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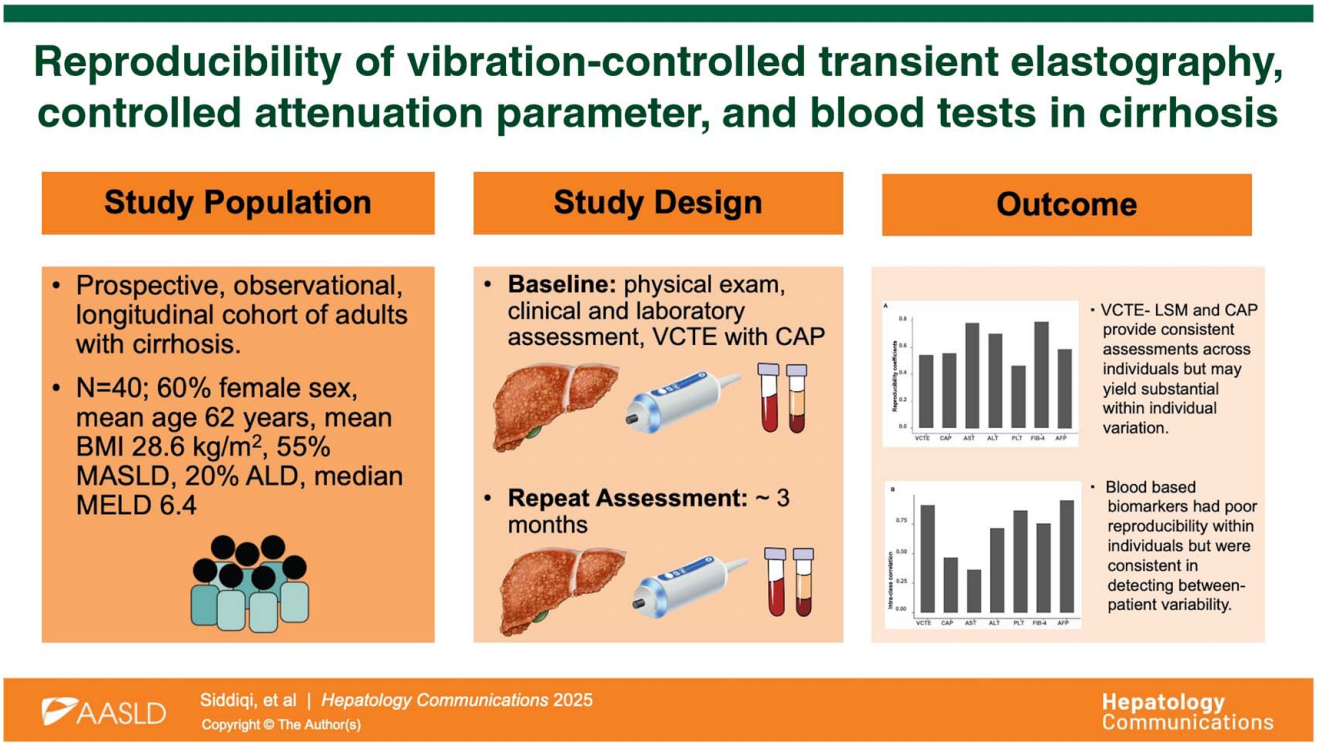
VISUAL ABSTRACT



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ORIGINAL ARTICLE

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Reproducibility of vibration-controlled transient elastography, controlled attenuation parameter, and blood tests in cirrhosis

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Abstract

Background: Qualification of non-invasive tests (NITs) and blood biomarkers for fibrosis severity and risk assessment is an unmet need in clinical care for cirrhosis. The paucity of reproducibility data for imaging and blood biomarkers in cirrhosis hinders their application for longitudinal monitoring. The aim of this study was to evaluate the reproducibility of imaging and blood biomarkers in a prospective cohort of adults with cirrhosis.

Methods: We prospectively enrolled adults with cirrhosis in an observational, longitudinal cohort study. Participants completed a research visit with vibration-controlled transient elastography (VCTE) with liver stiffness measurement (LSM) and controlled attenuation parameter (CAP) and blood testing, including AST, ALT, platelets, alpha-fetoprotein (AFP), and the Fibrosis-4 Index (FIB-4). Biomarkers were repeated a median of 3 months apart without any interim intervention. The *primary* outcome was the reproducibility of each biomarker as assessed by the reproducibility coefficient (RDC%), within-participant coefficient of variation (wCV), intraclass correlation coefficient (ICC), and Bland–Altman analysis.

Results: In total, 40 participants (mean age 62, 60% female, mean BMI 28.6 kg/m^2) had VCTE/CAP, 38 AST/ALT, and 26 had AFP at both time points. The RDC% for VCTE-LSM was 54.4, wCV 0.19, and ICC 0.91. VCTE CAP had an RDC% of 56, a wCV of 0.30, and ICC 0.47. AFP had an RDC% of 58, a wCV of 0.21, and an ICC of 0.95. RDC% for AST, ALT, and FIB-4 ranged from 70% to 79%. On Bland–Altman analyses, VCTE-LSM demonstrated the lowest relative bias (0.4%).

Abbreviations: AFP, alpha-fetoprotein; ALD, alcohol-associated liver disease; BMI, body mass index; CAP, controlled attenuation parameter; FIB-4, Fibrosis-4 Index; ICC, intraclass correlation coefficient; LoA, limits of agreement; LSM, liver stiffness measurement; MASLD, metabolic dysfunction–associated steatotic liver disease; MRE, magnetic resonance elastography; NIT, non-invasive test; RDC%, percent reproducibility coefficient; UCSD, University of California San Diego; VCTE, vibration-controlled transient elastography; wCV, within-participant coefficient of variation.

