



HAL
open science

The grade of obesity affects the noninvasive diagnosis of advanced fibrosis in individuals with MASLD

Y. Chouik, A. Aubin, M. Maynard-Muet, B. Segrestin, L. Milot, V. Hervieu,
F. Zoulim, E. Disse, M. Levrero, C. Caussy

► **To cite this version:**

Y. Chouik, A. Aubin, M. Maynard-Muet, B. Segrestin, L. Milot, et al.. The grade of obesity affects the noninvasive diagnosis of advanced fibrosis in individuals with MASLD. *Obesity*, 2024, 32 (6), pp.1114-1124. 10.1002/oby.24033 . inserm-04661849

HAL Id: inserm-04661849

<https://inserm.hal.science/inserm-04661849>

Submitted on 25 Jul 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution 4.0 International License

ORIGINAL ARTICLE

Clinical Trials and Investigations

The grade of obesity affects the noninvasive diagnosis of advanced fibrosis in individuals with MASLD

Yasmina Chouik¹ | Adrien Aubin² | Marianne Maynard-Muet^{1,3} |
 Bérénice Segrestin^{2,4} | Laurent Milot^{5,6} | Valérie Hervieu^{6,7} | Fabien Zoulim^{1,3,6} |
 Emmanuel Disse^{2,4,6} | Massimo Levrero^{1,3,6} | Cyrielle Caussy^{2,4,6} 

¹Hepatology Department, Croix-Rousse Hospital, Civil Hospices of Lyon, Inserm Unit 1052, Lyon, France

²Endocrinology, Diabetes and Nutrition Department, Lyon South Hospital, Civil Hospices of Lyon, Pierre-Bénite, France

³Lyon Cancer Research Center, Inserm Unit 1052, Scientific Research National Center, Lyon, France

⁴Lyon University, CarMen Laboratory, Inserm, National Institute for Agricultural Research (INRA), National Institute of Applied Sciences (INSA) Lyon, Claude Bernard University Lyon 1, Pierre-Bénite, France

⁵Radiology Service, Civil Hospices of Lyon, Edouard Herriot Hospital, Lyon, France

⁶Claude Bernard University Lyon 1, Lyon, France

⁷Pathological Anatomy Department, Civil Hospices of Lyon, Edouard Herriot Hospital, Lyon, France

Correspondence

Cyrielle Caussy, Endocrinology, Diabetes and Nutrition Department, Lyon Sud Hospital, 165 Chemin du Grand Revoyet, 69495 Pierre-Bénite CEDEX, France.

Email: cyrielle.caussy@chu-lyon.fr

Abstract

Objective: Metabolic dysfunction-associated steatotic liver disease (MASLD) is closely associated with obesity. We aimed to assess the impact of obesity on the performance of different noninvasive tests, including liver stiffness measurement (LSM) and Agile3+ (A3+), to detect advanced fibrosis (AF) in a population of patients with MASLD encompassing a wide range of BMI values.

Methods: A total of 479 patients with MASLD were consecutively included (Lyon Hepatology Institute). Clinical data and noninvasive tests, including FibroTest, LSM, A3+, Fibrosis-4 (FIB-4), magnetic resonance elastography, and liver biopsies, were collected. AF was determined by a composite endpoint, i.e., histological stage \geq F3, overt diagnosis of cirrhosis by magnetic resonance elastography, or concordant LSM \geq 9.6 kPa and FibroTest \geq F3.

Results: The median BMI was 35.0 kg/m², and the prevalence of AF was 28.6%. Patients with BMI \geq 35 versus $<$ 35 had a lower proportion of AF, i.e., 19.3% versus 38.1% ($p < 0.001$), but higher indeterminate status for AF (34.2% vs. 15.4%; $p < 0.001$). In the case of BMI \geq 35, LSM had lower specificity to rule in AF (77.9%) versus A3+ (90.4%), but A3+ had decreased sensitivity to rule out AF. A sequential LSM/A3+ strategy achieved high specificity to rule in AF and lowered the proportion of indeterminate cases in patients with BMI \geq 35.

Conclusions: The grade of obesity affects the detection of MASLD-related AF. A sequential use of LSM/A3+ could improve AF detection in patients with BMI \geq 35.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD), or metabolic dysfunction-associated steatotic liver disease (MASLD) based on the recent novel nomenclature [1], is the most common liver disease worldwide, affecting 25% of the global population with rising incidence over the years [2, 3]. The most critical determinant of overall prognosis and liver-related outcomes is the fibrosis stage, with a 1.9-

to 3.9-fold increase in all-cause mortality in patients with advanced fibrosis (AF; i.e., F3-F4) compared with others [4]. Therefore, identifying this subgroup of patients is key to optimizing their clinical management, including hepatocellular carcinoma surveillance, personalized weight loss management, cardiovascular prevention, and considering specific treatment in a clinical trial [5-7]. Therefore, several scientific society guidelines have recently recommended systematic screening for AF in high-risk

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial](https://creativecommons.org/licenses/by-nc/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2024 The Authors. *Obesity* published by Wiley Periodicals LLC on behalf of The Obesity Society.

populations, including patients with metabolic risk factors such as type 2 diabetes mellitus (T2DM) or obesity. Indeed, obesity is strongly associated with MASLD, and an increase in body mass index (BMI) is associated with the progression of MASLD [8–10].

The current screening strategy relies on noninvasive tests (NITs) such as Fibrosis-4 (FIB-4) score and liver stiffness measurement (LSM) by vibration-controlled transient elastography (VCTE) [1, 5–7, 11]. The LSM using VCTE is increasingly performed to assess liver diseases, and its ability to rule out the presence of AF at the cutoff below 8 kPa has been extensively validated [12]. However, its diagnostic performance to rule in the presence of AF is less accurate [13–15]. Liver biopsy is thereby considered in patients with elevated LSM, remaining the gold standard to stage liver fibrosis. Recently, concordant elevated LSM and patented blood-based tests such as FibroMeter or FibroTest have been validated as sufficiently performing to diagnose AF in secondary care [6]. Finally, the Agile 3+ (A3+) score was developed and validated for AF diagnosis in patients with NAFLD/MASLD [16], combining LSM by VCTE with routine clinical parameters. A3+ has demonstrated an improved diagnostic accuracy for the screening of AF by reducing the false-positive cases at the rule-in cutoff while reducing the proportion of patients in the indeterminate zone compared with LSM alone and with FIB-4 [16].

The severity of obesity and increase in BMI have been identified as factors affecting the diagnostic performance of NITs, whether blood-based biomarkers [17] or ultrasound-based imaging, including LSM [18–21]. However, the impact of the severity of obesity and BMI increase on the diagnostic performance of NITs for the detection of AF has not been investigated in a population encompassing a wide range of BMI values, to our knowledge. Therefore, we aimed at assessing the impact of the severity of obesity on the diagnostic ability to detect the presence of AF using data from a well-characterized population of patients with MASLD encompassing a wide range of BMI values who were consecutively enrolled on a liver assessment. This main objective was met by fulfilling the following aims: 1) to assess the impact of obesity severity on the detection of AF; 2) to compare the diagnostic performance of NITs (FIB-4, LSM, and A3+) for the detection of AF across different categories of obesity; and 3) to investigate the optimal noninvasive strategy using these NITs according to BMI categories.

METHODS

Study population

This was a cross-sectional study of adult patients with MASLD consecutively included in a monthly multidisciplinary board for suspected fibrotic metabolic dysfunction-associated steatohepatitis (MASH) at the Lyon Hepatology Institute (including both a hepatology and diabetology and nutrition department), Lyon University (Lyon, France), between March 2020 and December 2022.

All patients met the eligibility criteria for MASLD according to the new fatty liver disease nomenclature, including the presence of hepatic steatosis defined by ultrasound assessment and at least one adult cardiometabolic criterion [1]. All patients underwent comprehensive

Study Importance

What is already known?

