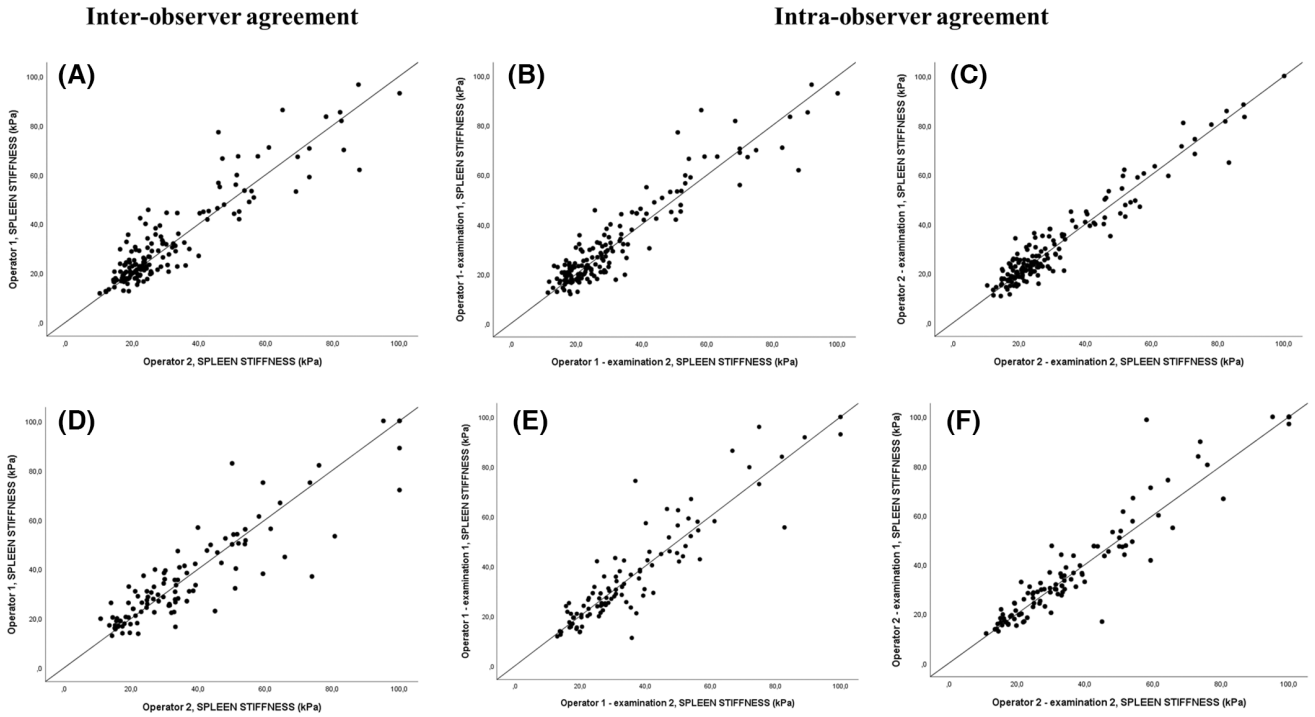

FIGURE 2 Interobserver agreement (A,D) and intra-observer agreement (B,C,E,F) on spleen stiffness measurement in patients with chronic liver disease (CLD). (A–C) Patients with CLD from Novara. (D–F) Patients with CLD from Milan

TABLE 4 Influence of different patient-related covariates on interobserver agreement calculated by intraclass correlation coefficient (ICC) in patients with CLD (Group A) and in patients with Ph- MNPs (Group B)

	CLD overall ICC (95% CI)	CLD Novara ICC (95% CI)	CLD Milan ICC (95% CI)	MPN ICC (95% CI)
Absence of splenomegaly	0.81 (0.75–0.85)	0.82 (0.76–0.87)	0.74 (0.59–0.84)	0.67 (0.40–0.82)
Presence of splenomegaly	0.91 (0.87–0.94)	0.91 (0.94–0.98)	0.94 (0.85–0.97)	0.92 (0.84–0.96)
BMI ≤ 24.9 kg/m^2	0.92 (0.89–0.95)	0.91 (0.88–0.90)	0.90 (0.83–0.96)	0.88 (0.77–0.94)
BMI > 24.9 kg/m^2	0.88 (0.85–0.92)	0.87 (0.82–0.91)	0.79 (0.79–0.85)	0.77 (0.56–0.89)
Absence of cirrhosis	0.84 (0.79–0.88)	0.77 (0.70–0.82)	0.83 (0.67–0.89)	—
Presence of cirrhosis	0.90 (0.91–0.96)	0.92 (0.86–0.95)	0.94 (0.90–0.97)	—

