EVALUATION OF AST/ ALT RATIO AS A MARKER OF LIVER FIBROSIS AND CIRRHOSIS IN PATIENTS WITH CHRONIC HEPATITIS C

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ABSTRACT

Objective: To assess the relation between serum AST/ALT ratio (AAR) and hepatic fibrosis and cirrhosis associated with chronic hepatitis C.

Study Design: A cross sectional study.

Place and Duration of Study: The study was conducted in the department of medicine Military Hospital Rawalpindi from Sep 2004 to Feb 2005.

Materials and Methods: Fifty diagnosed patients of chronic hepatitis C were selected whose liver biopsy was performed as a workup plan for treatment. Serum AST/ ALT ratio (AAR) was determined and degree of liver fibrosis noted on histopathology, using Knodell scoring system. ANOVA was applied to study the difference in AAR in different stages of liver fibrosis.

Results: The mean AAR was found to be higher with each increasing stage of liver fibrosis. The mean AAR in cirrhotics (1.34) was significantly higher compared to noncirrhotics (0.77), $p< 0.001$. AAR ≥ 1 had 100% sensitivity and negative predictive value in distinguishing cirrhotic from non-cirrhotic patients with 87% specificity and 45% positive predictive value.

Conclusion: There is only a modest relation between AAR and early hepatic fibrosis (stages 1-3) in patients with chronic hepatitis C, while AAR is significantly higher in patients with advanced fibrosis/ cirrhosis.

Keywords: AST, ALT, hepatitis, cirrhosis.

INTRODUCTION

Chronic Hepatitis C infection is an important cause of chronic liver disease worldwide, especially in the developing countries like Pakistan [1-5]. Majority of patients with chronic hepatitis C have asymptomatic mild elevation of serum transaminase levels without physical signs of liver disease. Symptoms develop in only about 6%, fatigue being most common [2]. The diagnosis of chronic hepatitis C is usually made by finding anti hepatitis C virus (HCV) antibodies in a patient with serum aminotransferase elevation or chronic hepatitis C on liver biopsy. However, assays for HCV RNA such as reverse transcriptase polymerase chain reaction (PCR) are the most sensitive tests for establishing a diagnosis. The natural history of hepatitis C is highly variable. Some patients have severe and progressive disease developing cirrhosis within a few years while others may take decades for end-stage liver disease [6].

Hepatic fibrosis is a reversible scarring response in patients with chronic hepatitis. It ultimately leads to nodule formation and cirrhosis. An accurate assessment of fibrosis is essential to guide management and predict prognosis .The histological evaluation of a liver biopsy specimen remains the gold standard for quantifying fibrosis. Recently there is increasing interest in the use of noninvasive markers to allow more frequent sampling and avoid the risks of percutaneous biopsy [7]. Examples of these markers include enzymes involved in extracellular matrix production and degradation, matrix molecules (e.g. Hyaluronic acid, collagen, laminin) , fibrogenic cytokines and pattern of serum aminotransferases [8-9].

The serum aminotransferases, Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT) are sensitive indicators of liver cell injury. The AST/ALT ratio is approximately 0.8 in normal subjects. In some settings, this ratio changes in characteristic ways that may suggest a particular diagnosis. This ratio may be useful as a noninvasive indicator of fibrosis and

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Received: 22 Sep 2007; Accepted: 11 Aug 2008

cirrhosis in patients with chronic hepatitis C [15-24].

The object of this study was to assess the relation between AST/ ALT ratio and hepatic fibrosis and cirrhosis associated with chronic hepatitis C.

PATIENTS AND METHODS

It was a cross-sectional study spanning over a period of 6 months; from Sep 2004 to Feb 2005. The data was collected prospectively. The study was carried out in the department of medicine, Military Hospital Rawalpindi, including indoor as well as outdoor patients. The study population consisted of 50 adult diagnosed patients of chronic hepatitis C having anti HCV antibodies, HCV RNA positive by PCR and serum ALT raised for more than six months. The majority of patients belonged to middle class socioeconomic group and was resident of urban and suburban areas of Rawalpindi. The sampling technique was convenient and non-probability. Patients with other conditions affecting liver enzymes were excluded such as HBV infection, thyroid disease, muscle disease, primary hepatic or metastatic lesions, passive congestion of liver, recent intramuscular injection or medications. Detailed history and appropriate investigations were carried out to exclude these conditions.

