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Research Article

Validity of Serum Markers for Fibrosis Staging in Chronic Hepatitis B and C Patients

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Introduction

According to latest report globally about 350 million people are affected by Hepatitis B virus and about 686,000 die every year from Hepatitis B related diseases[1,2]. Similarly, more than 185 million people around the world are infected with Hepatitis C virus, of whom 350,000 die each year[3,4]. Hepatic fibrosis, regardless of the underlying a etiology, is a consequence of accumulation of extracellular matrix components in the liver. This process is caused by persistent liver damage and consequent wound healing reaction, leading to cirrhosis, portal hypertension, and hepatocellular carcinoma (HCC), all these cumulatively leading to increased morbidity and mortality [5,6]. Thus accurate assessment of liver fibrosis is essential for successful individualized disease management for people with chronic hepatitis B and C7. Although liver biopsy, till date, remains the gold standard for diagnosis of liver fibrosis but it is far from optimal because of many associated complications [8,9,10]. To overcome these limitations multiple non-invasive modalities have been introduced. Various non-invasive parameters which could replace the biopsy of the infected liver include: - FIB-4[11], APRI[12], AST/ALT ratio[13], Kings Score[14], Frons index[15], Elastography[16] and Fibro scan[17]. Our study included the following three parameters as alternative to liver biopsy: FIB-4, APRI (Aspartate Aminotransferase to Platelet Ratio Index) and AST/ALT Ratio (Aspartate transaminase)/ (Alanine transaminase).

Materials and Methods

The current study was a hospital based prospective study which was conducted in the Department of Internal Medicine and Department of Gastroenterology, Government Medical College, Srinagar, J&K (INDIA). The study was approved by the respective ethical committees of the college. The study was conducted over a period of 36 months starting from August 2014 to July 2017. The study was approved by the respective ethical committees of the college. A total of 262 patients were included and out of them 172 were infected with hepatitis B and 90 patients were infected with hepatitis C. All Chronic Hepatitis B (CHB) and Chronic Hepatitis C (CHC) patients seen in the OPD or admitted in IPD were enrolled and investigated as per the study design. Patients were explained about the liver biopsy procedure, its advantages and possible adverse effects. Patient's history was taken, and physical examination was carried out. Written informed consent was obtained from each participant. Patients were ≥ 18 years of age of either sex. All patients' laboratory data (alanine aminotransferase [ALT], aspartate aminotransferase [AST], platelet count) were collected. FIB-4[12], APRI[13]were calculated by sterlings[11]and wai's[12] formulas respectively:

$$FIB-4=\frac{Age(Years)\times AST(U/L)}{Plateletcount(10^9/L)\times[ALT(U/L)^{1/2}}$$

$$APRI=\frac{AST(/ULN^*)}{Plateletcount(10^9/L}\times 100$$

(* where ULN = upper limit of normal for that laboratory)

Fibrosis stage was calculated by abstraction from liver biopsy reports. Fibrosis scores from different scoring systems (IASL[18], Metavir[19], Ishak[20], Knodell[21]) were mapped to a F0–F4 equivalency scale: F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with few septa; F3, numerous septa without cirrhosis; and F4, cirrhosis (Table 1). If the patient had more than one biopsy, the earliest biopsy with the highest fibrosis stage and available laboratory results was used for this analysis[18].

Table 1: Mapping of fibrosis stages from histological classification systems to a common F0–F4 scale. IASL: International Association for the study of liver.

Equivalent F0–F4 scale:	Fibrosis staging system			
	Metavir	Knodell	Ishak	IASL
F0 – No fibrosis	F0	Score 0	Stage 0	No fibrosis(0)
F1 – Fibrous portal expansion	F1	Score 1	Stage 1, 2	Mild portal fibrosis(1)
F2 – Few bridges or septa	F2	NA	Stage 3	Moderate fibrosis(2)
F3 – Numerous bridges or septa	F3	Score 3	Stage 4	Advanced fibrosis(3)
F4 – Cirrhosis	F4	Score 4	Stage 5, 6	Cirrhosis(4)

Statistical Analysis

We first validated predefined serum markers then developed and validated cut-offs of the serum markers for classification of cirrhosis (F4) or advanced fibrosis (F3–F4). The serum markers of interest were as follows: APRI, FIB-4 and ALT/AST ratio, as defined in the previous section. The endpoints of interest were the presence of advanced fibrosis (F3–4 vs F0–2) and the presence of cirrhosis (F4 vs F0–3) in case of Chronic Hepatitis C. However, in our study, in patients with chronic hepatitis B infection who underwent liver biopsy, no patient had a histological grade of F3 or F4. In such scenario, comparison was made between those with few bridges or septa (F2) and no fibrosis (F0). The data was entered in Microsoft Excel Spreadsheet. Continuous variables were summarized as mean and standard deviation (SD). Categorical variables were summarized as percentages. Radius of Curvature (ROC) curves were constructed for APRI and FIB-4 scores and AST/ALT ratio. Liver biopsy results was taken as standard. Area under ROC curve was reported along with its 95% confidence interval for APRI, FIB-4 and AST/ALT ratio. A p-value of <0.05 was considered as statistically significant.

