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Velacur ACE outperforms FibroScan CAP for diagnosis of MASLD

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Abstract

Background: As the prevalence of metabolic dysfunction-associated steatotic liver disease increases, it is imperative to have noninvasive alternatives to liver biopsy. Velacur offers a non-invasive, point-of-care ultrasound-based method for the assessment of liver stiffness and attenuation. The aim of this study was to perform a head-to-head comparison of liver stiffness and liver fat determined by Velacur and FibroScan using MRI-based measurements as the reference standard.

Methods: This prospective cross-sectional study included 164 adult participants with well-characterized metabolic dysfunction-associated steatotic liver disease. Patients underwent a research exam including Velacur, FibroScan and contemporaneous magnetic resonance elastography, and magnetic resonance imaging proton density fat fraction (MRI-PDFF) scans. The *primary outcome* was the presence of advanced fibrosis (>F2) as measured by magnetic resonance elastography and the presence of liver fat (>5%) as measured by MRI-PDFF.

Results: The mean age and body mass index were 57 ± 12 years and 30.6 ± 4.8 kg/m^2, respectively. The mean liver stiffness on magnetic resonance elastography was 3.22 ± 1.39 kPa and the mean liver fat on MRI-PDFF was $14.2 \pm 8\%$. The liver stiffness assessments by Velacur and FibroScan were similar for the detection of advanced fibrosis (AUC 0.95 vs. 0.97) and were not statistically different ($p = 0.43$). Velacur was significantly better than FibroScan (AUC 0.94 vs. 0.79, $p = 0.01$), for the detection of MRI-PDFF $> 5\%$ (diagnosis of metabolic dysfunction–associated liver disease).

Conclusions: Velacur was superior to FibroScan for liver fat detection with MRI-PDFF as the reference. Velacur and FibroScan were not statistically

Abbreviations: ACE, attenuation coefficient estimate; BMI, body mass index; CAP, controlled attenuation parameter; MASH, metabolic-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging proton density fat fraction; QIBA, Quantitative Imaging Biomarker Alliance.

different for liver stiffness assessment as defined by magnetic resonance elastography.

INTRODUCTION

Although liver biopsy remains the gold standard for the diagnosis of metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic-associated steatohepatitis (MASH), there are issues with morbidity[1,2] and misclassification due to sampling and interobserver and intraobserver variation.[3,4] As the number and prevalence of patients with MASLD and MASH increases,[5,6] it is imperative to have noninvasive alternatives to biopsy.

To evaluate MASLD and MASH, hepatic fibrosis and steatosis are essential measures that need to be assessed. Liver fibrosis is the main determinant of long-term patient outcomes,[7] while liver fat is a key indicator of disease. Liver stiffness has been shown in many studies to correlate well with fibrosis assessment on liver biopsy,[8–12] and shown to be a predictor of longer-term patient outcomes.[13,14] Multiple society guidelines advocate for noninvasive tests for the assessment of fibrosis using liver stiffness measurements in patients who are at risk of MASLD and MASH based on the presence of diabetes and/or metabolic syndrome.[2,15,16] The 2023 AASLD Practice Guidance on the clinical assessment and management of NAFLD specifically outlines a tiered approach, using both blood-based markers and imaging of liver stiffness and fat.[2] Noninvasive tests, specifically ultrasound attenuation, can be used to quantify liver fat, with 5% liver fat on magnetic resonance imaging proton density fat fraction (MRI-PDFF) indicating the presence of steatosis.

MRI methods of measuring both liver stiffness and liver fat have been shown to be accurate noninvasive alternatives to biopsy. Magnetic resonance elastography (MRE) is a type of elastography applied to the liver, which uses MRI to measure the shear wave propagation within the liver tissue. MRE has also been proven to have a high correlation with liver fibrosis when compared to liver biopsy[11] and to be the most accurate noninvasive method.

MRI is also the most accurate noninvasive test for assessing liver fat in patients with MASLD. Using MRI-PDFF, the amount of fat is compared to the amount of water, which can be directly measured in the liver of a patient. This method is now commonly part of the MRI software packages for many manufacturers. Although the exact methods may vary from manufacturer to manufacturer, they will be collectively referred to in this paper as MRI-PDFF. The high costs and complexity associated with MRI scans restrict its adoption and usefulness in many geographic locations affected by liver disease.

Vibration-controlled transient elastography is well validated across a broad range of liver diseases including hepatitis C, B, and MASLD/MASH, and is currently the most commonly used ultrasound-based imaging modality for the assessment of liver fibrosis and liver attenuation and is marketed as FibroScan (Echosens). FibroScan has a limitation in the higher range of body mass index (BMI), with a failure rate of up to 27% in obese individuals using the standard M probe, likely due to the larger skin capsular distance.[17,18] Assessment of steatosis by controlled attenuation parameter (CAP) score and liver stiffness is significantly affected by a skin capsular distance of >25 mm when using the FibroScan M probe in patients with MASLD.[19] The use of the obesity-specific (XL) probe has reduced the failure rate from 16% to 1.1% in individuals with BMI >28 kg/m^2.[20–22]

Shear wave absolute vibro-elastography is the ultrasound elastography method available on Velacur (Sonic Incytes Medical Corp.). This device uses similar shear wave production methods to that of MRE, creating a multifrequency steady-state shear wave. Velacur produces 2- and 3-dimensional images, allowing for full visualization of the liver with a portable platform. Using a sweep motion during data collection, Velacur captured a large volume of the liver and displayed the volumetric elasticity maps. Velacur uses ultrasound attenuation measurements, collected simultaneously with liver stiffness, to estimate the liver fat content.

