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Elastogram quality assessment score in vibration-controlled transient elastography: Diagnostic performance compared to digital morphometric analysis of liver biopsy in chronic hepatitis C

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Summary

Vibration-controlled transient elastography (VCTE) is widely used for noninvasive fibrosis staging in chronic hepatitis C. However, internal validation is based solely on variability and success rate and lacks reproducible quality indicators. We analysed the graphic representation of shear wave propagation in comparison with morphometric results of liver biopsy, eliminating observer variability bias. Individual elastograms were classified according to two morphologic criteria: extension of wave propagation (length of the graphic representation) and shear wave dispersal (level of parallelism displayed in the elastogram). Then, a score based on these criteria stratified the elastogram in classes I through III (highest to lowest technical quality). Liver stiffness results of each measurement were compared with collagen contents in liver biopsy by morphometric analysis. A total of 3243 elastograms were studied (316 patients). Digital morphometry in liver biopsy showed significant fibrosis in 66% of samples and advanced fibrosis in 31%. Elastogram quality analysis resulted in 1438 class I measurements (44%), 1070 class II (34%) and 735 class III. Area under the receiver operating curve (AUROC) for severe fibrosis according to class (I, II and III) was 0.941, 0.887 and 0.766, respectively. For advanced fibrosis, AUROCs were 0.977, 0.883 and 0.781, respectively. Spearman's correlation testing for all classes and levels of fibrosis demonstrated significant independent association ($r^2 = -.95$, $P < .01$). Our study is the first to propose measurable quality criteria for VTCE and to validate them against objective assessment of liver biopsy through digital morphometric imaging analysis. We concluded that VCTE performance is significantly influenced by quality assessment of individual measurements. Considering these criteria in clinical practice may improve accuracy.

KEYWORDS

chronic hepatitis C, digital morphometric analysis, elastogram, liver fibrosis staging, quality assessment

Abbreviations: AUROC, area under the receiver operating curve; CHC, chronic hepatitis C; CPA, collagen proportional area; LB, liver biopsy; LF, liver fibrosis; LS, liver stiffness; VCTE, Vibration-controlled transient elastography.

1 | INTRODUCTION

Chronic hepatitis C (CHC) affects over 70 million people worldwide with 500 000 liver-related deaths annually and 4 million new infections each year. Currently, CHC comprises 27% of world cases of cirrhosis and 25% of HCC occurrences. The risk of progression to cirrhosis 20 years after infection is estimated in 30% with 1%-3% per year risk of developing hepatocellular carcinoma (HCC) thereafter. Liver fibrosis (LF) is associated with disease progression and liver-related events, and therefore, baseline staging and longitudinal staging are central in CHC care.[1,2]

Noninvasive diagnostic approaches for liver fibrosis (LF) staging in CHC have been validated in different modalities including biomarkers and imaging techniques, mainly elastography. Elastography comprises different techniques aiming to characterize elastic properties of materials. Vibration-controlled transient elastography (VCTE—FibroScan®) has been shown to correlate well with histological evaluation through liver biopsy (LB) for diagnosis of both significant fibrosis (SF) and advanced fibrosis (AF). However, sensitivity and negative predictive values have consistently been reported as suboptimal, generally below 85%, especially in the lower stages of fibrosis.[3-8]

Vibration-controlled transient elastography measures liver stiffness (LS), expressed in kilopascals (kPa), and represents the elastic modulus of a liver tissue area derived from the propagation velocity of a mechanical shear wave generated from the transducer and measured by pulsed-echo ultrasound. A graphic spatiotemporal representation of the shear wave propagation through the liver parenchyma—the elastogram—is obtained with each measurement.

