ORIGINAL RESEARCH

To assess the diagnostic accuracies of APRI and FIB4 in predicting various stages of liver fibrosis in patients with non-alcoholic fatty liver disease (NAFLD) and to determine their correlation with Fibroscan

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ABSTRACT

Aim: To assess the diagnostic accuracies of APRI and FIB4 in predicting various stages of liver fibrosis in patients with non-alcoholic fatty liver disease (NAFLD) and to determine their correlation with Fibroscan.**Material and methods:** The patients were identified using ultrasound imaging and both males and females were included in the study. This research covered all individuals who were diagnosed with non-alcoholic fatty liver disease (NAFLD). The laboratory test findings that were assessed included those within the hospital records. The collected findings were all acquired during a one-month timeframe after a Fibroscan test. The standard range for serum alanine aminotransferase (ALT) in a laboratory is 30 - 65 U/L. The established upper limits for serum ALT levels were 45.25 U/L for men and 30.47 U/L for females. The usual reference range for serum aspartate aminotransferase (AST) is 15-37 U/L, whereas the normal reference range for platelet counts is 150-400 k/uL. **Results:**The average APRI and FIB-4 values for the participants in the research were 0.88±0.12 and 1.66±0.34, respectively. Non-alcoholic fatty liver disease (NAFLD) fibrosis was seen in 43.75% of the participants. Specifically, fibrosis stages G1, G2, G3, and G4 were found in 21.25%, 8.75%, 10%, and 3.75% of the participants, respectively. According to the FibroScan findings, 50% of the cases were categorized as F1, 31.25% as F2, 12.5% as F3, and 6.25% as F4. The mean values of AST/ALT, APRI, and FIB-4 were higher in the F3+F4 grade compared to the F1+F2 grade. When comparing mean AST/ALT, APRI, and FIB-4 based on fibroscan findings, a significant difference was seen in relation to APRI and FIB-4, with a p-value of less than 0.05. AST/ALT has the lowest sensitivity and specificity when it comes to predicting various stages of liver fibrosis in individuals with non-alcoholic fatty liver disease (NAFLD).**Conclusion:** Our findings indicate that APRI is the most effective marker for predicting advanced liver fibrosis when compared to the AST/ALT ratio. Additionally, APRI shows a similar level of accuracy as FIB-4, but exhibits the highest connection with FibroScan results. Thus, in situations where there are limited resources and FibroScan is not accessible, APRI serves as a suitable indicator for predicting significant liver fibrosis.

Keywords: NAFLD,FIB-4, APRI, AST,ALT

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is now the most widespread liver disease, impacting around two billion individuals worldwide. It has rapidly and discreetly reached epidemic levels, earning the nickname of a "silent epidemic[1-2]. In India, the situation is concerning, as the prevalence rate of non-alcoholic fatty liver disease (NAFLD) ranges from 14.6% to 42% [3]. It is estimated that the worldwide occurrence of NAFLD will increase to 56% during the next ten years [4]. NAFLD, or non-alcoholic fatty liver disease, is a common cause of chronic liver disease. It includes a range of conditions, starting with non-alcoholic fatty liver (NAFL) or simple steatosis, which can progress to non-alcoholic steatohepatitis (NASH), cirrhosis, and eventually hepatocellular