Conclusions: Prospective assessment of repeat biomarkers in adults with cirrhosis found that VCTE-LSM and CAP provide consistent assessments across individuals but may yield substantial within-individual variation. Blood-based biomarkers had poor reproducibility within individuals but were consistent in detecting between-patient variability. These data can inform ultrasound-based non-invasive testing qualification by defining thresholds that may reflect measurement variability rather than true biologic change over time.

Keywords: blood biomarkers, CAP, NILDA, NIT, repeatability

INTRODUCTION

Liver cirrhosis poses a major global health crisis, significantly contributing to morbidity and mortality, including the development of HCC and the need for liver transplantation.[1,2] Improving outcomes for individuals with cirrhosis relies heavily on early detection and treatment.[3,4] While liver biopsy is considered the gold standard for diagnosing cirrhosis, it is an invasive procedure that introduces adverse risks to patients.[5] In contrast, non-invasive tests (NITs) offer a safer alternative with demonstrated diagnostic and prognostic value.[5,6] Existing non-invasive modalities for identifying liver fibrosis and steatosis include ultrasound-based imaging tests such as vibration-controlled transient elastography (VCTE) with liver stiffness measurement (VCTE-LSM) and controlled attenuation parameter (VCTE-CAP).[5] In addition, blood-based tests, including AST, ALT, platelets, and the Fibrosis-4 (FIB-4) Index, have shown clinical utility in evaluating liver disease severity, and alpha-fetoprotein (AFP) has utility in screening for HCC.[7–9]

Despite the proven efficacy of NITs in assessing liver fibrosis severity, their regulatory qualification in patients with cirrhosis is a major unmet need. In particular, their potential use for longitudinal monitoring and assessing disease progression has not been validated, as studies have not yet been performed to assess their reproducibility across time and operators. Previously, our group investigated the same-day, same operator technical repeatability of NITs in patients with cirrhosis and demonstrated that VCTE had strong reliability and repeatability in liver stiffness measurements.[10] Reproducibility of diagnostic testing is a related but distinct concept that characterizes the extent to which a given test yields consistent results under varying conditions, such as different operators or at different times. Reproducibility is a critical test characteristic as it speaks to the reliability of results across real-world settings and their utility in guiding clinical and/or research decision-making, as it informs whether differences in results over time reflect true biologic change compared with test variability. The primary aim of this study is to evaluate the reproducibility of NITs in cirrhosis, including VCTE-LSM, VCTE-CAP, and blood-based biomarkers, across different days and operators. These NITs were chosen given their accessibility and cost-effectiveness.[11–13]

METHODS

Study design and participants

We prospectively enrolled adults with cirrhosis in an observational, longitudinal cohort study (San Diego Cirrhosis Registry) (Figure 1). Participants were

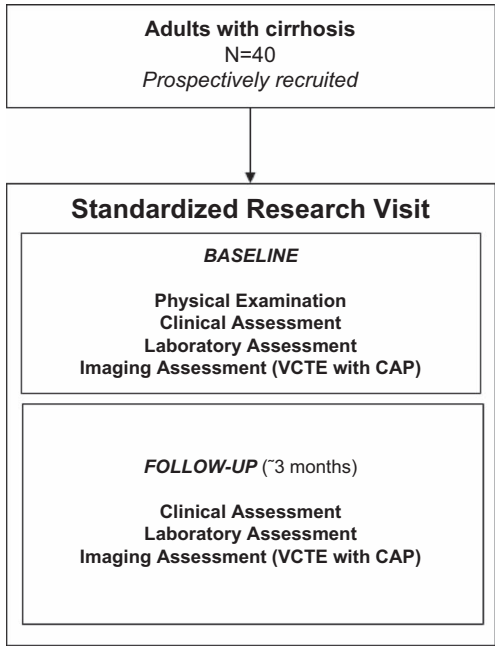

FIGURE 1 Study diagram of the San Diego Cirrhosis Registry. Abbreviations: CAP, controlled attenuation parameter; VCTE, vibration-controlled transient elastography.

recruited from hepatology, primary care, and community-based clinics in the greater San Diego area and underwent a standardized clinical evaluation at the University of California San Diego (UCSD), including demographics, medical history, and a physical examination with anthropometric measurements and vital signs. Before enrolling in the study, all participants provided written informed consent, and the study was approved by the UCSD Institutional Review Board. All all research was conducted in accordance with both the Declarations of Helsinki and Istanbul.

Inclusion and exclusion criteria

Inclusion criteria were as follows: (a) age $\geq$18 years old; (b) diagnosis of cirrhosis, based on histology, or imaging/liver stiffness measurement (LSM) data consistent with cirrhosis [magnetic resonance elastography (MRE) LSM $\geq$4.7 kPa or VCTE-LSM $\geq$11.8 kPa[14] *plus* platelet count $<$125K, or FIB-4 $\geq$2.67]; (c) able and willing to consent and participate in the study. Exclusion criteria were as follows: (a) liver disease other than cirrhosis; (b) current diagnosis of drug-induced liver injury; (c) receiving drug or placebo in treatment clinical trial currently or within the prior 30 days; (d) weight loss or gain of $\geq$5 kg in prior 3 months; (e) pregnant or nursing female; (f) known history of congestive heart failure; (g) ALT or AST $\geq$250 U/L; (h) clinically significant ascites, defined as need for paracentesis within the last 3 months, or furosemide dose more than 40 mg taken orally once a daily.