This prospective, open-label study compared the performance of Velacur and FibroScan. Both Velacur and FibroScan were used to measure liver stiffness and ultrasound attenuation, using MRE and MRI-PDFF as the noninvasive standards respectively. Both measures were compared to MRE and MRI-PDFF in a prospective cohort of patients with MASLD/MASH. The study took place at 5 centers in Canada and the United States.

METHODS

Study design

This was a prospective, cross-sectional, open-label, head-to-head comparison study of Velacur elasticity

(shear wave absolute vibro-elastography) and attenuation coefficient estimate (ACE) measurements versus vibration-controlled transient elastography and CAP using MRE and MRI-PDFF as the reference standard respectively.

Patients with well-characterized MASLD or MASH were recruited. Patients with a wide range of steatosis grades and fibrosis stages were included in the study based on prior assessment of liver measurements. Patients with diagnosed fatty liver were approached at the clinics at the time of their normally scheduled appointments or called ahead of an appointment to introduce them to the study. Patients were identified based on previous diagnosis and historical noninvasive testing. Patients enrolled at the University of California San Diego, who were already participating in fatty liver studies which included MRI scans, were approached as well to complete additional Velacur and FibroScan measurements. The MRE results were used to determine the final corresponding fibrosis stage for each patient. Cutoffs were defined based on the study of Hsu and colleagues. Given that most MRI scans were completed after enrollment, the final number of patients in each corresponding stage of fibrosis was not equal. MRI-PDFF percentages were used to evaluate liver fat and compared to the ultrasound attenuation measurements of both Velacur and FibroScan. Patients were scanned with Velacur and FibroScan on the same day and with MRE/MRI-PDFF within a 28-day window.

The study was conducted in accordance with Good Clinical Practices, informed consent, in writing, was obtained from each patient, and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in *a priori* approval by the appropriate institutional review committee (Beth Israel 2018P000730, WCG 1296038, UCSD 181679, Providence Health Care H20-03237, and University of British Columbia H20-03975). The study was registered with ClinicalTrials.gov (NCT04682600).

Study objectives

The primary objective was to perform a head-to-head comparison of Velacur versus FibroScan to determine liver stiffness and ultrasound attenuation to assess the presence of advanced fibrosis on MRE and the presence of liver fat as measured by MRI-PDFF.

Secondary objectives included comparing the AUROCs of Velacur and FibroScan at each stage of fibrosis and grade of steatosis, as well as comparing the overall correlation coefficients between the ultrasound and MRI-based measurements.

Inclusion and exclusion criteria

Patients between the ages of 19 and 75 years were included in the study. Only patients with MASLD and/or suspected MASH were enrolled. Liver disease needed to have been previously diagnosed or present in the past 12 months, by one of the following: biopsy, steatosis on abdominal ultrasound, MRI-PDFF $>12\%$, or FibroScan CAP score >230 dB/m.[23] Patients with at least 2 criteria for metabolic syndrome (obesity, hyperglycemia, dyslipidemia, and hypertension) and increased stiffness on FibroScan (>8 kPa) within 12 months were also included. As patients with different levels of fibrosis were enrolled, the requirements for stiffness on a historical FibroScan were adjusted to try to ensure the capture of patients at all fibrosis stages.

Excluded patients included those with viral hepatitis, other known causes of chronic liver disease, decompensated cirrhosis, serum alanine transaminase or aspartate aminotransferase $>5\times$ upper limit of normal on historical blood work within the past 3 months, individuals with a history of persistent ethanol abuse, or patients who were pregnant or planning to become pregnant during the study. Persistent ethanol use was defined as individuals with a history of persistent ethanol abuse (consumption >20 g EtOH/d for women, >40 g EtOH/d for men) for the course of more than 3 months in the past year. Patients with BMI >40 kg/m^2 (or using a cutoff based on MRI) were also excluded.

Imaging methods

MRE/MRI-PDFF

MRE and MRI-PDFF are the leading candidates for noninvasive measurements of liver stiffness and liver fat.[10,12,24,25] MRE was performed using the Resoundant system on all subjects. Subjects lie supine in the MRI bore with an active driver placed over the liver and secured in place. The parameters recommended by the Quantitative Imaging Biomarker Alliance (QIBA) for each individual manufacturer and magnet strength were used whenever possible.[26]

MRE and MRI scans were segmented manually by a radiologist. The “quality data,” as output by each MRI manufacturer, was used to determine which areas should be included. This is typically marked on the MRE images as a cross-hatched area. Segmenters were instructed to also avoid hot spots.[27] The T2-weighted images were compared to the segmented area to ensure that the traced areas were within the liver boundary and at least 1 cm from the liver capsule as recommended. The weighted average of the slices for each scan was computed and this mean result was used as the final measurement.[26]

Segmented areas of at least 2 cm in diameter, within the right lobe of the liver, were used to measure the MRI-PDFF results. Segmenters avoided vessels and the liver boundary was used to guide areas for measuring liver fat. The mean of all segmented areas was used as the final result.

