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Original Research Article

FIB-4 and APRI in Risk Assessment of NAFLD in Central India

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Abstract:

Introduction: Number of non-alcoholic fatty liver disease (NAFLD) cases is increasing day by day due to changes in food habits, exaggeration in metabolic syndrome, and lack of exercise. Test for diagnosis and staging of NAFLD Liver biopsy is the choice, but now a days numerous biochemical markers, scoring systems, and imaging studies are existing to diagnose and stage NAFLD which is allied to end-stage liver disease, hepatocellular cancer. Indices have been developed by researchers to assess liver fibrosis in NAFLD patients to avoid liver biopsy. In this study we aimed to compare fibrosis-4 (FIB-4), aspartate aminotransferase (AST) to platelet ratio index (APRI), with USG for the assessment of hepatic fibrosis in patients with NAFLD.

Material and Method: This cross-sectional study included patients with NAFLD conducted in People's College of Medical Sciences and Research Centre, Bhopal (M.P.). Cases and comparison group were selected from patients presenting to outpatient Department of Medicine and Radiology by systematic random sampling. Anthropometric features of the participants including age, gender, weight, height was recorded. All participants underwent USG and had their AST, ALT, and platelet count measured in a random blood sample, taken within 1 month of the USG.

Result: A total of 172 individuals were included, of which 86 cases are of NAFLD and 86 cases control with cases with mean age 44 yrs.47.3% had moderate risk and 14 % had low risk. The mean AST and ALT levels were and 59.11±30.70 U/L and 69.022± 36.40 respectively in NAFLD cases. FIB4 and APRI are correlated with r= 0.832 with P=0.00 which is significant FIB 4.

Conclusion: NAFLD can be assessed without invasion for fibrosis Our findings indicate that FIB-4 and APRI could play a role as a risk-stratification tool for a population health approach. NAFLD cases can progress to NASH and hepatocarcinoma so it should be diagnosed for fibrosis as early intervention.

Keywords: ALT alanine transaminase, AST aspartate transaminase, APRI AST platelet ratio index FIB-4 Fibrosis-4 Index, NAFLD non-alcoholic fatty liver disease, NASH nonalcoholic steatohepatitis.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is presently a very common liver disease. NAFLD is well-defined by pathologic accumulation of fat in the liver, and it have various anomalies ranging from simple fatty liver (steatosis) to non-alcoholic steatohepatitis (NASH) [1], while further developing to liver cirrhosis and hepatocellular carcinoma (HCC) [2]. The global prevalence of NAFLD is approximately 25%, and the prevalence in the USA has risen from 20.0% to 31.9% in the past years [3,4]. The estimated prevalence is 29.62% in Asia. [5]. The NAFLD prevalence in around is 9-32% in India reported by epidemiological studies. [6]. NAFLD is also closely related to multiple significant extrahepatic manifestations, including chronic kidney disease, cardiovascular disease (CVD), and some extrahepatic cancers resulting in an increased disease burden [7]. In the future, liver complications of NAFLD could be the most common reason for liver transplantation.

Abdominal ultrasonography (USG) is the most common imaging method for the assessment of NAFLD, with sensitivity and specificity of around 85% and 90%, respectively [8].

For diagnosis of NAFLD liver biopsy is an invasive diagnostic tool with little but significant hazard, and the decision of when to perform it remains to be controversial [5,9,10]. Therefore, it is necessary to search

for less aggressive methods for screening, distinguishing various NAFLD stages, and following their progression [11,6]. FIB-4 and APRI are the two scoring models for invasive diagnosis for fibrosis and risk assessment of NAFLD which have sufficient specificity, sensitivity and reproducibility.

FIB-4 index as the first step is usually the most common. Both cost-effective and highly sensitive tools is FIB-4 index to eliminate patients with advanced fibrosis. Moreover, higher scores may find patients at higher risk of non-liver- and liver-associated morbidity and mortality [9]. The FIB-4 index is easy to use in clinical practice and has a comparable diagnostic capacity for advanced fibrosis to that of magnetic resonance elastography [10].

