Comparative study between two 2D-Shear Waves Elastography techniques for the non-invasive assessment of liver fibrosis in patients with chronic hepatitis C virus (HCV) infection

Victor Bâldea, Felix Bende, Alina Popescu, Roxana Șirli, Ioan Sporea

Department of Gastroenterology and Hepatology, “Victor Babeș” University of Medicine and Pharmacy Timișoara, Romania

Abstract

Aims: We aimed to compare the diagnostic performance of two 2D-Shear Wave Elastography (2D-SWE) techniques for the non-invasive assessment of liver fibrosis in patients with chronic hepatitis C virus (HCV) infection using Transient Elastography (TE) as reference. Material and methods: We enrolled 208 consecutive patients with chronic HCV infection, in which liver stiffness (LS) was evaluated in the same session using two 2D-SWE techniques: 2D-SWE.GE and 2D-SWE.SSI using TE as the method of reference. LS measurements were considered failures when no value was obtained after 10 attempts. Results: Valid LSMs were obtained in 95.6% (199/208) of cases by 2D-SWE.GE, 92.7% (193/208) of cases by 2D-SWE.SSI, and in 94.7% (197/208) of cases by TE (p>0.05). The mean LS values by 2D-SWE.GE were significantly lower than those obtained by 2D-SWE.SSI: 10.3±3.8 kPa vs. 15±10.4 kPa (p<0.0001). 2D-SWE.GE LSMs correlated better with TE than 2D-SWE.SSI (r=0.75, p<0.0001 vs. r=0.57, p<0.0001, z test p=0.0012). Linear regression analysis showed a moderate correlation between LSMs obtained by 2D-SWE.GE and 2D-SWE.SSI (r=0.63, R²=0.4, P<0.0001). Pairwise comparison of receiver operating characteristics curves (ROC) found no significant differences between 2D-SWE.GE and 2D-SWE.SSI in identifying F≥2 fibrosis (0.97 vs. 0.96, P = 0.5650), F≥3 (0.97 vs. 0.95, P = 0.2935), or F=4 (0.97 vs. 0.96, p = 0.6914). Conclusions: Both 2D-SWE techniques had good feasibility for the noninvasive assessment of liver fibrosis. LS values obtained by 2D-SWE.GE were significantly lower than those obtained by 2D-SWE.SSI. No significant differences were found between both methods in staging liver fibrosis in patients with chronic HCV.

Keywords: liver stiffness; 2D-SWE; feasibility

Introduction

Chronic hepatitis C virus infection (HCV) has an estimated global prevalence of 1%, affecting more than 71 million persons worldwide [1]. Hepatic fibrosis is a common pathological pathway in patients with chronic hepatitis C (CHC), which may lead to cirrhosis and hepatocellular carcinoma, therefore a crucial step in the management of patients with chronic liver diseases is represented by the correct assessment of liver fibrosis [2].

Liver biopsy (LB), which is traditionally considered the gold-standard method for fibrosis assessment, stage classification and also for necro-inflammatory activity grading [3], has been gradually replaced during the last decade by several non-invasive fibrosis assessment methods. LB is an invasive procedure which can lead to complications such as bleeding, sepsis or even death [4-8]. Furthermore, the lack of availability of expert practitioners can lead to sampling errors and intra- and inter-observer variability, which could potentially lead to the up- or downstaging of liver fibrosis [4-8]. Taking these limitations into account, the number of LB performed have dropped significantly in the last years, especially due to the introduction of non-invasive methods for the assessment of the liver disease severity and progression, methods that were endorsed by several guidelines [9,10].
2D-Shear Wave Elastography (2D-SWE) is a relatively new ultrasound-based technique, that allows a real-time tissue examination by measuring the propagation speed of shear waves induced by focused ultrasonic beams. The ultrasound system captures the generated shear waves and estimates their speed. The shear wave speed is used to estimate tissue stiffness which is displayed using a color-coded image superimposed on a B-mode image. At the same time, elasticity is displayed as a color-coded elastogram that allows both a qualitative and quantitative liver stiffness (LS) estimation. The measurements performed are expressed in units of m/s or converted to Young’s modulus in kPa, the same as for Transient Elastography [9]. Nowadays, several US system manufacturers have developed elastography platforms that use different mechanisms to push or detect shear waves in individual commercial US systems. Importantly, the diagnostic performance and reference values for discriminating among fibrosis stages vary among manufacturers and the interchangeability of stiffness measurements obtained with different devices remains controversial [11-15].

The first 2D-SWE technique available was implemented on an Aixplorer system (Supersonic Imagine) and has already demonstrated good to excellent performance in assessing liver fibrosis in patients with chronic liver diseases (CLD) [16-19]. Since then, numerous studies evaluating 2D-SWE techniques have shown good correlations with liver histology and/or TE [17,20-24].

