Section: General Medicine

Original Research Article

COMBINATION OF AST TO PLATELET RATIO (APRI) AND FIB4 (FIBROSIS) SCORING TO DETECT AND STAGE FIBROSIS IN CHRONIC LIVER DISEASE

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Received : 05/01/2023
Received in revised form : 03/02/2023
Accepted : 16/02/2023

Keywords:
Chronic liver disease, APRI, FIB-4 scores, Non-invasive diagnosis, Fibrosis.

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DOI: 10.47009/jamp.2023.5.2.88

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2023; 5 (2); 415-419

Abstract

Background: Patients with chronic liver disease have been reported with a poor prognosis which can lead to liver cirrhosis. The current study aims to assess the combination of APRI and FIB-4 scores to detect fibrosis and stages of fibrosis in patients with chronic liver disease to better assess mortality, prognosis, and treatment outcome without using invasive techniques such as liver biopsy. **Materials and Methods:** The cross-sectional study was conducted at the Kanyakumari Government Medical College for a duration of the 1-year follow-up period among 100 patients. Patients diagnosed with liver cirrhosis were included in the current study, whereas patients with any other systemic disease or inflammation were excluded. Data collection was based on the detailed history interview, APRI, FIB-4 scores, general and systemic examination, and serum AST/ALT and platelet levels. **Result:** The current study reports a male predominance (60.0%) with an affected age group of 51-60 (33.0%). A significant difference was reported between the serum AST, ALT, and platelet levels with stages of liver fibrosis (p-value <0.0001). The use of APRI and FIB-4 scores accurately predict and differentiate liver fibrosis stages in patients with a cut-off value of 0.72 and 2.15. A sensitivity of 75% and specificity of 71.90% were seen for APRI scores, whereas the FIB-4 score reported 83.30% sensitivity and 67.16% specificity. **Conclusion:** The use of APRI and FIB-4 scores appears to be accurate in diagnosing stages of liver fibrosis and differentiating between stages F3 and F4 in chronic liver disease patients.

INTRODUCTION

The prevalence of deaths associated with chronic liver disease has been estimated to be more than 1.3 billion patients, with more than 2 million due to liver-related deaths occurring every year, accounting for a total of 3.5% of total deaths worldwide.[1] The development of liver fibrosis has consistently led to liver cirrhosis or hepatocellular carcinoma (HCC), which results in the worsening of conditions and poor prognosis, which ultimately results in the improvisation of the clinical outcomes and therapeutic regimens.[2-4]

As liver biopsy has remained the gold standard for diagnosing liver cirrhosis and histopathological findings, the method has reported contraindications and complications.[5] The fibrosis index based on four factors (FIB-4) for the diagnosis of liver fibrosis/hepatitis C comprised of age, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and platelet, which has proven to be accurate in classifying different stages of liver fibrosis in viral hepatitis and non-alcoholic fatty liver disease (NAFLD).[6] The use of FIB-4 has been reported to be more accurate in classifying stages of liver fibrosis better than the AST-to-Platelet ratio index (APRI), AST-to-ALT ratio index, age-spleen platelet ratio index, and enhanced liver fibrosis score.[7-9] However, most validations of these diagnostic markers have been seen under controlled conditions and have reported sensitivity and specificity at the extreme stages of liver fibrosis.[10] The use of APRI and FIB-4 has been seen in predicting stages of liver cirrhosis in specific regions like Taiwan and Iran with high accuracy and sensitivity among patients.[10,11]

The current study aims to assess the combination of APRI and FIB-4 scores to detect fibrosis and stages of fibrosis in patients with chronic liver disease to

better assess mortality, prognosis, and treatment outcome without using invasive techniques such as liver biopsy.

MATERIALS AND METHODS

The cross-sectional study was conducted at the Kanyakumari Government Medical College in the Department of General Medicine for 12 months. One hundred patients were screened and enrolled with a clinical diagnosis of liver cirrhosis.

Inclusion criteria: Patients diagnosed with chronic liver disease at the Kanyakumari Medical College were included.

Exclusion criteria: Patients who presented with other chronic inflammatory conditions and systemic illnesses were excluded.

During the enrolment, patients were screened, and selected patients based on the inclusion criteria and underwent detailed history interviews and various clinical examinations and investigations. APRI score (AST/upper limit of normal AST) *(100)/platelet count, FIB-4; age*AST/ALT* platelet count, including general and systemic examinations, were conducted.

The follow-up of selected cases was conducted with the collaboration of the Medical Gastroenterology Department at the Kanyakumari Government Medical College.

The data recorded during the overall study is represented as percentages and frequencies. Continuous variables were compared using the One-way ANOVA test, ROC curves (predictive cut-off value), and a significant difference <0.05 was used using the two-tailed test. The data analysis was performed using the IBM-SPSS version 21.0 (IBM-SPSS Science Inc., Chicago, IL).

