

# Is Aspartate Aminotransferase to Platelet Ratio Index a Better Noninvasive Score for Predicting Advanced Fibrosis in Nonalcoholic Fatty Liver Disease Patients?

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## ABSTRACT

**Background:** In the 21st century, nonalcoholic fatty liver disease (NAFLD) is the most prevalent liver disorder. The prevalence of NAFLD within the general population in India ranges from 9 to 53%. The gold standard for assessing the severity of liver fibrosis is liver biopsy. However, due to various difficulties involved with liver biopsy, it is imperative to identify different non-invasive tools that can replace liver biopsy.

**Methodology:** A prospective observational study of 130 patients meeting the inclusion criteria for NAFLD was done for a period of 18 months. We aimed to compare the performance characteristics of different noninvasive scores [fibrosis-4 (FIB-4) score, nonalcoholic fatty liver disease fibrosis score (NFS), and aspartate aminotransferase to platelet ratio index (APRI)] in predicting advanced fibrosis as assessed by FibroScan.

**Results:** In the study, 76.9% of patients were male. Advanced fibrosis was seen in 12.3% of the patients. Majority of the patients with advanced fibrosis had metabolic syndrome. Based on the area under the receiver operating characteristic curve (AUROC), the new cut-off for ruling out advanced fibrosis for FIB-4, NFS, and APRI were 1.18,  $-0.9$ , and 0.65, respectively, and APRI had the best AUROC (0.768).

**Conclusion:** Abnormal glycemic status and metabolic syndrome were risk factors for advanced fibrosis. The newly derived cut-offs for the FIB-4 score, NFS score, and APRI score had a better Negative predictive value compared to the original cut-offs.

**Keywords:** Aspartate aminotransferase to platelet ratio index score, FibroScan, Fibrosis-4 score, Nonalcoholic fatty liver disease, Nonalcoholic fatty liver disease fibrosis score.

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## INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) remains the most common liver disease in the 21st century.<sup>1</sup> It has become a primary reason for liver transplantation and exposes individuals to an elevated risk of extrahepatic morbidity and mortality.<sup>2,3</sup> It is currently estimated that 25% of people worldwide suffer from NAFLD.<sup>4</sup> In India, the general population's prevalence of NAFLD varies from 9 to 53%.<sup>5,6</sup> It is crucial to differentiate between various stages of NAFLD in clinical management, given the significantly distinct prognoses associated with each stage. Furthermore, liver fibrosis emerges as the most robust predictor of long-term outcomes among patients with NAFLD.<sup>7</sup>

Liver biopsy has traditionally been considered the gold standard for diagnosing NAFLD. Nevertheless, its invasiveness has deterred routine implementation. The need for noninvasive methods as an alternative to liver biopsy has emerged for the diagnosis and prognosis of patients with NAFLD.<sup>8</sup> These methods encompass scores such as the fibrosis-4 (FIB-4) score, nonalcoholic fatty liver disease fibrosis score (NFS), and aspartate aminotransferase (AST) to platelet ratio index (APRI). Additionally, radiological techniques such as transient elastography (TE)/FibroScan, which is an ultrasound-based method, are widely recognized as one of the most validated noninvasive approaches for assessing hepatic fibrosis.<sup>9</sup> In general practice, noninvasive scores are commonly recommended for excluding advanced fibrosis. In this study, we aimed to compare the performance characteristics of different noninvasive scores in predicting advanced fibrosis as assessed by FibroScan.

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## METHODOLOGY

This prospective observational study was carried out in the Department of Medical Gastroenterology at Apollo Hospitals, Chennai, Tamil Nadu, India for a period of 18 months. A total of 130 patients meeting the inclusion criteria for NAFLD were selected. The demographic details consisted of the age of the study population in years, gender, body mass index (BMI) [to be calculated by weight (kg)/height (m<sup>2</sup>)], and waist circumference [in centimeters (cm)]. Based on BMI, the study population was divided into the following two groups: People with BMI <23 kg/m<sup>2</sup> – lean/normal, and people

with BMI  $\geq 23$  kg/m<sup>2</sup> – overweight/obese.<sup>10</sup> Blood investigations consisted of a complete hemogram, liver biochemistry, Fasting and post-prandial blood sugars, lipid profile, glycosylated hemoglobin, and viral serology to rule out hepatitis B surface antigen (HBsAg) and hepatitis C virus (HCV). The grades of fatty liver documented by ultrasound of the abdomen were also recorded.

