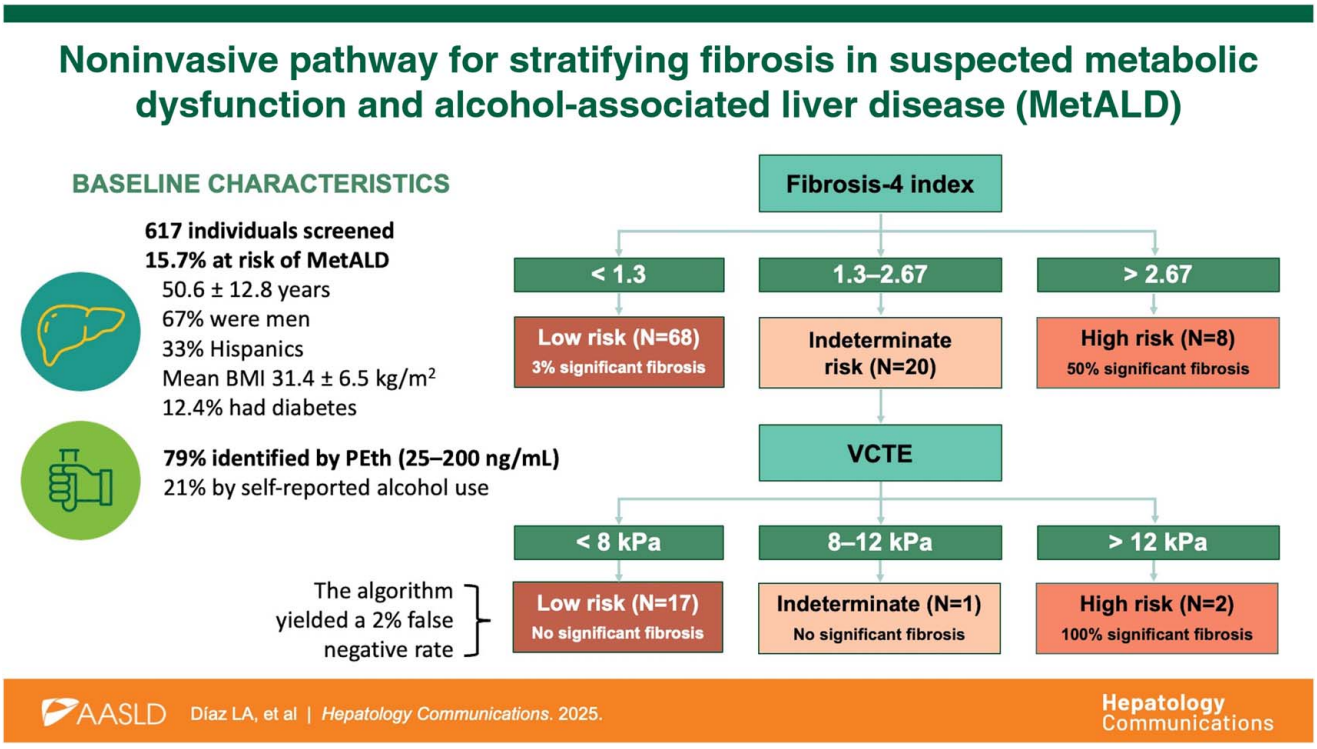
Noninvasive pathway for stratifying fibrosis in suspected metabolic dysfunction and alcohol-associated liver disease (MetALD)

VISUAL ABSTRACT



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Noninvasive pathway for stratifying fibrosis in suspected metabolic dysfunction and alcohol-associated liver disease (MetALD)

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Abstract

Background: Metabolic dysfunction and alcohol-associated liver disease (MetALD) may increase liver fibrosis progression, but data on screening are scarce. We aimed to assess the performance of noninvasive tests (NITs) for detecting significant fibrosis in individuals with suspected MetALD.

Methods: This is a cross-sectional study of prospectively enrolled adults identified as overweight or obese. We included adults with suspected MetALD defined by ≥ 1 of 5 cardiometabolic criteria and self-reported alcohol use within MetALD ranges or lower self-reported alcohol use but with phosphatidylethanol (PEth) levels ≥ 25 ng/mL. Clinical assessment included contemporaneous magnetic resonance elastography (MRE) and vibration-controlled transient elastography (VCTE). Significant fibrosis was defined as MRE ≥ 3.14 kPa (or VCTE ≥ 7.6 kPa if MRE was missing). Analyses included AUROCs.