RESULTS

Baseline characteristics, APRI score, and FIB-4 score

The current study was conducted with 100 patients with liver cirrhosis. A majority of the patients were in the age group of 51-60 years of age (33.0%), followed by 41-50 years of age (31.0%) [Table 1].

A male predominance was reported in the current study with 60 male patients (60.0%), whereas 40 patients were female (40.0%). The APRI score was calculated for the enrolled patients, revealing that 65.0% had an APRI score <1, followed by 34.0% of patients with an APRI score between 1-1.5 and one with an APRI score >1.5. Based on the FIB-4 analysis, 38.0% of patients were in a score of 1.45-3.25. 36.0% of patients with a score of <1.45, and 26.0% of patients with a FIB-4 score >3.25.

The clinical diagnosis revealed that liver fibrosis stage 1 (F1) in 37 patients (37.0%), followed by stage 2 (F2) in 27 patients (27.0%), stage 3 (F3) in 20 patients (20.0%), stage 4 (F4) with 16 patients (16.0%) respectively [Table 1].

Comparison of age, APRI score, and FIB-4 score with liver fibrosis stages

Based on the mean age of the patients F1 stage included 37 patients with a mean age of 47.97±9.57, followed by the F2 stage with 27 patients and a mean age of 49.93±8.64, F3 with 20 patients with a mean age of 51.30±9.93, and stage 4 comprising of 16 patients with a mean age of 53.25±10.97 respectively. However, the study did not report a significant difference between the age and stages of liver fibrosis [Table 2].

Patients in the F1 stage have a BMI of 29.12kg/m2, and those in the F2 stage have a BMI of 29.41kg/m2. Those in the F3 stage have a BMI of 29.10kg/m2, and those in the F4 stage have a BMI of 30.52kg/m2. There is no statistically significant variation in BMI between stages of liver fibrosis (p=0.165). In addition, fasting blood sugar levels in the F1 stage were 92 mg/dl, 92.48mg/dl in the F2 stage, 84.80mg/dl in the F3 stage, and 72mg/dl in the F4 stage. The difference in fasting blood sugar levels between liver fibrosis stages was not statistically significant (p=0.490). The triglyceride level of patients in the F1 stage is 189.05mg/dl, 191.89mg/dl in the F2 stage, 183.80mg/dl in the F3 stage, and 167.38mg/dl in the F4 stage. The difference in triglyceride levels between liver fibrosis stages was not statistically significant (p=0.634). The table for the comparison of BMI, fasting blood sugar, and triglyceride levels are represented in the supplementary data.

Comparison of AST and ALT levels with liver fibrosis stages

The comparison revealed a significant difference (p-value <0.0001) between the serum AST comparison and liver fibrosis stages with patients with F1 stage prevalent with 35.41±6.93 U/L, followed by F2 stage with 42.33±9.58, F3 stage with 44.80±8.16, and F4 stage with 48.63±6.93 respectively [Table 3].

A significant difference was also reported between ALT levels and liver fibrosis stage (p-value <0.0001), where elevated levels of ALT were reported with the increased staging of liver fibrosis (Table 3). The ALT level of patients in the F1 stage is 47.41 U/L, 54.19 U/L in the F2 stage, 57.95 U/L in the F3 stage, and 60.13 U/L in the F4 stage.

A decreased trend of platelet was reported based on the fibrosis stages, where F1 patients reported 159.59 109/L, F2 stage 114.67 109/L, F3 stage 95.25 109/L, and 96.69 109/L in stage F4. A significant difference was reported in the current study between the platelet levels and liver fibrosis stages (p-value <0.0001).

Distribution of APRI, FIB-4 score between liver fibrosis stage

The study reports a significant difference (p-value <0.0001) between APRI scores and the liver fibrosis stage, indicating an accurate diagnosis of stages of liver fibrosis in patients. The APRI score of patients in the F1 stage is 0.52, F2 stage 0.77, F3 stage 0.96, and in the F4 stage 1.10. Similarly, the FIB-4 score also revealed a significant difference between the

ISSN (O): 2687-5365; ISSN (P): 2753-6556

stages of liver fibrosis, with the F1 stage at 1.48, the F2 stage at 2.21, the F3 stage at 3.18, and the F4 stage at 3.49 with a p-value <0.0001 [Table 4].

Further assessment of performance indicators of APRI and FIB-4 scores in stages F3 and F4 revealed a cut-off value of 0.72 for APRI and >2.15 for FIB-4 scores. In addition, a sensitivity of 75% and specificity of 71.90%. A PPV of 60% and an NPV of 83.60% were reported for APRI scores. Furthermore, the FIB-4 score for predicting F3 and F4 stages was seen with a predicted cut-off of 83.20%. Specificity of 67.16%, PPV of 57.69% and NPV of 88.24% [Table 5].