Velacur

Velacur is a standalone ultrasound-based tool designed for the assessment of liver tissue stiffness and ultrasound attenuation measurements. The imaging procedure of Velacur is similar to a traditional ultrasound scanning procedure, in which the patient is asked to lie supine on an examination bed, with the operator seated next to them. A vibration source is placed under the patient, between the patient and the bed, to induce shear waves in the liver. The vibration source creates multifrequency steady-state shear waves, at 40, 50, and 60 Hz simultaneously. Ultrasound imaging through the patient's ribs is used to track the displacements of these waves.[28] Through tracking of the displacements, the shear wave velocity and thus tissue stiffness can be calculated. ACE measurements of the liver are calculated simultaneously.[29] Ten volumes were collected on all patients in the study.

Velacur is performed by a trained technician. All users were trained with the same training program at the start of the study by a Sonic Incytes trainer. The quality of the scans was assessed using an objective algorithm to measure shear wave propagation or goodness of fit for attenuation.[30] The algorithm measures the volume of the liver with shear waves. If the resulting shear wave volume is above a predetermined threshold, the elasticity measurement is considered valid. The presented result is the median of those volumes that passed the quality threshold. The quality of the elasticity and attenuation measures were assessed separately.

FibroScan

All FibroScan measurements were completed by a trained FibroScan user with over 50 completed scans. The M or XL probe was used as recommended by the FibroScan software. At least 10 measurements were taken from the patient's right lobe, using an intercostal approach, while the patient was lying supine on the bed. The median and IQR of 10 elasticity and attenuation results are presented. Patients with IQR/median $>30\%$ were labeled as invalid. Elasticity and attenuation IQR/median were assessed separately.

Patient preparation

Before all types of scans, patients fasted for at least 3 hours.

Blinding

Those reviewing the MRI results were blinded to the results of the Velacur scans. As the same operator often scanned the patient with both Velacur and FibroScan, the results were not blinded from each other.

Statistical analysis

The analysis population for elasticity included patients with valid measurements from Velacur, FibroScan, and MRE. The analysis population for attenuation/liver fat included patients with valid measurements from Velacur ACE, FibroScan CAP, and MRI-PDFF (Figure 1).

For each fibrosis stage, as measured by MRE defined by Hsu and colleagues, a receiver operator curve using the final Velacur elasticity measurement as a predictor of the fibrosis stage was constructed with an accompanying 95% CI for the AUC.

The AUC and 95% CIs for the FibroScan device were also calculated, using the FibroScan cutoffs recommended for clinical practice to categorize patients into fibrosis stages.[31] The AUC curves were constructed to compare the discriminatory ability of Velacur and FibroScan in determining mild (F0/F1) and moderate (F2/F3) and advanced fibrosis (F4), using MRE as the reference. Pearson correlation coefficients were calculated between MRE and both Velacur and FibroScan stiffness measurements.

A similar analysis was completed to measure the discriminatory ability of Velacur ACE results with MRI-PDFF, and the FibroScan CAP results with MRI-PDFF. In this case, the ability to discriminate patients with PDFF $>5.2\%$, $>11\%$, and $>17.1\%$ was measured.[25] An ROC curve using final Velacur and FibroScan attenuation measurements as a predictor of the presence of steatosis was constructed with an accompanying 95% CI for the AUC. Pearson correlation coefficients were calculated between Velacur and FibroScan attenuation measurements with MRI-PDFF.

DeLeong test was used to determine if the AUCs for Velacur and FibroScan were significantly different.[32] This test is designed to compare AUCs of correlated measures, such as 2 diagnostic tests performed on the same group of patients.

RESULTS

Patient characteristics

A total of 164 patients were screened and enrolled in the study. One hundred thirty patients were included in the elasticity analysis and 133 in the attenuation analysis. To be included, patients needed to have a valid MRI scan,[26,27] FibroScan IQR $<30\%$, and a valid Velacur

