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The Performance of Vibration Controlled Transient Elastography in a US Cohort of Patients with Non-alcoholic Fatty Liver Disease

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Abstract

Background—Identification of patients with Nonalcoholic Fatty Liver Disease (NAFLD) who have advanced fibrosis is crucial. Vibration Controlled Elastography (VCTE) is an alternative to biopsy; though published experience with VCTE in a U.S. population is limited.

Methods—We performed a prospective cohort of 164 biopsy-proven NAFLD patients evaluated with VCTE using an M probe and NAFLD Fibrosis Score (NFS) at baseline and a repeat VCTE at 6 months. Reliable liver stiffness measurements (LSM) were defined as 10 valid measurements and interquartile range (IQR) < 30% of the median.

Results—120 (73.2%) patients had reliable LSM. The median LSM for patients with and without F3–F4 (advanced) fibrosis were 6.6 kPa (5.3 – 8.9) and 14.4 kPa (12.1 – 24.3), respectively. The optimal LSM cutoff for advanced fibrosis was 9.9 kPa (sensitivity 95%, specificity 77%). Additionally, 100% of patients with LSM < 7.9 kPa did not have advanced fibrosis. A risk stratification strategy based on VCTE avoids the need for biopsy in at least the 74 (45.1%) patients correctly classified as low risk for advanced fibrosis. The area under the receiver operating curve (AUROC) of 0.93 (95% CI: 0.86–0.96). For the detection of F3-F4 fibrosis in patients with

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reliable VCTE, the AUROC of VCTE is superior to that of NFS (0.77), $p=0.01$. Patients who achieved a 5% weight loss at 6 month follow-up experienced improved LSM ($p = 0.009$), independent of changes in aminotransferase levels.

Conclusion—Reliable VCTE results can rule out advanced fibrosis and avoid the need for biopsy in at least 45% of US patients with NAFLD. However, 1 in 4 patients have uninterpretable studies using the M probe.

Keywords

Nonalcoholic Steatohepatitis; Cirrhosis; Obesity; Liver Disease; Hepatology

Introduction

Nonalcoholic fatty liver disease (NAFLD) is becoming the major cause of liver disease related morbidity and mortality in the United States and Europe. (1, 2) As recently demonstrated by Ekstedt and colleagues, the most important determinant of outcomes including mortality for patients with NAFLD is their fibrosis stage. (3) Accordingly, efficient and effective identification of patients with advanced fibrosis who are at risk for the complications of advanced liver disease and increased mortality is critical. The optimal risk-stratification strategy for patients with NAFLD, however, is unknown.

American Association for the Study of Liver Disease (AASLD) guidelines recommend a liver biopsy for patients with metabolic syndrome or elevated NAFLD fibrosis scores (NFS) – a freely available algorithm based on the alanine and aspartate aminotransferase levels, albumin, platelet count, body mass index and presence of diabetes mellitus. (4) Clinicians and patients alike are deeply interested in alternative strategies to the liver biopsy for a number of reasons. First, more than half of patients offered a liver biopsy refuse. (5) Second, biopsies are expensive and somewhat risky. (6, 7) Third, the liver biopsy is an imperfect gold-standard. Sampling error is common. (8)

In clinical practice, it is difficult to base treatment and screening decisions based on the NFS alone. Its results benefit from confirmation. Vibration controlled transient elastography (VCTE) is a candidate confirmatory test. An FDA approved, validated, point-of-care tool, VCTE can provide a non-invasive estimate of fibrosis in patients with NAFLD. (9) Furthermore, as demonstrated in two Italian cohorts by Petta et al, VCTE performs significantly better in the detection of advanced fibrosis than NFS. (10)

While the published experience with VCTE in the USA is increasing, specific reports on NAFLD are lacking. Prior studies of patients with NAFLD from France and Canada reported good test performance in populations with BMI > 30 kg/m². (11–13) Still, many worry that the higher BMI of American patients may result in poorer VCTE performance. Herein, we report a prospective assessment of VCTE for American patients with NAFLD.

