Diagnostic Performance of Non-Invasive Tests in Assessing Liver Fibrosis Among Type 2 Diabetes Mellitus

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ABSTRACT

Background: *Noninvasive tools for assessing liver fibrosis are essential, especially in patients with Type 2 Diabetes Mellitus (T2DM) who are at high risk of developing metabolic dysfunction-associated fatty liver disease (MAFLD). This study aimed to evaluate the correlation between the diagnostic accuracy of the Fibrosis-4 Index (FIB-4), aminotransferase-to-platelet ratio index (APRI), and NAFLD fibrosis score (NFS) and the diagnostic accuracy of FibroScan® in Indonesian patients with T2DM.* ***Methods:*** *This cross-sectional study enrolled 80 outpatients with T2DM. Liver fibrosis was evaluated using FibroScan®. FIB-4, APRI, and NFS were calculated using routine clinical and laboratory parameters. Correlations between noninvasive scores and liver stiffness measurement (LSM) were analyzed. Receiver operating characteristic (ROC) curve analysis was used to assess the diagnostic performance for significant fibrosis (≥F2) and cirrhosis (F3-F4).* ***Results:*** *MAFLD was present in 67.5% of subjects; significant fibrosis and cirrhosis were found in 25% and 7.5% of subjects, respectively. FIB-4 and NFS showed significant correlations with LSM ($\rho = 0.291$ and 0.296; $p < 0.01$), whereas APRI did not. FIB-4, APRI, and NFS demonstrated fair to good diagnostic performance for significant fibrosis (area under the curve (AUC) 0.693, 0.685, 0.693) and excellent performance for cirrhosis (AUC 0.825, 0.860, 0.870). Female sex and HOMA-IR were independent predictors of significant fibrosis; AST and platelet count were predictive of cirrhosis.* ***Conclusion:*** *FIB-4, APRI, and NFS are effective and affordable screening tools for initial fibrosis in patients with T2DM, particularly in low-resource settings. The combination of these measures may enhance the detection of at-risk individuals for referral and further management.*

Keywords: *Type 2 diabetes mellitus, fibrosis, non-alcoholic fatty liver disease, liver cirrhosis, diagnostic accuracy.*

INTRODUCTION

Metabolic dysfunction-associated fatty liver disease (MAFLD) has emerged as the leading cause of chronic liver disease worldwide, with a rapidly increasing prevalence that currently affects approximately 32% of the global population (1, 2). The region of Southeast Asia has the highest rate of MAFLD in Asia, whereas Indonesia has the highest MAFLD incidence rate, which exceeds 50%.[3,4] The condition known as MAFLD leads to liver complications and elevated cardiovascular disease risk, which remains the main cause of death for those affected.[3,5] Type 2 diabetes mellitus (T2DM) is a significant metabolic condition affecting both the development and progression of MAFLD.[1] The risk of developing severe liver fibrosis and cirrhosis remains high among patients with T2DM.[6]

Clinical symptoms associated with liver involvement in MAFLD may often be underrecognized because of overlapping medical signs, and standard liver screenings are frequently not included in diabetic treatment protocols, particularly in under-resourced healthcare settings.[1,4] The timely diagnosis of liver fibrosis is crucial for managing patient outcomes and preventing serious complications, including hepatocellular carcinoma and portal hypertension.[5,7]

Although liver biopsy is the gold standard procedure for diagnosing fibrosis, its invasive nature, cost, and associated risks limit its practicality, especially in resource-limited regions.[8,9] FibroScan® has become a commonly accepted noninvasive liver stiffness assessment tool through its application in transient elastography.[6,10-12] However, access to FibroScan® devices in many parts of resource-limited regions, including Indonesia, is limited because of their high cost, which affects widespread screening efforts.[3,13]

In response to these limitations, simple, serology-based noninvasive scoring systems, such as the Fibrosis-4 Index (FIB-4), aspartate aminotransferase to platelet ratio index (APRI), and NAFLD fibrosis score (NFS), have been developed. The scoring systems rely on standard clinical and laboratory values, which enable their application at the primary and secondary healthcare service levels.[1, 6, 7] The diagnostic accuracy of these scoring systems has been tested across different populations;[1] however, there is limited research validating their performance specifically in Indonesian patients with T2DM, a population with distinct genetic, metabolic, and epidemiological characteristics compared to other cohorts. This study aimed to evaluate the correlation between the diagnostic performance of FIB-4, APRI, and NFS and FibroScan® liver stiffness measurements (LSM) in Indonesian patients with T2DM, thereby addressing a critical gap in evidence for cost-effective, scalable fibrosis screening in resource-limited healthcare environments. By establishing the diagnostic utility of these noninvasive scores in this high-risk population, our findings aim to support early intervention practices and guide clinical practice development that can be applied in low- and middle-income nations.

METHODS

Study Design and Participants

The research was a cross-sectional observational analysis conducted at the outpatient clinic of Dr. Soetomo General Hospital in Surabaya, Indonesia, between January 2024 to September 2024. The study included all adult patients who received a T2DM diagnosis according to the American Diabetes Association standards. The study included patients who were at least 18 years old, had T2DM for more than 1 year, and were willing to undergo FibroScan® liver stiffness measurement. The study excluded patients who consumed more than 20 grams of alcohol daily for women and 30 grams for men, patients with known chronic viral hepatitis B or C and other chronic liver diseases, such as autoimmune hepatitis and hemochromatosis, patients with severe renal impairment (estimated glomerular filtration rate of <30 mL/min/1.73 m²) and active malignancy and pregnancy, and patients with missing clinical or laboratory data. The Institutional Ethical Review Board of Dr. Soetomo General Hospital (approval number: 0723/KEPK/VII/2023) approved the study, and all participants provided written informed

consent. The research began with 106 patients with T2DM; however, 26 participants were excluded due to hepatitis B (n = 13) or hepatitis C (n = 10) infections, resulting in 80 participants through consecutive sampling.

Data Collection

Each participant underwent a standardized evaluation during a single clinical visit. The collected data included demographic information along with clinical parameters such as age, sex, body mass index (BMI), waist circumference, blood pressure, history of hypertension, dyslipidemia, and insulin resistance determined by the Homeostasis Model Assessment for Insulin Resistance (HOMA-IR). The laboratory tests included fasting plasma glucose and hemoglobin A1c (HbA1c), aspartate aminotransferase[14] and alanine aminotransferase (ALT), platelet count, total cholesterol and triglycerides, and high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C). All laboratory tests were performed on the same day as the FibroScan® examination to maintain consistency.

Liver Fibrosis Assessment Using FibroScan®

The FibroScan® 630 Expert device from Echosens in Paris, France, performed noninvasive liver stiffness assessments by trained and certified technicians.[10,11] Each participant was required to abstain from food for at least 3 hours before the examination. The FibroScan® device selected its appropriate probe (M or XL) automatically through the skin-to-liver capsule distance measurement. The measurement results were valid when the device obtained at least ten successful acquisitions with an interquartile range (IQR)/median ratio of 30% or less. The interpretation of LSM values used validated thresholds to determine significant fibrosis (≥F2) at ≥8.2 kPa and advanced fibrosis (F3) at ≥9.7 kPa and cirrhosis (F4) at ≥13.6 kPa. In addition, the hepatic steatosis condition will be determined by the controlled attenuation parameter (CAP) values (S1–S3).