Patients were then subjected to FibroScan where the following values were considered for different grades of fibrosis based on liver stiffness measurement (LSM): F0–F1:  $\leq 8.1$  kPa; F2: 8.2–9.6 kPa; F3: 9.7–13.5 kPa; and F4:  $\geq 13.6$  kPa. Based on the controlled attenuation parameter (CAP) values, the degree of steatosis was graded as S0:  $\leq 301$  dB/m, S1: 302–330 dB/m, S2: 331–336 dB/m, and S3:  $\geq 337$  dB/m.<sup>11</sup> Based on LSM, the patients were divided into the following two groups: Patients with advanced fibrosis and patients without advanced fibrosis. Patients with  $\geq F3$  that is F3–F4 fibrosis were grouped as those with advanced fibrosis and those with  $F \leq F2$  that is F0–F2 fibrosis, were grouped as patients without advanced fibrosis.<sup>12</sup> Patients with a FIB-4 score  $>2.67$ , NFS score  $>0.676$ , and APRI score  $>1.5$  were considered to be at high risk of having advanced fibrosis.<sup>10</sup> The study was conducted after obtaining the institutional ethics committee’s approval.

**Statistical Analysis**

Data were entered in Microsoft Excel and analyzed by using the Statistical Package for the Social Sciences (SPSS), version 25.0, software. Shapiro–Wilk test was applied to check the normality of data. Descriptive statistics were represented with percentages for qualitative data and mean with standard deviation (SD) for quantitative data. Chi-square test and Fisher’s exact test were applied for the comparison of proportions. An independent t-test was applied for comparison of means. The receiver operating characteristic curve (ROC) analysis was done to find the cut-off values. Performance characteristics of noninvasive scores were assessed. Kappa statistics was applied to measure the agreement;  $p < 0.05$  was considered as statistically significant.

**RESULTS**

A total of 250 patients were screened, out of which 130 patients who met the inclusion criteria for the study were included.

**Baseline Characteristics of Patients with Nonalcoholic Fatty Liver Disease**

Out of 130 patients included in the study, most of them were males (76.9%). About 90.8% of the study population was either overweight/obese. About 36.9% of the included patients were diabetics. Most of the patients were normotensive (70%). Metabolic syndrome was present in 65.4% of the patients (Table 1).

The majority of the patients had grade 1 fatty liver (76.2%). Only 16 patients (12.3%) had advanced fibrosis based on LSM.

**Distribution of Cases based on Standard Cut-offs for Noninvasive Scores**

Based on the standard cut-off of FIB-4 score (Table 2A), NFS score (Table 2B) and APRI (Table 2C) for advanced fibrosis, only 5 patients (3.8%) had a FIB-4 score of  $>2.67$ , 3 patients (2.3%) had a NFS score of  $>0.676$ , and 2 patients (1.5%) had an APRI score of  $>1.5$ .

**Predictors of Advanced Fibrosis**

Weight (kg), BMI (kg/m<sup>2</sup>), waist circumference (cm), Fasting blood glucose (mg/dL), AST (U/L), ALT (U/L), CAP (dB/m), FIB-4 score, NFS

**Table 1:** Baseline characteristics of patients with NAFLD

Variable	Category	n (%)
Age (years)	18–27	3 (2.3)
	28–37	30 (23.1)
	38–47	47 (36.2)
	48–57	35 (26.9)
	$\geq 58$	15 (11.5)
	Sex	Male
Female		30 (23.1)
BMI (kg/m <sup>2</sup> )	$\geq 23$	118 (90.8)
	$< 23$	12 (9.2)
Glycemic status	Normal	50 (38.5)
	IFG	32 (24.6)
	DM	48 (36.9)
Hypertension	Yes	39 (30)
	No	91 (70)
Metabolic syndrome	Yes	85 (65.4)
	No	45 (34.6)
Grade of fatty liver on USG	1	99 (76.2)
	2	27 (20.8)
	3	4 (3.0)
LSM	Patients with advanced fibrosis (F4)	6 (4.6)
	Patients with advanced fibrosis (F3)	10 (7.7)
	Patients without advanced fibrosis (F2)	11 (8.5)
	Patients without advanced fibrosis (F0–F1)	103 (79.2)
CAP	S0	63 (48.4)
	S1	30 (23.1)
	S2	3 (2.3)
	S3	34 (26.2)
Increased WC		113 (86.9)
Hypertriglyceridemia		72 (55.4)
Low HDL		86 (66.2)

