



To determine the diagnostic accuracy of aspartate aminotransferase to platelet ratio index in detecting significant fibrosis in chronic hepatitis C patients by using histopathology as gold standard.

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ABSTRACT... Objective: The objective of the study was to: determine the diagnostic accuracy of AST to platelet ratio index in detecting significant fibrosis in chronic hepatitis C patients by using histopathology as gold standard. **Study Design:** Cross Sectional study. **Settings:** Department of Medicine, DHQ Hospital, Faisalabad. **Period:** 1st Oct 2017 to March 2018. **Material and Methods:** All patients (158) with chronic hepatitis were enrolled for medical OPD and emergency according to inclusion criteria. **Results:** In this study, out of 158 cases, 48.73%(n=77) were between 25-40 years while 51.27%(n=81) were between 41-60 years, mean+SD was calculated as 40.94+9.10 years, 55.06%(n=87) were male and 44.94%(n=71) were females, mean AST and platelet count was calculated as 1.68+0.54 and 191.0+43.75, frequency of significant fibroids in chronic hepatitis C patients by using histopathology as gold standard reveals as 53.16%(n=84) while 46.84%(n=74) had no findings of this morbidity. The diagnostic accuracy of AST to platelet ratio index in detecting significant fibrosis in chronic hepatitis C patients by using histopathology as gold standard was recorded which shows 51.27%(n=81) as true positive, 2.53%(n=4) false positive, 1.89%(n=3) false negative and 44.31%(n=70) were recorded as true negative, sensitivity, specificity, positive predictive value, negative predictive value and accuracy rate was computed as 96.43%, 94.59%, 95.29%, 95.89% and 95.57% respectively. **Conclusion:** The results of the study reveal that diagnostic accuracy of AST to platelet ratio for detection of significant fibrosis in chronic Hepatitis C patients was satisfactory and it may be used for the avoidance of invasive liver biopsy to initiate the antiviral therapy in these patients.

Key words: AST to Platelet Ratio Index, Chronic Hepatitis C, Diagnostic Accuracy, Significant Fibrosis.

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INTRODUCTION

Hepatitis C virus has become a dangerous form of infection that can cause a large number of cases of liver diseases throughout the world as in an estimate WHO said that around 170 million people around the world have been infected with hepatitis C virus and infected people can then develop chronic hepatitis C (15-20%), cirrhosis of liver and liver cancer if not treated properly in time. Hepatitis C infection can lead to two major pathological changes in liver i.e, fibrosis and necroinflammatory activity.¹

To know the stage of liver fibrosis is important in decision making of anti-viral treatment and

for prognosis of liver disease. As the antiviral treatment is usually not given to chronic hepatitis C patients having no or minimal fibrosis. On the other hand patients having significant fibrosis of liver must be given antiviral treatment to halt the progression to liver cirrhosis over a period 10-20 years.²

In chronic hepatitis C, the gold standard for diagnosing and staging liver fibrosis is liver biopsy. But it is an invasive test with the potential for serious complications requiring hospital admission or prolonged hospital stay, apart from possible sampling error and inter-observer variability.³ Also certain clinical conditions such

as thrombocytopenia and increased prothrombin time often prevent a biopsy being performed in these patients.⁴ Due to these limitations of liver biopsy, a noninvasive marker for detecting fibrosis and cirrhosis should be there and the test should be inexpensive, simple to perform and should have reliability and accuracy in detecting liver fibrosis.⁵ In the recent past a novel marker APRI i.e, Aspartate aminotransferase to Platelet Ratio Index has been reported in detecting liver fibrosis in chronic hepatitis C patients.⁶ This biochemical marker can detect liver fibrosis by establishing a relationship between serum levels of aspartate aminotranferase and platelet count of the patient.⁴ It has been reported that with the progression of hepatic fibrosis, there is an increase in serum AST levels while the platelet count of the patient gradually fall. As with progression of fibrosis, there is an increase in portal hypertension leading to enlargement of spleen causing sequestration and destruction of platelets. Another known cause for thrombocytopenia in liver disease is the decreased production of thrombopoietin by defective hepatocytes in chronic hepatitis C as the stage of liver fibrosis advances. The increase in AST levels is related to mitochondrial Injury due to HCV infection. Additionally with progression of liver fibrosis, there is a reduction in clearance of AST by defective hepatocytes causing an increase in serum AST levels.^{1,2} In a study done at Brazil, the sensitivity and specificity of APRI is 92.9% and 95.5% respectively at a cut off value of 0.9.² The prevalence of significant fibrosis in chronic hepatitis C according to one study done in Pakistan is 54%.¹

APRI is an inexpensive, easily available and simple blood test, so the rationale of my study is to use APRI for detecting significant fibrosis in chronic hepatitis C patients so that invasive liver biopsy can be avoided to initiate antiviral therapy in these patients.

