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Assessing spleen stiffness by point shear-wave elastography: Is it feasible and reproducible in patients with chronic liver disease? Is it useful to predict portal hypertension?

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Summary

Background and aims: To assess the feasibility and reproducibility of the spleen stiffness (SS) measurement by point shear-wave elastography (pSWE) in a cohort of compensated chronic liver disease (CLD) patients *[Cohort 1]* and to investigate pSWE accuracy to predict clinically relevant portal hypertension (PH) in a consecutive cohort of cirrhotics with endoscopic signs of portal hypertension *[Cohort 2]*.

Methods: *[Cohort 1]:* 186 consecutive CLD patients underwent abdominal ultrasound (US), liver stiffness (LS) and SS measurement by pSWE and transient elastography (TE) and liver biopsy. Inter-rater agreement of SS (pSWE) was evaluated by intra-class correlation coefficient (ICC). *[Cohort 2]:* 80 cirrhotics underwent US, LS and SS (by pSWE and TE), hepatic venous pressure gradient (HVPG) measurement and upper endoscopy. Linear correlations between LS or SS and HVPG and linear regression analysis were performed to establish determinants of HVPG > 16.

Results: *[Cohort 1]* SS measurement failure was 3.4% for pSWE and 13.8% for TE. For pSWE the ICC between two independent examiners was 0.74 (95% CI, 0.66-0.80). *[Cohort 2]:* SS measurement failure was 2.5% for pSWE and 48% for TE.

HVPG and LS did not correlate. Significant correlation was observed between HVPG and SS (r = 0.36, P = .001). At multivariate analysis only the presence of ascites and SS values significantly correlated with HVPG > 16, a threshold of high mortality risk cirrhosis.

Conclusions: Measuring SS by pSWE is feasible and reproducible in CLD and is applicable in most cirrhosis cases as a promising tool of prognosis and a surrogate marker of the HVPG threshold related to survival- and liver-related outcomes.

1 | INTRODUCTION

The evaluation of liver fibrosis and the diagnosis of cirrhosis are routinely performed by measuring liver stiffness (LS) using transient elastography (TE). TE has almost completely replaced liver biopsy in patients with chronic liver diseases (CLDs), especially those with a viral aetiology.[1,2] Besides TE, other elastographic techniques are currently available, such as acoustic radiation force impulse imaging (ARFI), which includes point shear-wave elastography (pSWE) and 2D-SWE imaging,[3-6] all with software integrated in the ultrasound (US) machine. The reference standard for assessing portal hypertension (PH) remains the measurement of the hepatic venous pressure gradient (HVPG). Data from the literature indicates that the diagnostic accuracy of LS measurement to indirectly evaluate the PH degree is not optimal,[7] probably as the dynamic progression of PH is independent from the severity of liver fibrosis and extra-hepatic haemodynamic changes, such as hyper-dynamic circulation, which occurs over the HVPG threshold of 10 mmHg, can account for this.[8,9] Thus, the spleen stiffness (SS) measurement is potentially an alternative test to assess the presence and severity of PH[10-16] in a non-invasive way. TE is currently the most commonly used technique to assess SS,[14,17,18] but measuring SS by ARFI methods and pSWE too has been evaluated for predicting the presence and degree of PH,[18-20] and has given promising data, whereas the role of these techniques in detecting any presence of OVs is still sub-optimal.[21-23]

We performed a prospective single-centre cohort study in order to investigate the feasibility and reproducibility of the SS measurement by using pSWE in a cohort of consecutive patients with CLDs of different aetiology who underwent liver biopsy. As a further step we investigated the accuracy of SS to predict the presence of clinically relevant PH values, correlated with a high risk of death in a second cohort of cirrhotic patients with endoscopic signs of portal hypertension.

