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ORIGINAL ARTICLE

Comparison of APRI, FIB-4 and fibroscan for detecting chronic liver disease severity among chronic Hepatitis B Patients in Pakistan.

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ABSTRACT… Objective: To compare aspartate aminotransferase to platelet ratio index (APRI), fibrosis-4 index (FIB-4), and fibroscan scores in evaluating severity of chronic liver disease (CLD) in chronic hepatitis B (CHB) patients. **Study Design:** Cross-sectional study. **Setting:** Department of Gastroenterology, Liaquat National Hospital and Medical College, Karachi, Pakistan. **Period:** 11th July 2024 to 10th January 2025. **Methods:** A total of 250 patients aged 18 years or above, and presenting with CHB were analyzed. Necessary laboratory investigations and Fibroscan evaluation were performed for the assessment of APRI and FIB-4 scores and fibrosis confirmation. Predictive ability of all scores was determined by plotting receiver operating characteristic curve (ROC), and determining area under the curve (AUC). Youden index was applied for the calculation of the optimal cut-off value of the score. **Results:** Total 22.0% were female and 78.0% were male patients. Median (IQR) scores for APRI, FIB-4, and Fibroscan were 0.74 (0.35-2.20), 1.32 (0.90-2.90), and 9.10 (5.30-16.00). The AUC indicates that the APRI score (AUC=0.980) is a better predictor of CLD severity than the FIB-4 score (AUC=0.929). The optimal cutoff for APRI score was 0.789 (sensitivity=85.3%, specificity=100%), 0.662 (sensitivity=92.2%, specificity=92.6%), and 0.858 (sensitivity=78.3%, specificity=100%). **Conclusion:** In CHB patients, APRI seems an excellent tool for determining the severity of CLD and showed the highest association with FibroScan results.

Key words: Chronic Liver Disease, Fibroscan, Fibrosis-4 Index, Hepatitis B Virus, Platelet.

INTRODUCTION

Hepatitis B virus (HBV) infection is a major global health concern, especially in developing countries.[1] Approximately 296 million individuals worldwide are estimated to be afflicted with HBV, with Sub-Saharan Africa and East Asia bearing a disproportionate amount of the burden.[2] WHO estimates an annual 1.5 million new HBV cases globally.[3] HBV has a complex course that primarily affects liver, where hepatocellular cycle damage and tissue regeneration occurs as a result of interaction between host immune response and viral proteins.[4-7] Repeated extracellular matrix deposition during this healing process causes liver fibrosis (LF) to worsen with time.[8]

Depending on the stage of chronic hepatitis B (CHB) and the extent of active liver inflammation and damage, advanced LF can progress quickly, slowly, or intermittently. To establish the prognosis of the disease, the urgency of treatment, and the responsiveness to medication, a thorough evaluation of LF is necessary. The liver disease severity at presentation is primary predictor of outcome.[9,10] Liver biopsy is positioned as the gold standard for LF grading, but it is known to have substantial drawbacks, such as sampling bias and the potential for adverse outcomes. Investigating precise, easy, and noninvasive methods for assessing LF is therefore crucial.[10,11] For the evaluation of LF, a variety of non-invasive models and imaging techniques have been created. Even while alanine aminotransferase (ALT) levels and other conventional blood tests are helpful in assessing disease activity, these have not been shown to be reliable predictors of LF on their own.[12]

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The Fibrosis-4 "(FIB-4)" index has been validated for several liver illnesses after being first created for HCV/ HIV co-infection.[13] In order to predict cirrhosis in HCV and severe LF, Wai et al.,[14] devised the "AST to platelet ratio index (APRI)".[14] FibroScan is an evidence-based, transient elastography (TE) tool. It is essential to have a low-cost, dependable, non-invasive technique that may be readily applied in clinical settings for the detection of LF. FIB-4 and APRI have not been widely assessed for their utility in the assessment of LF in the local studies so the present study was performed with an objective to determine the usefulness of the APRI, FIB-4, and Fibroscan scores in assessing the severity of CLD in patients with CHB.