When evaluating liver fibrosis in patients with NAFLD, a FIB-4 index < 1.3 is categorised as low risk, while a FIB-4 index ≥2.67 is categorized as high risk of fibrosis [12,13,14]. FIB-4 index can be easily calculated using routine clinical and biochemical indices, so it may be used for primary screening for advanced fibrosis in the general population. APRI is also fibrosis score with a ratio of AST to platelet count. It is categorised as <0.7 as low risk of fibrosis, while APRI score >1 as high risk of fibrosis.

Methods

This was a hospital based analytical cross-sectional study conducted in People's College of Medical Sciences and Research Centre, Bhopal (M.P). Cases and comparison groups were selected from patients presenting to outpatient department of medicine and radiology by systematic random sampling under the following.

Inclusion Criteria of NAFLD

- Patients in both gender in age group of 25 to 60 years of age.
- Diagnosed cases of NAFLD based on USG abdomen done in People's Hospital and non-alcoholics.

USG guidelines

Ultrasound features include any 4 of the following 5 sonographic features: (1) attenuation of image quickly within 4-5 cm of depth; [2] echogenic diffusely but particularly important to note brightness within the first 2-3 cm of depth; [3] liver uniformly heterogeneous; [4] thick subcutaneous depth (> 2 cm); and [5] liver fills entire field with no visible edges [18]

Non-Alcoholics

Either no alcohol or alcohol consumption less than 30g/ day in man and 20g /day in woman.

ALT >AST (even if normal)

Inclusion Criteria of comparison group

Patients in both gender in age group of 25 to 60 years of age.

- USG negative for NAFLD who had USG abdomen done in people's hospital.

Non-Alcoholics

Either no alcohol or alcohol consumption less than 30 g day in men and 20g/day in woman.

ALT > AST (even if normal)

Exclusion criteria for NAFLD cases and Comparison group

- Hepatitis A, B and C
- other liver diseases and Cancers
- Cardiac diseases
- Drugs causing liver injury- antitubercular drugs, anabolic steroids, amiodarone, atorvastatin and methotrexate.
- Persons not willing to participate in study.

Sampling Collection

After overnight fasting for 8-12 hours, approx.10ml blood sample for serum LFT and lipid profile in plain vials, for glucose in fluoride vial samples. Blood sample is centrifuged at 3000rpm for 10 minutes. The serum is separated and immediately stored in freezer at -20°C till further analysis for assays of emerging NAFLD biomarkers. Anthropometric parameters, including body weight and height, BMI, waist circumference (WC), and blood pressure (BP), will be measured. Fasting blood glucose, lipids, platelet count (CBC), and ALT, AST tests will be performed through automated analyzer – Biosystem BA 200.
The sample size was calculated 182 with 86 cases and 86 comparison Sample size is calculated from the below formula:

$$\text{Sample size n} = \frac{(Z_\alpha + Z_\beta)^2 \times S^2 \times 2}{D^2}$$

Where, $Z_\alpha = 1.96$ when α is 5%.
$Z_\beta = 0.842$ when β is 20%
Hence (power of study is 80%)
S = common standard deviation=0.75
D = mean difference= 0.3
APRI and FIB-4 were also calculated based on the following formulae:

$$\text{APRI: } \frac{\text{AST level /ULN}}{\text{Platelet count } (10^9/\text{L}) \times 100}$$

$$\text{FIB} - 4 = \frac{\text{Age (years)} \times \text{AST (U/L)}}{\text{PLT } (10^9/\text{L}) \times ALT^{1/2} \text{ (U/L)}}$$

- Serum ALT with 45.25 U/L as upper limit of normal in men and 30.47 in women.
- Serum AST with 15–37 U/L as the normal range.
- Platelet count with 150,000–400,000/µL as the normal range.

Data analysis, Statistical Package for the Social Sciences (SPSS) software (version 25.0, Armonk, NY: IBM Corp.) was used for data analysis. Mean, standard deviation, median, interquartile range (IQR), frequency, and percentages were used to describe the results. Continuous variables are presented as mean±standard deviation or median (min–max) values according to the distribution of the data. Categorical variables were presented as number (n) and percentage (%). Dependent Sample t-test or the Wilcoxon test was used to compare numerical data in dependent groups, according to the conformity of the data to the normal distribution. Distribution normality of quantitative variables were determined using the Kolmogorov–Smirnov normality test. Accordingly, Spearman's correlation was used to determine their correlations and the Mann-Whitney test was used for comparison by gender.

