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A Prospective Cross-sectional study to evaluate the utility of Fibroscan and Serum Biomarkers (APRI, FIB-4) for Non-Invasive Diagnosis of Liver Fibrosis in Metabolic dysfunction associated fatty liver disease (MAFLD) patients in a tertiary care center

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ABSTRACT

Introduction: Metabolic dysfunction associated fatty liver disease (MAFLD) is a more prevalent condition and a leading cause of chronic liver disease worldwide. It spans a spectrum from simple steatosis to metabolic dysfunction associated steatohepatitis (MASH), which can progress to fibrosis, cirrhosis, and hepatocellular carcinoma. Liver biopsy, the gold standard for diagnosing fibrosis, is invasive, costly, and carries risks, leading to a demand for non-invasive alternatives. FibroScan measures liver stiffness, while serum biomarkers, including the aspartate aminotransferase to platelet ratio index (APRI) and the fibrosis-4 (FIB-4) score, are inexpensive and accessible diagnostic options. This study aims to evaluate and compare the diagnostic accuracy of these non-invasive tools for liver fibrosis in non-Alcoholic Fatty Liver Disease.

Methods: This prospective, cross-sectional study included 120 MAFLD patients confirmed via imaging. FibroScan was used to assess liver stiffness, with cutoffs of >8.0 kPa and >12.0 kPa for significant (F2) and advanced (F3) fibrosis, respectively. APRI and FIB-4 scores were calculated using routine clinical parameters. Diagnostic accuracy was assessed using AUROCs, sensitivity, specificity, and correlation with histological fibrosis scores.

Results: FibroScan showed the highest accuracy (AUROC: 0.88 for F2, 0.91 for F3), followed by FIB-4 (0.79 for F2, 0.80 for F3) and APRI (0.75 for F2, 0.78 for F3). FibroScan demonstrated the strongest correlation with histological fibrosis ($\rho = 0.72$), while FIB-4 ($\rho = 0.68$) outperformed APRI ($\rho = 0.64$). Obesity and advanced age reduced sensitivity, particularly for FIB-4 and APRI.

Conclusion: FibroScan is the most accurate tool for non-invasive fibrosis assessment in MAFLD. FIB-4 provides a reliable, cost-effective alternative, while APRI serves as a simpler screening option, especially in resource-limited settings. These findings support integrating these tools into clinical practice to reduce reliance on liver biopsy.

Keywords: *cirrhosis, Fibroscan, fibrosis, steatohepatitis*

INTRODUCTION

Metabolic dysfunction associated fatty liver disease (MAFLD) is a global health concern, increasingly recognized as a leading cause of chronic liver disease. It encompasses a spectrum ranging from simple hepatic steatosis to metabolic dysfunction associated steatohepatitis (MASH), which may progress to liver fibrosis, cirrhosis, and hepatocellular carcinoma (1). Accurate detection of liver fibrosis is crucial for the prognosis and management of MAFLD. While liver biopsy remains the gold standard, its invasiveness, cost, and associated risks have prompted the need for non-invasive diagnostic alternatives (2). FibroScan, a transient elastography technique, measures liver stiffness and has emerged as a reliable tool for fibrosis assessment. Serum biomarkers such as the aspartate aminotransferase to platelet ratio index (APRI) and the fibrosis-4 (FIB-4) score, derived from routine clinical parameters, are also widely used to estimate fibrosis severity (3).

FibroScan demonstrates high diagnostic accuracy in distinguishing advanced fibrosis in MAFLD patients. Studies have shown its utility in stratifying patients based on fibrosis stages, with AUROCs often exceeding 0.80 (2). However, accessibility to FibroScan may be limited in resource-constrained settings, making serum biomarkers an attractive alternative. The APRI score incorporates AST levels and platelet counts, while FIB-4 additionally accounts for age and ALT levels, improving diagnostic accuracy for advanced fibrosis. Comparative studies have shown FIB-4 and APRI

scores to correlate significantly with FibroScan measurements, suggesting their potential as non-invasive substitutes (4,5).