- Metabolic dysfunction-associated steatotic liver disease (MASLD) is strongly associated with obesity.
- Liver stiffness measurement (LSM) may be less accurate in patients with severe obesity.
- A recently developed noninvasive test, Agile 3+ (A3+), has improved the positive predictive value (PPV) for advanced fibrosis (AF) diagnosis compared with other noninvasive tests in all patients with MASLD.

What does this study add?

- LSM has insufficient specificity and PPV for AF diagnosis in the case of BMI ≥ 35 kg/m².
- A3+ has better PPV but leads to an increase in the proportion of patients with indeterminate status for AF compared with LSM.
- A sequential strategy of LSM followed by A3+ maximizes PPV while reducing the proportion of patients in the indeterminate zone in patients with MASLD and BMI ≥ 35 .

How might these results change the focus of clinical practice?

- The use of the sequential strategy LSM/A3+ improves the detection of AF in patients with BMI ≥ 35 and may avoid unnecessary liver biopsies.

evaluation for other causes of steatotic liver disease, notably questioning on alcohol consumption and a search for drug-induced liver steatosis, viral hepatitis, autoimmune hepatitis, hemochromatosis, Wilson disease, glycogen storage disease, and cholestatic and vascular liver disease. Patients with evidence of another cause of liver disease or with excessive alcohol consumption (≥ 14 drinks/week for men and ≥ 7 drinks/week for women) were excluded.

Data collection

Pseudonymized clinical data, fasting labs, liver biopsy reports, and available NITs, including FIB-4, FibroTest, LSM using VCTE, and magnetic resonance elastography (MRE), were systematically extracted from electronic medical records. Biological parameters were collected within a median (interquartile range [IQR], 0–68) of zero days from LSM. We followed the Standards for Reporting of Diagnostic Accuracy Studies (STARD) guidelines (Table S1). The study was performed in strict compliance with the French reference methodology MR-004, established by the French National Commission on Informatics and Liberties (CNIL), and in accordance with the Declaration of Helsinki. Patients received written notice and could object to the use of their

data [22]. The study was approved by the Research Ethics Commission of Lyon University Hospital Institutional Review Board (IRB), 22_584.

Noninvasive evaluation of liver fibrosis

Noninvasive evaluation of liver fibrosis was performed by LSM using VCTE, magnetic resonance imaging (MRI)/MRE, and/or blood-based NITs (procedures described in online Supporting Information Methods). LSM cutoff values of 8 kPa and 9.6 kPa were used respectively to rule out and rule in AF as previously described [6, 13, 23–25]. The MRE cutoff value of 3.62 kPa was used to rule out AF and was demonstrated to have an excellent diagnostic performance [15]. Low and high cutoffs of 1.30 and 2.67 for FIB-4 [26, 27] and 0.451 and 0.679 for A3+, respectively, were used to rule out and rule in AF, respectively [16, 23].

Histological assessment

Liver biopsy was proposed to patients when deemed clinically indicated after multidisciplinary assessment for precise diagnosis of MASH and fibrosis staging. All liver biopsies were scored by two expert pathologists in MASLD at the Lyon Hepatology Institute, using the SAF (Steatosis, Activity, and Fibrosis) score [28, 29]. AF was defined by the presence of histological stage of fibrosis F3 or F4.

Definition and endpoints

The main endpoint was the presence of AF defined by composite diagnostic criteria following hierarchical steps:

1. If liver biopsy was performed, presence of F3 or F4 histological fibrosis stage.
2. If liver biopsy was not performed and MRI was available, presence of overt imaging diagnosis of cirrhosis.
3. If liver biopsy and MRI were not performed, concordant LSM \geq 9.6 kPa and FibroTest \geq F3 according to the European Association for the Study of the Liver (EASL) guidelines [6].

The absence of AF was defined by composite diagnostic criteria following hierarchical steps:

1. If liver biopsy was performed, presence of fibrosis stage $<$ F3.
2. If liver biopsy was not performed and MRI available, MRE $<$ 3.62 kPa and absence of overt diagnosis of cirrhosis.
3. If liver biopsy and MRI were not performed, concordant LSM $<$ 8 kPa and FibroTest \leq F2 according to the most recent EASL guidelines [6].

Indeterminate status for AF was defined as the absence of liver biopsy and MRI assessment and discordant LSM and FibroTest for the presence of AF.

The hierarchical determination of AF is shown in Figure S1.

Statistical analysis

Data were described using number (percentage) for categorical variables and median with IQR for continuous variables. Categorical variables were compared with the χ^2 or Fisher exact tests, and quantitative variables were compared using the *t* test or nonparametric tests (Mann–Whitney or Kruskal–Wallis tests) when appropriate.

The performance of LSM, A3+, and the sequential combination of LSM/A3+ for AF diagnosis was analyzed using the area under the receiver operating characteristic curve (AUROC) and 95% confidence interval (CI). Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated using the different cutoff values. The DeLong test was used to compare the different AUROCs. Two-sided *p* values $<$ 0.05 were considered statistically significant. Analyses were carried out on an intention-to-diagnose basis and considered all LSM values, including technical failure. Statistical analyses were performed using SPSS version 23 and GraphPad Prism version 9.4.1.

RESULTS

Baseline characteristics

The study population consisted of 479 adult patients, including 50.3% male individuals, with a median age of 59.0 years (IQR, 49.5–66.0). Median BMI was 35.0 kg/m² (IQR, 29.9–40.9). Class 2 or 3 obesity, defined by BMI \geq 35, was observed in 243 patients (50.7%). In this subgroup, serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and γ -glutamyltransferase (GGT) were significantly lower, whereas no difference was observed in T2DM frequency. The FibroScan XL probe was significantly more frequently used in patients with BMI \geq 35 (79.0% vs. 32.2%; *p* $<$ 0.001). Median LSM was not different between patients with BMI $<$ 35 and \geq 35 (9.3 vs. 9.4 kPa, respectively; *p* = 0.299). Median FIB-4 and FibroTest were significantly lower in patients with BMI \geq 35, whereas A3+ was not different in the two groups. The main characteristics and flow-chart of the study population are shown in Table 1 and Figure S2, respectively.

Higher BMI is associated with a decrease in the proportion of patients with determinate status for AF

Overall, the prevalence of AF was 28.6%. Approximately half of the cohort (46.6%) had no AF, and 24.8% showed an indeterminate status for AF (Figure S1). The detection of AF was significantly lower in patients with BMI \geq 35 (19.3%) compared with 38.1% in patients with BMI $<$ 35 (*p* $<$ 0.001), potentially due to the increased

TABLE 1 Baseline characteristics in the overall study population and stratified by BMI < 35 or ≥35.

