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Diagnostic Accuracy of Noninvasive Tests for Metabolic Dysfunction-associated Steatotic Liver Disease Across Age, Type 2 Diabetes, and Obesity Subgroups: A Multinational Study

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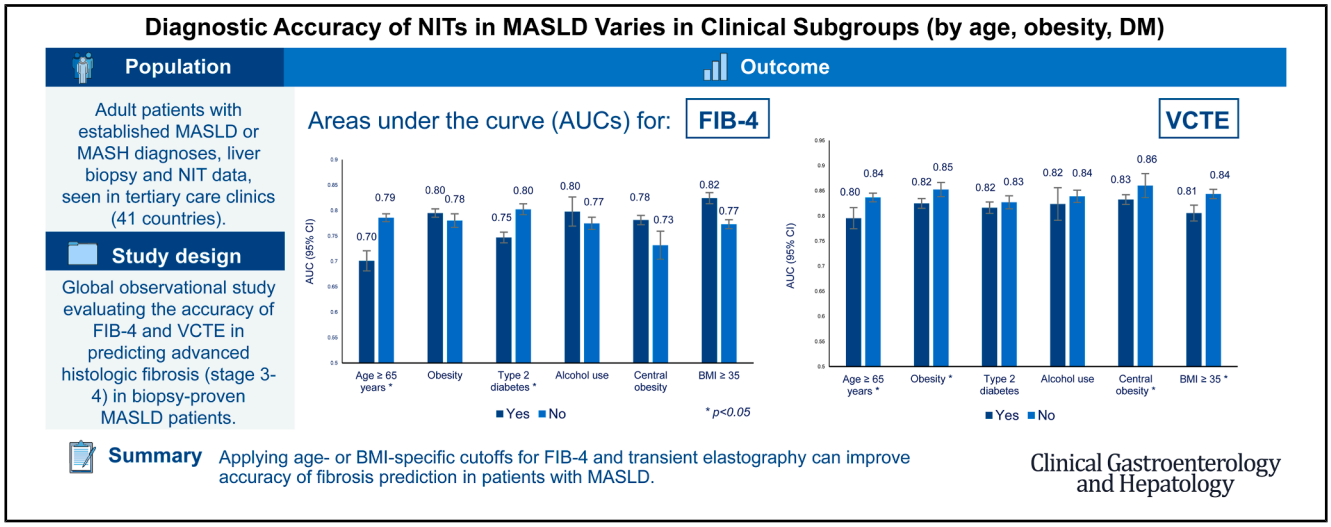
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Abbreviations used in this paper: **AUC, area under the receiver operating characteristic curve; AUDIT-C, Alcohol Use Disorders Identification Test-Concise; BMI, body mass index; CI, confidence interval; ELF, enhanced liver fibrosis; FIB-4, fibrosis-4 index; GNC, Global NASH/MASH Council; HCC, hepatocellular carcinoma; LSM, liver stiffness measurement; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic dysfunction and alcohol-associated liver disease; NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD Activity Score; NITs, noninvasive tests; NPV, negative predictive value; PEth, phosphatidylethanol; PPV, positive predictive value; ROC, receiver operating characteristic; SD, standard deviation; T2D, type 2 diabetes; VCTE, vibration-controlled transient elastography.**

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BACKGROUND & AIMS: **Noninvasive tests (NITs) are widely used to risk-stratify patients with metabolic dysfunction-associated steatotic liver disease (MASLD); however, their performance may vary according to patient characteristics. We evaluated the accuracy of NITs in a large, multinational MASLD cohort across select subpopulations.**

METHODS: **We analyzed 18,759 adults with biopsy-confirmed MASLD from 41 countries. NITs included FIB-4, liver stiffness measurement (LSM), and Agile-3+. Diagnostic performance for advanced fibrosis (F3–F4) was measured using areas under the curve (AUCs) across subgroups defined by age, sex, type 2 diabetes (T2D), obesity, and alcohol use. Subgroup-specific cutoffs were derived.**

RESULTS: **Advanced fibrosis was present in 37% of patients. Pooled AUCs were 0.79 for FIB-4, 0.83 for LSM, and 0.86 for Agile-3+. FIB-4 accuracy declined with age (AUC 0.70 in ≥65 years vs 0.79 in <65 years, *P*<.0001) and in middle-aged patients with T2D. The LSM performance remained stable across T2D status but was moderately reduced in patients with obesity and, more profoundly, morbid obesity (body mass index [BMI] >35 kg/m^2). Sex and alcohol use had minimal impact on AUCs. Age- and T2D-specific FIB-4 cutoffs varied substantially to maintain predefined accuracy (sensitivity or specificity). The cutoffs for LSM also differed based on patients' BMI, with lower diagnostic cutoffs for advanced fibrosis required in nonobese MASLD (sensitivity 80%: 8.8 kPa in lean, 9.0 kPa overweight, 9.6 kPa in obesity, 11.0 kPa in morbid obesity).**

CONCLUSIONS: **Accuracy of NITs for advanced fibrosis in MASLD is influenced by age, T2D, and obesity. Age-adjusted FIB-4 thresholds may enhance risk stratification. Imaging-based and composite NITs (LSM and Agile-3+) provide more consistent performance across MASLD subpopulations.**

Keywords: Biomarkers; Chronic Liver Disease; Diagnostic Thresholds; Metabolic Syndrome; Non-communicable Diseases; Outcomes; Steatohepatitis; Steatotic Liver Disease.