This study aims to evaluate and compare the diagnostic accuracy of FibroScan, APRI, and FIB-4 for non- invasive assessment of liver fibrosis in MAFLD. By addressing gaps in the comparative performance of these methods, the findings could optimize resource allocation and clinical decision-making, particularly in settings where liver biopsy or FibroScan is impractical. Ultimately, this research seeks to validate a reliable, accessible diagnostic strategy for MAFLD-related fibrosis.

AIM

To evaluate and compare the utility of FibroScan, the aspartate aminotransferase to platelet ratio index (APRI), and the fibrosis-4 (FIB-4) score in the non-invasive diagnosis of liver fibrosis in patients with Metabolic dysfunction associated fatty liver disease (MAFLD)

OBJECTIVES

- To assess the diagnostic performance of FibroScan for staging liver fibrosis in MAFLD.
- To determine the sensitivity and specificity of APRI in detecting advanced fibrosis.
- To analyse the correlation between FIB-4 scores and fibrosis severity in MAFLD.
- To estimate the effectiveness of FibroScan, APRI, and FIB-4 in distinguishing fibrosis stages.
- To analyze demographic and clinical factors affecting the accuracy of these diagnostic methods.

MATERIALS AND METHODS

Study Design and Setting: This was a prospective, cross-sectional study conducted at the General Medicine department in Chettinad Hospital & Research Institute. The study was carried out over a period of 3 months and included patients diagnosed with Metabolic dysfunction associated fatty liver disease (MAFLD) based on imaging criteria or histological evidence.

Study Design:

Adult patients (aged ≥18 years) with confirmed MAFLD through ultrasonography showing fatty infiltration of the liver and providing written informed consent were included. Exclusion criteria were Alcohol consumption >20 g/day for women and >30 g/day for men, Co-existing liver diseases (e.g., viral hepatitis, autoimmune hepatitis, or Wilson's disease), history of hepatotoxic drug use, prior liver transplantation and pregnancy or active malignancy.

Sample Size: The study recruited 120 participants to ensure adequate statistical power for comparing diagnostic methods. Sample size calculation was based on previous studies reporting an expected area under the receiver operating characteristic (AUROC) curve for FibroScan and serum biomarkers, assuming a power of 80% and a significance level of 5%.

Ethical Approval: The study was approved by the institutional ethics committee, and written informed consent was obtained from all participants before enrollment. The study was done for the duration of 3 months.

Data Collection

Demographic and Clinical Data: Demographic variables such as age, sex, and body mass index (BMI) were recorded. Clinical parameters including the presence of diabetes, hypertension, and hyperlipidemia were also documented.

Laboratory Tests: Venous blood samples were collected after an overnight fast. Laboratory tests included:

- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT).
- Platelet counts.
- Total cholesterol, triglycerides, and fasting glucose.

DIAGNOSTIC METHODS

1. **FibroScan (Transient Elastography):** FibroScan (Echosens, France) will be utilised to measure liver stiffness in kilopascals (kPa). Measurements were performed by an experienced operator using the M or XL probe based on patient BMI. Ten valid measurements were obtained, and the median value was recorded. A liver stiffness measurement

(LSM) cutoff of >8.0 kPa indicated significant fibrosis (F2), while >12.0 kPa indicated advanced fibrosis (F3–F4).

2. **APRI Score Calculation:** APRI was calculated using the formula:

$$\text{APRI} = \left(\frac{\text{AST(U/L)}}{\text{Upper Limit of Normal AST (U/L)}} \right) \times 100 \div \text{Platelet Count}(10^9/\text{L}).$$

A cutoff of 0.7 was used to identify significant fibrosis, and 1.0 was used for advanced fibrosis.

3. **FIB-4 Score Calculation:** FIB-4 was calculated using the formula:

$$\text{FIB-4} = \frac{\text{Age (years)} \times \text{AST (U/L)}}{\text{Platelet Count}(10^9/\text{L}) \times \sqrt{\text{ALT (U/L)}}}.$$

Cutoff values were set at 1.3 for significant fibrosis and 2.67 for advanced fibrosis.