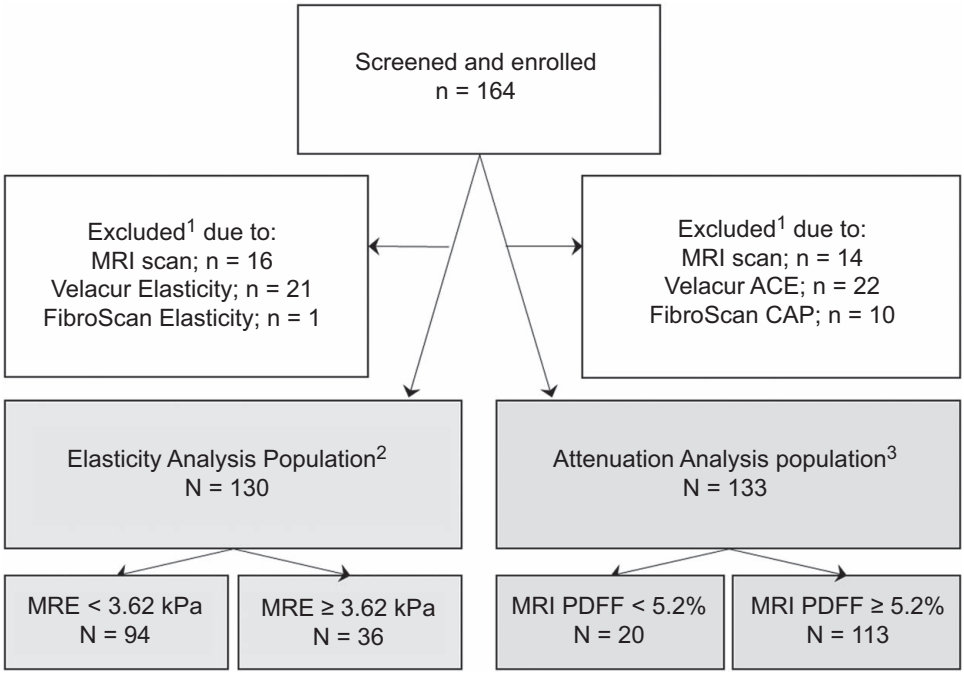

FIGURE 1 Patient flow diagram, showing the total enrolled patients and reasons for exclusion. Note that all reasons for exclusion are listed. A patient might have been excluded for more than one reason as the scans were not always completed sequentially. Abbreviations: ACE, attenuation coefficient estimate; CAP, controlled attenuation parameter; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging proton density fat fraction.

scan. The enrolled and excluded patients are summarized in Figure 1.

Fourteen patients did not complete an MRI scan. Of these patients, 1 failed MRI-specific screening, 10 were lost to follow-up, 2 withdrew the consent to complete the MRI after their other scans were completed, and 1 patient became uncomfortable in the MRI and ended the session early. The MRE portion of the MRI scan failed on 2 patients, as there were insufficient waves within the liver to make an accurate measurement.[26,27] The PDFF measurements for these 2 patients were included in the analysis.[26] A total of 21 Velacur elasticity scans were considered to be invalid based on the objective measure of shear waves and 1 patient had a FibroScan IQR/median $>30\%$. A total of 22 Velacur attenuation scans were considered to be invalid based on the objective ultrasound quality measure and 10 patients had a CAP IQR/median $>30\%$.

Table 1 describes the patient population. The average age of all patients was 57 ± 12 years old, with 56.1% female. The average BMI was 30.6 ± 4.8 kg/m^2. The average Fib-4 was 1.93 with 51.8% of patients having type 2 diabetes. None of the categories showed significant differences between all enrolled patients and the patients used in the elasticity or attenuation analysis populations. One patient was missing values for aspartate aminotransferase, and 1 missing for alanine transaminase. Between 4 (2%) and 11 (7%) patients were missing values for triglycerides, albumin, cholesterol, or gamma-glutamyl transferase. As these missing values were determined to be completely random, and not used in the primary analyses, these missing values were ignored in the means presented in Table 1.

The median time between the MRE and Velacur scans was 11 days. Of the patients included, 40 patients had MRI sessions which fell outside of the expected 28-day window. A sensitivity analysis was performed to evaluate the effect of out-of-window MRIs on the correlation of Velacur with MRI results. There were no differences in the results for the elasticity measurements between those who had an out-of-window MRI ($r = 0.86$ [0.75, 0.93] 95% CI) and those with an in-window MRI ($r = 0.86$ [0.81, 0.91] 95% CI) as indicated by the substantial overlap in the 95% CIs. As a result, all patients were included in the analysis of correlation coefficients and all other analyses.

Table 2 and Figure 2 summarize the imaging results for elasticity and liver fat/attenuation for each imaging modality.

Detection of advanced fibrosis and MRE staging

In this patient population, 28% (36/130) were classified based on MRE as having advanced fibrosis (≥F3, MRE ≥ 3.62 kPa). The AUC [95% CI] for Velacur to determine the presence of advanced fibrosis was 0.95 [0.92, 0.98]

TABLE 1 Baseline characteristics of participants and patients included in each analysis population

Patient characteristic	All enrolled	Elasticity comparison	Attenuation comparison
Total subjects	164	130	133
Age (y, mean ± std)	57 ± 12	57.8 ± 12	57.7 ± 12
Gender (% female)	56.1	53.1	53.4
BMI (kg/m^2, mean ± std)	30.6 ± 4.8	29.9 ± 4.49	30.1 ± 4.51
BMI proportion (%), <30, 30–35, 35–40, >40	45.7, 36.6, 14.0, 3.7	52.3, 33.1, 12.3, 2.3	50.4, 35.3, 11.3, 3.0
Fib-4 (mean ± std)	1.93 ± 1.8	1.91 ± 1.67	1.81 ± 1.52
Race (% White)	37.2	38.5	35.3
Diabetes (%)	31.1	33.1	32.3
AST (U/L, mean ± std)	39.8 ± 30.2	40.6 ± 29.9	41 ± 30.7
ALT (U/L, mean ± std)	50 ± 30.2	52.1 ± 29.9	52.8 ± 30.7
GGT (U/L, mean ± std)	61.8 ± 70.9	64.4 ± 75.2	65 ± 74.9
Platelets (10^9/L, mean ± std)	224 ± 87.5	218 ± 70.2	223 ± 72.3
Triglycerides (mg/dL, mean ± std)	164 ± 111	170 ± 119	172 ± 117
Cholesterol (mg/dL, mean ± std)	155 ± 49	155 ± 49.9	156 ± 50.5
Albumin (g/dL, mean ± std)	4.52 ± 0.365	4.58 ± 0.302	4.58 ± 0.3

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; BMI, body mass index; GGT, gamma-glutamyl transferase; T2DM, type 2 diabetes mellitus.

versus 0.97 [0.93, 0.99] for FibroScan. Both AUCs are considered to be good, at >0.85, and were not statistically different using the DeLeong test.