Results: Among 617 individuals screened, we identified 97 (15.7%) with suspected MetALD. The mean age was 50.6 ± 12.8 years, 67% were men, the mean body mass index was 31.4 ± 6.5 kg/m^2, 12.4% had diabetes, and 8% had significant fibrosis. Fibrosis-4 ≥ 1.3 demonstrated good performance for significant fibrosis (AUROC: 0.78, 95% CI: 0.58–0.98, sensitivity 80%, specificity 76%, positive predictive value 17%, and negative

Abbreviations: AASLD, American Association for the Study of Liver Diseases; AGA, American Gastroenterological Association; AUDIT, Alcohol Use Disorder Identification Test; CAP, controlled attenuation parameter; CONSORT, Consolidated Standards of Reporting Trials; EASL, European Association for the Study of the Liver; FIB-4, fibrosis-4; LSM, liver stiffness measurement; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction–associated steatotic liver disease; MetALD, metabolic dysfunction and alcohol-associated liver disease; MRE, magnetic resonance elastography; NIT, noninvasive test; NPV, negative predictive value; PDFF, proton density-fat-fraction; PEth, phosphatidylethanol; PPV, positive predictive value; SLD, steatotic liver disease; UCSD, University of California San Diego; VCTE, vibration-controlled transient elastography.

predictive value 98%). VCTE ≥8 kPa also had good performance (AUROC: 0.85, 95% CI: 0.66–1.00, sensitivity 80%, specificity 91%, positive predictive value 36%, and negative predictive value 99%). A stepwise approach using fibrosis-4 followed by VCTE yielded a low false negative rate (2% misclassified as low risk).

Conclusions: A clinical care algorithm utilizing a stepwise approach with fibrosis-4 and VCTE shows adequate performance in detecting significant fibrosis in individuals with suspected MetALD.

Keywords: FIB-4, fibrosis-4, MASH, MASLD, metabolic dysfunction–associated steatohepatitis, non-invasive testing, steatotic liver disease, transient elastography

INTRODUCTION

Steatotic liver disease (SLD) is the leading cause of chronic liver disease globally, affecting 37.9% of adults in the United States.[1] In 2023, a new nomenclature process provided objective criteria for dual metabolic dysfunction and alcohol-associated liver disease (MetALD).[2,3] Based on these clinical criteria, MetALD has been estimated at 2.6% of the overall population and 4.8% of individuals with excess weight in the United States.[1,4] However, the use of direct alcohol biomarkers has revealed that alcohol consumption is usually underreported in clinical practice.[5,6] Phosphatidylethanol (PEth) is an alcohol biomarker that can detect alcohol use for up to 4 weeks, being a potential candidate to facilitate classification into SLD subtypes.[7]

In metabolic dysfunction–associated steatotic liver disease (MASLD), the presence of significant fibrosis (fibrosis stage ≥2) and "at-risk metabolic dysfunction–associated steatohepatitis (MASH)"—defined as MASH with nonalcoholic fatty liver disease activity score ≥4 and significant fibrosis—has been associated with higher rates of hepatic decompensation and overall mortality as well as eligibility for pharmacotherapy and enrollment in clinical trials.[8–10] Current clinical guidelines from the American Association for the Study of Liver Diseases (AASLD), the American Gastroenterological Association (AGA), and the European Association for the Study of the Liver (EASL) recommend the use of the fibrosis-4 index (FIB-4) and a second assessment with vibration-controlled transient elastography (VCTE) to stratify risk in patients with MASLD.[11–15] However, there is no current data about the performance of these algorithms in patients with suspected MetALD. In this study, we aimed to assess the performance of this sequential algorithm for stratifying the risk of liver fibrosis in individuals with suspected MetALD.

METHODS

Study design

We prospectively enrolled individuals identified as overweight or obese who reside in the greater San Diego area into the "San Diego Liver Study" between February 2019 and July 2024. The San Diego Liver Study is a large, ongoing, prospective, population-based, multiethnic cohort study conducted at the University of California San Diego (UCSD).[4] We included adults fulfilling at least 1 out of 5 cardiometabolic risk factors according to the 2023 criteria and self-reported levels of alcohol use in the range of MetALD. Specifically, we considered individuals with alcohol use levels of 140–350 g per week for women and 210–420 g per week for men. For those who reported lower levels of alcohol use, we included patients with PEth ≥25 ng/mL as suspected MetALD with covert alcohol consumption. Individuals were included regardless of their fat liver content at the moment of enrollment to capture better individuals who could exhibit consequences of metabolic dysfunction and alcohol use over time.[16] All participants underwent MRI proton density fat fraction (PDFF) with magnetic resonance elastography (MRE) and same-day VCTE with controlled attenuation parameter (CAP) (Figure 1). The exclusion criteria were: (1) alcohol use >350 g/wk in women and >420 g/wk in men within the previous 2 years; (2) other causes of chronic liver disease; (3) secondary causes of hepatic steatosis, including medications, HIV infection, and nutritional disorders; (4) decompensated liver disease (defined as Child-Pugh score >B7); (5) major systemic illness; (6) contraindications to performing MRI; (7) pregnancy or attempting to become pregnant, and (8) history of liver transplantation. The study was approved by the UCSD Institutional Review Board, and all individuals provided written informed consent before enrollment.