After explanation of the procedure and obtaining consent, liver biopsy of the patients fulfilling inclusion criteria was performed. Serum sample was obtained at the same time for evaluation of the liver function tests including AST and ALT. These tests were performed on each sample on the same day. AST/ALT ratio was calculated. Degree of liver fibrosis was noted from Knodell score (Table-1) given on liver biopsy specimens.

Statistical Analysis

Values were expressed as mean ± SEM. The data was entered in SPSS version 10.0 for statistical analysis. ANOVA was applied to study the difference in AAR in different stages of liver fibrosis.

The AAR in different stages of fibrosis is graphically shown by plotting scattergram.

RESULTS

A total of 50 adult patients suffering from chronic hepatitis C were included in the study. Their age ranged from 24 to 50 years, with mean age of 35. Out of them, 34 (68%) were males while16 (32%) were females.

The mean values for AST, ALT, and AAR were 82.58 ± 41.77, 103.10 ± 63.76, and 0.86 ± 0.26, respectively. (Table-2)

There were 9 (18%) patients in stage-1 with mean AAR 0.72 ± 0.17. Stage-2 included majority of patients, with a total of 22 (44%). The mean AAR for this stage was 0.76 ± 0.16. There were 14 (28%) patients in stage-3 with mean AAR 0.91 ± 0.26.The fibrosis stage-4 or cirrhosis included 05 (10%) patients, and had the highest mean AAR (1.34 ±0.18), (Tables-3).

The mean AAR for non-cirrhotic patients (fibrosis stage 1-3) was 0.77 ± 0.22, while this ratio was significantly higher in patients with cirrhosis (fibrosis stage 4); 1.34 ± 0.18, p value < .001. To distinguish cirrhotic from non-cirrhotic patients, AAR ≥ 1 had 100% sensitivity, 87% specificity, 45% positive predictive value and 100% negative predictive value with 88% accuracy. The AAR in different stages of liver fibrosis is shown in the form of scatter plot (figure).

DISCUSSION

Significant progress has been made to develop reliable noninvasive tests for the monitoring of patients with chronic hepatitis C. However, none of the currently available

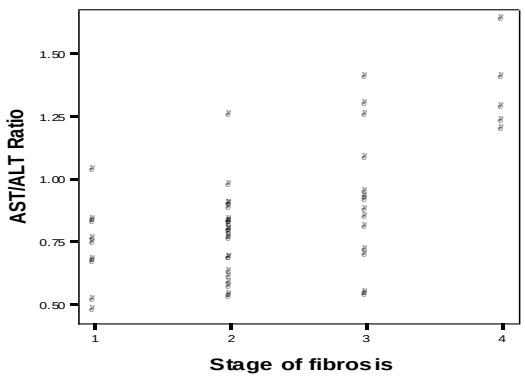

Figure: Showing relation of AAR to stages of liva fibrosis.

Table-1: Knodell score for degree of liver fibrosis

Fibrosis	Knodell Score	Stage of Fibrosis
No fibrosis	0	1
Fibrous portal expansion	1	2
Bridging fibrosis	3	3
Cirrhosis	4	4

Table- 2: Serum AST, ALT (U/L) and AST/ALT ratio

	AST	ALT	AST/ ALT Ratio
Mean	82.58	103.10	0.86
Std. Error of Mean	5.91	9.02	0.04
Std. Deviation	41.77	63.76	0.26
Minimum	33	33	0.47
Maximum	225	357	1.63

tests can completely replace liver histology. Because chronic hepatitis C has variable clinical course compounded by complex host, virus and environment factors, it is crucial to have noninvasive tests that can be used repeatedly to monitor such patients [9].