Quality criteria for VCTE results consist solely of technical indicators: the total amount of measurements and the success rate (ie, the number of valid measurements divided by total acquisitions) and variability assessments, such as the interquartile range and its relation to the median of valid measurements. Current published standards consider acceptable a 60% minimal success rate and <0.30 IQR/median (with <0.1 IQR/median as the optimal variability for interpretation of lower levels of fibrosis).[9]

Moreover, concern has been raised against liver biopsy as the gold standard for LF staging with regard to sampling and observer variability, therefore hindering performance indicators for comparators. Diagnosis of significant fibrosis (METAVIR stages $F < 2$ vs $F \geq 2$) was demonstrated to be particularly challenging with lowest inter- and intra-observer agreement and area under the receiver operating curves (AUROCs).[10-13] In that sense, fibrosis quantification in computerized liver fragment images through digital morphometric analysis was developed as an objective approach to histological examination of LB correlating with other markers of liver fibrosis progression (such as hepatic venous pressure gradient) and liver-related clinical events.[14-17]

We aimed to propose a set of quality criteria for VCTE measurements based on morphologic evaluation of the graphic representation of shear wave propagation—the elastogram. To further validate and assess diagnostic performance, we compared individual measurements with quantitative digital morphometric analysis of LB samples rather than pathologist-based histological analysis, providing an objective quantification and eliminating operator-related bias.

2 | METHODS

2.1 | Patients

From January 2014 to August 2016, adult patients chronically infected with hepatitis C virus were prospectively enrolled from a university hospital outpatient viral hepatitis clinic (State University of Campinas, Sao Paulo, SP, Brazil). Patients were included if they had HCV RNA detectability at least 6 months after initial seropositivity for anti-HCV antibodies, and a liver biopsy performed no longer than 6 months prior to enrolment (with liver fragments of at least 15 mm length and a minimum representation of 6 portal tracts). Patients who were co-infected with human immunodeficiency virus (HIV) or hepatitis B virus (HBV) were excluded, as were those with overt clinical diagnosis of cirrhosis (defined as the presence of ascites or endoscopic signs of portal hypertension) or previous liver transplantation.

Demographic and anthropomorphic characteristics comprise gender, weight, height, body mass index (BMI) and alcohol consumption. Biochemical, virological and haematological variables were included from routinely collected samples, and results were obtained from no more than 90 previous days, including ALT, AST, gamma-glutamyltransferase (GGT), alkaline phosphatase (AP) and platelet counts.

2.2 | Liver biopsy and digital morphometric analysis

LB was indicated by the assisting physician in the context of LF and necroinflammatory activity staging for evaluation of antiviral treatment. Ultrasound-guided LB samples of the right hepatic lobe, fixed in 10% formalin, embedded in paraffin, had 4-mm-thick sections stained with Masson's trichrome for morphometric analysis. Significant fibrosis was defined as $F \geq 2$ according to the METAVIR staging system. Advanced fibrosis and cirrhosis were diagnosed based on METAVIR levels, $F \geq 3$ and $F = 4$, respectively.

Image capture of the entire liver specimen section was performed on 40× optical magnification using Olympus DP72 microscope camera (Olympus Corporation, Tokyo, Japan) with 4140 × 3096 pixel resolution and ISO 1600. Unprocessed files were converted to TIFF format with minimum compression. Using Adobe PhotoShop version CC 2017, background, anatomic and handling artefacts (such as liver capsule, large portal tracts, vessel or biliary lumens, soft tissue, dusts or folds) were manually removed. Panoramic 32-bit RGB slide images were converted to 8-bit greyscale using the red channel as reference for optimum contrast enhancement of fibrous tissue (stained in blue). Histogram thresholding was performed using an automated algorithm resulting in a binary two-dimensional pattern. Collagen proportionate area (CPA) was measured by automated direct pixel counting of fibrous tissue in the binary pattern divided by the total