Characteristics	Overall (n = 479)	BMI < 35 kg/m ² (n = 236)	BMI ≥ 35 kg/m ² (n = 243)	p value*
Age (y)	59.0 (49.5–66.0)	61.0 (52.0–68.0)	57.0 (47.5–63.0)	<0.001
Male, n (%)	241 (50.3)	130 (55.1)	111 (45.7)	0.040
T2DM, n (%)	324 (67.8)	158 (66.9)	166 (68.3)	0.801
BMI (kg/m ²)	35.0 (29.9–40.9)	29.8 (26.9–32.2)	40.8 (37.4–45.0)	<0.001
AST (U/L)	35 (27–48)	37 (28–52)	33 (25–45)	0.012
ALT (U/L)	45 (32–70)	50 (34–77)	42 (29–64)	0.025
GGT (U/L)	54 (35–102)	62 (39–114)	47 (32–91)	0.016
Ferritin (μg/L)	117 (38–244)	122 (40–248)	116 (38–223)	0.296
Albumin (g/dL)	4.3 (4.0–4.6)	4.5 (4.2–4.7)	4.2 (4.0–4.4)	<0.001
Glucose (mmol/L)	6.2 (5.3–8.0)	6.1 (5.1–8.0)	6.3 (5.4–8.2)	0.117
HbA1c (%)	6.3 (5.7–7.6)	6.4 (5.7–7.6)	6.3 (5.7–7.6)	0.536
Platelet count (10 ⁹ /L)	240 (202–284)	233 (193–280)	248 (209–288)	0.020
Prothrombin time (%)	97 (91–116)	97 (92–103)	97 (91–106)	0.292
AST/ALT	0.76 (0.59–1.02)	0.74 (0.57–0.99)	0.77 (0.61–1.04)	0.320
FIB-4	1.26 (0.86–1.76)	1.34 (0.92–1.96)	1.17 (0.82–1.61)	<0.001
FibroTest	0.31 (0.16–0.56)	0.41 (0.23–0.62)	0.22 (0.12–0.40)	<0.001
A3+	0.506 (0.240–756)	0.549 (0.220–0.786)	0.489 (0.243–0.729)	0.501
LSM (kPa)	9.3 (7.4–12.4)	9.3 (6.8–12.6)	9.4 (7.7–12.3)	0.299
LSM (IQR)	1.3 (0.9–2.0)	1.2 (0.8–2.0)	1.5 (1.0–2.2)	0.803
IQR/median LSM ratio	0.14 (0.10–0.19)	0.13 (0.09–0.18)	0.15 (0.11–0.20)	0.093
CAP (dB/m)	330 (296–360)	319 (284–348)	341 (309–368)	<0.001
Unreliable LSM, n (%) ^a	22 (4.2)	10 (4.2)	10 (7.0)	0.947
Use of FibroScan XL probe, n (%)	268 (59.2)	76 (32.2)	192 (79.0)	<0.001
Liver biopsy performed, n (%)	179 (37.4)	111 (47.0)	68 (28.0)	<0.001
Histological stage of fibrosis, n (%)				
F0	3 (0.6)	1 (0.9)	2 (2.9)	–
F1	34 (7.1)	15 (13.5)	19 (27.9)	–
F2	58 (12.1)	37 (33.3)	21 (30.9)	–
F3	46 (9.6)	31 (27.9)	15 (22.1)	–
F4	38 (7.9)	27 (24.3)	11 (16.2)	–
Presence of AF, n (%)	137 (28.6)	90 (38.1)	47 (19.3)	<0.001
Indeterminate status for AF, n (%)	119 (24.8)	36 (15.3)	83 (34.2)	<0.001

Note: Median values are provided with IQR in parentheses unless otherwise noted as n (%).

Abbreviations: A3+, Agile 3+; AF, advanced fibrosis; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CAP, controlled attenuation parameter; FIB-4, Fibrosis-4; GGT, gamma-glutamyl transferase; HbA1c, glycated hemoglobin; LSM, liver stiffness measurement; T2DM, type 2 diabetes mellitus.

^aReliable LSM was defined as less than 10 valid measurements or IQR/median > 30%.

*p value determined by comparing patients with BMI ≥ 35 versus <35 using independent-samples t test, Mann–Whitney test, or χ^2 test as appropriate. Bold indicates significant $p < 0.05$.

proportion of indeterminate cases. The presence of AF across the different BMI categories is shown in Figure 1. Higher BMI was significantly associated with an elevated proportion of indeterminate status for AF (odds ratio [OR] = 1.09; 95% CI: 1.06–1.12; $p < 0.001$), i.e., BMI ≥ 35 (OR = 2.85; 95% CI: 1.83–4.44; $p < 0.001$). BMI ≥ 35 remained statistically and clinically significant after multiple adjustments for age and sex (adjusted OR = 2.65; 95% CI: 1.69–4.16; $p < 0.001$).

Overall diagnostic performance of NITs for the detection of AF

We next assessed the diagnostic performance of NITs for the detection of AF in the subgroup of patients with determinate status for AF and all NITs available ($n = 358$). As previously published [16], LSM and A3+ had similar diagnostic performance in the overall population with an AUROC of 0.91 (95% CI: 0.88–0.94) versus 0.91 (95% CI:

0.87–0.94), respectively ($p = 0.802$), whereas FIB-4 displayed a significantly lower diagnostic performance with an AUROC of 0.81 (95% CI: 0.76–0.84; $p < 0.001$) compared with LSM. There was no significant difference in LSM diagnostic performance using the FibroScan M probe or XL probe, i.e., AUROC of 0.94 (95% CI: 0.89–0.97) versus 0.89 (95% CI: 0.83–0.93; $p = 0.091$). The diagnostic accuracy of the different NITs for AF detection is shown in Figure 2 and Table S2.

Diagnostic performance of NITs for the detection of AF stratified by obesity severity

The AUROCs of FIB-4, LSM, and A3+ in patients without obesity and within each class of obesity are shown in Table S3. Subsequently, we focused on the diagnostic performance of NITs stratified by obesity severity comparing patients with BMI < 35 and ≥ 35 . FIB-4 tended to have a higher AUROC in patients with BMI ≥ 35 compared with others without reaching statistical significance ($p = 0.211$; Figure 2).

LSM had an excellent diagnostic accuracy in both patients with BMI ≥ 35 and < 35 with AUROCs of 0.90 (95% CI: 0.84–0.94) and

0.93 (95% CI: 0.88–0.96; $p = 0.373$), respectively (Figure 2). At the rule-out cutoff < 8 kPa, NPV was excellent (>98%) in both groups. However, at the rule-in cutoff ≥ 9.6 kPa, LSM had a lower ability to discriminate AF in patients with BMI ≥ 35 with specificity of 77.9% compared with 85.4% in patients with BMI < 35, resulting in a decreased PPV of 63.2% compared with 82.4%, respectively (Table 2).

Similar to LSM, A3+ had an excellent diagnostic accuracy in both patients with BMI ≥ 35 and < 35 with AUROCs of 0.92 (95% CI: 0.86–0.95) and 0.90 (95% CI: 0.85–0.94), respectively (Figure 2). At the rule-out cutoff < 0.441, A3+ had slightly lower sensitivity compared with LSM in both BMI ≥ 35 (90.9% vs. 98.9%) and BMI < 35 (93.6% vs. 97.9%), resulting in a lower NPV in both groups (Table 2).

Conversely, at the rule-in cutoff ≥ 0.679 , A3+ achieved better specificity than LSM in both BMI ≥ 35 (90.4% vs. 77.9%) and BMI < 35 (90.0% vs. 85.4%; Table 2). Therefore, the number of false-positive cases with A3+ was lower compared with LSM (Figure 3). However, the proportion of patients in the indeterminate zone was higher with A3+ compared with LSM in both BMI groups (Table 2; Figure 3).

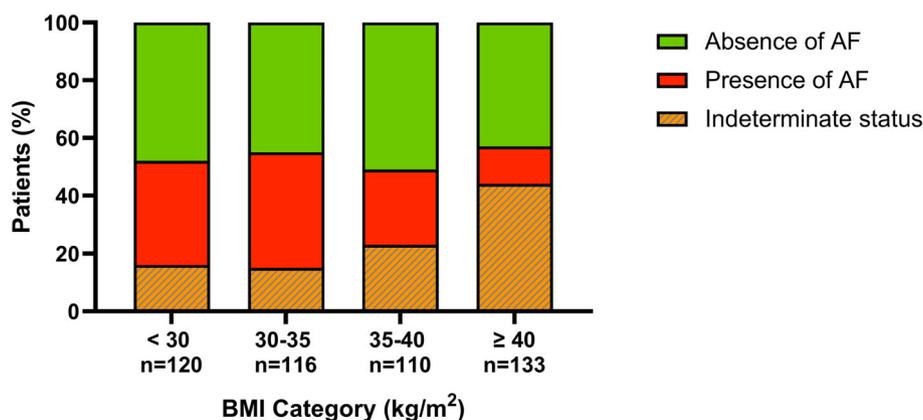


FIGURE 1 Distribution of advanced fibrosis (AF) status stratified by BMI categories. The proportion of patients with indeterminate status for AF (orange with stripes) progressively raises in parallel with an increase in the different BMI categories, whereas the prevalence of AF (in red) is lower in patients with BMI ≥ 35 kg/m². Patients with a low probability of AF are represented in green. [Color figure can be viewed at wileyonlinelibrary.com]