The subtype of metabolic dysfunction-associated steatotic liver disease (MASLD) known as metabolic dysfunction-associated steatohepatitis (MASH) is a progressive liver disease that can lead to cirrhosis, hepatocellular carcinoma (HCC), and liver-related death.[1–3] Globally, MASH affects an estimated 5% to 7% of the population, and this burden is expected to increase in the coming decades.[4] This increase is largely driven by the global epidemic of metabolic syndrome, type 2 diabetes (T2D), and obesity, which are major risk factors for MASH and are strongly associated with the development of significant and advanced hepatic fibrosis.[5,6] Consequently, the rising burden of MASH has direct implications for its associated fibrosis and related morbidity and mortality, underscoring the need for accurate, noninvasive fibrosis risk stratification.[7]

Historically, liver biopsy has served as the reference standard for staging hepatic fibrosis. However, its invasive nature, high cost, limited availability, and susceptibility to sampling error and procedural complications significantly

limit its use in routine clinical practice.[8] These limitations have spurred global efforts to develop and validate noninvasive tests (NITs) that can aid in risk stratification, guide clinical decision-making, and reduce the need for liver biopsy. Both blood- and imaging-based NITs have been incorporated into international guidelines and care pathways for identifying patients with advanced fibrosis.[1] The performance of these NITs has been evaluated using large international cohorts, allowing for assessment across different geographic regions.[9]

Most clinical algorithms for MASLD risk stratification employ a stepwise testing strategy, starting with broad screening (or case finding) of at-risk populations such as individuals with T2D or complicated obesity (obesity with one additional metabolic risk factors) or those with chronically elavated liver enzymes.[1] Initial assessment typically uses the Fibrosis-4 index (FIB-4) index due to its simplicity, accessibility, and low cost. For patients with indeterminate (1.3–2.67) or non-low FIB-4 scores (>1.3), second-line tests such as vibration-controlled transient elastography (VCTE) or enhanced liver fibrosis (ELF) test are commonly employed.[10,11]

Although these tools have generally shown acceptable diagnostic performance, emerging data suggest their accuracy may be influenced by individual patient characteristics including age, sex, ethnicity, body mass index (BMI), and presence of T2D.[12–14] These findings highlight the importance of understanding how NIT performance varies across clinically relevant subgroups to improve diagnostic accuracy and optimize risk stratification. Therefore, the aim of this study was to use a large, multinational cohort to systematically assess the diagnostic accuracy of commonly used NITs across clinically relevant patient subgroups with MASLD.

What You Need to Know

Background

Noninvasive tests (NITs) like FIB-4 and liver stiffness measurement (LSM) from transient elastography (TE) are used to risk stratify patients with metabolic dysfunction-associated steatotic liver disease (MASLD), but their accuracy may differ according to age, presence of type 2 diabetes (T2D) and obesity.

Findings

In 18,759 patients with MASLD and available liver biopsies, FIB-4 accuracy decreased with age and T2D, whereas LSM and Agile-3+ remained reliable across groups. Obesity modestly reduced LSM performance.

Implications for patient care

Applying age- and T2D-specific cutoffs may improve accuracy of NITs, particularly FIB-4. Agile-3+ and Agile-4 tests offer more consistent results, supporting better individualized risk stratification in MASLD management.

Methods

Study Sample

The present analysis utilized data from the Global MASLD project, an international initiative launched in 2023 by the Global NASH/MASH Council (GNC) involving collaborators from over 40 countries. Participating investigators obtained approval from their respective institutional review boards or equivalent ethics committees to collect clinical and histological data from patients. Deidentified datasets were shared under formal data use agreements and housed centrally in a secure electronic repository for aggregate analysis by the GNC.

Eligible participants were adults with a histologically confirmed diagnosis of MASLD or MASH and available liver biopsy data. Individuals were excluded if they were under 18 years of age at the time of biopsy, pregnant, lacked key demographic data (age, sex, country), had no valid liver biopsy record, or did not meet MASLD diagnostic criteria (defined as having hepatic steatosis with at least 1 cardiometabolic risk factor in the absence of excessive alcohol use or viral hepatitis[15]).

Data Collection and Definitions

Data elements collected included demographic information (age, sex, country of enrollment), anthropometric measures (BMI, waist circumference), and components of metabolic syndrome (T2D, hypertension, hyperlipidemia). Liver biopsy data encompassed fibrosis staging (F0–F4) and the nonalcoholic fatty liver disease (NAFLD) Activity Score (NAS). Collected NITs included liver stiffness measurement (LSM) via VCTE and biomarker-based scores derived from laboratory data collected at the time of or within no more than 1 year of the biopsy. FIB-4 scores were calculated using age, aminotransferases, and platelet counts. Additionally, Agile-3+ scores were derived using validated formulas incorporating both laboratory and VCTE data.[16]

Statistical Analysis

All collected demographic and clinical parameters, as well as NIT scores, were summarized as n (%) or mean ± standard deviation (SD). In case of missing data, only observed data was used for any analysis. Comparisons between groups were conducted using the Wilcoxon rank-sum test for continuous variables and Pearson's χ^2 test for categorical variables.

Performance of NITs to predict advanced fibrosis (F3–F4) was determined by assessing the respective

area under the receiver operating characteristic (ROC) curve (AUC) in pre-defined clinical subgroups: by age, sex, T2D, obesity, and alcohol use. The estimated AUCs were statistically compared between the subgroups using the DeLong test. Commonly used NIT cutoff values collected from literature were applied, and cutoff values that would return pre-determined accuracy were calculated for subgroups where substantial AUC deviation was observed.