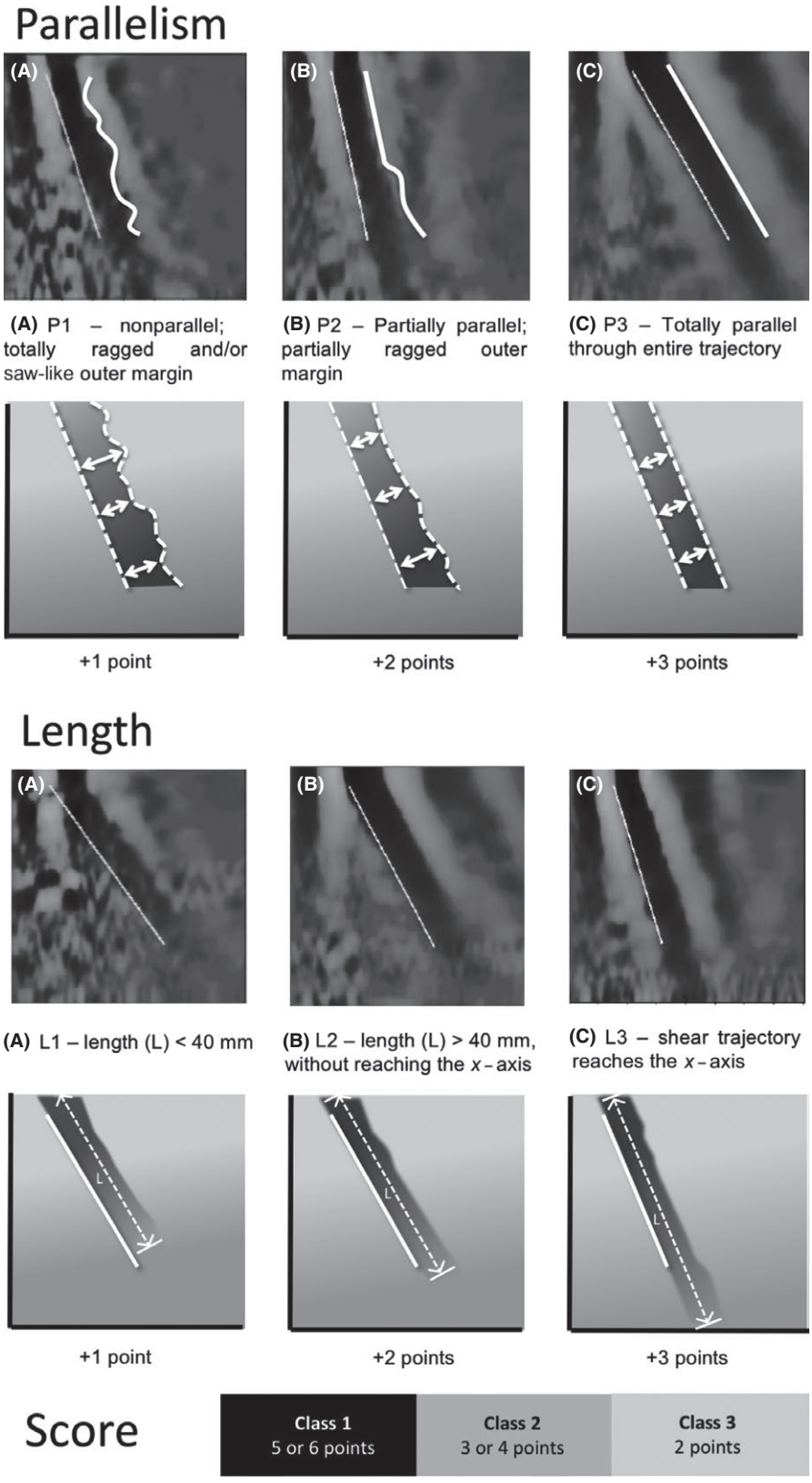

FIGURE 1 Elastogram quality score criteria

are of the liver specimen image. CPA thresholds for significant fibrosis and advanced fibrosis were 6.5% and 13.7%. METAVIR level correspondence[18] was considered specifically for Cohen's kappa correlation: F0—up to 3.0% CPA, F1—3.6%, F2—6.5%, F3—13.7% and F4—27.8%.

2.3 | Transient elastography and elastogram quality evaluation

Vibration-controlled transient elastography evaluates liver elasticity by mechanically generating a physical shear wave through a piston

with a 20-ms sinusoidal impulse. The propagation velocity of the shear wave is measured by a pulsed-echo ultrasound with a 3 MHz amplitude and 6000 Hz repetition frequency through an area of interest comprised of a cylinder with a 10 mm diameter and 40 mm length located from 25 to 65 mm bellow the skin (considering the M probe). Spatiotemporal propagation of the shear wave through the liver parenchyma is intercorrelated between successive echo pulses with each measurement and graphically represented in the elastogram with time index in the *x*-axis and vertical distance in the *y*-axis. The shear wave front is represented by a black negative line. Derivating from Green's elastodynamic function, Young's modulus is calculated based on the slope of the shear wave front using the following formula: $E = 3\rho V^2$ (where p represents mass density, which is constant in soft body tissue [1000 kg/m^3], and V is for shear wave velocity).