Methods

Patient population

The subjects for this study were prospectively enrolled in an NAFLD registry at Beth Israel Deaconess Medical Center (BIDMC) beginning in 2009 through 2014. All patients had biopsy proven NAFLD within 3 months of the VCTE examination. Patients with other chronic liver diseases or consumption of greater than 20 g alcohol daily were excluded from the registry. At the time of this study, there were 185 subjects overall, 169 (91.4%) of whom had a VCTE exam within 3 months of a liver biopsy, 164 with an M-probe. We excluded the 5 patients who received XL probe VCTE exams to maintain a consistent protocol (the XL probe was only available for the final 3 months of the study). Of these patients, 87 returned for a 6 month visit where a VCTE was performed. All patients received a comprehensive evaluation at study enrollment which included anthropomorphic indices (waist circumference, body mass index) and lipid profiles in addition to their liver-specific testing.

As described elsewhere, (14) each patient received standard instructions for lifestyle modifications. Patients were instructed to perform two days of resistance/weight training weekly in addition to aerobic exercise. This included either 150 minutes of moderate intensity exercises (increased heart rate with sweating) or 75 minutes of vigorous intensity exercises (sweating and hard breathing). Portion control, elimination of sugary beverages and limited saturated fats were universally recommended. A consultation with a nutritionist was made available to all patients and 33 (20%) attended at least one visit during the first 6 months of follow-up. No patient was receiving drug therapy (e.g. vitamin E) at the time of registration, nor were any prescribed during the first 6 months of follow-up. The study was approved by the BIDMC institutional review board.

Liver biopsy

Ultrasound guided liver biopsy was performed at the enrollment of the study. Biopsies were interpreted by specialized hepatopathologists and reported in standardized fashion according to the Brunt scoring system with specific mention of fibrosis stage and NAFLD activity score (NAS) as described previously. (15) NASH was defined by NAS score of 5 – 8. Advanced liver fibrosis was defined as fibrosis stages 3 – 4. Pathologists were unaware of non-invasive assessments.

Noninvasive fibrosis assessment: VCTE and NFS

All VCTE examinations were performed with the 'M' probe, which measures shear wave velocity at a depth of 25–65 mm. (9, 16) This velocity is converted mathematically into a liver stiffness measurement (LSM) which is depicted in kiloPascals (kPa). A successful VCTE exam was defined by the acquisition of 10 successful measurements where the interquartile range of the LSM does not exceed 30% of the median LSM. Therefore an 'uninterpretable' VCTE examination encompassed failures on one or both accounts. Each patient received their exam after 3 hours of fasting. (9, 17) All VCTE examinations were performed by two experienced technicians, both of whom have performed in excess of 500 LSM. Each examination was reviewed by a physician to determine the adequacy of the measurements.

We employed a strategy for non-invasive risk stratification that classified patients as low, indeterminate and high risk for advanced fibrosis. This strategy enhances the negative predictive value while allowing for an indeterminate range of LSM that deserve further evaluation. The optimal high risk cutoff for advanced fibrosis was derived from this dataset as described below. As is standard practice for non-invasive markers including the NFS and VCTE, (9, 10, 18, 19) we set the low risk LSM cutoff for advanced fibrosis to be <80% of the optimal cutoff. (9, 10, 18) An indeterminate LSM result was considered any value greater than a low risk score and below the optimal cutoff for advanced fibrosis. For example, if the optimal cutoff for advanced fibrosis is determined to be 10 kPa, then a low risk result would be < 8 kPa and indeterminate would be 8 – 9.9 kPa.

All patients had their NFS score assessed at the time of their VCTE examination. The NFS was calculated according to the published algorithm: $-1.675 + 0.037 \times \text{age (years)} + 0.094 \times \text{BMI (kg/m}^2) + 1.13 \times \text{diabetes (yes = 1, no = 0)} + 0.99 \times \text{AST/ALT ratio} - 0.013 \times \text{platelet count (} \times 10^9/\text{L)} - 0.66 \times \text{albumin (g/dL)}$. (19) The NFS cutoff consistent with advanced fibrosis and minimal fibrosis were 0.675 and -1.455, respectively, with the interval range considered indeterminate. (19) The presence of metabolic syndrome was determined using standard criteria based upon waist circumference, triglyceride and high-density lipoprotein levels, blood pressure measurements, and the presence of diabetes or elevated fasting glucose. (20)

