DIAGNOSTIC ACCURACY OF FIB-4, APRI AND AST/ ALT RATIO FOR PREDICTION OF FIBROSIS IN CHRONIC HEPATITIS B AND C PATIENTS

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ABSTRACT

Background and Objectives: Accurate assessment of liver fibrosis is essential for successful disease management for people with chronic hepatitis B (CHB) and chronic hepatitis C (CHC). Although liver biopsy remains gold standard for diagnosis of liver fibrosis, it has some limitations. To overcome these limitations multiple non-invasive modalities have been introduced. The main aim of our study was to validate the various fibrosis scoring systems with liver biopsy and give recommendations to replace it with these scoring systems if feasible in hepatitis B and C.

Methods: We included 62 patients, 32 (51.60%) had hepatitis B, and 30 (48.40%) had hepatitis C infection. These patients were enrolled from Out Patient Department and In Patient Department of Sri Maharaja Hari Singh Hospital, Srinagar. We examined the validity of commonly used liver fibrosis scoring systems: FIB-4 (Fibrosis-4 Index), APRI (Aspartate aminotransferase to Platelet Ratio) and AST (Aspartate Aminotransferase)/ ALT(Alanine Aminotransferase) ratio. Liver biopsy was histologically graded using Knodell, Ishak and Metavir grading systems. On basis of histopathological examination, the patients were divided into those with non-significant fibrosis (F0-F2) and significant fibrosis (F3-F4); and those without cirrhosis (F0-F3) and with cirrhosis (F4).

Results: In case of CHB patients, all 32(100%) belonged to non-significant fibrosis group (F0-F2) and none had cirrhosis. In case of CHC, 12(40%) patients had insignificant fibrosis while as 18(60%) had fibrosis to cirrhosis. The sensitivity and specificity of FIB-4 in detecting significant fibrosis was 91.7% and 88.9% respectively. For cirrhosis, these parameters were 100% and 81.8% respectively. The sensitivity and specificity of APRI in detecting significant fibrosis was 75% and 91.4% respectively and for cirrhosis, 87.5% and 82.4% respectively. The sensitivity and specificity of AST/ALT ratio in detecting significant fibrosis was 50% and 83.9% while for cirrhosis, 57.5% and 80.9% respectively.

Conclusion: Our study suggests that FIB-4 and APRI are excellent surrogate markers for liver fibrosis, ASL/ ALT is not a very sensitive marker. Among all, FIB-4 fared the best.

Keywords: Liver fibrosis, Non-invasive methods, Liver biopsy, Hepatitis B, Hepatitis C

INTRODUCTION

Globally, about 350 million people are affected by chronic hepatitis B (CHB), 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 chronic hepatitis C(CHC), of whom 350,000 die each year.[3,4] Hepatic fibrosis, regardless of the underlying aetiology, 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] Fibrosis and cirrhosis are of great significance, not only from prognostic point of view but also for deciding about the treatment in both Hepatitis B and C. Thus an accurate assessment of liver fibrosis is essential for successful individualised disease management for people with chronic hepatitis B and C.[7] Although liver biopsy, till date, remains the gold standard for the 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 affected 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 departments of Internal Medicine and Gastroenterology, Government Medical College, Srinagar, J&K (India). The study was approved by ethical committee of the college. The study was conducted over a period of 26 months starting from August 2014 to September 2016. A total of 62 patients were registered and out of them 32 were infected with hepatitis B and 30 patients were infected with hepatitis C. It was an open label study and the sample size was not defined at the beginning. All Chronic Hepatitis B (CHB) and Chronic Hepatitis C (CHC) patients seen in the OPD or admitted in IPD, who consented were enrolled and investigated as per the study design. Patients with the following conditions were excluded from the study: those with the presence of other causes of liver disease, hepatocellular carcinoma, prior liver transplantation, prior interferon therapy, immunosuppressive therapy, insufficient liver tissue for staging of fibrosis, and incomplete data on complete blood counts and/or liver panel, patients with any contraindication to liver biopsy, patients who refused to give consent to liver biopsy, diabetic patients, alcoholics, patients with co-infection with other virus like HBV, HIV and Pregnant females. Patients were informed 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 -e" 18 years of age and of either sex. All patients' laboratory data (alanine aminotransferase [ALT], aspartate aminotransferase [AST], platelet count) were collected. FIB-4[12], APRI[13]were calculated using the following formulas:

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

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

(* 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]

Statistical analysis

We first validated pre-defined serum markers then developed and validated cut-off values 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 CHC. However in our study, in patients with CHB infection who underwent liver biopsy, none 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.