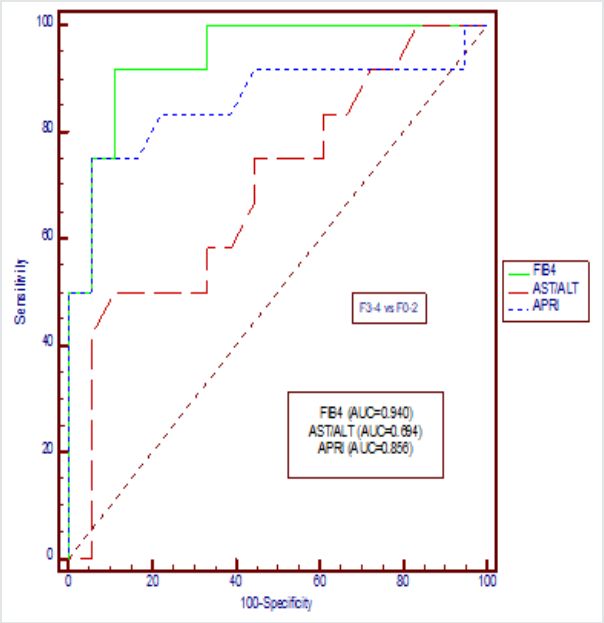

Figure 1.

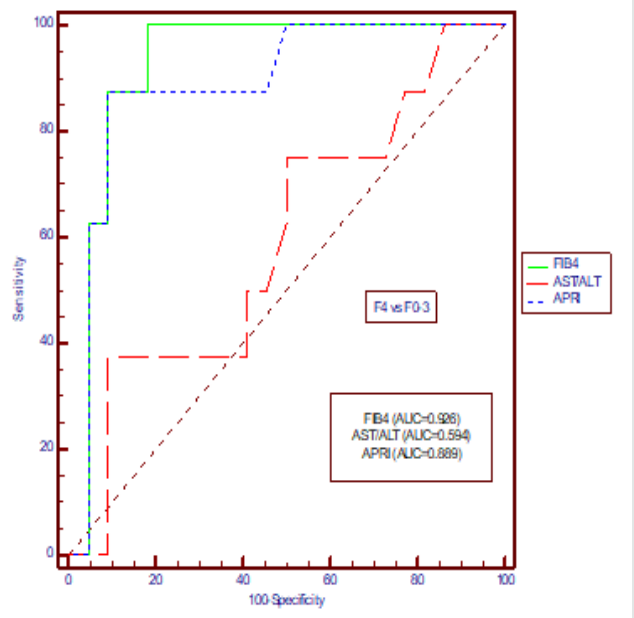

Figure 2.

Results

Out of 90 CHC patients, 18 belonged to 18-30-year age group, 36 patients belonged to 31-45 age group. Twenty-three patients were between 46-60 years of age whereas thirteen patients belonged to 61-75-year age group. Similarly, out of 172 CHB, 34 belonged to 18-30-year age group, 68 patients belonged to 31-45 age group. Fifty-five patients were between 46-60 years of age whereas fifteen patients belonged to 61-75-year age group. In our study out of 172 patients of CHB, 107 were male and 65 were females with male to female ratio of 1.6:1. Similarly out of 90 patients of hepatitis CHC, 56 were males and 34 were females and the male to female ratio was 1.6:1. On combining the two groups, out of 262 patients there was slight male preponderance with total male to female ratio of 1.6:1.

A. Chronic Hepatitis C

We compared AUROCs of the FIB-4 index with those of the other indices for the classification of advanced fibrosis and cirrhosis, respectively (Figure-1&2, Table 2&3).

Table 2: Comparison of ROC curves [F3-4 vs F0-2 among CHC study participants]. *Statistically Significant Difference (P-value<0.05).