This study aimed to compare the diagnostic performance of two 2D-SWE elastography techniques in terms of feasibility and liver fibrosis assessment in patients with chronic HCV infection, using Transient Elastography (TE) as reference.

**Material and methods**

**Study population**

The Institutional Review Board and the Research Ethics Committee of our University approved this study and informed consent from the patients was waived because of the retrospective nature of the study. This was a monocentric cross-sectional study conducted in a Department of Gastroenterology and Hepatology between January 2016 and November 2019. We enrolled 208 consecutive patients diagnosed with chronic hepatitis C virus (HCV) infection by the presence of HCV antibodies and detectable HCV-RNA for more than 6 months. The patients were referred to the ultrasound unit for liver fibrosis assessment and voluntarily accepted to undergo LSMs using TE and the 2D-SWE systems (SSI and GE).

Patients were asked to fast for at least 6 hours before performing LSMs. Data collected from the patient’s medical records included age, gender, body mass index (BMI), total bilirubin concentrations, alanine aminotransferase (ALT) levels, aspartate aminotransferase (AST) levels.

We excluded patients younger than 18 years, undergoing antiviral treatment, patients with ascites, under beta-blocker medication, with history of malignancy or with signs of liver congestion secondary to biliary obstruction or heart failure, and patients with focal liver lesions or end-stage renal diseases. We also excluded patients with significant alcohol consumption (ethanol intake >210 g per week for men and >140 g per week for women), those tested positive for hepatitis B surface antigen, those with primary biliary cholangitis, primary sclerosing cholangitis or autoimmune hepatitis, as well as those with AST and ALT higher than five times the upper limit of normal (ULN) values.

TE, 2D-SWE.GE and 2D-SWE.SSI were performed on the same day, by 4 different physicians, highly experienced and trained with each method and with more than 2 years of experience in the B-mode US, who were blinded to each other’s results.

**Elastography protocol**

**Transient elastography**

TE was performed in all subjects with a FibroScan® device (EchoSens, Paris, France) by experienced physicians, with more than 500 TE procedures performed, according to the EFSUMB and WFUMB guidelines [9,10]. Patients were asked to lie in a supine position, with the right arm in maximum abduction. Measurements were performed using the intercostal approach, in the right liver lobe. In each patient, we aimed for 10 valid LSMs, using the M probe (standard probe – transducer frequency 3.5 MHz) or by the XL probe (transducer frequency 2.5 MHz). M and XL probes were used according to the EASL-ALEH Clinical Practice Guidelines on M and XL probe selection [25]. LSMs were considered failures when no value was obtained after 10 attempts. Reliable measurements were defined as the median value of 10 valid LSMs with an interquartile range interval/median ratio (IQR/M) <30% [9].

To discriminate between TE fibrosis stages we used the following cut-off values, calculated in the Tschantzis et al meta-analysis; for significant fibrosis (F≥2): 7 kPa; for advanced fibrosis (F≥3): 9.5 kPa and for liver cirrhosis (F=4): 12 kPa [26].

**2D-Shear Wave Elastography**

The evaluation of LS using 2D-SWE was performed using two different systems: Aixplorer® ultrasound system (Hologic SuperSonic Imagine S.A., Aix-en-
Provence, France - 2D-SWE.SSI and LOGIQ E9 (GE Healthcare, Wauwatosa, Wisconsin, U.S.A) - 2D-SWE.GE. For both methods, LSMs were performed in each patient according to the EFSUMB and WFUMB guidelines [9,10]. Measurements were made using the intercostal approach, in the right liver lobe (liver segments V, VII, VIII) with the transducer positioned at a 90-degree angle to the liver capsule. Once an appropriate image was obtained, the shear wave region-of-interest (ROI) was placed at least 1 cm below the liver capsule, in an area free of large vessels, or other anatomical structures, while also avoiding SWS artefactual areas (reverberation, noisy areas from rib shadowing) [9]. LSMs were considered failures when no value was obtained after 10 attempts. Reliable measurements were defined as the median value of 10 valid LSMs for 2D.SWE.GE and 2D-SWE.SSI with an interquartile range interval/median ratio (IQR/M) <30% [9,10]. The operators who performed 2D-SWE.GE and 2D-SWE.SSI measurements were experienced in ultrasound, with more than one hundred 2D-SWE LSMs performed with each system. Examiners were blinded to clinical, biological, and other elastographic measurement data to avoid potential bias.

