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Performance of simple fibrosis scores in non-obese patients with nonalcoholic fatty liver disease

Running title: Fibrosis scores in non-obese NAFLD

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Introduction

Because only a minority of patients with nonalcoholic fatty liver disease (NAFLD) have advanced fibrosis and would eventually develop liver-related complications, current guidelines recommend initial assessment with non-invasive tests of fibrosis.¹⁻³ Most previous studies focused on overweight and obese patients. Despite a strong association between obesity and NAFLD, 3-30% of people with relatively normal body mass index (BMI) may still have NAFLD.^{4,5} Hence, this study aims to evaluate the performance of the common non-invasive tests in non-obese (BMI <25 kg/m²) and obese (BMI ≥25 kg/m²) NAFLD patients.

Methods

We prospectively recruited consecutive adult patients with biopsy-proven NAFLD at three tertiary referral centers in France, Malaysia and Hong Kong. Indications for liver biopsy included elevated liver tests and high metabolic burden suspicious of significant NAFLD. Patients with other chronic liver diseases, excessive alcohol consumption (>30 g per day in men and >20 g per day in women), secondary causes of fatty liver, and active malignancies were excluded. Liver histology was scored by experienced pathologists using the Nonalcoholic Steatohepatitis Clinical Research Network system.⁶ Non-invasive tests of fibrosis were performed within 1 week prior to liver biopsy. All patients underwent liver stiffness measurement (LSM) by both M and XL probes of vibration-controlled transient elastography. We used M probe results for patients with BMI <30 kg/m² and XL probe results for those with BMI ≥30 kg/m² or who had failed M probe examination.⁷ Receiver operating characteristic (ROC) curves were used to determine the accuracy of each non-invasive test in identifying advanced fibrosis (F3-4) in patients with different BMI. To account for different distribution of fibrosis stages in patients with different BMI, we also calculated and compared the Obuchowski indices.

Results

We included 709 patients, of whom 81 (11.4%) had BMI <25 kg/m². As expected, non-obese patients had lower fasting plasma glucose and less severe liver histology (**Supplementary Table 1**). 19.8% of non-obese patients and 39.0% of obese patients had advanced fibrosis. The failure rates of LSM by M and XL probes were 13.3% and 3.0% in 706 patients; 580 (82.2%) and 626 (88.7%) patients had reliable LSM by the two probes, respectively.

In both non-obese and obese patients, the AUROC for advanced fibrosis was the largest for LSM, followed by Fibrosis-4 index, NAFLD fibrosis score, aspartate aminotransferase-to-platelet ratio index, BARD score and the aspartate aminotransferase-to-alanine aminotransferase ratio (**Table 1**). The area under ROC curves for all of the non-invasive tests was numerically higher in the non-obese group. However, while LSM consistently performed better in the non-obese group, there was no significant difference in the Obuchowski indices for the simple fibrosis scores. At cutoffs proposed by the published literature, the sensitivities and specificities of the non-invasive tests in non-obese patients were comparable to or higher than those in obese patients. Because of ethnic differences in body fat distribution and definition of normal BMI, we stratified the analysis by ethnicity and showed similar findings both in Caucasians and Asians (**Supplementary Table 2**). Finally, using cutoffs of 30 and 35 kg/m², we again demonstrated a better performance of LSM in patients with lower BMI but not for the simple fibrosis scores (**Supplementary Tables 3 and 4**).

Discussion

The majority of NAFLD patients included in previous studies of non-invasive tests of fibrosis were obese. With the global rise in NAFLD, these tests will inevitably be used increasingly in patients with different BMIs. We show that all non-invasive tests perform equally as well in non-obese compared with obese patients. The same cutoffs can be used with similar or higher sensitivities and specificities. Furthermore, the negative predictive value of every non-invasive test was higher in the non-obese cohort due to a lower prevalence of advanced fibrosis. This suggests that non-invasive tests are well suited for excluding advanced fibrosis in non-obese patients, and further tests are needed in case of abnormal results.

Our study has the strength of a large sample size and multicenter design. However, there are also a few limitations. Firstly, the patients were from academic centers and the prevalence of advanced fibrosis was high. We expect the negative predictive values of the non-invasive tests to be even higher in the community.⁸ Secondly, because of the cross-sectional design, further studies are needed to define the role of non-invasive tests as monitoring tools.

In conclusion, non-invasive tests of liver fibrosis perform well in non-obese NAFLD patients, and the published cutoffs can be applied in this population. These tests are well suited for initial assessment in the general population or primary care settings.