Calculation of the Noninvasive Fibrosis Scores

Three noninvasive serological scoring systems were calculated for each patient to estimate liver fibrosis: FIB-4, APRI, and NFS. The FIB-4 Index was calculated using the following formula:[15]

$$FIB-4 = \frac{\left(Age\,[years] \times AST\,\left[\frac{U}{L}\right]\right)}{\left(Platelet\ count\,\left[\frac{10^9}{L}\right] \times \sqrt{ALT\,\left[\frac{U}{L}\right]}\right)}$$

The APRI was calculated as (14):

$$APRI = \left(\frac{AST\,\left[\frac{U}{L}\right]}{ULN\ AST\,\left[\frac{U}{L}\right]}\right) \times 100 \div Platelet\ count\,\left[\frac{10^9}{L}\right]$$

The APRI was calculated as:[14]

NFS was calculated using a combination of age, BMI, hyperglycemia status, AST/ALT ratio, platelet count, and serum albumin levels derived through the original published formula.[16] All scores were derived from laboratory values collected during the study visit.

Statistical Analysis

The statistical analysis was performed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). The assessment of continuous variables for normality included the presentation of normally distributed data as means ± standard deviation (SD) and non-normally distributed data as medians with interquartile ranges (IQR). The presentation of categorical variables included frequencies with percentages. The relationship between liver stiffness measurements and noninvasive fibrosis scores (FIB-4, APRI, NFS) was evaluated using Spearman's correlation coefficient. Receiver operating characteristic (ROC) curve analysis was used to evaluate the diagnostic accuracy of each fibrosis score for significant fibrosis and cirrhosis prediction, and the area under the curve (AUC) was calculated. The Youden index was used to determine the best cutoff value for each score. The results include sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). The study used univariate and multivariate logistic regression analysis to determine the independent factors that predicted significant fibrosis and cirrhosis. The statistical significance threshold was set at $p < 0.05$ for the two-tailed tests.

RESULTS

Baseline Characteristics of the Study Participants

This study included 80 patients with T2DM (the demographic, anthropometric, and clinical characteristics of participants at baseline are presented in **Table 1)**. The mean age was 54.8 ± 8.5 years, and females constituted 55.0% of the study population. The median BMI was 25.6 (IQR 5.7) kg/m², with the majority classified as overweight (23.8%) or obese (56.2%). Only 15.0% had a normal BMI and 5.0% were underweight.

The findings of the CAP measurement with FibroScan® were such that hepatic steatosis existed in 67.5% of patients, with a mean CAP value of 268.8±55.0 dB/m. Steatosis was graded as S1 in 7.5%, S2 in 27.5%, S3 in 32.5%, and S0 in 32.5% of patients. The median LSM was 5.6 kPa (IQR 3.0). Fibrosis staging showed that F0, F1, F2, F3, and F4 were present in 62.5%, 12.5%, 16.3%, 5.0%, and 3.8% of the patients, respectively. Significant fibrosis (LSM ≥ 8.2 kPa) and cirrhosis (LSM ≥ 13.6 kPa) in the T2DM group were present in 25.0% and 7.5% of patients, respectively. No participant had LSM ≥ 25 kPa, indicating the absence of clinically significant portal hypertension.

Table 1. Baseline Characteristics of Study Participants

Variable	Value
Age (years), mean ± SD	54.8 ± 8.5
Sex, n (%)	
Men	36 (45.0%)
Female	44 (55.0%)
BMI (kg/m²), median (IQR)	25.6 (5.7)
BMI category, n (%)	
Underweight (<18,5 kg/m²)	4 (5.0%)
Normal (18,5-22,9 kg/m²)	12 (15.0%)
Overweight (23-24,9 kg/m²)	19 (23.8%)
Obesities (>25 kg/m²)	45 (56.2%)
CAP, mean ± SD	268.8 ± 55.0
Steatosis Stage, n (%)	
S0 (CAP ≤237 dB/m)	26 (32.5%)
S1 (CAP 238-258 dB/m)	6 (7.5%)
S2 (CAP 259-289 dB/m)	22 (27.5%)
S3 (CAP ≥290 dB/m)	26 (32.5%)
LSM (kPa), median (IQR)	5.6 (3.0)
Fibrosis Stage, n (%)	
F0 (LSM ≤6,0 kPa)	50 (62.5%)
F1 (LSM 6,1-7,0 kPa)	10 (12.5%)
F2 (LSM 7,1-9.9 kPa)	13 (16.3%)
F3 (LSM 10,0-13,9 kPa)	4 (5.0%)
F4 (LSM ≥14,0 kPa)	5 (3.8%)
MAFLD Prevalence, n (%)	54 (67.5%)

The subgroup analysis showed that the prevalence of MAFLD was significantly higher in obese individuals than in their non-obese counterparts (84.4% vs. 45.7%, $p < 0.001$; **Supplementary Figure 1**). However, when subjects were grouped using a lower BMI threshold (non-overweight vs. overweight/obese), the difference in MAFLD prevalence did not reach statistical significance (50.0% vs. 71.8%, $p = 0.095$). Furthermore, within the MAFLD subgroup, the rates of significant fibrosis and cirrhosis were higher at 35.2% and 11.1%, respectively (**Supplementary Figure 2**).

Clinical and Laboratory Predictors of Hepatic Steatosis in Patients with T2DM

The research investigated the connection between hepatic steatosis, as determined by CAP values (S1–S3), and multiple clinical and laboratory indicators among patients with T2DM. The univariate analysis revealed that several metabolic parameters were significantly different between the participants with and without hepatic steatosis. The steatosis group had a significantly higher BMI than the non-steatosis group at 27.1 (6.4) and 23.9 (3.3), respectively ($p < 0.001$). Patients with steatosis had higher HbA1c values (8.6 [2.9] vs. 7.1 [2.7], $p = 0.019$) and HOMA-IR values (4.7 [5.5] vs. 2.0 [2.2], $p < 0.001$), indicating poorer glycemic control and higher insulin resistance.

In contrast, no substantial differences were observed in age (53.5 ± 7.7 vs. 57.5 ± 9.8 years, $p = 0.056$) or sex distribution (female: 55.5% vs. 53.8%, $p = 0.886$) between the groups. Lipid profile analysis showed that patients with hepatic steatosis had lower HDL levels (43.5 [11.3] vs. 49.5 [20.8], $p = 0.022$) with no significant differences in total cholesterol, triglycerides, and LDL levels. The liver enzymes AST and ALT, along with albumin, hemoglobin, white blood cell count, and platelet count, showed no statistical difference between the two groups (**Supplementary Table 1**).

To identify independent risk factors for hepatic steatosis, the study employed

multivariate logistic regression analysis. The analysis revealed two distinct risk factors, namely BMI increase (OR 1.205, 95% CI 1.034–1.405, $p = 0.017$) and elevated HOMA-IR (OR 1.325, 95% CI 1.014–1.730, $p = 0.039$). Neither HbA1c nor HDL levels remained significant in the adjusted model (**Supplementary Table 2**).

Clinical and Laboratory Predictors of Significant Liver Fibrosis in Patients with T2DM

Among the 80 patients with T2DM, significant liver fibrosis (defined as fibrosis stage ≥F2 on transient elastography) was detected in 25% of the subjects. Several clinical and laboratory factors were associated with significant fibrosis according to univariate analysis. Female sex was more prevalent in the fibrosis group compared with those without significant fibrosis (75.0% vs. 48.3%, $p = 0.038$). Participants with fibrosis had a poorer metabolic profile than the other participants. The fibrosis group had higher median HbA1c levels than the non-fibrosis group (9.3 [2.5] vs. 7.4 [2.5], $p = 0.005$). Similarly, HOMA-IR values were significantly higher (7.3 [9.6] vs. 2.9 [3.4], $p = 0.002$), as were triglyceride values (170.5 [119.5] vs. 122.0 [68.3], $p = 0.027$).

