EVALUATION OF DIAGNOSTIC ACCURACY OF APRI FOR PREDICTION OF FIBROSIS IN HEPATITIS C PATIENTS

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Background: Several non-invasive markers are being used to assess the structural liver damage in patients with chronic hepatitis C (CHC). We evaluated Aspartate aminotransferase (AST) to platelet ratio index (APRI) in comparison with Metavir scoring for assessing the severity of hepatic fibrosis in the CHC patients in district Rawalpindi. Methods: One hundred twenty CHC patients, naive for HCV treatment, underwent liver biopsy in tertiary care hospitals of district Rawalpindi, participated in the study. Liver biopsies were reviewed by Metavir scoring system. Serum AST was analyzed by IFCC method. Platelets were measured on a haematology Analyzer. Patients with mild fibrosis (F0, F1) were differentiated from significant fibrosis (F2, F3, F4) and those with mild/moderate fibrosis (F0, F1, F2) from advanced fibrosis (F3, F4) based on APRI score as compared to liver biopsy. Results: Liver biopsies examination revealed that out of 120 patients 10 (8.3%) had no fibrosis (F0), 46 (38%) portal fibrosis (F1), 34 (28%) septal fibrosis (F2), 21 (18%) bridging fibrosis (F3) and 9 (8%) cirrhosis (F4). APRI correctly classified 58 (48%) patients of significant fibrosis with AUC=0.82 (95% CI, 0.73–0.88) at cut-off 0.5 and 1.5 with negative predictive value (NPV). Positive predictive value (PPV), sensitivity and specificity of 78%, 72%, 66%, 83% and 58%, 90%, 41% and 90% respectively. Eighty-seven (66%) CHC patients were correctly classified for advanced fibrosis with AUC=0.87(95%CI 0.79-0.94) at cut-offs 0.90 and 1.75 with a 95%NPV at 0.90 and 78% PPV at 1.75. Conclusion: APRI could correctly identify significant fibrosis in 48% and advanced fibrosis in 66% cases with acceptable degree of diagnostic accuracy in CHC patients in our clinical practice.

Keywords: Chronic hepatitis C, APRI, liver biopsy, Metavir score, AST, diagnostic accuracy

INTRODUCTION
Hepatitis C virus is the most serious form of infection which accounts for high proportion of liver diseases throughout the world. According the WHO estimate 170 million individuals of the world population are infected with Hepatitis C virus (HCV).1 The prevalence of hepatitis C is 5.31% among healthy adults in Islamabad.2 Patients are at high risk (15–20%) of developing chronic hepatitis, cirrhosis and liver cancer if not properly treated in time.3 Degree of Hepatic fibrosis is the important factor for initiation of treatment in patients of hepatitis C.4 There are two major consequences of hepatitis C infection in liver, i.e., fibrosis and necroinflammatory activity. CHC patients with no or minimal fibrosis at presentation appear to progress slowly and treatment possibly could be delayed or withheld. On the other hand, patients with significant fibrosis progress almost invariably to cirrhosis over a 10–20 year period so antiviral treatment should be strongly considered.5

Liver biopsy is currently the most reliable standard for assessment of hepatic fibrosis and necro-inflammatory activity. This is an invasive indoor procedure subject to inter-observer variability and sampling error is up to 33% of biopsies.6 Biopsy length and fragmentation influences its reliability and histopathological results.7 Furthermore the biopsy could have serious complications such as bleeding, pain or puncture of the other organs such as kidney, lung or colon and rarely death. Moreover, liver biopsy cannot be recommended in elderly patients or patients with severe concomitant medical problems. Due to these limitations, liver biopsy cannot be performed in such patients.8

Realizing this need several non invasive biochemical markers for assessing the severity of hepatic fibrosis stage and monitoring the degree of liver damage in patients of chronic hepatitis C have been developed.9 Notable among these are fibrotest and hepascore which have exhibited good diagnostic accuracy.10,11 However, these scores require cumbersome calculation, use of specialized set of biochemical markers and are costly for a third world country like ours.