Statistical Analysis: All data were analyzed using SPSS software version 25.0. Continuous variables were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR), depending on the distribution. Categorical variables were presented as frequencies and percentages. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall diagnostic accuracy were calculated for FibroScan, APRI, and FIB-4 in detecting significant (≥F2) and advanced fibrosis (≥F3). AUROCs were used to compare the diagnostic performance of FibroScan, APRI, and FIB-

4. Pairwise comparisons were performed using the DeLong method. Spearman's correlation coefficient (ρ) was used to assess the relationship between FibroScan liver stiffness measurements, APRI, FIB-4, and histological fibrosis scores. Diagnostic performance was evaluated in subgroups based on BMI, age, and comorbidities (e.g., diabetes and metabolic syndrome).

Quality Assurance: FibroScan measurements were performed by certified operators to minimize variability. Laboratory tests were conducted in a centralized lab adhering to international standards. Data entry and analysis were cross-verified by two independent researchers to ensure accuracy.

RESULTS

A total of 120 MAFLD patients were included in the study, of which 58 (48.3%) were male, and 62 (51.7%) were female. The mean age of the cohort was 50.2 ± 11.5 years, with 47% of patients classified

as obese (BMI >30 kg/m²). Diabetes was present in 35% of the patients, and metabolic syndrome was observed in 42%.

Table 1: Demographic and Clinical Characteristics

Characteristic	Value (n=120)
Male, n (%)	58 (48.3%)
Female, n (%)	62 (51.7%)
Mean Age (years)	50.2 ± 11.5
BMI > 30 kg/m², n (%)	56 (46.7%)
Diabetes, n (%)	42 (35%)
Metabolic Syndrome, n (%)	50 (42%)

Diagnostic Accuracy of Non-Invasive Methods

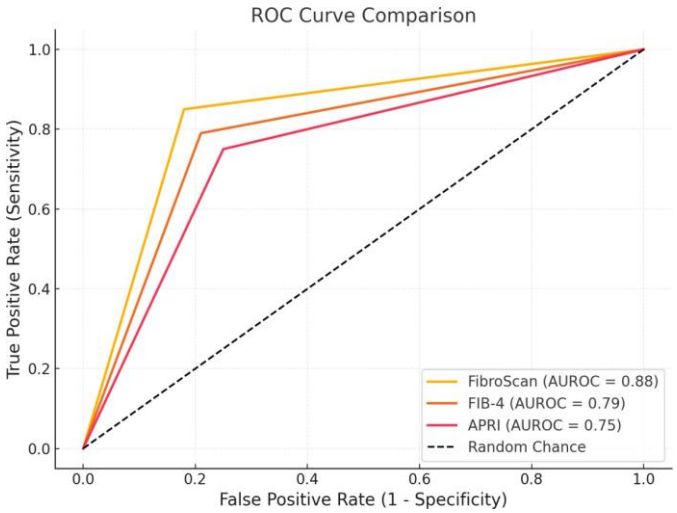
FibroScan demonstrated the highest AUROC (0.88), followed by FIB-4 (0.79) and APRI (0.75). Sensitivity and specificity of FibroScan were 85% and 82%, respectively, at a liver stiffness cutoff of 8.0 kPa. For FIB-4 and APRI, the optimal

cutoffs provided moderate sensitivity and specificity.

Table 2: Performance of FibroScan, APRI, and FIB-4 in Detecting Significant Fibrosis (≥F2)

Parameter	FibroScan	APRI	FIB-4
AUROC	0.88	0.75	0.79
Sensitivity (%)	85%	68%	73%
Specificity (%)	82%	78%	81%
Cutoff Value	8.0 kPa	0.7	1.3

Figure 1: ROC of FibroScan, APRI, and FIB-4 in Detecting Significant Fibrosis (≥F2)