The fibrosis group had lower platelet counts than the non-fibrosis group at (285.5 [106.5] vs. 318.0 [67.3], $p = 0.015$). The surrogate marker of advancing fibrosis also revealed this result. Other variables such as age, BMI, fasting glucose, cholesterol levels, liver enzymes (AST, ALT), albumin, hemoglobin, and white blood cell count were not significantly different between the groups (**Supplementary Table 3**).

Multivariate logistic regression analysis was conducted to identify independent predictors of significant fibrosis. Two variables remained significant: female sex (OR 5.110, 95% CI 1.106–23.601, $p = 0.037$) and HOMA-IR (OR 1.191, 95% CI 1.047–1.355, $p = 0.008$). HbA1c, triglyceride levels, and platelet count were not independently associated after adjustment (**Supplementary Table 4**).

Clinical and Laboratory Predictors of Cirrhosis in Patients with T2DM

Among the 80 patients with T2DM, 6 subjects (7.5%) were identified as having cirrhosis, defined as fibrosis stage ≥F3 on transient elastography. Cirrhosis was associated with significantly lower LDL levels (80.0 [25.75] vs. 106.5 [54.0] mg/dL, $p = 0.006$), lower platelet counts (237.0 [128.8] vs. 316.5 [61.8] × 10^9/L, $p = 0.022$), and higher AST levels (28.0 [21.8] vs. 19.0 [7.0] U/L, $p = 0.030$). No statistically significant differences were observed for age, sex, BMI, fasting glucose, HbA1c, HOMA-IR, lipid profile components other than LDL, ALT, albumin, hemoglobin, or white blood cell count (**Supplementary Table 5**).

Multivariate logistic regression analysis identified AST and platelet count as independent predictors of cirrhosis. The odds of cirrhosis were 18% higher for every unit increase in AST (OR 1.18, 95% CI 1.10–1.32, $p = 0.004$), whereas the odds were 3% lower for every unit decrease in platelet count (OR 0.97, 95% CI 0.95–0.99, $p = 0.009$). LDL, although significant in the univariate analysis, did not remain an independent predictor in the adjusted model ($p = 0.323$) (**Supplementary Table 6**).

Correlation Between Fibrosis Scores and FibroScan® Parameters (LSM and CAP)

This study aimed to establish the correlation between three noninvasive fibrosis scores (FIB-4, APRI, and NFS) and FibroScan® parameters, including LSM and CAP, in patients with T2DM. Spearman's correlation analysis indicated that none of the scores were significantly correlated with CAP, a measure of hepatic steatosis ($p > 0.05$ for all).

On the contrary, both FIB-4 and NFS were found to have a positive and statistically significant correlation with LSM, which is a measure of liver stiffness. The correlation coefficient (ρ) for FIB-4 was 0.291 ($p = 0.009$) and that for NFS was 0.296 ($p = 0.008$). In addition, the APRI score was not correlated with LSM or CAP ($p > 0.05$). This suggests that among the three noninvasive scoring systems, FIB-4 and NFS are more aligned with actual liver stiffness measurements and may be more useful in screening for liver fibrosis in patients with T2DM (**Figure 1**).

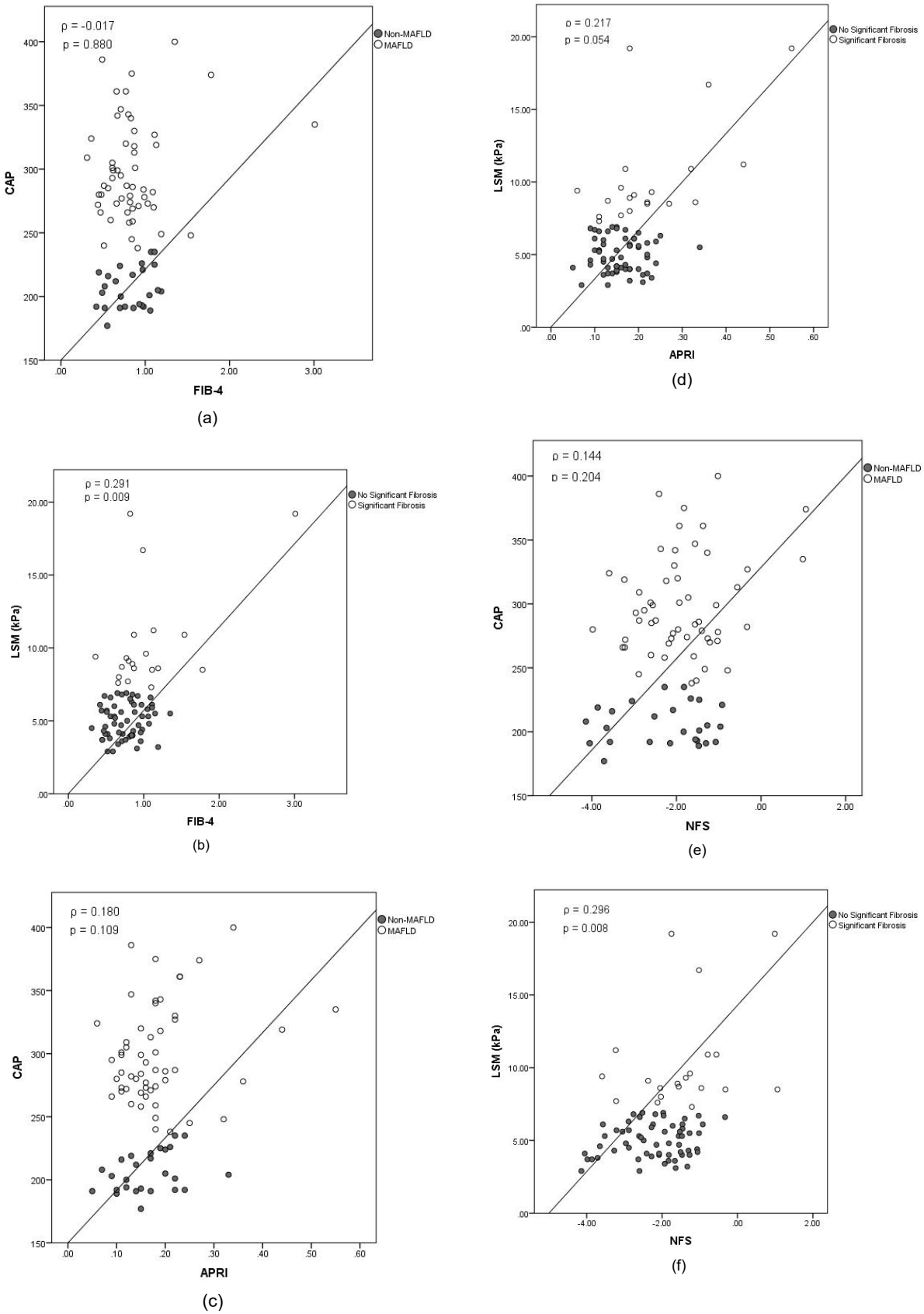

Figure 1. Correlation between FibroScan® parameters and non-invasive fibrosis scores (FIB-4, APRI, and NFS). Panel (a) shows the correlation between CAP and FIB-4; (b) LSM and FIB-4; (c) CAP and APRI; (d) LSM and APRI; (e) CAP and NFS; and (f) LSM and NFS. Only FIB-4 (ρ = 0.291, *p* = 0.009) and NFS (ρ = 0.296, *p* = 0.008) demonstrated significant positive correlations with LSM. None of the scores showed a significant correlation with CAP, which reflects hepatic steatosis.