2 | PATIENTS

2.1 | Cohort 1

From September 2015 onwards all the patients undergoing liver biopsy for diagnosis or during therapy at the "AM & A. Migliavacca" Center for Liver Disease of IRCCS Ospedale Maggiore Policlinico, Milan, were consecutively enrolled. The local Ethics Committee approved the study protocol and the informed consent by all the study participants was obtained. These were the inclusion criteria: serum ALT levels to be 1.5 times over the upper normal limit, either persistently or intermittently, against the presence of HBV/HCV serum markers; serum ALT levels to be 1.5 times over the upper normal limit, either persistently or intermittently, against the suspicion of alcoholic hepatitis, NASH or autoimmune/cholestatic disease. Any patients who presented with decompensated liver disease, human immunodeficiency virus co-infection and/or hepatocellular carcinoma were excluded.

2.2 | Cohort 2

In a 24-month period between September 2015 and May 2017 a second cohort of patients with endoscopic signs of portal hypertension, who underwent HVPG measurement for diagnostic and/or prognostic purposes at the same aforementioned, were consecutively enrolled. The local Ethics Committee approved the study protocol and the informed consent of all the study participants was obtained. The inclusion criteria were: patients with clinically significant PH, and those who already had clinical or endoscopic signs of portal hypertension and were tested for the haemodynamic response to the chronic treatment with nonselective beta-blockers. The study excluded those patients with any clinical conditions contra-indicating the HVPG measurement and patients with portal vein thrombosis.

3 | METHODS

Data collection: the data from both cohorts were recorded anonymised in case report forms. Blood test analysis was routinely performed on the subjects as outpatients or inpatients, and their clinical data were recorded. Recorded parameters from B-mode US were collected.

3.1 | Cohort 1

All the patients underwent abdominal US and SS measurements both with TE and shear-wave elastography immediately before liver biopsy guided by US. An experienced hepatologist performed the biopsy on the same day: a 16-G Menghini needle (Biomol; Hospital Service) was used under US guidance. The liver tissue was fixed in formalin and embedded in paraffin and 5-μm thick sections of liver tissue were stained with H&E and Masson tri-chrome, to be then examined by an expert liver pathologist, blind to the clinical data. Only those samples longer than 15 mm and including at least 12 complete portal tracts, were considered adequate. Liver fibrosis and necro-inflammatory activity were semi-quantitatively evaluated by the METAVIR scoring system.[24] A 4-point scale was applied to grade any necro-inflammatory activity (A) and any steatosis in liver specimens was arbitrarily graded from 0 to 3.

3.1.1 | Abdominal ultrasound

US abdominal scanning by standard equipment (iU22; Philips) was carried out on patients while fasting. The portal vein diameter (cm), portal flow velocity (cm/s) and spleen diameter (cm) were collected for every patient. The spleen was scanned along the longitudinal and transverse planes with an intercostal approach, a subcostal approach or both. The patient was kept in a supine or right-sided position up to the full completion of the organ visualisation. The longitudinal diameter was taken as the maximum measurement with splenic borders and angles clearly visible. The degree of steatosis on US scans was calculated referring to the decrease in the echo amplitude (eg the degree

of posterior beam attenuation caused by the high reflectivity of the fatty tissue), which shows attenuation in the posterior segments of the liver (grade 1), a loss of echoes from the diaphragm (grade 2) or a loss of echoes from the walls of the portal vein (grade 3).[25]

3.1.2 | Point shear-wave elastography

ElastPQ-pSWE (iU22; Philips) was performed by two examiners (MF and CBC), both with >3 years long experience in TE measurement and no previous experience in point shear-wave elastography measurements. Both examiners were blind to clinical, serological and histological data.

LS and SS were measured with iU22 US equipment (Philips Healthcare) using a convex probe and the ElastPQ technique, which applies a radiation force through a focused US beam to generate shear waves inside the tissue. The transducer was the C5-1 one (device iU22; Philips) with the *Abdominal Gen* preset and the general optimisation for B-mode, and the general setting for ElastPQ.