We compared the relative performance of noninvasive risk stratification using VCTE alone and combined VCTE/NFS. The combination testing strategy with sequential VCTE and NFS assessments was studied as described elsewhere. (9, 10, 21) Specifically, patients would receive a VCTE examination during their clinic visit (at the point of care) and have blood tests performed to allow for the determination of their NFS. In this strategy, patients can be classified as low risk if they have low risk results from both VCTE and NFS; high risk if both tests are concordant; or indeterminate if there is discordance between tests or concordant indeterminate values. Risk stratification strategies were evaluated based on their ability to exclude advanced fibrosis.

Outcomes

We chose multiple outcomes to report based on their interest to clinicians who utilize non-invasive tools. Our main goal was to assess the performance of risk stratification strategies based on VCTE examinations as well as combined testing with VCTE and NFS. To do so we created clinical decision algorithms based on low, indeterminate and high risk LSM and NFS scores to determine the number of patients correctly classified as low risk by VCTE alone or the combination strategy. High risk LSM was defined as any score greater than the optimal LSM for the determination of advanced fibrosis as judged by the receiver operating characteristics (ROC) of LSM. We had three secondary goals. First, we sought to assess the determinants of uninterpretable VCTE exams. Exposure variables employed for this analysis included all available baseline clinical characteristics with multivariate analysis of variables significant on univariate comparisons to determine the primary drivers. Second, we explored the effect of clinical variables on LSM as continuous variable using linear regression. Third, we assessed changes in the LSM over time with a focus on the effect of weight loss. Since

we felt, a priori, that BMI, necroinflammatory activity (vis-à-vis ALT, AST, NAS score), and fibrosis burden could determine the capacity for LSM change, we divided our analyses into subsets to address these potential effects.

Data Analysis

Data are summarized as mean + standard deviation for normally distributed, median [25th and 75th percentiles] for non-normally distributed continuous outcomes, or counts and percentages for categorical outcomes. A two-tailed p-value was considered significant when < 0.05 .

Logistic regression was performed to assess associations with the binary outcomes (uninterpretable VCTE, advanced fibrosis) with an odds ratio as its output. Linear regression was performed to assess continuous outcomes (liver stiffness measurements (LSM)). Multivariate analyses were performed to adjust for any variable found to be significant on univariate analysis, defined either by a p value < 0.05 or a confidence interval that did not cross 0. We also used ROC curves with 95% confidence intervals (CI) to determine the optimal cutoffs for continuous measurements (LSM, body mass index (BMI)) for binary outcomes (advanced fibrosis, uninterpretable VCTE examinations). We compared the area under the ROC (AUROC) for different diagnostic tests applied to the same patients within the data set using the non-parametric DeLong-test.

For univariate longitudinal assessments of LSM, we used paired Wilcoxon testing for matched-pairs to determine the significance of changes on follow up. We chose to divide baseline subgroups based on patients with values greater than the median or based on the presence or absence of advanced histology (NASH or fibrosis). For change results, we chose a 5% reduction in weight as a clinically meaningful cutoff based on prior studies demonstrating a significant reduction in hepatosteatosis with 5% weight loss. (22) We chose a 20% reduction in ALT or AST as half of the cohort experienced such decrements. JMP Pro statistical discovery software (version 11) was used for statistical analyses.

Results

Determinants of Liver Stiffness Reliability and Results

Among the 164 patients with VCTE exams at enrollment, 120 (73.2%) had reliable results. The demographics and clinical details of the whole cohort as well as comparisons between those with reliable and uninterpretable exams are depicted in Table 1. The major difference potentially explaining the occurrence of an uninterpretable exam is patient BMI with possible contributions from gender, diabetes and NFS.

