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Title: Agreement Between 2-dimensional Shear Wave and Transient Elastography Values for Diagnosis of Advanced Chronic Liver Disease

Short title: Agreement between 2D-SWE and TE values

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List of Abbreviations

LS, Liver Stiffness; VCTE, Vibration-Controlled Transient Elastography; 2D-SWE, 2-Dimensional Shear Wave Elastography; cACLD, compensated advanced chronic liver disease; BMI, Body Mass Index; PT, Prothrombin Time; GGT, Gamma-Glutamyl Transpeptidase; AST, Aspartate AminoTransferase; ALT, Alanine AminoTransferase; ALP,

aminotransferase/alanine aminotransferase ratio index; CAP, controlled attenuation parameter; IQR, InterQuartile Range; kPa, kilopascal; IQR/M, Interquartile range/Median; AUC, areas under the receiver operating characteristics curves; CI, confidence intervals

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Conflict of interest statement

VDL: received consultant fees from Echosens (Paris, France) and Supersonic Imagine (Aix-en-Provence, France). All other authors: Conflicts of interest: none

Authors' contributions

CC: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing

BL: Data curation, Investigation, Validation

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MID: Data curation, Validation

NM: Formal analysis, Software, Validation

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Background & Aims: Inter-platform variation in liver stiffness evaluation (LSE) could hinder dissemination and clinical implementation of new ultrasound methods. We aimed to determine whether measurements of liver stiffness by bi-dimensional shear wave elastography (2D-SWE) with a Supersonic Imagine apparatus are comparable to those made by vibration-controlled transient elastography (VCTE).

Methods: We collected data from 1219 consecutive patients with chronic liver disease who underwent LSE by VCTE and 2D-SWE (performed by blinded operators), on the same day, at a single center in France from September 2011 through June 2019. We assessed the ability of liver stiffness value distributions and 2D-SWE performances to identify patients with compensated advanced chronic liver disease (cACLD) according to the Baveno VI criteria, based on VCTE cut-off values.

Results: VCTE and 2D-SWE values correlated (Pearson's correlation coefficient, 0.882; $P < .0001$; Lin concordance coefficient, 0.846; $P < .0001$). The median stiffness values were 6.7 kPa with VCTE (interquartile range, 4.8–11.6 kPa) and 7.1 kPa with 2D-SWE (interquartile range, 5.4–11.1 kPa) ($P = .736$). 2D-SWE values were slightly higher in the low percentiles and lower in the high percentiles; the best match with VCTE values were at approximately 7–9 kPa. The area under the curve of 2D-SWE for identifying of VCTE values below 10 was 0.964 (95% CI, 0.952–0.976) and for VCTE values above 15 kPa was 0.976 (95% CI, 0.963–0.988), with Youden index-associated cut-off values of 9.5 and 13 kPa and best accuracy cut-off values of 10 kPa and 14 kPa, respectively. A 2D-SWE cut-off value of 10 kPa detected VCTE values below 10 kPa with 92% sensitivity, 87% specificity, and 91% accuracy.

Conclusions: Measurement of liver stiffness by VCTE or 2D-SWE produces comparable results. 2D-SWE accurately identifies patients with cACLD according to the Baveno VI criteria based on VCTE cut-off values. A 10 kPa 2D-SWE cut-off value can be used to rule out cACLD.

KEY WORDS: noninvasive, elasticity, ultrasonography, fibrosis, LSM

Need to Know

Background: Inter-platform variation in measurement of liver stiffness evaluation poses challenges to development and use of ultrasound-based elastography techniques.

Findings: Measurement of liver stiffness by vibration-controlled transient elastography or 2-dimensional shear wave elastography (2D-SWE LSE) produces comparable results. 2D-SWE accurately identifies patients with advanced chronic liver disease, and a 10 kPa 2D-SWE cut-off value can be used to rule out cACLD.

Implications for patient care: Liver stiffness can be evaluated in patients with chronic liver disease equally well by VCTE or 2D-SWE.

Liver stiffness (LS) has become an essential feature in the management of patients with chronic liver diseases. Although LS is often considered as a single entity, in recent years different diagnostic tools have been developed to quantify LS using specific technical approaches ¹. In the 2000s, vibration-controlled transient elastography (VCTE) with FibroScan[®] was the first tool with which LS was measured and studied. Since then, new techniques have been marketed, such as point-shear wave elastography (p-SWE) and several bi-dimensional shear wave elastography (2D-SWE) methods with diagnostic performances at least as good as VCTE ^{2,3}. Nevertheless, due to the longer experience and excellent level of evidence, VCTE remains the main technique endorsed by liver international societies and used in their clinical recommendations ^{4,5}. In 2015, the Baveno VI consensus workshop introduced the term of “compensated advanced chronic liver disease” (cACLD) to describe asymptomatic patients with severe fibrosis or cirrhosis. According to this consensus, LS values below 10kPa (obtained only with the VCTE technique) rule out cACLD, whereas LS values above 15kPa are highly suggestive of cACLD. Values between 10 and 15 kPa are suggestive of cACLD, but additional tests are needed for confirmation ⁵.