Clinical research evaluation visit

A standardized clinical evaluation was conducted for all participants at enrollment, including a detailed clinical history, an anthropometric exam, and phlebotomy with blood testing at the UCSD MASLD Research Center. An experienced clinical research member documented all details, including sex, age, height, weight, body mass index (BMI), and ethnicity. The history of alcohol intake was confirmed with the Alcohol Use Disorders Identification Test and the Skinner questionnaire. All study participants were informed to fast for a minimum of 12 hours before laboratory tests and to avoid changes in medications, physical activity, diet, and alcohol consumption between study visits. Participants completed imaging and blood tests at the time of enrollment, and again ~3 months after enrollment without any interim intervention. Participants were instructed to avoid changes in medications, physical activity, diet, and alcohol consumption between study visits. Medications, alcohol use, and vital signs were reassessed at the time of repeat NIT assessment.

VCTE-LSM and VCTE-CAP assessment

Participants underwent 2 ultrasound vibration-controlled transient elastography (VCTE) examinations with LSM and CAP using FibroScan Expert 630 (M Probe; XL Probe; Echosens, Paris, France) at 2 different time points ~3 months apart. The ultrasound examinations were performed by 2 different experienced operators at the MASLD Research Center at UCSD. Participants were told to fast for at least 4 hours before VCTE examinations. To be considered a valid VCTE exam, the IQR was $\leq$30%.

Blood biomarker assessment

Blood samples were collected after VCTE examinations and were analyzed for AST, ALT, AFP, platelet count, and components of the FIB-4 index calculated using:

$$\text{FIB}-4 = (\text{Age} \times \text{AST})/(\text{Platelet count} \times \text{Squareroot (ALT)}).$$

Reproducibility outcomes

The primary outcome was the reproducibility of each biomarker as assessed by the reproducibility coefficient (RDC%), within-participant coefficient of variation (wCV), intraclass correlation coefficient (ICC), and Bland–Altman analysis. The RDC% captures the extent of variability in repeated measures of a diagnostic test across different conditions, including different operators and time points. The RDC% represents the smallest detectable difference between 2 measurements taken on different days that can be interpreted as a true change, rather than measurement error, with a lower RDC% indicating high reproducibility.[15,16] The RDC% can therefore inform the threshold at which a change in measurements reflects a true change in disease status. The wCV assesses the reproducibility of a diagnostic test by quantifying the variability in repeated measures from the same individual under different-day/different-operator conditions. A lower wCV% indicates higher reproducibility and precision of that test for an individual. The ICC represents the proportion of total variation in a test measurement explained by between-patient differences rather than variance due to measurement error or inconsistency. ICC values range from 0 to 1, with 1 indicating perfect reproducibility, wherein all differences in measurement results are reflective of biologic differences between individuals. Bland–Altman analysis was performed to assess agreement between the repeated measurements to define clinical acceptability of variation across repeated measures. Bias in the Bland–Altman analyses represents the average difference between 2 sets of measurements for a given

biomarker. Limits of agreement (LoA) capture 95% of the differences between measures, with wide LoAs indicating poor reproducibility. Lastly, we assessed correlations between biomarkers at baseline and on repeat measures to assess how the repeatability of these measures may align on repeat assessments.

Statistical analysis

For participant characteristics, continuous variables were presented as mean (±SD) or median (IQR) if the distribution was not normal. *t* Tests, Wilcoxon rank sum, and chi-square or the Fisher exact test were used as appropriate for continuous and categorical variables. The RDC%, wCV, and ICC were calculated for VCTE-LSM, VCTE-CAP, and blood tests. RDC% values that are $<20\%$, between 20% and 50%, or $>50\%$ demonstrate excellent, moderate, and poor reproducibility, respectively. wCV values $>50\%$ indicate unstable measurements because the relative variability within subjects is comparable to their mean value. In addition, ICC values that are <0.20, between 0.2 and 0.75, and >0.75 demonstrate poor, moderate, and excellent agreement, respectively. This study was adequately powered based upon a priori sample size calculation in which 34 participants will be required to achieve a power of 80% with alpha = 5%. Sample size

