

HEPATITIS C;

VALIDITY OF ALANINE AMINOTRANSFERASE LEVELS IN PREDICTING HISTOLOGICAL CHANGES IN YOUNG ASYMPTOMATIC PATIENTS

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DR. RIZWANA KITCHLEW, FCPS, MRCP

Assistant Professor Medicine
FMH College of Medicine & Dentistry Shadman Lahore.

DR. ASIF HASHMI FCPS, DCN

Associate Professor Of Medicine
King Edward Medical College Lahore

DR. FUAD AHMAD SIDDIQI FCPS (MED)

H.No:157 St:9 Chaklala III Rawalpindi

ABSTRACT... Background: Liver biopsy the gold standard for the histological assessment in chronic hepatitis C is an invasive procedure with certain limitations. **Objective:** It was to evaluate the relation of serum ALT levels with the histological changes in healthy blood donors screened positive for HCV. **Study Design:** This cross sectional comparative study **Setting:** It was conducted at department of medicine Combined Military Hospital Lahore, from January to August 2004 **Method:** 76 apparently healthy blood donor soldiers age 20 – 49 years positive for HCV antibodies by third generation ELISA test, evaluated by medical history, physical examination, serum ALT levels , PCR test for HCV RNA and ultrasound abdomen were enrolled. Liver biopsy was done through percutaneous route and histology was graded according to Knodell scoring system. **Results:** Serum ALT levels showed a skewed distribution with mean of 130.9+96.9 IU/L and median of 8.5IU/L. Eleven patients had normal ALT (<40 IU/L). On histological analysis of liver biopsy specimen 17 had Knodell score ≤ 3 (mild inflammation), 38 had score between 4 and 7 (moderate inflammation) and 21 had > 8. Patients with score > 8 were older than the former groups. The difference was significant ($p=0.047$). Relation of ALT levels with stage of fibrosis and grade of inflammation was estimated using ANOVA it showed no statistical significance. Patients with stage 1 fibrosis had highest mean serum ALT levels ($p=0.108$). **Conclusions:** No association found between the ALT level & liver biopsy histological score. However patients with normal ALT levels usually had mild necroinflammatory changes.

Key words: Alanine Aminotransferase, Hepatitis C, Liver Biopsy, Knodell scoring.

INTRODUCTION

Chronic Hepatitis C develops in 85% of patients with acute Hepatitis C. Worldwide 170 million people are infected with it^{1,2}. According to the estimate of Centre for Disease Control the number of new cases of acute HCV infection in United States is about 19000 cases per year. Chronic hepatitis C is the most common chronic liver disease and accounts for 8000 to 13000 deaths each year in the United States of America³.

Hepatic histological evaluation is currently the gold standard to determine the degree of liver injury in chronic hepatitis C. Liver biopsy has been recommended to exclude other liver diseases and to establish the histologic stage of liver inflammation in patients with chronic hepatitis C^{4,5,6}. The level of necroinflammation reveals the degree of ongoing damage, whereas the fibrosis stage is indicative of the degree of histologic damage, the architectural remodeling and disease progression. Both these components have prognostic implications in the natural history of the disease and response to therapy.

Liver biopsy although the current standard of care for histological assessment has a number of limitations. The procedure is invasive, samples only a small portion of liver and is also subject to wide variations in interpretation. Complications of liver biopsy occur infrequently but patients are generally concerned about these risks plus the associated discomfort and cost. In view of these concerns about liver biopsy, several authors have looked at the correlation of levels of ALT and liver fibrosis/ inflammation but have failed to show a correlation between them.

It has been generally felt in our setup that patients are even more reluctant to get a liver biopsy done due to deep rooted social and cultural beliefs. Histological correlation with ALT is one of the most important factors to determine the urgency of treatment. We therefore embarked on studying this correlation in young male patients presenting to our unit. Such a correlation, if found, could help reduce the pre-treatment requirement of liver biopsy and thus the psychological and financial burden on less privileged patients of a third world country.

The purpose of this study was to determine whether degree of serum Alanine aminotransferase (ALT) elevation can predict level of histological damage in asymptomatic anti – HCV positive patients of chronic hepatitis C.

METHODOLOGY

This was a cross-sectional comparative study conducted at Combined Military Hospital Lahore during the period from January 2004 to August 2004. Non randomized apparently healthy blood donors, who were above 18 years of age and screened positive for HCV antibodies by third generation ELISA test were selected for the study. They met the diagnosis of chronic hepatitis C i.e anti HCV positive and PCR positive for HCV RNA(Roche Amplicor).

Ultrasound abdomen was done to exclude any hepatobiliary abnormality. Liver biopsy was conducted after obtaining the patient's consent, through percutaneous route, using Surecut needle (size 18G) after checking the coagulation profile. The biopsy specimens were immediately preserved in 10% formalin solution and transported to the laboratory. The same pathologist reported on all the liver specimens. All specimens were stained with routine and special stains.

