

Association of Liver Histology with Serum ALT Levels in Patients with Chronic Hepatitis C

Wajeeha Ahad¹, Ayaz Ahmed², M Fahad Waseem³, Muhammad Tahir⁴, Muhammad Tarique⁵

ABSTRACT:

Objective: To evaluate the incidence of liver damage based on grading of necro-inflammatory and fibrotic changes on hepatic cytology in patients suffering chronically with hepatitis C, presenting with alanine transaminase levels in normal ranges.

Methodology: A cross-sectional survey was accomplished at department of medicine, PAF Hospital Mushaf, Sargodha for six months of duration from April 2012 to October 2012. 100 cases were evaluated. Liver biopsy was done using large bore sure cut biopsy needle under all aseptic measures after ultrasound marking and sent in 10% formalin for histological studies of inflammation and necrosis. Liver damage was declared for patients having grade 1 or more activity on METAVIR scoring system.

Results: Majority of the patients were between 31-40 years of age and lowest age was 20 years. Average age of the patients was 33.2±7.4 years. Out of 100 patients, 47 patients (47.0%) were male while remaining 53 patients (53.0%) were females. Liver damage was found in 41.0% patients.

Conclusion: Liver biopsy should be performed for a clear diagnosis in patients suffering from HCV with alanine transaminase level within the normal ranges. Patients may suffer advanced hepatic disease despite normal levels of hepatic enzymes.

Keywords: Liver histology, Chronic hepatitis C, Normal alanine transaminase

INTRODUCTION:

Hepatitis is a disease that has been with us for a long time. It is contagion that damages the Liver. Many of the patients suffering from chronic hepatitis C have tenaciously ALT levels in normal ranges¹. The virus accountable for the disease is typically evident in the blood by polymerase chain reaction (PCR) test within a month after being infected. The antibodies that are produced in response of viral infection are usually evident within a month to one and a half year. Eradication rates of Hepatitis C virus are extremely inconsistent; upto 60 percent² of the patients remove the virus from their blood at some stage in acute phase, as revealed by normal levels of the liver enzymes Transaminase Alanine and Aspartate Transaminase. Though, many of the time infection is persistent³ and the majority of patients get

chronically ill, i.e., infection is long-lasting over half a year^{4,5}. Although liver enzymes levels commonly keep up a correspondence with the commotion of the ailment, even a normal stage could not leave out a grim histological damage. Therefore, these facts should remind the physician to perform a liver biopsy prior to therapy⁶. Reasons that have been accounted for the progression of the disease embraces increasing age, males are more prone to the disease, utilization of alcohol, subjects infected with human immunodeficiency virus (HIV), and fatty liver. Mild chronic hepatitis patients with slow or absent progression to cirrhosis suffers chronically with the disease and usually have doggedly normal ALT blood levels, though cirrhosis is can be observed in few of these patients⁷. However, Fibro test and Acti test estimate hepatic fibrosis and extent of necrotic inflammation⁸. In the study carried out by Syed and Sadiq at Jinnah Post Graduate Medical Centre Karachi in 2009, it was accomplished that elevated ALT blood levels are allied with more evident forms of necroinflammation and hepatic fibrosis. Though it was also established that severity of disease cannot be predicted using ALT levels as some patients with normal ALT levels had grade1 activity whereas others had severe necroinflammatory disease which supports the fact that liver biopsy is required to discover the complexity of liver. ⁹ When patients suffering from chronic hepatitis C were tested extensively; nearly half of the patients had normal serum ALT levels. The diagnosis of chronic hepatitis C should be confirmed by testing for HCV RNA. The existence of HCV RNA shows that the patient is currently suffering from viral infection regardless of normal ALT levels. While another study done by Sanai et al in Riyadh Military Hospital Saudi Arabia it was observed that none of the hepatitis C patient with normal ALT had normal liver histology¹⁰. The objective of this study was to find out the incidence of hepatic damage assessed following the METAVIR system in patients with hepatitis C with normal ALT

✉ **Dr. Wajeeha Ahad**
Medical Specialist
PAF Hospital Korangi Creek
Karachi
Email: wajeehas@yahoo.com

✉ **Dr. Ayaz Ahmed**
Medical Specialist
PAF Hospital Samungli
Quetta

✉ **Dr. M Fahad Waseem**
Medical Specialist
PAF Hospital Masroor
Karachi

✉ **Dr. Muhammad Tahir**
Medical Specialist
CMH Rawalpindi

✉ **Dr. Muhammad Tarique**
Medical Specialist
PAF Hospital Faisal
Karachi

Received: 08-11-16

Revised: 20-04-17

Accepted: 12-06-17

levels. Previous studies have shown differences in degree of damage and ALT levels.