An ideal non-invasive diagnostic test for hepatic fibrosis should be simple, readily available, inexpensive, and accurate. AST/ ALT ratio was used for the diagnosis of cirrhosis. However, these tests did not predict significant fibrosis.12 Wai et al reported a novel index for prediction of significant fibrosis and cirrhosis by combining AST and platelets in a model termed APRI.13

Hepatic fibrosis is the most important factor for estimating clinical outcome in patients of hepatitis. The objective of the study was to determine the diagnostic accuracy of APRI for hepatic fibrosis staging as compared to liver biopsy in the treatment-naïve CHC patients in tertiary care hospitals at Rawalpindi.

PATIENTS AND METHODS
The study was carried out at the department of Pathology, Army Medical College, and Rawalpindi-

Pakistan. The descriptive validation study was performed in accordance with declaration of Helsinki after approval of the institutional ethical committee.

A total of 120 untreated patients of CHC admitted from Sep 2007–Aug 2008 in tertiary care hospitals of district Rawalpindi were included by convenient sampling. 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 between 18–50 years of age of either sex. Patients were non-alcoholic and non-obese. They had positive anti HCV and PCR+. Patients having a co-existing liver disease including; chronic hepatitis B, Wilson’s disease, haemochromatosis, autoimmune hepatitis and Patients on steroids or immunosuppressant therapy were excluded.

Blood sample (2.5 ml) was collected in EDTA tubes. Complete blood count assessment including Hb and platelets were carried out on a haematology Analyzer –SYMEX KX-21 (Japan).

Blood (5 ml) was drawn in plain tubes for biochemical analysis. The routine liver function tests including serum ALT, AST, ALP, were determined by using pioneer diagnostic kits (USA) procedures based on IFCC methods on Selectra E (Vita lab Netherlands). Serum total bilirubin was estimated by Jendrassik and Grof method. The upper limit of AST for men was 35 IU/L and for females it was 31 IU/L.

Microscopic examination was carried out on formalin fixed sections of liver biopsies. Fibrosis and activity were staged by a single blinded pathologist according to the Metavir scoring system. Liver biopsies were examined for various changes in cellular appearance that are signs of ongoing inflammation, necrosis and fibrosis. The degrees of inflammation and fibrosis were recorded as F0=no fibrosis, F1=portal fibrosis without septa, F2=few septa, F3=numerous septa without cirrhosis and F4=cirrhosis. According to Metavir stages, significant fibrosis was defined by the presence of F2, F3, or F4 and the presence of F3 or F4 stages was labelled advanced fibrosis.

Statistical analysis was performed by SPSS software version 16 (Chicago IL). Data were expressed as mean (SD) unless otherwise stated. The variables included in the univariate analysis were age, sex, and platelet count, bilirubin, ALT, AST, and ALP. The APRI was calculated as: [(AST/upper limit of normal)/platelet count (10^9/L)]×100. (Wai et al.)

Multivariate analyses were used to identify variables associated with significant fibrosis. The predictive accuracies of these variables were tested by measuring the area under the receiver operating characteristics curve (AUROC). Based on the receiver operating characteristics curve, the best cut-offs points to predict the absence or presence of significant fibrosis and advanced fibrosis were chosen.

Diagnostic accuracy at these cut-offs was evaluated by calculating the sensitivity, specificity, PPV and NPV, respectively. Continuous variables were compared with the Student’s t-test. A p-value of less than 0.05 was considered significant.

RESULTS

One hundred and twenty diagnosed CHC patients consisting of males 83 (69%) and females 37 (30%) with mean (SD) age 37(10) years participated in the study.

Histopathological examination of liver biopsies demonstrated that the patient had all stages of fibrosis ranging from no fibrosis (F0) to cirrhosis (F4) according to the Metavir scores system (Table-1). The frequency of significant fibrosis was 54% and 26% for advanced fibrosis which were our main diagnostic targets. Mild to severe necroinflammatory activity was also graded.