Performance of FIB-4, APRI, and NFS in identifying hepatic steatosis

This study assessed the efficiency of FIB-4, APRI, and NFS in detecting hepatic steatosis among patients with T2DM, with FibroScan® CAP values used as a reference measure. The results revealed that there were no significant statistical differences in the mean scores of the three indices between the steatosis and non-steatosis groups. The median FIB-4 score was slightly lower in the steatosis group than in the non-steatosis group (0.80 [0.30] vs. 0.85 [0.50], $p = 0.600$). In addition, no differences were observed between the steatosis and non-steatosis groups for APRI values (0.17 [0.07] vs. 0.16 [0.10], $p = 0.513$) and NFS values (−1.94 [1.28] vs. −1.95 [2.07], $p = 0.297$) (**Supplementary Figure 3**).

To further assess the predictive accuracy, ROC curve analysis was conducted. All three scores had AUC values of <0.7, indicating poor performance in detecting steatosis. In detail, the AUC value of FIB-4 was 0.464 (95% CI: 0.323–0.604, $p = 0.600$), APRI was 0.545 (95% CI: 0.406–0.685, $p = 0.514$), and NFS was 0.572 (95% CI: 0.433–0.712, $p = 0.297$) (**Supplementary Table 7**).

Taken together, these findings indicate that FIB-4, APRI, and NFS, which were originally developed to measure liver fibrosis, are not suitable tools for identifying hepatic steatosis or MAFLD in T2DM populations.

Performance of FIB-4, APRI, and NFS in Identifying Significant Fibrosis

This study investigated the diagnostic performance of FIB-4, APRI, and NFS in detecting significant liver fibrosis (≥F2) in patients with T2DM using transient elastography as the reference standard. All three indices had higher scores in patients with significant fibrosis. The median FIB-4 score was 0.87 in the fibrosis group and 0.76 in the non-fibrosis group ($p = 0.010$). The APRI scores were also elevated (0.19 vs. 0.15, $p = 0.014$), as were the NFS values (−1.46 vs. −2.08, $p = 0.010$).

Next, ROC curve analysis was performed to determine the discriminatory ability of each score. FIB-4 and NFS achieved an AUC of 0.693 (95% CI: 0.559–0.827 for FIB-4; 0.548–0.837 for NFS), whereas APRI had a comparable AUC of 0.685 (95% CI: 0.538–0.831). At the optimal cutoff points, FIB-4 ≥ 0.655 demonstrated the highest sensitivity (95.0%) but low specificity (36.7%). APRI ≥ 0.155 achieved 80.0% sensitivity and 51.7% specificity. Meanwhile, NFS ≥ −1.265 showed the highest specificity (90.0%) but lower sensitivity (45.0%). The predictive values also varied: the NPV of FIB-4 was the highest at 95.6%, whereas NFS had the highest PPV at 60.0% (**Table 2**, **Figure 2**).

Table 2. Diagnostic Performance of FIB-4, APRI, and NFS for Identifying Significant Liver Fibrosis in T2DM Patients

Score	AUC (95% CI)	Youden Index	Cut-Off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	p
FIB-4	0.693 (0.559–0.827)	0.317	0.655	95.0	36.7	33.3	95.6	0.010*
APRI	0.685 (0.538–0.831)	0.317	0.155	80.0	51.7	35.6	88.5	0.014*
NFS	0.693 (0.548–0.837)	0.350	–1.265	45.0	90.0	60.0	83.1	0.010*

*Significant (p <0.05)

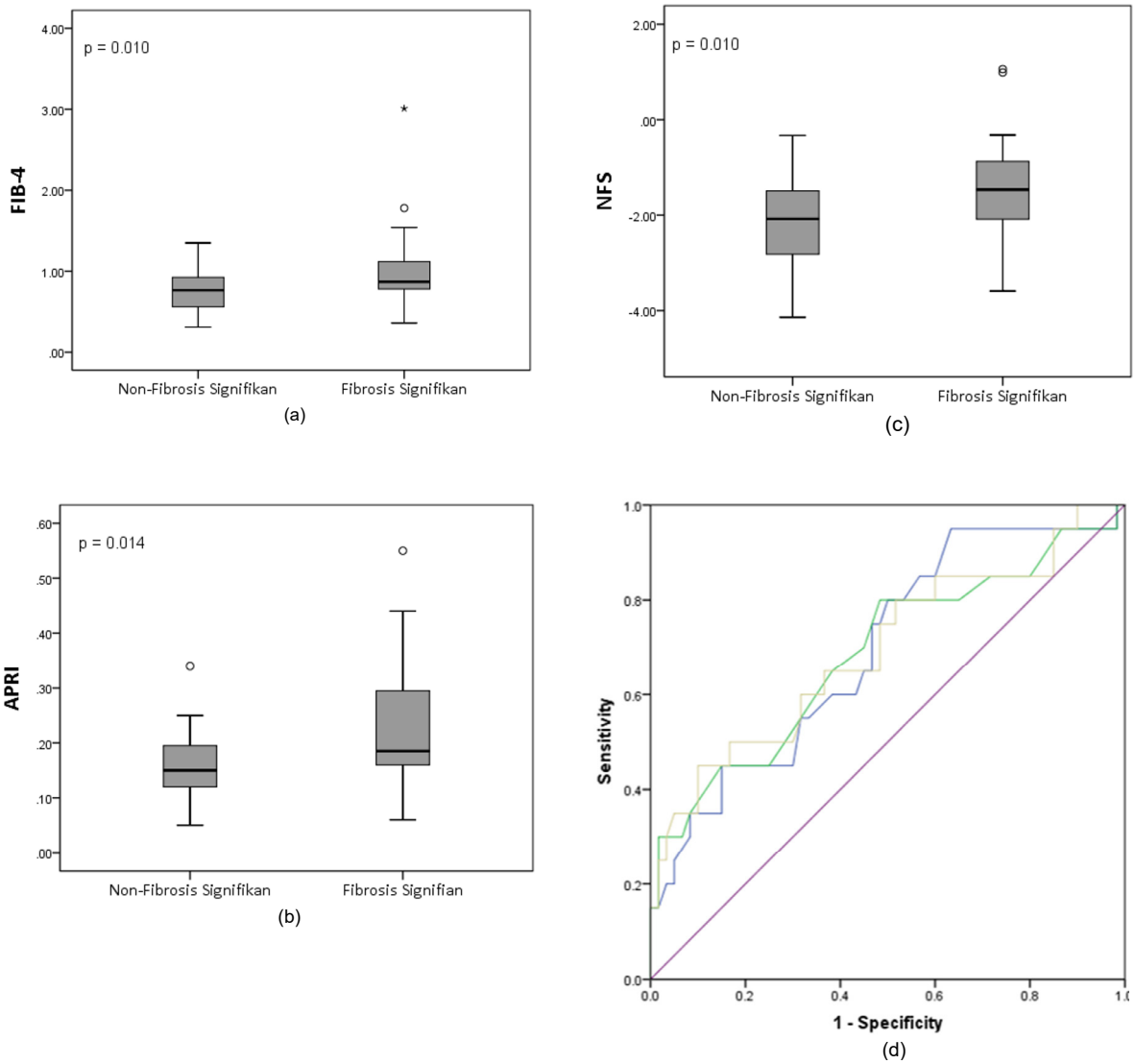

Figure 2. Comparison of non-invasive fibrosis scores between fibrosis and non-fibrosis groups and their diagnostic performance for identifying significant fibrosis in T2DM patients. Panel (a) shows the comparison of FIB-4 scores between patients with and without significant fibrosis (median 0.87 vs. 0.76, p = 0.010). Panel (b) illustrates APRI values in the two groups (median 0.19 vs. 0.15, p = 0.014). Panel (c) displays NFS values (median –1.46 vs. –2.08, p = 0.010). Panel (d) presents ROC curve analysis for FIB-4 (AUC 0.693), APRI (AUC 0.685), and NFS (AUC 0.693). FIB-4 and APRI showed high sensitivity (95.0% and 80.0%, respectively), while NFS demonstrated high specificity (90.0%).