Our cohort's mean BMI is 33.2 kg/m². The mean BMI of patients with uninterpretable VCTE is 37.2 kg/m² and 31.8 kg/m² among those with reliable results, $p = 0.0001$. In multivariate analysis of gender, diabetes, hypertension, and BMI only BMI is significantly associated with an uninterpretable LSM, beta coefficient 0.13 (95% CI 0.05 – 0.21), $p = 0.001$. The area under the receiver operating curve (AUROC) for the association of BMI with an uninterpretable test is 0.71. Derived from this analysis, the optimal cutoff is a BMI

of 36.65 kg/m². The odds ratio (OR) for an uninterpretable exam associated with a BMI of greater than 36.65 kg/m² is 8.76 95% CI (3.82 – 21.0).

We then examined the 120 patients with reliable exams to determine the clinical drivers of LSM. While univariate associations were present between LSM and age, BMI, diabetes, hypertension, AST, Alkaline phosphatase, active histologic NASH and advanced fibrosis, only advanced fibrosis held in multivariate analysis. Among these patients, the median LSM for patients with and without advanced fibrosis were 6.6 kPa (5.3 – 8.9) and 14.4 kPa (12.1 – 24.3), respectively.

Comparison of Non-invasive testing strategies

The ability of non-invasive tests to discriminate patients at risk for advanced fibrosis was examined in two ways. First, we sought to describe VCTE's test characteristics. The optimal cutoff – 9.9 kPa – has a sensitivity of 95% and specificity of 77% for advanced fibrosis. The positive and negative predictive values for this cutoff are 46.5% and 98.7%. The lowest LSM of a patient with advanced fibrosis was 8.4 kPa. Applying our pre-specified criteria, low risk results were those < 7.9 kPa. Indeterminate LSM was defined as any value between 7.9 and 9.89 kPa. The specificity and negative predictive value of the low risk cutoff (< 7.9 kPa) for advanced fibrosis are both 100%. A patient's LSM was associated with advanced fibrosis with an AUROC of 0.93 95% CI (0.86 – 0.96).

Conversely, the AUROC for NFS was much lower – 0.77 (95% CI = 0.63 – 0.97). Using Angulo et al's high (0.675) and low (–1.455) cutoffs, the respective sensitivity and specificity for advanced fibrosis were 19%/95% and 63%/70%. Seven of 82 (9%) patients with low NFS had advanced fibrosis. The presence of metabolic syndrome was associated with an AUROC of 0.66 95% CI (0.62 – 0.68). Comparing the AUROC from VCTE to NFS, VCTE is statistically superior, $p = 0.01$, and led to a lower misclassification rate (13% versus 17%). When the NFS was applied to the whole cohort of 164 patients (not just those with reliable VCTE), the AUROC was lower at 0.72 (95% CI = 0.60 – 0.82).

Second, we examined the performance of our non-invasive risk stratification strategy with VCTE (Figure 1). As above 120 subjects had reliable M-probe VCTE exams. Of these, a low risk VCTE result (<7.9 kPa) in 67 subjects (40.9% of the cohort) correctly classified all as not having advanced fibrosis (100% correct classification). Beyond that, patients were either classified as high (43, 26.2% with >9.8 kPa) or indeterminate risk (10, 6.1% with 7.9 to 9.8 kPa). 46.5% of patients with high risk LSM have advanced fibrosis (20/43) and 10% (1/10) of the patients with intermediate risk LSM have advanced fibrosis. All 10 patients with indeterminate results, had a follow up LSM obtained 6 months later. Seven of the 10 had a repeat LSM of < 7.9 kPa, none with advanced fibrosis. The remaining 3 of the 10 patients had LSM > 9.8 kPa, one with advanced fibrosis. Therefore, VCTE-based noninvasive risk stratification with low, indeterminate and high risk scores therefore has a 100% sensitivity and 75.5% specificity. Overall, this strategy avoids the need for biopsy in at least the 74 (45.1% of the total cohort) patients correctly classified as low risk for advanced fibrosis.