Although recent elastography techniques present interesting technological innovations and good to excellent diagnostic performances, their recognition and integration in the various clinical recommendations is very slow. This delayed recognition could be mainly due to their lower level of scientific evidence compared with VCTE, but other reasons should also be mentioned. Indeed, different proprietary elastography technologies generally give different LS values when used in the same patient. LS values are influenced by various system-specific factors, particularly shear wave vibration frequency and bandwidth ^{1,6}. Therefore, the availability of many ultrasound methods is associated with some drawbacks, especially in the daily practice, due to the more or less important variability of LS and cut-off values, in function of the specific characteristics of the used technique. For a clinician long accustomed to the LS values and cut-offs of VCTE, it can be daunting to switch to another set of thresholds and range of LS values ⁷. On the other hand, previous prospective studies designed to assess 2D-SWE diagnostic performances using the Aixplorer ultrasound machine (Supersonic Imagine, Aix-en-Provence, France), one of the first bi-dimensional shear wave technique to be developed, suggested that the LS value distribution and cut-offs of VCTE and 2D-SWE might be similar, despite their technical differences ^{2,8,9}.

cut-off values associated with cACLD according to the Baveno VI criteria. We also studied the distribution, correlation and concordance of LS values obtained using VCTE and 2D-SWE in a large cohort of patients with chronic liver disease who underwent LS assessment with both techniques on the same day.

Patients

From a prospective registry (clinical trial number 02060565), we retrospectively extracted all consecutive patients with chronic liver disease who underwent LS evaluation with both VCTE and 2D-SWE on the same day at our hospital, from September 2011 to June 2019. In total, 1219 patients met these inclusion criteria, including 266 patients who were previously included in a prospective study to analyse and compare the diagnostic performances of VCTE, 2D-SWE and p-SWE for fibrosis staging⁹. No patient with acute viral hepatitis or hemochromatosis were included. All health professionals who performed the LS measurements were experimented and blinded to the results of the other non-invasive method. Among the 1219 included patients, 416 had a liver biopsy performed within one week of LS measurement, with reliable results obtained in 334 patients with VCTE, and 380 with 2D-SWE. An ethics committee (Institutional Review Board CHU de Montpellier) approved the study design and waived the need of informed consent by the patients.

Morphological and laboratory parameters

For all patients, the following parameters were determined at the time of LS quantification: age, sex, body mass index (BMI), waist circumference, history of diabetes and of hypertension, aetiology of the chronic liver disease. The diagnosis of NAFLD was based on the presence of liver steatosis in the context of metabolic syndrome and without other known causes of chronic liver disease, and especially high alcohol consumption (i.e., >21 drinks, on average, per week in men and >14 drinks, on average, per week in women). A blood sample was collected to quantify the platelet count, international normalized ratio (INR), total bilirubin, gamma-glutamyl transpeptidase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), albumin, ferritin, cholesterol and triglyceride levels.

2D-SWE-SSI and transient elastography

LSE were performed by experienced operators, in a fasting patient, on the right lobe of the liver, through the intercostal spaces with the patient lying in dorsal decubitus and the right arm in maximal abduction. 2D-SWE-SSI measurements were performed using the Aixplorer™ ultrasound device (Supersonic Imagine, Aix-en-Provence, France). The operator targeted a right liver portion at least 6-cm thick and

median value (interquartile range (IQR)) of 3 measurements, expressed in kiloPascals (kPa), was used as the representative measurement. Measurements were classified as failed when no or little signal was obtained for all acquisitions. VCTE was performed with FibroScan (Echosens, Paris, France) using the M probe for all patients. The objective was to obtain a total of 10 valid measurements, with the maximum number of attempts set at 20. For VCTE as well as for 2D-SWE-SSI, LSE was considered as unreliable when IQR/M was ≥ 0.30 in patients with Median ≥ 7.1 kPa¹⁰.

Statistical analysis

Statistical analysis was performed using SPSS Statistics version 26 (SPSS statistics, IBM), and Stata software version 14.0 (Stata corporation, College Station, TX, USA). The sample normality was tested with the Shapiro-Wilk test. Quantitative data were expressed as mean \pm standard deviation or median (IQR), and compared using the two-sample *t* test or the Wilcoxon signed-ranks test, according to the data distribution. Categorical data were expressed as numbers (percentages) and compared using the Chi-square test. The influence of various clinical factors on LS quantification failure or unreliability using VCTE or 2D-SWE was analysed using stepwise forward multiple regression (R^2) according to Nagelgerke et al.¹¹. The variables that influenced each studied dependent variable (Spearman's correlation coefficient with a p value of $<.10$) were selected as independent variables. After excluding unreliable results, the mean, median, range, and IQR/M between VCTE and 2D-SWE were compared. The correlation between VCTE and 2D-SWE values was tested using the Pearson's correlation coefficient. A Bland-Altman plot was built to represent the differences between VCTE and 2D-SWE values¹². The Lin concordance coefficient *pc* was also computed¹³. This coefficient combines measures of precision and accuracy to determine whether the observed data deviate significantly from the line of perfect concordance (i.e. the 45° line). The variability between techniques was assessed by calculating the coefficient of variation, i.e. the ratio of absolute difference on the mean value of the two measurements: $|VCTE - 2D-SWE| / ((VCTE + 2D-SWE) / 2)$. Univariate and multivariate analyses were performed, as described above, to identify variables associated with the coefficient of variation. Finally, receiver operating characteristics (ROC) curves for 2D-SWE were built for the whole population and for patients with BMI $< 30 \text{ kg/m}^2$ to limit discrepancies linked to