Performance of FIB-4, APRI, and NFS in the identification of cirrhosis

In line with the findings for significant fibrosis, patients with cirrhosis also demonstrated significantly higher scores in all three scoring systems. The median FIB-4 scores were higher in the cirrhosis group than in the noncirrhosis group (1.06 [1.05] vs. 0.78 [0.36], p = 0.008). Similarly, the APRI scores were 0.34 [0.29] vs. 0.16 [0.08] (p = 0.003), and the NFS values were −0.90 [1.95] vs. −2.00 [1.20] (p = 0.035) (**Figure 3a-c**).

The ROC curve analysis further confirmed the strong discriminative performance of all three scores for cirrhosis detection. FIB-4 demonstrated the highest sensitivity (100.0%) with an AUC of 0.825 (95% CI: 0.680–0.971, p = 0.008), although its specificity was modest (54.1%). APRI had the best specificity (97.3%) and overall diagnostic accuracy (PPV 95.0%), with an AUC of 0.860 (95% CI: 0.702–1.000, p = 0.003). NFS also showed excellent specificity (91.9%) and PPV (90.0%), with an AUC of 0.760 (95% CI: 0.508–1.000, p = 0.035) (**Table 3**, **Figure 3d)**.

These findings highlight that FIB-4 has the highest sensitivity, making it an excellent initial

Table 3. Diagnostic Performance of FIB-4, APRI, and NFS for Identifying Cirrhosis in T2DM Patients

Score	AUC (95% CI)	Youden Index	Cut-Off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	p
FIB-4	0.825 (0.680–0.971)	0.541	0.815	100.0	54.1	15.0	100.0	0.008*
APRI	0.860 (0.702–1.000)	0.640	0.295	66.7	97.3	95.0	66.7	0.003*
NFS	0.760 (0.508–1.000)	0.586	–1.025	66.7	91.9	90.0	40.0	0.035*

*Significant (p <0.05)

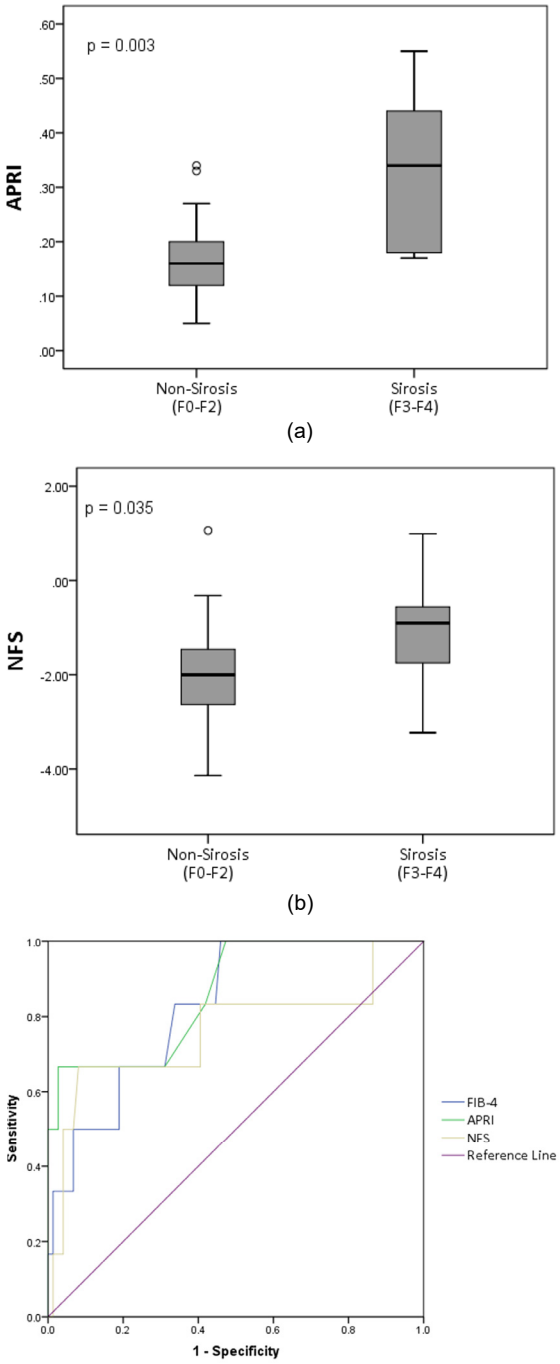

Figure 3. Comparison and diagnostic performance of FIB-4, APRI, and NFS for identifying cirrhosis in T2DM patients. Panel (a) compares FIB-4 scores between cirrhosis and non-cirrhosis groups (p = 0.008). Panel (b) shows APRI scores (p = 0.003), and panel (c) shows NFS scores (p = 0.035). Panel (d) displays the ROC curves for all three scores. FIB-4 demonstrated the highest sensitivity (100.0%), while APRI showed the best specificity (97.3%) and PPV (95.0%).

screening tool to rule out cirrhosis in clinical settings. In contrast, APRI and NFS had greater specificity (97.3% and 91.9%, respectively), supporting their utility in confirming cirrhosis when suspected. Based on this evidence, this study proposes that a stepwise algorithm incorporating FIB-4, APRI, and NFS represents a feasible and cost-effective strategy for identifying compensated cirrhosis among patients with T2DM, particularly in resource-limited settings where FibroScan® is not readily available (**Figure 4**).

DISCUSSION

This cross-sectional study evaluated the diagnostic performance of three noninvasive fibrosis scores FIB-4, APRI, and NFS against FibroScan® liver stiffness measurements in Indonesian patients with T2DM. Our findings demonstrated that FIB-4 and NFS correlated significantly with liver stiffness, whereas APRI did not, except in cirrhosis detection. This distinction underscores the importance of diabetes-specific interpretation of noninvasive scores, as metabolic alterations such as insulin resistance, chronic hyperglycemia, and systemic inflammation influence both disease progression and biomarker behavior. The novelty of this study lies in its focus on the Indonesian T2DM population, which remains underrepresented in global MAFLD research despite having one of the highest prevalence rates in Asia. We observed a MAFLD prevalence of 67.5%, consistent with international reports but higher than many Western cohorts.[17] This highlights the urgent need for tailored screening strategies in Indonesia, where the burden of diabetes and fatty liver disease is disproportionately high. This high prevalence makes it essential to include liver health checks in routine diabetic management plans, especially in low- and middle-income settings.[18]

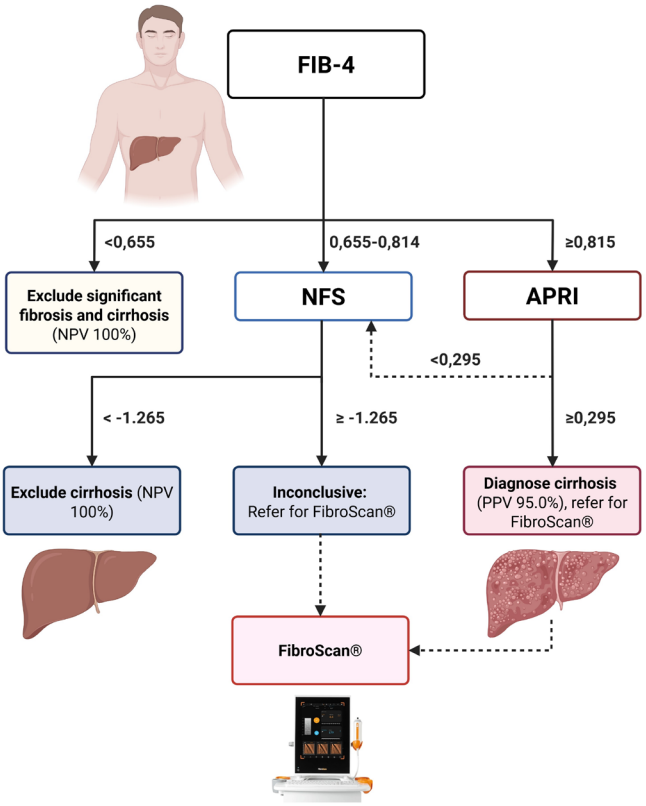

Figure 4. A stepwise algorithm incorporating three indices represents a feasible and cost-effective strategy for identifying cirrhosis among T2DM patients. The screening begins with FIB-4. A value <0.655 can safely exclude both significant fibrosis and cirrhosis (NPV 100%). Patients with FIB-4 between 0.655 and 0.814 undergo NFS calculation. If NFS <–1.265, cirrhosis is unlikely, higher NFS suggests referral for FibroScan®. For FIB-4 ≥0.815 combined with APRI ≥0.295, compensated cirrhosis can be clinically suspected, with a PPV of 95.0%.