Results

Of the 172 subjects enrolled 86 patients with NAFLD with a mean age of 44.12±10.18 years and 86 comparison group with a mean age of 42.70±11.30 years included in this study.39 (45.2%) were male and 47 (54.7) were female in cases with NAFLD and 44(51.2%) were male and 42 (48.8) were female in comparison group. General characteristics of the study participants are shown in Table 1. The mean AST and ALT levels were and 59.11±30.70 U/L and 69.022±36.40 respectively in NAFLD cases. The mean AST and ALT levels were and 79.50±97.08 U/L and 77.75± 38.65 respectively in comparison group. The mean platelet count was 193.746±62.406/ µL in NAFLD cases and 259.163±194.265 respectively in comparison group.

Table 1:

		Mean	Std. Deviation	t	df	P value
AGE	Positive	44.0000	10.18303			
	Control	42.7093	11.30525	.787	170	.433
WT	Positive	71.1938	9.66758	2.971	170	.003
	Control	66.9940	8.85114			
HT	Positive	167.5788	9.02754	.130	170	.897
	Control	167.4028	8.76315			
BMI	Positive	25.559	3.668	3.417	170	.001
	Control	23.936	2.437			
PLC	Positive	193.746	62.406	2.973	170	.003
	Control	259.163	194.265			
FIB4	Positive	1.835	1.039	1.604	170	.002
	Control	1.631	2.957			
APRI	Positive	.888	.614	2.904	170	.004
	Control	.905	1.381			

With reference to table 2. NAFLD cases in age group (20-35yrs) is 22.15 (n=19), in 35-50 yrs is 45.3% (n=39), above 50yrs is 32.6% (n=28) respectively. Other comparison group in age group (20-35yrs) is 26.7 (n=23), in 35-50 yrs. is 37.2% (n=32), above 50 yrs is 36.0% (n=31).

Table 2:

Age	NAFLD		CONTROL	
	Frequency	Percent	Frequency	Percent
20-35	19	22.1	23	26.7
35-50	39	45.3	32	37.2
50 and above	28	32.6	31	36.0
Total	86	100.0	86	100.0

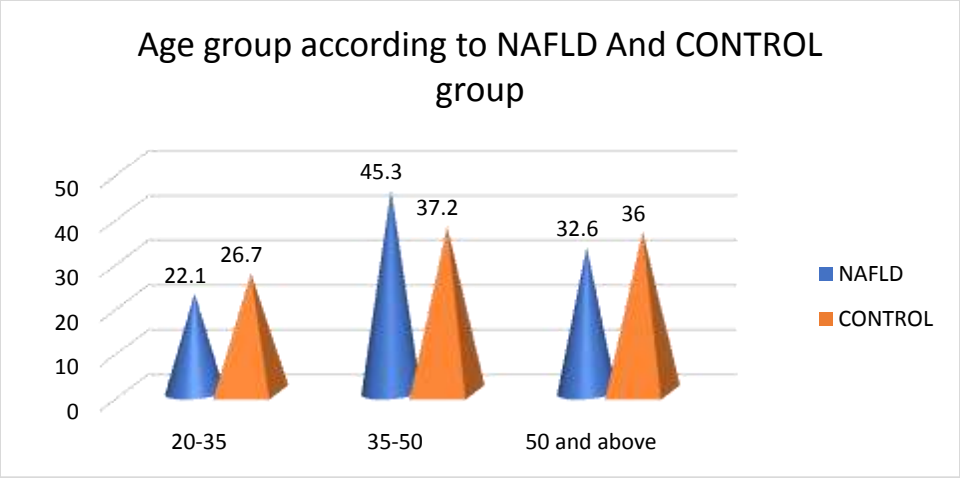

Figure 1:

When evaluating liver fibrosis in patients with NAFLD, a FIB-4 index < 1.3 is categorised as low risk, while a FIB-4 index ≥2.67 is categorized as high risk of fibrosis and between 1.3 and 2.67 is moderate risk. According to the FIB 4 score, 38.3% (n:33) of patients were low-risk, 47.7% (n:41) were intermediate-risk, and 14% (n:12) were at high-risk in NAFLD case (Table3). FIB4 score indifferent age group is significant with P value =0.03 with reference table 4 and graph 3. Among different indices, only FIB-4 was significantly correlated with age ($r = 0.272$, $P = 0.001$); however, the correlation was weak.

