

Liver Enzymes Correlation among Chronic Hepatitis C Patients with Virus Infection Fibrosis Progression

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Abstract

The main aim of the study is to identify the association between liver enzymes and virus infection fibrosis progression among the patients, suffering from HCV infection. The study has recruited 195 patients, and data has been gathered for a five years' period from January 2010 till March 2015. The laboratory analyses were conducted on the blood samples to evaluate the level of liver enzymes (ALT, AST, GGT). A slight increase in ALT levels was observed among the patients, who received treatment for HCV infection. The ALT level was estimated to be 48.04% for patients with negative PCR. There is no significant correlation between ALT levels and development of HCV, even when the serum levels of ALT are increased. The patients with negative or positive PCR were observed to have increased level of AST. A slight increase was observed in the negative HCV patients for mean GGT levels, as compared to the positive HCV patients. The hepatic enzymes depicted significant correlation with hepatitis infection.

Keywords: ALT, AST, Hepatitis, GGT, Enzymes.

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Introduction

Hepatic diseases play a major role in the development of morbid and mortal complications among male and female individuals. The most serious complication, related with the impaired hepatic functioning, is cirrhosis. Chronic hepatitis C has been identified as a major pathological manifestation for the development of cirrhosis¹. The prevalence rate of HCV among developed countries along with the Arab region had increased. The common factors for increased prevalence rate of HCV include transfusion of infected blood and blood products, IV drug, and sharing of non-sterilized medical equipment or needles. In order to diagnose chronic hepatitis C infection, noninvasive biochemical markers, serological test and molecular testing are comprehensively used².

Liver biopsy has been identified as a major standard for the evaluation of liver damage; however, patients usually refuse for it. Therefore, noninvasive methods are commonly utilized to diagnose the complications accordingly. Iron is considered as a major mineral, which plays a significant role in the metabolic processes. Along with the minerals, a substantial number of hepatic enzymes also play a vital role for the regulation of normal body processes and functioning^{3,4}.

Elevated liver enzymes that mainly include ALT, AST, and GGT are widely observed among the patients, suffering from hepatitis C infection. A past study has identified that serum iron markers along with liver enzymes were elevated while the patients were chronically infected with HCV³. Therefore, it is necessary to establish the correlation between the hepatitis C virus and liver enzymes among patients, with fibrosis progression.

Liver enzymes have a pivotal role in the control of various hepatic complications among patients. It is said that liver enzymes correlation is necessary to be identified among chronic hepatitis C patients, suffering from virus infection fibrosis progression⁵. Therefore, it is necessary to identify the correlation of hepatic enzymes among chronic

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hepatitis C patients. There is a need for adequate follow-up of the patients, infected with HCV to improve the understanding of chronic HCV infection and clinical consequences associated with the infection. The study has aimed to identify the correlation of liver enzymes among chronic hepatitis C patients, with virus infection fibrosis progression.

The process of necro-inflammation is associated with the presence of liver enzyme; including alanine aminotransferase and aspartate. When the liver damage starts, the alanine aminotransferase is released in the bloodstream. However, the deterioration of liver function is evaluated through a series of liver blood tests, which include the test of ALT. This procedure is used extensively by the physicians to diagnose HCV infection, but there is no strong association between the progression of fibrosis and presence of aminotransferases in the bloodstream. Therefore, ALT is considered as a significant sign for liver inflammation; however, it does not reflect the progression of liver fibrosis⁶.

A study revealed the increased rate of liver fibrosis among the HCV patients, having elevated levels of serum transaminase. However, no correlation was found between the hepatic fibrosis and viral load among the patients, infected with HCV⁷. Majority of the HCV infected patients do not experience liver related complication in the initial years of developing infection because HCV is considered as a slowly progressive chronic disease. Defining the hepatic decompensation, rate of progression of liver fibrosis and potential mediators for the condition are recognized as the severe risk factors and consequences of chronic HCV develop due to liver disease⁸.

The ALT levels are used for the diagnosis of acute condition of hepatitis as ALT levels remain elevated for about 1-2 months after the onset of hepatitis infection. However, ALT levels are not elevated among the patients, suffering from chronic hepatitis, because ALT generally returns to normal level in about 3-6 months. The natural course of HCV infection is comprised of four phases, which include⁹.

- Immune-tolerant phase - characterized by HbeAg positive, increased HCV infection, and minimum elevation of alanine transaminase
- Immune-clearance phase - characterized by increased liver inflammation
- Inactive carrier phase
- Reactivation of virus

The immune clearance phase in HCV infection is characterized by elevated ALT levels during the immune clearance phase. A study conducted by Hui et al.¹⁰ revealed that elevated levels of ALT are taken as a marker for immune clearance and used as predictive measure to evaluate the progression of disease. According to the

guidelines given by AASLD, the patients with HCV infection need to be monitored by every 3 months during their first year to verify them as inactive carrier of HCV¹¹.