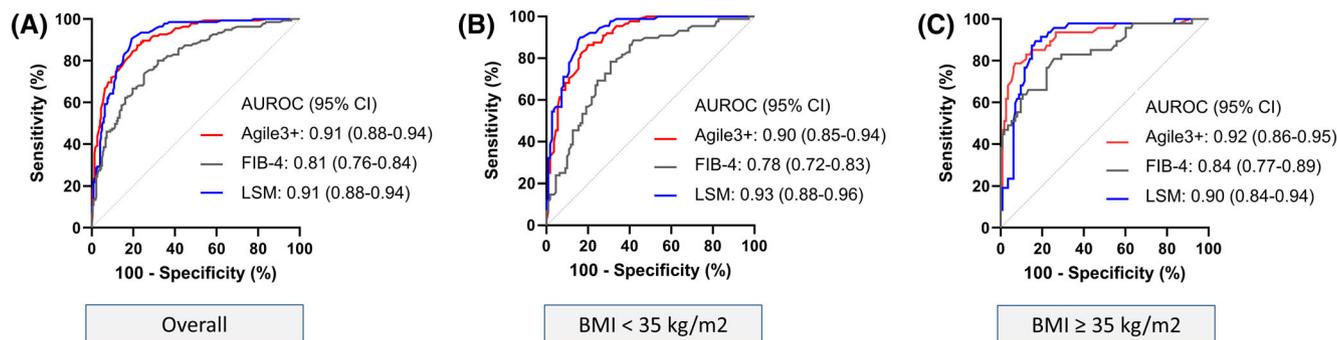


FIGURE 2 Diagnostic accuracy of noninvasive tests (NITs) for the detection of advanced fibrosis (AF). The area under the receiver operating characteristic curves (AUROCs) of Agile 3+ (A3+; in red), Fibrosis-4 (FIB-4; in gray), and liver stiffness measurement (LSM; in blue) are represented in (A) the overall population, in (B) patients with BMI < 35 kg/m², and in (C) patients with BMI ≥ 35 kg/m². [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Diagnostic performance of NITs for the detection of AF stratified by BMI ≥ 35 ($n = 160$) or BMI < 35 ($n = 198$)

NITs of AF	FIB-4	LSM	A3+	Sequential LSM/A3+
Rule-out cutoff	<1.30	<8 kPa	<0.451	LSM < 8 kPa/ LSM \geq 8 kPa and A3+ < 0.451
% patients (n)				
BMI < 35 kg/m ²	50.0 (99)	37.4 (74)	44.4 (88)	48.5 (96)
BMI \geq 35 kg/m ²	54.4 (87)	42.5 (68)	49.4 (79)	55.0 (88)
Se % (95% CI)				
BMI < 35 kg/m ²	73.9 (63.4–82.7)	98.9 (93.9–100.0)	90.9 (82.9–96.0)	90.9 (82.9–96.0)
BMI \geq 35 kg/m ²	83.0 (69.2–92.4)	97.9 (88.7–99.9)	93.6 (82.5–98.7)	93.6 (82.5–98.7)
Sp % (95% CI)				
BMI < 35 kg/m ²	69.1 (59.6–77.6)	66.4 (56.7–75.1)	72.7 (63.4–80.8)	80.0 (71.3–87.0)
BMI \geq 35 kg/m ²	70.0 (60.6–78.2)	59.3 (49.6–68.4)	68.1 (58.7–76.6)	75.2 (66.2–82.9)
NPV % (95% CI)				
BMI < 35 kg/m ²	76.8 (69.5–82.8)	98.6 (91.2–99.8)	90.9 (83.6–95.1)	91.7 (84.9–95.5)
BMI \geq 35 kg/m ²	90.8 (83.9–94.9)	98.5 (90.5–99.8)	96.2 (89.5–98.7)	96.6 (90.4–98.8)
PPV % (95% CI)				
BMI < 35 kg/m ²	65.7 (58.5–72.2)	70.2 (64.4–75.8)	72.7 (66.1–78.5)	78.4 (71.3–84.2)
BMI \geq 35 kg/m ²	53.4 (45.7–61.0)	50.0 (44.4–55.6)	55.0 (48.0–61.8)	61.1 (53.1–68.6)
Indeterminate zone	1.31–2.66	8.1–9.5 kPa	0.451–0.678	LSM \geq 8 kPa and A3+ = 0.452–0.678
% patients (n)				
BMI < 35 kg/m ²	36.9 (73)	14.6 (29)	19.2 (38)	16.2 (32)
BMI \geq 35 kg/m ²	38.8 (62)	13.8 (22)	20.0 (32)	15.0 (24)
Rule-in cutoff	≥ 2.67	≥ 9.6 kPa	≥ 0.679	LSM \geq 8 kPa and A3+ ≥ 0.679
% patients (n)				
BMI < 35 kg/m ²	13.1 (26)	48.0 (95)	36.4 (72)	35.4 (70)
BMI \geq 35 kg/m ²	6.9 (11)	43.8 (70)	30.6 (49)	30.0 (48)
Se % (95% CI)				
BMI < 35 kg/m ²	22.7 (14.5–32.9)	85.2 (76.1–91.4)	68.2 (57.4–77.7)	68.2 (57.4–77.7)
BMI \geq 35 kg/m ²	21.3 (10.7–35.7)	91.5 (79.6–97.6)	78.7 (64.3–89.3)	78.7 (64.3–89.3)
Sp % (95% CI)				
BMI < 35 kg/m ²	95.4 (89.7–98.5)	85.4 (77.5–91.5)	90.0 (82.8–94.9)	90.9 (83.9–95.6)
BMI \geq 35 kg/m ²	100.0 (96.8–100.0)	77.9 (69.1–85.1)	90.4 (83.2–95.0)	90.3 (83.2–95.0)
NPV % (95% CI)				
BMI < 35 kg/m ²	61.0 (58.1–63.9)	87.9 (81.3–92.3)	78.0 (72.1–82.9)	78.1 (72.3–83.0)
BMI \geq 35 kg/m ²	75.3 (72.1–77.4)	95.7 (89.6–98.3)	89.3 (80.9–94.2)	91.1 (85.4–94.7)
PPV % (95% CI)				
BMI < 35 kg/m ²	80.8 (62.3–91.4)	82.4 (74.7–88.1)	84.5 (75.4–90.7)	86.7 (76.6–91.7)
BMI \geq 35 kg/m ²	100.0 (NA)	63.2 (54.6–71.1)	66.7 (48.6–80.9)	77.1 (65.3–85.7)

Note: LSM and A3+ performance was assessed in intention-to-diagnose AF including patients with technical failure ($n = 14$).

Abbreviations: A3+, Agile 3+; AF, advanced fibrosis; FIB-4, Fibrosis-4; LSM, liver stiffness measurement; NA, not applicable; NIT, noninvasive test; NPV, negative predictive value; PPV, positive predictive value; Se, sensitivity; Sp, specificity.

Optimal algorithm for the detection of AF using a sequential use of LSM followed by A3+

Because we observed a higher NPV of LSM to rule out AF compared with A3+ and, conversely, a lower PPV of LSM to rule in AF, we have

next assessed the relevance of a sequential strategy using LSM followed by A3+. LSM was used as a first line at the low cutoff < 8 kPa to rule out AF, followed by A3+ at the low cutoff < 0.451 to rule out additional cases for AF and the high cutoff ≥ 0.679 to rule in AF (Figure 4A).