[Figure 1] demonstrates the ROC curve for APRI prediction of stage F3/F4 fibrosis, whereas, Figure 2 demonstrates the ROC curve for FIB-4 score prediction of liver fibrosis stages in patients.

Table 1: Distribution of age group

		Frequency	Percent
Age Group	<30	4	4.0%
	31-40	14	14.0%
	41-50	31	31.0%
	51-60	33	33.0%
	>61	18	18.0%
Gender	Male	60	60.0%
	Female	40	40.0%
APRI Score	<1	64	64.0%
	1-1.5	34	34.0%
	>1.5	1	1.0%
FIB-4 Score	<1.45	36	36.0%
	1.45-3.25	38	38.0%
	>3.25	26	26.0%
Liver fibrosis stage	F1	37	37.0%
	F2	27	27.0%
	F3	20	20.0%
	F4	16	16.0%

Table 2: Comparison of age between liver fibrosis stage

Age	N	Mean	SD	P value
F1	37	47.97	9.57	0.288
F2	27	49.93	8.64	
F3	20	51.30	9.93	
F4	16	53.25	10.97	
Total	100	50.01	9.68	

Table 3: Comparison of AST with liver fibrosis stage

Fibrosis stage	N	The mean level of AST	SD	P value
AST Comparison				
F1	37	35.41	6.93	<0.0001
F2	27	42.33	9.58	
F3	20	44.80	8.16	
F4	16	48.63	6.93	
Total	100	41.27	9.28	
ALT Comparison				
F1	37	47.14	7.26	<0.0001
F2	27	54.19	8.70	
F3	20	57.95	8.75	
F4	16	60.13	8.43	
Total	100	53.38	9.46	
Platelet levels comparison				
F1	37	159.59	38.53	<0.0001
F2	27	114.67	28.70	
F3	20	95.25	21.06	
F4	16	96.69	19.22	
Total	100	124.53	41.01	

Table 4: Comparison of APRI score with liver fibrosis stages

Liver fibrosis stages	N	APRI Score Mean	SD	P-value
F1	37	0.52	0.16	<0.0001
F2	27	0.77	0.24	
F3	20	0.96	0.28	
F4	16	1.10	0.27	
Total	100	0.77	0.31	
FIB-4 Score				
F1	37	1.48	0.55	
F2	27	2,21	1.01	

ISSN (O): 2687-5365; ISSN (P): 2753-6556

F3	20	3.18	1.05	<0.0001
F4	16	3.49	1.22	
Total	100	2.34	1.21	

Table 5: Performance indicators for APRI, FIB-4 score in F3/F4 stage patients

Score	APRI	FIB-4
Cut-off value	>0.72	>2.15
Sensitivity	75%	83.30%
Specificity	71.90%	67.16%
PPV	60%	57.69%
NPV	83.60%	88.24%

Table 6: Performance indicators of APRI and FIB-4 combinations scores in the F3/F4 stage patients

Sensitivity	80.5%
Specificity	75%
PPV	64.4%
NPV	87.3%

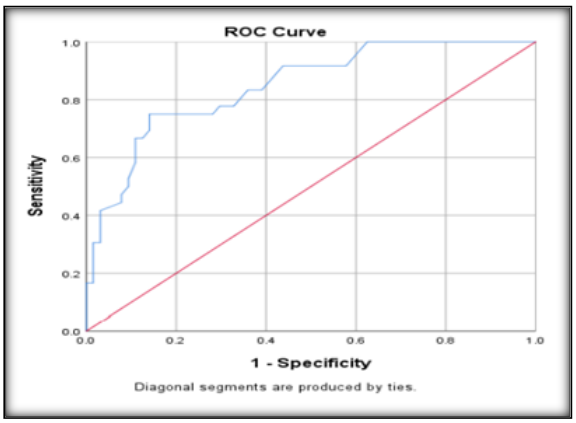

Figure 1: ROC curve for APRI predictions

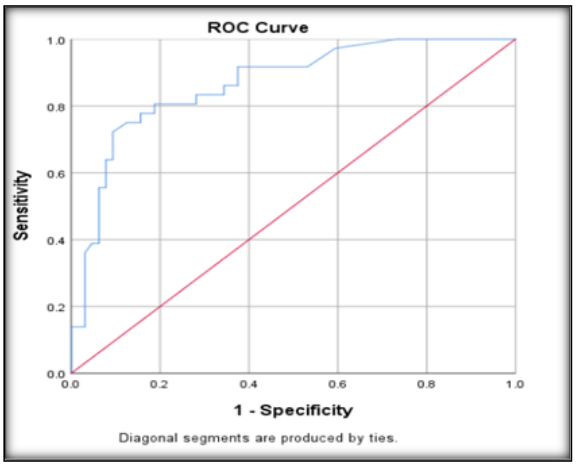

Figure 2: ROC curve for prediction of FIB-4 scores for F3/F4 stage of liver fibrosis

The APRI and FIB-4 score combination prediction for F3/F4 stages revealed a sensitivity of 80.5%, specificity of 75%, PPV of 64.4%, and NPV of 87.3%, respectively [Table 6].

