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ORIGINAL ARTICLE

A Simple and Reliable 2D-Shear Wave Elastography and UltraSound Coefficient Attenuation Parameter Technique in Chronic Liver Diseases

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Abstract

Background The performance and reliability criteria for Aixplorer MACH30 (SS) in chronic liver diseases (CLD) have not been validated.

Aims The objectives were to define the optimal procedure, the accuracy for fibrosis and steatosis diagnosis, and the reliability criteria using SS.

Methods Patients had 2D-shear wave elastography (SWE) and ultraSound-guided controlled attenuation parameter (SCAP) performed in triplicate at the mid-axillary line (MAL), posterior axillary line (PAL), and anterior axillary line (AAL). Performances of SWE and SCAP were defined using transient elastography (TE ≥ 9.5 kPa) and CAP (≥ 275 dB/m) using Fibroscan (FS) as reference and validated with liver biopsy (LB).

Results FS and SS data from 203 CLD patients were analyzed (55 ± 14 years; 59% male; MASLD 58%). Median TE and CAP were 6.4 kPa (2.5–66.9) and 270 dB/m (141–400). The best technique for the diagnosis of advanced fibrosis and significant steatosis was the median of three SWE values and three SCAP values at MAL, PAL, and AAL with an AUROC of 0.96 [95% CI 0.93–0.98] and 0.91 [95% CI 0.86–0.95]. Only skin-to-liver distance ≥ 2.4 cm ($p = 0.012$, 95% CI 1.37–13.38) was independently associated with discordance. The accuracy of SWE (≥ 8.5 kPa) and SCAP (≥ 0.44) was analyzed in 58 patients with LB. The PPV and NPV were 50% and 94%, and 71% and 88% for fibrosis and steatosis, respectively.

Conclusion A reliable diagnosis of advanced fibrosis and significant steatosis can be obtained with the median of three measurements in different liver portions using SS. The only non-reliable criterion is skin-to-liver distance ≥ 2.4 cm.

Keywords Fibrosis · Steatosis · Transient elastography · Shear wave elastography · Attenuation · Non-invasive tests

Abbreviations

FS	FibroScan®
TE	Transient elastography
CAP	Coefficient attenuation parameter
LSM	Liver stiffness measurement
SS	SuperSonic Aixplorer MACH 30®
SWE	2D-shear wave elastography
SCAP	UltraSound-guided CAP

Introduction

Chronic liver diseases represent a significant health problem worldwide. Viral hepatitis and alcohol abuse were the main etiologies associated with chronic liver disease. Nowadays, metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common liver disease, being present also in patients with history of alcohol intake, past chronic hepatitis C, and treated chronic hepatitis B patients [1]. Regardless of the etiology, liver fibrosis is one of the main prognostic factors in patients with chronic liver disease [2]. The presence of advanced fibrosis is associated with liver-related complications, such as clinical decompensation and the development of hepatocellular carcinoma [3]. Therefore, it is crucial to correctly assess the liver fibrosis stage during follow-up, knowing that it can be a real challenge in patients presenting diseases where the fibrosis distribution is highly heterogeneous [4, 5], as seen in patients with MASLD.

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Traditionally, liver biopsy is considered the "gold standard" method for the evaluation of liver disease etiology and the assessment of liver fibrosis stage and steatosis grade. However, it is an invasive procedure with risk of complications, possible sampling errors in heterogeneous diseases, and relative high costs [6–8]. Moreover, liver disease progression with worsening of fibrosis and/or steatosis is difficult to evaluate prospectively as multiple liver biopsies are generally not well accepted by patients. Consequently, non-invasive methods have been developed to simplify the follow-up of patients with chronic liver disease [9].