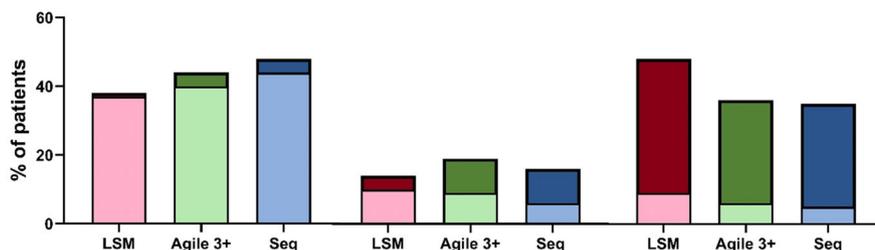
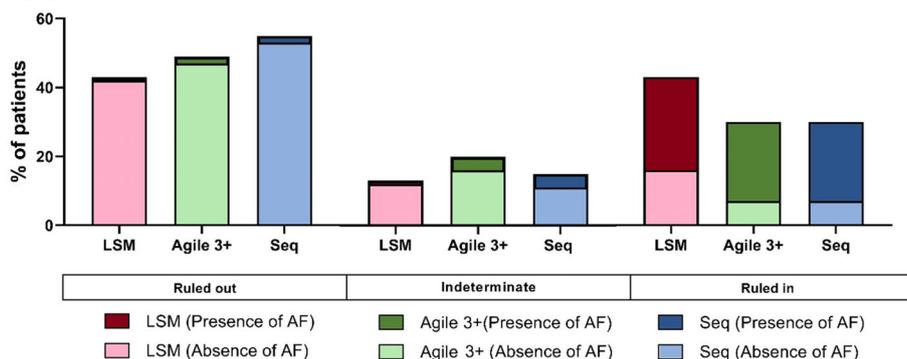
(A) BMI < 35 kg/m²

(B) BMI ≥ 35 kg/m²


FIGURE 3 Performance of liver stiffness measurement (LSM), Agile 3+ (A3+), and sequential LSM/A3+ to rule in and rule out advanced fibrosis (AF). The percentage of the patients in the rule-in zone using LSM in pink, A3+ in green, and the sequential strategy with LSM followed by A3+ in blue is presented in (A) patients with BMI < 35 kg/m² and (B) BMI ≥ 35 kg/m². The rule-out zone corresponds to the percentage of patients with low cutoffs of either LSM < 8 kPa, A3+ score < 0.451, or sequential LSM < 8 kPa and A3+ score < 0.451. The rule-in zone corresponds to the percentage of patients at the high cutoffs of either LSM ≥ 9.6 kPa, A3+ score ≥ 0.679, or sequential LSM ≥ 8 kPa and A3+ score ≥ 0.679. The indeterminate zone corresponds to patients between the low and high cutoffs of either LSM, A3+, or with sequential LSM ≥ 8 kPa and A3+ score between 0.451 and 0.679. The LSM/A3+/sequential (presence of AF) corresponds to patients classified as having AF using LSM/A3+/sequential LSM/A3+ cutoffs in dark pink, green, or blue, respectively. The LSM/A3+/sequential (absence of AF) corresponds to patients classified as having no AF using LSM/A3+/ sequential LSM/A3+ cutoffs in light pink, green, or blue, respectively.

At the rule-in cutoff, the sequential LSM/A3+ strategy enabled a maximization of specificity similar to A3+ alone in both groups (~90%), leading to an improved PPV compared with LSM, FIB-4, and A3+ (Table 2). The higher benefit in terms of increase in PPV was observed in patients with BMI ≥ 35 (77.1% compared with 66.7% for A3+ and 63.2% for LSM). In addition, the proportion of patients in the indeterminate zone was lower using the sequential LSM/A3+ strategy compared with A3+ in both BMI groups (Table 2; Figure 3).

Finally, the sequential LSM/A3+ strategy at the rule-out cutoff maintained excellent sensitivity > 90% in all patients but was lower than LSM. A decrease in NPV of the sequential LSM/A3+ compared with LSM was mostly observed in patients with BMI < 35, i. e., 91.7% versus 98.6%, respectively, but remained minimal in patients with BMI ≥ 35, i. e., 96.6% versus 98.5% (Table 2; Figure 3). The improved specificity at the rule-in cutoff compared with LSM was observed starting from BMI ≥ 35, whereas LSM alone seemed sufficiently accurate for lower BMI ranges (Figure S3; Table S4).

Sensitivity analysis

We then performed a sensitivity analysis on patients diagnosed with AF with liver biopsy or MRE ($n = 233$) to validate our findings and exclude any misclassification bias. Using more stringent criteria for the diagnosis of AF, our results remained similar, as well as statistically and clinically significant (Table S5). This analysis confirmed that a sequential LSM/A3+ at the high cutoff maximizes specificity and PPV similar to A3+ alone while reducing the proportion of patients in the indeterminate zone compared with A3+, especially in patients with BMI ≥ 35, whereas LSM or A3+ alone seemed sufficiently accurate for lower BMI ranges, as shown in Figure S4.

DISCUSSION

Using data from a well-characterized population of patients with MASLD enriched with patients with obesity and encompassing a wide range of BMI values, consecutively presented at a multidisciplinary

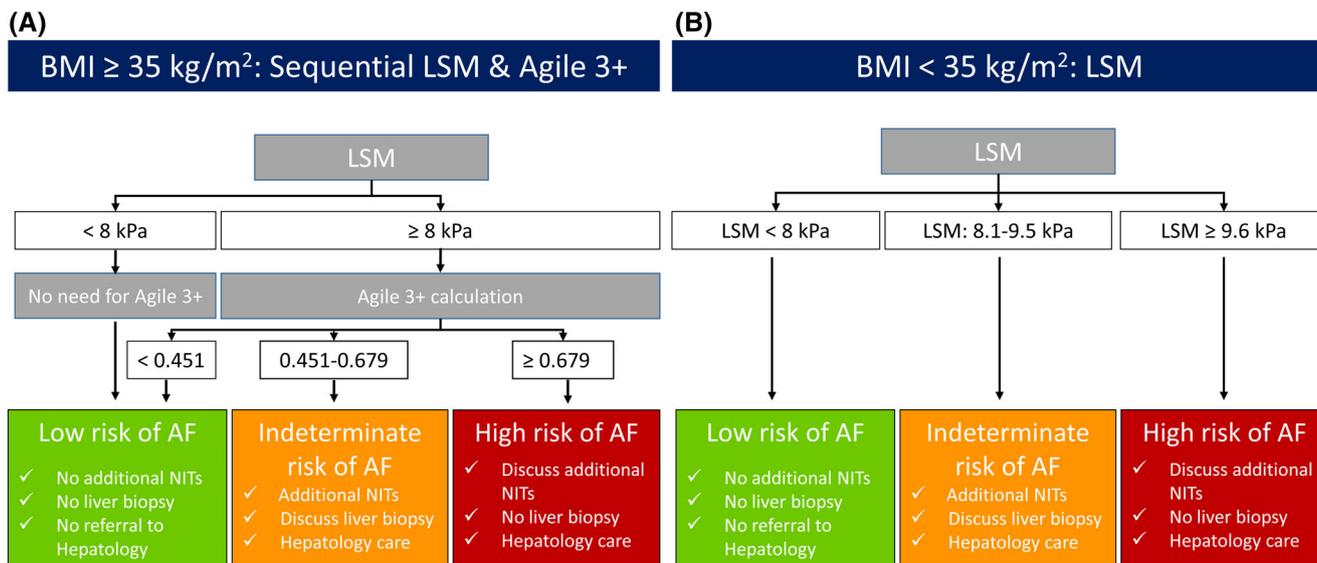


FIGURE 4 Strategy for advanced fibrosis (AF) risk stratification according to BMI in an obesity-enriched population. In (A) patients with BMI ≥ 35 kg/m²: sequential strategy of liver stiffness measurement (LSM)/Agile 3+ (A3+). After a first step of LSM using the low cutoff of 8 kPa to rule out AF, the A3+ score is calculated in all patients with LSM ≥ 8 kPa. Patients with LSM ≥ 8 kPa and A3+ score < 0.451 are reclassified and ruled out for AF resulting in a high negative predictive value (NPV) of 96.6%, whereas patients with LSM ≥ 8 kPa and A3+ score between 0.452 and 0.678 are classified as indeterminate for AF. Patients with LSM ≥ 8 kPa and A3+ score ≥ 0.679 are ruled in for AF with a positive predictive value (PPV) of 77.1%. In (B) patients with BMI < 35 kg/m², LSM < 8 kPa enables ruling out of AF with a high NPV of 96.6%. Patients with LSM ≥ 9.6 kPa are ruled in for AF with a PPV of 82.4%. [Color figure can be viewed at wileyonlinelibrary.com]

board for suspected fibrotic MASH, our study demonstrates that an increase in BMI significantly affects the ability to determine the presence of MASLD-related AF. We report a significantly higher proportion of patients with indeterminate status for AF in patients with BMI ≥ 35 compared with patients with BMI < 35 using a composite criterion according to recent scientific society guidelines [6].

