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Original Research Article

Evaluation of aspartate amino transferase to platelet ratio index as a non invasive marker for liver cirrhosis

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ABSTRACT

Background: Cirrhosis is a condition in which the liver slowly deteriorates and is unable to function normally due to chronic long lasting injury. Liver biopsy is considered as a gold standard for the diagnosis of cirrhosis and has many problems like bleeding, infective peritonitis which limit use of liver biopsies in all patients.
Methods: A comparative study was done (90 cases and 90 controls) who fulfilled the inclusion criteria in a tertiary center.
Results: The present study was conducted using a total of 180 participants, 90 USG diagnosed cases of liver cirrhosis was compared with 90 healthy controls. The mean AST level in the cirrhosis was 66.50±27.06 as compared to 21.26±6.52 in controls which was statistically significant. In this study the sensitivity and specificity of APRI was found to be 100.0% and 84.44% respectively, and the positive and negative predictive values were 86.54% and 100% respectively with significantly Area under the curve (AUC) (0.999, P>0.01).
Conclusions: A simple index like Aspartate platelet ratio index, consisting of 2 readily available laboratory results (AST level and platelet count), can predict cirrhosis with a high degree of accuracy.

Keywords: Aspartate platelet ratio index, Aspartate amino transferase, Complete blood count, Cirrhosis, Liver function test, Ultrasound

INTRODUCTION

Cirrhosis is the end-stage consequence of fibrosis of the liver parenchyma that results in nodule formation and altered hepatic function.[1] For the diagnosis of cirrhosis, liver biopsy is currently the gold standard for assessment of hepatic necroinflammatory activity and fibrosis. This is an invasive procedure which is subjected to inter-observer variability and sampling error of biopsies; biopsy length and fragmentation influences its reliability and histopathological results. There are a number of other complications like bleeding, pneumothorax, infective peritonitis which limit the use of liver biopsies in all patients.[2]

Several non-invasive biochemical tests like fibro test, hepascore, transient elastography, fibrospect, forns-index, AAR, ELF etc. are currently in use, requiring complex calculations and expensive biochemical assays.[1,3-6] An ideal non-invasive diagnostic test for hepatic fibrosis should be simple, readily available, reproducible, inexpensive, and accurate. Aspartate aminotransferase: Platelet Ratio Index (APRI) was reported as a novel index for prediction of significant fibrosis and cirrhosis.[7,8] APRI as simple bedside diagnostic tool has been

successfully evaluated in Western and some Asian populations.[9-11] But not many studies have been done in the Indian population. Hence, in the present study we tried to evaluate APRI as a non-invasive bedside marker of cirrhosis in a subset of Indian population and statistically determine its sensitivity and specificity as a diagnostic tool.

METHODS

This comparative study was conducted at the Mahatma Gandhi Medical College and Research Institute, Pillayarkuppam, Puducherry, India. All participants who attended the General Medicine OPD/In patient who were fulfilling the inclusion/exclusion criteria were taken up for the study from October 2016 until April 2018 by stratified random sampling.

Inclusion criteria

Cases

Patients above 18 years of age of either sex attending the OPD or admitted in medicine wards who had signs and symptoms and USG evidence of cirrhosis of liver.

Controls

Age and sex matched healthy volunteers from master health check-up.

Exclusion criteria

All patients with liver disorders other than cirrhosis, accompanying illnesses like hematological disorders, malignancy, and chronic disorders like diabetes, hypertension, cardiac diseases, renal failure, any surgical history or patient's unwillingness to participate in the study. The exclusion criteria for controls were the patient's unwillingness to participate in the study.

Procedure

APRI Score was calculated as {(AST/upper limit of normal)/platelet count (109/L)} × 100.

This study was done in compliance with declaration of Helsinki and it was approved by Institutional human ethics committee of Mahatma Gandhi Medical College and Research Institute, Puducherry, India.

Patients were subjected to detailed history and clinical examination. Socio-demographic profile was noted. LFT, CBC, USG abdomen, HBsAg, Anti HCV was done in all patients (Figure 1).

Data collection

All data was entered into a data collection performa sheet and were entered into Excel (MS Excel 2011). The Sheet had a visual map for marking and divided into indications for both genders. Other biographical data had also been collected.