Different non-invasive methods are now widely used for the first line assessment of liver fibrosis and steatosis [9, 10]. Transient elastography (TE) and controlled attenuation parameter (CAP) measured by FibroScan (EchoSens, Paris, France) were the first and most validated techniques developed for the diagnosis of fibrosis and steatosis, respectively [11, 12]. A reliable TE exam is performed by an experienced operator (> 100 examinations) following a standardized protocol with the patient, fasting for at least 2 h [13], in the supine position, right arm in full abduction, on the mid-axillary line with the probe-tip placed in the 9th to 11th intercostal space with at least 10 validated measurements and an interquartile range (IQR) that reflects variations among liver stiffness measurements (LSM) < 30% of the median value (IQR/LSM ≤ 30%) [13]. As only one point of the liver is analyzed, patients with heterogeneous liver disease could have under- or overestimated fibrosis staging. No direct liver visualization is possible and the evaluation of other segments out of the predefined location is not recommended and increases the rate of misdiagnosis.

Other ultrasound-based techniques have been described [10]. The detection of advanced fibrosis (F3–F4) using 2D-shear wave elastography (SWE) and significant steatosis (S2–S3) using ultraSound-guided CAP (SCAP) measured by Aixplorer MACH 30® (SS, Supersonic Imagine, Aix-en-Provence, France) is simple, safe, and overcomes several limitations of TE and CAP [14]. Published studies have described experienced operators (> 100 examinations) using a real-time B-mode ultrasound image to target a region of interest (ROI) through the intercostal space in the right liver portion, free of large vascular structures, and 15–20 mm depth below the liver capsule. The advantage of this technique is the direct visualization of different liver segments and could allow LSM and SCAP in more than one site which could be really useful in patients with heterogeneous liver diseases such as MASLD. Also, patients with liver nodules may have unreliable TE using FibroScan as measurements could be performed in tumor area, and 2D-SWE could overcame this limitation as the operator can directly choose a ROI to assess LSM and SCAP outside the nodule. Despite these advantages, optimal technical procedure and reliability criteria are not homogeneous in the literature, with the minimal number of measurements from 3 to 10 measurements at the same location in the right liver portion, the minimal size of ROI from 10 to 20 mm, and stability index superior to 90% [15–17]. No studies have reported SS examinations with SWE and SCAP measurements at different locations of the right liver portion. The aims of this study were to define the optimal technical procedure measuring different right liver portions, the performance for the detection of fibrosis and steatosis, and the reliability criteria using SS in patients with chronic liver disease independent of etiology.

Patients and Methods

Patient Selection

This cross-sectional study recruited prospectively 215 consecutive patients with chronic liver disease that underwent non-invasive tests (FS and SS) for fibrosis staging between March 2021 and October 2021 at Pitié-Salpêtrière Hospital, Paris, France. All patients gave their informed consent for the collection of anonymous data. Inclusion criteria were age higher than 18 years old and agreement to participate in the study. The exclusion criteria were failure to obtain reliable FS and/or SS.

Assessments

The following data were collected at the time of non-invasive tests: age, gender, etiology of liver disease, ongoing treatment, and body mass index (BMI). Routine laboratory tests (complete blood count, prothrombin time, total bilirubin, aminotransferases levels, gamma-glutamyltransferase, albumin, and lipid profile) and liver biopsy (fibrosis stage and steatosis grade) within 6 months of non-invasive tests were collected when available.

Two non-invasive tests using ultrasound-based techniques were performed in all patients. First, TE and CAP were performed by two experienced operators using FibroScan® 630 Expert with SmartExam. All patients had a minimum of 2-h-long fasting as recommended by manufactures and available clinical practice guidelines [13]. Patients were lying in supine position, with the right arm in abduction. The M probe (3.5 Hz frequency, measurements between 25 and 70 cm) was the initial choice, and the XL probe (2.5 Hz frequency, measurements between 35 and 85 cm) was used in accordance with the machine advice, usually in patients with BMI > 30 kg/m^2. The classical technique of 10 measurements at the mid-axillary line (MAL) was used (Fig. 1). Median TE values, lowest and highest TE values, type of probe, IQR/*M* values, number of valid measurements for TE, CAP, and standard deviation (SD) for CAP were registered.

