# Accuracy of Fibrosis-4 index and non-alcoholic fatty liver disease fibrosis scores in metabolic (dysfunction) associated fatty liver disease according to body mass index: failure in the prediction of advanced fibrosis in lean and morbidly obese individuals

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**Background and aim** While non-invasive scores are increasingly being used to screen for advanced fibrosis in metabolic (dysfunction) associated fatty liver disease (MAFLD), the effect of BMI on their clinical utility remains uncertain. This study assessed the usefulness of the Fibrosis-4 index (FIB-4) and the non-alcoholic fatty liver disease fibrosis score (NFS) in lean, overweight, obese, severely obese, and morbidly obese patients with biopsy-proven MAFLD.
**Methods** A total of 560 patients (28 lean, 174 overweight, 229 obese, 89 severely obese, 40 morbidly obese) were included. Diagnostic performances and optimal cut-off values for FIB-4 and NFS were calculated using receiver operating characteristic (ROC) curve analysis.
**Results** In both lean and morbidly obese patients with MAFLD, both FIB-4 and NFS failed to discriminate advanced fibrosis. Conversely, both scores showed acceptable diagnostic performances in exclusion of advanced fibrosis in overweight, obese, and severely obese patients. FIB-4 was able to exclude advanced fibrosis with the highest diagnostic accuracy in the subgroup of overweight patients (area under the ROC curve: 0.829, 95% confidence interval: 0.738–0.919).
**Conclusion** FIB-4 and NFS can confidently be used to exclude advanced fibrosis in overweight, obese, and severely obese patients. However, they do not appear clinically useful in lean and morbidly obese patients. Eur J Gastroenterol Hepatol XXX: 00–00
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## Introduction

Metabolic (dysfunction) associated fatty liver disease (MAFLD), formerly termed non-alcoholic fatty liver disease (NAFLD), affects approximately a quarter of the world's population and is associated with significant morbidity and mortality [1,2]. Despite recognition of the growing burden of MAFLD, significant challenges exist in the accurate and non-invasive diagnosis of the disease and in evaluating its severity. Liver biopsy remains the current reference standard, but this method has numerous limitations including its invasive nature, sampling errors, potential complications, and high cost [3]. In this scenario, clinical prediction models – derived from a combination of blood-based parameters, clinical predictors, and imaging modalities – are increasingly being used as non-invasive screening tools [4,5].

Accumulating evidence indicates that a patient's stage of liver fibrosis is the key prognostic determinant in patients with MAFLD. Accordingly, the presence of advanced fibrosis ($F \geq 3$) poses a higher risk of liver-related and cardiovascular complications, as well as an increased risk of mortality [6,7]. Therefore, research has been focusing on timely detection of advanced fibrosis as a means to improve clinical outcomes. Of the non-invasive screening tools, the Fibrosis-4 index (FIB-4) and the NAFLD Fibrosis Score (NFS) perform with the greatest accuracy in excluding advanced fibrosis, thus contributing to reducing the need for liver biopsy [8–10]. However, those clinical estimation models have not been validated in the case of obese patients and there is ongoing debate on how the optimal cut-off values may vary depending on the patient's BMI [11]. There is also lack of evidence in the screening utility of those scores in lean patients [12]. We therefore designed the current study to specifically address this issue, comparing the diagnostic performances of FIB-4 and NFS among patients having biopsy-proven MAFLD categorized according to their BMI values.

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**Keywords: fibrosis, metabolic (dysfunction) associated fatty liver disease, non-invasive scores, screening**