Statistical methods

Statistical analysis was carried out using SPSS version 19.0 (IBM SPSS, US) software with Regression Modules installed. Simple statistical methods such as Pie diagram and Bar charts will be used for the descriptive purpose. Chi-Square test will be used to determine the significance between the parameters observed in this study with similar studies of other authors. P <0.05 will be accepted as significant.

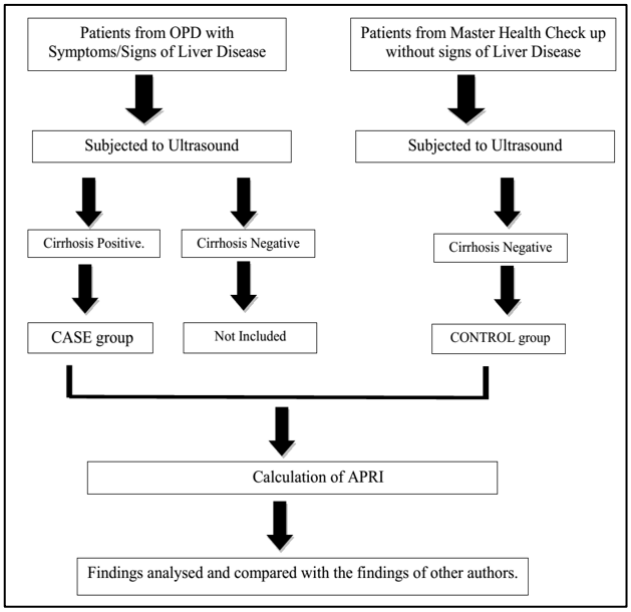

Figure 1: Selection process for cases and controls in the study.

RESULTS

The present study was a case-control study conducted among the patients admitted to MGMCRI with signs and symptoms of liver disease (cases) and patients attending the master health check-up OPD (controls). Present study was to evaluate Aspartate aminotransferase-to-platelet ratio index (APRI) as a bedside non-invasive marker for liver cirrhosis in a subset of Indian Population and to statistically determine its sensitivity and specificity as a marker in diagnosing liver cirrhosis.

In the present results section, Tables 1 and 2 shows the gender distribution and etiology of cirrhosis. Table 3 shows the mean differences of AST, Platelet count & APRI level among the study participants.

Cirrhosis among males (72.2%) was higher compared to females (27.8%). There exists no statistical significance among the cases and controls with respect to gender (Table 1).

Table 1: Gender distribution of the study participants.

Gender	Control (n=90)	Case (n=90)	p value
Male	70 (77.8%)	65 (72.2%)	0.741 (0.491)
Female	20 (22.2%)	25 (27.8%)	

Table 2: Distribution of alcohol usage among the study participants.

Alcohol consumption	Control (n=90)	Case (n=90)	Total
Yes	0 (0%)	55 (100.0%)	55 (100.0%)
No	90 (72.0%)	35 (28.0%)	125 (100.0%)
Total	90 (50.0%)	90 (50.0%)	180 (100.0%)

All the cases with cirrhosis had history of alcoholism while none of control group had history of alcoholism (Table 2).

In present study, the most common causes of cirrhosis were alcoholism (55%) followed by HBsAg (18%), HCV (15%) and cryptogenic cirrhosis (2%). None of the study participants were found to be HIV Positive. When tested for HBsAg, around 18 (20%) patients were found to be positive. None of the controls were found to have a positive HBsAg test. Of the cases, about 15 (16.67%) were found to be positive for HCV.

Table 3: Mean differences of AST, platelet count and APRI level among the study participants.

Variables	Control (n=90)	Case (n=90)	p value
AST	21.26±6.52	66.50±27.06	<0.001
Platelet count	268233.33± 65066.958	95266.67± 22350.527	<0.001
APRI	0.211129± 0.881807	1.901031± 1.0382859	<0.001

Table 4: Diagnostic efficiency of the APRI in predicting cirrhosis with different cut-off values.