LSMs using 2D-SWE.SSI were performed using a Single Crystal Curved Array XC6-1 convex probe (transducer frequency 1-6 mHz), and the examinations were performed at least 1 cm under the liver capsule, using a color-box of 3.5x2.5 cm in which a 10 mm diameter circular region of interest (ROI) was selected. LSMs were made while the patient was asked to suspend breathing in a neutral, relaxed state. A valid 2D-SWE measurement was considered when the color-box was homogeneously filled, thus allowing the operator to place the circular ROI in the color-box and record the LSM. A map colored in blue suggests a soft tissue, while a red-colored map represents a stiff tissue. For each subject, we calculated the median value of 10 valid LSMs. The results of LSMs were expressed in kPa.

LSMs using 2D-SWE.GE were performed using a C1-6-D curved array probe XDClear (transducer frequency 1.5-6 mHz). The SWE region-of-interest (ROI) was placed at least 1 cm below the liver capsule in a region free of large vessels or anatomical structures. Once an appropriate image was obtained, the patient was asked to suspend breathing in a neutral, relaxed state, and afterward image acquisition was initiated. We aimed to acquire 10 continuous shot SWE emissions during a 4-5 second window of suspended breathing. We then analyzed each SWE emission obtained and the measurements were performed by placing a circular region of interest (ROI) of 10 mm in diameter on the most homogenous, stable elastogram in each recorded emission until 10 LSMs were obtained. The median stiffness expressed in terms of Young’s Modulus within each measurement region was automatically recorded by the system in a worksheet. The results of LS measurements were expressed in kPa.

Statistical Analysis

Data were expressed as mean (± standard deviation) for continuous variables with a normal distribution, as median (interquartile range) for continuous variables without normal distribution, or absolute frequency (percentages) for nominal variables according to the one-sample Kolmogorov-Smirnov test results, as appropriate.

Chi-Squared analysis was used to determine whether the technical success and reliable LSMs of TE, 2D-SWE.GE and 2D-SWE.SSI were significantly different. Linear regression analysis was used to determine the factors involved in LSMs failures with all methods. The correlation between the two variables was assessed with Pearson’s r correlation coefficient. Z test was used for the comparison between two correlation coefficients. The two-sample t-test was used to assess whether there are significant differences between the mean LSMs of 2D-SWE.GE and 2D-SWE.SSI.

Linear regression was applied to evaluate the correlation between LSMs obtained by 2D-SWE.GE and 2D-SWE.SSI. The agreement between the two methods was assessed by Bland-Altman analysis. The diagnostic performance of 2D-SWE.GE and 2D-SWE.SSI for staging liver fibrosis as compared to TE (reference standard) was estimated using the area under the receiver operator characteristics (AUROC) curves analysis and the sensitivity (Se), specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV) were calculated according to the optimal cut-off points that maximized the Youden index (sum of sensitivity and specificity minus one). For comparing the AUCs we used the method described by Delong et al [27].

MedCalc software for Windows (v. 19.2.0) and the R software packages (v.3.3) were used for statistical computing. We considered a p-value of <0.05 as the threshold for statistical significance and a confidence level of 95% for estimating intervals.

Results

Baseline characteristics

We included a total of 208 patients with chronic HCV infection who underwent LSMs using TE, 2D-SWE.GE and 2D-SWE.SSI, out of which 29 patients had invalid LSMs by at least one elastographic technique. Finally, a total of 179 patients with valid LSMs by all three methods were analyzed. The main clinical and demographic
Patients with HCV, 2D-SW Elastography techniques for the non-invasive assessment of liver fibrosis

characteristics of the patients with valid LSMs are described in Table I.

**Feasibility of TE, 2D-SWE. GE and 2D-SWE.SSI**

The technical success rate of each method is presented in Table II. Failure of LSMs was observed in 11 patients by TE, in 9 patients by 2D-SWE.GE and in 15 patients by 2D-SWE.SSI. Failure of LSMs by TE were due to obesity in 7 patients and narrow intercostal spaces in 4 patients. Failed LSMs using TE occurred in 5 patients with the M probe and in 6 patients with the XL probe. Failure of LSMs by 2D-SWE.GE were due to obesity in 6 patients and poor compliance (inability to suspend breathing) in 3 patients which led to the inhomogeneous filling of the color box. Failure of LSMs by 2D-SWE.SSI were due to obesity in 8 patients, poor acoustic window in 2 patients, and poor compliance (inability to suspend breathing) in 5 patients which led to the inhomogeneous filling of the color box. We obtained reliable measurements in all the 179 patients using TE, 2D-SWE.GE and 2D-SWE.SSI. There was no significant difference between the technical success rate of TE, 2D-SWE.GE and 2D-SWE.SSI (p=0.428).

**Factors involved in the technical failure of TE, 2D-SWE.GE and 2D-SWE.SSI**

On logistic regression analysis, the only factor associated with the impossibility to obtain valid LSMs with all methods was higher BMI (all p<0.05) (Table III).