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Table 1. Performance of non-invasive tests of fibrosis in detecting F3-4 fibrosis in patients with BMI <25 and ≥25 kg/m²

| Non-invasive tests | Cutoffs | BMI <25 | | | | | | BMI ≥25 | | | | | | P |
|-----------------------------------|---------|---------------------|---------------------|-------|-------|------|------|---------------------|---------------------|-------|-------|------|------|-------|
| | | AUROC | OI | Se | Sp | PPV | NPV | AUROC | OI | Se | Sp | PPV | NPV | |
| Liver stiffness measurement (kPa) | 7.9 | 0.93 (0.87-0.98) | 0.94 (0.92-0.96) | 0.88 | 0.80 | 0.52 | 0.96 | 0.83 (0.80-0.87) | 0.91 (0.90-0.92) | 0.91 | 0.52 | 0.55 | 0.90 | 0.013 |
| | 9.6 | | | 0.69 | 0.92 | 0.69 | 0.92 | | | 0.81 | 0.69 | 0.62 | 0.85 | |
| NAFLD fibrosis score | -1.455 | 0.85 (0.73-0.96) | 0.86 (0.81-0.91) | 0.67 | 0.85 | 0.50 | 0.92 | 0.69 (0.64-0.73) | 0.87 (0.85-0.88) | 0.81 | 0.45 | 0.49 | 0.78 | 0.935 |
| | 0.676 | | | 0.083 | 0.98 | 0.50 | 0.82 | | | 0.22 | 0.93 | 0.66 | 0.64 | |
| APRI | 0.5 | 0.78 (0.63-0.94) | 0.89 (0.85-0.94) | 0.67 | 0.81 | 0.44 | 0.91 | 0.68 (0.64-0.73) | 0.86 (0.84-0.88) | 0.57 | 0.67 | 0.53 | 0.70 | 0.230 |
| | 1.5 | | | 0.083 | 0.96 | 0.33 | 0.82 | | | 0.081 | 0.981 | 0.74 | 0.62 | |
| FIB-4 | 1.30 | 0.86 (0.75-0.98) | 0.90 (0.86-0.94) | 0.75 | 0.77 | 0.43 | 0.93 | 0.73 (0.69-0.77) | 0.88 (0.86-0.89) | 0.73 | 0.64 | 0.58 | 0.78 | 0.359 |
| | 2.67 | | | 0.42 | -0.98 | 0.83 | 0.88 | | | 0.20 | 0.95 | 0.73 | 0.64 | |
| BARD score | 2 | 0.71 (0.56-0.86) | 0.83 (0.78-0.89) | 0.67 | 0.34 | 0.31 | 0.90 | 0.61 (0.56-0.66) | 0.81 (0.80-0.83) | 0.74 | 0.57 | 0.72 | 0.46 | 0.513 |
| AST-to-ALT ratio | 0.8 | 0.69 (0.55-0.83) | 0.84 (0.78-0.90) | 0.67 | 0.64 | 0.29 | 0.90 | 0.60 (0.55-0.65) | 0.82 (0.80-0.84) | 0.44 | 0.68 | 0.49 | 0.65 | 0.417 |
| | 1.0 | | | 0.25 | 0.87 | 0.30 | 0.84 | | | 0.24 | 0.86 | 0.52 | 0.63 | |

P values represent comparisons between the Obuchowski indices of non-invasive tests in patients with BMI <25 and ≥25 kg/m².

Numbers in brackets represent the 95% confidence intervals of AUROC.

ALT, alanine aminotransferase; APRI, AST-to-platelet ratio index; AST, aspartate aminotransferase; AUROC, area under the receiver-operating characteristics curve; BMI, body mass index; FIB-4, fibrosis-4 index; NAFLD, nonalcoholic fatty liver disease; NPV, negative predictive value; OI, Obuchowski index; PPV, positive predictive value; Sn, sensitivity; Sp, specificity

Performance of simple fibrosis scores in non-obese patients with nonalcoholic fatty liver disease

Supplementary materials

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Supplementary Table 1. Patient characteristics of NAFLD patients with BMI <25 and ≥25 kg/m²