Cut-off	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV
0.93	100.00% (95.98% - 100.00%)	84.44% (75.28% - 91.23%)	86.54% (79.89% - 91.23%)	100.00%
1.0	100.00% (95.98% - 100.00%)	84.44% (75.28% - 91.23%)	86.54% (79.89% - 91.23%)	100.00%

With regard to the platelet count, authors found that average platelet count for alcoholic cirrhosis patients was 99x103 cells/mm^3 and that of control group was 221x103 cells/mm^3. Average platelet count for HBsAg cirrhosis patients was 98.5x103 cells/mm^3 and that of control group was 1.92x103 cells/mm^3. Average platelet count for HCV cirrhosis patients was 84.0x103 cells/mm^3 and that of control group was 1.92x103 cells/mm^3.

Table 3 represents the mean difference of the parameters among the study participants. Independent sample t test was applied and it showed a statistical significance among the cases and controls for AST, Platelet count and APRI. Average AST values among cases are 21.26 IU and controls are 66.5 IU which was statistically significant.

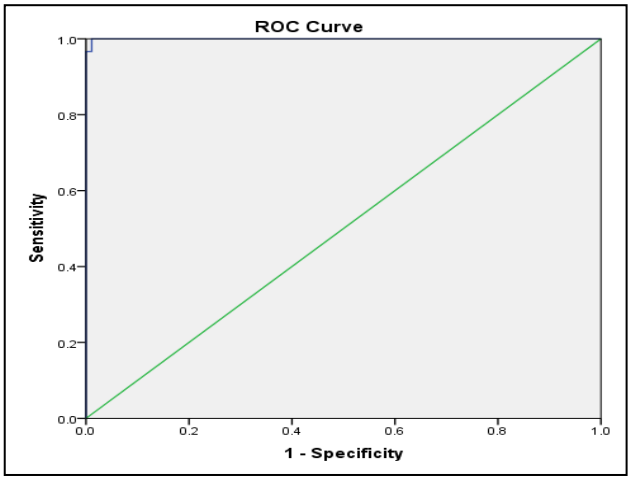

Figure 2: APRI as predictive marker for liver cirrhosis.

For both cut-off values of 0.93 and 1.0 sensitivity was 100% and sensitivity 84.44% with positive predictive values of 86.54%. Thus, there seems to be no difference between the cut-off values 0.93 and 1.0. Receiver Operating Characteristic (ROC) curve for aspartate amino transferase to platelet ratio index as a marker for liver cirrhosis revealed an area under the curve (AUC) value of 0.999 with a p value of <0.05 (Figure 2).

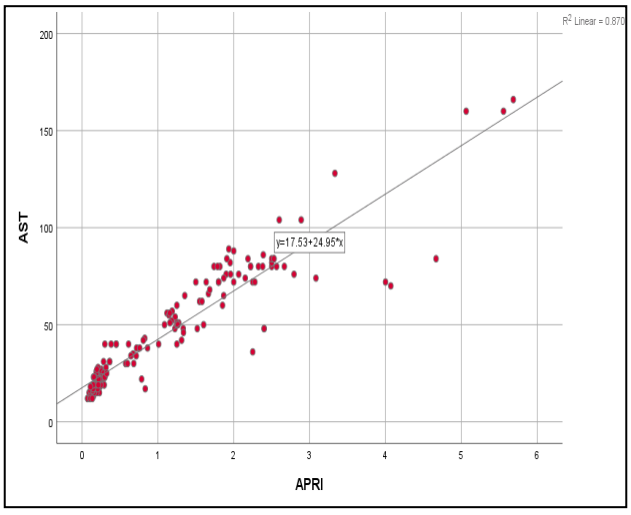

Figure 3: Correlation between the level of APRI and AST in cirrhosis cases (R 0.933, P <0.001).

Scatter plot shows correlation between APRI and level of AST in cirrhosis cases. Pearson correlation coefficient R was 0.933. There was statistically significant correlation (P <0.001) between APRI and level of AST in cirrhosis. This implies that as APRI increases AST values also increases (Figure 3).

Scatter plot shows correlation between APRI and level of Platelet in cirrhosis cases. Pearson correlation coefficient R was 0.933. There was statistically significant correlation (P <0.001) between APRI and level of AST in cirrhosis. This implies that as APRI increases platelet values decreases (Figure 4).