curve (AUC) and its 95% confidence intervals (CI) were calculated for 2D-SWE ability to classify patients in function of the absence/presence of cACLD defined according to the Baveno VI criteria for cACLD diagnosis (i.e. VCTE value <10kPa and >15kPa, respectively)⁵. Except for univariate analysis (p-value <.10), results were considered significant with p-value <.05.

Results

Patients

The characteristics of the 1219 patients are summarized in **Table 1**. The chronic liver disease aetiology was: alcohol use disorder (n=124; 10.2%), NAFLD (n=345; 28.3%), hepatitis C (n=346; 28.4%), hepatitis B (n=159; 13%), mixed viral hepatitis (n=47; 3.9%), sclerosing cholangitis, auto-immune hepatitis, primitive biliary cirrhosis, or overlap syndrome (n=69, 5.7%), drug-induced liver injury (n=36, 3%), unexplained chronic cytolysis (n=54, 4.4%), and follow-up after liver transplantation (n=39; 3.2%). The median BMI (IQR) was of 27 kg/m² ± 6.5 (14.9-54.7); 44.4% of patients had BMI values <25kg/m², 28.2% between 25 and 29.9 kg/m², and 27.4% ≥30kg/m². Among the 416 patients who had liver biopsy, 65 patients (15.6%) were F0, 112 (26.9%) were F1, 85 (20.4%) were F2, 73 (17.5%) were F3, and 81 (19.5%) F4.

Failures and reliability of LS measurements

The percentage of failed and unreliable measurements was higher using VCTE than 2D-SWE: 11.3% (138/1219) versus 8.3% (101/1219; p<.0001). LS quantification failure occurred in 6.4% of patients (78/1219) with VCTE and in 2.8% (34/1219) with 2D-SWE (p<.0001), including 17 patients (1.4%) in whom LS could not be measured with both VCTE and 2D-SWE. Unreliable results were obtained in 102 patients (8.4%): 60 (4.9%) with VCTE, 67 (5.5%) with 2D-SWE (p=0.52), and 25 (0.02%) with both techniques. Conversely, the percentage of reliable results was higher with 2D-SWE than with VCTE (91.7% versus 88.7%, p<.0001). In uni and multivariate analysis, the variables associated with failed or unreliable LS measurements are shown in **Table S1**.

LS measurement characteristics

median (IQR) LS values were 6.7 kPa (4.8-11.6) with VCTE, and 7.1 kPa (5.4-11.1) with 2D-SWE ($p=0.335$). The mean values (\pm SD) were 10.8 kPa (\pm 11.6) for VCTE and 10.1 kPa (\pm 8.8) for 2D-SWE ($p<.0001$). The median IQR/M values (IQR) were 11.9% (7.8 – 17.2) for VCTE, and 9.8% (5.4 – 16.1) for 2D-SWE ($p<.0001$).

The LS values obtained by VCTE and 2D-SWE were highly correlated (Pearson's correlation coefficient = 0.882, $p<.0001$); Lin coefficient = 0.846, $p<.0001$) (Scatterplot, **Fig. 1**). As shown in Fig 1 and confirmed in **Fig 2** showing the distribution of values according to medians weighted by percentiles, the 2D-SWE values tended to be higher in the low percentiles and lower in the high percentiles, with the best concordance of 2D-SWE and VCTE values (i.e. where curves cross each other) around 7-8 kPa in Fig 1 and around 8-9 kPa in Fig 2 (medians).

Differences in LS values and coefficient of variations

Comparison of the LS values obtained with the two techniques in a Bland-Altman plot (**Fig. 3**) showed that the mean (\pm SD) (i.e. 2D-SWE values minus VCTE value) and the median (IQR) difference between 2D-SWE and VCTE were -0.75 kPa (\pm 5.6) and 0.3 kPa (-1.4 – 1.5), respectively. In absolute value, the median (IQR) difference between 2D-SWE and VCTE was 1.5 kPa (0.7 – 2.9). 50% of 2D-SWE values were within \pm 1.5 kPa of the VCTE values, and 80% within \pm 3.5 kPa. Interestingly, the median difference (IQR) between both techniques tends to narrow in low values. Indeed, in patients with VCTE <20 kPa and <10kPa, 50% of 2D-SWE values were within \pm 1.3 kPa (0.6-2.5) and \pm 1.1 kPa (0.5-2.1) of the VCTE values, respectively. The variability between techniques, expressed as the coefficient of variation (IQR), was 19.8% (9.3 – 35.4). The variables associated with the coefficient of variation in univariate analysis are presented in **Table S2**. Only waist circumference ($R^2=0.011$) remained independently associated with the coefficient of variation in multivariate analysis. The LS value, as well as the CAP score, were not associated with discordances between techniques.