Liver stiffness was measured in the right lobe of the liver through intercostal spaces, the subject being kept supine with the right arm in maximal abduction. By real-time B-mode image the rater selected a vessel-free area, at least 1.5 cm below Glisson's capsule. There a fixed region of interest (ROI) sized 0.5 cm × 1.5 cm was outlined by moving a trackball. The maximum penetration of point shear-wave elastography was 7 cm deep and the ROI size was depth dependent: 0.5 cm × 1.5 cm at the depth of 4 cm. The patients were asked to hold their breath in an indifferent position while the rater pressed a button to launch the data acquisition. Only the examinations with at least 10 valid measurements expressed in kPa were considered reliable. The mean and median values of the successful measurements were considered representative of the SS only if the inter-quartile range (IQR) of all the valid measurements was less than 30% of the median values.

The US system monitors the shear-wave propagation by a Doppler-like US technique and measures the shear-wave velocity, displaying it in metres per second (m/sec) or in kPa through Young's modulus. $E = 3(vS^2 \times \rho)$, where E is the Young modulus, vS is the shear-wave speed and ρ is the density of the tissue in homogeneous isotropic tissues. If the amount of nonshear-wave motion exceeds the system threshold, no measurement is displayed. The measurements of spleen stiffness (Figure 1) were performed in the splenic parenchyma (always performed below 1.5 cm to the spleen capsule), through the intercostal space, the patient being kept supine with the left arm in maximal abduction. The US B-mode image allowed the rater to select an area without large vessels and the examiner to pick up a fixed region of interest (ROI), sized 0.5 × 1.5 cm, below the spleen capsule. The maximum penetration of the point shear-wave elastography was 7 cm deep. The patients held their breath in an indifferent position, while the operator pressed a button to acquire the measurement. Only those examinations with at least 10 valid measurements expressed in kPa were considered reliable. The mean and median value of the successful measurements were considered representative of the SS only if the inter-quartile range (IQR) of all valid measurements resulted less than 30% of the median values.

3.1.3 | Transient elastography

An independent investigator (MG), with >3 years long experience in TE measurement, performed spleen TE to assess SS, blind to clinical, serological and histological data. Spleen TE was performed in fasting conditions prior to liver biopsy. The measurements were acquired with the patient lying in the prone decubitus position and with the left arm in maximal abduction for the spleen. The probe was positioned on the spleen region, with access through the intercostal space. The ratio between the number of valid measurements and the total number of

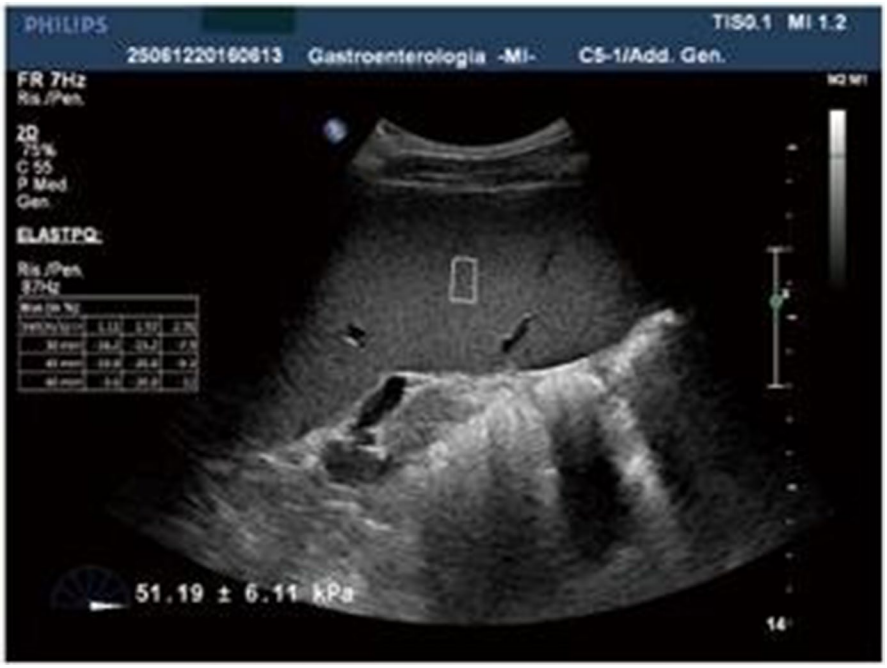

FIGURE 1 Example of spleen stiffness determination by point shear-wave elastography

measurements was calculated by the machine and the results were expressed in kPa as the median value of all the measurements. Only the examinations with at least 10 valid measurements and a success rate of 60% or higher, were considered reliable. In addition, the median value of successful measurements was considered representative of SS in any given patient only if the IQR of all validated measurements was less than 30% of the median values.[26-28]