| Characteristics | All | BMI <25 | BMI ≥25 | P |
|--------------------------------------|------------------|------------------|-------------------|--------|
| N | 709 | 81 | 628 | |
| Age (years) | 54±12 | 54±13 | 54±11 | 0.97 |
| Male sex, n (%) | 401 (56.6) | 41 (50.6) | 360 (57.3) | 0.25 |
| Ethnicity | | | | 0.008 |
| Caucasian | 282 | 26 | 256 | |
| Chinese | 338 | 52 | 286 | |
| Malay | 56 | 2 | 54 | |
| Indian | 30 | 1 | 29 | |
| BMI (kg/m ²) | 30.5±5.3 | 23.1±1.5 | 31.5±4.8 | <0.001 |
| Waist circumference (cm) | 102±14 | 85±6.5 | 104±13 | <0.001 |
| ALT (U/l) | 54.0 (35.0-85.5) | 39.5 (29.8-75.5) | 50.0 (33.0-85.0) | 0.43 |
| AST (U/l) | 38.0 (28.0-54.0) | 26.0 (19.8-35) | 35.0 (24.0-52.0) | 0.03 |
| GGT (U/l) | 66.0 (41.0-66.0) | 41.0 (30.5-72.7) | 60.0 (34.0-102.0) | 0.28 |
| Fasting glucose (mmol/l) | 6.9±2.5 | 6.3±2.0 | 7.0±2.5 | 0.008 |
| Hemoglobin A _{1c} (%) | 7.0±1.5 | 6.7±1.2 | 7.1±1.5 | 0.52 |
| Total cholesterol (mmol/l) | 4.8 ±1.2 | 4.8±1.1 | 4.8±1.2 | 0.58 |
| HDL-cholesterol (mmol/l) | 1.23±0.42 | 1.3±0.44 | 1.2±0.41 | 0.04 |
| LDL-cholesterol (mmol/l) | 2.6 ±1.6 | 2.6±0.9 | 2.6±0.8 | 0.56 |
| Triglycerides (mmol/l) | 1.5 (1.1-2.2) | 1.5 (1.1-2.2) | 1.5 (1.2-2.2) | 0.46 |
| Platelet count (x10 ⁹ /l) | 227.9±67.2 | 231.6±59.6 | 227.4±68.2 | 0.56 |

| | | | | |
|------------------------------------|----------------|-------------------|-------------------|--------|
| | | | | |
| Liver biopsy | | | | |
| Length of biopsy sample (cm) | 2.1±0.9 | 2.4±0.8 | 2.1±0.9 | 0.01 |
| Number of portal tracts | 9.0 (6.0-14.3) | 9.0 (7.0-14.8) | 9.0 (6.0-14.0) | 0.34 |
| Steatosis grade | 2 (1-3) | 2 (1-3) | 2 (1-3) | 0.23 |
| Lobular inflammation | 1 (1-2) | 1 (1-2) | 1 (1-2) | 0.21 |
| Ballooning | 1 (0-1) | 1 (0-1) | 1(1-1) | <0.001 |
| Fibrosis stage | 2 (1-3) | 1 (0-2) | 2 (1-3) | <0.001 |
| F0, n (%) | 105 (14.9) | 27 (33.3) | 78 (12.5) | |
| F1, n (%) | 210 (29.7) | 27 (33.3) | 183 (28.3) | |
| F2, n (%) | 130 (18.4) | 11 (13.6) | 119 (19.0) | |
| F3, n (%) | 157 (22.2) | 5 (6.2) | 152 (24.3) | |
| F4, n (%) | 104 (14.7) | 11 (13.6) | 93 (14.9) | |
| Liver stiffness measurement (kPa) | 9.3 (6.7-13.3) | 6.3 (4.6-8.6) | 7.2 (5.4-10.5) | <0.001 |
| NAFLD fibrosis score | -1.1 (1.6) | -2.3 (1.6) | 0.9 (1.5) | 0.70 |
| AST-to-platelet ratio index (APRI) | 0.4 (0.3-0.7) | 0.3 (0.2-0.5) | 0.4 (0.3-0.7) | 0.007 |
| Fibrosis-4 index (FIB-4) | 1.3 (0.9-1.9) | 1.0 (0.7-1.7) | 1.3 (0.9-1.9) | 0.009 |
| BARD score | 2.0 (1.3) | 1.3 (1.1) | 2.0 (1.3) | <0.001 |
| AST-to-ALT ratio | 0.77 (0.33) | 0.77(0.48) | 0.80 (0.30) | 0.02 |

Continuous variables are reported as mean (standard deviation) or median (interquartile range) and compared using unpaired *t* test or Mann Whitney U test as appropriate.