Abbreviation: CI, confidence interval.

interobserver agreement was significantly reduced by the absence of splenomegaly (ICC 0.92 in presence of splenomegaly vs. 0.67 in absence of cirrhosis). Overweight reduced moderately, but not significantly, interobserver agreement (ICC 0.88 in presence of BMI ≤ 24.9 kg/m^2 vs. 0.77 in patients with BMI > 24.9 kg/m^2).

SSM diagnostic performance in diagnosing esophageal varices in patients with cirrhosis

With regard to the presence of esophageal varices, we performed a subgroup analysis among the 98 patients with cirrhosis (48% prevalence of esophageal varices). For the diagnosis of esophageal varices (any size), the operative characteristics of SSM@100 Hz were AUROC = 0.76 (95% CI 0.65–0.87); the cutoff value ≥ 40 kPa showed 85% sensitivity, 54% specificity, with a corresponding LR- of 0.29 (95% CI 0.13–0.61) and LR+ of 1.81 (95% CI 1.23–2.67).

DISCUSSION

This study assesses in real practice the applicability and reproducibility of spleen stiffness measurement in patients with CLD or in patients with hematologic disease by means of the new FibroScan 630 Expert appliance equipped with a spleen-dedicated module (SSM@100 Hz). The study, which was conducted in two CLD referral centers, showed that SSM is feasible with a negligible failure rate and is highly reproducible with excellent interobserver and intra-observer agreement.

In the last decade, SSM by VCTE has emerged as a promising noninvasive tool with good diagnostic accuracy for predicting clinically significant portal hypertension and identifying high-risk varices in patients with advanced CLD.[3,4,16,23,24] Because chronic portal hypertension causes spleen congestion, hyperplasia, angiogenesis, fibrogenesis, enlargement, and hyperactivation of the lymphoid tissue,[25] SSM is well-suited to predict the presence and degree of portal hypertension and esophageal varices.[26,27] In addition, hyperdynamic circulation, splanchnic vasodilation, and portosystemic shunting as seen in clinically severe portal hypertension are not directly or indirectly quantified by liver elastography,[28] and LSM alone has limited accuracy in the detection or risk stratification of gastroesophageal varices.[29] SSM in adjunct to LSM can better stratify the severity of portal hypertension, and it has also been proposed as a tool for predicting hepatic decompensation and mortality in patients with cirrhosis.[4,30]

However, all of the studies that have so far assessed SSM have been conducted with a standard FibroScan appliance with no spleen-dedicated module, which is now available and has higher accuracy than the liver-dedicated module.[14,15] In such studies, SSM assessment (with the liver-dedicated module) was affected by a high failure rate of the examinations, ranging from 10% to 20%.[2-4,23,30,31] In addition, because the spleen is stiffer than the liver, VCTE examination dedicated to the liver on the spleen leads to SSM overestimation.[14] In fact, as shown by Calvaruso et al., the median value of spleen stiffness in 112 patients with cirrhosis was 117 kPa (range 81.7–149.5 kPa) when measured using a liver-dedicated module with a modified ceiling value of 150 kPa (instead of 75 kPa).[31]

In our study, the overall failure rate of SSM examination by VCTE with the spleen-dedicated module (SSM@100 Hz) was in all operators about 3%–4%, which is significantly lower than what previously reported with the liver-dedicated module (LSM@50 Hz)[2-4,23,30,31] and even lower than 7.5% as reported by the pilot study firstly using the new spleen-dedicated module.[15] This finding, equally reproduced in the two centers in Novara and Milan, was confirmed in patients with CLD, in patients with MPNs, and heathy volunteers, emphasizing the high applicability of SSM assessment by VCTE also in patients without CLD and in those with normal spleen size. This result is relevant, as SSM has been found to have a role also in hematological diseases, such as in predicting bone marrow fibrosis in patients with MPNs.[11-13]