Our results demonstrated that FIB-4 and NFS outperform APRI in detecting significant fibrosis, while APRI remains more reliable for cirrhosis confirmation. These results are similar to those found in other meta-analyses and validation studies that have indicated that these indices are more effective in diagnosing advanced fibrosis or cirrhosis than earlier stages.[19-21] The greater efficacy in detecting cirrhosis is partially attributed to the inclusion of AST and platelet count in the scoring systems, as these parameters typically decline with the progression of liver disease.[22] However, unlike some Western cohorts where male sex and obesity were stronger predictors (1), our study identified female sex and HOMA-IR as independent predictors of significant fibrosis. This difference may reflect unique genetic, hormonal, and metabolic characteristics in Southeast Asian populations, reinforcing the need for region-specific validation. Our finding aligns with a growing body of research indicating that insulin resistance significantly contributes to the pathogenesis of fibrosis in MAFLD, regardless of BMI or age.[23] The association with female sex, although less commonly reported, has been substantiated in several populations, as indicated in studies highlighting sex differences in liver disease. Factors such as hormonal regulation and fat distribution have been proposed to explain these disparities.[24] The identification of female sex and insulin resistance (HOMA-IR) as predictors of significant fibrosis is particularly noteworthy. While insulin resistance is a well-established driver of fibrogenesis, the association with female sex has been less frequently reported but is supported by emerging evidence suggesting hormonal regulation and fat distribution differences

Table 4. Summary of Key Studies Evaluating FibroScan®, FIB-4, APRI, and NFS in Type 2 Diabetes Mellitus (with MAFLD Prevalence, Diagnostic Accuracy & Predictors)

Study (Year)	Population	Tools Used	MAFLD / Steatosis	Advanced Fibrosis / Cirrhosis Findings	Predictors / Other Notes
Ciardullo et al., 2020 (30)	2,770 T2DM	FIB-4, NFS, APRI	Not reported	AF prevalence: 1% (APRI) vs 33% (NFS), large variability between scores	Scores differ widely in diabetics due to metabolic factors
Adrian et al., 2023 (31)	100 T2DM ± CKD	FibroScan®, FIB-4, NFS	Not reported	Significant fibrosis: 38% (CKD), 28% (non-CKD)	FIB-4 and NFS higher in CKD, but not independent predictors
Akin et al., 2023 (32)	316 T2DM	FibroScan®, FIB-4, NFS, APRI	89.7% NAFLD	APRI significantly higher in moderate–severe steatosis	FIB-4 & NFS showed similar classification performance
Amernia et al., 2023 (32)	T2DM NAFLD cohort	FibroScan®, APRI, FIB-4	Not reported	APRI was better for advanced fibrosis than FIB-4	APRI superior for cirrhosis identification
Pan et al., 2023 (32)	442 metabolic patients	FibroScan®, APRI, NFS	High prevalence reported	Higher APRI and NFS in hepatosteatosis	Consistent with metabolic risk patterns in T2DM
Tórrez et al., 2024 (Meta-analysis) (33)	>40,000 MAFLD/ diabetes	FIB-4, APRI, NFS	Variable	FIB-4 highest AUC for cirrhosis (0.83); moderate APRI performance	Confirms FIB-4 best for cirrhosis screening
Lee et al., 2021 (Systematic review) (2)	NAFLD cohorts including T2DM	FibroScan®, FIB-4, NFS, APRI	Not specified	FibroScan had highest AUC for mortality (0.86)	Reinforces variability of scores in diabetics
Blank et al., 2020 (34)	204 T2DM	LSM, FIB-4, APRI, NFS	Not reported	Diagnostic pathway sensitivity 47–96%	Highlights poor external discrimination in diabetes
Polyzos et al., 2018	NAFLD + T2DM subgroup	FIB-4, NFS	High NAFLD prevalence	Both scores validated for advanced fibrosis	External validation cohort in diabetics
This study (2025)	80 Indonesian T2DM	FibroScan®, FIB-4, APRI, NFS	67.5% MAFLD, consistent with global T2DM	AUC for ≥F2: 0.685–0.693. AUC for cirrhosis: 0.825–0.870	Predictors of significant fibrosis were female sex and higher HOMA-IR, while cirrhosis was associated with increased AST and lower platelet counts. APRI remained the most reliable score for confirming cirrhosis.

contribute to fibrosis risk. In patients with cirrhosis, AST levels were increased, and platelet counts were decreased. This finding agrees with the known pathophysiological sequence of liver fibrosis, where necro-inflammatory activity and portal hypertension lead to an increase in AST levels and thrombocytopenia due to splenic sequestration.[25,26] These findings confirmed that APRI remains relevant for assessing cirrhosis, although it has limitations regarding early-stage diagnosis.[27]

Given the high prevalence of MAFLD and its complications in diabetic patients, these simple, low-cost, serological scoring systems are a feasible screening tool, especially in primary care or in areas where FibroScan® is not available. These indices could facilitate earlier diagnosis and management of liver disease, ultimately leading to improved long-term outcomes and a reduced burden on tertiary care services.[28,29]

Table 4 provides an overview of key studies evaluating FibroScan® and non-invasive fibrosis scores in type 2 diabetes mellitus, showing consistently high rates of MAFLD and variable performance of serological tools across diabetic populations. Larger cohorts such as Ciardullo et al. reported wide discrepancies in advanced fibrosis prevalence depending on the index used, while studies incorporating FibroScan® (e.g., Idkhuu, Adrian, Akin) demonstrated substantial proportions of significant fibrosis and highlighted the influence of metabolic factors on test accuracy. Across multiple studies, FIB-4 and NFS generally performed better for identifying significant fibrosis, whereas APRI was more useful for cirrhosis confirmation. Meta-analyses and systematic reviews further supported the superior accuracy of FIB-4 for advanced fibrosis and the limitations of general NAFLD algorithms when applied to diabetic cohorts. Collectively, these findings align with our results and reinforce the need for diabetes-specific interpretation of non-invasive fibrosis assessments.

However, several limitations must be acknowledged. The lack of liver biopsy as a reference method may make it difficult to confirm the fibrosis stages, although FibroScan® is a recognized noninvasive alternative. The sample size is also small, possibly reducing the statistical power of the subgroup analysis and the generalizability of the results to other populations. Some confounders, such as other cardiovascular or renal diseases, may also affect the biochemical parameters included in these scores.

From a practical standpoint, our findings support the integration of simple, low-cost serological scores into routine diabetic care in Indonesia and similar low-resource settings. FibroScan® remains the most reliable tool but is often inaccessible due to cost and limited availability. In contrast, FIB-4 and NFS rely on standard laboratory parameters, making them feasible for widespread use at primary and secondary care levels. A stepwise approach—initial screening with FIB-4 or NFS, followed by FibroScan® confirmation when available—could optimize resource allocation, enable earlier diagnosis, and reduce the burden on tertiary care services.

