Determination of Diagnostic Accuracy of Aspartate Aminotransferase/Alanine Aminotranferase in Patients with Hepatic Cirrhosis Presented at Tertiary Care Hospital of South Punjab Pakistan

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ABSTRACT

Objective: To determine the diagnostic accuracy of Aspartate aminotransferase/Alanine aminotransferase ratio in hepatic cirrhosis keeping liver biopsy as a reference standard.

Study Design: Cross-sectional analytical study.

Place and Duration of Study: Department of Medicine, Nishtar Hospital, Multan and Combined Military Hospital, Multan Pakistan, from Dec 2019 to Mar 2020.

Methodology: Two hundred and fifty (250) patients were consecutively picked according to inclusion and exclusion criteria after approval of the institutional review board. Blood Samples were collected from patients for serum alanine amino-transferase and serum aspartate aminotransferase after informed consent who had undergone liver biopsy and Batt Ludwig was the staging system used to stage liver cirrhosis. They were interpreted at Nishtar Hospital Multan Pakistan and analyzed in Combined Military Hospital Multan Pakistan by using the Spectrophotometry technique by IFCC certified enzymatic method. Aspartate aminotransferase/Alanine aminotransferase ratio was derived which represents hepatic cirrhosis keeping liver biopsy as a reference standard.

Result: 230 patients out of 250, fulfilled the inclusion criteria. Kolmogorov smirnov test showed data is non-parametric. The Aspartate aminotransferase/Alanine aminotransferase ratio for diagnosing hepatic cirrhosis in patients with hepatic cirrhosis, its sensitivity, specificity, negative predictive value, positive predictive value and accuracy were 72%, 68%, 89%, 41%, and 69% respectively. The receiver operating curve proclaims that Aspartate aminotransferase/Alanine aminotransferase of 1.7 with an area under the curve was 0.795 which is consistent with histopathological findings of hepatic cirrhosis in liver biopsy.

Conclusion: To conclude, Aspartate aminotransferase/Alanine aminotransferase may be wielded as an incredible diagnostic tool for patients suffering from viral hepatic cirrhosis. Invasiveness and poor reproducibility associated with liver biopsy, Aspartate aminotransferase/Alanine aminotransferase ratio were found to be helpful to diagnose hepatic cirrhosis.

Keywords: Aspartate aminotransferase/Alanine aminotransferase ratio, Hepatic Cirrhosis, Liver biopsy.

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INTRODUCTION

Viral hepatitis infection is a universal health dilemma that has posed devastation to more than 0.85 billion individuals worldwide.[1] End-stage liver diseases, including cirrhosis and carcinoma, have escalated due to chronic hepatitis C and B. Antiviral therapy and vaccination have hampered hepatitis B virus infections, dwindled its reproduction, managed the disease itself and the subdued risk of its advancement. Still, the effects of such therapies on the hepatitis C virus are not compelling.[2] Even so, they can cease to be efficacious in primitivity, to pre-empt direct consequences.

The American Association for the study of Liver Diseases, the European Association for the study of the Liver, and the Asian Pacific Association for the Study of the Liver have laid down guidelines.[3] As stated by these, patients who suffer from hepatitis C and B have a Knodell histology activity index of ≥4 or moderate/ severe necro-inflammation [Scheuer Grade (G) ≥2] and fibrosis (Grade S ≥2) need treatment for these viruses.[4] The gold standard in the diagnosis of fibrosis in these patients is the biopsy of the liver. Non-dynamic assessment of histopathology, intra-subject and inter-subject variability, observer variability, invasive nature, and sample error are some of its hindrances.[5] Fibro-Scan and non-intrusive serum indicators or biomarkers like aspartate aminotransferase (AST) to platelet (PLT) ratio index and Fibrosis-4 (ALT, AST, and PLT] were reported to have prodigious diagnostic accuracy for liver fibrosis and liver cirrhosis.[6]

Nonetheless, for diagnosing necro-inflammation, the indicators mentioned earlier have insubstantial

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practicability. Currently, non-invasive biomarkers are used routinely. This outlook sets a need for a novel non-presumptuous indicator to identify liver necro-inflammation as well as antiviral therapy commencement.[7]