**Correlation between LSMs obtained by 2D-SWE.GE and 2D-SWE.SSI**

The two-sample t-test showed that the mean LS values obtained by 2D-SWE.GE and 2D-SWE.SSI differs significantly between adjacent fibrosis stages (Table IV, fig 1).

| Characteristics | n=179
|-----------------|-----|
| Gender: Male    | 66 (36.8) |
| Age (years)     | 59.8 ± 9.0 |
| Weight (kg)     | 73.9 ± 13.6 |
| Height (cm)     | 166.7 ± 9.2 |
| Body mass index (kg/m²) | 26.5 ± 4.2 |
| AST level (IU/L) | 27.7 ± 11.1 |
| ALT level (IU/L) | 27.8 ± 11.1 |
| Fibrosis stage by TE | |
| F0-1            | 33 (18.4) |
| F2              | 29 (16.2) |
| F3              | 22 (12.2) |
| F4              | 95 (53.2) |

Data are presented as number (%) or mean ± standard deviation; ALT = alanine aminotransferase, AST = aspartate aminotransferase.

Table II. The feasibility of liver stiffness measurements (LSMs) obtained by Transient Elastography (TE), Two-Dimensional Shear Wave Elastography by General Electric (2D-SWE.GE) and Two-Dimensional Shear Wave Elastography by SuperSonic Imagine (2D-SWE.SSI)

| Method       | Technique (N)   | Method feasibility (N) | Mean LS value (kPa) |
|--------------|-----------------|------------------------|---------------------|
|              |                 |                        | F0-1 (n=33) | F2 (n=29) | F3 (n=22) | F4 (n=95) |
| 2D-SWE.GE    | Convex probe (208) | Final analysis (179) | 5.5±0.8 | 7.6±1 | 9.0±1.1 | 13.2±2.8 |
|              |                 | Valid (199)            |          |        |          |          |
|              |                 | Invalid (9)            |          |        |          |          |
| 2D-SWE.SSI   | Convex probe (208) | Final analysis (179) | 6.5±1.1 | 9.0±1.9 | 10.9±2.1 | 20.7±11.5 |
|              |                 | Valid (193)            |          |        |          |          |
|              |                 | Invalid (15)           |          |        |          |          |
| TE           | M probe (159)   | Final analysis (179)  | 5.5±0.8 | 8.0±0.5 | 10.7±0.7 | 24.5±12 |
|              | XL probe (59)   | Valid (197)            |          |        |          |          |
|              |                 | Invalid (11)           |          |        |          |          |

Data are presented as number or mean ± standard deviation; N = number of patients, 2D-SWE.GE = Two-Dimensional Shear Wave Elastography by General Electric; 2D-SWE.SSI = Two-Dimensional Shear Wave Elastography by SuperSonic Imagine; TE = Transient Elastography.
Med Ultrason 2021; 0: 1-8

Table III. Regression analysis of factors involved in Transient Elastography (TE), Two-Dimensional Shear Wave Elastography by General Electric (2D-SWE.GE) and Two-Dimensional Shear Wave Elastography by SuperSonic Imagine (2D-SWE.SSI) failed liver stiffness measurements (LSMs).

| Parameter | TE | 2D-SWE.GE | 2D-SWE.SSI |
|-----------|----|-----------|------------|
| Age       | 0.89 | 0.10      | 0.13       |
| Gender    | 0.25 | 0.95      | 0.53       |
| BMI       | 0.0203 | 0.0013    | 0.0001     |
| ALT       | 0.86 | 0.33      | 0.38       |
| AST       | 0.62 | 0.96      | 0.92       |
| TB        | 0.32 | 0.50      | 0.71       |

2D-SWE.GE = Two-Dimensional Shear Wave Elastography by General Electric; 2D-SWE.SSI = Two-Dimensional Shear Wave Elastography by SuperSonic Imagine; TE = Transient Elastography; ALT = Alanine aminotransferase, AST = Aspartate aminotransferase; BMI = Body mass index; TB = Total bilirubin

Table IV. Differences in mean liver stiffness measurements (LSMs) between Two-Dimensional Shear Wave Elastography by General Electric (2D-SWE.GE) and Two-Dimensional Shear Wave Elastography by SuperSonic Imagine (2D-SWE.SSI) in different fibrosis stages.

| Fibrosis stage | 2D-SWE.GE (kPa) | 2D-SWE.SSI (kPa) | p-value |
|----------------|-----------------|-----------------|--------|
| Overall        | 10.3±3.8        | 15±10.4         | <0.0001|
| F0-1           | 5.5 ± 0.8       | 6.5 ± 1.1       | <0.0001|
| F2             | 7.6 ± 1         | 9.0 ± 1.9       | 0.0001 |
| F3             | 9.0 ± 1.1       | 10.9 ± 2.1      | 0.0003 |
| F4             | 13.2±2.8        | 20.7±11.5       | <0.0001|