Spleen stiffness assessment by VCTE with a spleen-dedicated module was highly reproducible in terms of both interobserver and intra-observer agreement. This is really an interesting and valuable finding, as no data have so far been available regarding the reproducibility of this technique. One should also consider that these results were accomplished in two different liver centers from two large cohorts of consecutive patients in a real-world setting. In the whole cohort of patients with CLD, the ICC for interobserver agreement was 0.90, which is an excellent value of reproducibility, and ICC for intra-observer agreement ranged from 0.91 to 0.96. Similar results were obtained in patients with MPNs with excellent interobserver agreement (ICC = 0.90). Furthermore, our study provides information on covariates that may affect the reproducibility of the examination in patients with CLD and MPNs. In patients with CLD, the reproducibility was negatively influenced by overweight, absence of cirrhosis and absence of splenomegaly, whereas in patients with MPNs reproducibility was negatively affected by overweight and absence of splenomegaly. In overweight patients, the ICC for interobserver agreement was slightly, but not significantly, reduced to 0.88 in CLD and moderately to 0.77 in patients with MPNs. This finding is not unexpected considering that overweight is a factor usually associated with more difficult examination due to deeper spleen parenchyma. Absence of splenomegaly was responsible for all cases of examination failure and significantly decreased reproducibility in both patients with CLD and MPNs. However, even in the presence of a normal spleen size, it is still feasible to measure SSM, as shown in healthy volunteers (1.6% failure rate). According to these findings, physicians should be aware that in the absence of splenomegaly, SSM reproducibility is fairly reduced and SSM readings should be more cautiously interpreted and may be confirmed in a further examination in patients with a normal spleen size. Another factor that had a significant effect on SSM reproducibility in patients with CLD was the absence of cirrhosis. Generally, excluding patients with porto-sinusoidal vascular disorders (2% in our study population) in which portal hypertension (and related splenomegaly) is not associated with cirrhosis, we can presume that in our patients with CLD, the absence of cirrhosis also means absence of splenomegaly. In actuality, in patients with CLD, SSM was highly significantly correlated with LSM.

In addition to its high reproducibility, the technique was easy and quick to perform (median time for examination = 50 s), confirming that the new spleen-dedicated module equipped with ultrasound probe for spleen localization improves the technique applicability.

The present study assesses SSM in healthy volunteers by means of VCTE with the new spleen-dedicated module. In Group C, the median SSM was 16.1 kPa (IQR = 14.6–18.7), slightly lower than the value previously reported for 52 healthy volunteers measured with the LSM@50 Hz liver-dedicated module (median = 25.7 kPa)[2] and expected because of the likely SSM overestimation caused by the liver probe.[14,16] The median age of the Group C subjects was slightly lower than that of the patients in Groups A and B. However, age was not related to SSM in a previous[2] as well as in the present study. Regarding spleen stiffness in healthy volunteers, some data are available, as obtained from different elastography techniques. In particular, using point shear-wave elastography, in a group of 100 healthy volunteers, the mean SSM was 18.14 (±3.08) kPa (17.73 [±2.91] kPa for males [n = 49] and 16.72 [±3.32] kPa for females [n = 51]).[32]

The robustness of our study stands on the large sample size of consecutive patients evaluated in two different tertiary liver centers, representative of an unselected CLD population, in which the proportion of patients with cirrhosis was about 30% and a broad etiological spectrum was represented. In addition, the inclusion of patients without CLD allowed us to broadly assess SSM applicability also in different settings. SSM mostly reflects a pathological process that involves the spleen parenchyma: Spleen damage can be caused not only by congestion of the spleen related to portal hypertension,[3-5,24] but also to the spleen involvement in different pathological conditions.

CONCLUSIONS

In conclusion, SSM by VCTE with the new spleen-dedicated module is a rapid, feasible, and user-friendly exam that has proven to be highly reproducible in two independent cohorts with excellent interobserver and intra-observer agreement. Interestingly, SSM reproducibility was not significantly influenced by overweight or obesity, making this technique largely applicable in patients with advanced CLD, in order to identify those with clinically significant and severe portal hypertension. Moreover, the present study provides proof that spleen stiffness can be reliably assessed in different clinical contexts, both in CLD and in other extrahepatic settings such as in hematologic diseases.

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CONFLICT OF INTEREST

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SUPPORTING INFORMATION

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

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