The patients had raised serum mean (SD) ALT 75 (24) IU/L; AST 69 (27) IU/L, serum ALP 203 (43) IU/L. The platelet count ranged from 120-365 (10^9/L) with mean (SD) 235 (59). Patients with F2–F4 had significantly (p<0.001) higher serum transaminase enzymes and lower levels platelet count as compared with F0–F1 (Table-2). These differences were also observed between patients with and without advanced fibrosis (F3–F4).

Box plot of AST platelet ratio index in relation to the Metavir score is shown in Figure-1.

ROC curves were plotted for APRI for predicting significant and advanced fibrosis and the best cut-off points were evaluated to predict the significant and advanced fibrosis respectively with an aim of achieving predictive values >80 in (Figure -2).

For patients with APRI of 0.5 or less, 32 of 43 (78% NPV) would not have significant fibrosis and Among the 53 patients who had significant fibrosis, only 11 (8%) would have APRI of 0.50 or less, PPV being 72%, 9 had a METAVIR stage F2 and 2 were F3. For patients with APRI greater than 1.5, 26 (90% PPV) would have significant fibrosis. Thus the best cut-offs were 0.5 and 1.5 for significant fibrosis. The accuracy for determination of significant fibrosis at cut-off 0.5 was 70% while it was lower 65% for 1.5 cut-offs.

Together, using APRI below the lower cut-off value (0.5) and above the higher cut-off value (1.5), 32 (27%) and 26 (21%) patients in accordance with liver biopsy could be classified as either without or with significant fibrosis, respectively. Thus liver biopsy could have been avoided in 58 (48%) cases.

Comparable results were obtained for the detection of advanced fibrosis (F3–F4). The AUROC
of APRI was 0.87 (95% CI, 0.79–0.94). The best determined diagnostic cut-offs were 0.90 and 1.75 based on ROC for advanced fibrosis. An APRI value ≤0.90 for excluding advanced fibrosis achieved a sensitivity of 90%, a specificity of 70%, NPV 95% and PPV 49%. Scores >1.75 could detect liver F3–F4 stages with an accuracy of 85%, a sensitivity of 56%, a specificity of 94%.

Together, using APRI below the lower cut-off value (0.90) and above the higher cut-off value (1.75), 63 (52%) and 17 (14%) patients in accordance with liver biopsy could be classified as either without or with advanced fibrosis.

Table-2: Comparison of serum AST, platelets and APRI score in different staging of Fibrosis according to METAVIR scoring (F0–F4)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>F0–F1 (n=56; 46%)</th>
<th>F2–F4 (n=64; 53%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT* (IU/L)</td>
<td>63 (17)</td>
<td>86 (25)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AST* (IU/L)</td>
<td>52 (15)</td>
<td>84 (27)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Platelets* (10^9/L)</td>
<td>267 (51)</td>
<td>207 (51)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>APRI</td>
<td>0.69 (0.44)</td>
<td>1.38 (0.78)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Table-3: Diagnostic Accuracy of the APRI Model in Predicting Significant Fibrosis (METAVIR F2–F4) and Advanced Fibrosis (METAVIR F3–F4)

<table>
<thead>
<tr>
<th>Diagnostic Accuracy</th>
<th>APRI Cutoff values</th>
<th>Patients (n=120)</th>
<th>Actual Fibrosis</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Significant fibrosis</td>
<td>0.90</td>
<td>120</td>
<td>F0–F1 (n=56)</td>
<td>83</td>
<td>66</td>
<td>72</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td>1.75</td>
<td>120</td>
<td>F2–F4 (n=64)</td>
<td>38</td>
<td>32</td>
<td>83</td>
<td>66</td>
</tr>
<tr>
<td>Advanced fibrosis</td>
<td>0.90</td>
<td>120</td>
<td>F0–F2 (n=90)</td>
<td>90</td>
<td>70</td>
<td>49</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>1.75</td>
<td>120</td>
<td>F3–F4 (n=30)</td>
<td>13</td>
<td>85</td>
<td>56</td>
<td>94</td>
</tr>
</tbody>
</table>

Abbreviations: APRI, Aspartate aminotransferase platelet ration index; PPV, positive predictive value; NPV, negative predictive value.
DISCUSSION