2D-SWE.SSI = Two-Dimensional Shear Wave Elastography by SuperSonic Imagine; 2D-SWE.GE = Two-Dimensional Shear Wave Elastography by General Electric

2D-SWE.GE LSMs correlated better with TE than 2D-SWE.SSI (r=0.75, p<0.0001 vs. r=0.57, p<0.0001, z test p=0.0012). Linear regression analysis showed a moderate correlation between LSMs obtained by 2D-SWE.GE and 2D-SWE.SSI (r=0.63, R^2=0.4, p<0.0001) (fig 2). The Bland-Altman analysis revealed that the mean difference in LSMs between 2D-SWE.GE and 2D-SWE.SSI was 4.68±8.5 kPa. The lower and upper limits of agreement (LoA) were -12.1 kPa (95% CI, -14.2 to -9.9 kPa) and 21.5 kPa (95% CI, 19.3 to 23.6 kPa). Overall, 4 out of 179 (2.2%) LSM values were out of the LoA (fig 3).
Diagnostic performance of 2D-SWE.GE and 2D-SWE.SSI in liver fibrosis staging

The AUROC values (95% CI) of 2D-SWE.GE and 2D-SWE.SSI for diagnosis of fibrosis stage F≥2, F≥3, and F=4 are illustrated in Table V and VI. Comparable diagnostic performance was observed between 2D-SWE.GE and 2D-SWE.SSI in identifying significant (F≥2) fibrosis (AUC of 0.97 vs. 0.96, p=0.56), advanced (F≥3) fibrosis (AUC of 0.97 vs. 0.95, p=0.29) and liver cirrhosis (F=4) (AUC of 0.97 vs. 0.96, p=0.69). Optimal LSM cut-off values determined by the Youden Index and their corresponding sensitivity, specificity, negative predictive values, and positive predictive values of 2D-SWE.GE and 2D-SWE.SSI in the identification of significant, advanced fibrosis and liver cirrhosis are illustrated in Table V and VI.

Discussion

Nowadays, almost all new ultrasound machines released on the market offer the possibility of implementing SWE applications, capable of performing good quality liver elastography measurements, leading to a significant increase in the availability of LS assessment techniques, and providing clinicians simple and useful support for better monitoring of large patient populations. Conventionally, many published papers have considered TE as an alternative to liver biopsy for liver fibrosis staging and a reference technique when evaluating the performance of other novel SWE techniques, including 2D-SWE [9,10]. However, we must be aware that TE has several limitations, the most important being the absence of direct visualization of the liver parenchyma and the impossibility or increased difficulty to obtain valid measurements in patients with ascites or obesity. Given the limitations of TE, 2D-SWE has been introduced to clinical practice as a simple, non-invasive and reproducible technique to evaluate the progression of CLD over time. There were several meta-analyses published which have shown good diagnostic performance of 2D-SWE techniques for the detection of liver fibrosis when compared to liver biopsy or TE [17,24,28,29].

Few studies have compared the diagnostic performance of two 2D-SWE techniques in terms of feasibility and performance in predicting different fibrosis stages [13-15] and to our knowledge, our present study is the first to compare two 2D-SWE techniques from different US system manufacturers in terms of feasibility and performance for predicting liver fibrosis in patients with chronic HCV infection.

Regarding the feasibility of the two 2D-SWE methods (2D-SWE.GE and 2D-SWE.SSI), the proportion of cases in which reliable LSMs were obtained was excellent for both techniques, with no significant differences when compared to TE (95.6% vs. 92.7% vs. 94.7%, p=0.428). Looking at the limits of TE, previously published studies have shown that higher BMI and narrow intercostal spaces can lead to failed or unreliable LSMs [30-32]. Regarding 2D-SWE there is evidence that LSMs are more difficult to obtain or in some cases impossible in overweight or obese subjects [16]. We analyzed factors involved in the failure of LSMs using all three methods