Clinical and laboratory data

All individuals underwent a standardized medical history, physical examination, laboratory testing, and anthropometric assessment at study entry. We used standardized, validated questionnaires to assess alcohol use, including the Alcohol Use Disorder Identification Test (AUDIT) to screen for current heavy drinking and/or active alcohol abuse or dependence,[17] and the lifetime drinking history questionnaire[18] to obtain quantitative indices of alcohol consumption patterns. Alcohol use was quantified using standard drinks, and calculations of average weekly alcohol intake were made based on 1 standard unit of alcohol equaling 14 g of ethanol.[19] Participants were instructed to fast for at least 8 hours before laboratory test collection. The FIB-4 index was calculated using the original formula, with FIB-4 values of <1.3 classified as low risk, 1.3–2.67 as indeterminate risk, and ≥ 2.67 as high risk in accordance with the AASLD, EASL, and AGA pathways, as these thresholds can identify liver fibrosis and predict all-cause and liver-related outcomes.[11–14] Although the FIB-4 index has a lower accuracy than other serum-based fibrosis markers, it is recommended due to its wide availability, simplicity, and low cost.[12]

PEth testing

Whole-blood samples for PEth testing were collected at the time of the research visit (ie, the same day of the collection of data on self-reported alcohol intake and blood tests) and sent to a national laboratory for analysis (ARUP Laboratories Test Directory, https://ltd.aruplab.com/Tests/Pub/3002598). Quantification of the PEth 16:0/18:1 homolog was performed using liquid chromatography-tandem mass spectrometry in whole blood.[20] The limit of quantification was set at 10 ng/mL. All PEth analyses were conducted blinded to patient data.

VCTE assessment

VCTE with CAP was performed using the FibroScan 502 Touch model. Technicians conducting the assessment were blinded to clinical, histologic, and biochemical information. The M-probe (3.5 MHz) was used for the initial evaluation of VCTE and CAP. The XL probe (2.5 MHz) was implemented when prompted by the automatic probe selection tool. Only examinations with 10 valid Fibroscan measurements were included in the study. Although multiple cut points have been identified and validated in SLD to stratify liver fibrosis risk, we defined VCTE <8 kPa as low risk, 8–12 kPa as indeterminate risk, and ≥ 12 kPa as high risk, for second-line testing, in accordance with the recommendations from the AASLD, AGA, and EASL clinical care guidelines for MASLD.[11,12,14]

MRI assessment

Magnetic resonance imaging using MRI-PDFF and MRE was performed at the UCSD MR3T Research Laboratory using a 3T research scanner (GE Signa EXCITE HDxt; GE Healthcare). The liver stiffness measurement (LSM) was obtained using 2D MRE at a frequency of 60 Hz. A radiologist blinded to clinical and laboratory data completed the interpretation of the acquired imaging. We used validated MRE cutoffs of ≥ 3.14 kPa to define significant fibrosis, ≥ 3.53 kPa for advanced fibrosis, and ≥ 4.45 kPa for cirrhosis.[21]

Endpoints

The primary endpoints were the diagnostic performances of FIB-4 and VCTE, using both currently recommended cut points for the identification of significant fibrosis in individuals with suspected MetALD, using MRE as the gold standard. In addition, we evaluated the diagnostic performance of the currently recommended clinical care algorithms.

Statistical analysis

Continuous variables were presented as mean $\pm$ SD or median and IQR (the latter if data were non-normally distributed). *t* tests or Wilcoxon rank sum and chi-square or Fisher exact test were used as appropriate for continuous and categorical variables, respectively.

AUROC analysis was performed for FIB-4 and LSM on VCTE to determine accuracy in predicting significant fibrosis (defined by an LSM on MRE ≥ 3.14 kPa).[21] In the few cases with missing MRE data, AUROC analysis was performed for FIB-4 exclusively, using a cutoff of VCTE ≥ 7.6 kPa to identify significant fibrosis.[22] Hepatic steatosis was defined by an MRI-PDFF $\geq 5\%$ (or a CAP ≥ 288 dB/m if MRI-PDFF was missing). Diagnostic tests were categorized as rule-in, indeterminate, and rule-out according to their respective rule-in and rule-out criteria using cutoffs previously published for the general population. AUROCs were compared using the methods outlined by Gonen et al, wherein pairwise tests compare the areas under the independent ROC curves. The diagnostic performances of FIB-4 and VCTE were expressed as sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) at prespecified cut points.[23] A sensitivity analysis for the diagnostic performance of FIB-4 and VCTE was performed in cases with hepatic

steatosis (defined by an MRI-PDFF ≥5% or CAP ≥288 dB/m). A p value ≤0.05 was considered statistically significant. All analyses were performed using SAS 9.4 (SAS Institute).

RESULTS

Characteristics of the study population

A total of 617 well-characterized individuals who were overweight or obese were enrolled in the San Diego Liver Study. Among them, 333 reported alcohol use, while 284 were lifetime abstainers or did not report alcohol use in the last 12 months. Ninety-seven (15.7%) individuals fulfilled the criteria for at-risk MetALD and were included in the analysis (20 individuals based on clinical alcohol use thresholds and 77 with PEth ≥25 ng/mL). In the entire cohort, the median alcohol intake was 77 [32–161] g/wk, while the median AUDIT scores were 5 [3–9], and the median PEth levels were 79 [41–200] ng/mL. The median alcohol intake was 258 [200–290] g/wk in those with self-reported alcohol consumption in the range of MetALD, and 48 [26–103] g/wk in those identified by PEth ($p < 0.0001$). However, when comparing individuals identified by self-reported alcohol use to those identified by PEth levels, we did not observe significant differences in the median AUDIT scores (6.5 [1.5–11] vs. 5,[3–7] $p = 0.563$, respectively) and median PEth levels (149 [17–336] vs. 74 [42–169] ng/mL, $p = 0.909$, respectively). Eighty-four of the 97 participants (87%) had LSM on MRE available, and 13 (13%) had VCTE exclusively. The Consolidated Standards of Reporting Trials (CONSORT) flowchart is shown in Figure 1. The mean age was 50.6 ± 12.8 years and 67% were men. The mean body mass index was 31.4 ± 6.5 kg/m^2, 12% had type 2 diabetes mellitus, 38% had hypertension, and 27% had hyperlipidemia (Table 1).