2D-SWE diagnostic performances and cut-off values for cACLD

In patients who had liver biopsy, the diagnostic performances of 2D-SWE and VCTE were of 0.89 (0.85-0.93) and 0.89 (0.85-0.94) for the diagnosis of cirrhosis, 0.86 (0.82-0.90) and 0.84 (0.80-0.89) for the diagnosis of advanced fibrosis, 0.81 (0.77-0.86) and 0.81 (0.77-0.86) for the diagnosis of significant fibrosis, respectively.

(i.e. VCTE value <10kPa, according to the Baveno VI criteria) was 0.948 (0.934-0.961) in patients with reliable results, and 0.964 (0.952-0.976) in the 811 patients with BMI <30kg/m² (**Fig. 4a**). The AUC (95%CI) value to define the ability of 2D-SWE to diagnose the presence of cACLD (i.e. VCTE value ≥15kPa, according to the Baveno VI criteria) was 0.969 (0.957-0.981) in patients with reliable results, and 0.976 (0.963-0.988) in patients with BMI <30kg/m² (**Fig. 4b**).

The diagnostic performances of the 2D-SWE cut-off values based on the Youden index, optimal accuracy, sensitivity ≥95%, specificity ≥95%, and on the fixed VCTE thresholds of 10 and 15 kPa are shown in **Table 2**. For ruling out cACLD, the 2D-SWE value associated with the Youden index was 9.5 kPa (sensitivity of 90%, specificity of 91% and accuracy of 90%), and those associated with the best accuracy was 10 kPa (sensitivity of 92%, specificity of 87%, and accuracy of 91%). For ruling in cACLD, the 2D-SWE values associated with the Youden index and the best accuracy were 13 kPa (sensitivity of 90%, specificity of 94% and accuracy of 94%) and 14 kPa (sensitivity of 86%, specificity of 97% and accuracy of 96%), respectively. With a threshold value of 15kPa, sensitivity decreased (81%) and specificity increased (98%), without loss of accuracy (95%).

Supplementary Figure S1 demonstrated a schematic representation of the 2D-SWE cut-offs associated with the Youden index and the best accuracy index in the whole study cohort, and in subgroups of patients with HCV (n=346) and NAFLD (n= 345).

Discussion

The results of our study show that the distribution of LS values obtained with 2D-SWE is very similar to the one obtained with VCTE. Indeed, among the 1219 patients with chronic liver disease, about 50% had 2D-SWE LS measurements within ±1.5 kPa, and 80% within ±3.5 kPa of those obtained by VCTE. Moreover, VCTE and 2D-SWE LS values displayed excellent correlation and concordance (Pearson correlation coefficient of 0.88 and Lin concordance coefficient of 0.85). 2D-SWE demonstrated excellent diagnostic performances for classifying patients according to the Baveno VI criteria, with AUC of 0.96 and 0.98 for ruling out and strongly suggesting cACLD, respectively. The 2D-SWE cut-off values associated with the Youden index and the best accuracy for ruling out cACLD were 9.5 kPa and 10kPa, which is very close or similar to the VCTE cut-off value of 10kPa. The use of a cut-off value of 10kPa for of 2D-SWE can therefore be recommended for clinical use. On the

accuracy for strongly suggesting cACLD were 13 and 14 kPa, respectively, which is moderately lower than that of VCTE (15kPa). On the basis of its excellent diagnostic performances (sensitivity, specificity, and accuracy higher than 90%), the 13kPa 2D-SWE cut-off is probably best suited for clinical practice. Conversely, the 2D-SWE cut-off values of 14 and 15 kPa were associated with better accuracy, but with a decrease in sensitivity and an increase in specificity. These results are of critical importance for clinical practice. By showing that the LS value distributions are very close for 2D-SWE and VCTE, and that the VCTE cut-off for ruling out cACLD can be applied to 2D-SWE with an excellent diagnostic performance, these results imply that these techniques could be interchangeably used in the clinical routine, depending on the local resources, and may help extending the capacity to perform LS measurements. Moreover, these results should accelerate the use of 2D-SWE in international recommendations alongside VCTE.

Almost all new ultrasound machines now systematically offer the possibility of performing good quality liver elastography measurements, and consequently the availability and supply of LS assessment techniques for better monitoring of large patients population have greatly increased. Moreover, as liver ultrasound is regularly recommended in patients with chronic liver disease, it is interesting to couple morphological exploration with liver elastography during the same examination, to propose a longitudinal follow-up of the disease, also because quantitative markers of fibrosis and steatosis have now become complementary and essential for the morphological ultrasound analysis. However, the development of liver ultrasound techniques is accompanied by many pitfalls and criticisms^{1,7}. One limitation is that every novel elastography technique is released to the market without clinical data on their technical and diagnostic performances, and therefore their real clinical added value is not clear. Regarding 2D-SWE, several studies have shown that it performs as well as or better than VCTE both from a technical point of view (excellent rates of reliable results and good reproducibility)^{3,14}, as confirmed in our current study, and in terms of diagnostic performance^{2,15,16}. The second main limitation is much more complex to deal with. Indeed, although LS quantifications using various techniques are overall well correlated, the stiffness value range and cut-off values are clearly not superimposable, because manufacturers apply proprietary patented calculation modes with slight to great differences in the technical aspects of the emission/propagation of the acoustic shear wave⁷. This absence of LS value uniformity is generally confusing for a clinician already accustomed to the range and cut-offs values of an