NFS alone and in combination with VCTE as risk stratification strategies did not enhance risk stratification in our cohort. (Supplementary Figure 1). Concordant low risk results between both VCTE and NFS, resulted in 13 fewer patients or 54 (32.9%) patients being correctly classified as low risk for advanced fibrosis. This is significantly lower than the proportion of biopsies correctly avoided using VCTE alone ($p = 0.03$). Beyond low risk results, the combination of VCTE and NFS does not improve indeterminate or high risk patient risk stratification further. For example, among the 10 patients with indeterminate VCTE exams, the 1 (10%) patient with advanced fibrosis had a low risk NFS value. At the same time, for the 44 patients with uninterpretable VCTE exams, the prevalence of advanced liver disease among low, indeterminate and high risk NFS values were 14.3% (3/21), 13.3% (2/15) and 20% (2/5).

Subgroup analysis: Sequential VCTE exams

Eighty-seven patients returned for VCTE examinations at 6 months (Table 3). Thirty-seven (42.5%) patients had a 20% improvement in their LSM while 17.2% had a 20% increase in LSM. Overall, patients experienced a 12.8% (95% CI=5.2 – 20.5) improvement in LSM. However, while many patients experienced an improvement in their LSM, the mean reduction in LSM was greater among those who lost $\geq 5\%$ of their weight than those who did not; 22.7% (95% CI = 8.2 – 37.1) and 8.1% 95% CI = -1.0 – 16.7), respectively ($p = 0.04$). Overall, 14 of 31 (45%) patients with LSM > 9.9 kPa experienced a decrease in LSM < 9.9 kPa on follow up compared to 5 of 56 (8.9%) who began < 9.9 and became ≥ 9.9 kPa. As shown in supplemental figure 2, the correlation between change in BMI and LSM was weak. However, changes in LSM classification (advanced fibrosis or not) were most associated with weight loss. Weight loss was associated with an OR of 5.40 95% CI (1.22 – 38.6, $p = 0.02$) for change in LSM from > 9.9 kPa to < 9.9 kPa. There were no baseline variables (fibrosis burden, NASH, gender, BMI, liver biochemistry) that were significantly associated with either an increase or decrease in LSM. The effect of a weight increase on LSM could not be assessed as only two patients experienced a $> 5\%$ weight gain. As shown in Table 3, the LSM at baseline and follow up for various baseline subgroups were significantly different for patients with NAS ≥ 4 and a steatosis score of 1. When change variables were examined, a 5% reduction in weight, but not a 20% reduction in ALT or AST, was significantly associated with a decrease in LSM ($p = 0.009$).

Discussion

NAFLD is a common, costly and potentially morbid condition. As the presence of advanced fibrosis in NAFLD is the strongest predictor of liver-related morbidity and mortality, (3) an efficient noninvasive risk stratification strategy to identify patients at high risk for advanced fibrosis is essential. While liver biopsy remains the gold standard, alternatives are urgently needed to reduce risks and costs as well as to satisfy patient preferences. In this prospective cohort study of consecutive patients enrolled at an American NAFLD clinic, we demonstrate three major findings. First, using a noninvasive risk stratification strategy with VCTE is extremely effective at ruling out advanced fibrosis, more so than the NAFLD fibrosis score. VCTE is highly sensitive but not specific; NFS is relatively insensitive but highly specific. Second, many patients, namely those with markedly elevated BMI are not candidates for

VCTE with an M probe but further study employing the XL probe in this population is needed. Third, we show that when patients are followed longitudinally, a 5% weight loss is associated with a decrease in liver stiffness measurement on 6-month follow-up.

This study extends the developing literature on non-invasive risk stratification in several important ways. First, while experience with VCTE is growing world-wide, data regarding its applicability in the American NAFLD population is limited. VCTE performance in other nations, mainly in Asia, has been encouraging. In a recent meta-analysis, the pooled sensitivity and specificity of various LSM cutoffs for advanced fibrosis were 85% and 85%. (11) In our hands, a cutoff of 9.9 kPa has a sensitivity of 95% and specificity of 77% for the presence of advanced fibrosis. Applying our noninvasive risk stratification strategy increases the sensitivity (and therefore negative predictive value) to 100% with a minimal decrement in specificity (75.5%). Accordingly, our data shows that for patients with reliable exams, mainly those with a BMI of 36 kg/m² or lower, VCTE with an M probe is an excellent tool for which clinicians may discern low from high risk patients, avoiding the need for biopsy in 45% patients presenting for evaluation at a US NAFLD clinic.