All statistical analyses were performed using SAS, version 9.4 (SAS Institute). The study received approval from the Western Institutional Review Board and from the respective Institutional Review Boards or equivalent supervisory institutions at each participating site. All research was conducted in accordance with both the Declarations of Helsinki and Istanbul, and all subjects had provided informed consent prior to enrollment to research studies in their respective sites.

Results

Study Population

A total of 18,759 patients with MASLD from 41 countries were included in the analysis, of whom 6872 (36.6%) had advanced fibrosis (F3–F4) and 11,887 (63.4%) had none, mild, or moderate fibrosis (F0–F2) (Table 1). Patients with advanced fibrosis were significantly older (56.7 ± 10.7 vs 47.6 ± 13.3 years; $P <$ .0001), more frequently female (56.8% vs 49.9%; $P <$ .0001), and had higher rates of obesity, T2D, hypertension, and hyperlipidemia when compared with those with F0 to F2 fibrosis (all $P <$ .0001) (Table 1). In patients with available waist circumference measurement, central obesity was also more prevalent in the advanced fibrosis group ($P <$ .0001) (Table 1). All studied NIT scores (FIB-4, LSM, and Agile-3) were significantly higher in patients with advanced histologic fibrosis by liver biopsy (all $P <$ .0001) (Table 1).

NIT Performance Across Clinical Subgroups

Quantified via AUC (with 95% confidence interval [CI]), the performance of the studied NITs for predicting advanced fibrosis in the pooled study population were as follows: FIB-4 0.79 (95% CI, 0.78–0.79), LSM 0.83 (95% CI, 0.83–0.84), Agile-3+ 0.86 (95% CI, 0.85–0.86). However, this performance varied significantly across some clinical subgroups (Table 2).

The discriminatory performance of all 3 NITs was significantly attenuated in older patients with MASLD: AUC of FIB-4 0.701 (95% CI, 0.682–0.720) in age ≥65 years vs 0.786 (95% CI, 0.778–0.794) in age <65 years ($P <$ .0001); AUC of LSM 0.795 (95% CI, 0.775–0.816) vs 0.837 (95% CI, 0.828–0.845), respectively ($P =$ .0003); AUC of Agile-3 0.804 (95% CI, 0.784–0.825) vs 0.859 (95% CI, 0.851–0.867), respectively ($P <$ .0001) (Table 2).

Sex-based differences in performance were minimal (Table 2). NIT performance was also consistent across those with and without alcohol use (all $P >$ .05) (Table 2).

In addition, FIB-4 showed notably poorer performance in patients with T2D compared with those without (AUC, 0.747; 95% CI, 0.737–0.757 vs 0.802; 95% CI, 0.792–0.813; $P <$ .0001). Although a similar trend was observed for Agile-3+ (AUC, 0.833; 95% CI, 0.823–0.844) vs 0.857; 95% CI, 0.846–0.869; $P =$ .0031) the performance was better in both groups. On the other hand, LSM maintained high and consistent AUCs regardless of T2D status ($P >$ .05) (Table 2).

Finally, there was a trend towards lower AUC of LSM in patients with obesity (AUC 0.825; 95% CI, 0.815–0.834 vs 0.852; 95% CI, 0.839–0.866; $P =$ .0012), central obesity (AUC, 0.832; 95% CI, 0.823–0.842 vs 0.860; 95% CI, 0.837–0.884; $P =$ .0317), or BMI >35 kg/m^2 (AUC, 0.806; 95% CI, 0.790–0.821 vs 0.844; 95% CI, 0.835–0.853; $P <$ .0001), whereas no similar associations with obesity (regardless of the definition) were observed for FIB-4 (all 1-sided $P >$ .05) (Table 2).

Because age and T2D are highly correlated, we evaluated the association of FIB-4 accuracy with T2D stratified by age (Table 3). There was a reduction in FIB-4 accuracy among patients with T2D in comparison to those without T2D in middle age groups: from 0.775 (95% CI, 0.752–0.798) to 0.729 (95% CI, 0.708–0.751) in the 45 to 54 year group and from 0.760 (95% CI, 0.739–0.782) to 0.717 (95% CI, 0.699–0.736) in the 55 to 64 year group (both $P <$ .05) (Table 3). However, no significant difference in AUC of FIB-4 was observed among younger or older patients with vs without T2D ($P >$ .05) (Table 3).

NIT Accuracy in Age-based Subgroups

Consistent with the AUCs described above, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) with established FIB-4 cutoffs varied substantially by age group (Table 4). However, commonly used cutoffs for LSM yielded relatively balanced performance, particularly those used to identify high-risk patients (15 kPa or 20 kPa) (Table 4).

The FIB-4 cutoffs required to achieve fixed accuracy varied substantially across age groups (Figure 1). In particular, to maintain consistent sensitivity of 80% (screening criterion, to identify low-risk patients), the FIB-4 cutoffs would vary between 0.41 (<25 years group) and 2.08 (≥81 years group) (Figure 1*A*). Similarly, for the specificity of 95% (diagnostic criterion, to identify high-risk patients), the age-specific FIB-4 cutoffs could be as low as 0.90 in patients <25 years vs as high as 4.10 in patients of 76 to 80 years (Figure 1*B*). After stratification by T2D status, we found that FIB-4 cutoff

Table 1. Demographic and Clinical Parameters of Patients With MASLD/MASH Included in the Study