Transient elastography was performed using FibroScan® model 502 (Echosense, Paris, France) M probe after 2-hour fasting, on the right liver lobe, through intercostal spaces with the patient in a supine position by a previously trained and experienced operator with over one thousand previous examinations and blinded to biochemical or histological data. According to the published literature, significant fibrosis was defined as liver stiffness results >7.1 kPa and >9.5 kPa for advanced fibrosis. Acceptable LS values represented the median of at least 10 valid measurements with <0.1 variability (represented by interquartile range/median - IQR/med), or <0.3 for LS values >7.1 kPa, and >60% success rate.

Initially, 4 different graphical characteristics were determined for each elastogram, namely width, length, parallelism and colour homogeneity. Bootstrapping samples (each comprising 1000 individual measurements) were evaluated, and regression analysis determined that length and parallelism were independently associated with higher accuracy. Elected criteria for elastogram quality assessment therefore were shear wave propagation length, representing adequate topographic measurement in the liver parenchyma; and shear ware displacement linearity, or parallelism in the spatiotemporal graphic, representing uninterrupted propagation and homogenous tissue in the area of interest. Each criterion was scored in three categories. For length, shear wave front propagation extending less than the 40 mm of measured area received 1 point, 2 points if it extended beyond the 40 mm measured area

TABLE 1 Baseline characteristics of subjects

Characteristic	Value (range)
Median age (years)	53 (26-71)
Gender (male)	61%
Ethnicity (Caucasians)	43%
Body mass index (BMI, kg/m^2)	27.2 (19.8-37.9)
BMI >25	32%
BMI >30	11%
Mean ALT (IU/mL)	39 (18-99)
Mean AST (IU/mL)	44 (20-114)
Mean GGT (IU/mL)	38 (11-287)
Mean AP (IU/ml)	104 (66-261)
Mean platelets (g/dL)	191 (78-306)
Treatment-naïve	64%
Nonresponders to PEG/RBV	36%
Median CPA (% of total area)	10.1
Significant fibrosis (CPA >6.5%)	66%
Advanced fibrosis (CPA >13.7%)	31%
Mean LB fragment length (mm)	17.6 (15.2-29.9)
Mean CAP on VCTE (db/m^2)	229 (157-389)

BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; AP, alkaline phosphatase; PEG/RBV, peginterferon/ribavirin; CPA, collagen proportionate area; LB, liver biopsy; VCTE, vibration-controlled transient elastography.

TABLE 2 Diagnostic performance of vibration-controlled transient elastography stratified by elastogram quality

	Elastogram classes		
	Class I	Class II	Class III
	Significant fibrosis		
Sensitivity	92.0	79.3	71.1
Specificity	97.1	85.1	80.2
Accuracy	93.6	81.3	74.2
Cohen's kappa value	0.82	0.79	0.71
Positive likelihood ratio	30.6 (19.4-51.0)	5.32 (4.15-6.82)	3.59 (2.78-4.64)
Negative likelihood ratio	0.08 (0.07-0.10)	0.24 (0.21-0.28)	0.36 (0.31-0.42)
	Advanced fibrosis		
Sensitivity	93.4	84.1	75.2
Specificity	98.4	88.4	83.2
Accuracy	96.9	87.0	80.6
Cohen's kappa value	0.92	0.85	0.77
Positive likelihood ratio	58.37 (36.2-95.7)	7.25 (5.91-8.90)	4.48 (3.64-5.51)
Negative likelihood ratio	0.07 (0.05-0.10)	0.18 (0.14-0.23)	0.30 (0.24-0.37)

and 3 points if the shear wave representation crossed the *x*-axis. For parallelism, if the outer edge of the shear wave front is irregularly serrated from the start of the measurement area, it received 1 point, an irregular and ragged outer edge that extends partially through the measurement area corresponds to 2 points and, finally, a completely linear and parallel outer edge received 3 points. The sum of the points received in the two previously described criteria corresponded to the final score classification of the individual elastogram: Class I for 5 or 6 points (representing the maximum measurement quality), class II for 3 or 4 points and class III for 2 points (representing the minimum measurement quality; Figure 1). For the purpose of multivariate analysis against other technical factors associated with accuracy, mean elastogram quality score was determined for the entire examination.