TABLE 1 Baseline characteristics of participants

	VCTE/CAP (N = 40)	AST/ALT/Plt/FIB-4 (N = 38)	AFP (N = 26)
Demographic profile			
Age (y)	62.2 (10.2)	62.4 (10.2)	62.1 (11.0)
Female, n (%)	24 (60.0%)	22 (57.9%)	15 (57.7%)
Type 2 diabetes mellitus, n (%)	18 (45.0%)	16 (42.1%)	11 (42.3%)
BMI (kg/m^2)	28.6 (4.8)	28.2 (4.8)	27.7 (4.5)
Obese[a], n (%)	12 (30.0%)	10 (26.3%)	6 (23.1%)
Race/ethnicity, n (%)			
White	15 (37.5%)	15 (39.5%)	13 (50.0%)
Hispanic	17 (42.5%)	15 (39.5%)	8 (30.8%)
Asian	3 (7.5%)	3 (7.9%)	3 (11.5%)
Etiology, n (%)			
MASLD	22 (55.0%)	20 (52.6%)	13 (50.0%)
ALD	8 (20.0%)	8 (21.0%)	6 (23.1%)
HCV	2 (5%)	2 (5.3%)	1 (3.8%)
Other	8 (20.0%)	8 (21.0%)	6 (23.1%)
Biochemical data			
AST (U/L), median (IQR)	47.2 (32.7)	47.3 (33.1)	42.9 (21.2)
ALT (U/L), median (IQR)	39.1 (20.1)	38.6 (20.2)	36.1 (18.8)
Platelet count (1000/mm^3), median (IQR)	142.9 (58.9)	142.4 (59.7)	149.7 (58.8)
HbA1c (%), median (IQR)	6 (1.3)	5.9 (1.3)	5.8 (1.3)
Total bilirubin (mg/dL), median (IQR)	1.0 (0.7)	1.1 (0.7)	1.1 (0.8)
INR, median (IQR)	1.2 (0.2)	1.2 (0.2)	1.2 (0.2)
Albumin (g/dL), median (IQR)	4.2 (0.5)	4.2 (0.5)	4.2 (0.5)
MELD, median (IQR)	6.4 (3.8)	6.6 (3.8)	6.9 (4.4)
MELD-Na, median (IQR)	6.7 (4.2)	6.9 (4.2)	7.3 (4.9)
FIB-4, median (IQR)	4.4 (4.0)	4.4 (4.0)	3.8 (2.9)
Child–Pugh, median (IQR)	5.2 (0.8)	5.2 (0.8)	5.3 (0.9)
Imaging			
VCTE (kPa), mean (SD)	24.5 (17.2)	25.0 (17.6)	25.2 (18.7)
CAP (dB/m), mean (SD)	259.3 (62.9)	256.1 (62.9)	255.8 (60.7)

Note: Mean values are provided with SD in parentheses, unless otherwise noted as n (%) or median (IQR).
[a]Obesity was defined as BMI ≥30 kg/m^2.
Abbreviations: AFP, alpha-fetoprotein; ALD, alcohol-associated liver disease; ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; CAP, controlled attenuation parameter; FIB-4, Fibrosis-4 Index; INR, international normalized ratio; MASLD, metabolic dysfunction–associated steatotic liver disease; MELD-Na, Model for End-Stage Liver Disease—Sodium; Plt, platelet count; VCTE, vibration-controlled transient elastography.

was estimated using the ICC with a moderate effect size (Cohen $d = 0.25$) and an alpha of 0.05. ICC was selected because it is a model-based statistic with known variance properties, allowing standard power analysis. However, RDC, on the other hand, is a descriptive metric that reflects absolute measurement error. While it is highly informative for clinical interpretation, it lacks a closed-form statistical distribution and is therefore not typically used for a priori power calculations. The coefficients of determination R^2 and corresponding p-values are reported. Statistical significance was defined as a 2-tailed p-value of ≤ 0.05. All statistical analyses were performed on SAS, version 9.4 (SAS Institute, Cary, North Carolina). Agreement between variables was assessed using Bland–Altman plots describing bias over the full range of measurements. Limits of agreement (LoAs) were calculated using a 95% CI, ± 1.96 SDs from the mean. Spearman correlation was conducted to assess the relationship between various biomarkers at baseline, at follow-up, and averaging both time points. No statistical adjustments for imaging or blood-based biomarkers were made.

RESULTS

Participant characteristics

A total of 40 participants (60.0% female; 42.5% were Hispanic and 37.5% White) were included in the study. The mean age and body mass index were 62 years and 28.6 kg/m^2, respectively (Table 1). Based on medical history, 55.0% had metabolic dysfunction–associated steatotic liver disease (MASLD), 20.0% had alcohol-associated liver disease (ALD), and 5.0% had HCV. Of the 40 participants, 38 had AST, ALT, platelet, and FIB-4 values and 26 had AFP values available at 2 different time points. There were no self-reported changes in patient lifestyle, activity level, medications, or alcohol use from baseline to follow-up. The average time between visits was 115 days. The median time between visits was 89 days.

Reproducibility of various biomarkers

VCTE-LSM

The mean VCTE for participants who underwent 2 separate examinations was 24.5 ± 17.2 kPa. The RDC % for VCTE-LSM was 54.4% with a 95% CI [0.429, 0.673]. The wCV was 0.19, indicating moderate variability in VCTE measurements (Table 2). The ICC was 0.91 with a 95% CI [0.83, 0.95], indicating excellent reproducibility.

VCTE-CAP

The mean CAP for participants who underwent 2 separate examinations was 259.3 ± 62.9 dB/m. The RDC% for CAP was 55.6% with a 95% CI [0.43, 0.68]. The wCV was 0.20, indicating moderate variability in CAP measurements (Table 2). The ICC with 95% CI for CAP was 0.46, indicating moderate reproducibility.

AST/ALT/Platelets/FIB-4

The mean AST and ALT for participants who underwent 2 separate blood draws were 47.2 ± 32.7 U/L and 39.1 ± 20.1 U/L, respectively. The mean platelet count was 142.9 ± 58.9 (1000/mm^3) and the mean FIB-4 was 4.4 ± 4.0. The RDCs% and 95% CIs for AST, ALT, platelet, and FIB-4 values were 78.2% [0.610, 0.970], 70.2% [0.544, 0.865], 46.2% [0.359, 0.570], and 79.0% [0.615, 0.978], respectively. The wCV was lowest for platelets at 0.167, and higher for AST, ALT, and FIB-4 at 0.282, 0.253, and 0.285, respectively (Table 2). The ICC with 95% CI indicated moderate agreement for ALT (0.715) and excellent agreement for platelets and FIB-4 at 0.864 and 0.758, respectively. In contrast, ICC with a 95% CI for AST had inferior agreement at 0.366.