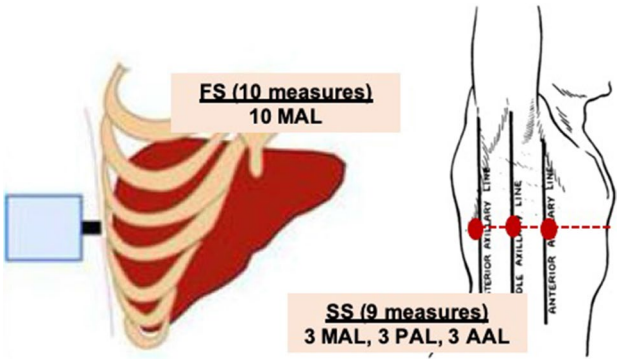

Fig. 1 Measurements of SWE and SCAP, using SS, were performed in triplicate at the mid-axillary line (MAL), posterior axillary line (PAL), and anterior axillary line (AAL) (total of nine values)

FS was considered non-reliable when IQR/$M > 30\%$, as previously described. The following published cut-offs for the diagnosis of advanced fibrosis (F3–F4) and significant steatosis (S2–S3) were used: ≥ 9.5 kPa and ≥ 275 dB/m [9]. Second, liver evaluation using Aixplorer® MACH 30 was performed immediately following FibroScan measurements by the same operator. Measurements of SWE, SCAP, Sound Speed plane-wave ultrasound (SSp), and viscosity plane-wave ultrasound were performed in triplicate at the mid-axillary line (MAL), posterior axillary line (PAL), and anterior axillary line (AAL), avoiding large vessels, bile ducts, and rib shadows (Fig. 1). Skin-to-liver capsule distance (SLD), minimum stability index (SI), and depth of the ROI were also evaluated in each patient.

When available, the performances of SWE and SCAP were also evaluated using liver biopsy (LB) as reference.

Statistical Analysis

The statistical analyses were performed using SPSS, version 29.0 (IBM SPSS Statistics).

Categorical variables were compared using χ^2 test or Fisher's exact test. Continuous variables were analyzed with the Student *t* test or Mann–Whitney *U* test as appropriate. Statistical significance was defined as $p < 0.05$ and all comparisons were two-tailed. Correlation analysis was performed using Spearman's correlation test.

The technique the simplest to perform and most reliable has been analyzed. Areas under receiver operating characteristics curves (AUROC) was determined for different techniques of SWE, SCAP, and SSp, using FS as reference. The optimal cut-off value was identified using the Youden index. Performances of SWE and SCAP for the diagnosis of advanced fibrosis and significant steatosis have been defined using TE (≥ 9.5 kPa) and CAP (≥ 275 dB/m) as reference [9]. Independent factors associated with discordance have been evaluated by logistic regression analysis using stepwise model. A 5% significance level was adopted. Finally, taking liver biopsy as the reference, the positive predictive value (PPV) and the negative predictive value (NPV) for the diagnosis of advanced fibrosis and significant steatosis were evaluated.

Table 1 Baseline characteristics of study population ($n = 203$)

Characteristics	$n = 203$
Age, years (mean ± SD)	55 ± 14.1
Male sex (%)	59
BMI, kg/m^2 (mean ± SD)	28.1 ± 5.9
Liver disease etiology (%)	
MAFLD	58
Viral hepatitis	23
Other	19
ALT, IU/mL (median ± SE)	36 ± 12.9
GGT, IU/mL (median ± SE)	42 ± 15.2
Platelets, cells/mm^3 (mean ± SD)	243 ± 65.8
TE, kPa (median, range)	6.4 (2.5–66.9)
TE ≥ 9.5 kPa (%)	23
Probe *M* (%)	86
CAP, dB/m (median, range)	270 (141–400)
CAP ≥ 275 dB/m (%)	51
SWE, kPa (median, range)	6.3 (3.8–63.3)
SLD, mm (median, range)	1.92 (1.02–4.03)
Depth, mm (median, range)	4.1 (2.90–6.40)
Minimum IS (median ± SD)	90 ± 9.3

Results

Patient Characteristics

Between March 2021 and October 2021, 215 patients with chronic liver disease were evaluated by non-invasive liver tests, of whom 203 patients presented reliable FS and SS evaluations. Twelve patients (5%) were excluded due to FS and/or SS failure: 9 non-reliable FS (IQR/$M < 30\%$), 1 FS not done due to pacemaker, 1 FS and SS failure due to low echogenicity, and 1 SS not done due to cognitive disorders due to patient inability to hold apnea. Mean BMI was significantly higher in patients with IQR/$M > 30\%$ (31.6 ± 5.8 vs. 28.1 ± 5.9 kg/m^2, $p = 0.048$, respectively).