carcinoma (HCC) and/or end-stage liver disease (ESLD). These conditions significantly impair liver function [2]. Severe instances of non-alcoholic fatty liver disease (NAFLD) may lead to hepatocellular carcinoma (HCC) even if cirrhosis is not present [4]. Both HCC and ESLD have a significant influence on life expectancy. The only viable option in such cases is liver transplantation, but only for individuals who meet the requirements to be considered ideal candidates for the procedure [2,5]. There is evidence suggesting that people with certain conditions are not just at a higher risk for liver problems, but also for heart problems such as hypertension, coronary artery disease, cardiac arrhythmias, or cardiomyopathy [6].Therefore, it is necessary for these individuals with NAFLD to have regular consultations with gastroenterologists for periodic monitoring. There should be tests with a specific threshold value that can definitively rule out fibrosis in NAFL patients. This would allow for careful monitoring and treatment to prevent or postpone the progression of fibrosis to its complex and difficult-to-manage phase. Additionally, these individuals will be safeguarded from receiving superfluous liver biopsies.Liver biopsy is widely regarded as the most reliable method for diagnosing simple steatosis and fibrosis in patients with non-alcoholic fatty liver disease (NAFLD). However, it is associated with several limitations and dangers. Additionally, the need for continuous monitoring of NAFLD patients to assess disease progression and response to therapy via repeated biopsies is impractical. Various blood tests, including specialized ones, or a combination of tests, have been used to assess potential liver scarring. However, none of these assays are flawless. Fibroscan is a rapid and convenient diagnostic conducted at the patient's bedside, taking just five minutes to complete. It provides instant results and is well-received by patients, with a high level of acceptability [8]. The use of the XL probe, instead of the M probe, has addressed the potential constraint of obesity on the effectiveness of the treatment. This modification is specifically intended for patients with a body mass index larger than 30 kg/m2 [9]. The fibroscan has the potential to replace liver biopsy as the most accepted and most reliable method [7]. However, the availability of this technology is restricted since it is quite expensive and requires educated professionals, which prevents its widespread usage for monitoring the general population in developing nations such as India [10]. The Fibrosis-4 (FIB-4) score system is used to assess the severity of liver fibrosis. It takes into account the patient's age, platelet count, aspartate transaminase (AST), and alanine transaminase (ALT). These factors may be readily obtained by a primary care physician and the test itself is affordable [11]. Fibrofast (FIB-5) is a cost-effective and non-invasive method used by primary care physicians to evaluate liver fibrosis. It assesses liver fibrosis by measuring ALT, AST, ALT/AST ratio, albumin, alkaline phosphatase (ALP), and platelet count, all of which are readily accessible.

MATERIAL AND METHODS

This research was a prospective, observational study done among 80 patients with non-alcoholic fatty liver disease (NAFLD). The patients were identified using ultrasound imaging and both males and females were included in the study. The research was done at the department of medicine, after approval from the Institutional Ethical Committee. This research covered all individuals who were diagnosed with non-alcoholic fatty liver disease (NAFLD). The research excluded individuals with evidence of other chronic liver illnesses such as hepatitis B or C, alcoholic liver disease, patients on hepatotoxic drugs, those with advanced liver disease, and those with acute fatty liver during pregnancy. Furthermore, those with excessively high body mass indexes (BMIs) or other factors that made them ineligible for Fibroscan scans, as well as those with clinical or ultrasound indications of decompensated cirrhosis, were excluded from the research. The laboratory test findings that were assessed included those within the hospital records. The collected findings were all acquired during a one-month timeframe after a Fibroscan test. The standard range for serum alanine aminotransferase (ALT) in a laboratory is 30 - 65 U/L.The established upper limits for serum ALT levels were 45.25 U/L for men and 30.47 U/L for females. The usual reference range for serum aspartate aminotransferase (AST) is 15-37 U/L, whereas the normal reference range for platelet counts is 150-400 k/uL. Liver enzymes were quantified utilizing a dimension clinical chemistry system, specifically the Flex Reagent Cartridge. The AST/ALT ratio was assessed for every patient, and the APRI score will be calculated using the following equation[12]:

FIB-4wasdeterminedbyusingthefollowingformula:

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

DIAGNOSTICCRITERIA

The grading of NAFLD fibrosis is as follows: grade (G) 1 indicates fibrosis in zone 3 and perisinusoidal and/or pericellular fibrosis; grade 2 indicates fibrosis in zone 3 and periportal fibrosis; grade 3 indicates bridging fibrosis; and grade 4 indicates nodule development and cirrhosis. The diagnostic criteria for severe fibrosis included the following cutoff values: APRI > 1, NAFLD score > 0.676, and FIB-4 score > 3.25 [13-15].

USGFINDINGS

US B-mode imaging enables the subjective assessment of the extent of fatty infiltration in the

liver. The grading is as follows: Absent (score 0) if the echotexture of the liver is within the normal range; A modest condition (score 1) is present when there is a small and widespread rise in liver echogenicity, with normal visibility of the diaphragm and the portal vein wall. In the case of a moderate increase in liver echogenicity with a slightly impaired appearance of the portal vein wall and the diaphragm, a score of 2 is given. A score of 3 is given in the case of a marked increase in liver echogenicity with poor or no visualization of the portal vein wall, diaphragm, and posterior part of the right liver lobe.