Furthermore, we highlight the impact of BMI ≥ 35 on the performance of NITs for AF detection. Indeed, we report lower and insufficient specificity and PPV of LSM at the rule-in cutoff in patients with BMI ≥ 35. We further observe better specificity and PPV of the A3+ score compared with LSM at the rule-in cutoff but lower sensitivity and NPV at the rule-out cutoff, as well as a higher proportion of patients in the indeterminate zone compared with LSM. Finally, we propose a new sequential strategy of LSM followed by A3+ to identify AF in patients with MASLD and BMI ≥ 35 and demonstrate that this sequential strategy maximizes PPV of the screening strategy while reducing the proportion of patients in the indeterminate zone in this population. To our knowledge, this is the first study assessing the impact of BMI on the screening strategy for the detection of MASLD/NAFLD-related AF using currently recommended NITs such as FIB-4, LSM, and the recently developed A3+.

The key novelties of our study are to provide estimates of the proportion of patients with indeterminate status for AF and to highlight the major impact of obesity severity on the accurate diagnosis of AF in patients with MASLD. This has important implications for clinical practice because obesity is strongly associated with MASLD. Here, half of our study population had BMI ≥ 35, with no significant difference regarding the proportion of T2DM, which is recognized as a

major risk factor for AF. The drop in the proportion of patients with determinate status for AF in patients with BMI ≥ 35 may be due to the lower frequency of liver biopsy performed in this population because it may be technically more challenging. Finally, potential stigma toward patients with severe obesity cannot be excluded, such as weight discrimination for the access to MRE or liver biopsy [30].

Intriguingly, patients with BMI < 35 had more elevated transaminases and GGT serum levels, lower platelet count, and higher values of FibroTest and FIB-4. AF detection was also higher, but this result is at least partially explained by fewer cases of patients with indeterminate status. Differences in biological tests may be due to different demographic characteristics in the two groups (older patients and overrepresentation of the male sex in the BMI < 35 group). However, there have been recent data suggesting that liver fibrosis is more frequent in lean patients with MASLD (BMI < 25) [31] and even in patients with MASLD without obesity [32]. Because the prevalence of MASLD increases with the presence of obesity [3], but not liver fibrosis, it may explain here the underrepresentation of severe forms in patients with BMI ≥ 35.

The impact of obesity on the diagnostic performance of first-line blood-based NITs in a cohort of biopsy-proven patients with MASLD enriched with severe obesity (BMI ≥ 40) has been recently studied [17]. Similar to our results, the authors reported an excellent diagnostic accuracy of FIB-4 for the detection of AF (AUROC of 0.89) but did not assess imaging-based biomarkers such as LSM or A3+ [17]. Another retrospective study reported a decrease in LSM diagnostic accuracy when BMI increased above 44 in patients who underwent bariatric surgery [20]. The impact of BMI on LSM diagnostic

performance may potentially be due to the increased skin-to-liver capsule distance in patients with obesity [19, 21]. Additionally, the adequate positioning of the probe for optimal acquisition may be more challenging in patients with increased waist circumference [21]. The development of the FibroScan XL probe for the assessment of LSM has considerably improved the accuracy of LSM using VCTE in patients with obesity [19], and we report a similar proportion of unreliable LSM in patients with BMI ≥ 35 and <35 . However, as previously reported, LSM lacks specificity to rule in AF at the cutoff ≥ 9.6 kPa in patients with severe obesity. Indeed, in our study population, the PPV of LSM to rule in AF dropped from 82.4% to 63.2% in patients with BMI ≥ 35 . Previous studies have suggested the need to raise the rule-in cutoff value of LSM in patients with severe obesity, thereby increasing the proportion of cases in the indeterminate zone [20]. Others have found that the use of the XL probe in patients with obesity enabled them to use the same threshold for AF diagnosis than in patients without obesity using the M probe [33]. Finally, in our study, the AUROC of LSM using the XL probe tended to be lower compared with the M probe without reaching significant statistical difference.

Recently, A3+ was developed and validated for AF detection in patients with biopsy-proven MASLD/NAFLD [16, 23, 34, 35]. These studies demonstrated a significant improvement in the AF diagnostic performance with fewer indeterminate results in patients from secondary and tertiary centers compared with LSM alone and FIB-4 [16, 23, 34, 35]. Our results show a similar diagnostic accuracy of A3+ compared with Sanyal et al. [16]. However, we demonstrate a clear impact of BMI ≥ 35 on the diagnostic accuracy of A3+ at the published rule-in and rule-out cutoffs. Indeed, the interest of A3+ for AF detection in our study population is less pronounced in patients with BMI < 35 because PPV is modestly improved at the cost of an increased number of patients in the indeterminate zone compared with LSM. However, a greater increase in PPV at the rule-in cutoff is observed in patients with BMI ≥ 35 using A3+ compared with LSM but remains relatively low, i.e., 66.7% versus 84.5% in patients with BMI ≥ 35 and <35 , respectively.

Therefore, we propose a two-step strategy using LSM followed by A3+ to further discriminate patients for the presence of AF using previously published cutoff values. This strategy leverages the improved PPV of A3+ at the rule-in cutoff ≥ 0.679 and the very high NPV of LSM at the rule-out cutoff < 8 kPa while minimizing the proportion of patients in the indeterminate zone. In patients with BMI ≥ 35 , this strategy increases the number of cases correctly ruled out while providing the highest PPV of 77.1% at the rule-in cutoff, thereby theoretically reducing the number of unnecessary liver biopsies.

There are several strengths in our study, including a large population of well-characterized patients with MASLD and the availability of numerous data, including different NITs, MRE, and histological assessment. The study population encompasses a wide range of BMI values, allowing head-to-head comparison of the diagnostic performance of NITs in balanced groups with BMI above and below 35. Furthermore, we used composite criterion to define AF, allowing us to consider several clinical situations and to better assess the diagnostic performance of NITs in their actual clinical context of use, in line with the most recent recommendations [6, 36]. Therefore, our data are complementary to

those of previous studies that have been performed in highly selective populations and included only patients with biopsy-proven MASLD but that are not representative of the real-life management of the majority of patients with MASLD [16, 23, 34, 35]. Although liver biopsy remains the gold standard for staging liver fibrosis, it has several limitations, including high cost, invasiveness with a risk of severe complication, sampling variability, and intra- and inter-observer variability [37, 38]. Therefore, it is usually not favored by the physician or the patient and rarely performed in clinical practice [39]. Moreover, cirrhosis diagnosis can be established in case of overt imaging features, especially using MRI [40, 41]. Finally, concordant NITs can provide a diagnostic accuracy comparable with liver biopsy [42], reinforced by the most recently validated EASL algorithm [6, 43]. Therefore, the most recent clinical practice guidelines and expert recommendations advocate liver biopsy only in patients with discordant NITs [6, 36]. Therefore, we used a composite endpoint to assess the presence of AF, allowing us to consider all of these clinical situations and avoid any selection bias by including patients without liver biopsy. However, because our composite hierarchical criterion for AF detection included a subgroup of 127 participants classified using concordant LSM and FibroTest, the analysis of the diagnostic performance of LSM and A3+ may be biased in favor of these NITs. Nevertheless, our findings remained clinically and statistically significant in the sensitivity analysis performed in the subgroup classified based on more stringent criteria (liver biopsy or MRE), thereby excluding potential misclassification bias using the composite endpoint.