A study revealed that around 25% of the patients presented serum ALT activity to be persistent with normal range, despite of the association between chronic HCV infection and elevated activity of ALT¹². Another study reported 26% of persistent normal aminotransferase levels among the co-infected patients with HCV¹³. There is variation in the natural history of chronic hepatitis C; and majority of the patients are not likely to develop liver cirrhosis if proper treatment is administrated. However, the progression of liver disease occurs over several decades; and the rate of progression is increased due to steatosis, alcohol consumption, old age, insulin resistance, and other co-infections¹³.

The progression of liver fibrosis after the development of hepatitis C is driven by different environmental, viral, and host related factors. The association between serum ALT and liver damage is unclear; therefore, the degree of liver damage is evaluated through liver biopsy¹⁴. The patients, who have persistent normal levels of ALT, are considered to be affected with mild degree of histological hepatic damage. A study was conducted to compare the inflammation and different stages of fibrosis among the HCV infected patients with elevated serum ALT levels. The results revealed that normal level of serum ALT is not an indication of healthy liver; therefore, histological evaluation of liver is necessary for the precise assessment of liver damage¹⁵.

A significant number of HCV infected patients with ALT levels are diagnosed with cirrhosis, moderate to severe fibrosis, and they may even develop hepatocellular carcinoma¹⁶. Normally, the patients suffer from hepatitis C, but have normal functioning of liver enzymes. This is because the rate of response to treatment is better among the patients, who suffer less liver damage. Apart from hepatic enzymes, viral load, and individual contraindications towards any treatment measure; viral genotype and presence of hepatic fibrosis should also be evaluated among the patients suffering HCV infection¹⁷.

Materials and Methods

A retrospective study has been conducted in Qatar University to examine the effects of iron depletion on chronic hepatitis C. The results were obtained over a five years period from January 2010 till March 2015. 195 patients with HCV were recruited in this study. The subjects were diagnosed with HCV through chemiluminescent microparticle immunoassay (CMIA), which has been verified by real-time PCR for RNA of the virus. Multiple results have been gathered for each patient, which reflected several follow-ups during the treatment course. All the incomplete results, which were not complied with the required tests, were excluded from the study.

Several laboratory analysis have been conducted through the blood samples including serum iron, ferritin, transferrin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and g-glutamyltransferase (GGT). The parameters were conducted in Hamad General Hospital's biochemistry laboratory. The ethical approval was taken from Medical Research Centre of Hamad Medical Corporation (HMC). The data has been analyzed using SPSS version 23.0. One-way ANOVA test has been applied to check the normality; whereas, p-value and correlation coefficient have been evaluated through paired t-test.

Results and Discussion

The patients, recruited in the study, were infected with chronic viral disease. The hepatic enzymes represented significant correlation with hepatitis infection; whereas, no significant correlation was observed between the liver enzymes (AST, ALT, GGT) and ferritin. Among 195 recruited patients, the prevalence rate of male patients was 73% and female patients was 27% (Figure 1).

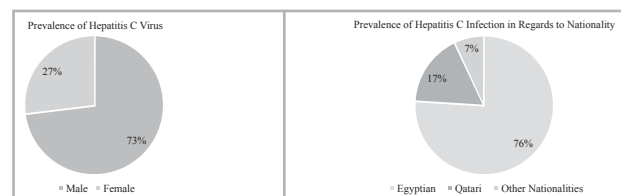


Figure-1: Gender-based prevalence of Hepatitis C Virus among 195 patients and Prevalence of HCV infection in regards to nationality among 195 patients.

(Source: Self-Generated in Microsoft Excel as per Data).

The highest rate of prevalence; i.e. 76% incidence rate, was observed among Egyptians; whereas, the prevalence rate of 17% was observed among Qatar nationals. The remaining 7% was distributed among Tunisian, Sudanese, Indian, Syrian, Somalian, Bangladeshi, Bahraini, and Canadian individuals (Figure 1).

A slight increase in ALT level was observed among patients, who received treatment for HCV infection. The ALT levels were increased to 57.00 $\mu\text{mol/L}$ (positive PCR) from 55.82 U/L (negative PCR) (Figure 2). The normal range for ALT level is 6-56 U/L. Considering the ALT levels, about 37.62% of the patients had increased level of ALT, and 62.37% of the patients with positive PCR were within normal range. The ALT level for patients with negative PCR was estimated to be 48.04%.

The hepatocytes are considered as the primary site for storing iron. The gradual hepatic iron deposition, cirrhosis, and development of hepatic fibrosis characterized the acquired defect, which lead to the excessive uptake of iron. A study stated that iron overload is the major factor for complicating chronic viral hepatitis leading to various hepatic disorders of multifactorial origin¹⁸. According to the study, no significant correlation was observed between ALT level and HCV ($r=0.40$, $P=0.695$)²³. Moreover, there

is no significant association between ALT levels and development of HCV, even when the serum levels of ALT are increased. Another study conducted by Young¹⁹ stated weak association between serum ALT levels and HCV.