AFP

The mean AFP for participants with AFP values available at 2 separate blood draws was 4.1 ± 2.9 ng/mL. The RDC% for AFP total was 58.4% with a 95% CI of [0.42, 0.75]. The wCV was 0.21, indicating moderate reproducibility of AFP measurements (Table 2). The ICC for AFP was the highest of all biomarkers at 0.95, indicating excellent agreement.

The RDC% and ICC for all biomarkers are demonstrated in Figures 2A, B, respectively.

Bland–Altman analyses

VCTE-LSM demonstrated low absolute bias (0.3 kPa) and the lowest relative bias (0.40%) by point estimate compared with other biomarkers (LoA = −54.7%, 55.5%) (Figure 3A). VCTE-CAP demonstrated low absolute bias (3 dB/m) and low relative bias (0.50%) compared with blood biomarkers (LoA = −56.8%, 55.8%) (Figure 3B). The blood biomarkers had greater absolute and relative biases than VCTE-LSM and VCTE-CAP on Bland–Altman analyses. The greatest absolute relative bias was observed for ALT (4.9%) (LoA = −65.6, 75.4), followed by AFP (4.2%) (LoA = −63.2, 54.8), FIB-4 (3.9%) (LoA = −75.8, 83.5), platelet (2.8%) (LoA = −49.2, 43.7), and AST (2.8%) (LoA = −76.3, 81.8) (Figures 3C–G) (Table 2).

TABLE 2 Reproducibility assessments for LSM by VCTE, CAP, AST, ALT, platelets, FIB-4, and AFP

Imaging/blood biomarkers	Number of patients	wCV	RDC% (95% CI)	ICC (95% CI)	Bias	Absolute relative bias (%)
VCTE median (kPa)	40	0.196	54.4% [0.429, 0.673]	0.910 [0.836, 0.951]	0.315	0.403
CAP median (dB/m)	40	0.201	55.6% [0.438, 0.688]	0.467 [0.182, 0.679]	3.275	0.496
AST (U/L)	38	0.282	78.2% [0.610, 0.970]	0.366 [0.055, 0.612]	3.895	2.759
ALT (U/L)	38	0.253	70.2% [0.544, 0.865]	0.715 [0.515, 0.841]	1.395	4.914
Platelet count (1000/mm3),	38	0.167	46.2% [0.359, 0.570]	0.864 [0.754, 0.927]	−3.711	2.780
FIB-4	38	0.285	79.0% [0.615, 0.978]	0.758 [0.584, 0.866]	0.663	3.876
AFP (ng/mL)	26	0.211	58.4% [0.426, 0.752]	0.952 [0.896, 0.978]	−0.258	4.195

Abbreviations: AFP, alpha-fetoprotein; ALT, alanine transaminase; AST, aspartate transaminase; CAP, controlled attenuation parameter; FIB-4, Fibrosis-4 Index; ICC, intraclass correlation coefficient; LSM, liver stiffness measurement; RDC%, percent reproducibility coefficient; VCTE, vibration-controlled transient elastography; wCV, within-participant coefficient of variation.

Correlation

Spearman correlation heatmaps were prepared to illustrate correlation at baseline, at follow-up, and by averaging both time points between variables (Figure 4). The 2 strongest correlation pairs were between AST and ALT, as well as platelets and FIB-4. AST and ALT had a strong positive correlation at baseline (rho = 0.75, $p < 0.01$), at follow-up (rho = 0.73, $p < 0.01$), and averaging both time points (rho = 0.73, $p < 0.01$). In addition, platelets and FIB-4 demonstrated a strong negative correlation at baseline (rho = −0.86, $p < 0.01$), at follow-up (rho = −0.88, $p < 0.01$), and averaging both time points (rho = −0.86, $p < 0.01$). There were no strong correlations between baseline, follow-up, or average measurements between VCTE measures and blood-based measures. Scatterplots to further illustrate the correlation between these pairs are demonstrated in Figure 5.

DISCUSSION

Main findings

In this prospective study of patients with cirrhosis, we assessed the different-day, different-operator reproducibility of VCTE-LSM, VCTE-CAP, and blood biomarkers, including AST, ALT, platelets, FIB-4 index, and AFP. Among the ultrasound-based imaging biomarkers, VCTE-LSM demonstrated a similar RDC% (54.4%) compared with VCTE-CAP (55.6%). Among individuals with cirrhosis undergoing longitudinal VCTE examinations using the same system by different operators, VCTE-LSM and CAP provide consistent assessments across individuals but may yield substantial within-individual variation. Blood-based biomarkers had poor reproducibility within individuals but were consistent in detecting between-patient variability. Within individuals, differences in LSM or CAP of $< 54\%$–56% may reflect measurement variability rather than a true physiological