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## Materials and methods

### Patients

This study was designed to be a retrospective analysis of data collected prospectively from patients referred to our outpatient clinics. We examined a total of 570 patients who had undergone liver biopsy with evidence of hepatic steatosis. Clinical, biochemical, and histologic data were retrieved from the electronic records held by the Turkish NAFLD Biobank database at the Institute of Gastroenterology, Marmara University (Istanbul). The procedures used in the data collection were described previously in detail [13–15]. The patients were classified according to BMI following the recommendations of the WHO as summarized in Table 1 [16]. In addition to liver biopsy providing evidence of hepatic steatosis and a diagnosis of MAFLD, the patients in our study fulfilled at least one of the following criteria: (1) BMI higher than 25 kg/m$^2$; (2) presence of diabetes mellitus type 2; (3) evidence of at least two of the metabolic dysfunction criteria for those having a BMI lower than 25 kg/m$^2$. The metabolic dysfunction criteria were as follows: (1) waist circumference ≥102/88 cm in men and women; (2) blood pressure ≥130/85 mmHg or specific drug treatment; (3) plasma triglycerides ≥150 mg/dl or specific drug treatment; (4) plasma high-density lipoprotein <40 mg/dl for men and <50 mg/dl for women or specific drug treatment; (5) prediabetes (i.e. fasting glucose levels 100–125 mg/dl or 2-h post-load glucose levels 140–199 mg/dl or glycated hemoglobin 5.7–6.4%); (6) homeostasis model assessment-insulin resistance (HOMA-IR) score ≥2.5; (7) plasma high-sensitivity C-reactive protein level >2 mg/L [17]. Patients not fulfilling any of the above criteria with evidence of hepatic steatosis were classified as 'NAFLD but not MAFLD' and were excluded from the analysis. This study conforms to the ethical principles for medical research as specified by the Declaration of Helsinki and it was approved by the Ethics Committee of the Faculty of Medicine at Marmara University. Owing to the retrospective nature of the study, the need for informed consent was waived.

### Calculation of Fibrosis-4 index and non-alcoholic fatty liver disease fibrosis score

To calculate the non-invasive scores we used the following universally accepted formulas. Specifically, we calculated FIB-4 as [18]: age (years) × aspartate transaminase (AST) (U/L)/platelets (10$^9$/L) × √alanine transaminase (ALT) (U/L), and NFS [19] as: −1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m$^2$) + 1.13 × impaired fasting glucose/diabetes (yes = 1, no = 0) + 0.99 × AST/ALT − 0.013 × platelet (×10$^9$/L) − 0.66 × albumin (g/dl).

**Table 1.** Classification of body mass index according to the WHO's criteria

| Classification | BMI (kg/m$^2$) |
|---|---|
| Lean | <25 |
| Overweight | 25 ≤ BMI < 30 |
| Obese (obesity class 1) | 30 ≤ BMI < 35 |
| Severely obese (obesity class 2) | 35 ≤ BMI < 40 |
| Morbidly obese (obesity class 2) | ≥40 |

### Liver histology

Liver biopsy was performed in those patients undergoing ultrasonographic examination who had elevated hepatic enzymes, clinically or radiologically diagnosed organomegaly, or who showed evidence of hepatic steatosis on liver ultrasound. The specimens were evaluated by a single, independent pathologist who had not been informed of the non-invasive score results. The pathologist followed NASH Clinical Research Network classification [20] and the steatosis, activity, the fibrosis score and fatty liver inhibition of progression algorithm [21]. In liver histology, absence of fibrosis (F) is defined as $F = 0$, presence of zone 3 perisinusoidal fibrosis only as $F = 1$, portal or periportal fibrosis in addition to zone 3 fibrosis as $F = 2$, bridging fibrosis in addition to previously mentioned fibrosis stages as $F = 3$ and cirrhosis as $F = 4$. A fibrosis stage of $F \geq 2$ is classified as significant fibrosis and $F \geq 3$ as advanced fibrosis [20].

### Statistical analysis

The categorical data were expressed as numbers and percentages, and compared using Pearson's chi-square test. The distribution of normality was evaluated with the Kolmogorov–Smirnov test. The skewed data were summarized as median (minimum–maximum) and examined with the Kruskal–Wallis test. The data were separately analyzed in all BMI categories. The optimal cut-off values for FIB-4 and NFS differentiating advanced fibrosis were calculated by finding the highest Youden's index (sensitivity + specificity − 1) using coordinate points of the receiver operator characteristic (ROC) curve. The diagnostic performance indicators [sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV)] were calculated according to the optimal cut-off values. All analyses were carried out using SPSS v.24 for Windows (IBM, Armonk, New York, USA). A two-tailed $P < 0.05$ was considered as statistically significant.