Among non invasive test for prediction of liver fibrosis, APRI is the simplest test with acceptable diagnostic accuracy. It employs routine lab parameters that is AST and platelet count and therefore is cost effective. It allows clinicians to use one formula to predict significant fibrosis as well as cirrhosis. Unlike APRI other non invasive markers currently in use in Europe and America like fibrotest and hepascore require specialized markers: haptoglobin, alpha2macroglobulin, Gamma glutamyl transferase, hyaluronic acid, thus increasing the test cost.10, 19

There is inverse relation between platelet count and AST level with progression of liver fibrosis. It is an established fact has that with increasing fibrosis and worsening portal hypertension; there is increased sequestration and destruction of platelets in the enlarged spleen.20 Hypersplenism is the most common cause of decreased platelet count related with cirrhosis and portal hypertension.21 Another cause for reduced platelets may be decreased production of thrombopoietin by hepatocytes.22 The increased AST level had been attributed to mitochondrial injury which may be associated with the HCV infection.23 In addition, progression of liver fibrosis may reduce the clearance of AST, leading to increased serum AST levels.24

The AUROC of APRI score for significant fibrosis prediction was comparable to that of the original study by Wai et al, 0.82 (0.73-0.88) vs. 0.88 (0.80-0.96) for diagnosis of significant fibrosis, in the present study and in the original, respectively.13 Silva et al reported for significant fibrosis AUC of 0.92.25 How ever latest studies comparing APRI with fibrotest and hepascore have shown lower accuracy rates than our data. Bourliere et al reported AUC of 0.76 and Cales P et al showed AUC 0.786 for significant fibrosis diagnosis.26-28

Bourliere et al reported that noninvasive markers of fibrosis may have different diagnostic accuracy depending on the prevalence of significant fibrosis in the studied population and that normal AST value can lead to APRI failure.29 This may explain the variability of results for APRI in different populations.

In our population, using our own diagnostic cut-off values significant fibrosis could be classified correctly according to liver biopsy in 48% and advanced fibrosis in 66% of patients. Our results were comparable to Wai et al who found,44% patients could be classified correctly for significant fibrosis.13 Silva et al also reported 44% accurate classification for significant fibrosis.25 The lower diagnostic cut off that best predicted significant fibrosis for APRI was 0.5 in our population. Wai et al reported it to be 0.5 and Trang et al reported 0.42.

The upper diagnostic cut-off was found to be 1.5 which was similar to by Wai et al.30-32

Very few studies have determined the diagnostic cut-offs for advanced fibrosis. The diagnostic cut-offs proposed by Trang et al are quite similar to ours for advanced fibrosis in his HIV-HCV co infected patients. Trang et al chose 0.71 and 1.85 based on AUC of 0.738 for APRI. Where as ours was 0.90 and 1.75 respectively for the prediction of absence and presence of advanced fibrosis.

Although APRI is a useful index for prediction of hepatic fibrosis. The limitation of this index is its inability to identify individual stages of fibrosis, it can only differentiate mild from significant fibrosis or mild/moderate from severe fibrosis and many patients remain unclassified after using the recommended cut-off values. The interval between the diagnostic cut-offs ≤0.90 and ≥1.5 is the grey zone where the patients remain unclassified. In these patients liver biopsy or some other diagnostic test with greater accuracy like fibrotest has to be performed for appropriate classification. Another difficulty is that each laboratory establishes a different value of the ULN and the appropriate definition of the upper limit of for AST remains uncertain. This may explain the lower diagnostic power and reproducibility of this test as compared with Fibro test in the literature.19

Recently sequential algorithms have been suggested which combine APRI with fibrotest, APRI is used as a screening test and those not classified by APRI under go fibro test. In this way diagnostic accuracy and test performance is further improved and greater number of liver biopsies avoided.33

In conclusion, APRI could identify 48% significant fibrosis and 66% advanced fibrosis with acceptable degree of diagnostic accuracy in chronic hepatitis patients in our clinical practice.

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