Table 3:

NAFLD		CONTROL	
Frequency	**Percent**	**Frequency**	**Percent**
33	38.4	41	47.7
41	47.7	39	45.3
12	14.0	6	7.0
86	100.0	86	100.0

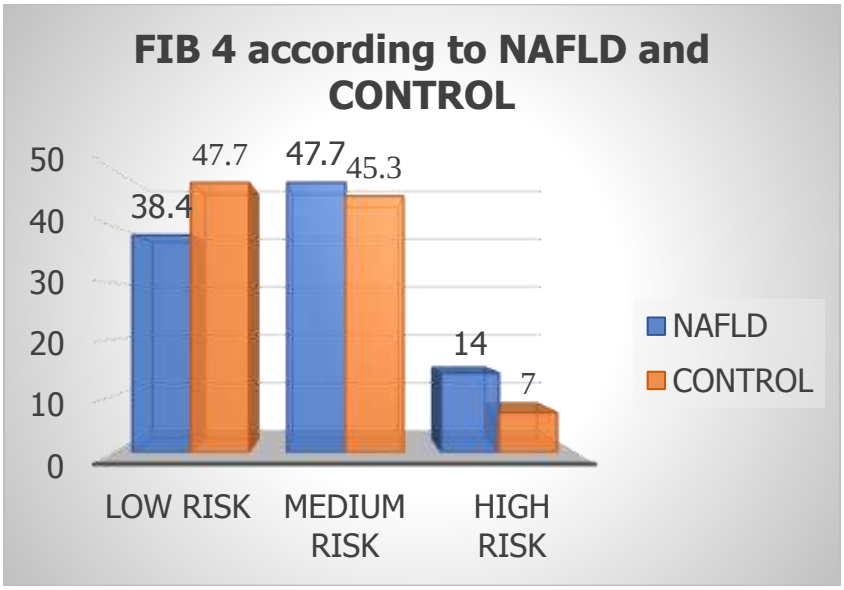

Figure 2:

Table 4:

AGE * FIB4

	Low risk	Medium risk	High risk	Total	Chi square value	df	P value
20-35	14	5	0	19	15.963	4	.003
35-50	14	19	6	39			
50 and above	5	17	6	28			