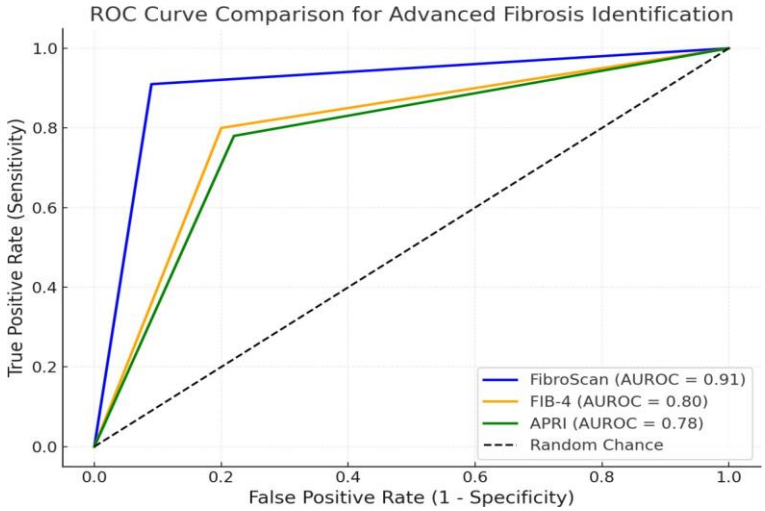


In identifying advanced fibrosis, FibroScan again outperformed APRI and FIB-4. The AUROC for FibroScan was 0.91 compared to 0.80 for FIB-4 and 0.78 for APRI. Sensitivity and specificity were highest for FibroScan at the cutoff of 12.0 kPa.

Table 3: Performance in Detecting Advanced Fibrosis (≥F3)

Parameter	FibroScan	APRI	FIB-4
AUROC	0.91	0.78	0.80
Sensitivity (%)	87%	71%	75%
Specificity (%)	84%	79%	83%
Cutoff Value	12.0 kPa	1.0	2.67

Figure 2: ROC in Detecting Advanced Fibrosis (≥F3)



Spearman's correlation coefficient revealed strong correlations between liver stiffness measured by FibroScan and both serum biomarkers. **FIB-4** showed the strongest correlation with FibroScan measurements (ρ = 0.72) and histological fibrosis (ρ = 0.68). **APRI** demonstrated moderate correlations with FibroScan and histological fibrosis scores (ρ = 0.67 and 0.64, respectively). **Platelet count** was negatively correlated with FibroScan and histological fibrosis scores, indicating lower platelet counts are associated with higher fibrosis. **Age** and **AST/ALT ratio** also showed significant but weaker correlations with FibroScan and histological fibrosis scores. **BMI** had a negative correlation with fibrosis measurements, likely due to its impact on FibroScan reliability.

Table 4: Correlation Analysis

Parameter	Correlation with FibroScan (ρ)	Correlation with Histological Fibrosis (ρ)	P-Value
APRI	0.67	0.64	**<0.001**
FIB-4	0.72	0.68	**<0.001**
Age	0.45	0.43	**<0.01**
Platelet Count	-0.58	-0.60	**<0.001**
AST/ALT Ratio	0.49	0.47	**<0.01**
BMI	-0.42	-0.40	**<0.01**

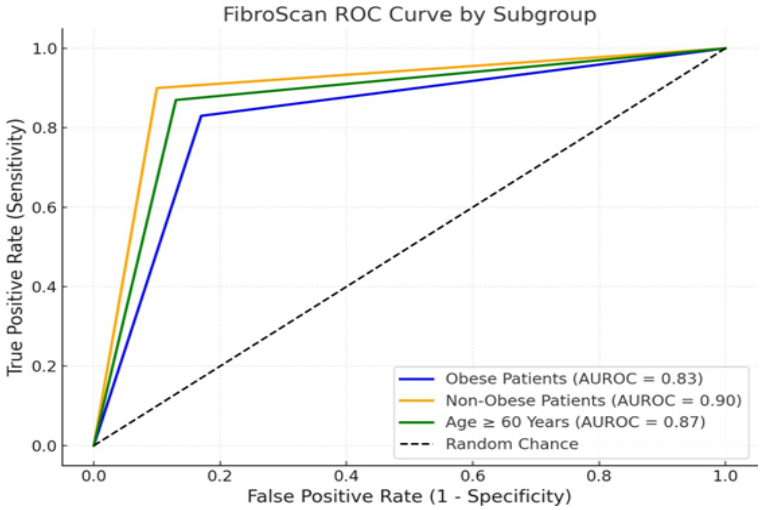
FibroScan accuracy was slightly reduced in obese patients (AUROC: 0.83 for significant fibrosis) compared to non-obese patients (AUROC: 0.90). Both APRI and FIB-4 had diminished sensitivity in patients aged ≥60 years, though specificity remained stable.