### Ethical approval

This study conforms to the ethical principles for medical research as specified by the Declaration of Helsinki and it was approved by the Ethics Committee of the Faculty of Medicine at Marmara University. Owing to the retrospective nature of the study, the need for informed consent was waived.

## Results

We identified a total of 569 patients and excluded nine lean NAFLD patients who did not fulfill the criteria of MAFLD. Thus, we included a total of 560 patients [296 men and 264 women, median age 48 (18–71) years] with biopsy-proven hepatic steatosis. **According FIB-4 367 (65.5%), 167 (29.8%) and 26 (4.6%) were classified as low, indeterminate and high risk for advanced fibrosis, respectively. A total of 322 (57.5%), 206 (36.8%) and 32 (5.7%) were estimated as low, indeterminate, and high risk according to NFS, respectively.** The general characteristics of the patients classified according to the BMI category are presented in Table 2, whereas histologic characteristics are shown in Table 3. The groups differed significantly in

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**Table 2.** General characteristics of the study population (*n* = 574)

| Characteristics | Lean (*n* = 28) | Overweight (*n* = 174) | Obese (*n* = 229) | Severely obese (*n* = 89) | Morbidly obese (*n* = 40) | Total (*n* = 569) | *P*-value |
|---|---|---|---|---|---|---|---|
| Age (years) | 45 (23–66) | 47 (18–70) | 48 (21–71) | 51 (18–68) | 47 (29–65) | 48 (18–71) | 0.136[a] |
| Sex (male/female) | 19 (67.9%) / 9 (32.1%) | 110 (63.2%) / 64 (36.8%) | 121 (52.8%) / 108 (47.2%) | 39 (43.8%) / 50 (56.2%) | 7 (17.5%) 33 (82.5%) | 296 (52.9%) / 264 (47.1%) | <0.001[b] |
| Diabetes mellitus type 2 (yes/no) | 12 (42.9%) / 16 (57.1%) | 55 (31.6%) / 119 (68.4%) | 89 (38.9%) / 140 (61.1%) | 46 (51.7%) / 43 (48.3%) | 23 (57.5%) / 17 (42.5%) | 225 (40.2%) / 335 (59.8%) | 0.004[a] |
| Hypertension (yes/no) | 6 (21.4%) / 22 (78.6%) | 50 (28.7%) / 124 (71.3%) | 76 (33.2%) / 153 (66.8%) | 38 (42.7%) / 51 (57.3%) | 20 (50%) / 20 (50%) | 203 (36.3%) / 357 (63.7%) | <0.001[a] |
| AST (U/L) | 39 (22–241) | 41 (12–148) | 43 (17–302) | 44 (11–166) | 31 (15–278) | 42 (11–302) | 0.023[b] |
| ALT (U/L) | 63 (26–343) | 68 (13–271) | 67 (12–323) | 63 (18–288) | 39 (12–227) | 66 (12–343) | 0.007[b] |
| Total cholesterol (mg/dl) | 227 (92–298) | 211 (74–417) | 211 (86–370) | 204 (79–419) | 199 (141–312) | 210 (74–419) | 0.718[b] |
| Triglycerides (mg/dl) | 197 (31–356) | 159 (38–1314) | 164 (37–1107) | 165 (39–448) | 175 (63–391) | 165 (31–1314) | 0.525[b] |
| HDL (mg/dl) | 42 (19–80) | 43 (18–74) | 45 (26–96) | 46 (28–91) | 44 (28–80) | 44 (18–96) | 0.284[b] |
| LDL (mg/dl) | 132 (35–186) | 136 (28–400) | 137 (15–400) | 131 (35–198) | 122 (65–233) | 133 (15–400) | 0.393[b] |
| Fasting blood glucose (mg/dl) | 97 (80–307) | 99 (70–270) | 101 (66–300) | 103 (77–269) | 105 (79–252) | 101 (66–307) | 0.156[b] |
| HOMA-IR | 4.1 (1.82–28.8) | 3.2 (0.6–21.8) | 4.1 (0.8–16.7) | 4.6 (0.4–17.9) | 4.5 (3.1–12.1) | 4.0 (0.4–28.8) | 0.004[b] |
| HbA1c (%) | 5.6 (4.8–8.7) | 5.7 (3.5–10.0) | 5.8 (4.0–11.1) | 6.0 (4.5–9.6) | 6.3 (4.5–10.2) | 5.8 (3.5–11.1) | 0.002[b] |