METHODS

This cross-sectional study was conducted at the Department of Gastroenterology, Liaquat National Hospital and Medical College, Karachi, Pakistan, from during 11th July 2024 to 10th January 2025. Approval from Institutional Ethics Committee was obtained (Letter number: 1066-2024-LNH-ERC, dated: July 10, 2024). A sample size of 38 was calculated by taking the anticipated value of area under curve (AUC) for APRI in the diagnosis of LF as 0.756,[15] with the power of the test at 80% and the confidence level at 95%. Because of the large patient turnover in this hospital, a total of 250 patients were analyzed. A non-probability consecutive sampling was applied for sampling. The inclusion criteria were patients of either gender, aged 18 years and above, and who had presented as patients of chronic HBV. The exclusion criteria were patients with hepatocellular carcinoma, alcoholic liver disease, NAFLD, or autoimmune hepatitis (on the basis of radiological evidence of cirrhosis, history of significant alcohol consumption, history of chronic abnormalities in liver profiles with serologic evidence of autoimmune liver disease, or evidence of chronic HBV or HCV infection based on serologic markers and history). Those who had liver transplantation and those who were on interferon therapy were also excluded from the current study. CHB was considered as serum HBsAg and detectable HBV DNA (> 6 months). Participants were explained about the study objective and its associated risks and benefits, along with the data secrecy, before obtaining written and informed consent from them. APRI score was calculated. APRI score greater than 0.89 was considered as the cut-off used for ruling in cirrhosis.[14] The FIB-4 score was calculated as: Age (year) x AST (U/L) / [(PLT (10^9/L)] x [ALT (U/L)]$^{1/2}$. A low FIB-4 cut-off of 1.45 can be employed to exclude patients who were not having advanced LF.[16] Transient elestrography (Fibroscan) was performed to obtain Fibroscan score. Based on the Fibroscan score, LF was labeled as F0-F1, F2, F3, and F4, or cirrhosis, for liver stiffness measurements of < 7kPa, 7-8.9 kPa, 9-12.49 kPa, ≥12.5 kPa.[17] The treating consultant finalized the diagnosis among patients who visited the outpatient clinic, identified to have CHB.

Data were analyzing using "IBM SPSS Statistics" version 26.0. The categorical data was expressed as frequency and percentage. The numerical data were shown as mean and standard deviation (SD), or median with inter-quartile range (IQR) depending on the assumption of normality. The normality assumption was evaluated using Shapiro-Wilk test. Predictive ability of all scores was determined by plotting receiver operating characteristic curve (ROC), and AUC was computed.[18] Youden index was applied for calculating the optimal cut-off value of the score. $P<0.05$ was taken as statistically significant.

RESULTS

Among total 250 patients in the current study, 195 (78.0%) were male. The median age, height, weight, BMI, and duration of disease were 38 (32-45) years, 165 (160-170) cm, 72 (65-75) kg, 26 (24.9-28.9) kg/m^2, and 21 (18–36) months, respectively. There were 176 (70.4%) patients, who belonged to urban areas of residence. No formal education was observed in 3.6% patients, however 63.6% got undergraduate education, and 32.8% had got graduation or higher degree (Table-I).

Median platelets, AST, ALT, and hemoglobin were 170mm3(105 mm3-255 mm3), 46IU/ml(41U/ml-50U/ml), 45U/ml (40U/ml-64U/ml), and 14.1 gm/dl (12.5 gm/dl -15.0 gm/dl). The median scores

for the APRI, FIB4, and fibroscan were 0.74 (0.35-2.20), 1.32 (0.90-2.90), and 9.10 (5.30-16.00). In our study, 51.6% of patients had severe Chronic Liver Disease, whereas 29.2% of patients had diabetes mellitus and 40% had hypertension. Table-2 is showing details with respect to comorbidites, and Fibroscan evaluation.