The median MRI-PDFF was 10.6% [4.5%–19.9%] and the median CAP was 286 [250–330] dB/m. Also, the median MRE was 2.2 [2.1–2.6] kPa and the median VCTE was 5.2 [4.1–6.7] kPa. Sixty-eight (70%) patients had evidence of liver steatosis, where 67 were identified by MRI-PDFF and 1 was identified by CAP. Using a composite estimation with LSM on MRE or VCTE (if MRE was missing) among the overall at-risk population, 8 (8%) individuals presented significant fibrosis (F2 = 4, F3 = 3, and F4 = 1) (Table 1). However, when we assessed the composite estimation of liver fibrosis risk, including the individuals with evidence of liver steatosis, only 6 out of 8 (75%) individuals were identified. At baseline, individuals identified by PEth versus by self-reported standardized questionnaire were more frequently men (73% vs. 45%, $p = 0.019$), had lower AST levels (26 vs. 35 U/L, $p = 0.032$), lower ALT levels (30 vs. 48 U/L, $p = 0.046$), a lower median FIB-4 (0.9 vs. 1.2, $p = 0.028$), and a lower median VCTE (5.1 vs. 6.2 kPa, $p = 0.029$) (Table 1).

Performance of noninvasive tests for the detection of significant fibrosis

Among individuals assessed by MRE, a FIB-4 ≥1.3 demonstrated good performance for significant fibrosis

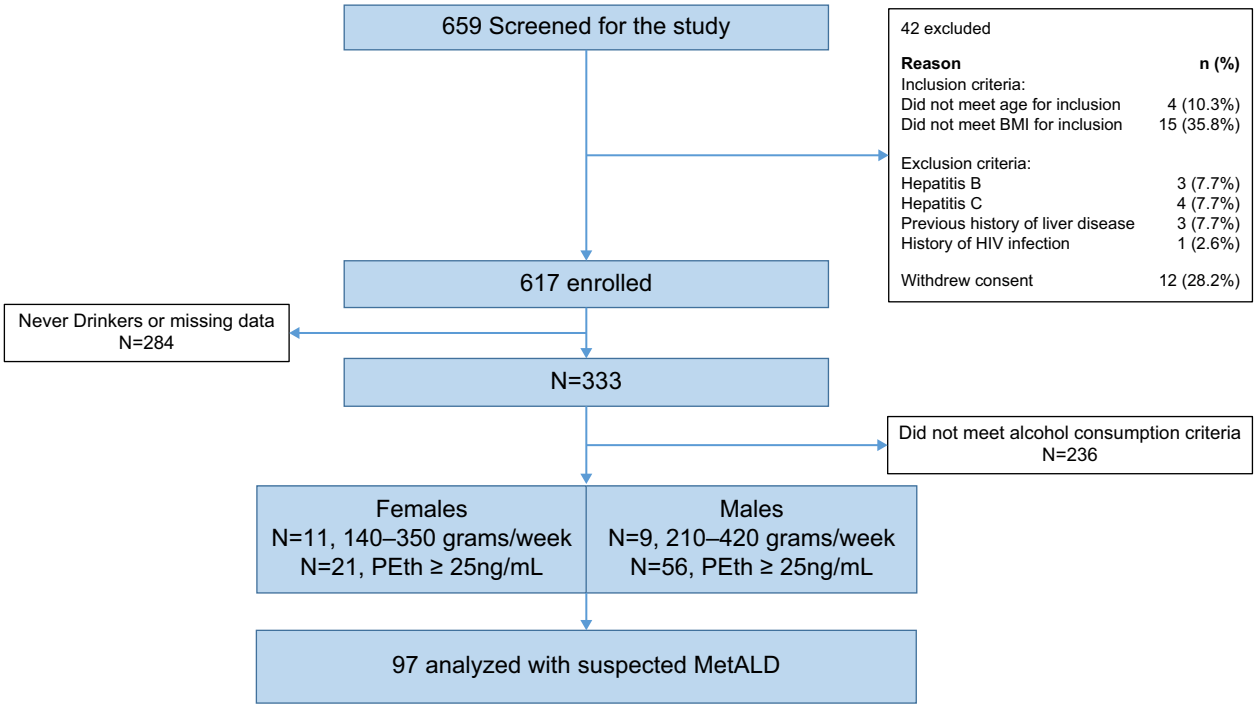

FIGURE 1 Consolidated Standards of Reporting Trials (CONSORT) diagram for the study population.