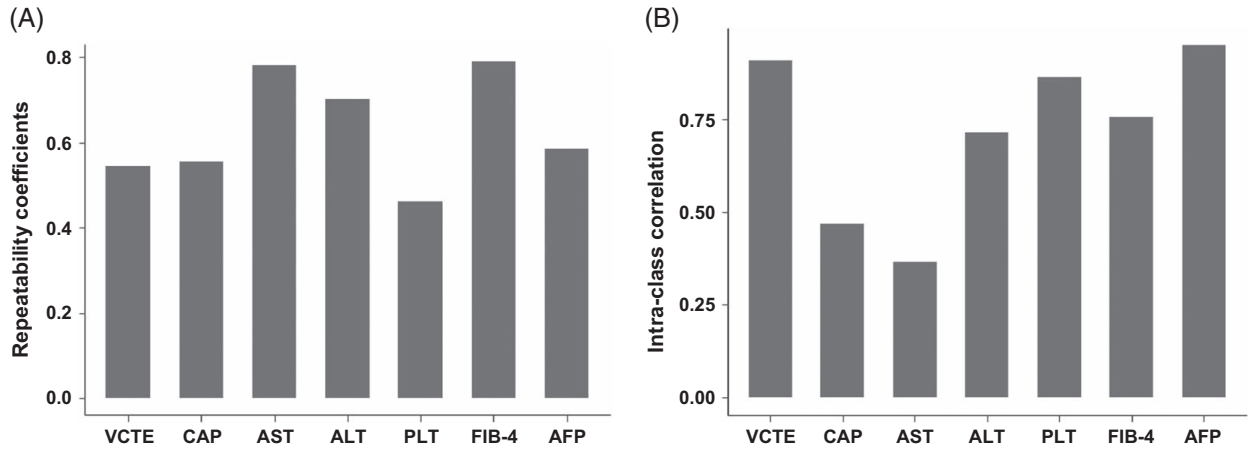

FIGURE 2 (A) Bar plot of reproducibility coefficients for all biomarkers. (B) Bar plot of intraclass correlation for all biomarkers. Abbreviations: AFP, alpha-fetoprotein; ALT, alanine transaminase; AST, aspartate transaminase; CAP, controlled attenuation parameter; FIB-4, Fibrosis-4 Index; PLT, platelet count; VCTE, vibration-controlled transient elastography.

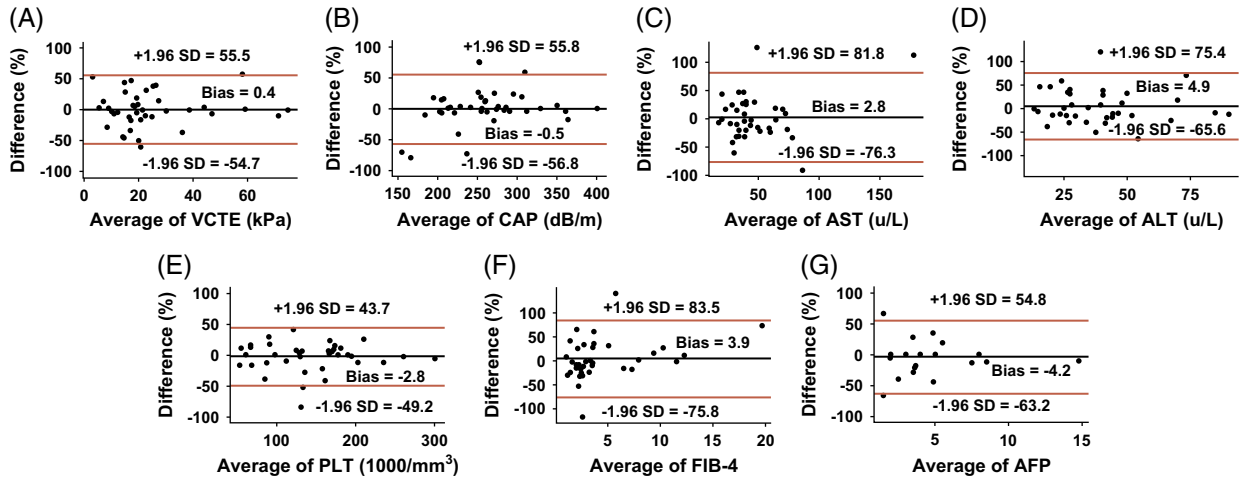

FIGURE 3 Bland–Altman analyses in VCTE (A), CAP (B), AST (C), ALT (D), platelet (E), FIB-4 (F), and AFP (G). Abbreviations: AFP, alpha-fetoprotein; ALT, alanine transaminase; AST, aspartate transaminase; CAP, controlled attenuation parameter; FIB-4, Fibrosis-4 Index; PLT, platelet count; VCTE, vibration-controlled transient elastography.

change in liver stiffness or hepatic steatosis. On Bland–Altman analyses, both VCTE-LSM and VCTE-CAP had low relative biases compared with blood biomarkers with broad LoA. Bland–Altman analyses of blood biomarkers demonstrated higher relative biases compared with ultrasound-based imaging modalities, with broad LOAs. Greater fluctuations observed in blood biomarkers are likely due to short-term metabolic or systemic influences to which these lab values are susceptible.[17] The strong positive correlation observed in AST and ALT was expected, as both hepatic enzymes typically fluctuate together.[18] The strong negative correlation observed between FIB-4 and platelets was also anticipated due to the mathematical calculation of FIB-4. These data will expand the evidentiary basis required for regulatory qualification, enhancing the diagnostic and prognostic accuracy of