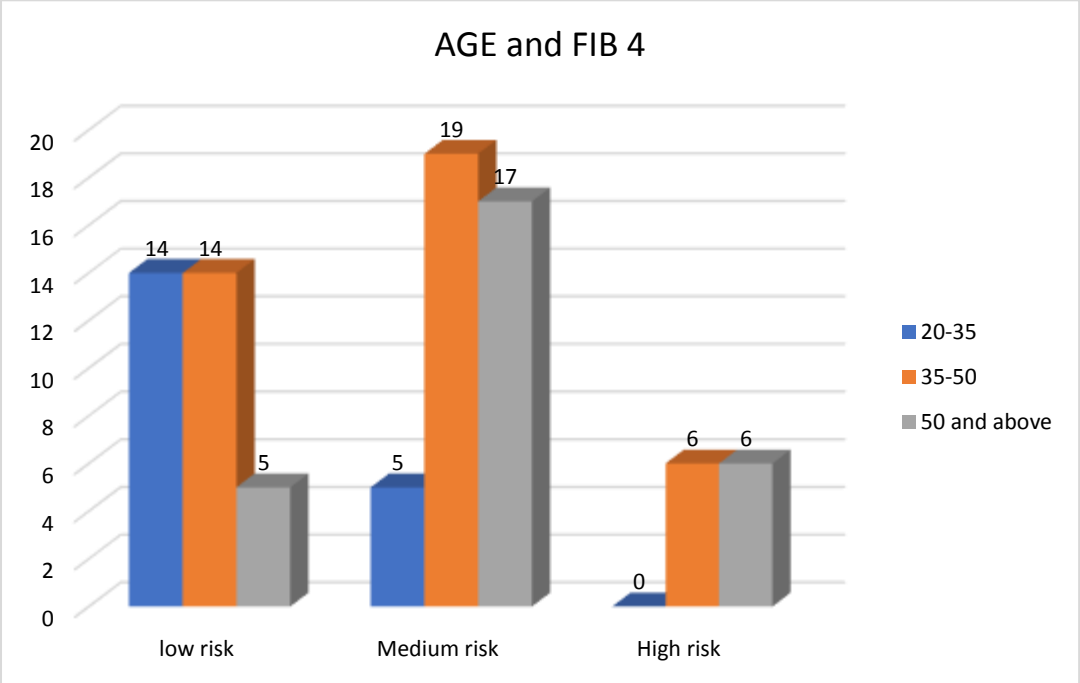

Figure 3:

APRI is also fibrosis score with a ratio of AST to platelet count. It is categorised as <0.7 as low risk of fibrosis, while APRI score >1 as high risk of fibrosis with intermediate risk between 0.7 and 1. According to the APRI score, 48.8% (n:42) of patients were low-risk, 27.9% (n:24) were intermediate-risk, and 23.3% (n:20) were at high-risk in NAFLD cases. Table5, Graph4. FIB4 and APRI are correlated with r= 0.832 with P=0.00 which is significant.

Table 5:

APRI	NAFLD		CONTROL	
	Frequency	Percent	Frequency	Percent
Low risk	42	48.8	45	52.3
Medium risk	24	27.9	23	26.7
High risk	20	23.3	18	20.9
Total	86	100.0	86	100.0

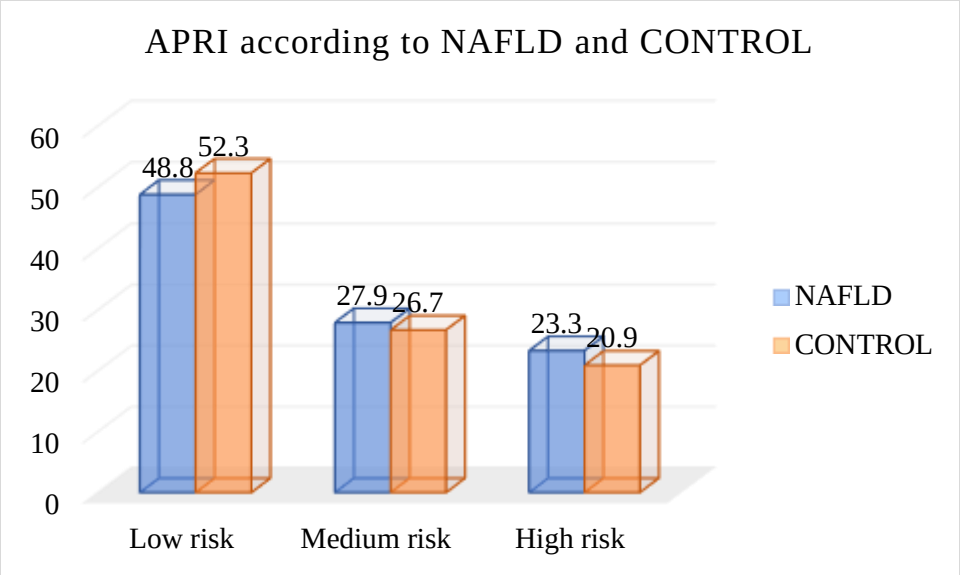

Figure 4:

APRI is more accurate for high-risk patient in comparison to FIB4 with reference to table 6.

Table 6:

NAFLD	FIB 4		APRI	
	Frequency	**Percent**	**Frequency**	**Percent**
Low risk	33	38.4	42	48.8
Medium risk	41	47.7	24	27.9
High risk	12	14.0	20	23.3
Total	86	100.0	86	100.0

Discussion

The main reason of end-stage liver disease, HCC, and liver transplantation is NAFLD throughout the world. Conventional ultrasonography is low cost, safe, and available, and the most commonly used imaging technique for screening for fatty liver [16]. In the current study, it has been showed that liver ultrasonography allows for reliable and exact detection of moderate-severe fatty liver compared to histology with sensitivity and specificity of 84.8% and 93.6%, respectively [8]. Moreover, European guidelines recommend using ultrasonography as first-choice to identify risk of NAFLD in adults [17].