	Advanced fibrosis (F3–F4)	None, mild, or moderate fibrosis (F0–F2)	*P*	All MASLD
No.	6872	11,887		18,759
Age, *y*	56.7 ± 10.7	47.6 ± 13.3	.0000	50.9 ± 13.1
Age <35	288 (4.2)	2220 (18.7)	.0000	2508 (13.4)
Age 35–64	4893 (71.2)	8412 (70.8)	.5324	13,305 (70.9)
Age ≥65	1691 (24.6)	1254 (10.6)	.0000	2945 (15.7)
Male	2971 (43.2)	5958 (50.1)	.0000	8929 (47.6)
Female	3901 (56.8)	5929 (49.9)	.0000	9830 (52.4)
Alcohol use (any)	329 (14.4)	1071 (15.5)	.2141	1400 (15.2)
BMI, kg/m^2	33.3 ± 6.8	33.8 ± 9.1	.0000	33.6 ± 8.3
Female waist, *cm*	107.4 ± 15.5	107.2 ± 18.8	.0074	107.2 ± 17.5
Male waist, *cm*	112.3 ± 15.6	106.3 ± 16.7	.0000	108.5 ± 16.6
Lean[a]	359 (5.3)	865 (7.4)	.0000	1224 (6.7)
Obese[a]	4902 (73.0)	8026 (69.1)	.0000	12,928 (70.5)
Central obesity[a]	4385 (90.4)	6206 (83.5)	.0000	10,591 (86.3)
BMI >35 kg/m^2	2300 (34.3)	3954 (34.1)	.7856	6254 (34.1)
T2D	4438 (65.6)	4345 (37.3)	.0000	8783 (47.7)
Hypertension	4097 (66.0)	5361 (47.1)	.0000	9458 (53.8)
Hyperlipidemia	3567 (58.4)	5646 (51.1)	.0000	9213 (53.7)
Fibrosis stage 0	0 (0.0)	2580 (21.7)		2580 (13.8)
Fibrosis stage 1	0 (0.0)	5819 (49.0)		5819 (31.0)
Fibrosis stage 2	0 (0.0)	3488 (29.3)		3488 (18.6)
Fibrosis stage 3	4488 (65.3)	0 (0.0)		4488 (23.9)
Fibrosis stage 4	2384 (34.7)	0 (0.0)		2384 (12.7)
FIB-4 score	2.26 ± 1.83	1.15 ± 0.95	.0000	1.56 ± 1.45
LSM, *kPa*	17.7 ± 11.6	8.86 ± 5.36	.0000	12.5 ± 9.5
Agile-3 score	0.818 ± 0.207	0.442 ± 0.284	.0000	0.597 ± 0.315
FIB-4 <1.30	1785 (27.2)	8023 (71.3)	.0000	9808 (55.0)
FIB-4 ≥2.67	1731 (26.3)	532 (4.7)	.0000	2263 (12.7)
FIB-4 ≥3.25	1160 (17.6)	297 (2.6)	.0000	1457 (8.2)
LSM <10 kPa	945 (21.4)	4575 (72.1)	.0000	5520 (51.3)
LSM ≥15 kPa	2017 (45.8)	430 (6.8)	.0000	2447 (22.8)
LSM ≥20 kPa	1243 (28.2)	177 (2.8)	.0000	1420 (13.2)
Agile-3+ ≥0.451	3881 (92.1)	2783 (46.2)	.0000	6664 (65.1)
Agile-3+ ≥0.678	3383 (80.3)	1560 (25.9)	.0000	4943 (48.3)
NAS ≥5	4055 (66.3)	3873 (40.0)	.0000	7928 (50.2)

NOTE. Data are presented as number (%) or mean ± standard deviation.
BMI, body mass index; FIB-4, Fibrosis-4 Index; LSM, liver stiffness measurement; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; NAS, NAFLD Activity Score; T2D, type 2 diabetes.
[a]Lean is defined as BMI <25 kg/m^2 or <23 kg/m^2 in patients of East Asian origin; obese is defined as BMI >30 kg/m^2 or >25 kg/m^2, respectively; central obesity is defined as waist circumference ≥102 cm in male, ≥88 cm in female or ≥85 cm or80 cm, respectively, in patients of East Asian origin.

Table 2. Accuracy (AUC With 95% CI) of NITs for Predicting Advanced Fibrosis in Subgroups of Patients With MASLD

	Subgroup 1	Subgroup 2	*P* value
NIT	**Age ≥65 y**	**Age <65 y**	
FIB-4 score	0.701 (0.682–0.720)	0.786 (0.778–0.794)	<.0001
LSM	0.795 (0.775–0.816)	0.837 (0.828–0.845)	.0003
Agile-3	0.804 (0.784–0.825)	0.859 (0.851–0.867)	<.0001
NIT	**Male**	**Female**	
FIB-4 score	0.783 (0.773–0.793)	0.789 (0.780–0.799)	.37
LSM	0.835 (0.824–0.846)	0.829 (0.818–0.840)	.47
Agile-3	0.863 (0.852–0.873)	0.848 (0.837–0.858)	.05
NIT	**Obesity**	**No obesity**	
FIB-4 score	0.795 (0.787–0.803)	0.780 (0.767–0.793)	.06
LSM	0.825 (0.815–0.834)	0.852 (0.839–0.866)	.0012
Agile-3	0.852 (0.843–0.861)	0.869 (0.856–0.882)	.0411
NIT	**T2D**	**No T2D**	
FIB-4 score	0.747 (0.737–0.757)	0.802 (0.792–0.813)	<.0001
LSM	0.816 (0.805–0.827)	0.827 (0.814–0.840)	.21
Agile-3	0.833 (0.823–0.844)	0.857 (0.846–0.869)	.0031
NIT	**Alcohol use**	**No alcohol use**	
FIB-4 score	0.798 (0.770–0.826)	0.775 (0.763–0.787)	.14
LSM	0.824 (0.792–0.855)	0.839 (0.827–0.851)	.38
Agile-3	0.837 (0.807–0.867)	0.851 (0.840–0.863)	.37
NIT	**Central obesity**	**No central obesity**	
FIB-4 score	0.781 (0.772–0.790)	0.732 (0.705–0.759)	.0006
LSM	0.832 (0.823–0.842)	0.860 (0.837–0.884)	.0317
Agile-3	0.854 (0.845–0.863)	0.859 (0.835–0.883)	.69
NIT	**BMI >35 kg/m^2**	**BMI <35 kg/m^2**	
FIB-4 score	0.824 (0.814–0.835)	0.773 (0.764–0.782)	<.0001
LSM	0.806 (0.790–0.821)	0.844 (0.835–0.853)	<.0001
Agile-3	0.846 (0.832–0.859)	0.862 (0.853–0.870)	.06