The characteristics of the included patients are described in Table 1. MASLD was the main etiology in 58% and viral hepatitis in 23%. Fifty-eight (29%) patients had a BMI ≥ 30 kg/m^2. Median TE and CAP were 6.4 kPa (2.5–66.9) and 270 dB/m (141–400). All included patients had IQR/$M \leq 30\%$ in accordance with the exclusion criteria.

Performance of SWE for the Diagnosis of Advanced Fibrosis

Forty-seven (23%) patients had advanced fibrosis (TE ≥ 9.5 kPa). Median SWE was 6.3 kPa (3.8–63.3). Taking FS as reference, the median of three SWE values (1st measurement at MAL, PAL, and AAL) had an AUROC of 0.96 [95% CI 0.93–0.98]. An excellent correlation was observed between TE and SWE (Fig. 2). The best cut-off value for the diagnosis of advanced fibrosis using SWE was ≥ 8.5 kPa, which was observed in 47 (23%) patients.

The etiology of liver disease had no impact on accuracy for the diagnosis of advanced fibrosis. The median of three SWE values (1st measurement at MAL, PAL, and AAL) had an AUROC of 0.96 [95% CI 0.93–0.99] in patient with MASLD and 0.98 [95% CI 0.95–1.00] in patients with chronic viral hepatitis.

Discordance between TE and SWE was observed in 18 (9%) patients: 9 patients had an underestimation and 9 patients had an overestimation of fibrosis stage. The factors associated with discordance were skin-to-liver distance (SLD) ≥ 2.4 cm ($p < 0.001$), depth ≥ 5.5 cm ($p < 0.001$), stability index < 70% ($p = 0.009$), and viscosity ≥ 2.4 ($p = 0.026$). In logistic regression, the only factor associated with discordance between the two exams was SLD ($p = 0.012$, 95% CI 1.37–13.38).

Performance of SS for the Diagnosis of Significant Steatosis

The performances of SCAP according to different technique methods are described in Table 2. The median of three SCAP values (1st measurement at MAL, PAL, and AAL) had an AUROC of 0.91 [95% CI 0.86–0.95] for the diagnosis of significant steatosis, which was not significantly different for the other technique methods (Fig. 3). The median of 1st SCAP measurement at MAL, PAL, and AAL was considered the best and simplest technique. The best cut-off for the diagnosis of significant steatosis (≥ S2) using SCAP was ≥ 0.44 dB/cm/MHz, which was observed in 107 (53%) patients.

Table 2 Performances of SCAP for the diagnosis of significant steatosis according to different technique methods, taking CAP measured by FS as reference

SS technique for the diagnosis of steatosis	AUROC	95% CI
SCAP measured 3 times at MAL (SCAPAMM)	0.87	0.82–0.92
SCAP measured 3 times at PAL (SCAPAPM)	0.80	0.74–0.87
SCAP measured 3 times at AAL (SCAPAAM)	0.85	0.80–0.90
SCAP measured 9 times (3 MAL, 3 PAL and 3 AAL) (SCAPMED)	0.90	0.86–0.95
SCAP measured 3 times (1st MAL, 1st PAL, and 1st AAL) (SCAP1MM)	0.91	0.86–0.95

When comparing the two techniques for steatosis evaluation using SS, SCAP correlated better than SSp with CAP values ($r = 0.68$, 95% CI 0.59–0.75, $p < 0.001$ vs. $r = -0.47$, 95% CI − 0.59 to − 0.34, $p < 0.001$, respectively).

