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## RESEARCH ARTICLE

# ASPARTATE AMINOTRANSFERASE -TO- PLATELET RATIO INDEX (APRI) FOR THE PREDICTION OF HEPATITIS C–RELATED FIBROSIS

***Shah NA, Chauhan Imran, Kadla SA, Irfan Ali, Asif iqbal, Afroza Jan, Muzafar Bindroo and Sakshi Sharma**

Srinagar, Jammu and Kashmir, 190010, India

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**ABSTRACT**

***Background:*** Chronic hepatitis C is a major public health problem affecting an estimated 150 million individuals globally. About 75–85% of newly infected persons develop chronic infection and 60–70% of them develop chronic liver disease; 5–20% develops cirrhosis and 1-5% die from cirrhosis or liver cancer. Assessment of liver disease severity is recommended prior to therapy. In chronic hepatitis C (CHC), liver biopsy is the gold standard method for assessing liver histology, however it is invasive and can have complications.

**Objective:** To determine the correlation of APRI score with the degree of histological liver fibrosis in chronic hepatitis C patients.

**Method**: This prospective study was carried out at the Postgraduate Department of Medicine, Division of Gastroenterology, Govt. Medical College, Srinagar, between july 2011 and july2013. A total of thirty patients of incidentally detected HCV positive patients were included. All these patients underwent liver biopsies and were evaluated according to Ishak modification for HAI for scoring necroinflammatory activity and staging. AST to Platelet Ratio Index (APRI) was calculated based on laboratory results performed on the day of liver biopsy.

**Results:** All the patients with APRI <0.5 had Ishak staging score ≤3 whereas all the patients with APRI ≥2.5 had Ishak staging score≥4. Among patients with APRI ≤1.50 only 12.5 % had fibrosis score of ≥4 whereas among patients with APRI ≥1.5, 73.33% had fibrosis score of ≥4. A significant correlation was observed between APRI and histopathological parameters like necro-inflammatory score, Staging (modified Ishak) and cirrhosis with p value of 0.019, 0.000 and 0.03 respectivelly.

**Conclusion:** APRI ≤0.50 rules out significant fibrosis whereas APRI ≥1.51 suggests significant fibrosis. APRI, a simple model incorporating readily available laboratory data is highly predictive of significant fibrosis in HCV infected patients.



## INTRODUCTION

Hepatitis C is a global disease with over 150 million patients all over the world infected with this virus (WHO 2013) .In USA approximately 2% or 5.2 million persons are HCV infected currently (Eric Chak *et al.*, 2011). In India the prevalence has not been studied systematically, several studies on voluntary or mixed donors have noted a prevalence of hepatitis C below 2% (Ashis Mukhopadhya *et al*., 2008). The natural history of HCV infection has been very difficult to assess because of the usually silent onset of the acute phase as well as the frequent paucity of symptoms during the early stages of chronic infection. About 75–85% of newly infected persons develop chronic infection and 60–70% of them develop chronic liver disease; 5–20% develop cirrhosis and 1-5% die from cirrhosis or liver cancer (Timothy *et al*., 2006).

****Corresponding Author: Shah NA,***
*Srinagar, Jammu and Kashmir, 190010, India.*

To estimate prognosis and guide management decisions, the accurate staging of hepatic fibrosis is a clinical and research priority. Currently, liver biopsy is the gold standard for this purpose Husain *et al.* (2007). Unfortunately, this procedure is limited by invasiveness, complications, sampling error, variability in pathological interpretation, and the reluctance of patients to undergo repeated biopsies to monitor disease progression, (Friedman *et al*., 2004). An important study by Abdi *et al.* (1979) showed that the yield of diagnosis of cirrhosis was 80% with one biopsy sample, which reached 100% when three biopsy samples were obtained and examined. Superiority of multiple samples was also supported in a study by Maharaj *et al.* (1986). There can easily be sampling errors, because only approximately.002% of the organ is biopsied, and inter- and intra-observer discrepancies of 10% to 20% in assessing hepatic fibrosis have been reported (Regev *et al*., 2002).

Sample size can affect the diagnostic accuracy of liver biopsy specimens, especially in cases of chronic hepatitis, because the biopsy represents approximately only 1/50,000 of the total mass of the liver (Lee *et al*., 1994). As antifibrotic therapies are developed, the assessment of fibrosis will have important practical implications (McHutchison *et al.*, 2006). Staging HCV infection is still mainly based on degree of histologic fibrosis in a liver biopsy sample, but there are many problems in relying on biopsy.