NOTE. The pooled AUC estimates (all MASLD) were as follows: FIB-4 0.79 (95% CI, 0.78–0.79), LSM 0.83 (95% CI, 0.83–0.84), and Agile-3+ 0.86 (95% CI, 0.85–0.86).
NOTE. Obesity is defined as BMI >30 kg/m^2 or >25 kg/m^2 in patients of East Asian origin, respectively; central obesity is defined as waist circumference ≥102 cm in male, ≥88 cm in female or ≥85 cm or ≥80 cm, respectively, in patients of East Asian origin.
AUC, area under the receiver operating characteristic curve; CI, confidence interval; FIB-4, Fibrosis-4 Index; LSM, liver stiffness measurement; NIT, noninvasive test; T2D, type 2 diabetes.

values needed to achieve 80% sensitivity for advanced fibrosis were lower in patients with T2D in the 56- to 70-year-old age range (Supplementary Figure 1*A*). For illustration, patients of 61 to 65 years of age can be considered low-risk with FIB-4 scores of <1.53 in the absence of T2D but only with <1.35 in the presence of T2D (Supplementary Figure 1*A*). However, high-risk cutoff values did not show a similar association with the presence of T2D when stratified by age (Supplementary Figure 1*B*).

Table 3. Accuracy (AUC with 95% CI) of FIB-4 by the Presence of T2D Within Age Subgroups

Age groups	T2D	No T2D	*P*
<45 y	0.713 (0.682–0.743)	0.722 (0.696–0.747)	.65
45–54 y	0.729 (0.708–0.751)	0.775 (0.752–0.798)	.0046
55–64 y	0.717 (0.699–0.736)	0.760 (0.739–0.782)	.0028
65–74 y	0.717 (0.692–0.743)	0.712 (0.679–0.744)	.79
≥75 y	0.638 (0.545–0.732)	0.642 (0.525–0.758)	.96

AUC, area under the receiver operating characteristic curve; CI, confidence interval; FIB-4, Fibrosis-4 Index; T2D, type 2 diabetes.

We conducted a similar age-stratified analysis for LSM using broader age categories (Figure 2*A*). Both low- and high-risk LSM cutoff values were higher in patients of ≥45 years of age in comparison to those <45 years but without further substantial increase with older age (Figure 2*A*). In addition, we ran a BMI-stratified analysis for LSM, and found that the LSM cutoffs for obese and especially morbidly obese patients were higher than those for lean and overweight individuals with MASLD (Figure 2*B*).

Discussion

In this large, multinational cohort of nearly 19,000 patients with MASLD and liver biopsy, we systematically

Table 4. Predictive Power (%) of Commonly Used NIT Cutoffs for Detection of Advanced Fibrosis in Age-based Subgroups of Patients With MASLD

Cutoff /age group	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
FIB-4 ≥2.67				
<35 y	4.0 (1.7–6.3)	99.1 (98.6–99.5)	35.5 (18.6–52.3)	88.8 (87.5–90.1)
35–64 y	22.3 (21.1–23.5)	95.8 (95.4–96.3)	75.9 (73.6–78.1)	67.7 (66.9–68.6)
≥65 y	41.7 (39.3–44.1)	84.9 (82.8–86.9)	79.0 (76.2–81.7)	51.7 (49.5–53.9)
FIB-4 ≥3.25				
<35 y	1.8 (0.2–3.4)	99.4 (99.1–99.8)	29.4 (7.8–51.1)	88.6 (87.4–89.9)
35–64 y	15.0 (14.0–16.1)	97.8 (97.5–98.1)	80.0 (77.4–82.6)	66.2 (65.3–67.0)
≥65 y	27.8 (25.7–30.0)	90.8 (89.2–92.5)	80.5 (77.3–83.8)	48.0 (46.0–50.1)
FIB-4 ≥1.30				
<35 y	18.6 (14.0–23.2)	94.5 (93.5–95.5)	30.5 (23.6–37.5)	89.9 (88.7–91.2)
35–64 y	69.7 (68.4–71.0)	71.8 (70.8–72.8)	59.2 (57.9–60.5)	80.1 (79.2–81.0)
≥65 y	91.2 (89.8–92.6)	26.8 (24.3–29.3)	62.9 (61.0–64.9)	69.1 (64.8–73.3)
FIB-4 ≥2.00				
<35 y	7.7 (4.5–10.8)	98.0 (97.4–98.6)	32.8 (21.3–44.3)	89.1 (87.8–90.4)
35–64 y	38.9 (37.5–40.3)	90.6 (90.0–91.3)	70.9 (69.2–72.7)	71.6 (70.7–72.5)
≥65 y	64.0 (61.7–66.4)	65.8 (63.1–68.5)	71.8 (69.5–74.1)	57.3 (54.7–59.9)
LSM ≥15 kPa				
<35 y	31.4 (24.6–38.3)	94.5 (93.2–95.8)	46.6 (37.6–55.6)	90.0 (88.3–91.7)
35–64 y	45.6 (43.9–47.3)	93.6 (92.8–94.3)	83.1 (81.3–84.9)	71.2 (70.1–72.4)
≥65 y	48.5 (45.6–51.5)	89.1 (86.9–91.4)	87.5 (84.8–90.1)	52.6 (49.8–55.4)
LSM ≥20 kPa				
<35 y	16.6 (11.1–22.1)	98.0 (97.2–98.8)	55.8 (42.3–69.3)	88.5 (86.7–90.2)
35–64 y	28.1 (26.5–29.7)	97.2 (96.7–97.7)	87.4 (85.3–89.4)	66.0 (64.9–67.2)
≥65 y	30.4 (27.6–33.1)	96.2 (94.8–97.6)	92.6 (89.9–95.3)	46.9 (44.4–49.5)
LSM ≥10 kPa				
<35 y	68.6 (61.7–75.5)	77.7 (75.3–80.1)	32.0 (27.3–36.7)	94.2 (92.7–95.7)
35–64 y	78.8 (77.4–80.2)	72.0 (70.7–73.4)	66.2 (64.7–67.7)	83.0 (81.8–84.2)
≥65 y	79.5 (77.1–81.9)	63.2 (59.6–66.7)	77.1 (74.7–79.6)	66.4 (62.8–69.9)