Second, the addition of NFS to VCTE worsened the performance of our noninvasive risk stratification strategy. On one hand, these results contrast with those of Petta and colleagues, who demonstrated an incremental benefit to combined NFS/VCTE testing. (23) On the other, these results confirm some of the pitfalls in the clinical use of the NFS. Petta et al's retrospective study included two cohorts with lower BMI (27.4 and 29.3 kg/m²) and falsely classified 4% of patients as low risk (including 7.3% in one of the cohorts). Similarly, in its American validation study, the NFS also misclassified low risk patients (12% had advanced fibrosis). (19) Furthermore, the performance of NFS in the detection of advanced fibrosis among our cohort was similar to most large studies of NFS including its validation study, (19) as well as that of McPherson et al (24) and Petta et al. (10) The incremental value of VCTE - what the NFS does not offer in this or prior studies - is the ability to confidently exclude advanced fibrosis at the point-of-care. However, the available data suggests that the natural history of NAFLD is often mild. (3, 25, 26) For this reason, an NFS based strategy which would fail to capture patients with advanced fibrosis is still cost-effective. (27)

Third, we found that a BMI > 36.65 was associated with uninterpretable VCTE results using the M-probe. BMI has had conflicting effects on the performance of VCTE. (23, 28, 29) It is generally accepted that higher BMI is associated with a higher likelihood of failed VCTE. Notably, the mean BMI of our cohort was 33.2 kg/m², compared to 24.4 in a recent study of VCTE variability, (30) 26.6 in a study of VCTE as screening among diabetics, (31) and 28.0 in the largest VCTE series in NAFLD to date (32) and 33.0 in a Canadian study. (12) We show that 1 in 4 patients with NAFLD evaluated at an American liver referral center will have an uninterpretable VCTE exam, using the M probe. It should be noted, however, that an uninterpretable exam is not, by itself, indicative of increased risk as advanced fibrosis and active NASH are evenly distributed between patients with reliable and uninterpretable results. Further research is needed to clarify the performance of VCTE in the US with studies utilizing the XL probe. For now, we place our results in the context of a non-invasive risk stratification strategy employing either MRE or liver biopsy in patients with uninterpretable VCTE.

Fourth, we demonstrate that a 5% weight loss was associated with a lower follow-up LSM. Indeed, patients with LSM consistent with advanced fibrosis who lost weight were more than 5-fold more likely to be reclassified as non-advanced fibrosis on follow-up. As recently shown by Petta et al in one Italian cohort, hepatic steatosis is a partial driver of LSM. (18) Notably, we found that only grade 1 steatosis is significantly linked to liver stiffness improvement following weight loss. As 5% weight loss has been shown to improve hepatosteatosis, (22) it is likely that those with grade 1 are most likely to experience that benefit of possible LSM improvements in the short-term.

These data must be understood within the context of the study design. First, this study was performed at a referral center in the Northeastern United States. While most of our patients were obese with 75% of the cohort between 29.4–36.5 kg/m², the baseline BMI of a given cohort is likely to determine the applicability of VCTE to one's practice. The prevalence of advanced fibrosis (17.7%) is likely higher than in general clinical practice which may mean that an even higher proportion of patients will have low risk LSM elsewhere. Second, VCTE may not be available in many settings where, therefore, NFS is a viable alternative. Third, we did not perform follow up biopsies to assess histological changes concurrent with LSM changes to tease out what precisely (fibrosis, steatosis or other factors) is accounting for the decrease in LSM. The weak overall correlation between changes in BMI and LSM suggests that there are important unmeasured determinants of longitudinal LSM changes including necroinflammation, fibrosis and intra- or inter-observer variations. (30) However, six-months is likely insufficient for changes in fibrosis and the lack of association between ALT or AST and change in LSM indicates that we would have been unlikely to detect any changes in necroinflammatory activity. Fourth, the multivariable analysis of factors contributing to liver stiffness suggests that there are unmeasured confounders of VCTE. Fifth, owing to confounding by liver biopsy's sampling variability, non-invasive metrics of liver fibrosis cannot distinguish fibrosis stages. (9) Binary risk categories (advanced fibrosis or not) are therefore more reliable and answer the most important question for patients and providers alike. (3, 26, 27) Finally, we did not assess the XL probe in this setting which may allow for fewer uninterpretable/failed VCTE exams.

