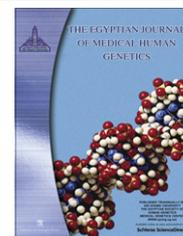




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ORIGINAL ARTICLE

# Correlation between alanine aminotransferase level, HCV-RNA titer and fibrosis stage in chronic HCV genotype 4 infection

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## KEYWORDS

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**Abstract** The relationship of serum alanine aminotransferase (ALT) level and viral replication to liver damage in chronic hepatitis C virus (HCV) patients remains unclear.

The aim of the present study was to determine whether the stage of fibrosis correlates with HCV-RNA titer and/or serum ALT level in patients with chronic hepatitis C (genotype 4) infection.

Clinical and biochemical characteristics were collected from 138 patients with chronic HCV genotype 4 infection. Quantitative HCV-RNA level measurement, HCV genotyping, and abdominal ultrasonography were investigated in all patients.

Liver biopsy was done for 80 patients and the remaining 58 patients were examined using Fibroscan.

Highly significant higher percentage of cases with high level of HCV viremia was found among patients with fibrosis stage 3 as compared to other stages of fibrosis. In contrast, grades of activity were independent of serum HCV-RNA titer.

Patients with stages 1 and 4 hepatic fibrosis had significantly higher levels of ALT than patients with other stages of fibrosis. In contrast, an insignificant correlation was found between ALT level and grade of necroinflammation.

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In conclusion neither ALT level nor HCV viremia can reflect the histological liver change accurately. As a result, liver biopsy or other noninvasive procedures that measure liver stiffness (i.e., Fibroscan) remain essential for accurate staging of liver fibrosis in patients with genotype 4 chronic HCV infection.

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## 1. Introduction

Patients infected with hepatitis C virus (HCV) have different clinical outcomes, ranging from acute resolving hepatitis to chronic liver disease including liver cirrhosis or hepatocellular carcinoma [1].

Egypt has the highest prevalence of HCV worldwide (15%) [2] and the highest prevalence of HCV-4, which are responsible for almost 90% of HCV infections [3].

Because the relationship of serum ALT (alanine aminotransferase) level to liver damage or viral replication in chronic HCV carriers remains unclear, liver biopsy is essential to evaluate the degree of liver damage in these subjects. However, it is practically difficult to perform liver biopsy in all asymptomatic healthy carriers with normal ALT level [4,5] and therefore, a noninvasive approach is required to make an accurate diagnosis.

Transient elastography (TE) using FibroScan is a new, non-invasive, and reproducible technique that evaluates tissue stiffness. Liver stiffness measurement (LSM) has been demonstrated to be a reliable tool for assessing the hepatic fibrosis, mainly in patients with chronic hepatitis. Because TE can be performed rapidly, painlessly, and has high patient acceptance, it is likely to become a common way of assessing fibrosis in routine practice [6].

Studies on the correlations between HCV-RNA titers or HCV genotype, and the severity of liver damage have shown conflicting results [7–11]. In addition, whether HCV-RNA titer is a better predictor of underlying liver injury than serum ALT is not known.

The aim of the present study was to determine whether the stage of fibrosis correlates with HCV-RNA titer and/or serum ALT level in patients with chronic hepatitis C (genotype 4) infection.

## 2. Methods

This study was conducted in the Gastroenterology and Hepatology Unit, Department of Internal Medicine, Ain Shams University Hospital; in the period between May 2009 and August 2011. A total of 138 patients with chronic HCV (genotype 4) infection were enrolled in the study.

All patients were subjected to the following.

History taking, thorough clinical examination, calculation of Body Mass Index (BMI), laboratory investigations including: fasting and post prandial blood glucose level, liver function tests,  $\alpha$  fetoprotein, prothrombin time and International Neutralization Ratio (INR), renal function tests, complete blood count, serum ceruloplasmin, ANA (Antinuclear Antibody), HIV and hepatitis C virus antibodies using ELISA technique, HBsAg, HBsAb, HBcAb, HBeAg and HBeAb.