The objective of the study was to determine the diagnostic accuracy of AST to platelet ratio index in detecting significant fibrosis in patients of chronic hepatitis C by using histopathology as gold standard

Chronic Hepatitis C

In our study we included the patients of chronic hepatitis C if both of following were present:

1. Evidence of HCV infection indicated by detection of HCV ribonucleic acid (RNA) on qualitative reverse transcriptase Polymerase Chain Reaction (rtPCR).
2. Elevation of liver enzyme, Alanine aminotransferase (ALT) > twice normal (normal level 10-40 IU/L) for >6 months.

Significant Fibrosis

Significant fibrosis was taken if on liver biopsy there was grade II-IV fibrosis according to Metavir classification of liver fibrosis which is as under:

Grade 0: No scaring.

Grade 1: Minimum scaring without septa.

Grade 2: few septa has formed and fibrosis extends to the areas in the liver that contains blood vessels.

Grade 3: Bridging fibrosis with numerous septa but no cirrhosis.

Grade 4: Cirrhosis or fibrosis of advanced stage leading to nodularity in liver.

AST to Platelet Ratio Index

Aspartate aminotransferase to platelet ratio index was measured according to formula; $[(AST \text{ of the sample/reference AST}) \times 100] / \text{plate count}$ Patients were considered as having fibrosis if APRI ≥ 0.9 .

Sensitivity

It was the ability of APRI to correctly detect patients who had significant fibrosis in chronic hepatitis C patients.

Specificity

It was the ability of APRI to correctly detect patient who did not have significant fibrosis in chronic hepatitis C patients.

Positive Predictive Value

It is the ability of the index to identify the patients actually having the disease.

Negative Predictive Value

It is the ability of the index to identify the patients not actually having the disease.

True Positive

When the significant fibrosis is diagnosed on both liver biopsy and APRI.

True Negative

When the significant fibrosis is not diagnosed on both liver biopsy and APRI.

False Positive

When the significant fibrosis is diagnosed on APRI but not on liver biopsy.

False Negative

When the significant fibrosis is diagnosed on liver biopsy but not on APRI.

MATERIAL & METHODS

This study was conducted at Department of Medicine, DHQ Hospital, Faisalabad from 1st Oct 2017 to 31st March 2018. This was a Cross Sectional Study, where non-probability consecutive sampling technique was used. The sample size was conducted by using WHO sample size calculator for sensitivity and specificity, Sensitivity=92.9%, Specificity=95.5%, prevalence= 54%, P=54% Absolute provision6%, d-4%, n=92, n= 155, sample size at-least= 158.

Inclusion Criteria

1. Age between 25-60 years
2. Both sexes
3. Diagnosed cases of chronic hepatitis C as evidence by detection of HCV-RNA on rtPCR and elevation of liver enzymes for more than 6 months.

Exclusion Criteria

1. All those patients who has been taking alcohol were excluded.
2. Patients with co-morbid conditions who can have high AST value e.g. MI, hemolysis, rhabdomyolysis were also excluded from the study.
3. Patients having hepatitis B & C co-infection.
4. Patients having hepatitis tumor either primary or metastatic.

After getting permission from hospital ethical committee, 48/ERC/201273/PMRC/PMC/150.

