

ALANINE AMINOTRANSFERASE/ASPARTATE AMINOTRANSFERASE RATIO REVERSAL AND PROLONGED PROTHROMBIN TIME: A SPECIFIC INDICATOR OF HEPATIC CIRRHOSIS

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Background: Both ALT/AST ratio reversal ($AST/ALT > 1$) and prolonged prothrombin time are separately related to hepatic cirrhosis. Ratio reversal means that in normal individuals ALT is more than AST and thus $ALT/AST > 1$ but with development of cirrhosis AST becomes $> ALT$ and so $AST/ALT > 1$ or $ALT/AST < 1$. This study was conducted with the idea that prolonged prothrombin time and reversed ($AST/ALT > 1$) ratio together can prove a more specific indicator with a high positive predictive value for the detection of hepatic cirrhosis in patients of chronic liver disease than either of the two alone. **Method:** This is a comparative cross sectional study. The data of hepatitis B & C patients was collected from the general medical ward and medical out patient department. Clinical and Ultrasonographic features, detected by a single ultrasonologist, were used to diagnose cirrhosis. Patients who were alcoholic were excluded from the study as alcohol itself causes ALT/AST ratio reversal. To avoid laboratory errors and variations the facilities of only a single specific laboratory were used for this study. The sensitivity and specificity of ALT/AST ratio reversal along with positive predictive value were calculated. Then prolonged prothrombin time (PT) and reversed ratio together were used and the results of these two groups were compared. **Results:** It was found that the reversal of ratio alone is 88% specific as an indicator of hepatic cirrhosis and almost 70% sensitive and have a positive predictive value of 94.5%. The statistical significance test based on ztest for difference of proportion yields: $z=6.96$ with a p value=0.0000. On the other hand, the prolonged PT and ratio reversal are 98% specific and 53.9% sensitive with a positive predictive value of 98.2%. ztest for difference of proportion yields here: $z=6.23$ with a p value=0.0000. **Conclusion:** ALT/AST ratio reversal alone has a high sensitivity and the combined effect of these two parameters increases the specificity as compared to either of the two alone. The high positive predictive value here shows that almost all the patients with reversed ratio and prolonged PT will have cirrhosis.

Key Words : ALT/AST ratio reversal, Prolonged PT, Hepatic Cirrhosis.

INTRODUCTION

Detection of cirrhosis in patients of chronic liver disease is very important from therapeutic point of view. Once a patient develops cirrhosis he is at the doorstep of complications. The gold standard for detection of hepatic cirrhosis is liver biopsy. Also, ultrasonography of abdomen can be equally good in hands of a good ultrasonologist.

In normal individuals ALT value is higher than AST value and so their ratio ALT/AST is more than 1. Reverse ratio means that AST value becomes greater than ALT value and so $AST/ALT > 1$.

The prothrombin time (PT) measures the clotting time from the activation of factor VII, through the formation of fibrin clot. This test measures the integrity of the extrinsic and common pathways of coagulation. It has a normal range of 10-14 seconds in normal healthy individuals and is prolonged in patients of chronic liver disease. Usually the monitoring with the serial values from a single laboratory is considered a useful way.

The aims and objectives of this study are to utilize these two investigations beyond their own exact values and to emphasize their importance to

avoid hepatic biopsy in patients of CLD to detect cirrhosis.

MATERIAL AND METHODS

Reverse ratio: In normal individuals ALT value is higher than AST value and so their ratio ALT/AST is more than 1. reverse ratio means that AST value becomes greater than ALT value and so $AST/ALT \sim 1$.

Subjects: The total number of cases were divided in two groups: first; patients having cirrhosis due to hepatitis B and/ C (study group). The other group comprised of those patients who had hepatitis B and/ C but had no radiological or clinical evidence of cirrhosis.

Apparatus: USG abdomen by a single ultrasonologist to see the hepatic features for cirrhosis.

Prothrombin time was measured by one stage prothrombin time. The reagent used for this, supplies a source of tissue thromboplastin and calcium, which activates factor VII and is therefore

sensitive to all extrinsic and common pathway factors.

The data for this comparative cross sectional study was collected from the General medical ward of Jinnah hospital Lahore.

Criterion of Cirrhosis: Cirrhosis was proven on ultrasonographic evidence and one of the three features of portal hypertension: haematemesis, ascites and splenomegaly. On USG all the features of cirrhosis were not found but only those patients were included who had at least two of the ultrasonographic features of cirrhosis (The features of cirrhosis on USG are: variable size of liver, irregular surface, non homogenous internal structure, coarse echo texture, compressed hepatic veins, irregular caliber of the intra hepatic portal vein branches, pseudo double barreled appearance, narrowing of segment IV, enlargement of caudate lobe, thickening of the wall of gall bladder and lax gall bladder. Splenomegaly and ascites were confirmed on USG and clinically while esophageal varices were confirmed on upper GI endoscopy.

Prolonged Prothrombin time: In order to avoid minor laboratory errors, in my study, I have considered the prothrombin time to be prolonged if it is 2 seconds or more above the control value.

Inclusion criteria

1. Patients having cirrhosis due to hepatitis B and/ C.
2. Since USG is operator dependent technique so, only those patients were included who got their USG done by the ultrasonologist who was selected for this study patients.

Exclusion criteria

1. All those patients who had been taking alcohol were excluded from the study as alcohol itself can cause reversal of AST/ALT ratio.
2. Patients with co-morbid conditions who can have high AST values eg. Myocardial infarction, hemolysis, rhabdomyolysis were also excluded from the study.