hindering its clinical use and integration in international guidelines. Regarding 2D-SWE, previous studies suggested that its LS values could be similar to those obtained by VCTE^{2,8,9,16}, but they were not designed for this goal. Our study confirmed that VCTE and 2D-SWE values are close, and importantly that the same 10kPa cut-off value can be used in clinical practice for ruling out cACLD. However, the 2D-SWE cut-off for ruling in cACLD is lower than that of VCTE (13 instead of 15kPa). Indeed, the relationship between the LS value distributions of two different techniques may be not strictly linear, and threshold values may, for example, be similar for low LS values, while show greater discrepancies for higher values, like in our sample, further complicating the task of standardizing the technique clinical applicability.

In 2013, the Quantitative Imaging Biomarker Alliance (QIBA) committee on Ultrasound Shear Wave Speed of the Radiological Society of North America, analysed and quantified the differences in elasticity values among the systems available at the time: VCTE (Echosens), real-time elastography (Philips iU22), p-SWE (ACUSON S2000), and 2D-SWE (SSI Aixplorer)⁶. This inter-laboratory study using elastic phantoms showed the presence of significant differences in elasticity values, depending on the used system and measurement depth. In 2015, similar results were reported by another study using phantoms with viscoelastic properties close to those observed in normal, slightly, and moderately fibrotic liver¹⁷. The inter-system variability increased with the measurement depth, but was not related to stiffness, as observed in our study. Unfortunately, these two studies on phantoms could not provide a conversion tool to easily switch from one technique to another. The notion of greater inter-variability according to the measurement depth is of interest for operators. However, VCTE has a fixed measurement depth, and experienced operators are already aware of the importance of performing ultrasound elastography measurements (any technique) in an area at least 1 cm away from the capsule, while remaining as superficial as possible in order not to lose too much signal and quality of the ultrasound window.

Our study has some limitations. First, measurements were made by different operators without precise knowledge of where the measurement was made with the other technique. This can be considered a strong point provided that the measurements performed with both techniques are well matched. Nevertheless, it would have been extremely interesting to carry out measurements with each technique at the same location in order to precisely analyse the

how 2D-SWE values compare to those of VCTE in clinical practice but was not designed to compare diagnostic performances between both techniques, and liver biopsy was lacking for many patients. Therefore, in patients who had large discrepancies, out of the limits of agreement of the Bland-Altman plot for some of them, possibly related to technical issues linked to overweight, it was not possible to say which value was the most accurate. In the same way, the impact of concordant values on diagnostic performances could not be assessed. These points are interesting and will need to design specific studies dealing with these objectives. Third, as suggested by manufacturers and literature, 10 measurements were performed with VCTE but 3 with 2D-SWE. Finally, this study concerns only the 2D-SWE technique with Supersonic Imagine. Although this was the first 2D-SWE technique to be developed and that many evidences are available on its technical and diagnostic performances, similar studies will have to be carried out for each technique put on the market in recent years.

In conclusion, the distributions of LS values obtained by 2D-SWE with Supersonic Imagine and by VCTE are very similar. 2D-SWE displays excellent diagnostic performances for ruling out and ruling in cACLD according to the Baveno VI criteria (i.e. VCTE values below 10kPa and above 15kPa, respectively). The same 10kPa cut-off value can be used with 2D-SWE in clinical practice for ruling out cACLD. These results should help the clinical implementation of the 2D-SWE technique, accelerate its integration in international guidelines and recommendations, and greatly help hepatologists in their clinical practice. Other studies based on phantoms or clinical data should be performed for all novel or recent elastography techniques to limit inter-platform variability.

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Table 1. Characteristics of the 1219 included patients

Variable	
Sex – Men: n (%)	712 (58.4)
Age (years)	53.3 ± 15 (15-86.3)
BMI (kg/m ²)	27 ± 6.5 (14.9-54.7)
<25, n (%)	541 (44.4)
25 to 29.9	344 (28.2)
≥30	334 (27.4)
Waist circumference (cm)	93.8 ± 17.1 (54-154)
Diabetes, n (%)	291 (23.9)
Hypertension, n (%)	413 (33.9)
Aetiology of chronic liver disease	
- Alcoholic	124 (10.2%)
- NAFLD, n (%)	345 (28.3%)
- hepatitis C	329 (27%)
- hepatitis B	159 (13%)
- mixed viral hepatitis	47 (3.9%)
- other causes	215 (17.6%)
VCTE (kPa)	6.7 (4.8-11.6)
2D-SWE (kPa)	7.1 (5.4-11.1)
Controlled Attenuation Parameter (dB/m)	248 ± 98 (100-400)
AST (IU/L)	60.3 ± 79.1 (14-1203)
ALT (IU/L)	69.4 ± 93.1 (5-961)
GGT (IU/L)	128.5 ± 189 (2-1788)
Total bilirubin (µmol/L)	17.4 ± 32 (4-481)
Platelet count (x10 ⁹ /L)	207 ± 82 (30-910)
International Normalized Ratio	1.08 ± 0.3 (0.8-4.2)
Alkaline Phosphatase (IU/L)	104.4 ± 88.2 (26-1303)
Albumin (g/L)	40.3 ± 4.7 (13-70)
Ferritin (µg/L)	260 ± 439 (5-6752)
Cholesterol (mmol/L)	5 ± 1.3 (1.2-11.8)