Liver biopsy is performed by a small number of specialists further, as biopsy is usually performed once on a patient, the ability to monitor a patient's liver fibrosis would benefit from an index based on serum fibrosis markers. A review study by Gebo *et al* in Hepatology (2002), compared liver biopsies with biochemical and serologic tests in predicting treatment outcomes for chronic hepatitis C. They found that a liver biopsy may have some usefulness in predicting efficacy of treatment of these patients, while biochemical and serologic tests have only a modest value in predicting fibrosis on a liver biopsy. Thus, several indices constructed from non-invasive serum-based biomarkers of fibrosis have been proposed and validated, usually within relatively small sets of treatment-naïve chronic hepatitis C patients (Castera *et al*., 2012). In 2003 Wai *et al*. (2003) published a study in which they validated the index known as APRI Score that establishes the relationship between serum aspartate aminotransferase levels and platelet count. The parameters are simple, inexpensive and available in the remotest locations. It was proposed as an alternative method to liver biopsy with satisfactory sensitivity and specificity.

APRI score = [(AST/upper limit NV AST) ×100]/number of platelets ($10^9$ /l) (Shaheen *et al*., 2007)

APRI is of more interest to clinicians because they are simple to calculate and readily available from hospital or clinic laboratories during usual patient care. That is, this simple calculations based on serum result would be useful to screen patients with high values needing biopsy and clinical follow-up and to provide a system for categorizing stage of illness. It is critical to determine which HCV patients have advanced fibrosis to gauge the urgency of treatment as well as the need for upper endoscopy for varices, hepatocellular cancer screening, and closer clinical monitoring of cirrhotic patients.
We carried out this study to predict the liver fibrosis using routine laboratory investigation. Further we studied the correlation of APRI score with the degree of histologic liver fibrosis in chronic hepatitis C patients.

## MATERIALS AND METHODS

**Patients and sample:** We conducted a prospective hospital based study over a period of two years from July 2011- July 2013. A total of thirty patients of incidentally detected Hepatitis C positive patients were included in the study. Both inpatients and out patients were included in the study. Those patients who were first time detected incidently positive for HCV infection either as a part of routine investigations or as a part of evaluation of abnormal liver function or symptoms of liver disease were included in the study. However patients who were already HCV positive, HCV positive patients who had history of organ transplantation, HCV positive patients on chronic dialysis for chronic renal failure, patients who were incidentally detected HCV positive but could not be taken for liver biopsy either due to procedural contraindication or due to patient refusal ,incidentally detected patients who underwent liver biopsy but an adequate liver tissue could not be obtained for histopathological examination study, patients who had concomitant hepatitis B infection were excluded from study.

After selection of the patients as per the criteria a thorough clinical examination of the patients was performed. They were evaluated for baseline investigation like Complete blood counts using Sysmax cell counter, Kidney Function Tests using Hitachi-925 automatic analyser, Liver Function Tests using Dimension Siemon analyser, PT / INR using Sysmax C-1500. Other investigations included: USG of Hepatobiliary system, EGD, Quantitative HCV RNA by Real time PCR using Cobas Ampliprep and Taqman,HCV Genotype by Real Time PCR using Cobas Ampliprep and Taqman. All the patients underwent liver Biopsy (using Bexter Liver Biopsy Needle) After obtaining the liver tissue it was sent in 10% formalin and was studied for detail histopathology with specific stress on following histopathological parameters: liver architecture , hepatocytes change, portal tract Inflammation, Lobular inflammation, Portal Tract Fibrosis, bridging fibrosis, Interphase Hepatitis, Necrosis, Cholestasis, Ductular Proliferation, Lymphoid Follicle Formation, Cirrhosis, Necro-inflammatory score, Staging (modified Ishak)

The total necro inflammatory score (maximum 18) was divided into following groups: minimal hepatitis (score 1-3), mild hepatitis (score 4-8), moderate hepatitis (score 9-12) and severe hepatitis (score 13-18). And seven groups according to the stage of the disease (0-6): No fibrosis(stage 0), Fibrous expansion of some portal areas, with or without short fibrous septa(stage 1), Fibrous expansion of most portal areas, with or without short fibrous septa(stage 2), Fibrous expansion of most portal areas, with occasional portal-portal (P-P) bridging(stage 3), Fibrous expansion of portal areas, with marked bridging portal-portal (P-P) as well as portal –central (P-C) (stage 4), Marked bridging (P-P and /or P-C) with occasional nodules (incomplete cirrhosis) (stage5) , Cirrhosis, probable or definite(stage 6). The histopathological evaluation was performed by a single expert pathologist who was provided the detail history of the patient, clinical findings, biochemical parameters, HCV RNA levels (quantitative) and HCV genotype.