Hepatitis C patients who fulfill the inclusion and exclusion criteria were enrolled in the study from OPD as well as from emergency of DHQ Hospital Faisalabad. We took the history of alcohol consumption as alcohol itself can cause increase in AST level. CBC was performed to exclude the patients of hemolysis. ECG was done to exclude MI and hepatitis B serology was done to exclude co-infection with hepatitis B. Hepatic tumor was ruled out on ultrasound abdomen. A detailed informed consent was taken from every patient or guardian if the subject was not in state of giving consent. The whole procedure of liver biopsy with its risks and hazards was explained to the every patient. Liver biopsy was done in the MU-IV DHQ Hospital, Faisalabad and the sample was sent to the pathology department Punjab Medical College Faisalabad for reporting. The biopsy specimens were reported by a single histopathologist. 5ml venous blood of every patient was taken prior to liver biopsy for serum transaminases and platelet count and sent to the Pathology laboratory DHQ Hospital Faisalabad where a senior pathologist done reporting. On getting the reports of liver enzymes and liver biopsy the results were matched. All the information was recorded on proforma by myself.

The collected data was then entered and analyzed by using SPSS V-10. For quantitative variable like age, AST level and platelet; Mean and Standard deviation were calculated. For qualitative variables like gender, true positive, false positive, true negative and false negative; Frequency and percentage were calculated and then sensitivity, specificity, positive predictive value, negative predictive value and accuracy were calculated by constructing 2x2 table as follows:

Liver Biopsy

| | | +ve | -ve |
|--|-----|-----------------------|-----------------------|
| Aspartate aminotransferase to Platelet ratio index | +ve | a (True positive) | b (False positive) |
| | -ve | c (False negative) | d (True negative) |

Sensitivity= $a/a+c \times 100$

Specificity= $d/b+d \times 100$

Positive predictive value= $a/a+b \times 100$

Negative predictive value= $d/c+d \times 100$

Diagnostic accuracy = $a+d/a+b+c+d \times 100$

RESULTS

158 patients of chronic hepatitis C were enrolled in the study after following the inclusion and exclusion criteria to determine the diagnostic accuracy of aspartate aminotransferase to platelet ratio index in detecting significant fibrosis in patients of chronic hepatitis C by using histopathology as gold standard.

Age distribution of the patients was done which shows that 48.73% (n=77) were between 25-40 years while 51.27% (n=81) were between 41-60 years, mean+sd was calculated as 40.94+9.10 years. (Table-I)

Gender distribution of the patients was done which shows that 55.06% (n=87) were male and 44.94% (n=71) were females. (Table-II)

Mean AST and platelet count was calculated as 1.68+0.54 and 191.0+43.75. (Table-III)

Frequency of significant fibrosis in patients of chronic hepatitis C by using histopathology as gold standard reveals as 53.16% (n=84) while 46.84% (n=74) had no findings of this morbidity. (Table-IV)

Diagnostic accuracy of APRI in detecting significant fibrosis in patients of chronic hepatitis C by using histopathology as gold standard was recorded which shows 51.27% (n=81) as true positive, 2.53% (n=4) false positive, 1.89% (n=3) false negative and 44.31% (n=70) were recorded as true negative. Sensitivity, specificity, positive predictive value, negative predictive value and accuracy were computed as 96.43%, 94.59%, 95.29%, 95.89% and 95.57% respectively. (Table-V)

| Age (in years) | No. of Patients |
|----------------|-----------------|
| 25-40 | 77 (48.73%) |
| 41-60 | 81 (51.27%) |
| Total | 158 |
| Mean+sd | 40.94+9.10 |

Table-I. Age Distribution. (n=158)

| Gender | No. of Patients |
|--------|-----------------|
| Male | 87 (55.06%) |
| Female | 71 (44.94%) |
| Total | 158 |

Table-II. Gender Distribution. (N=158)

| AST | Platelet |
|-----------|-------------|
| 1.68+0.54 | 191.0+43.75 |

Table-III. Mean AST and Platelet Count.

| Aspartate Aminotransferase to Platelet Ratio Index | Liver Biopsy | | Total |
|--|-------------------------------------|-------------------------------------|--------------------|
| | Positive | Negative | |
| +ve | a (True positive) 81 (51.27%) | b (False positive) 4 (2.53%) | a+b 85 (53.80%) |
| -ve | c (False negative) 3 (1.89%) | d (True negative) 70 (44.31%) | c+d 73 (46.20%) |
| Total | a + c 84 (53.16%) | b + d 74 (46.84%) | 158 (100%) |

Table-V. Diagnostic accuracy of AST to platelet ratio index in detecting significant fibrosis in chronic hepatitis c patients by using histopathology as gold standard. (n=158)