Accuracy of Cut-Off Values in Patients with Liver Biopsy

A total of 58 patients with chronic liver disease had liver biopsy performed within 6 months from non-invasive tests. All liver biopsy samples had a length of at least 10 mm

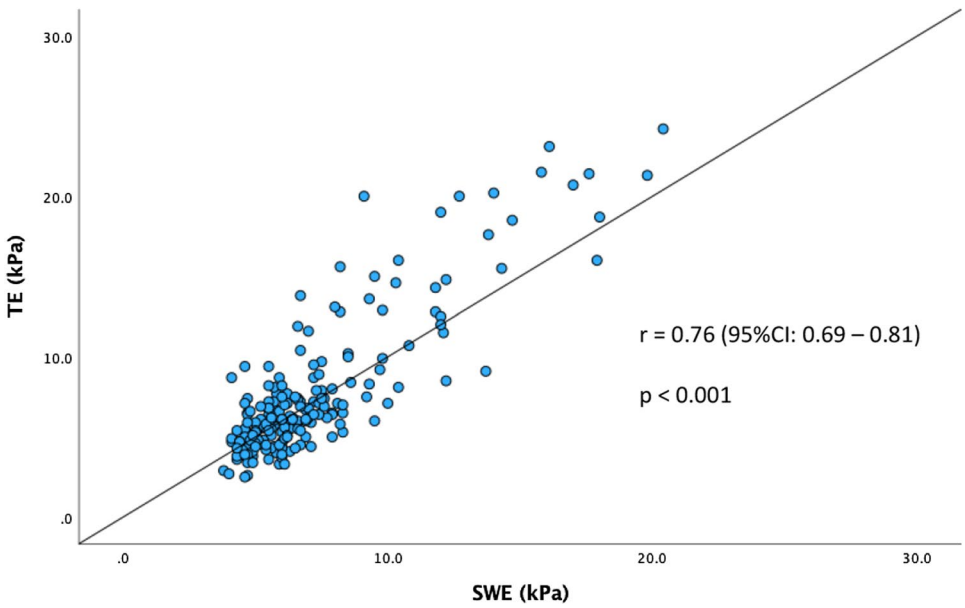

Fig. 2 Spearman's correlation between TE and SWE for the diagnosis of advanced liver fibrosis

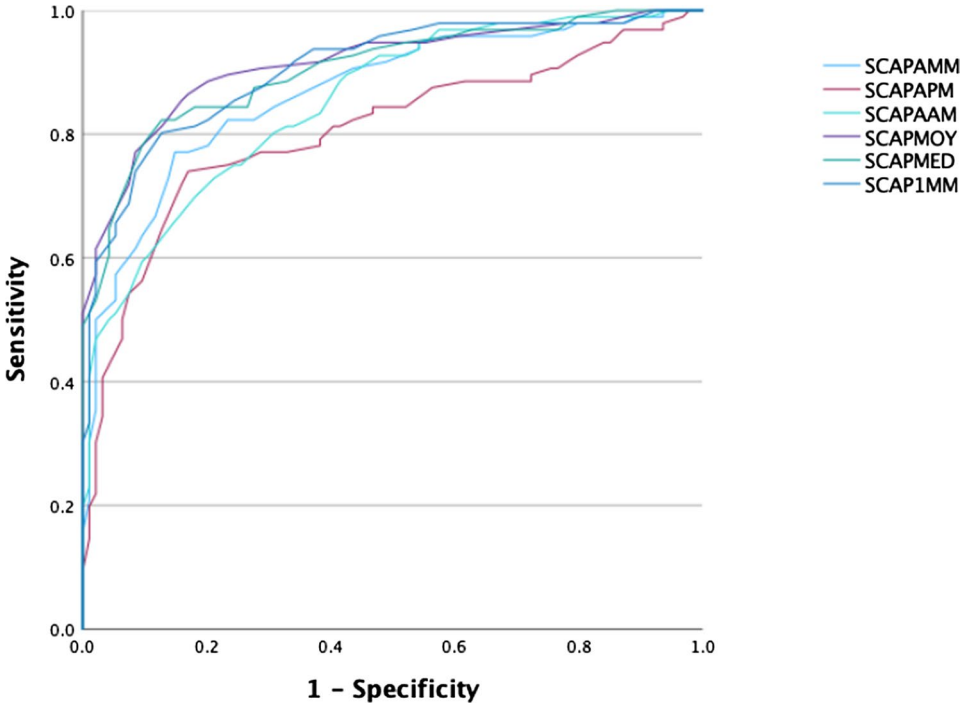

Fig. 3 AUROC curves for the best technique for the diagnosis of significant steatosis using SCAP. SCAP1MM is the median of 1st SCAP measurement at MAL, PAL, and AAL