HCV RNA (PCR) in serum, both quantitative and qualitative:

- Automated PCR (using Cobas Amplicor HCVv2.0, Roche molecular system) was used for qualitative HCV-RNA detection.
- Manual PCR (using Cobas Amplicor HCVv2.0, Roche molecular system) was used for quantifying HCV RNA.
- Interpretation of viremia: <200.000 IU/ml: low viremia, 200.000–2000.000 IU/ml: moderate viremia, >2000.000 IU/ml: high viremia.

HCV genotyping using INNO-LIPA HCVII test (INNO-LiPA HCV II, Innogenetics, Ghent, Belgium). This test is based on the reverse hybridization of 5' untranslated region PCR amplification product [12].

Abdominal ultrasonography (Aloka SSD620, Japan) using 3.5 MHz convex probe.

Fibroscan was done for 58 patients. Fibroscan is designed for noninvasive assessment of liver fibrosis and is based on elastometry (or one dimensional transient elastography), harder the tissue, faster the shear wave propagates [13].

The tip of the transducer probe was placed on the skin, between the ribs, at the level of the right lobe. Once the target area has been located, acquisition was triggered by pressing a button. The measurement depth is between 25 and 65 mm below the skin surface. In this study, at least five successful measurements were made in each patient. The median value of all successful acquisitions in each patient was recorded as the liver elastic modulus.

The operator who performed the liver stiffness measurement was unaware of neither the clinical nor the laboratory data of the patients. Results are expressed in kilopascals (kPa).

The values used to correlate elastometry with METAVIR scoring system are as follows: 0–2.9 kPa for F0, 3–5.9 kPa for F1, 6–8.9 kPa for F2, 9–16.9 kPa for F3 and 17–75 kPa for F4 [14].

Liver biopsy was done for 80 patients, ultrasonographically guided. METAVIR scoring system was used to assess the necroinflammatory grades of activity and stages of fibrosis.

METAVIR scoring system is one of the few validated scoring systems. This system assesses histological lesions in chronic hepatitis C using two separate scores, one for the necroinflammatory grade and another for the stage of fibrosis. These scores are defined as follows:

Stages of fibrosis (F): F0: no fibrosis; F1: portal fibrosis without septa; F2: portal fibrosis with rare septa, F3: numerous septa without cirrhosis; F4: cirrhosis.

Grades of activity (A): A0: no necroinflammatory activity; A1: minimal activity, A2: moderate activity, A3: severe activity.

The intra- and inter-observer variations of this METAVIR scoring system are lower than those of the widely used Knodell scoring system. For METAVIR fibrosis stage there is an almost perfect concordance [14].

Exclusion criteria:

1. Patients with decompensated cirrhosis.
2. Patients with hepatocellular carcinoma.
3. Patients with diabetes mellitus.
4. Patients with HBV co-infection.
5. Prior or current antiviral therapies.
6. Current or past history of regular or excessive alcohol consumption.
7. Other liver diseases such as alcoholic liver disease, non-alcoholic fatty liver disease (NAFLD), drug-induced hepatitis, other viral hepatitis, hereditary hemochromatosis, Wilson's disease, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis and  $\alpha 1$  antitrypsin deficiency.
8. Current intravenous drug abuse.
9. HIV infection.
10. Obese patients ( $BMI \geq 30$ ).
11. Patients refusing to be entitled in the study.

This study was approved by the local ethical committee of Ain Shams University Hospitals and a written consent was obtained from each individual before participation in the study.