The histological features were scored according to the Knodell scoring system (appendix A). Grading, staging and total scores were reported. The grades were I to III with maximum score of 18 {I=mild activity (score 0-3), II=moderate activity (score 4-7), III=severe activity(score 8-18)}. The stages were 1 to 4 (1= no fibrosis, 2= portal fibrosis, 3= bridging fibrosis, 4= cirrhosis) with a maximum score of 4. The total score was out of 22.

In accordance with Knodell scoring system the patients were divided into 2 groups: In group-I were those with histological activity index (HAI) of < 3 whereas group-II comprised of patients with HAI of > 3. Patients in group 1 were recommended follow-up rather than treatment provided their serum ALT levels were persistently normal. Patients in group-II were candidates for treatment.

Based on ALT levels, individuals were divided into two groups: Group-I with ALT levels of less than 40IU/L(normal levels) and group-II with ALT levels greater than 40 U/L. Association between serum ALT levels and degree of inflammation on liver biopsy, determined by the HAI Knodell score, was recorded.

The diagnostic value of ALT levels was assessed by determining the sensitivity, specificity and positive and negative predictive values. Comparisons of ALT levels between patients with high and low HAI Knodell scores was done.

Categorical variables are reported as frequency/ percentages while numerical data is reported as mean \pm sd. Data was analyzed on SPSS 10 statistical package. Pearson's Chi-square test was used for analysis of categorical data and Independent sample t-test was used for analysis of numerical variables. Multiple group comparisons was done with One Way Analysis of Variance (ANOVA) with Least Significant Difference (LSD) calculated for post hoc comparisons where appropriate. For all statistical tests a 'p' value < 0.05 was considered significant.

RESULTS

A total of 76 male patients with chronic hepatitis C infection were analysed in this study. Summary of the demographic, biochemical and histological analysis is presented in table-I. Mean age of the patients was 33.05 ± 6.25 years with a range of 20 - 49 years.

Serum ALT levels in the present study showed a skewed distribution with mean of 130.9 ± 96.9 and median of 98.5. Eleven patients(14.5%) had normal serum ALT levels (less than 40 IU/L) while the remaining 65 (85.5%)patients had serum ALT levels above 40 IU/L.

Histological analysis of liver biopsy specimens showed that 17 patients(22.4%) had Knodell score of less than or equal to 3 (mild inflammation), 38patients(50%) had a Knodell score between 4 and 7 (moderate inflammation) and 21 patients(27.6%) had a Knodell score greater than 8 (severe inflammation).

ANOVA for age distribution in the three necroinflammatory groups based on Knodell scores indicated that patients with scores above 8 were older than the other two groups and the difference was statistically significant ($p = 0.047$) as reported in table-II.

ANOVA was used to analyze differences in distribution of

Table-I. Demographics, biochemical and histological characteristics of patients

Total No:	76
Age (Mean±SD) years	33.1±6.3
Sex	All male
ALT (Mean ± SD) IU/L	130.9±96.9
ALT Median (IU/L)	98.5
Knodell Necroinflammatory score (Mean ± SD)	5.2 ± 2.7
Fibrosis Stage	
Stage 0	20 (26.3%)
Stage 1	43 (56.6%)
Stage 2	12 (15.8%)
Stage 3	1 (1.3%)
<i>ALT: Alanine Aminotransferase Levels</i>	

serum ALT levels in different grades of inflammation and stages of fibrosis determined on liver biopsy the results are presented in table3 & 4 respectively. There was no significant difference in the ALT levels between different grades of inflammation ($p = 0.14$). Stage1 of fibrosis showed the highest level of ALT with mean of 151+ 109.7 IU/L. However there was no significant difference in the ALT levels between different stages of fibrosis ($p = 0.07$).

The sensitivity of ALT levels in correctly identifying the true positives on Knodell scoring was found to be 88% and the specificity was 24%. The positive predictive value was 80% and negative predictive value was 36%.

DISCUSSION

Serum alanine aminotransferase (ALT) activity and aspartate aminotransferase (AST) activity are markers of liver cell damage⁷. Their elevation above the range of normal values is the most frequent feature of acute or chronic hepatitis C. However, serum aminotransferase activity elevation is not specific, because it is seen in numerous liver disorders of various etiologies. It is also poorly sensitive, since ALT and AST can remain within the normal range for long periods of time in cases with chronic HCV infection, inspite of progressive liver

Table-II. Age distribution in different grades of necroinflammatory response.

Groups	Necro-Inflammatory Score	n	Mean±Std	Age in years	
				Minimum	Maximum
1	0-3	17	31.7±6.5	20	48
2	4-7	38	32.5±5.6	22	49
3	8-12	21	35.6±6.4	24	48
	Total	76	33.1±6.3	20	49

Table-III. Analysis of mean serum ALT by grade of inflammation

Necroinflammatory	No	ALT IU/L (Mean ± SD)
0-3	31	109.3±69.9
4-7	35	136.8±108.5
8-12	10	177.3±115.5
<i>ALT: Alanine Aminotransferase Levels</i>		

Table-IV. Analysis of mean serum ALT by fibrosis stage

Fibrosis Score	No	ALT IU/L (Mean±SD)
Stage 0	20	90 ± 51.4
Stage 1	43	151 ± 109.7
Stage 2/3	13	125 ± 90.2
<i>ALT: Alanine Aminotransferase Levels</i>		

disease^{8,9}.