(median 25 mm, range 10–80 mm). Advanced fibrosis (METAVIR fibrosis ≥ F3) and significant steatosis (steatosis ≥ S2) were observed in 14 and 31 patients, respectively. Taking liver biopsy as reference, the median of three SWE values had an AUROC of 0.88 [95% CI 0.79–0.97] for the diagnosis of advanced fibrosis. SCAP had an AUROC of 0.83 [95% CI 0.72–0.93] for the diagnosis of significant steatosis. The accuracy of cut-off values for SWE (≥ 8.5 kPa) for advanced fibrosis and SCAP (≥ 0.44 dB/cm/MHz) for significant steatosis was analyzed. There was only 2 false-negatives for fibrosis (PPV = 50%, NPV = 94%) and 2 false-negatives for steatosis (PPV = 71%, NPV = 88%).

Discussion

This study has four main findings. First, a simple and reliable SWE using Aixplorer MACH 30 to evaluate different liver portions showed a good performance and a strong agreement for the diagnosis of advanced fibrosis when considering TE as the gold standard. Second, these results are confirmed using liver biopsy as the reference method, defining the best SWE cut-off for advanced fibrosis of 8.5 kPa. Third, the best technique with the best performance for the assessment of significant steatosis can be obtained with the median of three measurements (1st mid-axillary line, 1st posterior axillary line, and 1st anterior axillary line) using SS. And last, the only non-reliable criterion regarding the exam was skin-to-liver distance ≥ 2.4 cm.

There are few studies evaluating the performance of 2D-SWE for the diagnosis of advanced fibrosis and steatosis. Popa et al. [18] evaluated the performance of Aixplorer MACH 30 for the diagnosis of significant fibrosis, steatosis, and inflammation in patients with MASLD. TE was also their comparison parameter. Our study included patients with viral hepatitis in addition to MASLD, which could validate this technique to several etiologies commonly seen in clinical practice. Likewise, the authors found a strong correlation between TE and SWE. Regarding steatosis, SSp correlated better than SCAP with CAP values. The best SSp and SCAP cut-off values for predicting the presence of significant steatosis were 1524 m/s and 0.5 dB/cm/MHz, respectively. In contrast, our study showed that SCAP using SS correlated better with CAP than SSp. The best SCAP cut-off value was 0.44 dB/cm/MHz for significant steatosis. This difference may be explained by the fact that Popa et al. have used a much higher CAP cut-off value (310 dB/m) than the cut-off used in our study (275 dB/m).

Patients with heterogeneous liver diseases represent a real challenge for the correct assessment of liver fibrosis. Kawamura et al. [19] described that liver heterogeneity may explain the discordance between biopsy- and magnetic resonance elastography-based fibrosis staging. In the training cohort including 155 patients with MASLD, 89% of discordance between biopsy and MRE-based advanced fibrosis was observed in case of LSM heterogeneity. Thus, heterogeneous spatial distribution of liver fibrosis would be better assessed by exams evaluating different liver portions. The median of three SWE measurements (1st mid-axillary

line, 1st posterior axillary line, and 1st anterior axillary line) using SS overcomes this issue and had an excellent accuracy for the diagnosis of advanced fibrosis. Of note, the NPV for liver fibrosis was 94%, which shows that only 6% of patients would be misclassified regarding fibrosis when SWE was applied.

Another study by Popa et al. [14], with 133 patients with chronic liver diseases, found a cut-off of 8.4 kPa for advanced fibrosis, quite similar to ours, considering TE as the gold standard. Although our study was based in TE results, we included a validation cohort of 58 patients with liver biopsy, which reinforces the accuracy of our results. Moreover, one single cut-off value has been described for advanced fibrosis and significant steatosis regardless of etiology as there was no impact of etiology on diagnostic performance in our study. The proposition of one SWE cut-off for all etiologies simplifies its use in daily clinical practice.