Unless otherwise indicated, results are expressed as mean \pm standard deviation (range).

n, number; na, non-available; s.d., standard deviation; NASH, Non-alcoholic steatohepatitis; BMI, body mass index; VCTE, Vibration-Controlled Transient Elastography; 2D-SWE, 2-Dimensional Shear Wave Elastography; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma glutamyltransferase.

Table 2. Optimal cut-off values of liver stiffness measurements using 2D-SWE for ruling out (VCTE <10kPa) or strongly suggesting (VCTE ≥15 kPa) compensated advanced chronic liver disease according to the Youden's index [best (sensitivity+specificity)-1], best accuracy ((true positive + true negative)/total), sensitivity ≥95%, specificity ≥95%, and for the fixed VCTE thresholds of 10 and 15 kPa.

<i>Aim</i>	<i>2D-SWE cut-off</i>	<i>Cut-off value</i>	<i>Sensitivity</i>	<i>Specificity</i>	<i>PPV</i>	<i>NPV</i>	<i>Accuracy</i>
		<i>(kPa)</i>	<i>(%)</i>	<i>(%)</i>	<i>(%)</i>	<i>(%)</i>	<i>y</i>
							<i>(%)</i>
<i>VCTE</i>	Youden index	<i>9.5</i>	90	91	96	78	90
<i><10 kPa</i>	Best accuracy	<i>10</i>	92	87	95	81	91
	10 kPa	<i>10</i>	92	87	95	81	91
	≥95% Sensitivity	<i>11</i>	95	82	93	86	91
	≥95% Specificity	<i>8.5</i>	84	95	98	70	87
<i>VCTE</i>	Youden index	<i>13</i>	90	94	89	95	94
<i>≥15 kPa</i>	Best accuracy	<i>14</i>	86	97	86	97	96
	15 kPa	<i>15</i>	81	98	81	98	95
	≥95% Sensitivity	<i>11</i>	95	88	95	88	89
	≥95% Specificity	<i>13</i>	90	94	89	95	94

Figures legends

Figure 1

Scatterplot of VCTE and 2D-SWE LS values with regression line (solid line). The Pearson correlation coefficient was 0.882 ($p < .0001$). The Lin coefficient that quantifies the deviation of the regression line from the line of perfect concordance (dotted line) was 0.846 ($p < .0001$). 2D-SWE values tends to be slightly higher than VCTE for low values and lower for high values with an area where 2D-SWE and VCTE values are the most concordant (schematically represented by the zone where the lines of perfect concordance and correlation intersect) between 7 and 8 kPa.

Figure 2

Distribution of 2D-SWE (dashed line) and VCTE (solid line) values as expressed as medians weighted by percentiles. The X axis represents the percentiles and the Y axis the liver stiffness in kPa. Peaks of the curves are the median (50th percentile). 2D-SWE values tend to be higher than VCTE values in low percentiles and lower in high percentiles with curves crossing around 8-9 kPa.