Sensitivity = $a / (a + c) \times 100 = 96.43\%$

Specificity = $d / (d + b) \times 100 = 94.59\%$

Positive predictive value = $a / (a + b) \times 100 = 95.29\%$

Negative predictive value = $d / (d + c) \times 100 = 95.89\%$

Accuracy rate = $a + d / (a + d + b + c) \times 100 = 95.57\%$

| Significant fibroid | No. of Patients |
|---------------------|-----------------|
| Yes | 84 (53.16%) |
| No | 74 (46.84%) |
| Total | 158 |

Table-IV. Frequency of significant fibroids in chronic hepatitis c patients by using histopathology as gold standard. (n=158)

DISCUSSION

Liver fibrosis is the main underlying pathology causing liver dysfunction in chronic liver disease due to any cause. Liver fibrosis progressively leads to chirosis that can cause liver failure, portal hypertension and in some cases hepatocellular carcinoma. The process of liver fibrosis can be stopped or even reversed by starting anti-fibrotic therapies if detection of fibrosis done at earlier stages and thus progression of liver cirrhosis can be prevented. For these reasons, an inexpensive, simple and easily available test that can be used as an alternative to more invasive liver biopsy for detecting liver fibrosis is needed.

Our findings regarding frequency of significant fibrosis are in agreement with a local study showing the prevalence of significant fibrosis in chronic hepatitis C as 54%.¹

Our results are comparable with a study done at Brazil, in which the sensitivity of APRI was 92% and the specificity was 95% with a cut off value of 0.9.²

A meta analysis showed that in chronic hepatitis C patients the summary AUCs of the aspartate aminotransferase to platelet ratio index for significant fibrosis was 0.76 [95% CI: 0.74-0.79] and for cirrhosis it was 0.82 [95%CI: 0.79-0.86], with an APRI threshold of 0.5, the sensitivity and specificity were 81% and 50% respectively with a 40% prevalence of significant fibrosis. The negative predictive value (NPV) at this threshold was 80%. However For cirrhosis, at a threshold of 1.0%, the sensitivity and specificity were 76% and 71% respectively with a 15% prevalence of cirrhosis and at this threshold the negative predictive value was 91%; thus the primary strength of the index is to exclude the HCV related

significant fibrosis.⁷

Another study⁸ assessed the accuracy of APRI for detection of liver fibrosis in HCV related liver disease and to determine the heterogeneity in wide application of clinical practice and the study concluded that the index shows accuracy of moderate degree for the detection of liver fibrosis in chronic hepatitis C patients and by using APRI, the need for liver biopsy for detection of hepatic fibrosis among patients of chronic hepatitis C can be minimized.

In another study of 270 patients, done by Wai and colleagues⁹, the relationship of some simple laboratory tests to the significant fibrosis and cirrhosis was looked for. After analyzing multiple laboratory parameters, they concluded that APRI was the most accurate index for detection of significant fibrosis and cirrhosis.

Wenwen Jin and colleagues¹⁰ also analyzed the role of aspartate aminotransferase to platelet ratio index in detecting significant fibrosis and cirrhosis in patients of hepatitis B, and they recorded a sensitivity of 84% at the threshold of 0.5.

WG Shin and others¹¹ revealed that among non-invasive markers, APRI showed best area (0.86) under the receiver operating characteristic curve, thus APRI has the highest accuracy in detecting significant fibrosis in patients of chronic hepatitis B. Lin CS and colleagues¹² were also of the same view.

However, we are of the view that AST to platelet ratio is a simple, cheap and readily available alternative to invasive liver biopsy to initiate the antiviral therapy in chronic hepatitis C patients.

CONCLUSION


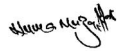




The study revealed that AST to platelet ratio index has good diagnostic accuracy for detection of significant fibrosis in patients of chronic Hepatitis C and it can be used to avoid invasive liver biopsy to initiate the antiviral therapy in these patients.

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AUTHORSHIP AND CONTRIBUTION DECLARATION

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| 4 | Talha Munir | Data Interpretation. |  |
| 5 | Arfan Mahmood | Liver Biopsy. |  |
| 6 | Awais Khalid | Data Interpretation. |  |