CI, confidence interval; FIB-4, Fibrosis-4 Index; LSM, liver stiffness measurement; MASLD, metabolic dysfunction-associated steatotic liver disease; NIT, noninvasive test; NPV, negative predictive value; PPV, positive predictive value.

evaluated the diagnostic performance of widely used NITs across key clinical subgroups defined by age, sex, T2D, obesity, and alcohol consumption. Our findings reveal important and clinically actionable variation in test performance, particularly influenced by age, T2D, and obesity.

Age emerged as the most influential modifier of diagnostic accuracy. All NITs, especially FIB-4, demonstrated significantly lower discriminative ability in older adults. Commonly used FIB-4 thresholds performed variably across age groups, and cutoffs required to achieve predefined diagnostic targets (eg, high sensitivity or specificity) differed substantially by age. These findings strongly support the implementation of age-adjusted FIB-4 thresholds, which may reduce false-positive referrals in older populations and improve the detection of true positives in younger adults.

In clinical practice, interpretation of age-adjusted FIB-4 thresholds may depend on the prevalence of high-risk MASLD. Indeed, although sensitivity- and specificity-based cutoffs are mathematically independent of the prevalence rates, the clinical meaning of "low-risk" and "high-risk" categories is often tied to observed PPV and/or NPV. In the present biopsy-based cohort, the prevalence of advanced fibrosis was relatively high (37%). Given that, when applied to a lower prevalence population (eg, primary care settings), low-risk thresholds would be expected to still yield high NPV and, therefore, function well as rule-out tools, whereas high-risk thresholds would have lower PPV than reported in this study. It is also important to note that some of the observed subgroup differences in NIT performance may reflect intrinsic properties of score construction rather than purely biological effects. Indeed, age is directly incorporated into FIB-4, and therefore reduced specificity and attenuation of discrimination in older adults are not unexpected. However, we observed not only age-related shifts in optimal cutoffs but also substantial reductions in AUC, suggesting diminished discrimination beyond threshold inflation alone. This finding likely reflects increasing biological heterogeneity, competing comorbidities, and other drivers of aminotransferase elevation in the older patients with MASLD.