Data Analysis

Tables 1 and 2 show the number of patients of CLD with reversed ratio and both reversed ratio and prolonged prothrombin time respectively.

It can be seen in the graphical representation. In graph 1, the first bar of each doublet represents the reversal of ratio while the second bar stands for normal ratio patients. Similarly, in graph 2, first bar of each doublet represents the reversed ratio and prolonged PT while the second bar is for the group which either has both the values normal or a single value normal.

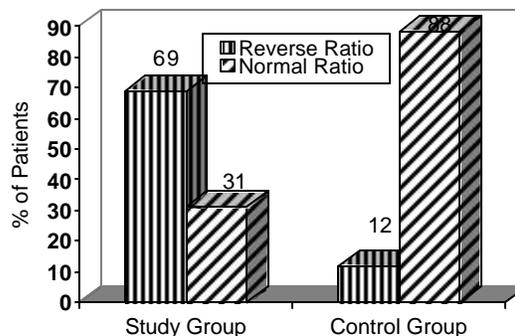


Figure 1. Reversal of Ratio in Study & Control groups

Table 1. Reversal of Ratio in patients with Cirrhosis and without Cirrhosis

	Reversed ratio	Normal ratio	Total
With Cirrhosis	108	42	150
Without Cirrhosis	06	44	50
Total	114	86	200

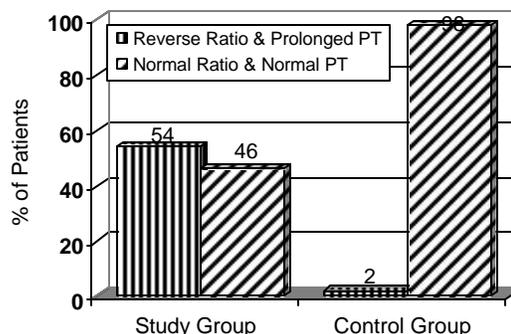


Figure 2. Both Ratio Reversal & Prolonged PT

Table 2. Reversal of Ratio and Prolonged PT in patients with and without Cirrhosis

	Reversed ratio & Prolonged PT	Normal ratio &/ Normal PT	Total
With Cirrhosis	55	47	102
Without Cirrhosis	01	49	50
Total	56	96	152

RESULTS

According to this data, for ratio reversal, the percentage sensitivity (the number of patients who have reversed ratios out of 100 cirrhotic patients) is approximately 70% and the percentage specificity (the number of non cirrhotic patients who do not show this reversal) is 88% with a positive predictive value of 94.5%. In statistical analysis of data z-test is used to find the difference of proportion. Here this data had a z value of 6.96 and a p value of 0.0000. This shows that there is a significant difference

between the study group and control group reversal of ratio. Or in other words, hepatic cirrhosis significantly increases the incidence of reversal of ratio. Combined sensitivity of prolonged PT and reversed ratio falls down to 53.9% but the specificity goes up to 98% as almost all those patients of hepatitis in this study who had both prolonged PT and reversed ratio had cirrhosis. The positive predictive value here was 98.2%. Here $z=6.23$ and p value =0.0000. This again shows the significant difference between the two groups.

The positive predictive value here approaches 100% which shows that almost all the patients with reversed ratio and prolonged PT will have cirrhosis.

DISCUSSION

Reversal of aminotransferase ratio in cirrhotic patients can be the only detectable feature in some cases. It was detected by Sheth et al. who found in their study 17 patients who had no other evidence of cirrhosis except reversal of this ratio¹. Some researchers have combined low platelet count with reversal of ratio to enhance the yield, e.g. Pohl A et. al. has used platelet count with reversal of ratio finding a specificity of 99.1%, but the sensitivity is low, 41.2%². So, by using PT with reversed ratio, the specificity is almost the same but the sensitivity is better in my study. They found that an AST/ALT ratio of >1 in combination with a platelet count of $<150,000$ can predict advance stage of fibrosis and cirrhosis in patients with chronic hepatitis C infection. In these patients, a liver biopsy may not be necessary³.

A value of $>$ or $= 1$ for the ratio of aspartate amino-transferase to alanine aminotransferase (the AST/ALT ratio) has been shown to have a positive predictive value of 100% for the diagnosis of cirrhosis in patients with chronic hepatitis C⁴ which in my study, where both hepatitis B and C patients were studied was 94.5%. The reversal of ratio is being used not only in diagnostic purposes but also for prognostic and treatment response purposes as well.

Certain researchers found results which were not as good as were others. Park GJ. et al. found

that although relatively insensitive, an AST:ALT $>$ or $= 1$ is highly specific but not diagnostic for the presence of cirrhosis in patients with chronic HCV infection. The ratio reflects the grade of fibrosis in these patients⁵.

The ALT/AST ratio has also been studied for some other purposes as well. The following study references may not be directly related to my study but certainly emphasize the importance of ratio reversal detection. A Korean group of researchers found that the AST/ALT ratio in the cirrhosis group were significantly higher ($p<0.01$) than those in the normal and fatty liver group, mild hepatitis group and moderate to severe hepatitis group⁶.

CONCLUSION

Reversal of ALT/AST ratio alone has a high sensitivity (approximately 70%) and with prolonged PT has a high specificity (approximately 100%) and positive predictive value 98% which shows that all those who have reversed ratio and prolonged PT will have cirrhosis.

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