In conclusion, VCTE is a useful tool for clinicians caring for patients with NAFLD. VCTE reliably determines which patients are at low risk for advanced liver disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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What is known

1. Nonalcoholic Fatty Liver Disease (NAFLD) is the most common liver disease
2. The complications of NAFLD are confined primarily to patients with advanced fibrosis
3. Risk stratification of all patients with NAFLD by biopsy is impractical

What this study adds

1. Vibration Controlled Transient Elastography (VCTE) is a reliable tool for risk stratification but as many as 25% of patients will have unreliable exams
2. Liver stiffness can be reduced with as little as 5% weight loss
3. VCTE performs better than the NAFLD Fibrosis Score given its superior sensitivity for advanced fibrosis

Figure 1. Clinical Decision Making is Aided by Liver Stiffness Measurements

In this flow chart depicting a noninvasive risk stratification strategy using VCTE, we show how patients can be categorized as low, indeterminate or high risk for advanced fibrosis in the first clinic visit. We offer input on further management after risk stratification. kPa = kilopascal, LSM = liver stiffness measurement, MRE = magnetic resonance elastography, VCTE = Vibration Controlled Transient Elastography

Table 1

Demographics and Clinical Characteristics of Patients with and without Reliable Liver Stiffness Measurements (LSM)

	Whole Cohort (n = 164)	Reliable LSM (n = 120)	Uninterpretable LSM (n = 44)	P value*
Sex (n male, %)	96 (58.5%)	76 (63.0%)	20 (45.5%)	0.02
Age (mean years $\pm$ SD)	51.1 (12.6)	50.4 (12.7)	52.9 (12.0)	0.38
BMI (median, IQR)	32.2 (29.3 – 36.4)	31.3 (28.7 – 35.1)	36.7 (31.4 – 45.5)	0.0001
Hispanic (n, %)	23 (14.2%)	17 (14.4%)	6 (14.0%)	1.0
Diabetes Mellitus (n, %)	45 (27.4%)	27 (22.5%)	18 (40.9%)	0.04
Hypertension (n, %)	72 (43.9%)	46 (38.3%)	26 (59.1%)	0.04
Hyperlipidemia (n, %)	63 (3.4%)	42 (35.0%)	21 (47.7%)	0.35
ALT (median IU/L, IQR)	65 (42 – 89)	65 (44 – 95)	57 (39 – 83)	0.25
AST (median IU/L, IQR)	42 (31 – 58)	42 (30 – 59)	42 (32 – 56)	0.49
Alkaline Phosphatase (median IU/L, IQR)	74 (63 – 86)	74 (64 – 88)	73 (60 – 84)	0.44
Ferritin (median mg/dL, IQR)	228 (98 – 379)	239 (131 – 424)	122 (86 – 355)	0.20
Platelet Count (median 10^9 , IQR)	248 (209 – 294)	250 (213 – 298)	231 (197 – 284)	0.36
Albumin (mean mg/dL, SD)	4.50 (0.42)	4.50 (0.43)	4.51 (0.40)	0.77
Metabolic Syndrome (n, %)	63 (38.4%)	41 (34.2%)	22 (50.0%)	0.07
Advanced Fibrosis (n, %)	29 (17.7%)	21 (17.5%)	8 (18.1%)	0.81
Steatosis Score 2 (n, %)	125 (76.1%)	95 (79.1%)	30 (68.1%)	0.75
NAS score > 4 (n, %)	79 (48.2%)	58 (48.3%)	21 (47.7%)	1.0

*The p-values presented reflect the comparison between patients with reliable and uninterpretable LSM

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, LSM = liver stiffness measurement, NAS = Nonalcoholic Fatty Liver Disease Fibrosis Score

Table 2

The Effect of Clinical Characteristics on Liver Stiffness Measured by the M Probe