We acknowledge different limitations to our study. Because VCTE was not systematically performed on the same day as the blood tests, we cannot exclude potential bias due to the intrinsic variability of the different variables. However, the diagnostic performance of the blood-based biomarkers and their combination with LSM was similar to those that have been previously published in the literature [16, 26]. In addition, all liver biopsy specimens were evaluated by a single hepatopathologist, inducing a potential misclassification of some patients for liver fibrosis. The study included patients discussed at the MASH multidisciplinary board for suspected fibrotic MASH; therefore, the population is enriched with more severe cases compared with the general population of patients with MASLD. Therefore, potential selection bias cannot be excluded. Although a recent study reported that the diagnostic performance of blood-based NITs was also affected by race and ethnicity [44], we were not able to study the impact of race and ethnicity in our study. Finally, the study was performed in a single tertiary center expert in the clinical management of patients with MASLD. Therefore, the reproducibility of our results needs to be confirmed in larger independent cohorts that include different clinical settings.

Systematic screening for AF is now unanimously recommended by several society guidelines in high-risk populations, including patients with obesity [1, 5–7, 11]. Thus, more individuals with BMI ≥ 35 are expected to be enrolled in these screening programs using the currently available and recommended NITs. Our findings will help clinicians to better understand the impact of BMI categories when interpreting these NITs using the recommended cutoff values to rule in or rule out AF. Although there remains a critical need to improve the diagnostic performance of currently available NITs to rule

in AF in patients with a high BMI, i.e., ≥ 35 , our proposed sequential LSM/A3+ strategy could already improve AF screening in this population. Indeed, the sequential LSM/A3+ algorithm is easy to implement because it is based on previously validated cutoffs of LSM and A3+. Moreover, this strategy is largely available, with no additional cost or procedures, and applying the calculation of A3+ only in patients with LSM ≥ 8 kPa saves clinical time. Finally, this strategy provides an immediate benefit for the patients because it could lower the number of indications for liver biopsy and additional NITs and ultimately minimize health care costs (Figure 4). Further studies encompassing a broader population to limit potential bias are needed to validate the finding that the sequential LSM/A3+ strategy could improve the detection of AF in patients with BMI ≥ 35 .[○]

AUTHOR CONTRIBUTIONS

Yasmina Chouik: analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript, and approval of the final submission. Adrien Aubin, Marianne Maynard-Muet, Bérénice Segrestin, Fabien Zoulim, Emmanuel Disse, and Massimo Levrero: data collection, critical revision of the manuscript, and approval of the final submission. Laurent Milot: imaging analysis, data collection, critical revision of the manuscript, and approval of the final submission. Valérie Hervieu: anatomicopathologic analysis, data collection, critical revision of the manuscript, and approval of the final submission. Cyrielle Caussy: study concept and design, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript, and approval of the final submission. All authors approved the final version of this article.

CONFLICT OF INTEREST STATEMENT

Cyrielle Caussy received consultant fees from Gilead Sciences, Inc.; Novo Nordisk A/S; AstraZeneca plc; Eli Lilly and Company; E-Scopics; MSD; Bayer AG; and Corcept and Echosens, as well as grant support from Gilead Sciences, Inc. Massimo Levrero received consultant fees from Gilead Sciences Inc.; Inventiva Life Sciences; and MSD. Bérénice Segrestin received consultant fees from Lilly and Novo Nordisk A/S. The other authors declared no conflict of interest.

ORCID

Cyrielle Caussy  <https://orcid.org/0000-0001-8089-2907>

REFERENCES

- Rinella ME, Lazarus JV, Ratziu V, et al. A multi-society Delphi consensus statement on new fatty liver disease nomenclature. *Hepatology* Published online. 2023;24:1966-1986. doi:10.1097/HEP.0000000000000520
- Younossi ZM. Non-alcoholic fatty liver disease - a global public health perspective. *J Hepatol*. 2019;70(3):531-544. doi:10.1016/j.jhep.2018.10.033
- Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology*. 2016;64(1):73-84. doi:10.1002/hep.28431
- Sanyal AJ, Van Natta ML, Clark J, et al. Prospective study of outcomes in adults with nonalcoholic fatty liver disease. *N Engl J Med*. 2021;385(17):1559-1569. doi:10.1056/NEJMoa2029349
- Kanwal F, Shubrook JH, Adams LA, et al. Clinical care pathway for the risk stratification and Management of Patients with nonalcoholic fatty liver disease. *Gastroenterology*. 2021;161(5):1657-1669. doi:10.1053/j.gastro.2021.07.049
- European Association for the Study of the Liver. EASL clinical practice guidelines on non-invasive tests for evaluation of liver disease severity and prognosis - 2021 update. *J Hepatol*. 2021;75(3):659-689. doi:10.1016/j.jhep.2021.05.025
- Cusi K, Isaacs S, Barb D, et al. American Association of Clinical Endocrinology Clinical Practice Guideline for the diagnosis and Management of nonalcoholic fatty liver disease in primary care and endocrinology clinical settings: Co-sponsored by the American Association for the Study of Liver Diseases (AASLD). *Endocr Pract*. 2022;28(5):528-562. doi:10.1016/j.eprac.2022.03.010
- Loomis AK, Kabadi S, Preiss D, et al. Body mass index and risk of nonalcoholic fatty liver disease: two electronic health record prospective studies. *J Clin Endocrinol Metab*. 2016;101(3):945-952. doi:10.1210/jc.2015-3444
- Fabbrini E, Sullivan S, Klein S. Obesity and nonalcoholic fatty liver disease: biochemical, metabolic, and clinical implications. *Hepatology*. 2010;51(2):679-689. doi:10.1002/hep.23280
- Non-alcoholic Fatty Liver Disease Study Group; Lonardo A, Bellentani S, Argo CK, et al. Epidemiological modifiers of non-alcoholic fatty liver disease: Focus on high-risk groups. *Dig Liver Dis*. 2015;47(12):997-1006. doi:10.1016/j.dld.2015.08.004
- ElSayed NA, Aleppo G, Aroda VR, et al. 4. Comprehensive medical evaluation and assessment of comorbidities: Standards of Care in Diabetes-2023. *Diabetes Care*. 2023;46(suppl 1):S49-S67. doi:10.2337/dc23-S004
- Castera L, Friedrich-Rust M, Loomba R. Noninvasive assessment of liver disease in patients with nonalcoholic fatty liver disease. *Gastroenterology*. 2019;156(5):1264-1281.e4. doi:10.1053/j.gastro.2018.12.036
- Eddowes PJ, Sasso M, Allison M, et al. Accuracy of FibroScan controlled attenuation parameter and liver stiffness measurement in assessing steatosis and fibrosis in patients with nonalcoholic fatty liver disease. *Gastroenterology*. 2019;156(6):1717-1730. doi:10.1053/j.gastro.2019.01.042
- Vuppalanchi R, Siddiqui MS, Van Natta ML, et al. Performance characteristics of vibration-controlled transient elastography for evaluation of nonalcoholic fatty liver disease. *Hepatology*. 2018;67(1):134-144. doi:10.1002/hep.29489
- Hsu C, Caussy C, Imajo K, et al. Magnetic resonance vs transient elastography analysis of patients with nonalcoholic fatty liver disease: a systematic review and pooled analysis of individual participants. *Clin Gastroenterol Hepatol*. 2019;17(4):630-637.e8. doi:10.1016/j.cgh.2018.05.059
- Sanyal AJ, Foucquier J, Younossi ZM, et al. Enhanced diagnosis of advanced fibrosis and cirrhosis in individuals with NAFLD using FibroScan-based Agile scores. *J Hepatol*. 2023;78(2):247-259. doi:10.1016/j.jhep.2022.10.034
- Qadri S, Ahlholm N, Lønsmann I, et al. Obesity modifies the performance of fibrosis biomarkers in nonalcoholic fatty liver disease. *J Clin Endocrinol Metab*. 2022;107(5):e2008-e2020. doi:10.1210/clinem/dgab933
- Caussy C, Chen J, Alquirish MH, et al. Association between obesity and discordance in fibrosis stage determination by magnetic resonance vs transient elastography in patients with nonalcoholic liver disease. *Clin Gastroenterol Hepatol*. 2018;16(12):1974-1982.e7. doi:10.1016/j.cgh.2017.10.037
- Myers RP, Pomier-Layrargues G, Kirsch R, et al. Discordance in fibrosis staging between liver biopsy and transient elastography using the FibroScan XL probe. *J Hepatol*. 2012;56(3):564-570. doi:10.1016/j.jhep.2011.10.007
- Eilenberg M, Munda P, Stift J, et al. Accuracy of non-invasive liver stiffness measurement and steatosis quantification in patients with