Liver cirrhosis due to chronic viral hepatitis infection is omnipresent with the highest predominance in Africa and Asia. As stated by recent studies, the number of suspected annual deaths from liver cancer and liver decompensation is 340,000 and 310,100, respectively.[8] Ergo, an unambiguous assessment for liver fibrosis in cases with hepatitis is crucial. Besides, it being pertinent in directing when and if to commence antivirals, it is also important to visualize the clinical forecast over the years. This study aimed to assess the predictability of the non-invasive index of AST/ALT in comparison to the abdominal ultrasound as a marker of cirrhosis.[9] The ratio of serum aspartate aminotransferase (AST) to alanine aminotransferase (ALT) manifested efficacious by existing studies emphasizing patients having liver diseases with diverse etiologies. This ratio of aminotransferases was also an element of the discriminant score of cirrhosis, established to identify advanced fibrosis or cirrhosis, implementing non-invasive methods.[10]

In this study, we scrutinized the ratio between AST and ALT against the chronic liver disease of multiple etiologies retrospectively in an attempt to establish the permanence of a correlation between the proportion of AST/ALT and operative liver damage.

METHODOLOGY

This study was carried out at Combined Military Hospital and Nishtar Hospital, Multan Pakistan from December 2019 to March 2020, after approval from the Institutional Review Board. 250 individuals of various age groups, presenting at Nishtar Hospital and Combined Military Hospital, Multan Pakistan were a part of this study. A sample size of 230 was calculated considering a confidence level of 95%, a proportion of cases of 70.5% and a 5% margin of error.[11]

Inclusion Criteria: Patients with cirrhosis due to hepatitis with a comprehensive spectrum of clinical signs and symptoms like biliousness, upper gastrointestinal bleed, ascites, and hepatic encephalopathy, who underwent liver biopsy were included in the study.

Exclusion Criteria: Patients with hepatic cirrhosis due to other causes or patient with hepatic encephalopathy were excluded.

Liver tissue for biopsy was received in 10% Formalin and its gross and microscopic segments were examined under the microscope. Samples of blood were taken from patients who had undergone liver biopsy using a nonprobability consecutive sampling technique with informed consent. For every patient, 3.0ml blood (venous) was accumulated within a tube containing plain gel, for determining Serum Alanine Aminotransferase (ALT) and Serum Aspartate Aminotransferase (AST) levels. Analysis of serum ALT and AST was done on a chemistry analyzer by using a spectrophotometry procedure by an IFCC recommended assay. A liver biopsy was performed in the histopathology department of Combined Military Hospital, Multan Pakistan and its findings are used as the reference standard for hepatic cirrhosis.

Statistical Package for Social Sciences (SPSS) version 23.0 was used for the data analysis. Median with a range of age and mean and standard deviation had been calculated for the quantitative variables, serum ALT, and AST. Various variables such as specificity, sensitivity, Positive Predictive Value (PPV), Negative Predictive Value (NPV), and likelihood ratios were calculated. ROC was applied to get the value of AST/ALT which would be consistent with histopathological findings in liver biopsy. The level of significance was set at 5%.

RESULTS

Out of 250 patients, 230 patients met the inclusion criteria. The AST/ALT ratio for diagnosing hepatic cirrhosis in patients with viral hepatitis, its sensitivity was 72%, specificity was 68%, Negative Predictive Value (NPV) was 89%, Positive Predictive Value (PPV) was 41%, and accuracy was 69% respectively (Table-I).

Table-I: Variables indicating diagnostic accuracy of aspartate aminotransferase/alanineaminotransferase stimulation test.

Test	Specificity	Sensitivity	Positive Predictive Value	Negative Predictive Value	Positive Likelihood Ratio	Negative Likelihood Ratio	Accuracy
ALT/AST Ratio	68%	72%	41%	89%	2.07	0.42	69 %

Kolmogorov Smirnov test was applied which showed $p<0.01$ which indicated the data was non-parametric. Spearman correlation and Chi-square correlation were applied between AST/ALT and liver biopsy

as shown in Table-II, which indicates a significant association between AST/ALT ratio and liver biopsy.

Batt Ludwig is the staging system used to stage liver cirrhosis in liver biopsy. These 4 stages include; portal fibrosis, peri-portal fibrosis, bridging fibrosis and definite cirrhosis respectively.

Table-II: Chi-Square test and spearman's correlation results.

	AST/ALT	Liver Biopsy	*p*-value
Chi-Square	31.896	31.277	< 0.01
Spearman's	1.000	1.000	< 0.01

The curve of receiver operating characteristic (ROC) when drawn to check cut off of the AST/ALT ratio of 1.7 showed the area under the curve at nearly 0.795 (Figure), imparting that test diagnosed hepatic cirrhosis due to viral hepatitis.