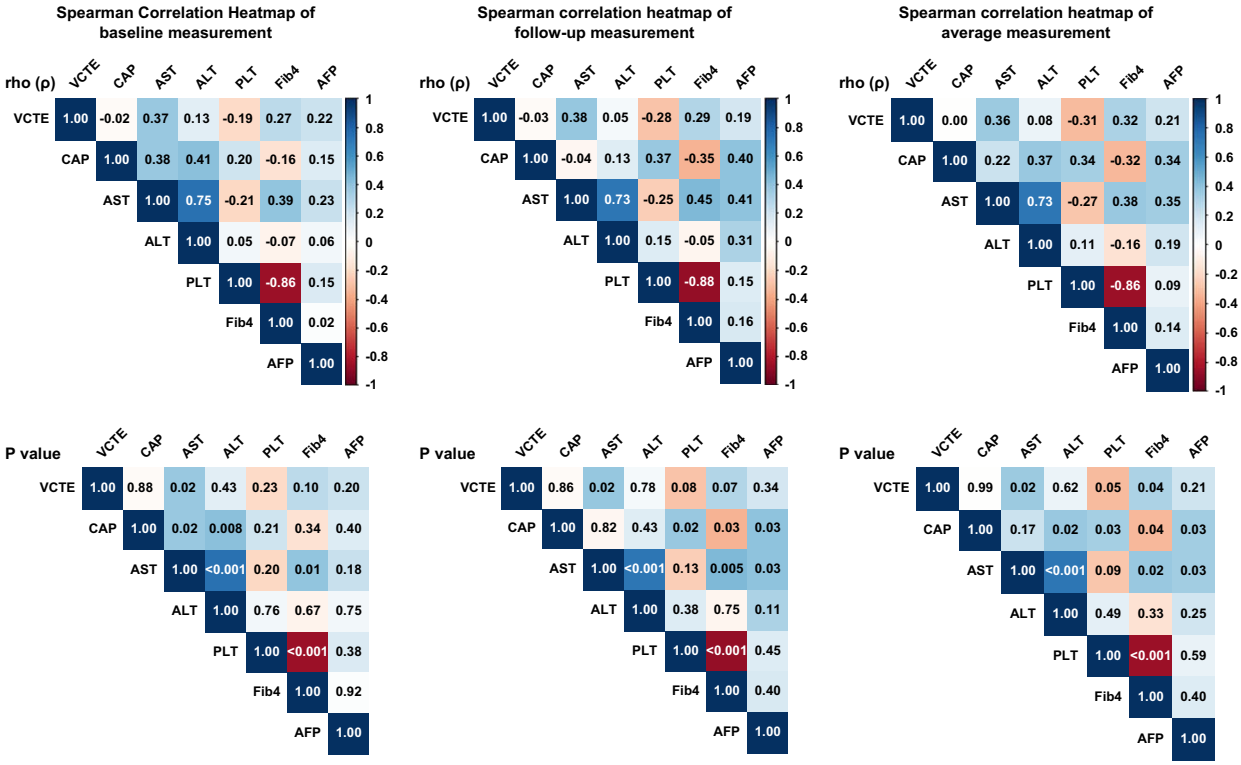

FIGURE 4 Spearman correlations of baseline, follow-up, and average measurement for all biomarkers. Abbreviations: AFP, alpha-fetoprotein; ALT, alanine transaminase; AST, aspartate transaminase; CAP, controlled attenuation parameter; FIB-4, Fibrosis-4 Index; PLT, platelet count; VCTE, vibration-controlled transient elastography.

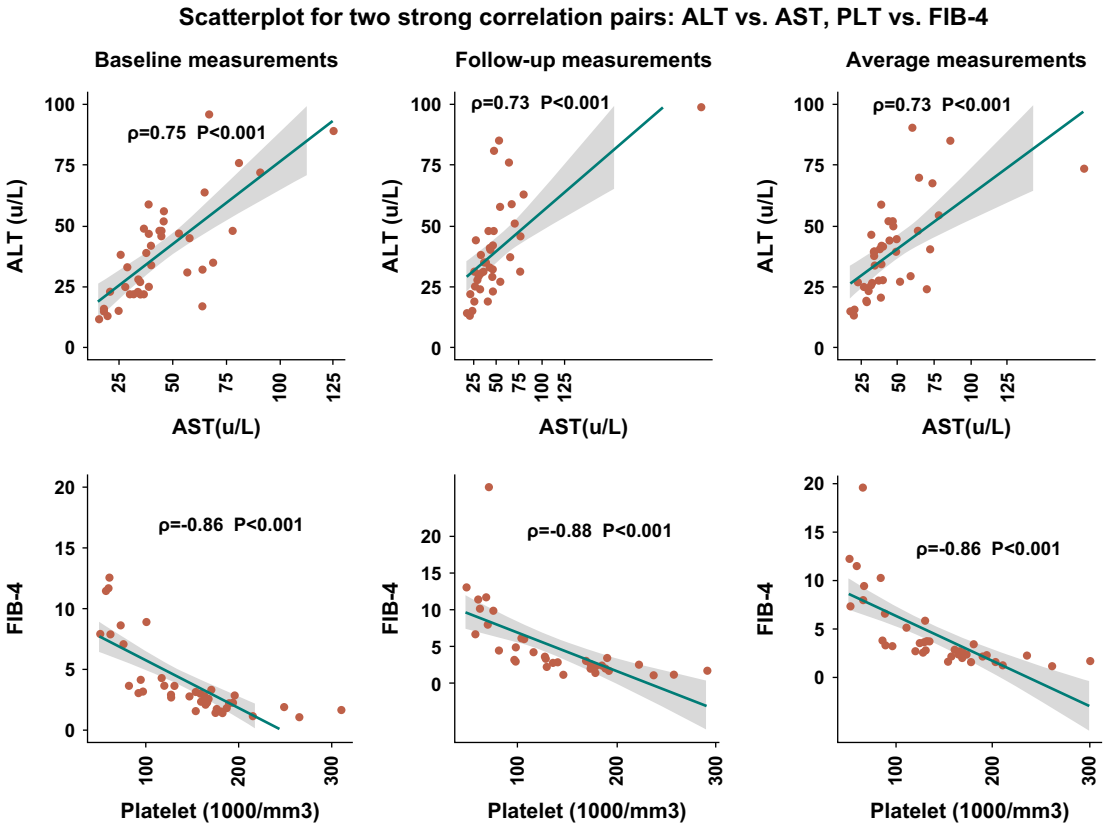

FIGURE 5 Scatterplot of baseline, follow-up, and average measurement for 2 strong correlation pairs (ALT vs. AST) and (PLT vs. FIB-4). Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; FIB-4, Fibrosis-4 Index; PLT, platelet count.

non-invasive approaches in clinical trials and routine care for patients with cirrhosis.