RESULTS

Out of 30 CHC patients, 9 (23.3%) belonged to 18-30 year age group, 12 (37.5%) patients belonged to 31-45 age group. Five patients were between 46-60 years of age whereas only one patient belonged to 61-75 year age group. Similarly out of 32 CHB, 14 (43.8%) belonged to 18-30 year age group, 12 (37.5%) patients belonged to 31-45 age group, 5 patients were between 46-60 years of age whereas only one patient belonged to 61-75 year age group. In our study, out of 32 patients of CHB, 20 were male and 12 were females with male to female ratio of 1.6:1. Similarly, out of 30 patients with CHC, 19 were males and 11 were females and the male to female ratio was1.7:1. On combining the two groups, out of 62 patients there was slight male preponderance with total male to female ratio of 1.69:1.

I .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 [Tab 2, Fig 1 &2].

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 0.321for 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.

II. Chronic hepatitis B:- in case of CHB [Fig 3, Table 3], comparison was done between AUROCs

Table 1: Mapping of fibrosis stages from histological classification systems to a common F0–F4 scale

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)

IASL: - International Association for the Study of Liver

Table 2: Comparison of fibrosis markers in CHC

Biomarker	AUC	SE	95% CI	Comparison	P-value
FIB-4	0.926	0.051	0.769 to 0.989	FIB-4 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	0.070	0.721 to 0.974	FIB-4 vs APRI	0.374

**Statistically Significant Difference (p-value<0.05)*

Table 3: Cross comparison of fibrosis markers in CHB

Biomarker	AUC	SE	95% CI	Comparison	P-value
FIB-4	0.839	0.095	0.667 to 0.944	FIB-4 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	FIB-4 vs APRI	0.732

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).

FIB-4 in distinguishing F3, F4 vs. F0-F2 was >2.30 with sensitivity and specificity of 91.7% and 88.9% respectively. The optimal cut-off of FIB-4 in distinguishing F3, F4 vs F0-F2 was >2.30 with

Table 4: Diagnostic accuracy of various biomarkers

Marker		Optimal Cut-off	Sensitivity (%)	Specificity (%)
F3-4 vs F0-2	**FIB-4**	> 2.30	91.7	88.9
(CHC)	**AST/ALT**	> 1.35	50.0	83.9
	APRI	> 1.66	75.0	91.4
F4 vs F0-3	**FIB-4**	> 2.50	100	81.8
(CHC)	**AST/ALT**	> 1.43	57.5	80.9
	APRI	> 1.74	87.5	82.4
F2 vs F0-1	**FIB-4**	> 1.33	86.3	78.5
(CHB)	**AST/ALT**	> 0.54	71.2	73.6
	APRI	> 0.68	80.1	82.9

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.

Cut-off Values for Predicting Fibrosis and Cirrhosis Using FIB-4 in CHC [Table 4].

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 CHC 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. Then the 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 were derived. The optimal cut-off values of 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 [Table 4]

Table 4: Diagnostic accuracy of various biomarkers

Marker		Optimal Cut-off	Sensitivity (%)	Specificity (%)
F3-4 vs F0-2	**FIB-4**	> 2.30	91.7	88.9
(CHC)	**AST/ALT**	> 1.35	50.0	83.9
	APRI	> 1.66	75.0	91.4
F4 vs F0-3	**FIB-4**	> 2.50	100	81.8
(CHC)	**AST/ALT**	> 1.43	57.5	80.9
	APRI	> 1.74	87.5	82.4
F2 vs F0-1	**FIB-4**	> 1.33	86.3	78.5
(CHB)	**AST/ALT**	> 0.54	71.2	73.6
	APRI	> 0.68	80.1	82.9

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.

DISCUSSION

Outcome and management of hepatitis B and C depends on the severity of fibrosis in an individual, this was true during the days of interferon therapy of hepatitis C and holds true today also for both diseases. Liver biopsy is highly invasive having some morbidity and even mortality while Fibroscan is either not freely available or is costly, Fibrosis markers are simple to calculate from readily available baseline investigations. So if we can predict fibrosis without liver biopsy and at no additional cost, it will contribute in the management of hepatitis B and C. 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 value obtained for APRI score 1.66 was similar to study conducted by Shehab *et al*[22] where the cut-off value 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 Holmberg *et al.*[23]However in case of CHB, FIB-4 has definitely been 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 limitations of our study were the small sample size and hepatitis B patients not with significant fibrosis.

CONCLUSION

The results of our study suggest that FIB-4 and APRI are excellent surrogate markers for liver fibrosis with FIB-4 being the best amongst the two while ASL/ALT is not a very sensitive marker. Though on the basis of our results we do recommend the use of FIB-4 as a surrogate marker for liver fibrosis across all age groups but in the field of research there is always a scope for further studies by including a larger number of patients.

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