Table V. Performance of Two-Dimensional Shear Wave Elastography by General Electric (2D-SWE.GE) for the diagnosis of significant fibrosis, advanced fibrosis, and liver cirrhosis

| Method | AUROC Value (95% CI) | P Value | Youden Index | Cutoff value (kPa) | Sensitivity (95% CI) | Specificity (95% CI) | PPV (95% CI) | NPV (95% CI) |
|--------|---------------------|---------|--------------|-------------------|---------------------|---------------------|--------------|--------------|
| F≥2    | 0.97 (0.94-0.99)    | <0.0001 | 0.83         | 7.7               | 86.3 (79.6-91.4)    | 96.9 (84.2-99.9)    | 99.2 (95.7-100) | 61.5 (47.0-74.7) |
| F≥3    | 0.97 (0.93-0.99)    | <0.0001 | 0.85         | 8.3               | 94.8 (89.2-98.1)    | 90.3 (80.1-96.4)    | 94.9 (89.2-98.1) | 90.3 (80.1-96.4) |
| F=4    | 0.97 (0.93-0.99)    | <0.0001 | 0.84         | 9.7               | 92.6 (85.4-97.0)    | 91.6 (83.6-96.6)    | 92.6 (85.4-97.0) | 91.7 (83.6-96.6) |

AUROC = area under the receiver operating characteristics curve, C = confidence interval, PPV = positive predictive value, NPV = negative predictive value.

Table VI. Performance of Two-Dimensional Shear Wave Elastography by SuperSonic Imagine (2D-SWE.SSI) for the diagnosis of significant fibrosis, advanced fibrosis, and liver cirrhosis

| Method | AUROC Value (95% CI) | P Value | Youden Index | Cutoff value (kPa) | Sensitivity (95% CI) | Specificity (95% CI) | PPV (95% CI) | NPV (95% CI) |
|--------|---------------------|---------|--------------|-------------------|---------------------|---------------------|--------------|--------------|
| F≥2    | 0.96 (0.93-0.98)    | <0.0001 | 0.87         | 8.5               | 87.6 (81.2-92.5)    | 100 (89.4-100)      | 100 (97.2-100) | 64.7 (50.1-77.6) |
| F≥3    | 0.95 (0.91-0.98)    | <0.0001 | 0.84         | 11.1              | 89.7 (82.8-94.6)    | 95.1 (86.5-99.0)    | 97.2 (92.1-99.4) | 83.1 (72.3-91.0) |
| F=4    | 0.96 (0.93-0.98)    | <0.0001 | 0.85         | 12.3              | 91.5 (84.1-96.3)    | 94 (86.7-98.0)      | 94.6 (87.8-98.2) | 90.8 (82.7-95.9) |

AUROC = area under the receiver operating characteristics curve, C = confidence interval, PPV = positive predictive value, NPV = negative predictive value.
Our data also showed a moderate correlation between 2D-SWE.GE and 2D-SWE.SSI \( (r=0.63, \ R^2=0.4, \ p<0.0001) \), results which could be accountable to the narrow range of LS values in patients with low-grade fibrosis versus a wide range for significant fibrosis since most patients included in our study had advanced fibrosis or liver cirrhosis. The mean LS values were significantly higher for 2D-SWE.SSI than 2D-SWE.GE across all fibrosis stages \( (15\pm10.4 \ \text{kPa} \ vs. \ 10.3\pm3.8 \ \text{kPa}, \ p=0.0001) \). We also found that 2D-SWE.GE LS values correlated better with TE than 2D-SWE.SSI \( (r=0.75, \ p=0.0001 \ vs. \ r=0.57, \ p<0.0001) \). A possible explanation could be that although LS values are overall well correlated, the stiffness value range is not superimposable, since each US systems manufacturer uses its proprietary patented acquisition software that sometimes differs significantly in the emission or propagation of the acoustic shear wave \[33,34\].

We analyzed a large cohort of HCV patients and estimated the best cut-off values based on the Youden index for predicting significant, advanced fibrosis and liver cirrhosis, by 2D-SWE.GE and 2D-SWE.SSI, using TE as the reference method, which are presented in Table \( V \) and VI. Our results are similar to other published studies evaluating the 2D-SWE.GE and 2D-SWE.SSI techniques. According to the meta-analysis of 2D-SWE.SSI performed by Herrmann et al \[17\] in which liver biopsy was considered as reference, the AUCs in the prediction of significant, advanced fibrosis, and liver cirrhosis were 0.86, 0.92, and 0.93 in patients with chronic HCV. In our study, the AUCs for predicting significant, advanced fibrosis and liver cirrhosis were 0.95, 0.95, and 0.96. In a study performed by Abe et al. \[35\] which included patients with chronic HCV, who had liver biopsy performed, 2D-SWE.GE exerted excellent diagnostic performance for staging significant, advanced fibrosis and liver cirrhosis, with AUCs of 0.91, 0.94, and 0.95, respectively, results which are similar to our findings with AUCs of 0.97, 0.97, and 0.97.

Also, we found comparable diagnostic performance of 2D-SWE.GE and 2D-SWE.SSI in identifying significant \( (F\geq2) \) fibrosis \( (\text{AUC of 0.97 vs. 0.96, p=0.56}) \), advanced \( (F\geq3) \) fibrosis \( (\text{AUC of 0.97 vs. 0.95, p=0.29}) \) and liver cirrhosis \( (F=4) \) \( (\text{AUC of 0.97 vs. 0.96, p=0.69}) \).

