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ASPARTATE AMINOTRANSFERASE-ALANINE AMINOTRANSFERASE RATIO PREDICTS CIRRHOSIS IN PATIENTS WITH CHRONIC HEPATITIS C

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ABSTRACT

Object: To confirm the usefulness of aspartate aminotransferase - alanine aminotransferase ratio (AST/ALT ratio) in predicting cirrhosis in patients with chronic hepatitis C.

Design: A prospective non interventional study.

Place and Duration of Study: Combined Military Hospital, Kharian.

Patients and Methods: Fifty Five patients with chronic hepatitis C were included in the study. Groups included were the patients admitted with sign and symptoms of chronic liver disease due to hepatitis C, blood donors found incidently to be Anti – HCV positive and the persons rejected from embassies duet to Anti-HCV postitive serostatins. The sera of the patients were tested for AST and ALT. Liver biopsy of each patient was performed. Histological Activity Index (HAI) of the specimens was scored on the basis of Knodell score. AST/ALT ratio was correlated with the histological stage (i.e. degree of fibrosis), and the histological grade (i.e. inflammatory activity). The mean AST/ALT ratio in 17 cirrhotic patients (1.11 ± 0.18) was higher than in 38 noncirrhotic patients (0.72 ± 0.23; $p < 0.05$). A ratio ≥ 1 had 97.36% specificity and 93.75% positive predictive value in distinguishing cirrhotic from noncirrhotic patients with 88.23% sensitivity and 94.87% negative predictive value. The ratio correlated positively with histological stage but not with the grade. Two Patients out of 17 cirrhotic patients (12%) had no clinical or biochemical features suggestive of chronic liver disease except for an AST/ALT ratio more than one.

Conclusion: It is concluded that AST/ALT ratio ≥ 1 is highly specific for the presence of cirrhosis in patients with chronic hepatitis C. This ratio reflects the fibrosis stage in these patients. This ratio can be considered as a dependable marker of fibrosis in patients with chronic hepatitis C.

Keywords: AST, ALT, cirrhosis, chronic hepatitis

INTRODUCTION

Hepatitis C Virus (HCV) infection is a major cause of chronic liver disease in the United States and various other parts of the world including Pakistan [1] . There are some 175 million chronic HCV carriers throughout the world . In United States, 1.8 % persons are HCV antibodies positive with an estimated 74 % with detectable HCV RNA[2] . About 85% HCV infected individuals become chronically infected, out of which 10-20% develop cirrhosis of liver. About 7 % of cirrhotic patients develop hepatocellular carcinoma [3].

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The specific symptoms and physical findings of chronic liver disease are frequently absent until patients develop hepatic decompensation. Thus, clinical examination is often unreliable in assessing the severity of disease in patients with chronic hepatitis C.

The histological evaluation of a liver biopsy specimen remains the gold standard for determining the activity of HCV related liver disease and histological staging remains the only reliable predictor of prognosis and the likelihood of disease progression [4]. The invasive and costly procedure of liver biopsy is associated with risk of complications and discomfort. Considerable efforts are being made by research workers to find some simple, safe, inexpensive means to non-invasively assess the severity of liver disease in patients with chronic hepatitis C .

Despite the general lack of correlation between serum ALT concentrations and liver histology in chronic hepatitis C , some investigators have observed that the AST/ALT ratio may be useful for predicting the presence of cirrhosis . In one study of 139 patients, the mean AST / ALT ratio was higher among patients with cirrhosis than in those without cirrhosis [5]. An AST : ALT ratio ≥ 1 had 100% specificity and 53% sensitivity for cirrhosis using corresponding liver biopsy specimen as gold standard . The usefulness of this ratio was confirmed in some other studies as well [6-10]. However, few studies showed limited value of AST/ALT ratio in predicting the presence of cirrhosis [11-13]. Thus, the clinical utility of this ratio remains uncertain and needs further study.

The objective of this prospective study was to confirm the usefulness of AST/ALT ratio in predicting cirrhosis and to correlate the ratio with histological grade (inflammatory activity) and stage (degree of fibrosis) in patients with chronic hepatitis C.

