

# Is there a Correlation between Degree of Viremia and Liver Histology in Chronic Hepatitis C?

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## Abstract

**Objective:** To determine the correlation between degree of histological liver damage and serum HCV RNA level in patients of chronic hepatitis C, in order to evaluate the usefulness of HCV RNA estimation as an alternate to liver biopsy.

**Methods:** This non-interventional descriptive study, was carried out at the department of Pathology, Army Medical College, Rawalpindi, Pakistan between April and September 2002. Core needle liver biopsies of fifty five patients of chronic hepatitis C were evaluated according to Knodell's histological activity index system. The patients were categorized into four subgroups depending upon the grade and stage of disease according to Desmet's classification, and into three groups according to degree of viremia.

**Results:** Five patients had mild viremia, 43 moderate and 7 had severe viremia. Seven patients had minimal disease, 9 mild, 22 moderate and 17 had severe chronic hepatitis. Eight patients had no fibrosis, 20 had fibrous portal expansion, 19 bridging fibrosis, and 8 patients had cirrhosis. No significant correlation was found between serum HCV RNA levels and grade or stage of the disease, with correlation coefficients of  $r_s = -.054$  and  $r_s = .034$  respectively. Moreover, no individual component of the HAI correlated with serum HCV RNA levels.

**Conclusion:** Serum HCV RNA level does not determine the degree of hepatic injury precisely and liver biopsy

## Introduction

Hepatitis C is a global disease with worldwide prevalence estimated to be around 3%.<sup>1</sup> Due to the paucity of authentic epidemiological studies in Pakistan, it is difficult to comment on the exact prevalence of HCV infection in our country. In healthy blood donors, the prevalence varies from 0 to 29.89% and in general population from 4 to 25.7%.<sup>2</sup>

Liver biopsy and histological evaluation are considered to be the gold standard, to determine the degree of liver injury in chronic hepatitis C.<sup>3</sup> In an attempt to standardize the histological evaluation of chronic hepatitis, Knodell et al.<sup>4</sup> in 1981 described a semi quantitative method of scoring liver biopsies that scores four different sets of histological features: Periportal necrosis with or without bridging necrosis, portal inflammation, intralobular degeneration and necrosis, and hepatic fibrosis. The first three features with a score of 0 to 18, evaluate the necroinflammatory component of the disease and therefore are a measure of histological activity or grade of the disease. The fourth component, fibrosis, with a score of 0 to 4 evaluates the histological stage of the disease. The summation of individual component scores provides a total histological activity index (HAI) with a score of 0 to 22.

Although liver biopsy is a safe procedure in experienced hands, the risk of complications is still about 3%.<sup>5</sup> Most of these complications are mild like pain and bleeding, but severe complications like pneumothorax and septic

shock, have generated a need to evaluate whether non invasive tests such as serum ALT and HCV RNA estimation, can adequately predict the degree of hepatic damage, to be used as alternate tests for liver biopsy.

The purpose of this study was to determine the correlation between degree of histological liver damage and serum HCV RNA level, in our setup, to evaluate whether HCV RNA estimation can replace liver biopsy in management of chronic hepatitis C.

## Materials and Methods

A non-interventional descriptive study carried out at the department of Pathology, Army Medical College, Rawalpindi, Pakistan between April and September 2002.

A total of fifty five patients of chronic hepatitis C admitted in Military Hospital and Fauji Foundation Hospital, Rawalpindi were included in the study. The sampling technique was convenient non-probability.

Patients of all ages and both sexes, whose serum HCV RNA estimation had been carried out at Armed Forces Institute of Pathology (AFIP), Rawalpindi were included, with exception of those having a coexisting liver disease which could alter the state of liver damage, including: chronic hepatitis B, Wilson's disease, hemochromatosis, alcoholic liver disease and autoimmune hepatitis. Patients who had previously received antiviral therapy were also excluded from the study.