Table 5: Subgroup Analysis

Subgroup	FibroScan (AUROC)	APRI (AUROC)	FIB-4 (AUROC)
Obese Patients	0.83	0.72	0.76
Non-Obese Patients	0.90	0.77	0.81
Age ≥ 60 Years	0.87	0.70	0.75

The ROC curves for FibroScan, APRI, and FIB-4 highlight the superior diagnostic performance of FibroScan in differentiating fibrosis stages. FIB-4 performed better than APRI across all fibrosis thresholds.

Figure 3: ROC Curve Analysis



DISCUSSION

Non-alcoholic fatty liver disease (NAFLD), recently termed as Metabolic dysfunction associated fatty liver disease (MAFLD), is identified as a leading cause of liver-related morbidity and mortality worldwide, driven by the global epidemic of obesity and metabolic syndrome. Accurate assessment of liver fibrosis is highly imperative, as fibrosis severity is a strong predictor of outcomes, including cirrhosis, liver failure, and hepatocellular carcinoma (1). This study compared the diagnostic performance of FibroScan, APRI, and FIB-4 in identifying significant and advanced fibrosis in patients with NAFLD. The findings underscore the utility of non-invasive diagnostic tools, particularly FibroScan and FIB-4, in evaluating fibrosis severity and guiding clinical decision-making.

Our study demonstrated that FibroScan, a transient elastography technique, had the highest diagnostic accuracy among the three methods for detecting both significant (≥F2) and advanced fibrosis (≥F3). The AUROCs of FibroScan were 0.88 and 0.91 for significant and advanced fibrosis, respectively, outperforming both APRI and FIB-4. These findings align with prior studies, such as those by Bouhamou et al., who reported an AUROC of 0.91 for FibroScan in identifying advanced fibrosis in NAFLD patients

(2). The high sensitivity (85%) and specificity (82%) of FibroScan at a cutoff of 8.0 kPa for significant fibrosis make it a reliable tool in clinical practice.

In obese individuals, excess subcutaneous fat can interfere with elastography signals, potentially leading to reduced accuracy. In our study, the AUROC of FibroScan in obese patients was slightly lower (0.83) compared to non-obese patients (0.90), consistent with previous reports (3). The FIB-4 score emerged as the second most accurate tool, with AUROCs of 0.79 for significant fibrosis and 0.80 for advanced fibrosis. The strong correlation between FIB-4 and both FibroScan ($\rho = 0.72$) and histological fibrosis scores ($\rho = 0.68$) supports its utility as a non-invasive diagnostic tool. Notably, FIB-4 outperformed APRI in our study, particularly in detecting advanced fibrosis. This superiority is consistent with previous research, such as the findings by Calzadilla Bertot et al., who reported a higher diagnostic accuracy of FIB-4 compared to APRI in NAFLD patients (6). The age dependence of FIB-4 also poses a limitation, as elevated scores in older individuals may not always reflect true fibrosis. Age- adjusted cutoffs have been proposed to address this issue and warrant further validation (4).

APRI, calculated using AST and platelet count, demonstrated moderate diagnostic accuracy, with AUROCs of 0.75 for significant fibrosis and 0.78 for advanced fibrosis. While its performance was inferior to both FibroScan and FIB-4, APRI remains a valuable tool, particularly in resource-limited settings where access to advanced imaging modalities is restricted. The simplicity of APRI, requiring only routine laboratory tests, makes it an attractive option for widespread implementation.

However, the sensitivity of APRI (68% for significant fibrosis and 71% for advanced fibrosis) was relatively low in our cohort, limiting its ability to rule out fibrosis in MAFLD patients. This aligns with previous studies, such as those by Sowjanya et al., who reported similar limitations in APRI's diagnostic performance (7). Despite these shortcomings, APRI's specificity (78–79%) and ease of use justify its role as an initial screening tool, particularly in settings where FibroScan or liver biopsy is unavailable.