DATAANALYSIS

The acquired data was imported to spreadsheets and analyzed with SPSS version 25.0. The findings are reported using the statistical measures of means ± standard deviation, as well as percentages and tables. The Student's t-test was used to compare continuous variables, while the Chi-square test or two-tailed Fischer's exact test was used to evaluate categorical characteristics, depending on the situation. A P-value less than or equal to 0.05 was deemed statistically significant.

RESULTS

Among the total of 80 participants, there were 55 men and 25 females. Therefore, there was a prevalence of males in this research. The average age of the participants in the research was 48.46±5.22 years. 68.75% of the patients were found to be overweight. The prevalence of hypertension, diabetes, and hyperlipidemia among the individuals was reported as 31.25%, 18.75%, and 10% accordingly (table 1).

Table1:Basic parameter of the participants

Parameter	Number	Percentage
Gender		
Male	55	68.75
Female	25	31.25
Age		
Below 30	5	6.25
30-40	21	26.25
40-50	36	45
50-60	14	17.5
Below 60	4	5
Mean Age	48.46±5.22	
Comorbidity		
Overweight Obese	55	68.75
Diabetes	15	18.75
Hypertension	25	31.25
Hyperlipidemia	8	10

The average APRI and FIB-4 values for the participants in the research were 0.88±0.12 and 1.66±0.34, respectively. Non-alcoholic fatty liver disease (NAFLD) fibrosis was seen in 43.75% of the participants. Specifically, fibrosis stages G1, G2, G3, and G4 were found in 21.25%, 8.75%, 10%, and 3.75% of the participants, respectively. According to the FibroScan findings, 50% of the cases were categorized as F1, 31.25% as F2, 12.5% as F3, and 6.25% as F4 (table 2).

Table2:APRI,FIB-4,NAFLDfibrosisandfibroscan

Parameter	Mean	SD
APRI	0.88	0.12
FIB-4	1.66	0.34
Grade	**Number**	**Percentage**
GO	45	56.25
G1	17	21.25
G2	7	8.75
G3	8	10
G4	3	3.75
Fibroscan		
F1	40	50
F2	25	31.25
F3	10	12.5
F4	5	6.25

The mean values of AST/ALT, APRI, and FIB-4 were higher in the F3+F4 grade compared to the F1+F2 grade. When comparing mean AST/ALT, APRI, and FIB-4 based on fibroscan findings, a significant difference was seen in relation to APRI and FIB-4, with a p-value of less than 0.05 (table 3).

Table3:ComparisonofAST/ALT,APRIandFIB-4score

Parameter	F1+F2		F3+F4		Ttest	Pvalue
	Mean	SD	Mean	SD		
AST/ALT	0.76	0.14	0.95	0.17	1.15	0.11
APRI	0.39	0.08	1.22	0.22	3.98	0.003
FIB-4	0.97	0.15	2.64	0.18	6.88	0.001

Table 4 revealed a statistically significant positive association between APRI and FIB-4 in relation to fibrosis stages, as determined by the Pearson correlation test.

Table4:CorrelationoffibroscanwithAST/ALT,APRIandFIB-4

Parameter	rvalue	p value
AST/ALT	0.23	0.11
APRI	0.55	0.001
FIB-4	0.72	0.001

Among patients with non-alcoholic fatty liver disease (NAFLD), the FIB-4 test has superior sensitivity in predicting various stages of liver fibrosis, whereas the APRI test exhibits the highest specificity. Therefore, in this investigation, APRI and FIB-4 were shown to be similar in their ability to predict liver fibrosis. Table 5 demonstrates that AST/ALT has the lowest sensitivity and specificity when it comes to predicting various stages of liver fibrosis in individuals with non-alcoholic fatty liver disease (NAFLD).

Table5:DiagnosticefficacyofAST/ALT,APRIandFIB-4consideringfibroscanasgoldstandard

Parameter	Sensitivity	Specificity
AST/ALT	61.45	75.15
APRI	83.55	90.77
FIB-4	95.89	78.76