TABLE 1 Demographic and clinical characteristics of patients with suspected MetALD, including differences between individuals identified by clinical criteria (140–350 g per week in women and 210–420 g per week in men) and lower self-reported levels of alcohol use, but a positive PEth (≥25 ng/mL) testing

Variable	Overall (N = 97)	Clinical criteria (N = 20)	PEth (N = 77)	p[a]
Demographic and clinical data				
Age (y)[b]	50.6 (12.8)	53.7 (10.5)	49.7 (13.3)	0.220
Sex (men), n (%)	65 (67.0)	9 (45.0)	56 (72.7)	0.019
Race/ethnicity, n (%)				0.867
White	49 (50.5)	10 (50.0)	39 (50.6)	
Hispanic	32 (33.0)	8 (40.0)	24 (31.2)	
Asian	8 (8.3)	1 (5.0)	7 (9.1)	
Other	8 (8.3)	1 (5.0)	7 (9.1)	
Body mass index (kg/m^2)[b]	31.4 (6.5)	30.4 (4.3)	31.6 (7.0)	0.353
Weight (kg)[b]	93.6 (19.0)	89.4 (18.6)	94.7 (19.1)	0.268
Obesity, n (%)	52 (53.6)	11 (55.0)	41 (53.2)	0.889
Type 2 diabetes mellitus, n (%)	12 (12.4)	5 (25.0)	7 (9.1)	0.119
Hypertension, n (%)	37 (38.1)	9 (45.0)	28 (36.4)	0.479
Hyperlipidemia, n (%)	26 (26.8)	5 (25.0)	21 (27.3)	0.838
Biochemical profile[c]				
AST (U/L)	28.0 (20.0–39.0)	34.5 (25.0–45.0)	26.0 (19.0–37.0)	0.032
ALT (U/L)	32.0 (22.0–55.0)	47.5 (28.5–57.0)	30.0 (21.0–52.0)	0.046
Platelet count (×10^9/L)	238.5 (205.5–292.0)	217.0 (181.0–282.0)	241.0 (206.0–297.0)	0.110
LDL cholesterol (mg/dL)	108.5 (85.0–141.0)	97.0 (70.0–143.0)	111.0 (88.0–141.0)	0.180
Triglycerides (mg/dL)	119 (78.0–172.0)	106.5 (76.5–193.0)	127.0 (82.0–171.0)	0.600
HbA1c (%)	5.5 (5.3–5.9)	5.5 (5.2–6.2)	5.5 (5.3–5.8)	0.951
Blood-based scores and imaging[c]				
FIB-4 index	0.9 (0.7-1.4)	1.2 (0.9-2.3)	0.9 (0.7-1.4)	0.028
FIB-4 categories, n (%)				0.247
<1.3	68 (70.8)	11 (57.9)	57 (74.0)	
1.3–2.67	20 (20.8)	5 (26.3)	15 (19.5)	
≥2.67	8 (8.4)	3 (15.8)	5 (6.5)	
MRE (kPa)	2.2 (2.1–2.6)	2.1 (1.9–2.9)	2.2 (2.1–2.6)	0.802
MRI-PDFF (%)	10.6 (4.5–19.9)	17.3 (5.3–29.6)	8.5 (3.9–19.8)	0.197
VCTE (kPa)	5.2 (4.1–6.7)	6.2 (5.1–7.8)	5.1 (3.9–6.5)	0.029
VCTE categories, n (%)				0.106
<8 kPa	81 (86.2)	15 (75.0)	66 (89.2)	
8–12 kPa	7 (7.4)	2 (10.0)	5 (6.8)	
≥12 kPa	6 (6.4)	3 (15.0)	3 (4.0)	
CAP (dB/m)	286 (250–330)	296 (234–333.5)	284.5 (253–327)	0.879
Significant fibrosis[d]	8 (8.3%)	4 (20.0%)	4 (5.2%)	0.054

[a]*p* values from the *t* test or Wilcoxon rank sum, where appropriate. Categorical variables are shown as N (%) and *p* values from the chi-square test or Fisher exact test, where appropriate.
[b]Mean and SD.
[c]Median and IQR [25–75].
[d]Defined as MRE ≥3.14 kPa (or VCTE ≥7.6 kPa if MRE was missing). A total of 84 patients had a liver stiffness measurement on MRE and 13 a liver stiffness on VCTE exclusively to estimate the prevalence of significant fibrosis.
Abbreviations: CAP, controlled attenuation parameter; FIB-4, Fibrosis-4; HbA1c, glycated hemoglobin; MetALD, metabolic dysfunction and alcohol-associated liver disease; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging proton density fat fraction; PEth, phosphatidylethanol; VCTE, vibration-controlled transient elastography.

with an AUROC of 0.78 (95% CI: 0.58–0.98), sensitivity of 80%, specificity of 76%, PPV of 17%, and NPV of 98%. VCTE ≥8kPa also demonstrated a good performance in predicting significant fibrosis, with an AUROC of 0.85 (95% CI: 0.66–1.00), sensitivity of 80%, specificity of 91%, PPV of 36%, and NPV of 99% (Table 2 and Figure 2A). When we assessed the composite endpoint for significant fibrosis (MRE

≥3.14 kPa or a VCTE ≥7.6 kPa if MRE is missing), FIB-4 ≥1.3 evidenced a similar performance predicting significant fibrosis, with an AUROC of 0.75 (95% CI: 0.58–0.92), sensitivity of 75%, specificity of 75%, PPV of 21%, and NPV of 97% (Table 2 and Figure 2B). In addition, similar results were observed when we assessed the noninvasive test (NIT) performance in individuals with concurrent liver steatosis, exclusively (Table 2).

