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Study of fibro Q test, AAR & APRI indices as markers of fibrosis in chronic liver disease

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Abstract

Introduction: Liver biopsy and ultrasound are the gold standard methods to assess liver fibrosis in chronic liver disease (CLD). Recently Fibrosis Quotient test (Fibro Q test), AST: ALT Ratio (AAR) & AST: Platelet Ratio Indices (APRI) are the three non-invasive and simple indices proposed for assessing liver fibrosis in CLD.

Objectives of the study: To know the efficacy of the indices- Fibro Q test, AAR, APRI as markers of fibrosis in CLD and to know which among these indices would be a high sensitive marker in estimating fibrosis.

Materials and Method: The study includes 60 subjects, out of which 30 were clinically diagnosed as CLD and were confirmed by abdominal ultrasound (USG) and 30 were age and sex matched healthy controls. Fasting blood sample was collected; and AST, ALT, prothrombin time and platelet count were analysed. Fibro Q test, AAR & APRI were calculated. Receiver operating characteristic (ROC) curves were constructed to compare the accuracy of these three non-invasive tests in predicting significant fibrosis in patients with CLD.

Results: Fibro Q, AAR, APRI were significantly increased in cases compared to controls. Fibro Q is a better marker than AAR & APRI, in the prediction of significant liver fibrosis.

Conclusion: Fibro Q test, AAR & APRI indices are efficient markers to evaluate liver fibrosis in patients with CLD. Fibro Q, a novel non-invasive test, is a high sensitive marker than AAR & APRI.

Keywords: AAR- Aspartate Amino Transferase – Alanine Amino Transferase Ratio; APRI- Aspartate Amino Transferase-Platelet Ratio Index**;** CLD- **C**hronic Liver Disease; Fibro Q test-Fibrosis Quotient test.

Introduction

CLD stages vary from mild hepatic inflammation without fibrosis to advanced hepatic fibrosis and cirrhosis.(1) Liver fibrosis results in cirrhosis that can in turn lead to liver failure and hepatocellular carcinoma.(2,3) CLD of different aetiologies are causes of morbidity and mortality. Assessment of the stages of liver disease is important for diagnosis, treatment, to estimate the prognosis.

Liver biopsy & ultrasound are the standard methods for assessing fibrosis in CLD. Liver biopsy is an invasive method. Biopsy has disadvantages like patient discomfort, hospitalization for 4–6 hours after biopsy & sometimes associated with serious complications. The use of ultrasound for the confirmation of complications during biopsy procedures increases the cost of treatment and may also increase the duration of hospitalization. The accuracy of liver biopsy is limited due to sampling error and intra- and inter-observer reporting in histological staging.(1) Although only few patients progress to clinical stages of fibrosis, early identification may significantly prevent cirrhosis and hepatic carcinoma.

Many non-invasive markers for assessing fibrosis have been developed and used by physician. They have been evaluated in different studies, and some were found to be highly accurate in the assessment of liver fibrosis when compared with liver biopsy and ultrasound.(1) Fibro Q test (FQT), Aspartate amino transferase – Alanine amino transferase ratio (AAR) & Aspartate amino transferase- platelet ratio index (APRI) are the three non-invasive and simple indices proposed for assessing fibrosis in CLD.

Hence, the aim of this study was to evaluate and compare the diagnostic accuracies of FQT, AAR and APRI for the prediction of significant fibrosis and cirrhosis in patients with CLD.

Objectives of the study

- To know the efficacy of the indices- Fibro Q test, AAR, APRI as markers of Fibrosis in CLD.
- To know which among these indices would be the high sensitive marker of liver fibrosis.

Materials and Method

Our study included 60 subjects, out of which 30 were clinically diagnosed as CLD and were confirmed by abdominal ultrasound and 30 were age matched healthy controls. This study was conducted in tertiary care hospital. Study had no conflicts of interest & Institutional Ethical Clearance was obtained. Informed consent from all the individual participants was obtained.

Inclusion criteria: Patients diagnosed as chronic liver disease by clinicians & confirmed by ultrasonography.

Exclusion criteria: Patients with a history of gastrointestinal bleeding, liver diseases such as Wilson's disease, hemochromatosis, alpha 1-antitrypsin

deficiency, biliary disease, hepatocellular carcinoma, active intravenous drug abuse and liver transplantation.