ALT, alanine aminotransferase; APRI, AST-to-platelet ratio index; AST, aspartate aminotransferase; BMI, body mass index; FIB-4, fibrosis-4 index; GGT, gamma-glutamyl transpeptidase; HDL, high density lipoprotein; LDL, low density lipoprotein; NAFLD, nonalcoholic fatty liver disease

Supplementary Table 2. AUROC of non-invasive tests to detect F3-4 fibrosis in NAFLD patients stratified by race and BMI

| Non-invasive tests | Caucasian | | Asian | |
|-----------------------------------|------------------|------------------|------------------|------------------|
| | BM<25 | BMI≥25 | BM<25 | BMI≥25 |
| Liver stiffness measurement (kPa) | 0.97 (0.90-1.0) | 0.78 (0.72-0.84) | 0.91 (0.81-1.0) | 0.86 (0.81-0.90) |
| NAFLD fibrosis score | 0.89 (0.76-1.0) | 0.67 (0.59-0.74) | 0.77 (0.55-1.0) | 0.70 (0.63-0.76) |
| APRI | 0.75 (0.56-0.95) | 0.69 (0.61-0.76) | 0.78 (0.54-1.0) | 0.68 (0.61-0.74) |
| FIB-4 | 0.86 (0.68-1.0) | 0.72 (0.65-0.79) | 0.90 (0.78-1.0) | 0.73 (0.67-0.80) |
| BARD score | 0.75 (0.56-0.95) | 0.65 (0.57-0.72) | 0.69 (0.43-0.94) | 0.56 (0.49-0.63) |
| AST-to-ALT ratio | 0.64 (0.40-0.88) | 0.66 (0.59-0.73) | 0.75 (0.60-0.90) | 0.54 (0.47-0.61) |

ALT, alanine aminotransferase; APRI, AST-to-platelet ratio index; AST, aspartate aminotransferase; AUROC, area under the receiver-operating characteristics curve; BMI, body mass index; FIB-4, fibrosis-4 index; NAFLD, nonalcoholic fatty liver disease

Supplementary table 3. Performance of non-invasive tests of fibrosis in detecting F3-4 fibrosis in patients with BMI <30 and ≥30 kg/m²

| Non-invasive tests | Cutoffs | BMI <30 | | | | | | BMI ≥30 | | | | | | P |
|-----------------------------------|---------|---------------------|---------------------|------|------|------|------|---------------------|---------------------|------|------|------|------|-------|
| | | AUROC | OI | Se | Sp | PPV | NPV | AUROC | OI | Se | Sp | PPV | NPV | |
| Liver stiffness measurement (kPa) | 7.9 | 0.88 (0.85-0.92) | 0.93 (0.92-0.95) | 0.52 | 0.60 | 0.39 | 0.72 | 0.80 (0.75-0.85) | 0.90 (0.89-0.92) | 0.79 | 0.67 | 0.62 | 0.82 | 0.008 |
| | 9.6 | | | 0.78 | 0.85 | 0.73 | 0.88 | | | 0.58 | 0.81 | 0.67 | 0.74 | |
| NAFLD fibrosis score | -1.455 | 0.75 (0.69-0.80) | 0.87 (0.85-0.89) | 0.72 | 0.65 | 0.52 | 0.82 | 0.68 (0.62-0.74) | 0.86 (0.84-0.89) | 0.87 | 0.34 | 0.48 | 0.78 | 0.561 |
| | 0.676 | | | 0.11 | 0.98 | 0.71 | 0.68 | | | 0.30 | 0.88 | 0.65 | 0.64 | |
| APRI | 0.5 | 0.73 (0.67-0.80) | 0.87 (0.85-0.90) | 0.59 | 0.72 | 0.52 | 0.77 | 0.66 (0.60-0.72) | 0.86 (0.84-0.88) | 0.56 | 0.67 | 0.54 | 0.68 | 0.473 |
| | 1.5 | | | 0.13 | 0.98 | 0.81 | 0.69 | | | 0.04 | 0.97 | 0.50 | 0.59 | |
| FIB-4 | 1.30 | 0.78 (0.73-0.83) | 0.89 (0.87-0.91) | 0.77 | 0.67 | 0.54 | 0.85 | 0.71 (0.65-0.77) | 0.88 (0.86-0.90) | 0.71 | 0.76 | 0.59 | 0.65 | 0.293 |
| | 2.67 | | | 0.23 | 0.97 | 0.82 | 0.71 | | | 0.19 | 0.94 | 0.68 | 0.62 | |
| BARD score | 2 | 0.60 (0.53-0.67) | 0.80 (0.78-0.82) | 0.52 | 0.60 | 0.39 | 0.72 | 0.63 (0.57-0.70) | 0.82 (0.80-0.84) | 0.91 | 0.32 | 0.48 | 0.84 | 0.233 |
| AST-to-ALT ratio | 0.8 | 0.59 (0.52-0.66) | 0.81 (0.78-0.83) | 0.40 | 0.70 | 0.40 | 0.70 | 0.63 (0.56-0.69) | 0.83 (0.80-0.85) | 0.50 | 0.64 | 0.49 | 0.65 | 0.272 |
| | 1.0 | | | 0.19 | 0.87 | 0.43 | 0.68 | | | 0.28 | 0.84 | 0.55 | 0.63 | |

P values represent comparisons between the Obuchowski indices of non-invasive tests in patients with BMI <30 and ≥30 kg/m². Numbers in brackets represent the 95% confidence intervals of AUROC.