Data are presented as median (minimum–maximum) or counts and percentages. Significant *P* values are marked in bold.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; LDL, low-density lipoprotein.
[a]Chi-square test.
[b]Kruskal-Wallis test.

**Table 3.** Histological characteristics of the study population (*n* = 574)

| Characteristics | Lean (*n* = 37) | Overweight (*n* = 175) | Obese (*n* = 229) | Severely obese (*n* = 89) | Morbidly obese (*n* = 40) | Total (*n* = 569) | *P*-value |
|---|---|---|---|---|---|---|---|
| Steatosis | | | | | | | 0.204 |
| S1, n (%) | 9 (32.1) | 36 (20.7) | 58 (25.3) | 12 (13.5) | 14 (35) | 129 (23) | |
| S2, n (%) | 10 (35.7) | 69 (39.7) | 93 (40.6) | 41 (46.1) | 14 (35) | 227 (40.5) | |
| S3, n (%) | 9 (32.1) | 69 (39.7) | 78 (34.1) | 36 (40.4) | 12 (30) | 204 (36.4) | |
| Lobular inflammation | | | | | | | |
| 0, n (%) | 1 (3.6) | 12 (6.9) | 17 (7.4) | 4 (4.5) | 1 (2.5) | 35 (6.3) | 0.601 |
| 1, n (%) | 14 (50) | 64 (36.8) | 88 (38.4) | 30 (33.7) | 13 (32.5) | 209 (37.3) | |
| 2, n (%) | 11 (39.3) | 75 (43.1) | 96 (41.9) | 37 (41.6) | 22 (55) | 241 (43) | |
| 3, n (%) | 2 (7.1) | 23 (13.2) | 28 (12.2) | 18 (20.2) | 4 (10) | 75 (13.4) | |
| Ballooning | | | | | | | 0.615 |
| 0, n (%) | 1 (3.6) | 11 (6.3) | 14 (6.1) | 3 (3.4) | 1 (2.5) | 30 (5.4) | |
| 1, n (%) | 15 (53.6) | 85 (48.9) | 108 (47.2) | 33 (37.1) | 21 (52.5) | 262 (46.8) | |
| 2, n (%) | 12 (42.9) | 78 (44.5) | 107 (46.7) | 53 (59.6) | 18 (45) | 267 (47.7) | |
| Activity | | | | | | | 0.546 |
| A0, n (%) | 0 (0) | 5 (2.9) | 4 (1.7) | 1 (1.1) | 0 (0) | 10 (1.8) | |
| A1, n (%) | 2 (7.1) | 12 (6.9) | 21 (9.2) | 2 (2.2) | 1 (2.5) | 38 (6.8) | |
| A2, n (%) | 9 (32.1) | 36 (20.7) | 54 (23.6) | 21 (23.6) | 9 (22.5) | 129 (23) | |
| A3, n (%) | 8 (28.6) | 62 (35.6) | 69 (30.1) | 24 (27) | 15 (37.5) | 178 (31.8) | |
| A4, n (%) | 9 (32.1) | 59 (33.9) | 81 (35.4) | 41 (46.1) | 15 (37.5) | 205 (36.6) | |
| Fibrosis | | | | | | | **0.010** |
| F0, n (%) | 13 (46.4) | 62 (35.6) | 69 (30.1) | 12 (13.5) | 12 (30) | 168 (30) | |
| F1, n (%) | 8 (28.6) | 52 (29.9) | 76 (33.2) | 25 (28.1) | 11 (27.5) | 172 (30.7) | |
| F2, n (%) | 3 (10.7) | 32 (18.4) | 45 (19.7) | 22 (24.7) | 7 (17.5) | 109 (19.5) | |
| F3, n (%) | 3 (10.7) | 24 (13.8) | 31 (13.5) | 20 (22.5) | 8 (20) | 86 (15.4) | |
| F4, n (%) | 1 (3.6) | 4 (2.3) | 8 (3.5) | 10 (11.2) | 2 (5) | 25 (4.5) | |
| Significant fibrosis ($F \geq 2$), n (%) | 7 (25) | 60 (34.5) | 84 (36.7) | 52 (58.4) | 17 (42.5) | 220 (39.3) | **0.001** |
| Advanced fibrosis ($F \geq 3$), n (%) | 4 (14.3) | 28 (16.1) | 39 (17) | 30 (33.7) | 10 (25) | 111 (19.8) | **0.005** |