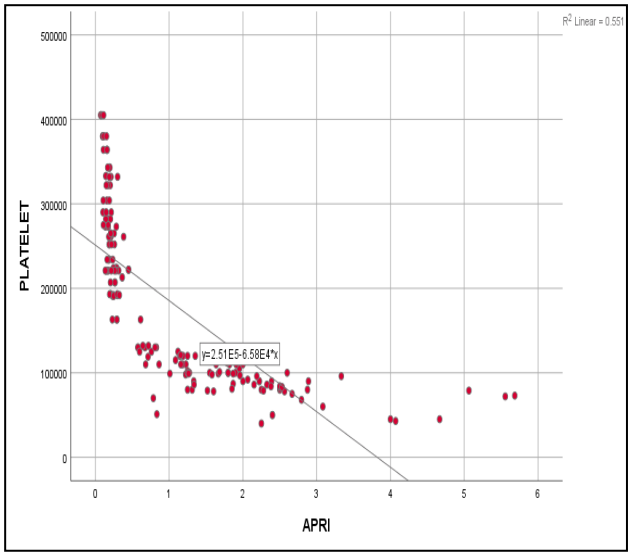

Figure 4: Correlation between the level of APRI and Platelet in cirrhosis cases (R -0.742, P <0.001).

DISCUSSION

The present study was conducted using a total of one eighty participants, 90 patients of liver cirrhosis diagnosed by ultrasound (case), and 90 from master health checkup (controls). Out of the cases majority of them were males 70 (77.8%) and 20 (22.2%) were female. Among the 90 healthy participants (control), 65(72.2%) were male and 25 (278%) were female. In present study out of 90 cases most common cause of cirrhosis were alcoholic (55%), followed by hepatitis B (18%), hepatitis C (15%) and cryptogenic (2%). None of the patients were HIV positive.

In present study Mean platelet count in alcoholic cirrhosis was 99x103 cells/mm^3 and that of non-cirrhosis were 221x103cells/mm^3, with p value <0.05. In a study by Xianghoung et al, mean platelet count among cirrhosis was lower when compared to our study (43×109 /L), p value <0.05).[12] In another study by Murali et al, they found significant correlation between Platelet and alcoholic liver cirrhosis with the median platelet count of less than 70x103cells/mm^3 was effective for ruling in alcoholic cirrhosis and a platelet count greater than 200x103 cells/mm^3 significantly decreased the likelihood of having cirrhosis.[13]

A recent meta-analysis by Udell et al, identified thrombocytopenia as the single most important laboratory test for identifying cirrhosis of varying etiologies.[14]

In present study mean platelet count for HbsAg cirrhosis patients was 98.5x103 cells/mm^3 and that of non-cirrhosis were 1.92x103 cells/mm^3 which was significantly reduced. In a similar study by Ceylan et al, observed that the MPV was lower among patients with severe fibrosis compared with patients with milder fibrosis.[15]

In contrast Turhan et al, reported that MPV was significantly higher in an inactive HBsAg carrier group compared with a control group.[16] Thrombocytopenia is the most common and first hematologic index abnormality to develop in cirrhosis. This explains the use of platelet count as an indirect marker in some of the non-invasive assessments of hepatic fibrosis.[1]

In present study participants mean serum albumin in cirrhosis patients (3 g/dL) were significantly reduced when compared to the control group (4.6 g/dL). Similar study was done by Wai et al, found significant median serum albumin concentration of 4.00 g/dl in cirrhotic patients.[7]

Patients with advanced cirrhosis almost always have hypoalbuminemia caused both by decreased synthesis by the hepatocytes and water and sodium retention that dilutes the content of albumin in the extracellular space.[17]

In present study patients with cirrhosis, total serum cholesterol level was decreased with mean value of 107 mg/dL in cases and 178 mg/dL in controls with a significant negative correlation compared with the control group. The more severe the liver damage is, the more decline in lipid levels are detected, especially total cholesterol levels.

In present study patients with cirrhosis TGL level was decreased with mean value of 89 mg/dL and 134 mg/dL in controls. Authors found that lower lipids levels are seen in patients with Cirrhosis of liver. Total cholesterol and TGL were significantly lower in cirrhotic patients than in the comparison group. Furthermore, the amount of decrement in the serum total cholesterol had a positive correlation with the severity of liver damage.