Characteristics		Frequency (% age)
Gender	Male	195 (78.0%)
	Female	55 (22.0%)
Age (years)	≤ 35	113 (45.2%)
	36-50	101 (40.4%)
	>50	36 (14.4%)
Body mass index (kg/m^2)	Obese	18 (7.2%)
	Non-obese	232 (92.8%)
Residential status	Urban	176 (70.4%)
	Rural	74 (29.6%)
Education	No formal education	9 (3.6%)
	Under graduate	159 (63.6%)
	Graduate or above	82 (32.8%)

Table-I. Demographic profile (n=250)

Characteristics		Frequency (% age)
Co-morbidity	Diabetes	73 (29.2%)
	Hypertension	100 (40.0%)
Fibrosis stages (on Fibroscan)	F0-F1	121 (48.4%)
	F3	57 (22.8%)
	F4	72 (28.8%)
Chronic liver disease severity (on Fibroscan)	Severe	129 (51.6%)
	Non-severe	121 (48.4%)

Table-II. Clinical profile of the study patients (n=250)

AUC indicated that the APRI score (AUC=0.980) was a better predictor of CLD severity than the FIB4 score (AUC=0.929). The optimal cut-off for the APRI score was 0.789 (specificity = 85.3%, specificity = 100%), 0.662 (specificity = 92.2%, specificity = 92.6%), and 0.858 (specificity = 78.3%, specificity = 100%), while the optimal cutoff for the FIB4 score was 1.24 (specificity = 85.3%, specificity = 85.1%), 0.98 (specificity = 100%, specificity = 70.2%), and 1.06 (specificity = 92.2%, specificity = 77.7%), as shown in Table-III.

AUC for APRI and FIB-4 scores for the prediction of the severity of CLD was calculated as 0.980 (p<0.001) and 0.929 (p<0.001), respectively (Figure-1).

Tool	Score	Sensitivity	Specificity	Youden index
AST to platelet ratio index	0.789	85.3%	100%	0.853
	0.662	92.2%	92.6%	0.848
	0.858	78.3%	100%	0.783
Fibrosis-4	1.24	85.3%	85.1%	0.704
	0.98	100%	70.2%	0.702
	1.06	92.2%	77.7%	0.699

Table-III. Optimal cut-off for the prediction for the detection of severe CLD (n=250)

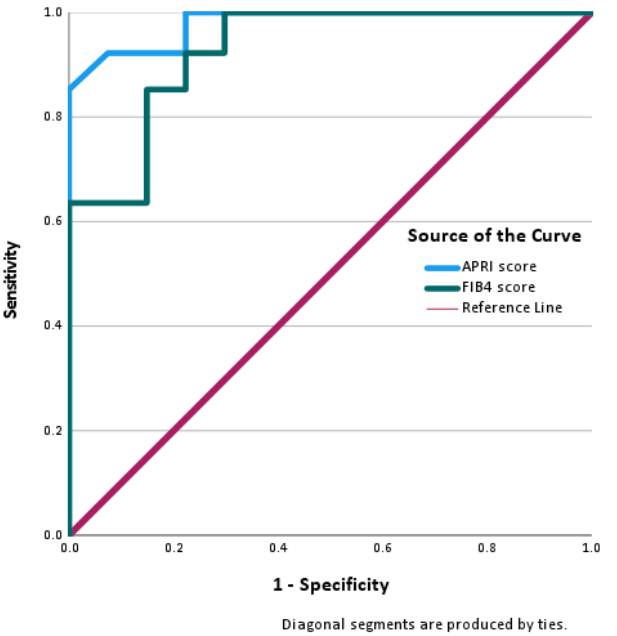

Figure-1. ROC analysis for APRI and FIB-4 scores for the prediction of CLD severity