3.1.4 | Clinical and laboratory data

The following clinical and laboratory data were collected and recorded for every patient: sex (male/female), age (in years), body mass index (BMI), alanine aminotransferase (ALT, UI/L), aspartate aminotransferase (AST, UI/L), gamma-glutamyl transferase (GGT, UI/L). Commercially available enzyme immunoassays were used to determine: serum hepatitis B surface antigen, antibodies to hepatitis B core antigen, anti-HCV antibodies, serum HCV RNA as detected by nested reverse transcription (RT)-PCR using primers to the 59 noncoding region. The minimum detectable level was 20 IU/mL.

3.2 | Cohort 2

All the enrolled patients underwent abdominal US and SS measurements (pSWE and TE) and HVPG was measured on the same day or in a few cases 3 days after.

3.2.1 | Abdominal ultrasound

US abdominal scanning was performed by standard equipment (iU22; Philips) on patients while fasting. The portal vein diameter (cm), portal flow velocity (cm/s) and spleen diameter (cm) were collected for every patient. The methods were the same applied in the examination of the first cohort.

3.2.2 | Point shear-wave elastography

For the SS measurement ElastPQ-pSWE was performed by a single examiner, with >3-year experience in elastographic techniques and blind to clinical, serologic and histological data. The method and the US equipment were the same as for the examination of the first cohort of patients.

3.2.3 | Transient elastography

A single rater performed spleen TE to assess SS, blind to clinical, serological and histological data, according to the same method as that already described with regard to Cohort 1 examination.

3.2.4 | Clinical and laboratory data

The following clinical and laboratory data were collected and recorded for every patient: sex (male/female), age (in years), body mass index (BMI), cirrhosis aetiology, OVs presence (yes/no), oesophageal severity (small vs large varices, eg F1 vs F2-F3), previous bleeding episode (yes/no) and platelet count (mmc).

3.2.5 | HVPG measurement

A venous introducer was placed in the right internal jugular vein under local anaesthesia. A balloon catheter was guided under fluoroscopy into the main right hepatic vein to obtain the wedged hepatic venous pressure (WHVP) and free hepatic venous pressure (FHVP) measurements. The portal pressure gradient (HPVG) was calculated as the difference between WHVP and FHVP. All the measurements were performed in triplicate, and permanent tracings were read by an experienced investigator, blind to the clinical conditions of patients. The mean arterial pressure (MAP; mmHg) was measured by automatic sphygmomanometer every 5 minutes. The patient's heart rate was checked by continuous electrocardiogram monitoring.

4 | STATISTICAL ANALYSIS

The categorical data were reported as counts (percentages) and the continuous variables as means and standard deviations or medians (ranges), as appropriate. The study was carried out and reported according to STARD (Standards for Reporting Studies of Diagnostic Accuracy).

4.1 | Cohort 1

The inter-rater agreement on the pSWE measurements was assessed by intra-class correlation coefficient (ICC), with its 95% confidence interval (CI). Agreement was considered as “poor” (ICC = 0.00-0.19), “fair” (ICC = 0.20-0.39), “moderate” (ICC = 0.40-0.75) or “excellent” (ICC > 0.75).[29] The effect on the agreement of the following factors was also assessed (by calculating ICC for sub-groups of patients): study period (first year vs second year), sex, age (≤45 vs ≥45 years), body mass index, BMI (≤25 vs ≥25 kg/m^2), ALT (≤40 vs >40), GGT (≤50 vs >50) and alkaline phosphatase levels (≤110 vs >110) and aetiology (HCV vs other aetiology).