In context with published literature

Prior to the current study, the reproducibility of imaging and blood biomarkers in individuals with cirrhosis was not known. A previous study examined the reproducibility and repeatability of shear-wave and transient elastography in adults with MASLD; however, this study was not limited to patients with cirrhosis.[19] The current study builds upon our previous study that examined the same-day repeatability of VCTE in patients with cirrhosis[10] by evaluating new data on the reproducibility of NITs using different operators on different days.

Strengths and limitations

The strengths of this study include a prospective study design, different-day examinations, standardized evaluation for measurements by experienced operators, and comprehensive inclusion and exclusion criteria. The limitations of this study include limited geographic diversity in the cohort. All participants of this study were recruited and enrolled within the greater San Diego area. Our recruitment encompasses heterogeneous communities and diverse patient characteristics, however. Although powered to assess reproducibility characteristics of each NIT, further validation cohorts among a larger number of patients may be required to validate these results. As the RDC is sensitive to within-subject variability, a larger sample size would yield more precise estimates of the RDC. Future studies with larger cohorts are warranted to validate and refine these reproducibility thresholds.

Implications for clinical practice and research

The reproducibility estimates reported here are critical for defining thresholds that indicate true biological or clinical changes, as opposed to measurement variability. The reproducibility estimates reported here are critical for defining thresholds that indicate true biological or clinical changes, as opposed to measurement variability. This is especially important in clinical trials, where accurate detection of treatment effects is paramount. In clinical care, reliable measurements are needed to guide decision-making and provide a mechanism for longitudinal disease monitoring and assessment of treatment effectiveness. These findings

pave the way for broader adoption of NITs, ensuring their integration as standardized tools in both research settings and routine practice, which ultimately improves outcomes for patients with cirrhosis.

AUTHOR CONTRIBUTIONS

Study concept and design: Rohit Loomba; data acquisition: Rohit Loomba, Monica A. Tincopa, Claude B. Sirlin, Harris Siddiqi, and Egbert Madamba; data analysis and interpretation: Meng Yin, Hao Wu, Harris Siddiqi, Monica A. Tincopa, and Rohit Loomba; drafting of the manuscript: Harris Siddiq; critical revision and approval of the final manuscript: all authors.

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CONFLICTS OF INTEREST

Rohit Loomba serves as a consultant to Aardvark Therapeutics, Altimmune, Anylam/Regeneron, Amgen, Arrowhead Pharmaceuticals, AstraZeneca, Bristol-Myers Squibb, CohBar, Eli Lilly, Galmed, Gilead, Glympse Bio, Hightide, Inipharma, Intercept, Inventiva, Ionis, Janssen Inc., Madrigal, Metacrine, Inc., NGM Biopharmaceuticals, Novartis, Novo Nordisk, Merck, Pfizer, Sagimet, Theratechnologies, 89bio, Terns Pharmaceuticals, and Viking Therapeutics. In addition, his institutions received research grants from Arrowhead Pharmaceuticals, AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli Lilly, Galectin Therapeutics, Galmed Pharmaceuticals, Gilead, Intercept, Hanmi, Inventiva, Ionis, Janssen, Madrigal Pharmaceuticals, Merck, NGM Biopharmaceuticals, Novo Nordisk, Pfizer, Sonic Incytes, and Terns Pharmaceuticals. He is also a co-founder of LipoNexus Inc. The Mayo Clinic and Meng Yin have intellectual property and a financial interest related to magnetic resonance elastography technology. Disclosed money paid to the Mayo Clinic for patents and royalties related to MR elastography technology and methods; disclosed money paid to Meng Yin for stock/stock options from Resoundant. Dr Sirlin reports payment to institution for research grants from ACR, Bayer, Foundation of NIH, GE, Gilead, Pfizer, Philips, Siemens, V Foundation; payment to institution for lab service agreements with OrsoBio, Enanta, Gilead, ICON, Intercept, Nusirt, Shire, Synageva, Takeda; payment to institution for institutional consulting for BMS, Exact Sciences, IBM-Watson, Pfizer; Personal consulting for Altimmune, Ascelia Pharma, Blade, Boehringer, Epigenomics, Guerbet, Livivos, and Novo Nordisk; payment to self for royalties and/or honoraria from Medscape, Wolters Kluwer, and HealthProMatch; ownership of stock options in Livivos; unpaid advisory board position in Quantix Bio; executive position for Livivos (Chief Medical Officer, unsalaried position with stock options and stock) through June 28, 2023; Principal Scientific Advisor to Livivos (unsalaried position with stock options and stock) since June 28, 2023; payment to self for serving as a speaker for HealthProMatch; support for attending meetings and/or travel from Fundacion Santa Fe, Congreso Argentino de Diagnóstico por Imágenes, Stanford, Jornada Paulista de Radiologia, Ascelia Pharma, RSNA, Sociedad Radiológica de Puerto Rico, Hospital Español Auxilio Mutuo de Puerto Rico, Paris MASH, and Liver Forum; member (no payment) of Data Safety Monitoring board for National Cancer Institute funded Early Detection Research Network; equipment loans to institution from Butterfly, GE, Siemens, and Mayo; provision of contrast material to institution from Bayer.

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