**Table 1** Correlation between stages of fibrosis and other studied parameters.

Fibrosis score	Mean $\pm$ SD	F	P
<i>Age (years)</i>			
FS0, N = 10	39.3 $\pm$ 9.1	3.2	0.01
FS1, N = 29	41.3 $\pm$ 9.2		
FS2, N = 56	37.3 $\pm$ 8.2		
FS3, N = 29	43.6 $\pm$ 9.1		
FS4, N = 14	44.0 $\pm$ 10.6		
<i>Body mass index (kg/m<sup>2</sup>)</i>			
FS0, N = 10	23.5 $\pm$ 1.3	4.2	0.003
FS1, N = 29	28.6 $\pm$ 4.9		
FS2, N = 56	26.3 $\pm$ 3.6		
FS3, N = 29	28.0 $\pm$ 4.1		
FS4, N = 14	28.3 $\pm$ 3.5		
<i>ALT (IU/l)</i>			
FS 0, N = 10	39.0 $\pm$ 32.3	4.0	0.004
FS1, N = 29	82.6 $\pm$ 63.5		
FS2, N = 56	50.9 $\pm$ 24.1		
FS3, N = 29	62.0 $\pm$ 38.0		
FS4, N = 14	74.3 $\pm$ 41.9		
<i>Albumin (g/dl)</i>			
FS0, N = 10	4.2 $\pm$ 0.2	3.1	0.01
FS1, N = 29	4.0 $\pm$ 0.3		
FS2, N = 56	4.0 $\pm$ 0.2		
FS3, N = 29	3.9 $\pm$ 0.3		
FS4, N = 14	3.9 $\pm$ 0.3		
<i>Direct bilirubin (mg/dl)</i>			
FS0, N = 10	0.18 $\pm$ 0.2	1.4	0.2
FS1, N = 29	0.20 $\pm$ 0.1		
FS2, N = 56	0.23 $\pm$ 0.2		
FS3, N = 29	0.29 $\pm$ 0.2		
FS4, N = 14	0.26 $\pm$ 0.2		

### 2.1. Statistical methods

The data were collected, coded and entered to a personal computer (P.C.) IBM compatible 2.6 GHz. The data was analyzed with the program Statistical Package for Social Science (SPSS) under Windows version 11.0.1. The following tests were used: calculation of the mean value, Student's *t*-test, one way analysis of variance (ANOVA), and Chi-square test. The probability of error (*P*) was expressed as following:

*P*-value > 0.05: non-significant (NS).

*P*-value  $\leq$  0.05: significant (S).

*P*-value < 0.01: highly significant (HS).

## 3. Results

A total of 138 patients with chronic HCV (genotype 4) infection were enrolled in the study. Most patients were men (78.3%), their mean age was 40.3 years and their mean BMI was 27.2 kg/m<sup>2</sup>.

On correlating the stages of fibrosis to other studied parameters, the following was found.

Significant higher mean ALT levels were found among patients with fibrosis stages 1 and 4 as compared to other stages of fibrosis (*P* = 0.004) (Table 1).

Significant higher mean age was found among patients with fibrosis stages 3 and 4 as compared to other stages of fibrosis (*P* = 0.01) (Table 1).

A significant lower BMI was found among patients with stage 0 fibrosis as compared to other stages of fibrosis (*P* = 0.003) (Table 1).

Significant lower mean albumin levels were found among the cases with fibrosis stages 3 and 4 as compared to other stages of fibrosis (*P* = 0.01) (Table 1).

A highly significant higher percentage of cases with high level of HCV viremia was found among patients with fibrosis stage 3 as compared to other stages of fibrosis (*P* = 0.000) (Table 2).

On correlating the grades of histological activity (among the 80 patients who underwent liver biopsy) to other studied parameters, the only significant correlation was found between the grades of activity and the stages of fibrosis (*P* = 0.000) (Tables 3–5).

## 4. Discussion

While there are many studies regarding the correlation of liver damage with serum HCV-RNA titer, ALT level, and HCV genotypes, the conclusions are quite different [15–20]. The current study investigated the correlation between serum HCV-RNA titer, ALT level, and the severity of liver damage in patients with chronic HCV (genotype 4) infection.

In general, chronic hepatitis C patients with elevated ALT levels and high HCV-RNA titers in the sera are considered to have active HCV replication in the liver and to be at risk for continued liver injury. Also, the serum ALT level is recognized as a marker reflecting the degree of the histological damage and has served as a parameter for starting therapy or judging response to antiviral treatment in chronic hepatitis C

**Table 2** Correlation between stages of fibrosis and level of HCV viremia.

	Low viremia		Moderate viremia		High viremia		$\chi^2$	<i>P</i>
	No.	%	No.	%	No.	%		
FS0, <i>N</i> = 10	7	70.0	3	30.0	0		29.1	0.000
FS1, <i>N</i> = 29	10	34.5	12	41.4	7	24.1		
FS2, <i>N</i> = 56	19	33.9	32	57.1	5	8.9		
FS3, <i>N</i> = 29	10	34.5	8	27.6	11	37.9		
FS4, <i>N</i> = 14	11	78.6	3	21.4	0			