**Analysis and Statistics**

The results were analysed using SPSS version 20 (USA). The students't' test. Chi square test was used to calculate the p value. A p value <0.05 was taken as significant. Furthermore correlation parameters were also evaluated from the same software.

## RESULTS

The age of the patients ranged between 16 to 76 years with a mean age of 45.65 years. Most of the patients were in the age group 46-60 years. 60 % of the studied population were male and 40% were females

**Table1.Correlation between APRI and Histopatholog**

| Histopathological changes | | APRI range | | | | | | Total |
|---|---|---|---|---|---|---|---|---|
| | | 0-0.5 | 0.51-1.00 | 1.01-1.50 | 1.51-2.0 | 2.01-2.50 | =>2.51 | |
| Cirrhosis | Absent | 02 (3.33%) | 08 (26.67%) | 03 (10%) | 01 (3.33%) | 01 (3.33%) | 02 (6.67%) | 17 (56.67%) |
| | occasional nodule | 00 0.00% | 01 (3.33%) | 00 0.00% | 00 0.00% | 03 (10%) | 02 (6.67%) | 06 (20%) |
| | definite cirrhosis | 00 0.00% | 01 (3.33%) | 01 (3.33%) | 02 (6.67%) | 00 0.00% | 03 (10%) | 07 (23.33%) |
| Total | | 02 (6.67%) | 10 (33.33%) | 04 (13.33%) | 03 (10%) | 04 (13.33%) | 07 (23.33%) | 30 (100%) |
| Necro - inflammatory score | 1 | 00 0.00% | 01 (3.33%) | 00 0.00% | 00 0.00% | 00 0.00% | 00 0.00% | 01 (3.33%) |
| | 2 | 00 0.00% | 02 (6.67%) | 02 (6.67%) | 00 0.00% | 01 (3.33%) | 00 0.00% | 05 (16.67%) |
| | 3 | 00 0.00% | 03 (10%) | 00 0.00% | 01 (3.33%) | 00 0.00% | 00 0.00% | 04 (13.33%) |
| | 4 | 01 (3.33%) | 02 (6.67%) | 00 0.00% | 00 0.00% | 00 0.00% | 00 0.00% | 3 (10%) |
| | 5 | 00 0.00% | 00 0.00% | 00 0.00% | 01 (3.33%) | 00 0.00% | 00 0.00% | 1 (3.33%) |
| | 6 | 00 0.00% | 01 (3.33%) | 02 (6.67%) | 00 0.00% | 00 0.00% | 01 (3.33%) | 04 (13.33%) |
| | 7 | 00 0.00% | 00 0.00% | 00 0.00% | 00 0.00% | 01 (3.33%) | 03 (10%) | 04 (13.33%) |
| | 8 | 00 0.00% | 01 (3.33%) | 00 0.00% | 00 0.00% | 00 0.00% | 02 (6.67%) | 03 (10%) |
| | 9 | 01 (3.33%) | 00 0.00% | 00 0.00% | 01 (3.33%) | 01 (3.33%) | 01 (3.33%) | 04 (13.33%) |
| | 13 | 00 0.00% | 00 0.00% | 00 0.00% | 00 0.00% | 01 (3.33%) | 00 0.00% | 01 (3.33%) |
| Total | | 02 (6.67%) | 10 (33.33%) | 04 (13.33%) | 03 (10%) | 04 (13.33%) | 07 (23.33%) | 30 (100%) |
| Staging (modified Ishak) | 0 | 01 (3.33%) | 07 (23.33%) | 03 (10%) | 00 0.00% | 00 0.00% | 00 0.00% | 11 (36.67%) |
| | 1 | 00 0.00% | 02 (6.67%) | 00 0.00% | 00 0.00% | 01 (3.33%) | 00 0.00% | 03 (10%) |
| | 2 | 00 0.00% | 00 0.00% | 00 0.00% | 01 (3.33%) | 00 0.00% | 00 0.00% | 01 (3.33%) |
| | 3 | 01 (3.33%) | 00 0.00% | 00 0.00% | 00 0.00% | 00 0.00% | 00 0.00% | 01 (3.33%) |
| | 4 | 00 0.00% | 00 0.00% | 00 0.00% | 00 0.00% | 00 0.00% | 02 (6.67%) | 02 (6.67%) |
| | 5 | 00 0.00% | 00 0.00% | 00 0.00% | 00 0.00% | 02 (6.67%) | 02 (6.67%) | 04 (13.33%) |
| | 6 | 00 0.00% | 01 (3.33%) | 01 (3.33%) | 02 (6.67%) | 01 (3.33%) | 03 (10%) | 08 (26.67%) |
| Total | | 02 (6.67%) | 10 (33.33%) | 04 (13.33%) | 03 (10%) | 04 (13.33%) | 07 (23.33%) | 30 (100%) |