TABLE 2 Imaging results of the elasticity and attenuation analysis populations

Patient characteristic	Elasticity comparison	Attenuation comparison
Total subjects	130	133
MRE (kPa, mean ± std)	3.22 ± 1.39	—
Velacur elasticity (kPa, mean ± std)	6.13 ± 1.68	—
Velacur elasticity scan invalid (%)	12.8	—
FibroScan VCTE (kPa, mean ± std)	10.1 ± 7.61	—
FibroScan VCTE IQR >30% (%)	0.61	—
M probe used (%)	62.3	61.7
MRI-PDFF (%, mean ± std)	—	14.2 ± 8.37
Velacur ACE (dB/m, mean ± std)	—	290 ± 64.5
Velacur ACE scan invalid (%)	—	13.4
FibroScan CAP (dB/m, mean ± std)	—	309 ± 52.9
FibroScan CAP IQR >30% (%)	—	6.1
MRI-PDFF (%, mean ± std)	—	14.2 ± 8.37

Abbreviations: ACE, attenuation coefficient estimate; CAP, controlled attenuation parameter; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging proton density fat fraction; VCTE, vibration-controlled transient elastography.

MRE cutoffs from Hsu and colleagues were used to determine the presence of advanced fibrosis and estimate the fibrosis stage of each patient. The cutoffs were 2.61, 2.97, 3.62, and 4.69 kPa. The number of patients falling into stages for F0-F4 was 57, 13, 24, 21, and 15, respectively.

The AUCs for Velacur for each fibrosis stage were 0.82, 0.88, 0.95, and 0.97 and 0.89, 0.90, 0.97, and 0.99 for FibroScan. The DeLeong test was used to on each staging AUC to determine if the AUCs for Velacur and FibroScan were significantly different.[32] None of the differences in AUC were statistically different between Velacur and FibroScan.

Table 3 describes the AUC and *p* value for each fibrosis stage. Velacur and FibroScan were not shown to be significantly different at any stage.

Detection of steatosis and MRI-PDFF grading

MRI-PDFF was used to measure the liver fat fraction.[25,33,34] A 5.2% cut point was used to determine the presence of steatosis, which is used for the diagnosis of MASLD.[25] At 5.2%, the AUC [95% CI] for Velacur was 0.94 [0.88, 0.98] versus 0.79 [0.65, 0.89] for FibroScan CAP. The AUC for Velacur is both greater and statistically significant ($p = 0.01$).

5.2%, 11%, and 17.1% were chosen as clinically relevant cutoffs based on meta-analysis papers to estimate the steatosis grades of S0 to S3[25] and discussion with physicians of clinically relevant numbers for mild, moderate, and severe liver fat. In