The significant decline in the serum total cholesterol and TG levels in cirrhotic patients compared with healthy people has been confirmed earlier in other studies, which is reasonably expected since liver biosynthesis has been reduced. For instance, the similar results were obtained in a study by Ghadir MR et al, studied 160 patients with chronic liver diseases in which there is significant decline in the serum total cholesterol and TG levels of patients.[18]

In contrast, study by Phukan et al, reported serum triglyceride level was significantly higher in cirrhotic cases than in controls.[19]

Reduced levels of cholesterol, HDL, LDL and TG are a feature of liver cirrhosis as reported previously by an Iranian study.[18] This Iranian study also stated that while cholesterol, HDL and LDL significantly reduced with worsening severity of cirrhosis, TG levels did not. Another Indian study found that except TG, all other lipid variables were low.[20] Present study reported significant reductions in cholesterol, HDL, LDL and TG with increasing severity of cirrhosis. However, malnutrition is a contributory factor as well. Lipids can thus be used to assess progression of liver disease indicative of development of malnutrition.

The present study predicted the efficiency of APRI as a bedside non-invasive marker for cirrhosis and this study showed that APRI is a fair and accurate non-invasive marker for cirrhosis with high specificity and sensitivity. The low cost and easy availability of two variables (AST and platelets) make APRI a useful and simple bedside test.[21] This study showed the AST level in cirrhosis patients was significantly increased (66.50±27.06 IU) than that in control (21.26±6.52). This may be attributed to chronic liver disease with associated hepatocyte death, as evidenced by elevated serum transaminase levels, results in inflammation followed by fibrosis.[22]

The platelet count was significantly lower in cirrhosis cases (95266.67±22350.527) as compared to control (268233.33±65066.958). This may be due to defect in the function of the liver which produce most of the coagulation factors and thrombopoietin hormone and some of the complications of liver cirrhosis(secondary hyper fibrinolysis, accelerated intravascular coagulation and splenomegaly) may lead to reduced platelet count.[23] On the other hand, the level of APRI was also significantly higher in cirrhosis cases (1.901031±1.0382859) in comparison to that in control subjects (0.211129±0.881807). Also, in this study the level of AST and platelet count was not significantly affected by gender, Furthermore, no significant difference was observed between cirrhosis genders for the level of APRI. In our study there is significant correlation between the level of AST and APRI and between the level of platelets count and APRI. Finally based on the diagnostic efficiency of APRI by ROC curve shown the Area under the curve (AUC) of APRI for predicting cirrhosis was significantly 0.999 and sensitivity and specificity of APRI was found to be 100.0% and 84.44% respectively. Positive and negative predictive values were 86.54% and 100% respectively.

The significant correlation between the level of AST and APRI and between the level of platelets count and APRI in cirrhotic patients compared with healthy people has been confirmed earlier in other studies. For instance, the same results were obtained in a study done by Jain et al, the sensitivity and specificity of the APRI test was found to be 96% and 96.1% respectively with negative predictive value (NPV) and Positive predictive value (PPV) of 96% and 96.1% respectively. Wai et al.; have found that using the cut-off APRI values of 1.00 and 2.00, as determined by the ROC curves, significant fibrosis could be predicted accurately in 51% and cirrhosis in 81% of patients. The AUC of APRI for predicting significant fibrosis and cirrhosis in the validation set were 0.88 and 0.94, respectively.[7]

In a study by Sirli R et al, found that APRI results had 81% sensitivity and 50% specificity in predicting significant fibrosis and that with a cut-off value of 1, the sensitivity and specificity for predicting cirrhosis were 76% and 71%, respectively.[24]

However, the Meta-analysis by Jin et al, suggested limited value of APRI in identifying hepatitis B related significant fibrosis and cirrhosis, and Jason et al, in 2015 reported serum and imaging non-invasive markers of fibrosis may have insufficient accuracy when used in isolation; however, a combination of markers may allow sufficient accuracy to systematically identify patients with cirrhosis.[10,11]

CONCLUSION

This study concludes that the APRI can predict cirrhosis with a high degree of efficiency, the sensitivity and specificity of APRI was found to be 100.0% and 84.44% respectively, also positive and negative predictive values were 86.54% and 100% respectively. There is no significant difference observed between cirrhosis genders for the level of APRI and it can be used in areas where facilities for liver biopsy and advanced imaging techniques are not available.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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