**Cirrhosis:** Cirrhosis was absent in 17(56.67%) of the cases, occasional nodule present in 6(20%) of the cases whereas definite cirrhosis was present in 7(23.33%) of the cases.

None of the patients with APRI <0.5 had cirrhosis whereas among patients with APRI > 2.5, 3(10%) had definite cirrhosis, 2(6.67%) had occasional nodule and 6.67% had absent cirrhosis. Among patients with APRI <1.5, 3(10%) patients had occasional to definite cirrhosis whereas among patients with APRI > 1.5, 11 (33.34%) had occasional to definite cirrhosis.

**Necroinflammatory score:** Minimal hepatitis (score 1-3), mild hepatitis (score 4-8), moderate hepatitis (score 9-12) and severe hepatitis (score 13-18) were observed in 33.33%, 50%, 13.33% and 3.33% of the patients respectively.

All the patients with severe hepatitis had APRI > 1.5 whereas among patients with minimal hepatitis, 8 (26.67%) had APRI < 1.5 and 2(6.67%) patients had APRI >1.5.

**Staging:** Stage 0,1,2,3,4,5 and 6 were observed in 11(36.67%), 3(10%), 1(3.33%), 1(3.33%), 2(6.67%), 4% (13.33%) and 8(26.67%) of the patients respectively.

Among patients with APRI <0.5 none of the patients had Ishak stage ≥4 and the maximum Ishak stage observed was 3 seen in 1(3.33%) patient .Among patients with APRI < 1.5, 2(6.67%) patients had Ishak stage more than ≥4 (i.e stage 4,5 and 6) whereas among patients with APRI > 1.5, 12(40%) with Ishak stage ≥4. Among patients with Ishak stage 0 all the patients had APRI < 1.5 whereas none of the patients with APRI >1.5 had Ishak stage 0.

## DISCUSSION

In our study the minimum and maximum fibrosis score in patients with APRI 0-0.5 was 0 and 3 respectively whereas minimum and maximum fibrosis score in patients with APRI >2.51 was 4 and 6 respectively. All the patients with APRI >2.51 had Ishak staging ≥4.

Statistically significant correlationexist between APRI and Ishak staging (p value 0.000). The result of our study is in accordance with study conducted by Aurora Loaeza–del Castillo *et al*. (2008) in which they concluded that APRI in values in CHC of ≤0.3 and ≤0.5 rule out significant fibrosis and cirrhosis and a value of ≥ 1.5 rules in significant fibrosis. In our study, 1 (3.33%) patient had APRI of <0.3 having Ishak stage score 0 i.e. no fibrosis. In patient with APRI <0.5 the maximum APRI was 3 i.e. no significant fibrosis or cirrhosis. In patients group with APRI > 1.51, 2 (6.67%), 4 (13.33%) and 4 (13.33%) patients had fibrosis score of 4, 5 and 6 respectively. Result of HAI in our study revealed that all except one patient with HAI score in between 9-18 (moderate to severe hepatitis) had APRI >1.5. Statistically significant correlation exist between HAI and APRI (p value 0.005). To the best of our knowledge none of the study compared HAI with APRI. A significant correlation was observed between APRI and histopathological parameters like necro inflammatory score, Staging (modified ishak) and cirrhosis with p value of 0.019, 0.000 and 0.03 respectively.

**Conclusion**

APRI ≤0.50 rules out significant fibrosis whereas APRI ≥1.51 rules in significant fibrosis. APRI, a simple model incorporating readily available laboratory data is highly predictive of significant fibrosis in HCV infected patients.

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