## Data Collection Procedure

Histological evaluation was done on formalin fixed, paraffin embedded sections of core needle liver biopsies, stained with hematoxylin and eosin. Reticulin stain was also used in routine for evaluation of fibrosis. Knodell's HAI system<sup>4</sup> was used to evaluate separate scores for amount of periportal and bridging necrosis (0-10), intralobular degeneration and necrosis (0-4), portal inflammation (0-4), and hepatic fibrosis (0-4), with a total score of 0-22. According to Desmet's classification [6] patients were placed in four groups depending upon the grade of the disease (0-18):

- a. Minimal chronic hepatitis C (1-3)
- b. Mild chronic hepatitis C (4-8)
- c. Moderate chronic hepatitis C (9-12)
- d. Severe chronic hepatitis C (13-18)

And four groups according to the stage of the disease (0-4):

- a. No fibrosis (0)
- b. Fibrous portal expansion (1)
- c. Bridging fibrosis (3)
- d. Cirrhosis (4)

The patients were placed in three groups according to serum HCV RNA level, estimated by Polymerase chain reaction (PCR) at AFIP Rawalpindi:

- a. Mild viremia <10<sup>6</sup> copies/ml
- b. Moderate viremia 10<sup>6</sup>-10<sup>8</sup> copies/ml
- c. Severe viremia >10<sup>8</sup> copies/ml

## Statistical Analysis

The correlation of various grades and stages of liver damage with degree of hepatitis C viremia was assessed by calculation of Spearman rank correlation coefficients, using the software programme SPSS version 10.

## Results

The age of the patients ranged between 17 to 50 years with a mean age of 32.5 years. Most of the patients were in the third and fourth decades. The male to female ratio was 2:1. Majority (40%) of the patients had moderate disease, followed by severe hepatitis. Twenty (36.4%) patients had fibrous portal expansion, with almost similar number having bridging fibrosis (Table 1). Out of 55 patients, 5 had mild viremia, 43 moderate and 7 had severe viremia. Photomicrographs showing varying degrees of inflammation, necrosis and fibrosis, in our patients are depicted in Figure.

### Level of Viremia vs Grade of disease

Table 2 clearly shows that there is no relationship between grade of the disease and level of viremia, as one patient with mild viremia had severe chronic hepatitis and one patient with severe viremia had minimal hepatitis. Moreover, there is no relationship of other sets of grades of liver disease with level of viremia.

Calculation of the Spearman rank correlation coefficients revealed Spearman rho (rs) = -0.054 for Viremia vs Grade. Value of the correlation coefficient being very near to zero, shows that no significant correlation exists between level of viremia and grade of liver disease.

### Level of Viremia vs Stage of disease

Likewise, no relationship could be seen between level of viremia and stage of the disease (Table 2), since 6 patients with moderate viremia had no fibrosis, while only one patient with severe viremia had cirrhosis. The Spearman rho of 0.034 for Viremia vs Stage showed no significant correlation between the two variables.

### Correlation of level of viremia with individual components of HAI

The coefficients of correlation between level of viremia and portal inflammation, intralobular degeneration and necrosis, and periportal necrosis were also calculated and the values of all three (0.033, 0.021 and 0.005 respectively) were indicative of a lack of significant correlation.

## Discussion

Hepatitis C has an alarmingly high rate of developing chronicity and there is no vaccine available, due to marked genomic variation in the virus. Treatment with interferon  $\alpha$  as a single agent or in combination with ribavirin, has shown promising results in a large number of patients.<sup>7,8</sup> Liver biopsy forms the backbone of the current protocol<sup>9,10</sup> for initiation of antiviral treatment. Presence of moderate or severe necro-inflammation, and fibrous portal expansion or bridging fibrosis, along with persistently elevated ALT and positive HCV RNA, are the indications for initiation of treatment and presence of cirrhosis is a relative contraindication. Similarly, in patients with no fibrosis and minimal necro-inflammation, observation with 6 monthly serial estimation of serum ALT and liver biopsy every 3-4 years is recommended.

Due to the complications and expense of liver biopsy there has been a considerable enthusiasm to search for alternate, non-invasive tests like serum ALT or HCV RNA estimation. Numerous studies have shown a poor correlation between serum ALT levels and histological activity.<sup>11-</sup>

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Due to the complications and expense of liver biopsy there has been a considerable enthusiasm to search for alternate, non-invasive tests like serum ALT or HCV RNA estimation. Numerous studies have shown a poor correlation between serum ALT levels and histological activity.<sup>11-13</sup> Therefore there is little role of serum ALT estimation as an alternate for liver biopsy. But the interest in the role of serum HCV RNA estimation has been kept alive by a few studies, which show a linear relationship between degree of liver injury and level of viremia.<sup>14,15</sup> However most of the studies done on this subject, around the world, have shown no significant correlation between the two.<sup>16-22</sup>

This study like others (Table 3) found no correlation between level of viremia and grade or stage of liver disease, as well as with individual components of HAI.<sup>19,21</sup> We therefore conclude that serum HCV RNA level does not determine the degree of hepatic damage precisely, and although it has an important role in the management of chronic hepatitis C, it cannot be used as an alternate to liver biopsy.

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