The level of aminotransferase activity has no prognostic value and is not related to the severity and outcome of acute or chronic liver disease¹⁰⁻¹². The diagnosis and the prognosis of chronic hepatitis C are currently based on histological examination of liver biopsy^{4,13,14}. Several interpretation scores have been proposed, the three most widely used being the Knodell's score, the Metavir score, and the Ishak's score¹⁵⁻¹⁸. On Liver Biopsy Samples the first parameter measured is Necro-inflammatory activity, the main predictor of liver disease outcome. Indeed, the patients with a high activity score are at risk of rapid fibrosis progression and cirrhosis. Fibrosis assessment also has prognostic significance, because it allows to differentiate: the patients with no or mild fibrosis, who generally have early disease or are slow progressors; the patients with severe fibrosis, who have more advanced disease and are at higher risk of developing cirrhosis and its complications.

The histological evaluation of liver is currently the gold standard to determine the degree of liver injury in chronic

hepatitis C. This study was conducted to evaluate whether degree of elevation of noninvasive and less resource consuming hepatic markers like serum ALT can predict level of histological damage. No significant association was found between HAI or Knodell score and serum ALT. Most cross-sectional studies have reported the same^{7,8,11,19}.

Serum ALT has been the most commonly investigated non invasive marker in a number of studies¹⁹⁻²². It was associated with fibrosis stage in 11 of 15 studies with sensitivity ranging from 61% to 71% and specificity ranging 66% to 94%. However, in other studies no statistically significant association was found^{11,12}.

Our study shows that determination of serum ALT alone cannot evaluate the extent of liver injury in patients with chronic HCV infection, liver biopsy is more sensitive and accurate in this respect as shown in various studies. However, patients with normal ALT levels usually have mild necroinflammatory changes on liver biopsy as already reported in previous studies^{8,11,23,24}.

In patients with normal ALT, the role of liver biopsy

Annex-A

Knodell Histological Activity Index Grade and Stage

Inflammation

Portal:

- Grade 0 no inflammation
- Grade 1 peri-portal inflammation no hepatocellular necrosis
- Grade 2 inflammation with mild interface hepatitis
- Grade 3 severe portal inflammation with moderate interface hepatitis
- Grade 4 marked inflammation with severe interface hepatitis

Lobular:

- Grade 0 no inflammation
- Grade 1 minimal, no necrosis (inflammatory cells within the lobule)
- Grade 2 moderate inflammatory cells with occasional liver cell necrosis
- Grade 3 marked inflammation with severe focal liver cell necrosis
- Grade 4 extensive inflammation with bridging necrosis

Fibrosis:

- Stage 1 none or mild peri-portal fibrosis
- Stage 2 peri-portal fibrosis with/without extension and portal-portal bridging
- Stage 3 portal-central bridges but no nodular formation
- Stage 4 probable or definite cirrhosis

remains the subject of debate. In approximately 40% of cases of chronic HCV, serum ALT levels are persistently normal. Affected persons with normal ALT levels usually have mild chronic hepatitis with slow or absent progression to cirrhosis^{2,4,7,23,24}. Our study reported the same. However, some of these patients have histologically very severe or advanced disease^{9,24-28}. In one study approximately 20% of such patients had extensive fibrosis or cirrhosis²⁶. In patients with persistently normal ALT levels the rate of progression of fibrosis is slow than those with high ALT levels but the duration of infection is longer in patients with chronic hepatitis C who have persistently normal ALT levels.²⁹ Therefore, we suggest that patients with persistently normal ALT levels must have liver biopsy to unearth clinically subtle but advanced liver disease. Further studies are required to establish the role of liver biopsy in the subset of patients with normal aminotransferase levels. Our sample size was limited to 76 cases. Larger prospective studies are required.

CONCLUSIONS

Serum ALT levels are sensitive in picking the necroinflammatory changes in chronic hepatitis C. However the level of ALT is not related to degree of histological change in liver, as individuals with normal ALT had mild to moderate histological changes. The later did not have fibrosis more than stage 1. So it can be assumed that individuals with normal ALT will have relatively mild disease.

- 1) There is no significant relation between serum ALT level and degree of hepatic injury in individual patients.
- 2) Patients with higher necroinflammatory score were older suggesting a longer duration disease.
- 3) Liver Biopsy remains the gold standard for assessing the degree of histological changes in patients with chronic hepatitis C.

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Correspondence Address:

Dr. Rizwana Kitchlew
H.No. 90 St.No. 3 Cavalry Ground Lahore Cantt
riz102403@yahoo.com

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Yesterday is but today's memory,
tomorrow is today's dream.

Kahlil Gibran