Data are presented as counts and percentages and compared with the chi-square test. Significant *P* values are marked in bold.

terms of sex, comorbidities (diabetes mellitus, hypertension), AST, ALT, glycated hemoglobin, HOMA-IR, and stage of fibrosis.

According to the ROC curve analysis, FIB-4 failed to discriminate patients with advanced fibrosis in both lean and morbidly obese individuals ($P = 0.325$ and $P = 0.512$, respectively). Additionally, ROC curve analysis revealed a failed discrimination performance for NFS in these two BMI categories ($P = 0.511$ and $P = 0.116$, respectively). The results of ROC curve analysis identified the optimal cut-off values for FIB-4 and NFS in the identification of advanced fibrosis (Table 4 and Figs. 1 and 2). Accordingly, FIB-4 in overweight individuals showed the best diagnostic performance in our study sample (area under the ROC curve: 0.829, 95% confidence interval: 0.738–0.919). Overall, all the optimal cut-off values in both FIB-4 and NFS indicated a higher NPV and a relatively lower PPV.

## Discussion

In this study, we examined the feasibility and diagnostic accuracy of FIB-4 and NFS for the screening of advanced fibrosis in a sample of patients with biopsy-proven MAFLD categorized according to their BMI. Our results specifically highlighted their poor discrimination capability in lean and morbidly obese patients.

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**Table 4.** The optimal cut-offs of fibrosis-4 index and non-alcoholic fatty liver disease fibrosis score according to BMI categories

| | Optimal cut-off | AUROC | Confidence interval | Sensitivity (%) | Specificity (%) | Positive predictive value | Negative predictive value |
|---|---|---|---|---|---|---|---|
| FIB-4 | | | | | | | |
| Overweight | 1.21 | 0.829 | 0.738–0.919 | 86 | 76 | 0.407 | 0.965 |
| Obese | 1.28 | 0.794 | 0.726–0.861 | 85 | 67 | 0.344 | 0.955 |
| Severe obese | 1.26 | 0.759 | 0.653–0.866 | 77 | 71 | 0.575 | 0.857 |
| Total | 1.22 | 0.775 | 0.728–0.822 | 76 | 70 | 0.381 | 0.922 |
| NFS | | | | | | | |
| Overweight | −1.51 | 0.785 | 0.685–0.885 | 71 | 80 | 0.400 | 0.935 |
| Obese | −1.39 | 0.792 | 0.723–0.861 | 85 | 64 | 0.324 | 0.953 |
| Severe obese | −0.39 | 0.746 | 0.633–0.859 | 63 | 80 | 0.613 | 0.810 |
| Total | −1.48 | 0.761 | 0.712–0.811 | 79 | 65 | 0.353 | 0.925 |

AUROC, area under receiver operating curve; FIB-4, Fibrosis-4 index; NFS, non-alcoholic fatty liver disease fibrosis score.