- severe and morbid obesity. *Hepatobiliary Surg Nutr.* 2021;10(5):610-622. doi:10.21037/hbsn-20-787
21. Castéra L, Foucher J, Bernard PH, et al. Pitfalls of liver stiffness measurement: a 5-year prospective study of 13,369 examinations. *Hepatology.* 2010;51(3):828-835. doi:10.1002/hep.23425
 22. Caussy C, Telliam C, Al-Nuaimi B, et al. Comparison of pathway referrals for liver fibrosis risk stratification performed in diabetology and nutrition clinics. *Diabetes Metab Syndr Obes.* 2023;16:1721-1729. doi:10.2147/DMSO.S407511
 23. Noureddin M, Mena E, Vuppalanchi R, et al. Increased accuracy in identifying NAFLD with advanced fibrosis and cirrhosis: independent validation of the Agile 3+ and 4 scores. *Hepatol Commun.* 2023;7(5):e0055. doi:10.1097/HCP.0000000000000055
 24. Petta S, Vanni E, Bugianesi E, et al. The combination of liver stiffness measurement and NAFLD fibrosis score improves the noninvasive diagnostic accuracy for severe liver fibrosis in patients with nonalcoholic fatty liver disease. *Liver Int.* 2015;35(5):1566-1573. doi:10.1111/liv.12584
 25. Petta S, Wong VWS, Cammà C, et al. Improved noninvasive prediction of liver fibrosis by liver stiffness measurement in patients with nonalcoholic fatty liver disease accounting for controlled attenuation parameter values. *Hepatology.* 2017;65(4):1145-1155. doi:10.1002/hep.28843
 26. Sterling RK, Lissen E, Clumeck N, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. *Hepatology.* 2006;43(6):1317-1325. doi:10.1002/hep.21178
 27. Imbert-Bismut F, Ratziu V, Pieroni L, Charlotte F, Benhamou Y, Poinard T. Biochemical markers of liver fibrosis in patients with hepatitis C virus infection: a prospective study. *Lancet.* 2001;357(9262):1069-1075. doi:10.1016/S0140-6736(00)04258-6
 28. Kleiner DE, Brunt EM, Van Natta M, et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. *Hepatology.* 2005;41(6):1313-1321. doi:10.1002/hep.20701
 29. Bedossa P, Poitou C, Veyrie N, et al. Histopathological algorithm and scoring system for evaluation of liver lesions in morbidly obese patients. *Hepatology.* 2012;56(5):1751-1759. doi:10.1002/hep.25889
 30. Ryan L, Coyne R, Heary C, et al. Weight stigma experienced by patients with obesity in healthcare settings: a qualitative evidence synthesis. *Obes Rev.* 2023;24(10):e13606. doi:10.1111/obr.13606
 31. Nabi O, Lapidus N, Boursier J, et al. Lean individuals with NAFLD have more severe liver disease and poorer clinical outcomes (NASH-CO study). *Hepatology.* 2023;78(1):272-283. doi:10.1097/HEP.0000000000000329
 32. Ye Q, Zou B, Yeo YH, et al. Global prevalence, incidence, and outcomes of non-obese or lean non-alcoholic fatty liver disease: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol.* 2020;5(8):739-752. doi:10.1016/S2468-1253(20)30077-7
 33. Wong VWS, Irls M, Wong GLH, et al. Unified interpretation of liver stiffness measurement by M and XL probes in non-alcoholic fatty liver disease. *Gut.* 2019;68(11):2057-2064. doi:10.1136/gutjnl-2018-317334
 34. Miura K, Hayashi H, Kamada Y, et al. Agile 3+ and Agile 4, noninvasive tests for liver fibrosis, are excellent formulae to predict liver-related events in nonalcoholic fatty liver disease. *Hepatol Res.* 2023;23:978-988. doi:10.1111/hepr.13938
 35. Pennisi G, Enea M, Pandolfo A, et al. AGILE 3+ score for the diagnosis of advanced fibrosis and for predicting liver-related events in NAFLD. *Clin Gastroenterol Hepatol.* 2023;21(5):1293-1302.e5. doi:10.1016/j.cgh.2022.06.013
 36. Wattacheril JJ, Abdelmalek MF, Lim JK, Sanyal AJ. AGA clinical practice update on the role of noninvasive biomarkers in the evaluation and management of nonalcoholic fatty liver disease: expert review. *Gastroenterology.* 2023;S0016-5085(23):881-888. doi:10.1053/j.gastro.2023.06.013
 37. Bedossa P, Dargère D, Paradis V. Sampling variability of liver fibrosis in chronic hepatitis C. *Hepatology.* 2003;38(6):1449-1457. doi:10.1016/j.hep.2003.09.022
 38. Davison BA, Harrison SA, Cotter G, et al. Suboptimal reliability of liver biopsy evaluation has implications for randomized clinical trials. *J Hepatol.* 2020;73(6):1322-1332. doi:10.1016/j.jhep.2020.06.025
 39. Anstee QM, Hallsworth K, Lynch N, et al. Real-world management of non-alcoholic steatohepatitis differs from clinical practice guideline recommendations and across regions. *JHEP Rep.* 2022;4(1):100411. doi:10.1016/j.jhepr.2021.100411
 40. Ito K, Mitchell DG, Gabata T, Hussain SM. Expanded gallbladder fossa: simple MR imaging sign of cirrhosis. *Radiology.* 1999;211(3):723-726. doi:10.1148/radiology.211.3.r99ma31723
 41. Harbin WP, Robert NJ, Ferrucci JT. Diagnosis of cirrhosis based on regional changes in hepatic morphology: a radiological and pathological analysis. *Radiology.* 1980;135(2):273-283. doi:10.1148/radiology.135.2.7367613
 42. Majumdar A, Campos S, Gurusamy K, Pinzani M, Tsochatzis EA. Defining the minimum acceptable diagnostic accuracy of noninvasive fibrosis testing in cirrhosis: a decision analytic modeling study. *Hepatology.* 2020;71(2):627-642. doi:10.1002/hep.30846
 43. Canivet CM, Costentin C, Irvine KM, et al. Validation of the new 2021 EASL algorithm for the noninvasive diagnosis of advanced fibrosis in NAFLD. *Hepatology.* 2023;77(3):920-930. doi:10.1002/hep.32665
 44. Bril F, Gray M. Noninvasive tests to identify liver fibrosis in metabolic dysfunction-associated steatotic liver disease are affected by race. *Obesity.* 2024;32(3):612-622. doi:10.1002/oby.23960

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Chouik Y, Aubin A, Maynard-Muet M, et al. The grade of obesity affects the noninvasive diagnosis of advanced fibrosis in individuals with MASLD. *Obesity (Silver Spring).* 2024;32(6):1114-1124. doi:10.1002/oby.24033