METHODOLOGY:

This was a cross sectional study conducted at department of medicine, PAF Hospital Mushaf, Sargodha. Study was carried out over a period of six months from April 2012 to October 2012. Data comprised of 100 patients selected via non probability convenient sampling. Sampling error was calculated to be 10%. Liver damage was assessed using METAVIR scoring criteria. Inclusion criteria comprised of patients presenting to the OPD with chronic hepatitis C during the study duration. Diagnosis was confirmed using HCV RNA levels and anti HCV antibody +ve for more than 6 months, ALT less than 40 U/L and Patients of both genders, age between 18- 60 years were included in the study. Subjects with previous history of therapy like interferon for treatment of the disease (treatment non-responders), Pregnant women and lactating mothers, Hepatitis BsAg positive, patients with History of Chronic hepatic disorders like Autoimmune hepatic disorders, hepatocellular carcinoma and Alpha1 Anti Trypsin deficiency, a platelet count less than 100 x 10⁹/L or Prothrombin time (PT) more than 3 seconds of control were excluded from the study design.

100 Patients fulfilling inclusion/exclusion criteria were enrolled after informed consent from Medical OPD of PAF Hospital Mushaf, Sargodha. Demographics like Name, gender, age & address was noted. Then liver biopsy was done by the researcher herself using large bore sure cut biopsy needle under all aseptic measures

after ultrasound marking and sent in 10% formalin for histological studies of inflammation and necrosis in PAF hospital Mushaf laboratory by single histopathologist, effect modifiers were controlled by following exclusion criteria. All the patients had a biopsy sample compatible with chronic hepatitis C as assessed by the METAVIR scoring system (grades the stage of fibrosis on a five-point scale, F0 = no fibrosis, F4 = cirrhosis, and histological activity on a four-point scale, A0 = no activity, A3 = severe activity). Liver damage was declared for patients having grade 1 or more activity on METAVIR scoring system and report of histopathology was gathered. SPSS version 16 was used to analyze the data. A Descriptive statistical analysis was executed. Data on continuous variables was reported as mean±standard deviation like age and METAVIR score and data on categorical variables like gender, Liver damage (Yes/No) were presented as frequency and percentage.

RESULTS:

100 Patients fulfilling inclusion/exclusion criteria were examined in this study. Age of majority patients was between 31-40 years and the lowest age reported was 20 years. Mean age of the patients was 33.2±7.4 years (Table 1). Out of 100 patients, 47 patients (47.0%) were male while 53 patients (53.0%) were female. Frequency of liver damage was based on grading of necroinflammatory and fibrotic changes on liver histology in Chronic patients, presenting with normal ALT was 41.0% (Table 2).

Table:1

Distribution of cases by age

Age in Years	Incidence of the disease	Percentage
< 20	3	3
20-30	30	30
31-40	41	41
41-50	18	18
51-60	8	8
Total	100	100

Table: 2

Distribution of cases by sex and Liver Damage

Sex	Number	Percentage
Male	47	47
Female	53	53
Liver damage	Number	Percentage
Yes	41	41
No	59	59

DISCUSSION:

Hepatitis C virus (HCV) is a globally prevalent pathogen and a leading cause of death and morbidity.¹¹ The most recent estimates of disease burden show an increase in sero-prevalence over the last 15 years to 2.8%, equating to >185 million infections worldwide.¹² About 10 million of the inhabitants are affected with the disease in Pakistan¹³. The adult personnel, patients with haemodialysis or blood transfusion are mostly affected with the disease¹⁴. The major diagnostic tool is hepatic biopsy in Elevated serum ALT (eALT). On the other hand, now days, a few hepatitis C patients may be seen cirrhotic regardless of normal enzyme levels (ALT). In fact ALT levels are commonly variable, revealing that ALT levels in normal ranges may not exactly be a sign of the course of the hepatitis. The efficacy of rise of serum ALT levels in forecasting of severity of hepatic damage in chronic patients is questionable¹⁵. A study found that 5% of patients with normal ALT levels had cirrhosis and 3% had bridging fibrosis¹⁶. As the usefulness of serum ALT levels in predicting the severity of Hepatitis C virus infection is uncertain so we aim to compare histological scoring of liver pathology in patients with chronic HCV infection with normal or elevated serum ALT. Previous studies have shown that Hepatitis C can be found with elevated serum ALT or with normal serum ALT¹⁷. Histological evaluation of hepatic biopsy specimens is the important way for measuring fibrosis¹⁸. There is no association of HCV RNA and serum ALT levels and degree of hepatic injury in individual persons. Liver histological assessment is necessary for the clinical assessment of patients suffering chronically with the disease¹⁹.

Mc Cormick in his study observed that there was no patient having normal ALT levels in grade 3 and 4 fibrosis¹⁹. Significant fibrosis has been reported, with large variation among studies, when inclusion criteria and length of base line follow up was different²⁰. Studies have shown AST/ALT ratio increased with liver histological progression. The ratio ≥ 1 was predominantly in cirrhotic patients²¹.

In present study frequency of liver damage based on grading of necroinflammatory and fibrotic changes on liver histology in chronic disease patients, having ALT levels in normal ranges was 41.0%. Some studies have suggested that up to 25% of patients with chronic hepatitis C virus infection have persistently normal aminotransferase levels (10% to 40%, according to different studies).^{22,23,24} Another study showed that approximately 30% of patients with chronic hepatitis C have normal serum alanine aminotransferase (ALT) levels and another 40% have ALT levels that are less than twice the upper limit of the normal range²⁵. Few studies have shown mean viral load significantly higher in chronic HCV patients with persistently normal ALT levels²⁶.

CONCLUSION:

In conclusion, liver biopsy is suggested for a clear diagnosis in patients suffering from HCV with alanine

transaminase level within the normal ranges. Patients may suffer advanced hepatic disease inspite of having normal levels of hepatic enzymes.

REFERENCES:

1. Arif A, Ahmed W, Alam SE, Qureshi H. Active disease in chronic hepatitis C patients with normal alanine aminotransferase. *J Coll Physicians Surg Pak*. 2012 Aug 1; 22(8):488-91
2. Căruntu FA, Benea L. Acute hepatitis C virus infection: Diagnosis, pathogenesis, treatment. *Journal of Gastrointestinal and Liver Diseases*. 2006 Sep;15(3):249
3. Kamal SM. Acute hepatitis C: a systematic review. *The American journal of gastroenterology*. 2008 May 1;103(5):1283-97
4. Cox AL, Netski DM, Mosbrugger T, Sherman SG, Strathdee S, Ompad D, et al. Prospective evaluation of community-acquired acute-phase hepatitis C virus infection. *Clinical Infectious Diseases*. 2005 Apr 1;40(7):951-8
5. Mohammadi M, Talei G, Sheikhian A, Ebrahimzade F, Pournia Y, Ghasemi E, et al. Survey of both hepatitis B virus (HBsAg) and hepatitis C virus (HCV-Ab) coinfection among HIV positive patients. *Virology journal*. 2009 Nov 18;6(1):202
6. Bartos V, Krkoska D, Slavik P, Lauko L, Adamkov M. Histological status of the liver in relation to serum aminotransferase levels in patients with chronic hepatitis C. *Bratislavske lekarske listy*. 2006 Dec;108(12):522-5
7. McPhee SJ, Papadakis MA, Tierney LM, editors. *Current medical diagnosis & treatment 2010*. New York: McGraw-Hill Medical; 2010
8. Ngo Y, Munteanu M, Messous D, Charlotte F, Imbert-Bismut F, Thabut D, et al. A prospective analysis of the prognostic value of biomarkers (FibroTest) in patients with chronic hepatitis C. *Clinical chemistry*. 2006 Oct 1;52(10):1887-96
9. Syed SI, Sadiq S. Histopathological grading and staging in liver biopsies of Hepatitis-C patients and their association with ALT levels. *Pak J Med Sci*. 2010 Jul 1;26(3):644-8
10. Sanai FM, Benmoussa A, Hussaini H, Ashraf S, Alhafi O, Abdo AA, et al. Is serum alanine transaminase level a reliable marker of histological disease in chronic hepatitis C infection? *Liver International*. 2008 Aug 1; 28(7):1011-8
11. Cooke GS, Lemoine M, Thursz M, Gore C, Swan T, Kamarulzaman A, et al. Viral hepatitis and the Global Burden of Disease: a need to regroup. *J Viral Hepat*. 2013;20: 600–601
12. Hanafiah MK, Groeger J, Flaxman AD, Wiersma ST. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. *Hepatology*. 2013; 57: 1333–42
13. Raja NS, Janjua KA. Epidemiology of hepatitis C virus infection in Pakistan. *J Microbiol Immunol Infect*. 2008; 41(1):4
14. Sy T, Jamal MM. Epidemiology of hepatitis C virus (HCV) infection. *Int J Med Sci*. 2006; 3(2): 41–6
15. Pradat P, Alberti A, Poynard T, Esteban JI, Weiland O, Marcellin C, et al. Predictive value of ALT levels for histologic findings in chronic hepatitis C: a European collaborative study. *Hepatology*. 2002 Oct 1; 36(4):973-7
16. Taraneh DM, Naseer ED, Muhammad B, Ali AH, Babak H, Ali RS et al. Relationship between serum ALT levels and liver histology in chronic hepatitis C infected patients. *Indian J Gastro* 2005; 24: 49-51

17. Bhatta SA, Shaikh NA, Akhter SS. Liver histology in hepatitis C virus positive patients with normal and elevated alanine amino transferase levels. *J Pak Med Assoc.* 2009 Dec; 59: 832-4
18. Afdhal NH, Nunes D. Evaluation of liver fibrosis: a concise review. *The American journal of Gastroenterology.* 2004 Jun 1; 99(6): 1160-74
19. McCormick SE, Goodman ZD, Maydonovitch CL, Sjogren MH. Evaluation of liver histology, ALT elevation, and HCV RNA titer in patients with chronic hepatitis C. *Am J Gastroenterol.* 1996 Aug; 91(8): 1516-22
20. Alberti A, Benvegna L, Boccato S, Ferrari A, Sebastiani G. Natural history of initially mild chronic hepatitis C. *Digestive and liver disease.* 2004 Oct 31; 36(10):646-54
21. Anderson FH, Zeng L, Rock NR, Yoshida EM. An assessment of the clinical utility of serum ALT and AST in chronic hepatitis C. *Hepatol Res.* 2000 Jul;18(1):63-71
22. Shiffman ML, Diago M, Tran A, Pockros P, Reindollar R, Prati D, et al. Chronic hepatitis C in patients with persistently normal alanine transaminase levels. *Clin Gastroenterol Hepatol.* 2006; 4: 645-52
23. Gholson CF, Morgan K, Catinis G, Favrot D, Taylor B, Gonzalez E, Balart L. Chronic hepatitis C with normal aminotransferase levels: a clinical histologic study. *Am J Gastroenterol.* 1997; 92: 1788-92
24. Persico M, Perrotta S, Persico E, Terracciano L, Folgori A, Ruggeri L, et al. Hepatitis C virus carriers with persistently normal ALT levels: biological peculiarities and update of the natural history of liver disease at 10 years. *J Viral Hepat.* 2006; 13: 290-6
25. Bacon BR. Treatment of patients with hepatitis C and normal serum aminotransferase levels. *Hepatology.* 2002; 36(5 Suppl 1):S179-84
26. Ito H, Yoshioka K, Ukai K, Watanabe K, Yano M, Ishigami M, et al. *Hepatol Res.* 2004 Sep; 30(1):11-7