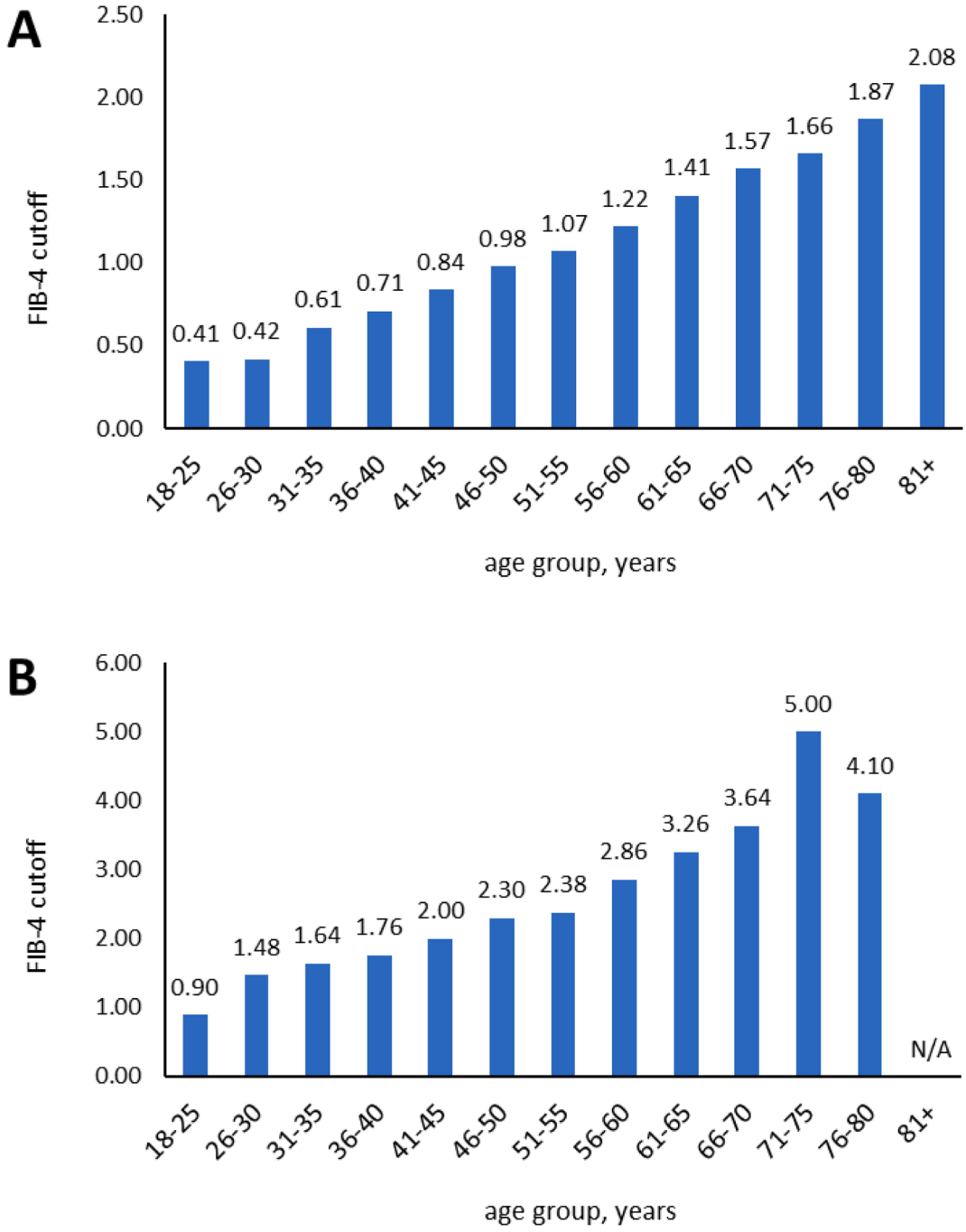


Figure 1. Cutoff for FIB-4 score cutoff needed to achieve (*A*) sensitivity of 80%, (*B*) specificity of 95% in age-based subgroups of patients with MASLD. N/A, not available.

In addition to age, T2D and obesity also negatively impacted NIT performance, although to varying degrees across different tools. In fact, T2D was associated with a reduced accuracy of FIB-4 in select age groups. In contrast, LSM showed stable performance irrespective of T2D status, and Agile 3+ retained high diagnostic accuracy with only modest attenuation. Obesity, particularly at higher BMI thresholds (>35 kg/m^2), was associated with diminished LSM performance, but did not significantly affect FIB-4. The modest reduction in LSM accuracy among patients with obesity and morbid obesity is consistent with prior elastography literature and likely reflects technical limitations related to increased subcutaneous and visceral adiposity, although obesity-related alterations in hepatic fibrogenesis may also contribute. Collectively, these observations highlight the limitations of single-parameter biomarkers in metabolically complex populations and underscore the potential value of composite scoring systems and imaging-based modalities for fibrosis risk stratification in patients with T2D or obesity.

Importantly, sex and alcohol consumption history did not materially affect NIT performance, supporting the continued use of unified thresholds across these

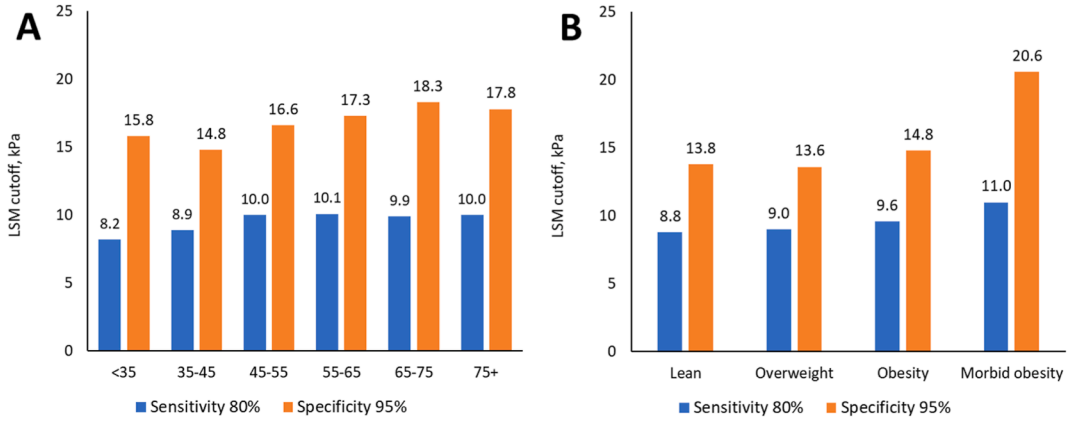


Figure 2. Cutoffs for LSM needed to achieve sensitivity of 80% and specificity of 95% with LSM in (*A*) age- and (*B*) BMI-based subgroups of patients with MASLD. Footnote: Lean is defined as BMI <25 kg/m^2 or <23 kg/m^2 in patients of East Asian origin; overweight is defined as BMI ≥ 25 kg/m^2 to <30 kg/m^2 or ≥ 23 kg/m^2 to <25 kg/m^2, respectively; obesity is defined as BMI ≥ 30 kg/m^2 to <35 kg/m^2 or ≥ 25 kg/m^2 to <30 kg/m^2, respectively; morbid obesity is defined as BMI ≥ 35 kg/m^2 or ≥ 30 kg/m^2, respectively.

subgroups. This finding is particularly relevant for the metabolic dysfunction and alcohol-associated liver disease (MetALD) subgroup, in which diagnostic performance appears to be preserved.[17] Nevertheless, underreporting of alcohol consumption, in the absence of a blood-based biomarker such as phosphatidylethanol (PEth) or a validated questionnaire such as the Alcohol Use Disorders Identification Test-Concise (AUDIT-C), may compromise the validity of assessing alcohol-related effects on NITs. Future studies should therefore evaluate the performance of these NITs following more accurate assessment of alcohol consumption.[18]

The consistent performance of Agile 3+ and LSM across nearly all evaluated strata suggests that these tools may be preferable when diagnostic reliability across diverse populations is a clinical priority.