The strong correlations observed between FibroScan, FIB-4, and histological fibrosis scores highlight the validity of these non-invasive tools in assessing liver fibrosis. FibroScan demonstrated the highest evidence for histological fibrosis ($\rho = 0.72$), followed closely by FIB-4 ($\rho = 0.68$). These findings support the growing consensus that non-invasive methods can effectively replace liver biopsy in many clinical scenarios (8). However, liver biopsy remains the gold standard for definitive diagnosis, particularly in cases with discordant non-invasive results or co-existing liver conditions. Subgroup

analysis revealed notable variations in diagnostic performance based on patient characteristics. In obese patients,

FibroScan and serum biomarkers showed reduced accuracy, likely due to technical and biological factors. Obesity is known to affect the reliability of transient elastography due to signal attenuation and increased liver fat content. Similarly, serum biomarkers such as APRI and FIB-4 may be influenced by obesity-related changes in platelet counts and liver enzyme levels (9).

Age also emerged as a significant factor influencing diagnostic accuracy. Older patients had higher FIB- 4 scores due to the inclusion of age in the calculation, which may lead to overestimation of fibrosis severity. Age-adjusted cutoffs for FIB-4 have been proposed to address this limitation and could improve its utility in elderly populations (10).

The findings of this study have important clinical implications. FibroScan, with its high diagnostic accuracy, should be considered the first-line non-invasive tool for fibrosis assessment in MAFLD patients. However, its limited availability and cost may restrict its use in certain settings. In such cases, FIB-4 serves as a reliable alternative, offering comparable accuracy for advanced fibrosis detection. APRI, while less accurate, can be used as an initial screening tool in resource-limited settings, with further evaluation using FibroScan or FIB-4 for patients with intermediate or high APRI scores (11).

This study has several advantages, including the prospective design and robust statistical analysis. The inclusion of a diverse MAFLD cohort enhances the generalizability of the findings. However, certain limitations must be acknowledged. First, the study was conducted at a single center, which may limit the external validity of the results. Second, the impact of metabolic comorbidities on the diagnostic performance of non-invasive methods warrants further investigation. Future research should focus on validating age- and BMI-adjusted cutoffs for FIB-4 and APRI to improve their diagnostic accuracy in specific subpopulations. The development of composite scoring systems that integrate FibroScan and serum biomarkers could further enhance diagnostic precision. Additionally, the role of emerging non-invasive techniques, such as magnetic resonance elastography (MRE) and machine learning-based predictive models, should be explored in comparison to FibroScan, APRI, and FIB-4.

CONCLUSION

This study reveals the utility of FibroScan, APRI, and FIB-4 as non-invasive tools for diagnosing and staging liver fibrosis in patients with non-alcoholic fatty liver disease (NAFLD). FibroScan emerged as the most accurate diagnostic method, demonstrating superior sensitivity and specificity for both significant and advanced fibrosis. The findings validate its role as a first-line tool in clinical settings where transient elastography is accessible. Among serum biomarkers, FIB-4 exhibited better diagnostic performance than APRI, particularly in identifying advanced fibrosis, underscoring its reliability as a cost-effective alternative in resource-limited settings. APRI, while less accurate, remains valuable as a screening tool due to its simplicity and widespread availability. The strong correlations observed between these non-invasive methods and histological fibrosis scores support their clinical validity and their potential to reduce reliance on liver biopsy. However, factors such as obesity and age were shown to influence the diagnostic accuracy of these methods, emphasizing the need for adjustments in specific subpopulations. Future research should focus on refining diagnostic cutoffs, particularly for age- and BMI-adjusted FIB-4 scores, and exploring the integration of these tools with advanced imaging modalities or emerging biomarkers to enhance diagnostic precision. Ultimately, the adoption of these non-invasive methods can facilitate early diagnosis and risk stratification in MAFLD, improving patient outcomes and reducing the burden of invasive procedures in clinical practice.

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