Biomarker	AUC	SE	95% CI	Comparison	P-value
FIB4	0.94	0.041	0.788 to 0.994	FIB4 vs AST/ALT	0.019*
AST/ALT	0.694	0.103	0.500 to 0.848	AST/ALT vs APRI	0.255
APRI	0.856	0.085	0.680 to 0.957	FIB4 vs APRI	0.321

Table 3: Comparison of ROC curves [F4 vs F0-3 among CHC study participants]. *Statistically Significant Difference (P-value<0.05).

Biomarker	AUC	SE	95% CI	Comparison	P-value
FIB4	0.926	0.051	0.769 to 0.989	FIB4 vs AST/ALT	0.007*
AST/ALT	0.594	0.123	0.400 to 0.768	AST/ALT vs APRI	0.042*
APRI	0.889	0.07	0.721 to 0.974	FIB4 vs APRI	0.374

The AUROC for FIB-4 in differentiating F3–F4 from F0–F2 was 0.940 (95% CI: 0.788–0.994) when compared with AST/ALT Ratio with p value of 0.019 and AUROC for APRI was 0.856(95% CI: 0.680–0.957) when compared with FIB-4 with p value of 0.321 for CHC. The AUROC for FIB-4 in differentiating F4 from F0–F3 was 0.926 (95% CI: 0.769–0.989) when compared with AST/ALT Ratio with p value of 0.007 and AUROC for APRI was 0.070(95% CI: 0.721–0.974)) when compared with FIB-4 with p value of 0.374 for CHC.

B. Chronic Hepatitis B

In case of CHB, comparison was done between AUROCs of the FIB-4 index with those of the other indices for the classification of those with few bridges or septa (F2) and no fibrosis (F0); and fibrous portal expansion (F2 vs F0-F1)(Figure-3,Table 4). The AUROC for FIB-4 in differentiating F2 from F0–F1 was 0.839 (95% CI: 0.667–0.944) when compared with AST/ALT Ratio with p value of 0.038 and AUROC for APRI was 0.801(95% CI: 0.614–0.915) when compared with FIB-4 with p value of 0.732 for CHB.

Table 4: Comparison of ROC curves [F2 vs F0-1 among CHB study participants]. *Statistically Significant Difference (P-value<0.05).

Biomarker	AUC	SE	95% CI	Comparison	P-value
FIB4	0.839	0.095	0.667 to 0.944	FIB4 vs AST/ALT	0.038*
AST/ALT	0.644	0.152	0.455 to 0.804	AST/ALT vs APRI	0.164
APRI	0.801	0.088	0.614 to 0.915	FIB4 vs APRI	0.732

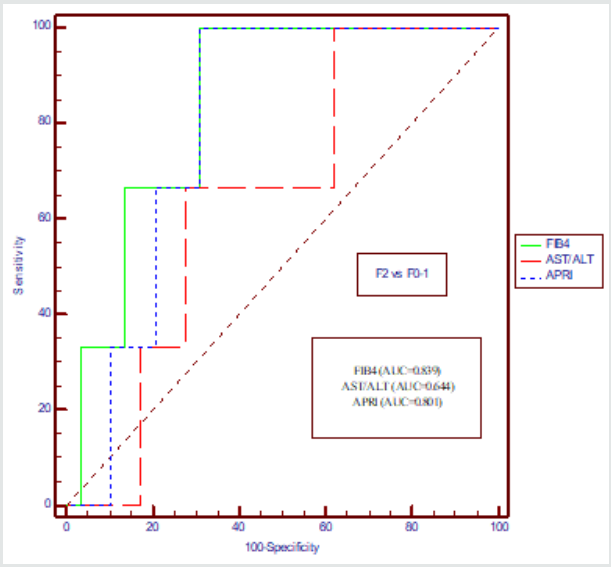

Figure 3.

Cut-off Values for Predicting Fibrosis and Cirrhosis Using FIB-4 in CHC

Based on the AUROC analysis in the previous section, FIB-4 had the best overall utility for prediction of advanced fibrosis and cirrhosis in a chronic hepatitis C population compared with the other two markers, as FIB-4 score outperformed the other serum markers and was superior to AST/ALT ratio and almost similar to APRI. We next derived optimal cut-off values of FIB-4 for distinguishing the lower end of liver stage (F0–F2) and upper end of liver stage (F3, cirrhosis) for CHC. The optimal cut-off of FIB-4 in distinguishing F3,F4 vs F0-F2 was >2.30 with sensitivity and specificity of 91.7% and 88.9% respectively. For APRI, optimal cut-off was >1.66 with sensitivity and specificity of 75% and 91.4% respectively and for AST/ALT ratio optimal cut-off was >1.35 with sensitivity and specificity of 50% and 83.9% respectively.