DISCUSSION

Numerous blood biochemical indicators may currently be used to create LF determinant scores.[20-23] TE which gauges liver stiffness among imaging techniques, and APRI and FIB-4 scores are suggested by WHO and experts as non-invasive diagnostic techniques for LF in chronic viral hepatitis.[22] Guidelines claim that FibroScan is a great method of evaluating LF because it is non-invasive.[23] Two well-researched non-invasive techniques for detecting liver cirrhosis and LF are the APRI and FIB-4.[24]

The current study revealed that the median scores for APRI, FIB-4, and Fibroscan were 0.74 (0.35-2.20), 1.32 (0.90-2.90), and 9.10 (5.30-16.00), respectively. A total of 129 (51.6%) patients had severe CLD. The AUC indicated that the APRI

score was a best predictor of CLD severity than the FIB-4 score (AUC=0.929 vs AUC=0.980). In terms of the detection of severity of CLD, the optimal cut-off for the APRI score was 0.789 (specificity=85.3%, specificity=100%), 0.662 (specificity=92.2%, specificity=92.6%), and 0.858 (specificity=78.3%, specificity=100%), while the optimal cut-off for the FIB-4 score was 1.24 (specificity=85.3%, specificity=85.1%), 0.98 (specificity=100%, specificity=70.2%), and 1.06 (specificity=92.2%, specificity=77.7%). In another study, the findings showed that APRI could rule in individuals with CHB who had LF of any degree (with a PPV of 90.8%). Additionally, this index has the best AUROC for detecting LF of any grade when compared to FIB-4.[25] According to the accurate evaluation of LF by the APRI, the requirement for Fibroscan was decreased in more than two-third of Chinese patients with CHB which is consistent with these findings.[25] According to Yue et al, bridging LF (F ≥ 3) was identified using an APRI cut-off of 0.8.[25] Compared to FIB-4, a study by Sha et al[26], claimed that most reliable and non-invasive indicator for predicting F2/F3 LF was the APRI score.

The APRI index has also been recommended by the WHO for evaluating LB in CHB, with a threshold of 0.5 to 1.5 for severe LF.[27] Although, in a study, 0.536 was the cut-off of APRI for F3/F4 LF, falling under the range previously stated, many people with substantial LF were missed when Fibroscan screening was conducted using these WHO cut-offs. In contrast, another study's cut-off resulted in a sensitivity of almost 90% in this regard, and an NPV of 95.4% was able to identify F3/F4 LF with APRI values below 0.536.[19] Another research found that the AUC of FIB-4 among severe LF as 0.82 at a cut-off of 1.571.[28] Studies done to distinguish F3/F4 from F0-F2 LF, FIB-4 produced better specificity with comparable AUC to APRI.[29,30] In another research, APRI found that cirrhosis ($p < 0.01$) had a higher AUC mean of 0.818 (0.776-0.861) and severe LF ($p<0.01$) had an associated AUC mean (95% CI) of 0.756 (0.714-0.797).[15] While result of another study indicated the AUROC for the same as 0.818, which is considerably superior of a meta-analysis SROC curve that evaluated APRI for cirrhosis showed the area under the ROC curve to be 0.75.[24]

This study had some limitations as well. Being a single center study restricts generalizability of the present study that warrants verification in the large multi-centric trials. Prognostic evaluation of various non-invasive risk stratification tools be considered in the future studies.

CONCLUSION

The study concluded that when compared to FIB-4, APRI showed strongest high correlation with Fibroscan findings and was the most useful marker for excluding the severity of CLD in CHB patients. As a result, APRI seems to be the most effective Fibroscan alternative for determining the degree of CLD in patients with CHB. It can recommend lifestyle changes, refer patients to more advanced stages of treatment, and assist in selecting further potentially invasive testing.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORSHIP AND CONTRIBUTION DECLARATION	
1	**Rana Ahsan:** Data collection, Drafting, Proof reading, Responsible for data's integrity, Approved for publication.
2	**Mansoor ul Haq:** Conception and designed, Proof reading, Critical revisions, Approved for publication.