4.2 | Cohort 2

Univariate and multivariate logistic regression analyses were performed to establish any factors associated with the risk of having a HVPG measurement >16 mmHg, which is a threshold of high mortality risk cirrhosis.[30-34] Age (<55 vs >55), BMI, ascites (yes/no), cirrhosis aetiology (alcoholic or alcoholic + virus vs other), previous bleeding episode (yes/no), pSWE SS measurements, liver steatosis detected at US (yes/no), PTL count (<150 vs >150), spleen diameter (cm), portal flow velocity (cm/sec; <18 vs >18) and Giannini's score (<909 vs >909) were considered as potential predictors of HVPG measurements higher than >16. The variables that resulted statistically significant at univariate analysis were considered for multivariate analysis. The c statistic was used to assess the performance of

the logistic models.[35] We chose the best cut-off value for SS measurement, in identifying HVPG > 16, according to the maximum value of positive likelihood ratio. Sensitivity, specificity, positive (LR+) and negative (LR−) likelihood ratios were reported with their 95% confidence intervals (CIP values ≤ 0.05 two sided were considered statistically significant). All the study statistics was performed by SAS software (release 9.4; SAS Institute Inc).

5 | RESULTS

5.1 | Cohort 1

5.1.1 | Patient demographics

One hundred and eighty-six CLD patients were consecutively enrolled, of whom 105 (56%) presented chronic hepatitis C, whereas the remaining ones (44%) had chronic viral hepatitis B, autoimmune/cholestatic liver disease or metabolic (NAFLD-NASH) liver disease. The main demographic, clinical and laboratory characteristics of the patients are provided in Table 1.

5.1.2 | SS measurement: feasibility and reproducibility

In five patients, the measurement of SS was not possible because of earlier splenectomy performed for trauma.

5.1.3 | Point shear-wave elastography

In 175 of 186 patients (94%), we achieved the valid measurement of SS by pSWE. Six failures (ie no valid measurement obtained) occurred. The SS median values and range were 15.3 kPa (4.5-53.3).

TABLE 1 Main clinical and demographic characteristics of the 186 consecutive patients who concomitantly underwent liver and spleen ElastPQ®-pSWE, liver and spleen transient elastography and liver biopsy

Patients characteristics	Mean ± SD, median (range)
Males, number (%)	116 (62)
Age, y	52.7 ± 13.3
BMI (kg/m^2)	25.2 ± 4.1
ALT (IU/L, n.v. <38)	53 (30-52)
GGT (IU/L, n.v. <50)	86 (39-179)
Alkaline phosphatase (IU/L, n.v. 40-129)	117 (77-179)
Platelet count (10^3/L)	213 (134-256)
Portal vein diameter (cm)	1.1 (0.90-1.22)
Portal vein velocity (cm/s)	1.9 (16.8-22.4)
Spleen diameter (cm)	11.8 (10-13.5)

Abbreviations: ALT, alanine aminotransferase; BMI, body mass index; GGT, gamma-glutamyl transferase; mean ± SD, median (range); n.v., normal values.

The inter-observer agreement on SS measurement was found very good with an ICC of 0.74 (95% CI, 0.66-0.80). The learning curve for the assessment of SS by pSWE was calculated, dividing the study period in two parts (first year and second year). Interestingly, among the clinical and temporal variables considered and summarised in Table 2, the period of study resulted the only determinant of ICC: the inter-observer agreement was good with an ICC of 0.70 (95% CI, 0.58-0.77) in the first year, whereas it was found good-to-excellent with an ICC of 0.87 (95% CI, 0.79-0.92) in the second year of the study.

5.1.4 | Transient elastography

In 159 of 186 patients (85%), we achieved the valid measurement of SS by TE. Twenty-two failures occurred. The SS median values and range for TE were 33.8 kPa (6.6-75).

5.2 | Cohort 2

5.2.1 | Patients' demographics

Eighty patients presenting with liver cirrhosis were consecutively enrolled, the disease aetiology being: viral (HCV or HBV) in 37 patients (46.25%), alcoholic in 18 patients (22.5%), both viral and alcoholic in 9 patients (11.25%) and metabolic (NAFLD-NASH) in 16 patients (20%). Table 3 provides the main demographic, clinical and laboratory characteristics of the patients.