Sample collection & processing: After obtaining informed consent, 5 ml of fasting blood sample was collected from all the subjects. 1 ml of blood sample was collected in EDTA vacutainer for analyzing platelet count, another 1 ml of blood sample was collected in separate vacutainer along with 100 µl of 3.2% trisodium citrate as an anticoagulant, for analyzing Prothrombin time. Remaining 3 ml of blood sample was allowed to clot for 30 min and centrifuged at 2000 rpm for 5 min. Serum was separated & used for estimating AST & ALT.

Serum Aspartate Amino Transferase (AST) & Alanine Amino Transferase (ALT) levels were determined using an autoanalyzer (Erba manheim- XL 640) by IFCC Kinetic method. Prothrombin time was assessed by in vitro diagnostic reagent- Uniplastin. The platelet count was performed on an automated hematology analyser- Sysmex Cell counter.

Using the above parameters and age of the patient, Fibrosis Quotient test (Fibro Q test), AST: ALT Ratio (AAR) & AST-Platelet Ratio Indices (APRI) were calculated as follows.

- Fibro Q test = (10 × Age (years) × AST × PT / (PLT × ALT))
- AST : ALT Ratio
- APRI = AST level (U/L) × 100

Platelet count (Lakhs/cmm)

Statistical analysis was performed online using Vassar stats & Graph pad prism. p value <0.05 was considered as statistically significant. To evaluate the diagnostic accuracy of the fibrosis prediction tests, following statistical parameters like sensitivity, specificity, Receiver operating characteristic (ROC), positive predictive value (PPV) & negative predictive value (NPV) were calculated. ROC curves were constructed to compare the accuracy of these three non-invasive tests in predicting significant fibrosis in patients with CLD.

Results

The mean age group of cases & controls in the study were 41.09±8.83 and 40.3±14.4 years respectively. Case group included 30 patients of which 4 were females and 26 were males. In control group 3 were females and 27 were males. The different causes of CLD in the study group were hepatitis (8), non-alcoholic fatty liver disease (4), alcoholic liver disease (16) & primary biliary cirrhosis (2) (Table 1). AST levels in cases & controls were 79.3±66.12 IU/L and 19.8±6.56 IU/L respectively with p value of 0.0002. ALT levels in cases & controls were 42.58±36.92 IU/L and 14.05±5.60 IU/L respectively with p value of 0.0013. Prothrombin time was also increased significantly in cases (2.16±1.06) compared to controls (1.09±0.14) with a p value of 0.0001. Platelet count was decreased significantly in cases (1.35±0.53) compared to controls (2.38±0.45) with a p value of 0.0001 (Table 2).

Fibro Q, AAR & APRI were significantly increased in cases compared to controls. The increase in Fibro Q test in cases was highly significant (p-0.0001) when compared to controls. There was a significant increase in AAR (p-0.003) & APRI (p-0.001) in CLD patients when compared to controls (Table 2).

The sensitivity of Fibro Q was 94% when compared to AAR & APRI of 71% & 87% respectively. The specificity of Fibro Q was 100% when compared to AAR & APRI of 90% & 95% respectively. The PPV & NPV was 100% & 91% for Fibro Q, 92% & 66% for AAR and 96% & 82% for APRI respectively. The area under the receiver operating characteristic curve (AUC) was 0.9902 for Fibro Q test when compared to AUC of 0.76 for AAR and 0.93 for APRI (Table 3, Fig. 1, 2 & 3).

According to our study, Fibro Q had p value of 0.0001, AUC was 0.9902 with specificity and positive predictive valve of 100%. Hence Fibro Q can be considered as highly sensitive marker than AAR & APRI in the prediction of significant fibrosis in CLD.