CAP, controlled attenuation parameter; DM, diabetes mellitus; HDL, high-density lipoprotein; IFG, impaired fasting blood glucose; LSM, liver stiffness measurement; USG, ultrasonography; WC, waist circumference

**Table 2A:** Performance of FIB-4 score

FIB-4 reference	LSM	
	Patients with advanced fibrosis (F3–F4)	Patients without advanced fibrosis (F0–F2)
$>2.67$ (n = 5)	3 (18.8%)	2 (1.8%)
$\leq 2.67$ (n = 125)	13 (81.2%)	112 (98.2%)
Total	16 (100.0%)	114 (100.0%)

Kappa value = 0.24;  $p = 0.001$

score, APRI score values were higher in patients with advanced fibrosis as compared to patients without advanced fibrosis.

Of the 16 patients who had advanced fibrosis, 15 of them (93.8%) had metabolic syndrome.

**Table 2B:** Performance of NFS score

NFS Ref	LSM	
	Patients with advanced fibrosis (F3–F4)	Patients without advanced fibrosis (F0–F2)
	n (%)	n (%)
>0.676 (n = 3)	3 (18.8%)	0 (0.0%)
≤0.676 (n = 127)	13 (81.2%)	114 (100.0%)
Total	16 (100.0%)	114 (100.0%)

Kappa value = 0.29;  $p < 0.001$

**Table 2C:** Performance of APRI

APRI reference	LSM	
	Patients with advanced fibrosis (F3–F4)	Patients without advanced fibrosis (F0–F2)
	n (%)	n (%)
>1.5 (n = 2)	2 (12.5%)	0 (0.0%)
≤1.5 (n = 128)	14 (87.5%)	114 (100.0%)
Total	16 (100.0%)	114 (100.0%)

Kappa value = 0.2;  $p < 0.001$

**Table 2D:** Performance characteristics of noninvasive scores compared to FibroScan

Performance characteristics	Noninvasive scores		
	FIB-4 > 2.67	NFS > 0.676	APRI > 1.5
Sensitivity	18.75%	18.75%	12.50%
Specificity	98.25%	100.00%	100.00%
Positive likelihood ratio	10.69	–	–
Negative likelihood ratio	0.83	0.81	0.88
PPV	60.00%	100.00%	100.00%
NPV	89.60%	89.76%	89.06%
Accuracy	88.46%	90.00%	89.23%

However, our analysis also showed that out of 85 patients who had metabolic syndrome, 15 of them had advanced fibrosis. At a standard cut-off, FIB-4 above 2.67 could identify only 3 patients with metabolic syndrome, NFS above 0.676 could identify 3 patients with metabolic syndrome and APRI above 1.5 could identify only 1 patient with metabolic syndrome at high risk for advanced fibrosis.

### Performance Characteristics of Noninvasive Scores Compared to FibroScan

The FIB-4 score had a specificity of 98.25%, the NFS score had a specificity of 100%, and the APRI had a specificity of 100%. The noninvasive scores had a better specificity but a poor sensitivity as depicted in Table 2D.

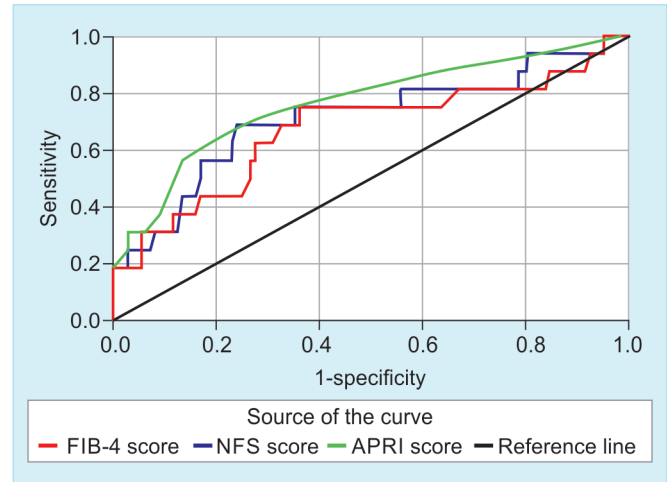
In the present study, the APRI score with an AUROC of 0.768 performed better than the NFS score who had an AUROC of 0.714, and the FIB-4 score who had an AUROC of 0.675 in identifying patients with advanced fibrosis (≥F3 fibrosis) based on FibroScan (Table 3; Fig. 1).