Characterization and performance of NITs in clinical care algorithms

A total of 2% of individuals categorized as low risk by FIB-4 (<1.3) had significant fibrosis by MRE. With VCTE, 2% of individuals categorized as low risk (<8 kPa) had significant fibrosis on MRE. Applying the AASLD, EASL, and AGA pathways using FIB-4 and VCTE in the population with suspected MetALD, 68 (71%) had a low-risk FIB-4, 20 (21%) had an indeterminate FIB-4, and 8 (8%) had a high-risk FIB-4. Of the 20 patients with indeterminate FIB-4, 17 (85%) had a low-risk VCTE, 1 (5%) had an indeterminate VCTE, and 2 (10%) had a high-risk VCTE (Figure 3). The sum of indeterminate-risk and high-risk groups requiring specialty referral is 11 (11%) of the total population, and 20 (21%) required VCTE testing before specialty care. Also, the false negative rate of participants classified as low risk who truly have significant fibrosis was 2 (2%) of the entire cohort.

DISCUSSION

To date, limited data validate the performance of NITs for stratifying the risk of liver fibrosis in individuals with MetALD.[6] In this study, we have analyzed a prospectively enrolled well-characterized population-based cohort for liver disease, targeting individuals identified as overweight or obese. In this population, 15.7% evidenced a moderately high alcohol intake, with 79% of them identified by PEth testing and 21% using self-reported alcohol use within the threshold criteria for MetALD. Despite differences in self-report alcohol use in both groups, the median AUDIT and PEth levels between those identified by self-report and those with PEth ≥25 ng/mL were similar. In addition, 8% of participants with suspected MetALD exhibited significant fibrosis. FIB-4 and VCTE exhibited good performance in predicting the presence of significant fibrosis, particularly with a high NPV. The algorithms integrating both NITs also had an adequate performance, with a low false negative rate to identify significant fibrosis (2%).

Liver fibrosis, particularly advanced fibrosis and cirrhosis, is the main predictor of liver-related death in individuals with SLD.[10,24] In our study, 4 individuals with suspected MetALD had significant fibrosis, 3 advanced fibrosis, and 1 cirrhosis, representing a prevalence of 8% of at least significant fibrosis. This finding is particularly noteworthy given that our cohort is a middle-aged population without known preexisting liver disease. To note, we included all patients at risk of fibrosis in the analysis regardless of the presence of liver steatosis, to better capture all individuals who could have MetALD, including those who can persist with liver fibrosis even after a decrease in liver fat content.[5] Using this approach, we identified 2 more individuals with significant fibrosis. In addition, the stratification of liver fibrosis can facilitate the initiation of treatment by addressing the leading risk factors for liver disease, such as excess weight or alcohol use.[25] Screening programs for liver fibrosis in individuals who consume alcohol could also impact clinical practice, facilitating early diagnosis of liver disease and decreasing rates of alcohol use.[26]

Several modeling studies have shown that screening for liver fibrosis by using NITs is a cost-effective strategy among individuals with MASLD.[27–29] This benefit is explained by the reduction of unnecessary referrals from primary care as well as the reduction in liver disease progression by being identified early, in the era of new effective emerging therapies for SLD.[30–32] For example, a cost-effectiveness study conducted among individuals with MASLD in midlife found that the use of different modalities of NITs and algorithms for screening in patients with MASLD is cost-effective; it reduces the estimated 10-year mortality rate from 1365 to 10,000 with no testing to 1329 of 10,000.[33] Other modeling studies in the United States showed that the screening strategies for high-risk MASLD resulted in additional costs compared with zero screenings.[31] However, the incremental cost-effectiveness ratio ranges from $26,913 to $27,884 per quality-adjusted life year among individuals with type 2 diabetes mellitus and $23,265–$24,992 per quality-adjusted life year in individuals with obesity.[31] A recent study, including 16 centers from the United States, Europe, and Asia, has also supported the effectiveness of this 2-step approach in classifying patients at different risk levels for liver-related events, indirectly supporting its cost-effectiveness by reducing unnecessary liver biopsies and focusing resources on high-risk patients with MASLD.[34] Although there is limited data on cost-effectiveness in MetALD screening, the aforementioned data from MASLD suggest that the implementation of NITs to screen for liver fibrosis should be reasonable, especially given the potentially higher risk of progression of fibrosis in MetALD compared with MASLD.[25,35]

Despite the benefits of using NITs in primary care, they have some limitations in clinical practice. In the case of FIB-4, the specificity for advanced fibrosis is lower in individuals aged ≥65 years and can

TABLE 2 Diagnostic accuracy of NITs for patients with suspected MetALD in predicting at least significant liver fibrosis