	Univariate Analysis Beta coefficient (95% CI)	Multivariate Analysis Beta coefficient (95% CI)	P value
Sex (male)	0.05 (−1.51 – 1.60)		
Age (per year)	0.14 (0.02 – 0.26)	0.08 (−0.026 – 0.20)	0.09
BMI (per unit)	0.34 (0.02 – 0.67)	0.20 (−0.10–0.46)	0.13
Hispanic (yes / no)	1.12 (−1.16 – 3.40)		
Diabetes Mellitus (yes / no)	2.13 (0.40 – 3.87)	0.02 (−1.24 – 2.13)	0.98
Hypertension (yes / no)	1.39 (0.12 – 2.89)	0.20 (−1.65 – 1.26)	0.79
Hyperlipidemia (yes / no)	0.12 (−1.68 – 1.45)		
ALT (per unit)	0.011 (−0.017 – 0.039)		
AST (per unit)	0.048 (0.007 – 0.089)	0.01 (−0.03 – 0.04)	0.57
Alkaline Phosphatase (per unit)	0.078 (0.022 – 0.134)	0.04 (−0.007 – 0.09)	0.11
Ferritin (per unit)	0.0047 (−0.005 – 0.015)		
Platelet Count (per unit)	−0.023 (−0.045 – −0.001)		
Albumin (per unit)	−1.43 (−4.85 – 1.99)		
Steatosis Grade (per unit)	1.20 (−0.99 – 3.38)		
NAS score > 4 (yes / no)	2.04 (0.60 – 3.49)	0.43 (0.93 – 1.79)	0.53
Advanced Fibrosis (yes/no)	6.07 (4.47 – 7.67)	5.66 (3.45 – 7.04)	< 0.0001

Associations that are significant in univariate analysis (those with confidence intervals that do not cross zero) are tested in the multivariate regression analysis. The beta coefficient represents the change in liver stiffness per unit change in the exposure variables listed in the first column.

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, NAS = Nonalcoholic Fatty Liver Disease Fibrosis Score

Table 3

The Association of Baseline Factors and Change Variables with Changes in Liver Stiffness Measurements (LSM) after 6 months

Baseline Factors	Baseline value kPa (IQR)	Follow up LSM kPa (IQR)	P value
BMI > 31.3 kg/m ²	8.5 (6.0 – 14.3)	9.2 (5.7 – 13.9)	0.44
ALT > 60 IU/L	8.3 (5.6 – 11.0)	7.6 (5.3 – 10.5)	0.25
AST > 40 IU/L	8.3 (5.7 – 11.8)	7.1 (5.3 – 11.5)	0.27
NAS 4	6.9 (5.4 – 10.6)	5.9 (5.1 – 8.7)	0.04
NAS > 4	8.7 (5.5 – 11.5)	8.6 (5.3 – 12.9)	0.65
Steatosis grade 1	6.2 (4.5 – 7.5)	5.2 (3.7 – 6.2)	0.02
Steatosis grade > 1	7.9 (5.6 – 10.6)	7.1 (5.4 – 10.3)	0.31
F0–F2 Fibrosis	6.7 (5.4 – 9.7)	5.9 (4.9 – 8.9)	0.08
F3–F4 Fibrosis	13.7 (10.3 – 23.5)	14.8 (10.9 – 20.0)	0.41
Change Variables			
5% Weight loss	6.7 (5.3 – 9.4)	5.7 (4.4 – 7.9)	0.009
20% ALT decrease	7.3 (5.4 – 10.2)	6.1 (4.6 – 9.1)	0.14
20% AST decrease	7.3 (5.5 – 10.1)	6.1 (4.6 – 9.2)	0.35

Longitudinal liver stiffness are described according to baseline and changing factors. The cutoffs for baseline BMI, ALT and AST were chosen as they are the median values for the cohort with longitudinal LSM ; the NAS score was chosen as 5 represents active nonalcoholic steatohepatitis and the fibrosis strata represent those with and without advanced fibrosis.

ALT = alanine aminotransferase, AST = aspartate aminotransferase, IQR = interquartile range, BMI = body mass index, NAS = Nonalcoholic Fatty Liver Disease Fibrosis Score