In our study, we examined the relation between AST/ALT ratio and hepatic fibrosis in chronic hepatitis C patients in our population. Mean AAR value was found to be higher for each increasing stage of fibrosis. The mean AAR for non-cirrhotic patients (fibrosis stage 1-3) was 0.77±0.22, while this ratio was significantly higher in patients with fibrosis stage 4 or cirrhosis (1.34±0.18) This finding was comparable with previous studies; 0.60 versus 1.05 in work by Sheth et al [14]. Seventy four versus 1.18 in study by Imperiale et al 20and 0.87 versus 1.2 in research work by Butt et al. [14, 15, 20].

Additionally, Sheth et al found that mean ALT values were comparable in non-cirrhotics (127.7 ± 16.6) and cirrhotics (128.0 ± 14.0) while mean AST value in patients with cirrhosis (118.5 ± 10.2) was greater than the mean AST value (71.3 ± 6.3) in patients without cirrhosis [14]. Similar mean AST and ALT values for non-cirrhotics and cirrhotics were noted by Imperiale and co-workers [20]. Above findings suggest that AST/ALT ratio increases with increasing liver fibrosis in patients with chronic hepatitis C. The reason for the increase in the AST/ALT ratio with increasing liver fibrosis and cirrhosis is not completely understood. As noted in present study and majority of the related research work, the mean AST value in the cirrhotic patients was significantly higher than in non-cirrhotic, whereas mean ALT values were similar in both the groups. Thus, this relative increase in the AST values in cirrhotics could explain the greater AST/ALT ratio. With disease progression, the relative activities of AST and ALT are altered. The sinusoidal liver cells have a possible role in the clearance of AST from the serum [22]. Therefore, it is possible that with increasing fibrosis, sinusoidal function is progressively impaired, resulting in a relative increase in the serum AST levels.

Although present study showed increasing mean AAR value for each increasing stage of liver fibrosis, there was considerable overlap between individual AAR values in fibrosis stage 1-3. By applying ANOVA, there was no statistically significant difference in AAR values for fibrosis stage 1-3, however AAR was significantly higher in stage 4 when compared to other stages ($p< 0.001$).

We also found that AAR ≥ 1 had 100% sensitivity and negative predictive value in distinguishing cirrhotic from non-cirrhotic patients with 87% specificity and 45% positive predictive value, with an accuracy of 88%.

Table-3: Frequency of stages of liver fibrosis and corresponding mean AAR (n=50)

Stage of fibrosis	Frequency with percentage	Mean AAR	Std Deviation	Min AAR	Max AAR
Stage-1	09 (18%)	0.72	0.17	0.47	1.03
Stage-2	22(44%)	0.76	0.16	0.52	1.25
Stage-3	14(28%)	0.91	0.26	0.53	1.40
Stage-4	05(10%)	1.34	0.18	1.19	1.63

However, total number of cirrhotic patients in our study was too small (n=5) to reliably interpret this ratio. Seth et al showed that a ratio ≥1 had 100% specificity and positive predictive value in distinguishing cirrhotics from non-cirrhotics with 53.2% sensitivity and 80.7% negative predictive value [14]. More recently, the usefulness of AAR in predicting cirrhosis in chronic hepatitis C has been challenged by Imperiale et al who found much lower sensitivity and specificity [16].

Therefore, although AST/ ALT ratio is an emerging noninvasive marker of liver fibrosis in chronic hepatitis C patients, it can not currently replace liver biopsy as a preferred diagnostic tool. Other biochemical and serological noninvasive tests have heterogeneous evidence in predicting fibrosis in liver biopsy specimens, with panels of such tests showing more success [9, 10, 23].

With increasing knowledge about hepatitis C and its treatment options, noninvasive markers of liver fibrosis and cirrhosis are increasingly required. As advances in treatment continue, it may become useful to use noninvasive predictors to estimate the likelihood of a therapeutic response and monitor disease progression in chronic hepatitis C. They could have special role in management of patients with bleeding diathesis or in a clinical setting where liver biopsy cannot be readily obtained.

CONCLUSION

Although mean AAR increases with increasing stage of hepatic fibrosis in patients with chronic hepatitis C, the statistically significant difference in AAR value is noted only in advanced fibrosis (stage 4/cirrhosis).

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