NIT	Cut point	AUROC (95% CI)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	True + (%)	False + (%)	False – (%)	True – (%)
Performance predicting significant fibrosis (defined by LSM on MRE ≥3.14 kPa exclusively) (N = 84)										
FIB-4	≥1.3	0.78 (0.58–0.98)	80	76	17	98	5	23	1	71
FIB-4	≥2.67	0.69 (0.45–0.93)	40	97	50	96	2	2	4	92
VCTE	≥8 kPa	0.85 (0.66–1.00)	80	91	36	99	5	9	1	85
VCTE	≥12 kPa	0.79 (0.55–1.00)	60	99	75	97	4	1	2	93
Performance predicting significant fibrosis (defined by LSM on MRE ≥3.14 kPa or a VCTE ≥7.6 kPa if MRE is missing) (N = 97)										
FIB-4	≥1.3	0.75 (0.58–0.92)	75	75	21	97	6	23	2	69
FIB-4	≥2.67	0.73 (0.54–0.91)	50	95	50	95	4	4	4	88
Performance predicting significant fibrosis (defined by LSM on MRE ≥3.14 kPa exclusively) in individuals with evidence of liver steatosis (an MRI-PDFF ≥5% or a CAP ≥288 dB/m if MRI-PDFF is missing) (N = 68)										
FIB-4	≥1.3	0.77 (0.51–1.00)	75	78	20	98	5	20	2	73
FIB-4	≥2.67	0.74 (0.46–1.00)	50	98	67	96	3	2	3	92
VCTE	≥8 kPa	0.82 (0.57–1.00)	75	89	33	98	5	11	2	82
VCTE	≥12 kPa	0.74 (0.46–1.00)	50	98	67	96	4	2	3	91
Performance predicting significant fibrosis (defined by LSM on MRE ≥3.14 kPa or a VCTE ≥7.6 kPa if MRE is missing) in individuals with evidence of liver steatosis (an MRI-PDFF ≥5% or a CAP ≥288 dB/m if MRI-PDFF is missing) (N = 67)										
FIB-4	≥1.3	0.71 (0.50–0.93)	67	76	21	96	6	22	3	69
FIB-4	≥2.67	0.73 (0.51–0.95)	50	95	50	95	4	4	4	87

Abbreviations: CAP, controlled attenuation parameter; FIB-4, fibrosis-4 index; LSM, liver stiffness measurement; MetALD, metabolic dysfunction and alcohol-associated liver disease; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging proton density fat fraction; NIT, noninvasive tests; NPV, negative predictive value; PPV, positive predictive value; VCTE, vibration-controlled transient elastography.

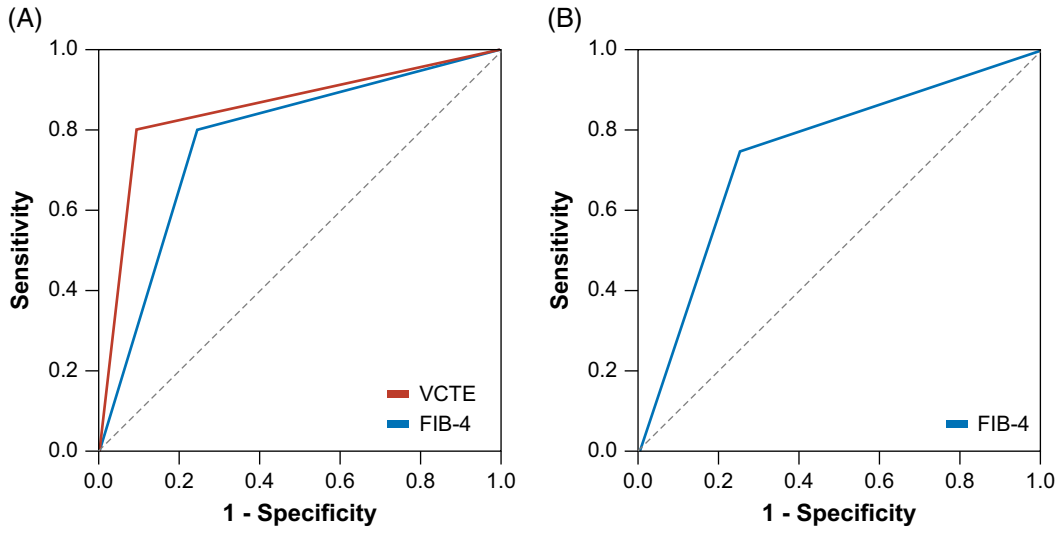

FIGURE 2 Receiver operating characteristic curves for FIB-4 and VCTE to predict significant fibrosis in individuals with suspected MetALD using (A) MRE ≥ 3.14 exclusively and (B) MRE ≥ 3.14 or VCTE ≥ 7.6 kPa (if MRE missing). Abbreviations: FIB-4, fibrosis-4; MetALD, metabolic dysfunction and alcohol-associated liver disease; MRE, magnetic resonance elastography; VCTE, vibration-controlled transient elastography.