**Table 3** Correlation between grades of histological activity and other studied parameters.

Grades of activity	Mean $\pm$ SD	<i>F</i>	<i>P</i>
<i>Age (years)</i>			
Grade 1, <i>N</i> = 21	37.7 $\pm$ 9.4	1.5	0.2
Grade 2, <i>N</i> = 36	38.0 $\pm$ 8.6		
Grade 3, <i>N</i> = 20	40.1 $\pm$ 8.1		
Grade 4, <i>N</i> = 3	48.3 $\pm$ 11.1		
<i>Body mass index (kg/m<sup>2</sup>)</i>			
Grade 1, <i>N</i> = 21	25.3 $\pm$ 3.2	1.1	0.3
Grade 2, <i>N</i> = 36	26.8 $\pm$ 4.0		
Grade 3, <i>N</i> = 20	27.3 $\pm$ 3.7		
Grade 4, <i>N</i> = 3	28.0 $\pm$ 4.2		
<i>ALT (IU/l)</i>			
Grade 1, <i>N</i> = 21	43.5 $\pm$ 33.7	2.4	0.07
Grade 2, <i>N</i> = 36	59.0 $\pm$ 44.1		
Grade 3, <i>N</i> = 20	73.9 $\pm$ 33.9		
Grade 4, <i>N</i> = 3	37.3 $\pm$ 17.9		
<i>Albumin (g/dl)</i>			
Grade 1, <i>N</i> = 21	4.2 $\pm$ 0.2	2.4	0.06
Grade 2, <i>N</i> = 36	4.0 $\pm$ 0.3		
Grade 3, <i>N</i> = 20	4.0 $\pm$ 0.3		
Grade 4, <i>N</i> = 3	3.8 $\pm$ 0.2		
<i>Direct bilirubin (mg/dl)</i>			
Grade 1, <i>N</i> = 21	0.14 $\pm$ 0.1	1.2	0.2
Grade 2, <i>N</i> = 36	0.19 $\pm$ 0.2		
Grade 3, <i>N</i> = 20	0.19 $\pm$ 0.1		
Grade 4, <i>N</i> = 3	0.33 $\pm$ 0.4		

[1]. However, a number of studies showed ambivalent results in the relationships among the degree of histological damage, serum ALT level, HCV-RNA titers and HCV genotype. While Zechini and colleagues found a correlation between serum ALT level and liver damage [16], Puoti and colleagues argued such a correlation [17].

The current study revealed an insignificant correlation between ALT level and the grades of necroinflammation ( $P = 0.07$ ). Strikingly, patients with stages 1 and 4 hepatic fibrosis had significantly higher levels of ALT than patients with other stages of hepatic fibrosis ( $P = 0.004$ ).

These findings are totally discordant to the findings of Liu and colleagues [18] who found that the level of serum ALT was not markedly related to the stages of liver fibrosis but was statistically linked with the grades of liver necroinflammatory activity.

These conflicting results could be attributed to the differences in HCV genotypes and the ethnicity of the population

**Table 4** Correlation between grades of histological activity and level of HCV viremia.

	Low level viremia		Moderate viremia		High viremia		$\chi^2$	<i>P</i>
	No.	%	No.	%	No.	%		
Grade 1, <i>N</i> = 21	14	66.7	5	23.8	2	9.5	0.1	0.7
Grade 2, <i>N</i> = 36	20	55.6	10	27.8	6	16.7		
Grade 3, <i>N</i> = 20	13	65.0	0		7	35.0		
Grade 4, <i>N</i> = 3	3	100.0	0		0			

studied. Also these findings suggest that serum ALT level cannot serve as a parameter to assess liver damage in the patients with chronic hepatitis C virus infection. It is not easy to explain the reason for the poor correlation between ALT level and the severity of liver damage. In general, ALT is released by direct virus-related cytopathic activity and/or by an immune-mediated process [18]. Some studies suggested that the cellular immune response in patients of HCV infection with persistent normal ALT levels is less activated than in patients with abnormal ALT levels [20,21]. Also, Calabrese and colleagues proposed that hepatocyte apoptosis has an important role since chronic liver damage and hepatocyte cell loss by apoptosis could occur in HCV-infected patients without overt ALT level changes, explaining the progressive nature of liver disease that was presented in patients with a normal ALT level [22].