PATIENTS AND METHODS

This prospective study was conducted at Combined Military Hospital Kharian from February 2001 to September 2001. A total number of 55 patients of chronic hepatitis C on the basis of clinical , biochemical , serological, ultrasonographical and histological criteria were included in this study / survey .

Following groups of persons with chronic hepatitis C were included .

- The patients admitted with symptoms / signs of chronic liver disease due to hepatitis C.
- Blood donors found incidentally to be anti-HCV positive.
- The persons rejected from embassies due to anti-HCV positive serostatus.

The HBsAg +ve cases and those with the history of drugs or alcohol abuse, antiviral or immunosuppressive therapy and any serious medical illness like diabetes mellitus , chronic renal failure and advanced liver disease were excluded from the study .

The biochemical parameters recorded for all the patients were serum bilirubin, transaminases, total proteins including albumin and globulin, ferritin and iron. The haematological parameters included prothrombin time with INR, Blood Hb , TLC , DLC, and platelet count.

All the patients were thoroughly examined and ultrasound was performed . The sera of the patients were tested for HBsAg and anti-HBc to rule out Hepatitis B virus, and for anti-HCV to confirm exposure to hepatitis C virus. The detection of HCV viremia was done by polymerase chain reaction (PCR).

Liver biopsy of the patients was done and evaluated for histological changes by classified pathologist. Histological Activity Index (HAI) was scored on the basis of Knodell score .

The statistical analysis was done by Students' t test . The statistical significance was $p < 0.05$.

RESULTS

A total of 55 patients were included in the study with the mean age 41 years (range from 19 to 59 years). Among these, 44 were male and 11 were female.

Out of 55 patients, 38 patients (69.9%) were found as non cirrhotic and 17(31.1%) were found cirrhotic on liver biopsy. The Knodell HAI score (excluding fibrosis) was 1-3 in 18 patients, 4-8 in 21 patients and 9-12 in 16 patients. Stage 1 fibrosis was found in 15 patients, stage 3 fibrosis in 4 patients and stage 4 in 17 patients. Stage 0 (no fibrosis) was detected in biopsy specimen of 19 patients (table-1).

Table-1: Histological activity index (HAI): distribution of patients in relation to histological grade and stage on liver biopsy.

HAI Grade	No of Patients
1-3	18
4-8	21
9-12	16
HAI Stage	**No of Patients**
0	19
1	15
3	4
4	17

Table-2: Correlation of ALT and AST levels with activity (grade) on liver biopsy.

		ALT			AST		
Grade	No of Patients	Mean	Min	Max	Mean	Min	Max
1	18	220	66	486	142	30	296
2	21	188	56	402	112	28	254
3	16	196	58	364	168	46	272

Table-3: Correlation of AST and ALT levels with fibrosis (stage) on liver biopsy.

		ALT			AST		
Fibrosis (stage)	No of Patients	Mean	Min	Max	Mean	Min	Max
0	19	190	40	288	110	26	216
1	15	242	32	308	102	18	258
3	4	124	30	196	120	32	178
4	17	118	24	178	132	35	204

No significant correlation was seen between the levels of ALT and activity (grade) on liver biopsy . The mean ALT level was 220 (66 - 486) in patients with grade 1 activity, whereas a mean level 188 (56 – 402) was found in grade 2 , and a mean level of 196 (58 – 364) in grade 3 activity. Similarly, no significant correlation was seen between the level of AST and grade on liver biopsy. The mean AST levels were 142 (30 – 296), 112(28 – 254) and 168(46 – 272) in relation to grade 1 ,2 and 3 respectively (table-2).

No significant correlation was found between the individual levels of AST and ALT and the stage on liver biopsy (table-3).

Table-4: Test characteristics of AST/ALT ratio (AAR) for all patients (taking liver biopsy as gold standard to indicate cirrhosis).

	Cirrhosis	No Cirrhosis	Total
AAR ≥ 1	15	1	16
AAR ≤ 1	2	37	39
Total	17	38	55

The above data shows following results indicating the statistical significance of AST/ALT ratio.