A validation subanalysis comprised of 10% of the total study population was carried out to assess interobserver agreement in elastogram classification between two independent observers. Intraclass correlation was determined for the entire study population.

2.4 | Statistical analysis

Collected data were analysed with descriptive statistical analysis using SPSS software version 17 (SPSS Inc., Chicago, IL, USA) and OpenEpi version 3.03a (Emory, USA). Continuous variables were analysed with Student's *t* test or Mann-Whitney test, where appropriate. Categorical variables were compared using Chi-squared test or Fisher's exact *t* test. Diagnostic performance was assessed using AUROC, accuracy, sensitivity, specificity, positive and negative likelihood ratios. Correlation between morphometric quantitative analysis of LB and VCTE measurements was performed with kappa and Spearman's correlation test. Reproducibility was evaluated with intraclass correlation. Significance was two-sided and defined as <.05 type I error probability.

2.5 | Ethical considerations

Study design, protocols, patient enrolment, data collection and storage were in accordance with ethical considerations supported by the updated 1975 Declaration of Helsinki. Patients were included in the study after written informed consent was obtained. The study was reviewed and approved by Ethics Committee for Research of the School of Medical Sciences—State University of Campinas (UNICAMP).

3 | RESULTS

A total of 3243 individual VCTE measurements were included in the final analysis corresponding to 316 patients with median age of 53 years. Caucasians comprised of 74% of study population and 61% were male. Mean levels of ALT, AST and platelets were 44, 39 IU/mL and 191 000, respectively. Body mass index over 25 was present in 32% of subjects and scored >30 in 11% (Table 1).

3.1 | Digital morphometric analysis of LB

Collagen proportional area in all analysed samples ranged from 1.7% to 34.3% (median value 10.1%). Significant fibrosis was detected in

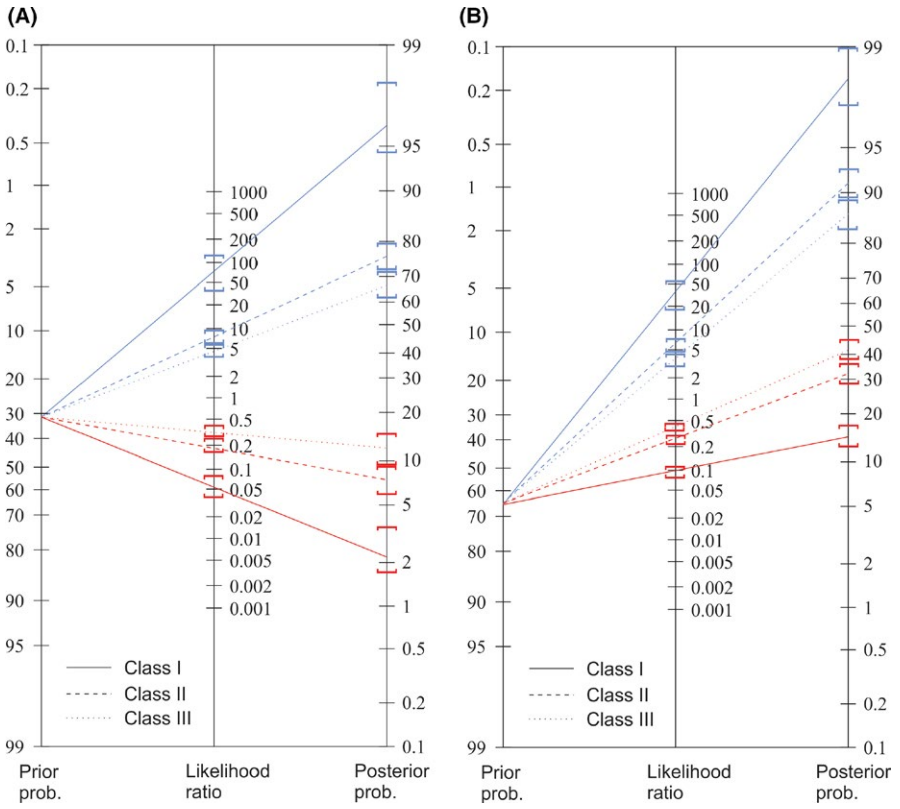

FIGURE 2 Fagan nomogram of vibration-controlled transient elastography diagnostic likelihood stratified by elastogram quality class. A, Advanced fibrosis; B, Significant fibrosis

66% of LB (mean CPA 9.7%) and advanced fibrosis in 31% (mean CPA 16.6%). Eleven per cent of LB samples had CPA over 27.8%, corresponding to established cirrhosis. (Table 1).