Similarly, the optimal cut-off of FIB-4 in distinguishing F4 vs F0-F3 was >2.50 with sensitivity and specificity of 100% and 81.8% respectively. For APRI, optimal cut-off was >1.74 with sensitivity and specificity of 87.5% and 82.4% respectively and for AST/ALT ratio optimal cut-off was >1.43 with sensitivity and specificity of 57.5% and 80.9% respectively.

Cut-off Values for Predicting few bridges or septa (F2) and no fibrosis (F0); and fibrous portal expansion (F2 vs F0-F1) in CHB

Similarly, the optimal cut-off of FIB-4 in distinguishing few bridges or septa (F2) and no fibrosis (F0); and fibrous portal

expansion (F2 vs F0-F1) was >1.33 with sensitivity and specificity of 86.3% and 78.5% respectively. For APRI, optimal cut-off was >0.68 with sensitivity and specificity of 80.1% and 82.9% respectively and for AST/ALT ratio optimal cut-off was >0.54 with sensitivity and specificity of 71.2% and 73.6% respectively[Table 5].

Table 5: Diagnostic accuracy of various biomarkers.

Marker		Optimal Cutoff	Sensitivity (%)	Specificity (%)
F3-4 vs F0-2 (CHC)	FIB4	> 2.30	91.7	88.9
	AST/ALT	> 1.35	50	83.9
	APRI	> 1.66	75	91.4
F4 vs F0-3 (CHC)	FIB4	> 2.50	100	81.8
	AST/ALT	> 1.43	57.5	80.9
	APRI	> 1.74	87.5	82.4
F2 vs F0-1 (CHB)	FIB4	> 1.33	86.3	78.5
	AST/ALT	> 0.54	71.2	73.6
	APRI	> 0.68	80.1	82.9

Discussion

While analysing our results for these markers, FIB-4 was found out to be a better marker for detecting the degree of fibrosis in CHC. In early stages of fibrosis (F0-F2), keeping a cut-off value >2.3, the sensitivity and specificity of FIB-4 was 91.7% and 88.9% respectively. At further advanced degree of fibrosis i.e., cirrhosis, the sensitivity of cut-off value of >2.5 for FIB-4 reaches 100%.

The cut-off valve obtained of APRI score 1.66 was similar to study conducted by [22]where the cut-off valve of APRI has been 1.5, the sensitivity and specificity of APRI has been more than 75% and 91.4% for F0-F2 and F3, F4 (significant fibrosis) score. The APRI score in similarity with FIB-4 score is quite valuable in advanced stage of fibrosis (cirrhosis), but in early stages of fibrosis the APRI score has not been of much significance, though the effect can be attributed to very less number of patients in this group. The higher sensitivity and specificity pattern obtained from FIB-4 and APRI score was not reflected by AST/ALT ratio in our study, with the sensitivity and specificity falling to 50% and 37% to stages F3 and F4 respectively. The superiority of FIB-4 and APRI with AST/ALT ratio in predicting the fibrosis is validated by the study conducted by [23]. However in case of CHB,FIB-4 has definitely being shown to be almost close to liver biopsy in predicting the histopathology of liver. The other two scoring systems like APRI and AST/ALT ratio have not proved to be better than FIB-4. The results of the study conducted by Yilmaz et al. [24] reported that APRI had acceptable accuracy for assessment of fibrosis with CHC but same was not applicable for CHB, though we had no patients of advanced fibrosis, but even on comparing the patients of mild with moderate fibrosis, APRI was not as significant marker with AUC of 0.644 and 95% CI of 0.455 to 0.804. FIB-4 again served as a significant marker to distinguish patients of mild fibrosis (F0, F1) from patients with moderate fibrosis with AUC of 0.839 and 95% CI (0.667 to 0.944) and p-valve of 0.038. The studies conducted by Zhang et al. [25] in the past revealed FIB-4 as a diagnostic marker to discriminate between patients of early fibrosis and advanced fibrosis.

The advantage of our study was its prospective design and adoption of strict inclusion and exclusion criteria. The disadvantage of our study was the small sample size.

Conclusion

Thus, our study suggests that FIB-4 and APRI are excellent surrogate markers for liver fibrosis while ASL/ALT is not a very sensitive marker. Among all these scores FIB-4 is the best. On the basis of our results, we recommend use of FIB-4 as a surrogate marker for liver fibrosis across all age groups. We further recommend that larger number of patients to be undertaken in future studies.

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