5.3 | Spleen stiffness measurement feasibility

5.3.1 | SS by pSWE

In 78 of 80 patients, we achieved valid SS measurement by point shear-wave elastography. Two failures (2.5%) occurred. The SS median values and range in kPa for pSWE were 30.6 (4.56-55.1).

TABLE 2 ElastPQ®-pSWE intra-observer agreement on the assessment of SS: intra-class correlation coefficient (ICC) with 95% confidence intervals (CI) according to different temporal and clinical variables

Variables	ICC (95% CI)
First year of study	0.70 (0.58-0.77)
Second year of study	0.87 (0.79-0.92)
Sex	
Male	0.76 (0.66-0.83)
Female	0.70 (0.56-0.81)
Age: ≤45	0.72 (0.49-0.86)
BMI: <25	0.71 (0.58-0.80)
ALT: <40	0.72 (0.62-0.80)
GGT: >50	0.73 (0.63-0.80
Alkaline phosphatase: <110	0.69 (0.58-0.79
>110	0.80 (0.71-0.87)
Overall	0.74 (0.66-0.80)

TABLE 3 Main clinical and demographic characteristics of the 80 consecutive patients who concomitantly underwent spleen stiffness measurement by ElastPQ®-pSWE, transient elastography and hepatic venous pressure gradient (HVPG)

Patients characteristics at time of shear-wave elastography and HVPG measurement	
Males, n (%)	47 (59)
Age, no. of years, mean ± SD	59 ± 13
Body mass index (kg/m^2), mean ± SD	25.6 ± 3.8
Ascites at US, n (%)	26 (33)
OV F0-F1, n (%)	36 (45)
OV F2-F3, n (%)	44 (55)
HVPG ≥ 16, n (%)	46 (57.5)
Previous bleeding episode, n (%)	16 (20)
Liver steatosis at US, n (%)	23 (28.7)
Platelet count (10^3/L), median (range)	89 (68-121)
Portal vein diameter (cm), median (range)	1.2 (1.0-1.3)
Portal vein velocity (cm/s), median (range)	17 (14-21)
Spleen diameter (cm), median (range)	14.3 (13-16)

5.3.2 | SS by TE

In 54 of 80 patients, we achieved the valid measurement of splenic stiffness by TE. Twenty-six (32.5%) failures occurred. The SS median values and IQR for TE in kPa were 72 (21-75).

5.4 | HVPG results (the reference standard)

The correlation of HVPG with platelet count, spleen diameter and US Doppler parameters is provided with the corresponding p value in Table 4. Among these variables, the platelet count (R = −0.21) and the hepatic artery RI (R = 0.23) significantly correlated with HVPG. We looked at the correlation between HVPG and SS in the cohort of 80 cirrhotic patients to find a significant correlation (r = 0.36, *P* = .001) (see Figure 2).

TABLE 4 Correlation between hepatic venous pressure gradient value and clinical data

Variables	r	*P*
PLT	−.21	.05
Portal flow velocity (cm/sec)	−.19	.08
RI of hepatic artery	.23	.05
RI of splenic artery	.08	.45
Spleen diameter	.08	.45
RI of renal artery	.18	.1

Abbreviations: PTL, platelets; RI, resistive index.

By contrast, the correlation between LS and HVPG did not show any statistical significance (r = 0.10, *P* = .10), thus confirming previous data that indicated scarce correlation in patients with HVPG > 10 mmHg.[9]

5.5 | Main determinants of the HVPG value

Given the significant correlation between HVPG (as a continuous variable) and SS, we investigated the main determinants of HVPG > 16 mmHg. The correlation between HVPG > 16 mmHg and clinical, imaging and laboratory variables, is reported in Table 5.

At univariate analysis the determinants of HVPG > 16 mmHg were: age > 55 years (*P* = .04), the presence of ascites at US examination (*P* = .04) and SS value obtained by SWE (*P* < .001). At multivariate analysis the variables that remained independently associated with HVPG > 16 mmHg were: SS by SWE (*P* < .001), and the presence of ascites at US examination (*P* = .01).