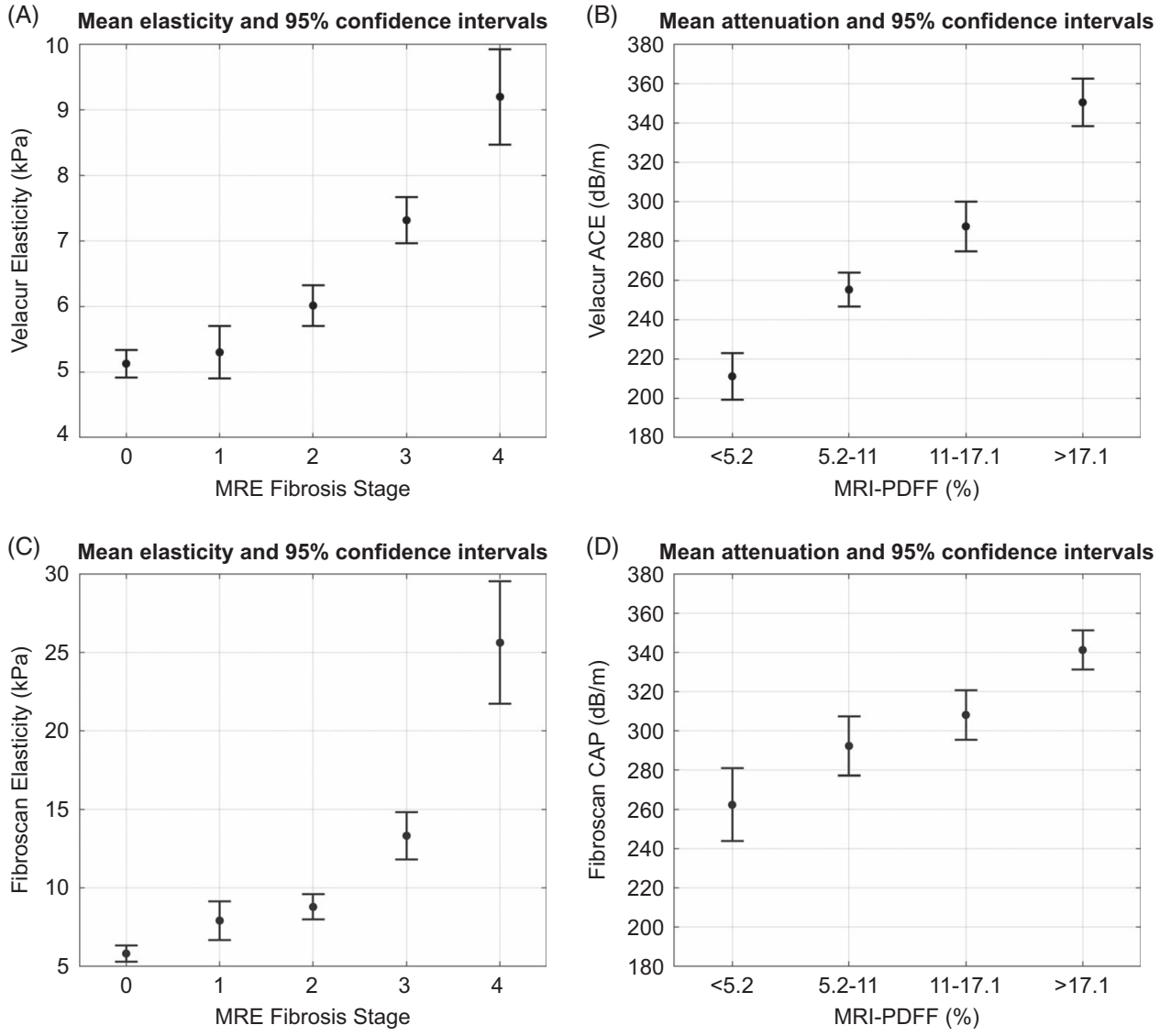

FIGURE 2 The staging for Velacur (A) and FibroScan (C) liver stiffness as defined by MRE cutoffs Grading of liver fat by Velacur ACE (B) and FibroScan CAP (D) based on MRI-PDFF measurements. Abbreviations: ACE, attenuation coefficient estimate; CAP, controlled attenuation parameter; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging proton density fat fraction.

the <5.2%, 5.2%–11%, 11%–17.1%, and >17.1% ranges, 20, 36, 30, and 47 patients were included, respectively.

Table 4 describes the AUC and *p* value for each MRI-PDFF cutoff. Velacur was also shown to be superior at each of the MRI-PDFF cutoffs.

Correlation coefficients

Correlation coefficients (*r*) and 95% CI between the MRE and liver stiffness measurements according to Velacur and FibroScan were 0.86 [0.80–0.90] and 0.91 [0.87–0.93], respectively.

TABLE 3 Comparison of the area under the operator receiving curve [95% CIs] for Velacur and FibroScan elasticity measurements

Fibrosis stage	MRE cutoff (kPa)	AUC (Velacur E) [CI]	AUC (FibroScan VCTE) [CI]	*p*
0/1–4	2.61	0.83 [0.72, 0.88]	0.89 [0.82, 0.94]	0.05
0–1/2–4	2.97	0.88 [0.79, 0.92]	0.90 [0.85, 0.94]	0.5
0–2/3–4	3.62	0.95 [0.92, 0.98]	0.97 [0.93, 0.99]	0.4
0–3/4	4.69	0.97 [0.93, 0.99]	0.99 [0.96, 1.00]	0.2

Abbreviation: VCTE, vibration-controlled transient elastography.

TABLE 4 Comparison of the area under the operator receiving curve [95% CIs] for Velacur and FibroScan attenuation measurements

MRI-PDFF value	AUC (Velacur ACE)	AUC (FibroScan CAP)	*p*
0–5.2%/ > 5.2%	0.94 [0.88, 0.98]	0.79 [0.65, 0.89]	0.01
0–11%/ > 11%	0.91 [0.86, 0.95]	0.77 [0.68, 0.86]	0.001
0–17.1%/ > 17.1%	0.93 [0.88, 0.96]	0.79 [0.71, 0.86]	< 0.001

Abbreviations: ACE, attenuation coefficient estimate; CAP, controlled attenuation parameter; MRI-PDFF, magnetic resonance imaging proton density fat fraction.

The correlation coefficient for ultrasound attenuation measurements versus MRI-PDFF liver fat percentages was 0.84 [0.78–0.88] for Velacur ACE versus 0.57 [0.44–0.68] for FibroScan CAP. The scatter plots of Velacur and FibroScan results versus MR imaging are shown in Figure 3.

DISCUSSION

Main findings

Using MRE and MRI-PDFF as the reference for this study, Velacur was superior to FibroScan CAP in