Sensitivity	=	88.23%
Specificity	=	97.36 %
False positive	=	2.63%
False negative	=	11.76%
Positive Predictive value	=	93.75%
Negative Predictive value	=	94.87%
Diagnostic efficacy	=	94.54%

There was poor correlation found between AST/ALT ratio and grade of the liver biopsy but a significant correlation was found between AST/ALT ratio and the histological stage to indicate cirrhosis. The test characteristics of AST/ALT ratio for all patients (taking liver biopsy as gold standard to indicate cirrhosis), showed 97.36% specificity and 88.23 % sensitivity of

AST/ALT ratio in predicting cirrhosis (table-4).

Table-5: Comparison of mean AST and ALT levels in patients with cirrhosis and those without cirrhosis.

	Cirrhosis			Chronic hepatitis without cirrhosis		
	Mean	Min	Max	Mean	Min	Max
AST	132.6	35	204	138.4	18	296
ALT	118	24	178	213	30	486

The comparison of the mean AST and ALT levels in patients with cirrhosis and those without cirrhosis showed raised levels of AST as compared to ALT in cirrhotic patients and raised levels of ALT as compared to AST in non cirrhotic patients (table-5). A significantly higher AST/ALT ratio ($p < 0.05$) was found in patients with cirrhosis as compared to those without cirrhosis (table-6).

Table-6: AST/ALT ratio in patients with cirrhosis and those without cirrhosis.

	AST/ALT Ratio (Mean ± Standard Deviation)
Cirrhosis	1.11 ± 0.18
Chronic hepatitis Without cirrhosis	0.72 ± 0.23

DISCUSSION

The validity and clinical utility of AST/ALT ratio in assessing severity of liver disease has been evaluated by many research workers in their retrospective studies. Most of the investigators demonstrated that an AST/ALT ratio ≥ 1 was a reliable marker for predicting the presence of cirrhosis [6-10]. In one study, it was found that an AST/ALT ratio ≥ 1 had 100% positive predictive value for the presence of cirrhosis [5].

In this study, we also confirmed the usefulness of AST/ALT ratio as a means of separating the patients with cirrhosis, from those without cirrhosis. We also verified the existence of relationship of this ratio with severity of the liver disease. Generally, the levels of AST and ALT were raised in non-cirrhotic patients as compared to those with cirrhosis. This finding was consistent with an earlier local study [7].

No significant correlation was found between the individual levels of ALT or AST with grade or stage on liver biopsy. In our study, a significant correlation was found between AST/ALT ratio and the histological stage on liver biopsy. Out of 17 patients with cirrhosis, AST/ALT ratio was ≥ 1 in 15 patients, and out of 38 non-cirrhotic patients, only one patient had AST/ALT ratio >1. Hence, the sensitivity, specificity and positive predictive value of this ratio were 88.23%, 97.36% and 93.75% respectively, so this ratio was found significant in separating the cirrhotic from non-cirrhotic groups.

The results of this study were compared with International studies done by Sheth and colleagues [5], and Reedy and colleagues [12]. The positive predictive values in the former two studies were 100% and 77% respectively, whereas our study has demonstrated 93.75% positive predictive value for the presence of cirrhosis. So, our results are more close to those of Sheth and colleagues.

Our study revealed that the mean AST/ALT ratio among cirrhotic patients was elevated significantly ($p < 0.05$, Students' t-test) than the patients with hepatitis. These findings were consistent with the study as conducted by Butt AR and colleagues [7]. Similar results were demonstrated by Giannini E and colleagues, as well as Sheth and colleagues [5,6].

This study confirms that the low cost, non-invasive parameter that is AST/ALT ratio is highly specific for the presence of cirrhosis in patients with chronic hepatitis C and can be considered as a dependable marker of fibrosis in patients with chronic hepatitis C.

CONCLUSION

Liver biopsy is considered as gold standard for assessing the severity of liver injury but the invasive and costly procedure of liver biopsy is associated with risk of complications and discomfort. It is recommended that further research work should be done on large population samples to finally accept the usefulness of AST/ALT ratio as an alternate to liver biopsy. Other non-invasive markers may be evaluated along with this ratio for more accurate results.

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