### Performance Characteristics of Newly Derived Cut-offs of Noninvasive Scores Compared to FibroScan

Based on the ROC curve, cut-offs were derived to exclude advanced fibrosis. Table 4 shows the sensitivity, specificity, positive predictive

**Table 3:** Area under the receiver operating characteristic curve

Test result variable(s)	Area under the curve				
	Standard Area	Standard error	p-value	Asymptotic 95% confidence interval	
				Lower bound	Upper bound
FIB-4 score	0.675	0.083	0.024	0.512	0.838
NFS score	0.714	0.078	0.006	0.560	0.868
APRI score	0.768	0.070	0.001	0.631	0.906



**Fig. 1:** Area under receiver operator curve

**Table 4:** Performance characteristics of newly derived cut-offs of noninvasive scores compared to FibroScan

Performance characteristics	Noninvasive scores		
	FIB-4 ≥ 1.18	NFS ≥ -0.9	APRI ≥ 0.65
Sensitivity	75.00%	68.75%	68.75%
Specificity	64.04%	76.32%	75.44%
Positive likelihood ratio	2.09	2.9	2.8
Negative likelihood ratio	0.39	0.41	0.41
Positive predictive value	22.64%	28.95%	28.21%
Negative predictive value	94.81%	94.57%	94.51%
Accuracy	65.38%	75.38%	74.62%

value (PPV), negative predictive value (NPV), and overall accuracy (OA) of the noninvasive scores.

The sensitivity and specificity of the newly derived cut-off for the FIB-4 score were 75%; 64.04%, for the NFS score were 68.75%; 76.32%, and for the APRI score was 68.75%; 75.44%.

### Comparison between the Standard and Newly Derived Cut-off for Advanced Fibrosis in the Present Study

Upon utilizing the recently established cutoff values for FIB-4 score, NFS score, and APRI score, the sensitivity to detect advanced fibrosis increased but was modest. However, the NPV increased even further which would help exclude advanced fibrosis. In the present study, the newly derived cut-off for FIB-4 score of ≥1.18 had the best sensitivity (75%) and negative predictive value. NFS score ≥ -0.9 had the best specificity (76.3%) (Table 5).

## DISCUSSION

This single-center study comprised 130 participants with NAFLD. The study assessed the performance of noninvasive scores by comparing them with FibroScan, employed as the reference standard for patients with NAFLD.

In this study, male preponderance was seen, 90.8% of the patients were either overweight/obese, and abnormal blood glucose levels were seen in 61.5% of the patients. These findings were similar to most of the studies.<sup>13-17</sup> Metabolic syndrome was seen in approximately two-third of the patients in the present study.

Patients with advanced fibrosis had a higher FIB-4 score when compared to those without advanced fibrosis. Similar findings were seen in the studies by Fallatah et al.,<sup>13</sup> McPherson et al.,<sup>16</sup> Shamseya et al.,<sup>17</sup> Mohamed et al.,<sup>18</sup> and Kolhe et al.<sup>19</sup>

The NFS score was higher in patients with advanced fibrosis in the present study. Similar findings were seen in the studies by McPherson et al.,<sup>16</sup> Shamseya et al.,<sup>17</sup> and Mohamed et al.<sup>18</sup>

Patients with advanced fibrosis had a higher APRI score. Similar findings were seen in the studies by Fallatah et al.,<sup>13</sup> McPherson et al.,<sup>16</sup> Mohamed et al.,<sup>18</sup> and Kolhe et al.<sup>19</sup>

### Performance of Noninvasive Scores based on Standard Cut-offs

Aspartate aminotransferase to platelet ratio index had the best AUROC in the present study. Similar findings were seen in the study by Amernia et al. and Mahady et al. where FibroScan was the reference standard,<sup>14,15</sup> In the study by Kolhe et al. where liver biopsy was the reference standard, APRI had the best AUROC.<sup>19</sup> Table 6 depicts the performance of noninvasive scores based on standard cut-offs across various studies.