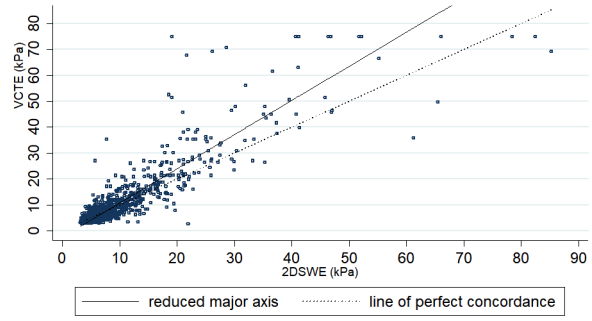
Figure 3

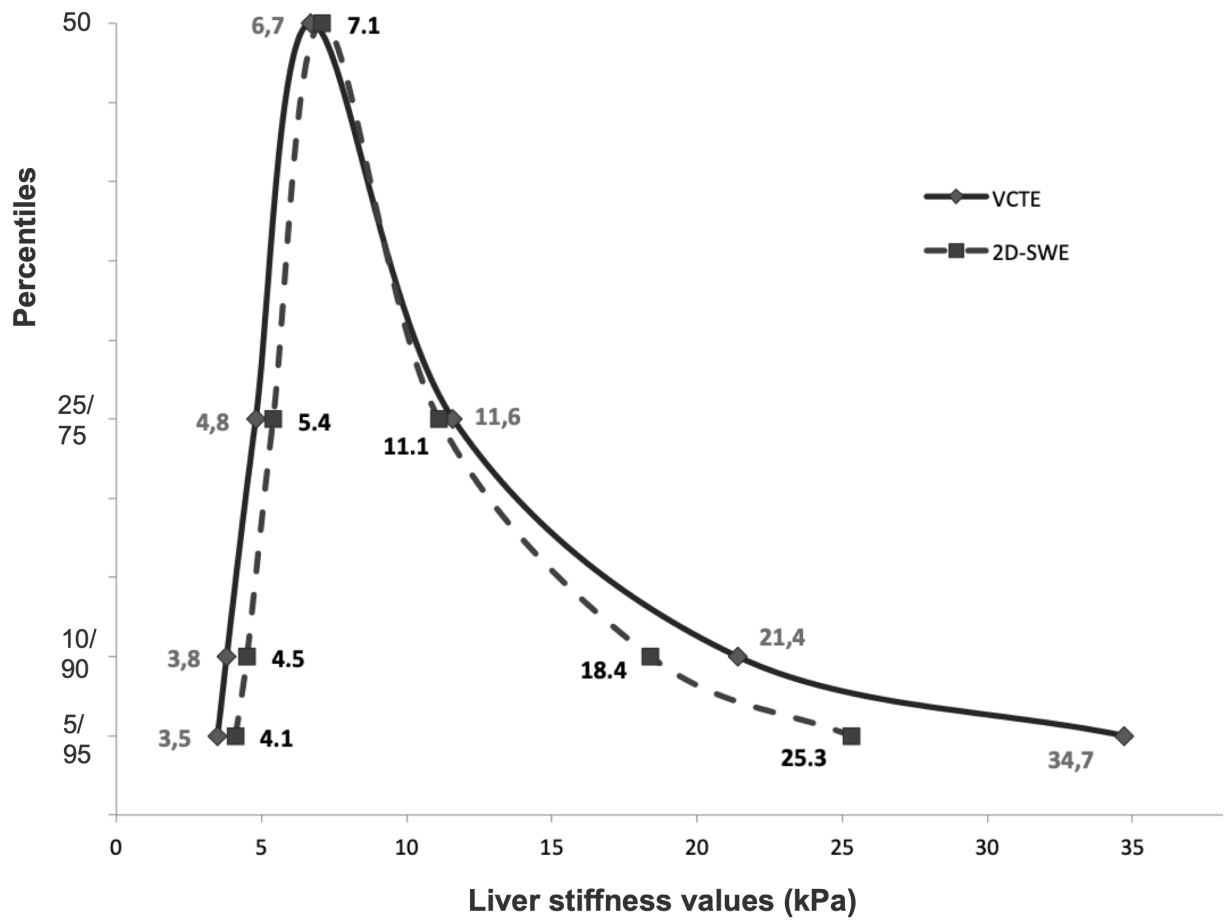
Bland-Altman plot showing the differences of LS values between VCTE and 2D-SWE in function of the mean values obtained with the two techniques.

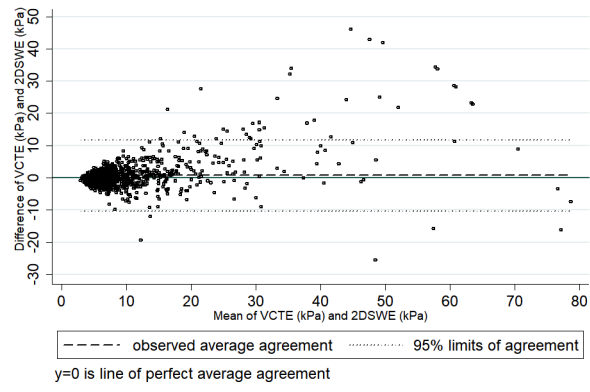
Horizontal lines indicate the mean difference (+0.75 kPa, dashed line), and the limits of agreement, which are defined as the mean difference ± 1.96 times the standard deviation of the differences (-10.3 and +11.8 kPa, dotted lines).

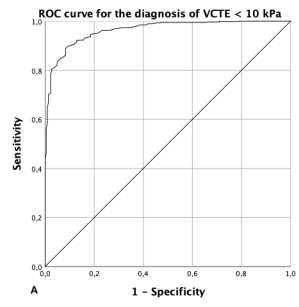
Figure 4

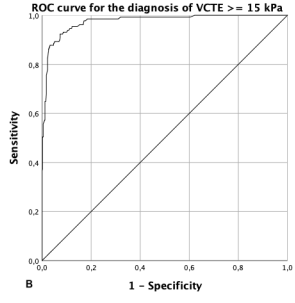
ROC curves of 2D-SWE performance for ruling out (A) and ruling in (B) compensated advanced chronic liver disease according to the Baveno VI criteria (VCTE < 10 kPa, and VCTE ≥ 15 kPa) in 811 patients with BMI < 30 kg/m² and reliable liver stiffness results. The AUC values (95% CI) were 0.964 (0.952-0.976) and 0.976 (0.963-0.988), respectively.