Our study has some limitations, the first being the relatively small number of patients with intermediate stages of liver fibrosis \( (F\geq2 \text{ or } F\geq3) \) since most of our patients had liver cirrhosis. Further limitations are represented by the single-center design of the study, the inclusion of patients only infected with HCV, and the unavailability of a liver biopsy for comparative analysis, hence our results do not apply to the general population. However, the purpose of our study was to demonstrate the non-inferiority of 2D-SWE techniques in staging liver fibrosis when compared to TE. Therefore, further larger multicentric studies are warranted to confirm our results, with the inclusion of patients with liver diseases of different etiologies.

**In conclusion,** our data have shown that both 2D-SWE techniques have good feasibility for the noninvasive assessment of liver fibrosis. Based on our results, 2D-SWE.GE and 2D-SWE.SSI have proven to be a valuable alternative to TE in the management of HCV patients. With the availability of a B-mode image and the possibility of choosing the optimal ROI, both 2D-SWE techniques can successfully overcome the technical limitations of TE, thus improving the non-invasive approach for the assessment of liver fibrosis in patients with chronic HCV.

**Conflict of interest:** none

**References**

1. Asrani S, Devabhavi H, Eaton J, Kamath PS. Burden of liver diseases in the world. J Hepatol 2019;70:151-171.
2. Wang JH. Application of ultrasound liver elastography to the diagnosis and monitoring of liver disease. J Med Ultrasound 2019;27:1-2.
3. Gebo KA, Herlong HF, Torbenson MS, et al. Role of liver biopsy in management of chronic hepatitis C: A systematic review. Hepatology 2002;36(5 Suppl 1):S161-S172.
4. Regev A, Berho M, Jeffers LJ, et al. Sampling error and intraobserver variation in liver biopsy in patients with chronic HCV infection. Am J Gastroenterol 2002;97:2614-2618.
5. Seeff LB, Everson GT, Morgan TR, et al. Complication Rate of Percutaneous Liver Biopsies Among Persons With Advanced Chronic Liver Disease in the HALT-C Trial. Clin Gastroenterol Hepatol 2010;8:877-883.
6. Standish R, Cholongitas E, Dhillon A, Burroughs AK, Dhillon AP. An appraisal of the histopathological assessment of liver fibrosis. Gut 2006;55:569-578.
7. Bedossa P, Dargere D, Paradis V. Sampling variability of liver fibrosis in chronic hepatitis C. Hepatology 2003;38:1449-1457.
8. Castéra L, Nègre I, Samii K, Buffet C. Pain experienced during percutaneous liver biopsy. Hepatology 1999;30:1529-1530.
9. Dietrich CF, Bamber J, Berzigotti A, et al. EFSUMB Guidelines and Recommendations on the Clinical Use of Liver Ultrasound Elastography, Update 2017 (Long Version). Ultraschall Med 2017;38:e48.
10. Ferraoli G, Wong VW, Castéra L, et al. Liver Ultrasound Elastography: An Update to the World Federation for Ultrasound in Medicine and Biology Guidelines and Recommendations. Ultrasound Med Biol 2018;44:2419-2440.
11. Sigrist RMS, El Kaffas A, Jeffrey RB, Rosenberg J, Willmann JK. Intra-Individual Comparison between 2-D Shear Wave Elastography (GE System) and Virtual Touch Tissue Quantification (Siemens System) in Grading Liver Fibrosis. Ultrasound Med Biol 2017;43:2774-2782.

12. Yoo J, Lee JM, Joo I, Yoon JH. Assessment of liver fibrosis using 2-dimensional shear wave elastography: a prospective study of intra- and inter-observer repeatability and comparison with point shear wave elastography. Ultrasound 2020;39:52-59.

13. Ryu H, Ahn SJ, Yoon JH, Lee JM. Reproducibility of liver stiffness measurements made with two different 2-dimensional shear wave elastography systems using the comb-push technique. Ultrasonography 2019;38:246-254.

14. Sporea I, Bende F, Popescu A, Lupusoru R, Fofii R, Sirli R. Are there different cut-off values for staging liver fibrosis using 2D-SWE implemented on different systems from the same manufacturer? Med Ultrason 2020;22:7-12.

15. Ferraioli G, De Silvestri A, Lissandrin R, et al. Evaluation of Inter-System Variability in Liver Stiffness Measurements. Ultraschall Med 2019;40:64-75.