In our study, based on the area under the receiver operating characteristic curve (AUROC) cut-off with the best sensitivity and specificity for the FIB-4 score was  $\geq 1.18$ , for NFS score was  $\geq -0.9$ , and for APRI score was  $\geq 0.65$ , respectively.

However, our analysis has also shown that out of 85 patients who had metabolic syndrome, 15 of them had advanced fibrosis. At

a standard cut-off, FIB-4 above 2.67 could identify only 3 patients with metabolic syndrome, NFS above 0.676 could identify 3 patients with metabolic syndrome and APRI above 1.5 could identify only 1 patient with metabolic syndrome at high risk for advanced fibrosis. Thus, patients with metabolic syndrome may have a different cut-off for noninvasive scores in identifying those at high risk for advanced fibrosis. This however would need validation in a larger cohort study.

In a resource-limited setting where FibroScan is not available based on the high negative predictive value obtained from the derived cut-offs in the present study, advanced fibrosis could be excluded without the need for FibroScan.

The high negative predictive value of the newly derived cut-offs would aid clinicians in a resource-limited setting to clear patients for major surgery by excluding advanced fibrosis. However, the newly derived cut-offs would need validation in a larger cohort study.

## CONCLUSION

Patients with impaired fasting blood glucose levels, diabetes mellitus, and metabolic syndrome are at a risk for advanced fibrosis. Furthermore, APRI had the best area under the receiver operator curve (0.768) in the study. The recently determined cut-off values for FIB-4 score, NFS score, and APRI score demonstrated improved negative predictive values compared to the original cut-offs, along with enhanced sensitivity. However, it is important to note that the sensitivity was found to be modest. The newly derived cut-offs can be used to exclude patients with advanced fibrosis in the absence of FibroScan in a resource-limited setting, however, this needs validation in a larger cohort study.

### Limitations

- This was a single-center study, with a limited sample size.
- The number of patients with advanced fibrosis was less (only 16 patients).
- The gold standard test of liver biopsy was not performed.
- The newly derived cut-offs need validation in a larger cohort.

**Table 5:** Comparison between the standard and newly derived cut-off for advanced fibrosis in the present study

Variable	Cut-off	Sensitivity	Specificity	PPV	NPV	OA
FIB-4 score	Standard cut-off > 2.67	18.75	98.25	60	89.6	88.46
	Cut-off derived in present study $\geq 1.18$	75	64	22.6	94.8	65.4
NFS score	Standard cut off >0.676	18.75	100	100	89.76	90
	Cut-off derived in present study $\geq -0.9$	68.8	76.3	28.9	94.6	75.4
APRI score	Standard cut off >1.5	12.5	100	100	89.06	89.23
	Cut-off derived in present study $\geq 0.65$	68.8	75.4	28.2	94.5	74.6

OA, overall accuracy

**Table 6:** Performance of noninvasive scores based on standard cut-offs

Study	Performance of noninvasive scores based on standard cut-offs		
	Best test	AUROC	Reference standard
Present study	APRI > NFS > FIB-4	0.768 > 0.714 > 0.675	FibroScan
Amernia et al. <sup>14</sup>	APRI > FIB-4 > AST/ALT	0.923 > 0.913 > 0.720	FibroScan
Mahady et al. <sup>15</sup>	APRI > FIB-4 > NFS	0.71 > 0.64 > 0.63	FibroScan
McPherson et al. <sup>16</sup>	FIB-4 > AST/ALT > NFS	0.86 > 0.83 > 0.81	Liver biopsy
Mohamed et al. <sup>18</sup>	FIB-4 > NFS > APRI	0.936 > 0.916 > 0.907	Liver biopsy
Kolhe et al. <sup>19</sup>	APRI > FIB-4 > FIB-5	0.95 > 0.78 > 0.75	Liver biopsy
Shah et al. <sup>20</sup>	FIB-4 > NFS > Goteborg University Cirrhosis Index	0.802 > 0.768 > 0.743	Liver biopsy

## CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

PDB: Participated in data acquisition, literature search, manuscript preparation, and manuscript editing.

SAP: Participated in conceptualization and manuscript editing.

KRP: Data literature search and manuscript editing.

PP: Conceptualization and manuscript editing.

NM: Participated in manuscript editing.

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