Our findings corroborate previous observations that select clinical parameters, namely, age for FIB-4 and BMI for LSM, may act as effect modifiers of NIT performance.[19–22] In one prior study of patients with MASLD with longitudinal follow-up, high FIB-4 and LSM were associated with differential risks of clinical events across age and BMI strata, respectively: elevated FIB-4 conferred a greater relative hazard in younger individuals, whereas the prognostic impact of elevated LSM was most pronounced among lean individuals and attenuated with increasing BMI.[22] In the current study, we observed that diagnostic accuracy for advanced fibrosis varied by these same parameters so that FIB-4 performed better in younger patients, whereas the accuracy of LSM was highest in leaner individuals. Together, these results suggest that both the diagnostic and prognostic utility of NITs may be modulated by patient-level factors, underscoring the importance of context-specific interpretation when applying NITs in clinical practice and trial design.

This study makes several novel contributions to MASLD literature. Although prior research has suggested reduced specificity of FIB-4 in older individuals and lower accuracy of various NITs in patients with metabolic comorbidities, our analysis quantifies these effects in a substantially larger and more globally diverse cohort. We further demonstrate that the impact of T2D on FIB-4 performance is age-dependent, with the greatest reduction in accuracy observed among middle-aged groups. This observation may inform age-specific screening strategies in diabetic populations. Finally, we provide practical guidance by proposing age- and diabetes-specific FIB-4 thresholds that could be seamlessly integrated into clinical algorithms and decision support tools.

Although current guidelines recommend sequential risk stratification using FIB-4 followed by imaging such a LSM by VCTE, the performance of such algorithms is inherently determined by the subgroup-specific behavior of their individual components. In this context, our findings provide mechanistic insight into why 2-step pathways may perform differently across patient populations.[1] In particular, age-related attenuation of FIB-4 discrimination highlights the importance of age-adjusted thresholds at the initial screening step, whereas the relatively stable performance of LSM across most subgroups supports its role as a confirmatory test in guideline-recommended algorithms. Formal evaluation of subgroup-specific 2-step algorithms will be an important focus of future studies, particularly in lower-prevalence, real-world screening settings. Furthermore, the development and validation of first-line NITs based on simple, widely available data that are not influenced by age, T2D, or obesity may offer advantages in terms of simplicity and applicability across diverse populations. Such novel tests could potentially replace FIB-4 in the future.

Despite the large international cohort, this study has several limitations. First, although liver biopsy remains the gold standard for fibrosis staging, centralized histopathological review was not feasible in this international cohort, potentially introducing inter-site

variability. Second, although we focused on commonly used NITs, we did not include emerging biomarkers (eg, ELF, NIS4) or advanced imaging techniques (eg, magnetic resonance elastography), which merit future investigation. Third, although our cohort is diverse, findings may not be fully generalized to the primary care setting, where patient characteristics and access to diagnostic tools may differ. Lastly, alcohol consumption was assessed by self-report, which is prone to recall and social desirability bias, potentially affecting MASLD vs MetALD classification. Despite this, by leveraging the large and globally diverse Global MASLD dataset, our study validates prior single-center findings and adds robust subgroup-level insight. Additionally, the stable performance of Agile 3+ across multiple subgroups reinforces the emerging value of multi-parametric models that integrate clinical and biochemical variables.

The findings reported in this study carry important implications for both clinical practice and health care policy. Because FIB-4 is widely used for MASLD triage, reliance on fixed cutoffs may lead to substantial misclassification, particularly in older adults and individuals with T2D. Our results support a shift toward personalized thresholds and, where feasible, broader adoption of imaging-based methods and/or composite indices. Such approaches may improve detection of advanced fibrosis, optimize referral pathways, and reduce unnecessary investigations, which is particularly relevant in primary care where MASLD is prevalent in patients with T2D and, therefore, fibrosis screening is increasingly emphasized.

Conclusion

In summary, this large multinational analysis shows that the diagnostic performance of widely used NITs for advanced fibrosis in MASLD varies substantially across clinical subgroups. FIB-4 is particularly influenced by age and T2D, whereas LSM and Agile 3+ maintain more consistent accuracy across populations, although LSM performance is moderately attenuated in patients with morbid obesity. These findings support the use of subgroup-specific thresholds for FIB-4 and a broader reliance on composite scores such as Agile 3+ for risk stratification in diverse clinical settings. Future MASLD guidelines should incorporate personalized cutoffs and composite diagnostic approaches to improve diagnostic precision and reduce disparities in care.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2026.01.016.

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Author Contributions
ZMY was responsible for study design, data interpretation, manuscript writing and critical review of the final manuscript. MS was responsible for data analysis, data interpretation, manuscript writing and critical review of the final manuscript. AR and LdA were responsible for data management, manuscript writing and critical review of the final manuscript. FN was responsible for study's oversight and critical review of the manuscript. All other authors were responsible for data collection, data management, data interpretation, manuscript writing and critical review of the final manuscript. All authors had access to the study data.

Conflicts of interest
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Data Availability
Deidentified data used in this study may be available upon written request to the corresponding author.