The absence of liver biopsy as a reference standard and the relatively small sample size limit the generalizability of our findings. Larger, biopsy-confirmed studies across diverse Indonesian cohorts are needed to validate these results. Future research should also explore the integration of novel biomarkers and imaging modalities to refine risk stratification algorithms.

CONCLUSION

This study demonstrated that the FIB-4, APRI, and NFS are practical, noninvasive tools with moderate to excellent diagnostic performance for assessing liver fibrosis and cirrhosis in patients with type 2 diabetes mellitus. FIB-4 and NFS showed statistically significant correlations with FibroScan® liver stiffness measurements, whereas APRI exhibited superior performance in detecting cirrhosis. Female sex and elevated HOMA-IR were independent predictors of significant fibrosis, whereas AST levels and platelet counts were predictive of cirrhosis. These findings support the integration of simple fibrosis scores into routine diabetic care, particularly in settings where FibroScan® is not readily available. Further studies with larger, biopsy-confirmed cohorts are needed to validate these results and refine risk stratification algorithms for early detection and intervention in patients with MAFLD-related liver disease.

ACKNOWLEDGMENTS AND AFFILIATION

Not Applicable.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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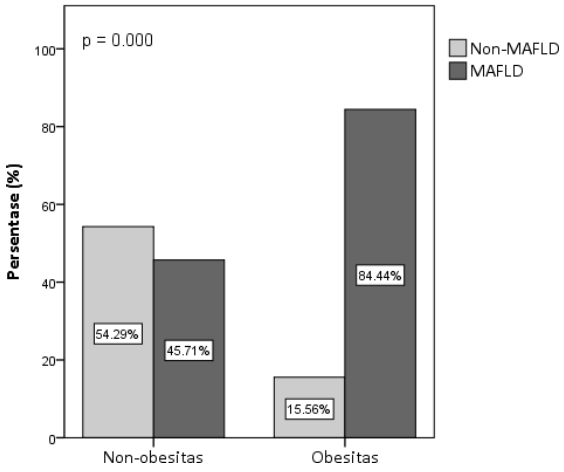
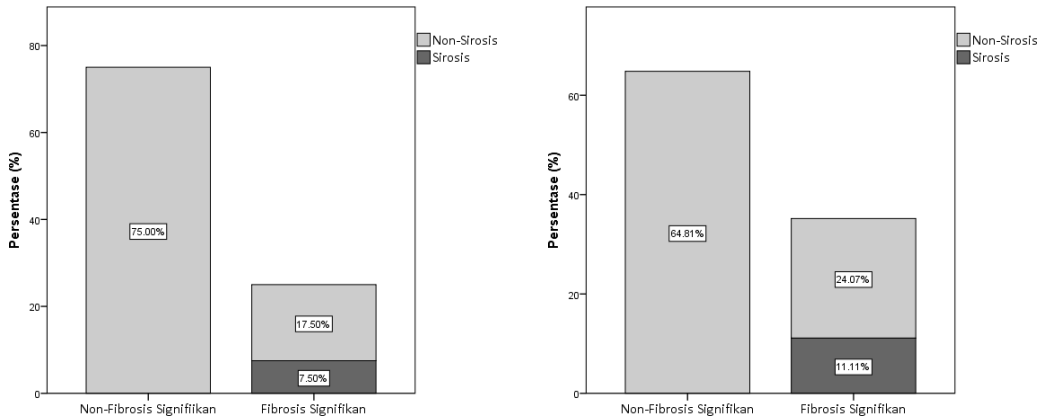
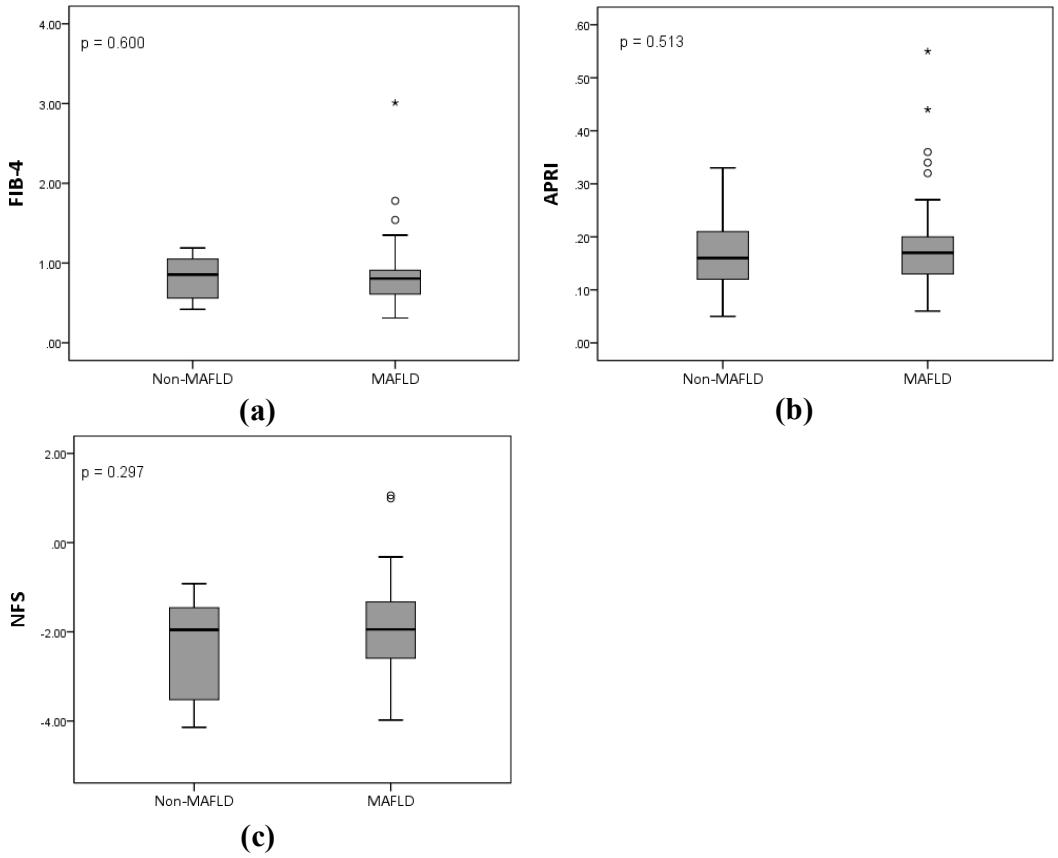
SUPPLEMENTARY FIGURES



Supplementary Figure 1. Prevalence of MAFLD in obese vs. non-obese subjects with T2DM.
Obese participants (BMI ≥25 kg/m²) showed a significantly higher prevalence of MAFLD compared to non-obese individuals (84.4% vs. 45.7%, $p < 0.001$). No statistically significant difference in MAFLD prevalence was observed when using the lower threshold of overweight/obesity (non-overweight vs. overweight/obese: 50.0% vs. 71.8%, $p = 0.095$).



Supplementary Figure 2. Prevalence of significant fibrosis and cirrhosis in the total T2DM population and the MAFLD subgroup. Panel (a) shows that 25.0% of the overall T2DM population had significant fibrosis and 7.5% had cirrhosis. Panel (b) illustrates that among patients with MAFLD, the prevalence increased to 35.2% for significant fibrosis and 11.1% for cirrhosis.No patients had LSM values ≥25 kPa indicative of clinically significant portal hypertension.