3.2 | VCTE and elastogram quality assessment

Overall, mean LS was 8.7 ± 2.1 kPa (range: 3.9-26.5 kPa). Fifty-eight per cent (1881) of VCTE measurements showed significant fibrosis and 34% (1103) pointed to advanced fibrosis. Considering final LS results (in accordance with the previously described internal validation success rate and variability criteria), significant fibrosis and advanced fibrosis were diagnosed in 69% and 30% of patients, respectively. Mean IQR/median ratios and success rate for significant fibrosis and advanced fibrosis measurements were 0.19 and 0.07, respectively. Overall mean success rate was 0.88 ± 0.07. Mean LS and fibrosis level distribution did not differ across elastogram quality classes.

Score-based quality assessment classified 1438 (44%) class I elastograms (mean score 5.511 ± 0.502), 1070 (34%) class II (mean score 3.644 ± 0.496) and 735 (22%) class III. Intraclass correlation for all classes was >0.9, and interobserver agreement in the validation study was 0.92.

For class I elastograms, LS ranged from 4.2 to 23.9 kPa (mean: 7.9 kPa). For significant fibrosis, sensitivity, specificity, positive and negative likelihood ratios were 92%, 97%, 30.6 and 0.08, respectively; for advanced fibrosis, sensitivity, specificity, positive and negative likelihood ratios were 95%, 99%, 67.1 and 0.05. Class II VCTE measurements yielded LS ranging from 3.9 to 21.4 kPa (mean: 8.8) with sensitivity, specificity, positive and negative likelihood ratios for significant fibrosis of 79%, 85%, 5.32 and 0.24 and for advanced fibrosis of 84%, 88%, 7.25 and 0.18, respectively. Considering class III elastograms, sensitivity, specificity, positive and negative likelihood ratios for significant fibrosis were 71%, 80%, 3.59 and 0.36, respectively; and 75%, 83%, 4.48 and 0.30, respectively, for advanced fibrosis (Table 2, Figure 2). AUROCs for class I, II and III measurements were 0.941, 0.870 and 0.766, for significant fibrosis and 0.977, 0.883 and 0.781, respectively, for advanced fibrosis (Figure 3).

Spearman's coefficient for AUROC and elastogram classes demonstrated significant positive correlation between classes in both significant fibrosis and advanced fibrosis ($r^2 = -.95$, $P = .002$). On multivariate analysis (considering mean elastogram quality score, success rate and IQR/median), mean elastogram quality was the only technical aspect independently associated with diagnostic accuracy (OR: 4.91, 95% CI: 2.40-6.17; Figure 3).