16. Ferraioli G, Tinelli C, Dal Bello B, et al; Liver Fibrosis Study Group. Accuracy of real-time shear wave elastography for assessing liver fibrosis in chronic hepatitis C: A pilot study. Hepatology 2012;56:2125-2133.

17. Herrmann E, de Lédinghen V, Cassinotto C, et al. Assessment of biopsy-proven liver fibrosis by two-dimensional shear wave elastography: An individual patient data-based meta-analysis. Hepatology 2018;67:260-272.

18. Sporea I, Bota S, Gradinaru-Taşcău O, Sirli R, Popescu A, Jurchiș A. Which are the cut-off values of 2D-Shear Wave Elastography (2D-SWE) liver stiffness measurements predicting different stages of liver fibrosis, considering Transient Elasticity (TE) as the reference method? Eur J Radiol 2014;83:e118-e122.

19. Dhyani M, Grajo JR, Bhan AK, Corey K, Chung R, Samir AE. Validation of Shear Wave Elastography Cutoff Values on the Supersonic Aixplorer for Practical Clinical Use in Liver Fibrosis Staging. Ultrasound Med Biol 2017;43:1125-1133.

20. Bende F, Sporea I, Sirli R, et al. Performance of 2D-SWE. GE for predicting different stages of liver fibrosis, using Transient Elasticography as the reference method. Med Ultrasound 2017;19:143-149.

21. Cassinotto C, Bourlier J, de Lédinghen V, et al. Liver stiffness in nonalcoholic fatty liver disease: A comparison of supersonic shear imaging, FibroScan, and ARFI with liver biopsy. Hepatology 2016;63:1817-1827.

22. Gao Y, Zheng J, Liang P, et al. Liver Fibrosis with Two-dimensional US Shear-Wave Elastography in Participants with Chronic Hepatitis B: A Prospective Multicenter Study. Radiology 2018;289:407-415.

23. Jamialahmadi T, Nematy M, Jangoo A, et al. Measurement of Liver Stiffness with 2D-Shear Wave Elastography (2D-SWE) in Bariatric Surgery Candidates Reveals Acceptable Diagnostic Yield Compared to Liver Biopsy. Obes Surg 2019;29:2585-2592.

24. Zhang W, Zhu Y, Zhang C, Ran H. Diagnostic Accuracy of 2-Dimensional Shear Wave Elastography for the Staging of Liver Fibrosis: A Meta-analysis. J Ultrasound Med 2019;38:733-740.

25. European Association for Study of Liver; Asociacion Latinoamericana para el Estudio del Higado. EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis. J Hepatol 2015;63:237-264.

26. Tsoschatzis EA, Gurusamy KS, Ntaoula S, Cholangitis E, Davidson BR, Burroughs AK. Elastography for the diagnosis of severity of fibrosis in chronic liver disease: A meta-analysis of diagnostic accuracy. J Hepatol 2011;54:650-659.

27. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988;44:837-845.

28. Kim JR, Suh CH, Yoon JM, Lee JS, Cho YA, Jung AY. The diagnostic performance of shear-wave elastography for liver fibrosis in children and adolescents: A systematic review and diagnostic meta-analysis. Eur Radiol 2018;28:1175-1186.

29. Feng JC, Li J, Wu XW, Peng XY. Diagnostic Accuracy of SuperSonic Shear Imaging for Staging of Liver Fibrosis. J Ultrasound Med 2016;35:329-339.

30. Castéra L, Foucher J, Bernard PH, et al. Pitfalls of liver stiffness measurement: A 5-year prospective study of 13,369 examinations. Hepatology 2010;51:828-835.

31. Sporea I, Șirli R, Mare R, Popescu A, Ivașcu SC. Feasibility of Transient Elasticity compared with M and XL probes in real life. Med Ultrason 2016;18:7-10.

32. Grădinaru-Taşcău O, Sporea I, Bota S, et al. Does experience play a role in the ability to perform liver stiffness measurements by means of supersonic shear imaging (SSI)? Med Ultrasound 2013;15:180-183.

33. Piscaglia F, Salvatore V, Mulazzani L, Cantisani V, Schiavone C. Ultrasound Shear Wave Elastography for Liver Disease. A Critical Appraisal of the Many Actors on the Stage. Ultraschall Med 2016;37:1-5.

34. Cassinotto C, Lopyuade B, Guiu B, et al. Agreement Between 2-Dimensional Shear Wave and Transient Elastography Values for Diagnosis of Advanced Chronic Liver Disease. Clin Gastroenterol Hepatol 2020;18:2971-2979.e3.

35. Abe T, Kuroda H, Fujiwara Y, et al. Accuracy of 2D shear wave elastography in the diagnosis of liver fibrosis in patients with chronic hepatitis C. J Clin Ultrasound 2018;46:319-327.