Supplementary Figure 3. Comparison of FIB-4, APRI, and NFS values between patients with and without hepatic steatosis. Panel (a) shows the distribution of FIB-4 values in patients with and without steatosis, with no significant difference observed between groups (median 0.80 vs. 0.85, p = 0.600). Panel (b) illustrates APRI values, which were similarly non-discriminatory (median 0.17 vs. 0.16, p = 0.513). Panel (c) presents NFS values, which also did not significantly differ (median –1.94 vs. –1.95, p = 0.297). These findings indicate that none of the three scores effectively differentiate hepatic steatosis status in T2DM patients.

SUPPLEMENTARY TABLES

Supplementary Table 1. Bivariate Analysis of Clinical and Laboratory Characteristics **Associated with Hepatic Steatosis in T2DM Patients (n = 80)**

Variable	Non-Steatosis (S0) (n = 26)	Steatosis (S1–S3) (n = 54)	p
Age (years)	57.5 ± 9.8	53.5 ± 7.7	0.056
Female sex (%)	14/26 (53.8%)	30/54 (55.5%)	0.886
BMI (kg/m²)	23.9 (3.3)	27.1 (6.4)	<0.001*
Fasting glucose (mg/dL)	120.5 (39.5)	139.5 (89.5)	0.172
HbA1c (%)	7.1 (2.7)	8.6 (2.9)	0.019*
HOMA-IR	2.0 (2.2)	4.7 (5.5)	<0.001*
Total cholesterol (mg/dL)	190 (68.5)	177 (52.8)	0.221
Triglycerides (mg/dL)	116.0 (90.0)	141.5 (96.8)	0.159
HDL (mg/dL)	49.5 (20.8)	43.5 (11.3)	0.022*
LDL (mg/dL)	108.0 (54.8)	100.0 (32.9)	0.208
AST (U/L)	19.0 (7.8)	19.0 (7.3)	0.773
ALT (U/L)	19.5 (10.5)	19.5 (14.5)	0.510
Albumin (g/dL)	4.3 ± 0.3	4.3 ± 0.4	0.240
Hemoglobin (g/dL)	12.8 (2.2)	13.3 (2.6)	0.122
WBC (×10⁹/L)	7.7 (2.7)	8.1 (3.4)	0.237
Platelet (×10⁹/L)	309.0 (113.8)	309.0 (67.5)	0.380

Supplementary Table 2. Multivariate Logistic Regression for Independent Predictors of Hepatic Steatosis (n = 80)

Variable	B	OR (95% CI)	p-value
IMT	0.186	1.205 (1.034–1.405)	0.017*
HbA1c	0.169	1.184 (0.850–1.650)	0.318
HOMA-IR	0.281	1.325 (1.014–1.730)	0.039*
HDL	–0.043	0.958 (0.911–1.007)	0.094

Supplementary Table 3. Univariate Analysis of Clinical and Laboratory Predictors of Significant Liver Fibrosis in T2DM Patients (n = 80)

Variable	Non-Significant Fibrosis (F0–F1) (n= 60)	Significant Fibrosis (≥F2) (n = 20)	p
Age (years)	54.4 ± 9.1	56.0 ± 6.8	0.483
Female sex (%)	29/60 (48.3%)	15/20 (75.0%)	0.038*
BMI (kg/m²)	25.5 (5.03)	25.9 (8.4)	0.617
Fasting glucose (mg/dL)	123.5 (64.7)	178.5 (104.7)	0.112
HbA1c (%)	7.4 (2.5)	9.3 (2.5)	0.005*
HOMA-IR	2.9 (3.4)	7.3 (9.6)	0.002*
Total cholesterol (mg/dL)	181.5 (59.0)	175.0 (66.5)	0.586
Triglycerides (mg/dL)	122.0 (68.3)	170.5 (119.5)	0.027*
HDL (mg/dL)	45.0 (14.0)	45.0 (13.0)	0.252
LDL (mg/dL)	106.5 (53.5)	90.5 (52.3)	0.124
AST (U/L)	19.0 (6.8)	20.5 (9.6)	0.233
ALT (U/L)	19.0 (11.0)	21.5 (18.5)	0.446
Albumin (g/dL)	4.4 ± 0.3	4.3 ± 0.3	0.105
Hemoglobin (g/dL)	12.9 (2.1)	13.6 (3.0)	0.092
White blood cell count	7.8 (3.0)	8.6 (3.6)	0.417
Platelet count (×10⁹/L)	318.0 (67.3)	285.5 (106.5)	0.015*

Supplementary Table 4. Multivariate Logistic Regression Analysis of Clinical and Laboratory Predictors of Significant Liver Fibrosis in T2DM Patients (n = 80)

Variable	B	OR (95% CI)	p
Female sex	1.631	5.110 (1.106–23.601)	0.037
HbA1c (%)	0.266	1.305 (0.947–1.799)	0.104
HOMA-IR	0.175	1.191 (1.047–1.355)	0.008
Triglycerides (mg/dL)	0.007	1.007 (0.999–1.014)	0.090
Platelet count (×10⁹/L)	–0.009	0.991 (0.981–1.002)	0.111

Supplementary Table 5. Univariate Analysis of Clinical and Laboratory Predictors of Cirrhosis in T2DM Patients (n = 80)

Variable	Non-Cirrhosis (F0–F2) (n = 74)	Cirrhosis (≥F3) (n = 6)	p
Age (years)	54.5 ± 12.0	57.7 ± 8.75	0.217
Female sex (%)	39/74 (52.7%)	5/6 (83.3%)	0.147
BMI (kg/m²)	25.5 (5.7)	26.5 (5.4)	0.648
Fasting glucose (mg/dL)	132.0 (84.5)	120.5 (109.8)	0.416
HbA1c (%)	7.8 (2.7)	9.2 (2.1)	0.217
HOMA-IR	3.3 (4.8)	4.9 (9.2)	0.661
Total cholesterol (mg/dL)	181.5 (57.5)	156.0 (52.0)	0.079
Triglycerides (mg/dL)	132.5 (81.8)	162.5 (205.5)	0.273
HDL (mg/dL)	45.0 (15.3)	43.0 (8.3)	0.269
LDL (mg/dL)	106.5 (54.0)	80.0 (25.75)	0.006*
AST (U/L)	19.0 (7.0)	28.0 (21.8)	0.030*
ALT (U/L)	19.0 (12.3)	27.5 (53.3)	0.084
Albumin (g/dL)	4.4 ± 0.4	4.3 ± 0.5	0.584
Hemoglobin (g/dL)	13.2 (2.2)	13.2 (4.9)	0.985
White blood cell count	8.0 (3.5)	7.8 (3.6)	0.674
Platelet count (×10⁹/L)	316.5 (61.8)	237.0 (128.8)	0.022*

Supplementary Table 6. Multivariate Logistic Regression Analysis of Predictors of Cirrhosis in T2DM Patients

Variable	B	OR (95% CI)	p
LDL (mg/dL)	–0.027	0.97 (0.92–1.03)	0.323
AST (U/L)	0.167	1.18 (1.10–1.32)	0.004*
Platelet count (×10⁹/L)	–0.028	0.97 (0.95–0.99)	0.009*

Supplementary Table 7. Diagnostic Performance of FIB-4, APRI, and NFS for Identifying Hepatic Steatosis in T2DM Patients

Score	AUC (95% CI)	Youden Index	Cut-Off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	p
FIB-4	0.464 (0.323–0.604)	0.084	0.575	81.5	26.9	34.9	41.1	0.600
APRI	0.545 (0.406–0.685)	0.118	0.105	92.6	19.2	35.6	55.5	0.514
NFS	0.572 (0.433–0.712)	0.232	–3.395	96.3	26.9	38.8	77.7	0.297