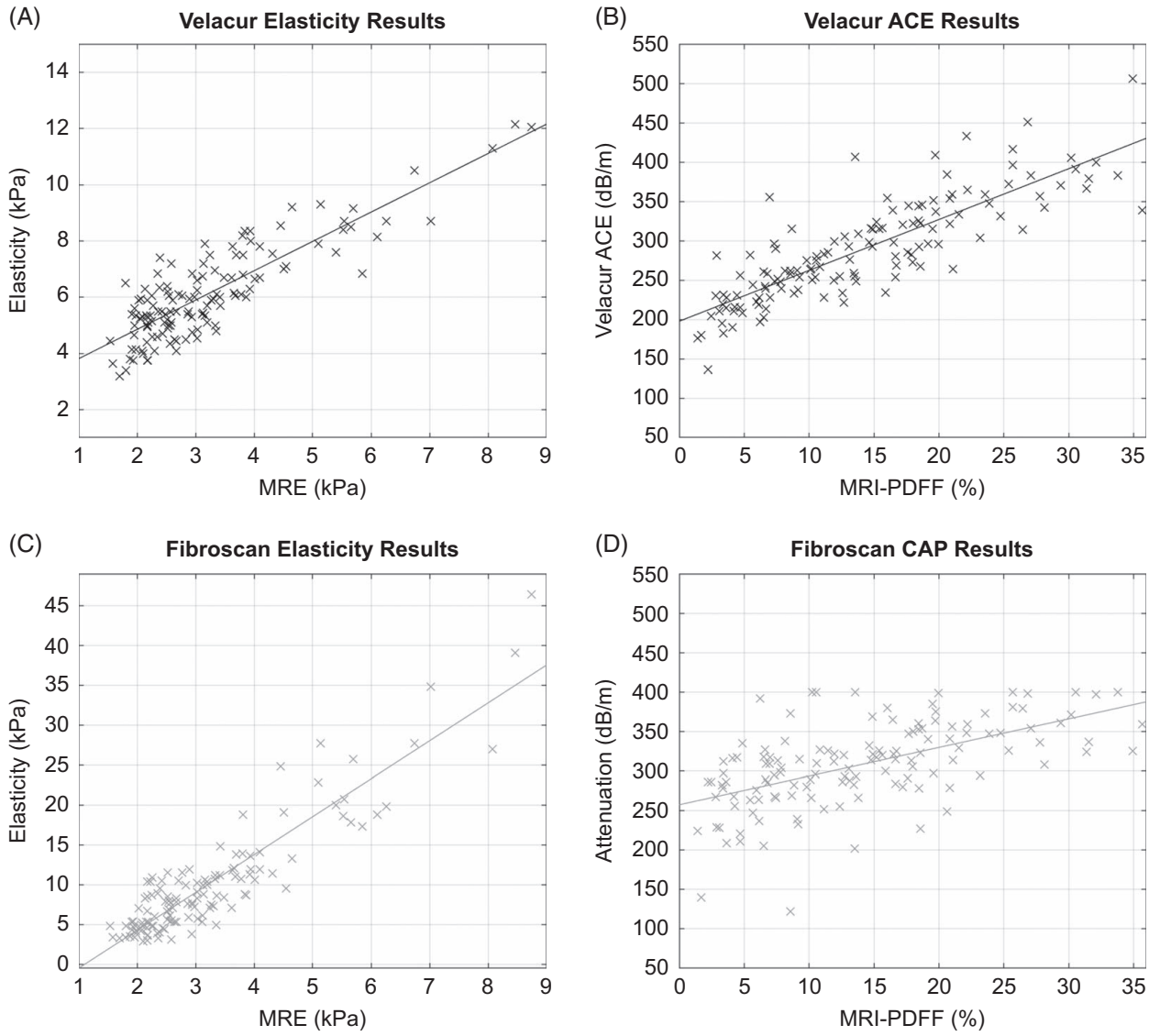

FIGURE 3 Scatter plots showing the correlations between the results of Velacur (A) and FibroScan (C) measurements of liver stiffness as compared to MRE. Scatter plots showing the correlations between the results of Velacur (B) and FibroScan (D) measurements of ultrasound attenuation as compared to MRI-PDFF. Abbreviations: ACE, attenuation coefficient estimate; CAP, controlled attenuation parameter; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging proton density fat fraction.

detecting the presence of steatosis and was equivalent to FibroScan in its ability to detect advanced fibrosis.

Velacur was able to differentiate patients with different levels of liver stiffness and liver fat with AUCs >0.8, and equal to or greater than FibroScan. This shows a level of agreement that is at or higher than most biomarkers used for the stratification of patients with MASLD and MASH.

In all stages of fibrosis, as designated by MRE cutoffs, analysis with the DeLeong test showed that there was no significant difference between the AUC of Velacur and FibroScan. Both modalities show excellent discriminatory ability with AUCs >0.8 at each stage. When looking at the box plots in Figure 2, there is less overlap of stages for F1 and F2 for Velacur than FibroScan. This is particularly important, as patients with F2 or greater are considered to have significant fibrosis in the evolution toward cirrhosis.[7] These are also the patients who will be most likely to receive the new treatments for MASLD and MASH as they become available.[35,36]

When looking at the attenuation measurements from Velacur and FibroScan versus the MRI-PDFF results, again the AUCs are satisfactory, all above 0.8. The correlation coefficients between Velacur and FibroScan versus the MRI-PDFF were 0.84 and 0.57, respectively, which tracks with the generally higher AUC for Velacur ACE than FibroScan CAP. In all levels of steatosis, the AUC for Velacur ACE was higher and also statistically significant using the DeLeong test.

Strengths and limitations

Although this study did not compare the outputs of Velacur to biopsy, the current "gold standard," MRE and MRI-PDFF have been shown to correlate well with biopsy,[8–10,12] and correlate with patient outcomes in patients with cirrhosis.[13] MRE and MRI-PDFF are used in clinical trials and more often than biopsy in clinical practice. Biopsy is more often considered the gold standard for fibrosis measurements, but due to problems with sampling size, incongruent reads, and patient risk, biopsy is less commonly used for the diagnosis and staging of patients with MASLD and MASH outside of clinical trials. In the diagnosis of fibrosis stage, there is currently no perfect standard to measure against, as all current standards suffer from some drawbacks, or are inherently surrogate markers. When reviewing the results of this study, it is important to appreciate that, due to the repeatability and reproducibility issues of biopsy, even a perfect biomarker would not exceed an AUC of 0.9, and an AUC of 0.8 would be considered excellent.[37]

MRI-PDFF was used as the standard for liver fat, as it is able to directly measure the number of free protons associated with triglycerides. The cutoffs chosen, 5%, 11%, and 17%, are associated with normal, mild/moderate, and severe liver fat. As there is greater uncertainty and variability in the literature between the absolute MRI-PDFF as they relate to the steatosis grade,[25,34] it was decided to not convert the MRI-PDFF fat fraction percentages to steatosis grades.