As for the relationship between serum HCV-RNA titer and liver histological damage, studies have shown different and conflicting results. Some showed no relationship [23–24], while others revealed significant correlations between serum HCV-RNA titer and liver damage [25]. The current study showed a highly significant higher levels of HCV-RNA titer among the patients with stage 3 hepatic fibrosis ( $P = 0.000$ ). In contrast, grades of activity were independent of serum HCV-RNA titer ( $P = 0.7$ ).

The mechanism of liver damage caused by HCV is not yet fully understood and could be attributed to either direct cytopathic damage by HCV or immune-mediated hepatic injury induced by HCV [18].

The results of the current study further indicate that liver damage is not caused by HCV directly, and immune-mediated liver injury may be the major cause.

Patient's age is a well known factor that is associated with the responsiveness to Pegylated interferon  $\alpha$ /ribavirin therapy in chronic HCV infection. Generally, it is believed that younger individuals (usually < 40 years of age) respond better to IFN- $\alpha$  treatment than older persons [26–27]. The obvious

**Table 5** Correlation between grades of histological activity and stages of fibrosis.

Fibrosis	Activity								$\chi^2$	P
	1		2		3		4			
	No.	%	No.	%	No.	%	No.	%		
FS0, N = 10	9	90.0	1	10.0						
FS1, N = 21	8	38.1	10	47.6	3	14.3				
FS2, N = 21	4	19.0	12	57.1	5	23.8			57.3	0.000
FS3, N = 17			11	64.7	6	35.3				
FS4, N = 11			2	18.2	6	54.4	3	27.3		

explanation is that older HCV patients are likely to have more advanced liver disease, such as fibrosis and cirrhosis (themselves predictors of poor virological responses) [28].

Cross sectional studies have indicated that the age at acquisition of HCV infection is positively associated with the rate of fibrosis progression [29]. Furthermore, the importance of considering age in a patient who is initiating therapy for chronic HCV infection has been highlighted by a recent study by Davis and coworkers [30] who developed a multicohort natural history model for predicting disease outcomes and the benefits of therapy in HCV-infected patients. Also, Asselah et al. undertook a prospective cross sectional analysis of 290 individuals with chronic hepatitis C infection. Higher levels of fibrosis were correlated with the age at infection [31]. In accordance with these reports, the current study revealed a significant correlation between age and stage of fibrosis as patients with stages 3 and 4 hepatic fibrosis had significantly higher mean age than patients with other stages of fibrosis ( $P = 0.01$ ).

Chronic hepatitis C (CHC) can be considered not only as a viral disease but also as a special type of metabolic disease [28]. Insulin resistance, obesity, and steatosis are associated with a higher risk of fibrosis progression in chronic HCV infection [32–33]. Despite excluding obese patients, the current study revealed a significant correlation between BMI and stage of fibrosis. Patients with stage 0 hepatic fibrosis had significantly lower mean BMI than patients with other stages ( $P = 0.003$ ). This result highlights the importance of metabolic factors in fibrosis progression in chronic HCV genotype 4 infection (even in non obese patients).

Regarding the relation between grades of necroinflammation activity and stages of hepatic fibrosis, the current study revealed a highly significant correlation between grades of necroinflammatory activity and stages of fibrosis ( $P = 0.00$ ,  $r = 0.663$ ). This result confirms other reports which found a significant correlation between higher levels of fibrosis and higher grades of hepatic necroinflammation [31–34]. Also, McCaughan and George suggested that progressive inflammation may underlie the observed non-linear rates of fibrosis progression in chronic HCV infected patients [34].

In Conclusion, neither serum HCV-RNA titer nor serum ALT level can reflect the histological liver change accurately. As a result, liver biopsy or other noninvasive procedures that measure liver stiffness (transient elastography “Fibroscan”) remain essential for accurate staging of liver fibrosis in patients with chronic HCV (genotype 4) infection.

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