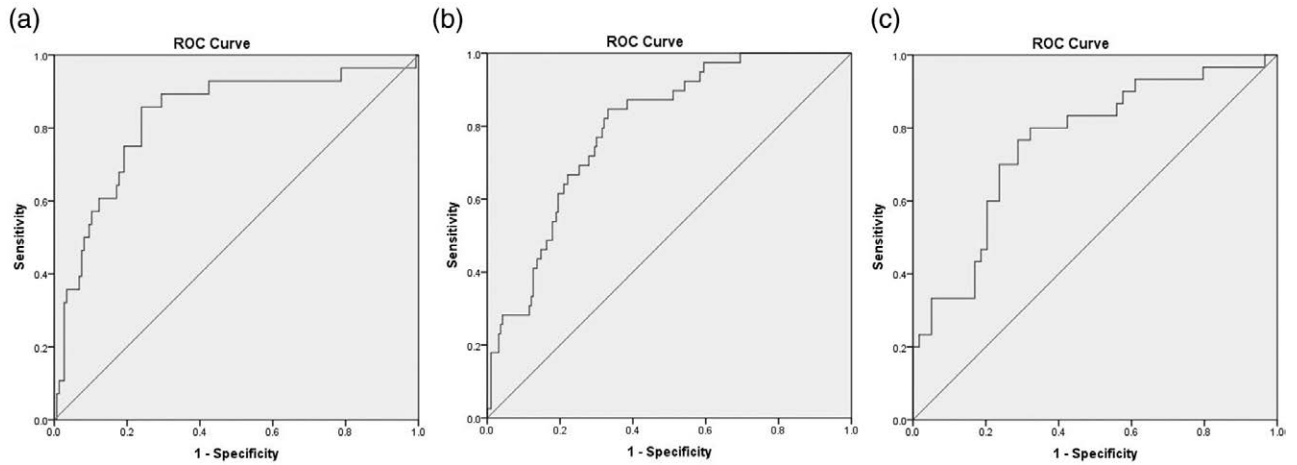



**Fig. 1.** Receiver operating characteristic curve analysis of the fibrosis-4 index in identifying advanced fibrosis in our sample of patients with biopsy-proven metabolic fatty liver disease (*n* = 537). (a) Analysis of overweight patients. (b) Analysis of obese patients. (c) Analysis of severely obese patients.