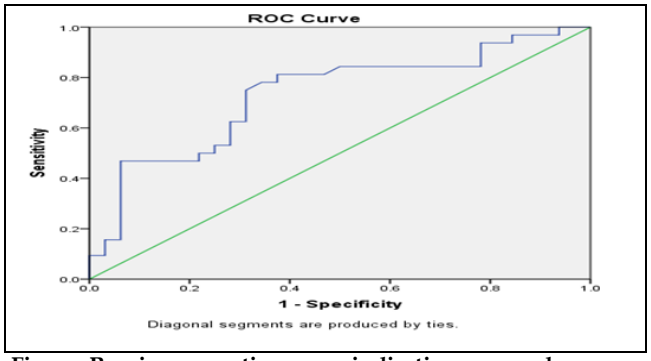

Figure: Receiver operating curve indicating area under curve.

DISCUSSION

Chronic viral hepatitis is amongst the most established and lethal causes of liver-associated disorders, which may progressively lead to catastrophic outcomes like hepatic fibrosis, cirrhosis, and liver cancer.[11] Fibrosis due to chronic viral hepatitis can be a reversible occurrence. Early diagnosis of hepatic fibrosis due to viral hepatitis and its effective management can hinder the progression of reversible to irreversible fibrosis.[12] The establishment of an essential approach that can determine the level of hepatic fibrosis is pivotal and has become a fundamental challenge. Literature portrays liver biopsy as momentous for diagnosing liver fibrosis. Despite being the gold standard in the diagnosis of fibrosis of the liver, liver biopsy has restrictions in being invasive, having subject variability, and poor reproducibility.[13] Imaging techniques and serological biomarkers may also be used as indicators of liver fibrosis but using them independently for the diagnosis of hepatic fibrosis remained a rhetorical question. Ultrasound has been long used to determine the progression and level of hepatic fibrosis.[14] Alteration in serological biomarkers, such as APRI, FIB-4 and AST/ALT ratio has been established, associated and confirmed as indicators of liver fibrosis in liver cirrhosis especially those infected by hepatitis viruses, can also speak of the progression of hepatic fibrosis.[15] In our study, AST/ALT ratio is estimated to have diagnostic accuracy by used as the reference standard of liver biopsy in 230 patients with viral hepatitis who were at different stages of hepatic fibrosis.

In our study, clinical data of these 230 patients with chronic viral hepatitis were dissected. The result showed the ratio of AST/ALT was higher in patients as juxtaposed with healthy individuals. This suggests that the proportion of AST/ALT can also be used as an indicative marker in patients with hepatic cirrhosis, which is in synchronization with previous studies. The results of these have revealed that the AST/ALT ratio had shown an immense association with hepatic cirrhosis, and patients with high values should be given immediate attention for early diagnosis, early management, and prevention of complications. ROC curve analysis had also been conducted to examine the clinical importance of this indicator further. The area under the curve exhibited that AST/ALT might be used as an ideal marker.

The ratio of AST/ALT had been used as a non-invasive indicator for evaluating the extent of fibrosis in chronic liver disease. In one study conducted at the University of Santa Catarina,[16] its specificity as a non-invasive indicator of fibrosis due to chronic liver disease is generally low, particularly in the diagnosis of less progressive stages of fibrosis while in our study AST/ALT ratio is proved to be a good specific marker and area under the curve (0.661 ± 0.055) of this study was also low as compared to area under cover calculated in our study (0.795). Similar results had been reported in another study by Lackner *et al*.[17]

In our study, the value for AST/ALT is found to be 1.7 with sensitivity, specificity, negative predictive value, positive predictive value and accuracy was 72%, 68%, 89%, 41%, and 69% respectively. Findings reported in the study by Giannini *et al*,[18] who had been found the value of AST/ALT to be ≥1 as a cutoff value for diagnosing fibrosis in cirrhosis, while Sheikh *et al*,[19] had been reported a higher cut off value (≥1.5) for

diagnosing fibrosis in cirrhosis, with a sensitivity of 44% and a specificity of 91%.

LIMITATION OF STUDY

Our study has some limitations. Due to a lack of patient outcome data. Moreover, our study sample consisted of patients who presented to medical OPDs for investigations of jaundice and were not the true representative of the population.

CONCLUSION

To conclude, AST/ALT may be utilized as a diagnostic tool for patients who have hepatic cirrhosis due to viral hepatitis and avoid limitations with invasiveness and poor reproducibility associated with liver biopsy.

RECOMMENDATIONS

A synchronous prospective study in various centres may be instigated which will cement reciprocity between AST/ALT and hepatic cirrhosis.

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Individuals who participated are appreciated by authors.

Conflict of Interest: None.

Author's Contribution

AY: Sample collection, WH: Manuscript writing, MAAS: Study planning, MY: Data interpretation, SE: Statistical review, QUA: Manuscript review.

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