DISCUSSION

This research aimed to determine the diagnostic accuracies of APRI and FIB 4 in predicting various stages of liver fibrosis in patients with non-alcoholic fatty liver disease (NAFLD) and to assess their connection with fibroscan results. The study design was prospective and observational. The research enrolled 80 patients with non-alcoholic fatty liver disease (NAFLD) of both genders, detected with ultrasound imaging (USG). Among the total of 80 patients, 55 were identified as men while the remaining 25 were identified as females. Therefore, there was a prevalence of male dominance in this research. The average age of the participants in the research was 48.46±5.22 years. In a research conducted by Layal Al Danaf, a total of 73 patients were discovered. Among them, there were 45 males with an average age of 50.24 ± 15.71 and 28 females with an average age of 57.28 ± 15.07. In their research, Ome Z. Pérez-Gutiérrez et al[17] found that there was an equal distribution of males and females, with a mean age of 48.6 ± 12.7 years. In a research conducted by Hind I. Fallatah et al[18], it was found that 53.3% of the participants were male, with an average age of 50.2 years. The results of our investigation were comparable to their findings. Male patients often have more severe liver disorders across many causes compared to females. The observed phenomena may be attributed to the protective influence of female sex hormones on the advancement of hepatic fibrosis.

Non-alcoholic fatty liver disease (NAFLD) fibrosis was seen in 43.75% of the participants. Specifically, fibrosis stages G1, G2, G3, and G4 were found in 21.25%, 8.75%, 10%, and 3.75% of the participants, respectively. The mean values of AST/ALT, APRI, and FIB-4 were higher in the F3+F4 grade compared to the F1+F2 grade. When comparing mean AST/ALT, APRI, and FIB-4 based on fibroscan findings, a significant difference was seen specifically in relation to APRI and FIB-4, with a p-value of less than 0.05. This research found a statistically significant positive link between APRI and FIB-4 when compared to fibrosis stages. This correlation was validated using a Pearson correlation test. In their research, Layal Al Danaf[16] categorized 29 patients as F0 (Normal), 13 as F0-F1 (Normal-Mild Fibrosis stage), 14 as F2-F3 (Mild-Moderate Fibrosis stage), 5 as F3-F4 (Moderate-Severe Fibrosis stage), and 12 as F4 (Cirrhosis). In a study conducted by Hind I. Fallatah et al[18], it was found that there was a notable disparity in the stiffness scores for APRI and the FIB-4 calculations between patients with advanced fibrosis (F2 or higher) and those with mild to moderate fibrosis (F2 or lower). Specifically, 44 patients (36%) had advanced fibrosis, while 78

patients (64%) had mild to moderate fibrosis. As to the study conducted by Ome Z. Pérez-Gutiérrez et al[17], there were no significant differences in the levels of ALT and AST across the groups.Among patients with non-alcoholic fatty liver disease (NAFLD), the FIB-4 test has superior sensitivity in predicting various stages of liver fibrosis, whereas the APRI test exhibits the highest specificity. Therefore, in this investigation, APRI and FIB-4 were shown to be similar in their ability to predict liver fibrosis. The sensitivity and specificity of AST/ALT in predicting various stages of liver fibrosis among NAFLD patients are the lowest.

Hind I. Fallatah et al[18] found a strong and favorable relationship between the Fibroscan findings and the AST/ALT ratios, the APRI scores, and the FIB-4 results. These findings align closely with the results of our investigation. In this research, the AST/ALT ratio was shown to be the least effective among the several non-invasive approaches in distinguishing between mild to moderate and severe fibrosis. In their investigation, Ome Z. Pérez-Gutiérrez et al[17] also reported comparable results. When we apply these findings to our whole population and analyze the diagnostic accuracy, it indicates that APRI can effectively rule out the existence of severe fibrosis. The APRI has a benefit in that it utilizes two variables that are often used and a straightforward formula for computation, yet it is unable to determine values for uncertain fibrosis. The sample size of patients included in this study may be relatively small compared to the national prevalence data for non-alcoholic fatty liver disease (NAFLD). However, this limitation is mitigated by the rigorous criteria used for participant selection. It is important to note that this study did not utilize liver biopsy, which is considered the most accurate method for diagnosing NAFLD. This decision was made due to the potential complications associated with the procedure, and it is not advisable to recommend liver biopsy for every patient with NAFLD.

CONCLUSION

Our findings indicate that APRI is the most effective marker for predicting advanced liver fibrosis when compared to the AST/ALT ratio. Additionally, APRI shows a similar level of accuracy as FIB-4, but exhibits the highest connection with FibroScan results. Thus, in situations where there are limited resources and FibroScan is not accessible, APRI serves as a suitable indicator for predicting significant liver fibrosis. It aids in making decisions regarding additional evaluations, referral to higher levels of care, and potentially making lifestyle changes or prescribing medications.

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