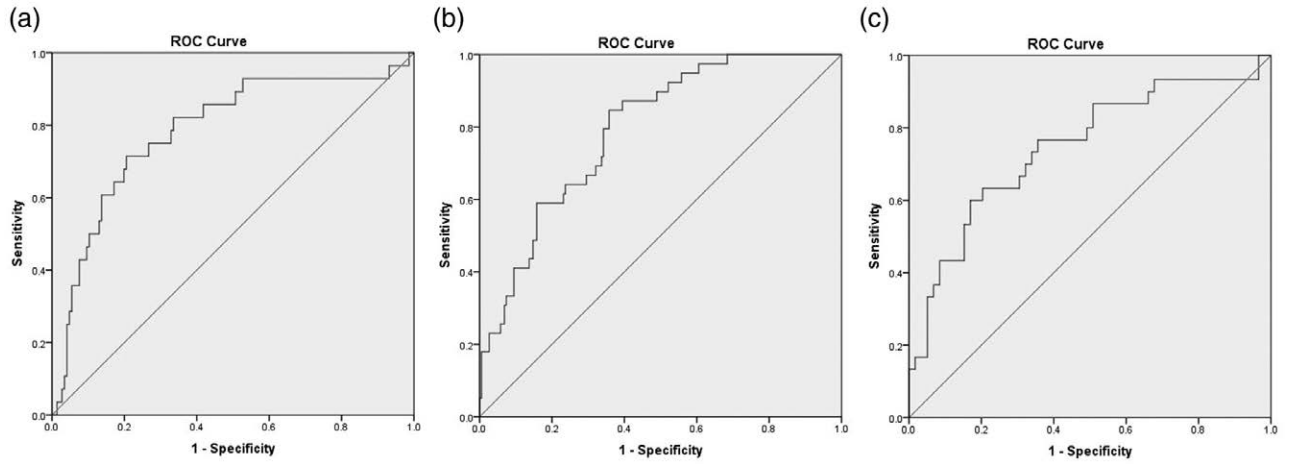



**Fig. 2.** Receiver operating characteristic curve analysis of the non-alcoholic fatty liver disease fibrosis score in identifying advanced fibrosis in our sample of patients with biopsy-proven metabolic fatty liver disease (*n* = 537). (a) Analysis of overweight patients. (b) Analysis of obese patients. (c) Analysis of severely obese patients.

Patients with advanced fibrosis are at increased risk of experiencing liver-related and liver-unrelated complications [6,21]. Moreover, as recommended in the recent international consensus for the definition of MAFLD, disease severity is described by activity and fibrosis stage, which makes these factors the major focus of therapeutic interventions [20]. Therefore, from a clinical perspective, the timely detection and monitoring of advanced fibrosis are paramount. Obesity is an important factor in development of severe liver histology in different clinical settings [22,23]. On the other hand, there is increasing evidence suggesting that both obese and non-obese patients benefit from the timely provision and maintenance of a weight loss regime to facilitate hepatic steatosis reduction and the extent/severity of liver fibrosis, contributing to reducing overall morbidity and mortality [24,25].

Consistent with previously reported studies, non-invasive scores were clinically useful in ruling out advanced fibrosis rather than detection of it [8–11]. This confirms the clinical inadequacy of non-invasive scores in the detection

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of advanced fibrosis. In this scenario, the use of transient elastography has increasingly gained clinical relevance by providing improved diagnostic accuracy. However, the application of this imaging technique in routine practice remains limited due to its restricted availability in clinical practice [26]. As recommended previously, FIB-4 and NFS should be used in first-line triaging of advanced fibrosis using a stepwise approach in combination with more accurate diagnostic modalities [27,28].

Recent clinical investigations have been focusing on the significance of FIB-4 and NFS thresholds to predict advanced fibrosis in various clinical settings. A modification of these thresholds remains contentious [29,30]. Our research, unlike previously reported studies, detected an optimal cut-off at (unexpectedly) lower values both in FIB-4 and NFS, corresponding approximately to the cut-off reported as previously indicating low risk of advanced fibrosis [18,19]. The questions as to whether the cut-offs for these tests should change in light of different clinical settings remains unanswered.

Owing to their high NPVs, both FIB-4 and NFS are mainly clinically useful in ruling out advanced fibrosis. For the sake of decreasing potential uncertainty related to grey zone created by dichotomous cut-offs, recently it is recommended that patients with a FIB-4 cut-off >1.3 should be referred to secondary care, whereas the other patients should be followed-up under primary care settings [31,32]. In the light of this knowledge, we also chose to use monochotomous cut-offs for FIB-4 and NFS.

The principal limitation of this study is the differing advanced fibrosis rates among the BMI categories, which may have an impact on diagnostic performance and interpretation. Conversely, prevalence of advanced fibrosis according to the BMI categories in our study population was roughly comparable with the published literature [12,30]. **Moreover, we conducted our analysis with a population of Caucasian ethnicity. For Asians, lower cut-offs were defined for obesity** [33]**. Therefore, our results may not be applied to Asians and need to be validated in different populations.** These limitations notwithstanding, the strength of this study lies in its prospective data collection and large sample size. In addition, our research was the first study to evaluate and compare the diagnostic performance of non-invasive scores in all BMI categories.

In summary, we demonstrated for the first time that FIB-4 and NFS are characterized by a poor diagnostic performance in the discrimination of advanced fibrosis in lean and morbidly obese patients with MAFLD, but not in patients who were in the overweight, obese, and severely obese categories. These data highlight the urgent need for non-invasive screening tools for advanced fibrosis specifically in lean and morbidly obese patients.

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### *Conflicts of interest*

There are no conflicts of interest.

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