In this study female were more as compared to male in study population in contrary to NAFLD is more prevalent in men than in premenopausal women but occurs at an even higher rate in postmenopausal women[17].In our study NAFLD cases were more in 35-50 yrs is 45.3% while the mean age of population was over 50 years in other study.[18] We found that serum AST activity was correlated with liver fibrosis in patients with NAFLD independent of age and BMI. Serum ALT and AST activities have been widely used by clinicians to access the liver function and damage same was shown by Dai et al (2022).[19] Serum AST and ALT activities have the advantage of low cost and availability for detection of liver injury, establishing their measurement as important biomarkers in identifying the presence of liver fibrosis. Liver biopsy is still necessary to detect fibrosis status and patients with NASH. However, liver biopsy is invasive, costly, less suitable for population-level screening, and shows inter-observer variability[19].

Patients with NAFLD may have mild or moderate elevations in AST and ALT, though normal aminotransferase levels don't exclude NAFLD. Elevated AST and ALT values have been shown to usually be 2–5 times the upper limit of normal, giving patients with NAFLD may have mild or moderate elevations in AST and ALT, although normal aminotransferase levels do not exclude NAFLD. The results of the current study revealed APRI as the best index to differentiate moderate and high risk of liver fibrosis from low risk as compared to FIB-4.

On contrary the diagnostic accuracy of APRI and AST/ALT ratio has been reported to be low for diagnosing advanced fibrosis in patients with NAFLD in one study [20]. The higher diagnostic performance of

APRI in our study, contrary to previous findings, can be due to the measurement accuracy of laboratory parameters in the APRI formula as the cause of fibrosis in our study is NAFLD as well as. APRI scores perform better than FIB-4 for identifying significant fibrosis in patients with NAFLD but do not have PPVs so high to be considered diagnostic tool. APRI scores perform better than FIB-4 for identifying significant fibrosis in patients with NAFLD but do not have PPVs so high to be considered diagnostic tool. [21]

FIB-4 and APRI have been recommended by many guidelines, including the World Health Organization (WHO) guidelines to determine the stage of fibrosis in countries with limited resources [22,23,24].

FIB-4 was the only index significantly correlated with age in our study probably because it includes age in its formula. However, contradictory to our findings, FIB-4 has been reported to have better performance compared to APRI in NAFLD [25].

In the current study, it is showed that APRI and FIB 4 scores to be used in the follow up of of NAFLD patients at early stages with no clear indication for liver biopsy same was shown by Fallatah e al.[26].

Fibrosis-4 index (FIB-4) is a clinical score based on common clinical parameters such as age, aspartate aminotransferase [AST], alanine aminotransferase [ALT], and platelets and has been shown to have the best diagnostic accuracy for advanced fibrosis when compared with other non-invasive clinical scores.

Recent suggestion shows that, FIB-4 also has prognostic value with diagnostic accuracy and can predict adverse outcomes among patients with NAFLD.

Limitations with our study is diagnosis of fibrosis with USG and not with liver biopsy. USG limitation appears to be obesity [13,14]. For excluding advanced fibrosis in morbidly obese patients with NAFLD, a recent study reported that FIB-4 and APRI are valuable [27]. Non-invasive evaluation of fibrosis severity is important in management of NAFLD patients, because of the fibrosis stage is a determinant of mortality.

Conclusion

We found APRI and FIB 4 to be the best indices to foresee advanced liver fibrosis and risk stratification of NAFLD. Thus, with minimal invasion and resources APRI and FIB 4 are appropriate indices for the prediction of significant liver fibrosis, contributing to decision, for further investigations. Lifestyle modifications can be suggested based on the diagnosis of indices.

Conflict of Interest: Nothing to declare.

Ethical Approval: No funding/financial support was received for the conduct of this research or for the preparation of this article. IEC and RAC approval was taken from People's University, Bhopal.

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