A pSWE cut-off of 38.8 kPa showed the following diagnostic accuracy to predict a HVPG > 16 mmHg: sensitivity at 47.8%

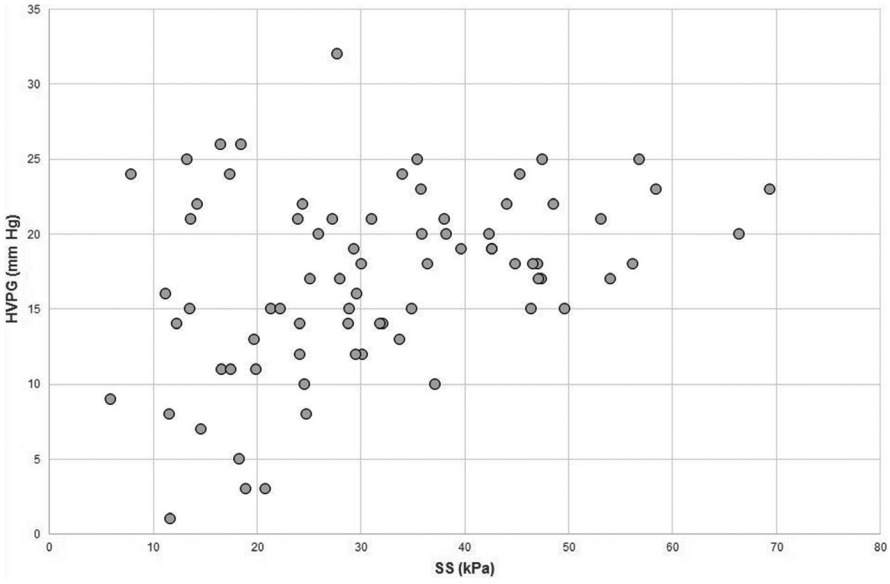

FIGURE 2 Correlation between the hepatic venous pressure gradient (HVPG) value and spleen stiffness (SS) in 80 consecutive patients who concomitantly underwent SS measurement by ElastPQ®-pSWE and HVPG

TABLE 5 Results of both univariate and multivariate analysis: main determinants of hepatic venous pressure gradient >16

Variables	Univariate analysis *P*	Multivariate analysis *P*
Aetiology (alcohol vs others)	n.s.	—
Ascites (yes/no)	.04	.01
Previous bleeding (yes/no)	n.s.	—
Age (≤55 vs >55)	.04	n.s.
BMI (≤ 25 vs >25 kg/m^2)	n.s.	—
Spleen diameter	n.s.	—
Liver steatosis at US (yes/no)	n.s.	—
Portal flow velocity (>18 vs <18 cm/s)	n.s.	—
PLT count (≤150 vs >150)	n.s.	—
Giannini's score (≤909 vs >909)	n.s.	
SS by SWE (kPa)	<.001	<.001

Abbreviations: BMI, body mass index; n.s., not significant; SS, spleen stiffness; SWE, shear-wave elastography.

(33.0%-63.2%), specificity at 93.3% (77.9%-99.2%), LR + 7.2 (1.8-28.3) and LR − 0.55 (0.41-0.74), PPV at 91.6% (73.0-98.9%) and NPV 53.8 (39.4-67.7%).

6 | DISCUSSION

In the first part of this study, we have assessed the values of SS for a cohort of consecutive CLD patients of different aetiology undergoing liver biopsy. The inter-observer reproducibility of SWE in the assessment of SS resulted as good-to-excellent with an overall ICC of 0.74. In the analysis of the determinants of the ICC value, the temporal variable, that is, the period of the study, was the only variable associated with ICC: in the first period of the study we had good reproducibility for SS, with ICC of 0.70, but we obtained a better result in the second period, with ICC of 0.87, after 100 examinations performed. This data suggests that ARFI techniques, such as pSWE, come with a learning curve to achieve reliable results. An interesting finding is also the higher feasibility of pSWE in assessing SS as compared to TE (96% vs 89%) making the former reliable in the majority of cirrhotic patients. The higher applicability of pSWE vs TE in assessing SS was expected. In fact, the opportunity of directly visualising the ROI within the splenic parenchyma sensibly reduces the rate of failures or indeterminate results especially in patients with a small spleen size.