ALT, alanine aminotransferase; APRI, AST-to-platelet ratio index; AST, aspartate aminotransferase; AUROC, area under the receiver-operating characteristics curve; BMI, body mass index; FIB-4, fibrosis-4 index; NAFLD, nonalcoholic fatty liver disease; NPV, negative predictive value; OI, Obuchowski index; PPV, positive predictive value; Sn, sensitivity; Sp, specificity

Supplementary table 4: Performance of non-invasive tests of fibrosis in detecting F3-4 fibrosis in patients with BMI <35 and ≥35

kg/m²

| Non-invasive tests | Cutoffs | BMI <35 | | | | | | BMI ≥35 | | | | | | P |
|-----------------------------------|---------|---------------------|---------------------|------|------|------|------|---------------------|---------------------|------|------|------|------|-------|
| | | AUROC | OI | Se | Sp | PPV | NPV | AUROC | OI | Se | Sp | PPV | NPV | |
| Liver stiffness measurement (kPa) | 7.9 | 0.85 (0.81-0.88) | 0.92 (0.91-0.93) | 0.75 | 0.81 | 0.68 | 0.85 | 0.72 (0.62-0.82) | 0.88 (0.85-0.91) | 0.73 | 0.51 | 0.52 | 0.73 | 0.009 |
| | 9.6 | | | 0.56 | 0.91 | 0.77 | 0.79 | | | 0.57 | 0.71 | 0.58 | 0.70 | |
| NAFLD fibrosis score | -1.455 | 0.71 (0.69-0.78) | 0.87 (0.85-0.89) | 0.78 | 0.58 | 0.52 | 0.82 | 0.63 (0.52-0.73) | 0.87 (0.84-0.91) | 0.88 | 0.20 | 0.44 | 0.70 | 0.756 |
| | 0.676 | | | 0.17 | 0.96 | 0.69 | 0.66 | | | 0.34 | 0.84 | 0.61 | 0.64 | |
| APRI | 0.5 | 0.73 (0.66-0.76) | 0.87 (0.85-0.89) | 0.60 | 0.70 | 0.53 | 0.75 | 0.63 (0.53-0.74) | 0.87 (0.84-0.90) | 0.49 | 0.67 | 0.52 | 0.64 | 0.923 |
| | 1.5 | | | 0.11 | 0.98 | 0.75 | 0.66 | | | 0.00 | 0.97 | 0.00 | 0.57 | |
| FIB-4 | 1.30 | 0.76 (0.71-0.80) | 0.88 (0.87-0.90) | 0.74 | 0.66 | 0.56 | 0.82 | 0.69 (0.60-0.79) | 0.89 (0.87-0.92) | 0.73 | 0.65 | 0.61 | 0.76 | 0.553 |
| | 2.67 | | | 0.25 | 0.96 | 0.76 | 0.69 | | | 0.08 | 0.96 | 0.57 | 0.59 | |
| BARD score | 2 | 0.63 (0.57-0.68) | 0.81 (0.79-0.83) | 0.70 | 0.51 | 0.44 | 0.75 | 0.61 (0.51-0.72) | 0.83 (0.80-0.86) | 0.88 | 0.27 | 0.47 | 0.75 | 0.332 |
| AST-to-ALT ratio | 0.8 | 0.60 (0.55-0.66) | 0.81 (0.79-0.83) | 0.43 | 0.69 | 0.44 | 0.68 | 0.65 (0.55-0.75) | 0.85 (0.81-0.88) | 0.53 | 0.60 | 0.49 | 0.64 | 0.090 |
| | 1.0 | | | 0.24 | 0.86 | 0.49 | 0.67 | | | 0.24 | 0.84 | 0.52 | 0.60 | |

P values represent comparisons between the Obuchowski indices of non-invasive tests in patients with BMI <35 and ≥35 kg/m².

Numbers in brackets represent the 95% confidence intervals of AUROC.

ALT, alanine aminotransferase; APRI, AST-to-platelet ratio index; AST, aspartate aminotransferase; AUROC, area under the receiver-operating characteristics curve; BMI, body mass index; FIB-4, fibrosis-4 index; NAFLD, nonalcoholic fatty liver disease; NPV, negative predictive value; OI, Obuchowski index; PPV, positive predictive value; Sn, sensitivity; Sp, specificity