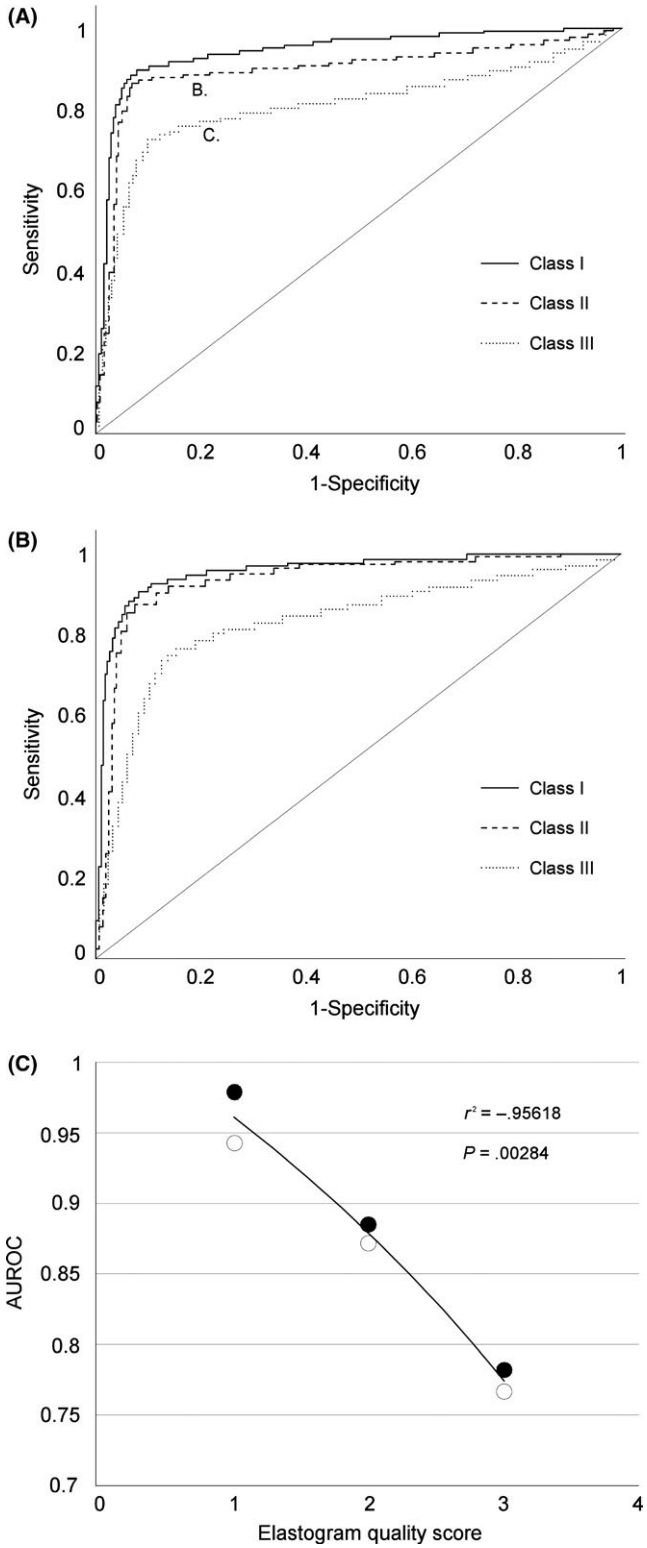

FIGURE 3 Plotted area under the receiver operating curves (AUROCs) for vibration-controlled transient elastography (VCTE) according to elastogram quality score and Spearman's correlation. A, AUROC for VCTE in advanced fibrosis; B, AUROC for VCTE in significant fibrosis; C, Spearman's correlation

4 | DISCUSSION

Our study is the first to propose and validate objective criteria to assess the quality of VCTE individual measurements. Elastogram

TABLE 3 Logistic regression of factors associated with diagnostic accuracy in vibration-controlled transient elastography

	Correctly classified patients	Incorrectly classified patients	OR (95% CI)	*P* value
Success rate	90.1	88.9	1.99 (0.91-3.35)	.067
IQR/med (LS < 7.1)	0.19	0.22	2.11 (0.86-3.01)	.152
IQR/med (LS > 7.1)	0.07	0.08	0.95 (0.77-2.58)	.470
Elastogram quality score	5.57	3.84	4.91 (2.40-6.17)	<.001

classification was based on morphologic characteristics of the spatiotemporal representation of shear wave propagation in the liver tissue. Wave front representation length and parallelism were used to assess quality. Physically, these attributes are conditioned by tissue homogeneity, where structures such as portal or hepatic vein branches or biliary ducts can deflect and alter the mechanical wave trajectory and therefore the parallelism in the elastogram; and extension, in the sense that measurements executed deeper and more central in the right lobe are more likely to provide longer shear displacement and allow for more accurate velocity assessment before attenuation. Such attributes have been previously explored in early developmental research in liver elastography techniques using phantom elements as models and therefore provide the closest resemblance to ideal physical conditions for Young's modulus calculation.[18-22]

Vibration-controlled transient elastography diagnostic performance in CHC has been consistently stronger for advanced fibrosis than that for significant fibrosis. In a meta-analysis of thirty-five studies, mean AUROC for significant fibrosis was 0.85 (95% CI: 0.80-0.89) and for advanced fibrosis was 0.89 (95% CI: 0.88-0.91).[3] One of the largest studies to assess single cut-off approach for significant fibrosis diagnosis found 67% sensitivity and 89% specificity.[4] Dual cut-off strategies for ruling in and out significant fibrosis have been proposed with varying performance.[23] Our results demonstrate that using a single >7.1 kPa cut-off for significant fibrosis on class I measurements yielded unprecedented >90% sensitivity and specificity with 0.941 AUROC.