overestimate liver fibrosis risk.[36] In individuals with obesity and MASLD, the FIB-4 can also exhibit lower sensitivity to detect advanced fibrosis, leading to misclassification.[37] Race and ethnicity can also impact the validity of NITs and algorithms in routine clinical practice. For example, a recent study including individuals with MASLD from the United States and Latin America showed that Hispanic ethnicity was associated with a higher risk of false negative rates in the algorithms to identify significant fibrosis.[38] Active alcohol use can increase FIB-4 and LSMs on VCTE values, and this can be found significantly in those with higher levels of alcohol use.[39,40] This study showed that only 11% of patients would require a further referral to be seen by a Hepatologist, and encouragingly, a low false negative rate (2%). Our results are in line with a prior study that found a good performance of FIB-4 in predicting advanced fibrosis in MetALD.[41]

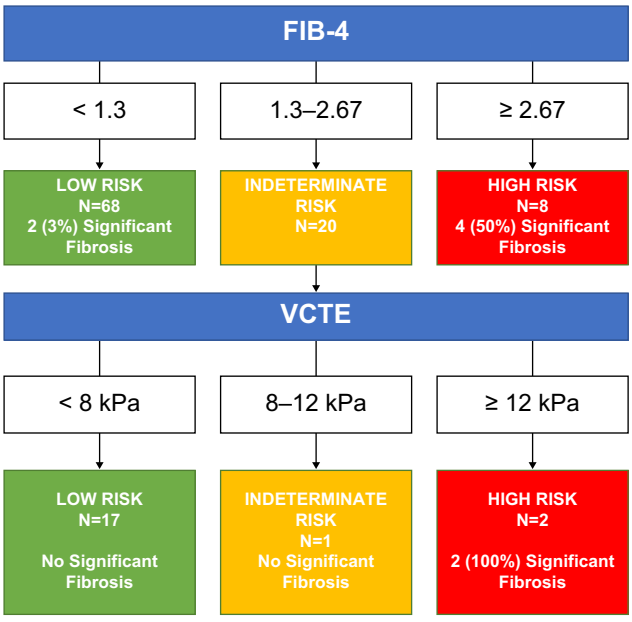

FIGURE 3 Performance of the sequential pathway using FIB-4 and VCTE in individuals with suspected MetALD. Abbreviations: FIB-4, fibrosis-4; MetALD, metabolic dysfunction and alcohol-associated liver disease; VCTE, vibration-controlled transient elastography.

To our knowledge, our study is the first to report the performance of clinical care algorithms to detect significant fibrosis in individuals with suspected MetALD. However, limitations should be noted. This was a cross-sectional single-center study that included patients with a low prevalence of liver fibrosis.[38] This lower prevalence of significant liver fibrosis could be due to a lower number of cardiometabolic risk factors than other populations or that they did not have evident liver disease at the time of referral.[5] Although our population may not fully represent the broader MetALD population, it is closer to the reality observed in primary care and outpatient services in the United States.[42] As mentioned before, race and ethnicity can impact the natural history of SLD and the performance of NITs.[5,38] Thus, our cohort exhibited wide diversity and included 33% Hispanic participants. However, because our cohort was derived from a single ongoing study in Southern California with specific inclusion criteria, the external validity of our findings may be limited. Populations with markedly different metabolic profiles or alcohol consumption patterns (for instance, lean individuals with MetALD or those with heavier alcohol use than allowed in our study) might exhibit a different prevalence of fibrosis and possibly different performance of NITs. MRE was utilized in the majority of our patients to identify liver fibrosis; liver biopsy data were

not collected for comparison. However, we would suggest that MRE is an accurate NIT of fibrosis and has high specificity, which makes it well-suited for this application,[21,22,43] while liver biopsy is not exempt from limitations and potential adverse effects.[44]

When looking to the future of MetALD, further studies with larger cohorts and extended follow-up periods are needed to better assess the long-term outcomes of these NITs in MetALD. In addition, the efficacy of standardizing the use of alcohol using biomarkers should be evaluated within SLD criteria to ensure that individuals are accurately classified into MetALD subtypes.[6] Given the success of integrated programs in patients with heavy alcohol use, future research should explore the combined approach of liver disease screening alongside alcohol use counseling to more effectively target this high-risk population. Lastly, a comprehensive approach from a public health perspective is needed,[45] due to the low existence of public health policies addressing SLD[46,47] and the potential impact of policies addressing metabolic dysfunction and alcohol in clinical practice.[48–50]

In conclusion, we have demonstrated that in a well-characterized cohort of individuals living with overweight or obesity, 15.7% exhibited evidence of moderately high alcohol consumption, indicating that they may have MetALD. A stepwise approach using FIB-4 and VCTE may have adequate performance in detecting patients with significant fibrosis in individuals with suspected MetALD, with a low false negative rate in individuals who truly have significant fibrosis. Our findings support the applications of current society guidelines for MASLD to the MetALD population. Further studies are needed to validate these findings in other cohorts of individuals with MetALD.

AUTHOR CONTRIBUTIONS

Luis Antonio Díaz and Rohit Loomba conceived and designed the study. Rohit Loomba was responsible for its conceptualization and execution. Lisa Richards and Egbert Madamba collected and organized the data samples. Luis Antonio Díaz drafted the initial manuscript. All authors critically reviewed and revised the manuscript, and all approved the final version.

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CONFLICTS OF INTEREST

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