**2D-SWE performances
HCV patients**



Youden index thresholds



Best accuracy thresholds

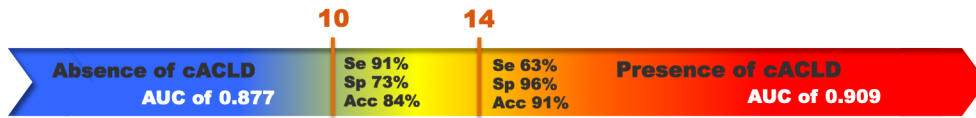


VCTE thresholds

**2D-SWE performances
NAFLD patients**



Youden index thresholds

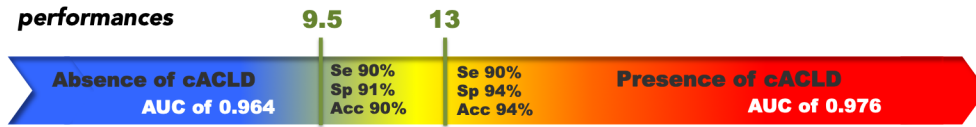


Best accuracy thresholds



VCTE thresholds

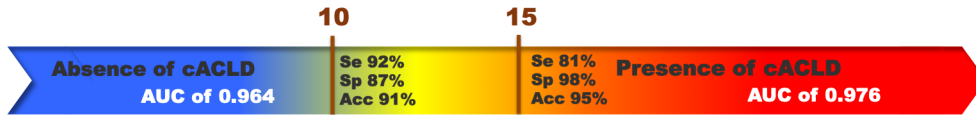
2D-SWE performances



Youden index thresholds



Best accuracy thresholds



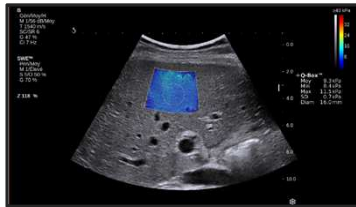
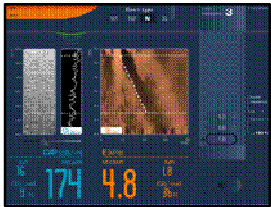
VCTE thresholds

Background: Inter-platform variation in measurement of liver stiffness evaluation poses challenges to development and use of ultrasound-based elastography techniques.

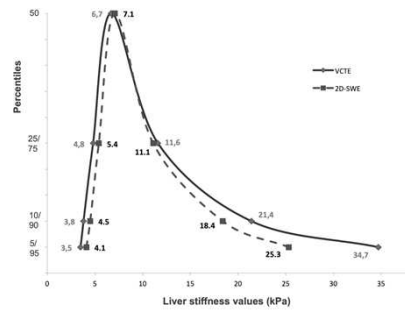
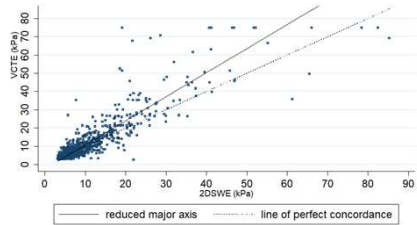
Findings: Measurement of liver stiffness by vibration-controlled transient elastography or 2-dimensional shear wave elastography (2D-SWE LSE) produces comparable results. 2D-SWE accurately identifies patients with advanced chronic liver disease, and a 10 kPa 2D-SWE cut-off value can be used to rule out cACLD.

Implications for patient care: Liver stiffness can be evaluated in patients with chronic liver disease equally well by VCTE or 2D-SWE.

1219 patients with chronic liver disease

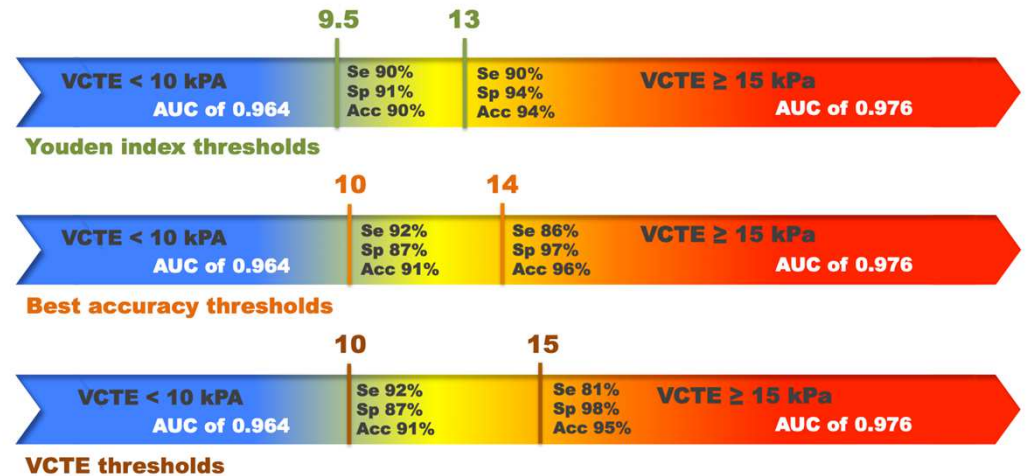


VCTE and 2D-SWE performed the same day



Correlation coefficient of 0.882
Concordance coefficient of 0.846
Best concordance between 7 - 9 kPa

2D-SWE performances and cut-offs for identifying VCTE lower than 10 kPa and higher than 15 kPa according to Baveno VI recommendations



Clinical Gastroenterology
and Hepatology