The present study also contributed to identify the technique with the best performance regarding the accuracy for the diagnosis of liver stiffness and steatosis. We found that the best AUROC of 0.96 [95% CI 0.93–0.98] and 0.91 [95% CI 0.86–0.95] was obtained by the median among the measures regarding three different regions such as AAL, MAL, and PAL for liver stiffness and steatosis, respectively. Veiga et al. aimed to assess the correlation between single to multiple measurements of liver and spleen stiffness and to evaluate interhepatic lobe variability of liver stiffness measurement (LSM) using 2D SWE in patients with hepatosplenic schistosomiasis [20]. A total of four stiffness measurements were performed in the right lobe (RL), left lobe (LL), and spleen. They found an excellent correlation between the first measurement and the median of four measurements for the RL, LL and spleen. However, they used a different equipment and chose different topographies compared to ours. Thus, this is the first study evaluating the best technique with measurements at different locations in the right liver portion when using the Aixplorer MACH 30 in patients with chronic liver diseases, represented mostly by viral hepatitis and MASLD. This technique is particularly useful in patient with heterogeneous liver diseases.

In the present study, we found a discordance between SWE and TE of 9%. This might have been related to the 23% of patients with obesity in this study. SWE may be less impacted by obesity as extra pressure on the probe reduces the thickness of the fatty layer between the probe and the rib cage, and the depth of SWE measurements can be adapted to go down to 10–12 cm. On the other hand, TE has the XL probe that may overcome the limit that higher BMI may impact on the success of the exam. Among the factors associated with discordance were SLD $\geq$ 2.4 cm, depth $\geq$ 5.5 cm, stability index $<$ 70% and viscosity $\geq$ 2.4. However, the only independent factor associated with discordance between the two exams in logistic regression was SLD. Although this result might have been biased by the high proportion of patients with MASLD (58%) with a high BMI (mean of 28 kg/m^2), this finding also reinforces what have already been shown in previous studies where SLD was also the main challenge for a successful exam independently of what equipment was used [15, 21].

Our study has some limitations. We compared our main results using TE as the gold standard instead of liver biopsy, and only a smaller sample of patients had liver biopsy to validate our results. Nonetheless, misdiagnosis is also possible with liver biopsy as a result of sampling errors and in patients with heterogeneous diseases and different fibrosis stages within the liver. Also, we did not have MRI–PDFF to assess steatosis in our patients. Although MRI–PDFF has a high sensibility to detect significant steatosis, it is highly expensive and not widely available, being mainly proposed in the management of patients with liver nodules. Another issue might be the high prevalence of MASLD as the main etiology of the studied population. However, MASLD is currently the most prevalent liver disease worldwide and it is important to evaluate this population that has many challenges when using non-invasive methods to establish both liver stiffness and steatosis. The second most prevalent etiology in our study was viral hepatitis which is also frequent. This way, we believe we have covered the most common liver diseases population in this study. It is important that our results may be validated in higher groups of MASLD and viral hepatitis patients independently, including those with chronic HCV infection who attained sustained virological response which has still some unanswered questions including liver stiffness cut-offs for defining liver fibrosis [22].

In conclusion, in this first study that evaluated the performance of SWE and SCAP using Aixplorer MACH 30 and the best accurate technique when using this equipment, we defined that 2D-shear wave elastography and ultrasound-based Controlled Attenuation Parameter by MACH 30 are quick and reliable non-invasive tools for the diagnosis of advanced fibrosis and significant steatosis in patients with chronic liver disease irrespective of etiology. It can be obtained with the median of three measurements (1st mid-axillary line, 1st posterior axillary line, and 1st anterior axillary line). Results for patients with skin-to-liver distance higher or equal to 2.4 cm might be regarded with caution since this impacts the reliability of the exam.

Declarations

Conflict of interest Christiane Stern: consultancy for Echosens, speaker fees for Hologic. Ann Ngo, Cristiane Villela-Nogueira, Dominique Thabut, and Vlad Ratziu state that they have no conflict of interest to declare.

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