Although an even distribution of patients into fibrosis stages was attempted, many more patients in the F0/F1 range were enrolled than expected (70/130, 54%). As the MRE was completed after enrollment, and no historical MRE was available, many patients were enrolled based on other historical measurements. Future studies will focus on patients with known cirrhosis and precirrhosis to validate these findings in patients with higher levels of fibrosis. On the other hand, this distribution is more representative of the overall MASLD population in which point-of-care noninvasive assessments are likely to be used.

It should also be noted that most users in this study, although fully trained, were novice users of Velacur. It has been shown in other elastography systems, such as FibroScan, that at least 50 scans are needed to achieve competency with a device.[21,38] Due to the novel nature of Velacur, having users complete such a training period was impractical. Velacur does include a software feature to measure the quality of the scan, using a mixture of ultrasound and shear wave features. We did see a marked increase in the quality of scans as the study progressed but as the sites began at different times, it is difficult to qualify at this time. We expect to see that in future studies, with users who are more experienced and a better understanding of the learning curve, would show a better overall correlation with MRE and MRI-PDFF. Work is underway to quantify the learning curve for future studies.

CONCLUSIONS

Velacur ACE was superior to FibroScan CAP for steatosis detection. Velacur and FibroScan were not statistically different for liver stiffness assessment.

Velacur has been shown capable of discriminating patients with an AUC >0.8 for both liver stiffness and steatosis as measured by MRE and MRI-PDFF. Velacur is able to achieve a discriminatory ability as high as or higher than FibroScan in all stages of fibrosis and steatosis qualification.

As the number of patients requiring liver assessment for MASLD increases across the world, additional, accurate, accessible, and ideally noninvasive tools are needed and Velacur has shown to be an accurate point-of-care option for assessing liver stiffness and attenuation.

DATA AVAILABILITY STATEMENT

Data will not be made publicly available.

AUTHOR CONTRIBUTIONS

Study design: Rohit Loomba, Eric M. Yoshida, Caitlin Schneider, Michael P. Curry, and Nezam H. Afdhal. Data acquisition: Rohit Loomba, Eric M. Yoshida, Tarek Hassanein, Alnoor Ramji, and Michael P. Curry. Data analysis and interpretation: Caitlin Schneider and Emily Pang. Original draft: Caitlin Schneider. Revision of the manuscript: All authors. All authors had access to the data, and approved the final draft of the manuscript as well as the authorship list.

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The study was sponsored by Sonic Incytes Medical Corp.

CONFLICTS OF INTEREST

Rohit Loomba: serves as a consultant for Aardvark Therapeutics, Altimmune, Anylam/Regeneron, Amgen, Arrowhead Pharmaceuticals, AstraZeneca, Bristol-Myer 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, Thera Technologies, 89 bio, 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, Intercept, Inventiva, Ionis, Janssen, Madrigal Pharmaceuticals, Merck, NGM Biopharmaceuticals, Novo Nordisk, Merck, Pfizer, Sonic Incytes, and Terns Pharmaceuticals. Co-founder of LipoNexus Inc. Alnoor Ramji: AR Advisor/consultant for Abbvie, Gilead, Intercept, Janssen, Novo Nordisk. Speaker: Abbvie, Amgen, Gilead, Intercept, Janssen, Novo-Nordisk. Grant/research support from Abbvie, Assembly, Galmed, Gilead, Intercept, Janssen, Merck, Novartis, Novo-Nordisk, and Pfizer. Tarek Hassanein: Advisory Committee or Review Panel for AbbVie, Bristol-Myers Squibb, Gilead, Mallinckrodt, Merck, and Organovo. Consulting for AbbVie, Bristol-Myers Squibb, Gilead, Mallinckrodt, Merck, and Organovo. Speaking and Teaching for AbbVie, Bristol-Myers Squibb, and Gilead. Receives grant/research support from AbbVie, Allergan, Amgen, Biolinq, Bristol-Myers Squibb, Cytodyn, Assembly, AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, CARA, DURECT Corporation, Enanta, Escient, Fractyl, Galectin, Gilead, Grifols, HepQuant, Intercept, Janssen, Merck, Mirum, Novartis, Novo Nordisk, Nucorion, Pfizer, Provepharm, Regeneron, Salix Pharmaceuticals, Sonic Incytes, Terns Pharmaceuticals, and Valeant. Eric M. Yoshida: Dr Eric M. Yoshida is an investigator of clinical studies sponsored by Sonic Incytes, Gilead Sciences, Pfizer, Madrigal, Novodisk, Intercept, and Genfit. He has received honoraria for CME lectures sponsored by Intercept Canada. He has received an unrestricted research grant from Paladin Laboratories. Caitlin Schneider: Sonic Incytes employee. Michael P. Curry has received research support from Sonic Incytes, Mallinckrodt, and Gilead and consulting fees from Sonic Incytes, Mallinckrodt, Alexion, and Albireo. Nezam H. Afdhal has received consulting fees from Gilead, Glaxo Smith Kline, Jannsen, Sonic Incytes, Precision Biosciences, and Intercept Pharmaceuticals. He has stock in Allurion. He is the director, Liver Institute for Education and Research. Emily Pang has no conflicts to report.

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