DISCUSSION

APRI and FIB-4 scores, as two non-invasive diagnostic methods, have been seen to predict liver fibrosis with acceptable diagnostic accuracy. In different liver disease conditions such as hepatitis and NAFLD, both methods are non-invasive and reported with reproducible results in large community-based cohort studies.[12] The current study reports an accurate diagnosis of liver fibrosis stages using APRI and FIB-4 scores.

The study was conducted among patients aged from <30 to >61 years, out of which the 51-60 age group was most prevalent with chronic liver disease with a male predominance. The clinical diagnosis revealed 37 patients in the F1 stage, followed by 27% in the F2 stage, 20% patients in the F3 stage, and 16% patients in the F4 stage, which was also seen in the study conducted by Teshale et al. and Abdelkar et al.[10-12]

The present study reported a significant correlation between AST, ALT, platelet, APRI, and FIB-4 scores with fibrosis (p-value <0.0001). In addition, the current study reports a significant correlation between the APRI and FIB-4 assessment in patients with a cut-off value of>0.72 and >2.15, respectively. In addition, based on the ROC curve analysis, an overall sensitivity of 75% and specificity of 71.90% was seen for APRI diagnostic results. In contrast, FIB-4 was reported with a sensitivity of 83.30% and specificity of 67.16%. Both scores could predict the stages of liver fibrosis in patients with high accuracy and specificity. Similar study findings were reported by Kuo et al. by using the APRI and FIB-4 scores in a large-community-based study with 180,359 patients. The study reports a highly accurate diagnosis of stages of liver fibrosis in patients with chronic liver disease concerning hepatitis with a significant difference.[12] Regarding the long-term changes in APRI score and FIB-4 scores, Abdelkader et al. reported a long-term improvement of APRI and FIB-4 scores along with liver stiffness which can be achieved in chronic hepatitis patients.[13]

In addition, a retrospective cross-sectional study also reported accurate diagnosis of fibrosis stages by using APRI and FIB-4 scores among 119 patients with a significant difference. Our study findings of elevated AST and ALT levels based on the fibrosis stage were similar to those of Amorim et al.[14]. A decrease in platelet levels was reported in the current study with increasing stages of liver fibrosis, similar to Sterling et al., in a retrospective analysis among

ISSN (O): 2687-5365; ISSN (P): 2753-6556

832 patients where an elevation of AST/ALT levels was seen with decreased levels of platelet with successive fibrosis stages.[6]

Our study findings also revealed higher APRI scores based on the liver fibrosis stages, similar to Teshale et al., who also reported elevation of APRI scores and FIB-4 scores with successive fibrosis levels from F1 to F4 stages (p-value <0.05).[10] The cross-sectional study by Amernia et al. among 205 NAFLD patients reported a significant correlation of FIB-4 score (r = 0.572), APRI score (r = 0.667), and AST/ALT levels (r = 0.251) with a p-value <0.0001 respectively. In addition, the study also reported similar cut-off values for APRI scores (0.702) for differentiation of F3 and F4 stages from F2 and F1 stages with 84.1%, 88.2%, 66.1%, 95.3%, and 87.3%.[11] In contrast to our specificity and sensitivity for APRI and FIB-4 scores, lower findings were reported by Teshale et al.[10]

The development of non-invasive indicators for diagnostic and prognostic purposes in cases of liver fibrosis is a clinical and research priority worldwide. Much research has been conducted to validate the efficacy of non-invasive serological markers for fibrosis. However, the available evidence shows that the threshold levels fluctuate. Variations in study populations, co-morbidities, ethnicity, the prevalence of severe fibrosis, cirrhosis, and reference range utilized for AST and ALT values may all impact the results and help to explain the inconsistencies.

CONCLUSION

APRI and FIB-4 scores have reported an accurate and highly specific diagnosis of liver fibrosis stages to differentiate between stage 3 and stage 4 of fibrosis. An early assessment with such a non-invasive method can be useful in identifying poor prognosis, worsening of the condition among patients with liver fibrosis, and preventing the development of liver cirrhosis.

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ISSN (O): 2687-5365; ISSN (P): 2753-6556