In the second part of the study, given the good feasibility and reproducibility of the SS measurement by pSWE, we have studied the SS potential role in predicting PH and prognosis. In fact, some recent studies[21] have reported encouraging results, even better than those reported for LS,[7] regarding the SS ability to predict PH and its clinical complications. To date, little data are available regarding the measurement of SS and PH, using HVPG as the reference standard.[36]

In the cohort of 80 cirrhotic patients for whom HVPG was measured, the majority of patients had decompensated disease, with HVPG > 16 mmHg in 58% of cases and 67.5% of them had ascites. The feasibility of SWE in assessing SS in this cohort was very good, with only two failures. At variance, the feasibility of SS measurement by TE in the same cohort was low, with 26 failures. This result was not surprising, as the presence of ascites is an obstacle in obtaining reliable LS and SS values. Ultimately, the possibility to place the ROI in the splenic parenchyma under direct visualisation provides pSWE with a further advantage over TE, in patients with ascites, making the assessment of SS by pSWE feasible in the majority of decompensated patients.

An interesting point highlighted by our results concerns the important difference in kPa observed for the median SS values measured by pSWE and by TE (33 kPa vs 72 kPa, respectively). A major limitation of TE results from a ceiling effect of the measurement (maximum: 75 kPa), which does not affect pSWE. However, the SS values obtained by pSWE tend to be generally lower than those obtained by TE. The reason of this finding is still unknown, but is probably related to intrinsic characteristics of the two devices and/or the modality of acquiring stiffness measurements.

As the second step of our cirrhotic cohort analysis we looked at the determinants of the HVPG value. The clinical variables and most of the echo-Doppler data that we considered for the analysis, apart from the platelet count and the hepatic artery RI (which had a weak association), did not show any significant correlation with HVPG. Only SS (pSWE) had statistically a significant correlation with HVPG. Based on this finding, we studied the value of SS in predicting the dynamic component of PH, by dividing the population in two groups and using the HVPG cut-off value of 16 mmHg, which is the threshold for increased risk of mortality in cirrhotic patients.[37-39] In our cohort 57.5% of patients had a HVPG > 16 mmHg. At univariate analysis the main determinants of HVPG > 16 mmHg were: age > 55 years (P = .04), ascites at US examination (P = .04) and, importantly, SS value obtained by SWE (P < .001). However, at multivariate analysis the variables independently associated with HVPG > 16 were: SS (pSWE) (P < .001) and the presence of ascites at US examination (P = .01). These findings lead to several observations. Firstly, the fact that the SS value is the main factor associated with determinants of the HVPG value clinically related to a negative prognosis in cirrhotics, opens to the possibility of using SS as a surrogate marker not only of the HVPG measurement but also as a predictor of clinically relevant outcomes, such as the risk of mortality in cirrhotic patients. A SS value higher than 38.0 kPa was highly specific for HVPG > 16 mmHg with only a few false positive results (two cases), thus allowing to stratify patients with worse prognosis because of their higher risk of negative clinical outcomes. On the other hand, as expected for this subset of patients already presenting with endoscopic signs of portal hypertension, the sensitivity of the technique was quite low.

Moreover, the availability and safety of SWE support its wide use as a repeatable test to follow the course of a patient's liver disease and to detect at an early stage, firstly, the onset of PH and, then, the risks of clinical decompensation and death.

In conclusion, SS measurement is a very promising tool for the clinical work-up and follow-up of cirrhotic patients. Interestingly, SS measurement by SWE predicts the presence of PH and the risk of clinical decompensation. It is a useful tool to stratify patients according to the different levels of risk concerning disease progression and significantly relevant outcomes.

Given the technical differences that exist among the different elastographic devices, we point out that measurement methodology and results interpretation should be standardised in order to obtain both accurate and reliable results.

AUTHORSHIP STATEMENT

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