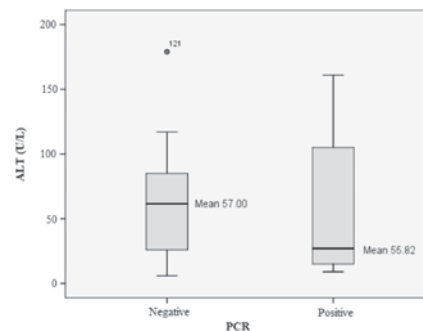


Figure-2: Effect of HCV on ALT in negative and positive PCR patients.

(Source: Self-Generated in SPSS as per Data).

Approximately 20-30% of the patients suffering from chronic HCV infection were diagnosed with normal ALT levels; and mild histological damage was seen among such patients. A study conducted by Sanai et al.²⁰ demonstrated ALT as a poor indicative marker for the diagnosis of inflammation and fibrosis among chronic HCV patients. An increase in ALT levels up to 27% of cases was demonstrated among the patients with normal ALT, when the patients were monitored for 5 years²¹.

The results of AST levels for negative and positive PCR patients were 53.25 U/L and 48.93 U/L respectively (Figure 3). Both the values for negative and positive PCR were increased as compared to the normal value; i.e. 5-34 U/L. The patients with negative or positive PCR were observed to have increased levels of AST. The positive PCR results for 38.61% of the patients were abnormal; whereas, approximately 61.39% of the patients had positive PCR. The normal levels of AST were observed among 31.68% of the patients with negative PCR and abnormal results were observed among 68.32% of the patients with negative PCR.

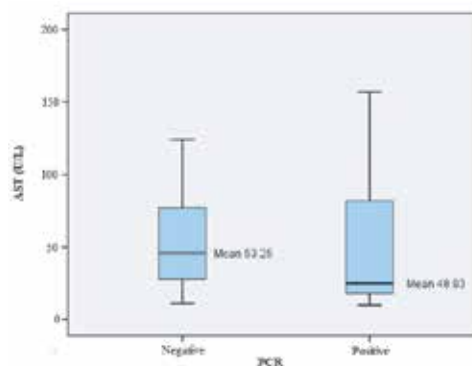


Figure-3: Effect of HCV on AST (U/L) in negative and positive PCR patients.

(Source: Self-Generated in SPSS as per Data).

The mean value of GGT for positive and negative HCV was 61.15 U/L and 62.95 U/L respectively; whereas, its reference range is between 9-64 U/L (Figure 4).

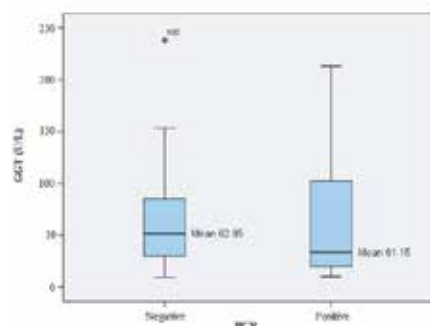


Figure-4: Effect of HCV on GGT (U/L) in negative and positive PCR.

(Source: Self-Generated in SPSS as per Data).

A slight increase for mean GGT levels was observed in HCV negative patients, as compared to the HCV positive patients. 91.55% of the patients depicted normal levels of GGT before receiving any treatment. However, the normal GGT levels were decreased to 73.24% after the treatment initiation.

Table I shows the correlation of liver enzymes (ALT, AST, GGT) and iron markers with HCV load after initiation of treatment.

Table-I: Summary of p-values and r-values for liver enzymes after receiving treatment.

Parameters	PCR	N	Mean	SD	r- value	p-value
ALT (U/L)	(Initially/ Positive PCR)	102	55.82	50.94	0.362	0.812
	(Follow up/ Negative PCR)	102	57.00	33.32		
AST (U/L)	(Initially/ Positive PCR)	101	48.93	44.90	0.444	0.294
	(Follow up / Negative PCR)	101	53.25	28.40		
GGT (U/L)	(Initially/ Positive PCR)	94	61.15	51.30	0.543	0.723
	(Follow up / Negative PCR)	94	62.95	51.06		

Similarly, serum AST levels are not useful indicator to diagnose the degree of liver inflammation and fibrosis among the patients, suffering from chronic HCV infection. However, it may serve as a monitoring response for the patients, who received alpha-interferon treatment. However, a study revealed that the GGT levels can be considered for the prediction of advanced histological liver damage among the patients, suffering from chronic HCV infection^{22,23}.

Conclusion

The prevalence of HCV is higher among males as compared to the females. None of the liver function tests including the test for ALT, AST, and GGT found significant association with HCV viral load. The results

concluded that a significant proportion of patients with persistent normal ALT levels represented various histological signs of fibrosis. There might be many reasons for representing minor changes in the functioning of liver enzymes; even after receiving treatment. For instance, body requires time to recover from any infection; therefore, the liver enzyme are not able to depict the dramatic changes. Although, the degree of fibrosis developing in liver might be mild, but sometimes marked changes are observed in the hepatic cells. A few cases may even reported about the presence of cirrhosis. The study has stated slight correlation between ALT, AST, and GGT with HCV viral load, but no significant correlation has been observed for p-values of ALT, AST, and GGT.

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