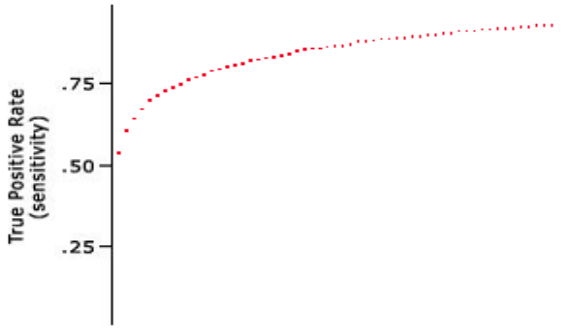

Fig. 1: ROC (AUC) of FQT

ROC-AUC of FQT= 0.99

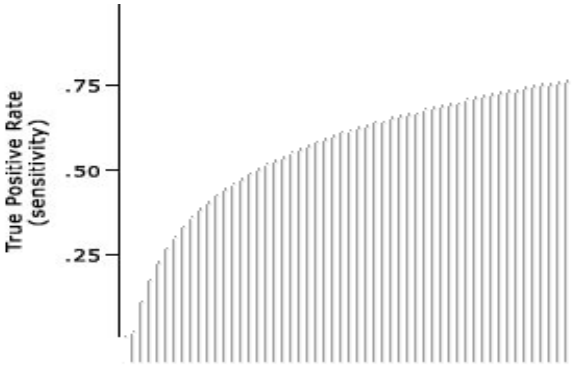

Fig. 2: ROC (AUC) of AAR

ROC-AUC of AAR=0.76

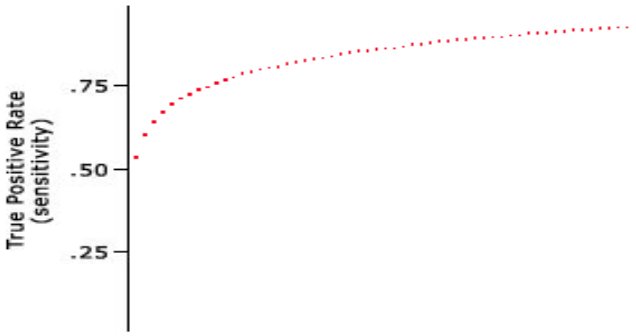

Fig. 3: ROC (AUC) of APRI

ROC-AUC of APRI=0.93

Table 1: Different causes of CLD in study group

Causes of CLD	Number of patients
Hepatitis	8
Non-alcoholic fatty liver disease	4
Alcoholic fatty liver disease	16
Primary biliary cirrhosis	2

Table 2: Comparison of age and other parameters between cases & controls

Variables	Cases n=30	Control n=30	p value (<0.05)
Mean age(years)	41±8	40±14	
Sex of the participants Male-M, Female-F	M-26, F-4	M-27,F-3	
AST(U/L)	79.3±66.12	19.8±6.56	0.0002
ALT(U/L)	42.58±36.92	14.05±5.60	0.0013
PT(INR)	2.16±1.06	1.09±0.14	0.0001
Platelet count (lakhs/cmm)	1.35±0.53	2.38±0.45	0.0001
FQT	2.55±2.4	0.28±0.13	0.0001 ***
AAR	2.3±1	1.4±0.4	0.003*
APRI	65±50	8.3±2.6	0.001**

p value<0.05 is considered as statistically significant

Table 3: Sensitivity, Specificity, Positive predictive valve, Negative predictive valve & AUC of the three indices of liver fibrosis

	FQT	AAR	APRI
Sensitivity	94	71	87
Specificity	100	90	95
PPV	100	92	96
NPV	91	66	82
ROC-AUC	0.99	0.76	0.93

Discussion

CLD is an imbalance between fibrogenesis and fibrolysis, due to which excess collagen deposition occurs, leading to fibrosis and later scar formation yielding hepatic cirrhosis.[4] In liver fibrosis, appearance of new biomarkers in the serum occurs due to the underlying pathological changes[3] The gold standard for diagnosing fibrosis is liver biopsy. Scoring system of liver fibrosis is assessed by collagen staining of biopsied liver sample. Major limitations of liver biopsy are fibrosis staging system,[5] sampling error[6] and inter-observer variation by pathologists in staging the fibrosis.[7] Hence for assessing fibrosis in CLD, there are few serum based non-invasive markers. These can be analyzed frequently and also helps in assessing the efficacy of the treatment.

The individual markers for assessment of liver fibrosis are:

- Liver function tests (aspartate aminotransferase: AST and alanine aminotransferase: ALT) which reflect hepatocyte damage,
- Bilirubin and Alkaline phosphatase for biliary obstruction and
- Albumin and Prothrombin time (PT) for biosynthetic function of liver.