In an attempt to predict accuracy, intrinsic technical factors associated with VCTE are used for internal validation, such as variability and success rate and have been evaluated in prospective studies with mixed results. Higher (>0.20) IQR/median correlates with discordance between LS and LB METAVIR staging, and optimal values are still under debate. Currently accepted standards (less than 0.1 variability with acceptable <0.30 for LS values >7.1) were used and reflect reliable or very reliable results. However, although statistically significant, AUROC for significant fibrosis of measurements with lowest variability scores is 0.886. Success rate has also been classically associated with improved performance; however, recent studies show that achieving higher values is not an independent predictor of accuracy.[24-29] Our results introduce a new approach to internal examination validation, based not on variability, but demonstrating the impact of individual measurement quality, which were, on multivariate analysis, the only technical variability independently associated with correct patient classification (Table 3).

Also, histological analysis of LB as the gold standard for noninvasive LF staging modalities poses important issues. Sample variability, especially in lower fibrosis levels, has been found to occur in over 55% of cases when left and right lobe fragments are compared.[12] More importantly, inter- and intra-observer variability are considerable with low kappa correlation values even for experienced liver pathologists. Digital morphometric collagen quantification compared to standard pathological examination has found AUROCs for LB assessment of adjacent fibrosis levels to be <0.85 for F4 vs F3 and <0.70 for F3 vs F2, with overall performance in significant fibrosis staging of 0.89.[30] In fact, theoretical models for expected AUROCs of hypothetical comparators in different scenarios stratified by levels of LB diagnostic performance demonstrated that in real world settings is mathematically impossible even for a perfect test to score higher than 0.90 AUROCs.[11] Therefore, we elected digital morphometric analysis as our gold standard as it offers an objective and quantifiable evaluation of LF with very good reproducibility and has been shown to correlate well with liver-related outcomes.[10,31] However, specific METAVIR stage correspondence thresholds still lack sufficient validation and therefore were not considered for comparison. Nonetheless, in the current paradigm of CHC care, as well as for many other causes of chronic liver diseases, significant and advanced fibrosis diagnosis is more important than specific METAVIR-based staging.

Other potential limitations of our study include the relatively low prevalence of advanced cirrhosis (8% of LS >20 kPa) not allowing to assess score performance in this setting and, also, high overall success rate in VCTE measurements (>85%) possibly undermining the analytical power of multivariate analysis to determine its impact on diagnostic accuracy. Moreover, although internally validated by double-blind observation of a sample of total subjects, the elastogram quality criteria and score require external validation to assess reproducibility across different patient populations. Also, in the final proposed quality criteria, both evaluated parameters were treated as categorical variables; indeed, in the initial analysis, elastogram length was calculated as a continuous measurement; however, applicability in clinical practice would be conditioned to specific measuring equipment. Comparing AUROCs for elastogram length as a continuous variable (directly measured) or as a categorical, intuitively assessed variable, resulted in less than −0.004 variability, and therefore, we elected a more

intuitive visual scoring system for easier clinical applicability. Finally, digital morphometric analysis of LB, considered to be an important strength factor for our results, still lacks methodological standards for image capture and processing, potentially affecting comparisons between different techniques. Further studies are required to establish diagnostic performance of elastogram quality scoring in other causes of chronic liver disease.

Among a variety of elastography-based technologies for LF staging, VCTE remains one of the most studied and scientifically substantiated with established prognostic implications both as a static point-based risk estimation and in longitudinal patient follow-up. However, previous performance results have been suboptimal in discriminating lower fibrosis stages and, perhaps, hindered by an imperfect gold standard. We propose a new approach to validate and stratify VCTE measurements based on elastogram quality, potentially allowing for selection of high-quality measurements demonstrably able to predict significant fibrosis and advanced fibrosis with higher accuracy than any previous report. Furthermore, as attention is drawn to the importance of longer follow-ups in order to evaluate fibrosis dynamics in treated and untreated populations, correlation of LS measurements is paramount. In that sense, moving beyond an exclusively variability-based quality indicator is welcome, and objectively scoring individual measurements can provide stronger basis for comparing results in clinical decision-making.

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