These tests only provide information about important aspects of liver function but cannot assess severity of liver fibrosis or cirrhosis individually.[8] Some studies have reported that due to the limitations of individual markers to assess liver fibrosis, indices combining the markers improve diagnostic accuracy.[9,10]

Fibro Q, AAR & APRI were considered as few non-invasive markers for assessing liver fibrosis in CLD which involved combination of markers like AST, ALT, platelet count & prothrombin time.[1] A series of indices of non-invasive serum markers showed 93-95% accuracy in the detection significant liver fibrosis and a reduction of 50% biopsy in this subset of patients. Liver fibrosis stage is correctly diagnosed in only 65% of cases, if the biopsy is at least 15 mm long, 75% if it is at least 25 mm long and the optimal size of biopsy should be 40 mm. However, most biopsies do not fulfil these optimal criteria.[11,12] Data analyzing the discordance between liver biopsy and the indices showed that this discordance was attributed to biopsy in 5% and for the indices 2%.[13] These shortcomings of liver biopsy lead to underestimation of the diagnostic accuracy of non-invasive markers. The error in the liver biopsy report itself makes it impossible to distinguish a perfect non-invasive marker from less valid assays.[14] This supports the assumption that non-invasive markers might be underestimated using liver biopsy as reference method.

Several studies have suggested APRI as a useful non-invasive marker for hepatic fibrosis in patients with CLD.[15-20] Hence APRI can be used as marker for fibrosis in CLD which is in accordance to our study. Loaeza-del-Castillo et al and Calès has showed that the APRI tend to increase with the degree of fibrosis in patients with non-alcoholic fatty liver disease.[21,22]

Etiologically different stages of fibrosis require the use of indices that assay fibrogenesis, oxidative stress markers, in addition to liver specific marker. The limited number of variables in APRI may minimize its potential in monitoring the basic events in scar formation. Yilmaz et al., demonstrated that APRI should be used with caution because their sensitivity in predicting fibrosis is strongly influenced by the etiology of fibrosis.[23] An additional limitation of APRI is its inability to identify mild forms of liver fibrosis. In fact, AST levels in serum and platelet counts become altered mainly in advanced stages of hepatic disease; thus, APRI could be ineffective in detecting early liver fibrosis.

AAR was raised significantly in CLD patients in our study and hence efficient as a marker of fibrosis but was less sensitive than FQT & APRI. Fujii calculated AAR & APRI indices in hepatitis C patients & concluded that these indices are as good as non-invasive laboratory tests to predict fibrosis.[24]

Lackner & Kim[25,26] study showed diagnostic accuracies of AAR and APRI index in chronic hepatitis C & CLD and observed that diagnostic accuracy of APRI was superior to that of AAR for prediction of fibrosis, which is in accordance to our study. Liu demonstrated a low accuracy of APRI and AAR for predicting significant fibrosis in viral hepatitis C carriers with persistently normal ALT levels.[27]

Bourlier et al studied Fibro Q test & APRI and reported 90% accuracy in diagnosing CLD, in whom liver biopsy was avoided in 46% & 45% respectively and concluded Fibro Q test as a better marker than APRI, which is in accordance with our study.[28]

Sabastiani et al reported that FQT is more sensitive than APRI in diagnosing advanced fibrosis with >95% and 94% accuracy respectively, which is in accordance with our study and the study also showed that the requirement for liver biopsy was decreased by 60–70%.[12]

Hsieh evaluated patients with chronic viral hepatitis & calculated the Fibro Q, AAR and APRI for assessment of liver fibrosis & concluded that Fibro Q performed better than APRI, but was equal to AAR, in the prediction of significant fibrosis.[29]

According to our study, all three indices are efficient as markers of fibrosis in CLD but Fibro Q test is highly sensitive than AAR & APRI.

Conclusion

Fibro Q test, AAR & APRI indices are efficient markers to evaluate liver fibrosis in CLD patients. Fibro Q, a novel non-invasive test, is highly sensitive marker than AAR & APRI. Therefore, utilization of non-invasive biomarkers for liver fibrosis can significantly reduce the requirement of liver biopsies in CLD patients.

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