Correlation between ALT level, HCV RNA titer and fibrosis stage in chronic HCV genotype 4 infection

Reham Al Swaff

Department of Internal medicine, Faculty of medicine, Ain Shams University, Cairo, Egypt.
Reham Al Swaff MD, MRCP (UK)
Lecturer of internal medicine, Ain Shams University, Cairo, Egypt
drrehamalswaff@yahoo.com

Abstract: Summary: Background: the relationship of serum ALT level and viral replication to liver damage in chronic 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. **Methods:** 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. **Results:** Highly significant higher percentage of cases with high level of HCV viraemia 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 stage 1and 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. **Conclusion:** neither ALT level nor HCV viraemia can reflect the histological liver change accurately. As a result, liver biopsy or other non invasive procedures that measures liver stiffness (i.e.: Fibroscan) remains essential for accurate staging of liver fibrosis in patient with genotype 4 chronic HCV infection.
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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].

Because the relationship of serum ALT (alanine aminotransferase) level to liver damage or viral replication in chronic HCV carriers remain 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 [2, 3] and therefore, noninvasive approach is required to make an accurate diagnosis.

Transient elastography (TE) using FibroScan is a new, noninvasive, and reproducible technique that evaluates tissue stiffness. Liver stiffness measurement (LSM) has been demonstrated to be a reliable tool for assessing 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 [4].

Studies on the correlations between HCV RNA titers or HCV genotype, and the severity of liver damage have shown conflicting results [5-9]. 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.

Methods:

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 , laboratory investigations including: fasting and post prandial blood glucose level, liver function tests, Alpha fetoprotein ,prothrombin time and INR, renal function tests, complete blood count, 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 Ammplicor HCVv2.0, Roche molecular system) was used for qualitative HCV RNA detection.
  - Mannual PCR (using Cobas Ammplicor HCVv2.0, Roche molecular system) was used for quantifying HCV RNA.
  - Interpretation of viraemia: < 200.000 IU/ml: low Viraemia, 200.000 - 2000.000

IU/ml: moderate viraemia, >2000.000 IU/ml: High viraemia.

- HCV genotyping_using INNO-LIPA HCVII test, this test is based on reverse hybridization of 5' untranslated region PCR amplification product.
- Abdominal ultrasonography (Aloka SSD620, Japan) using 3.5 MHZ convex probe.
- **Fibroscan** was done for 58 patients. Fibroscan is designed for non invasive assessment of liver fibrosis and is based on elastometry (or one dimensional transient elastography), the harder the tissue, the faster the shear wave propagates [10].
  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 5 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 KiloPascal (KPa).
  The values used to correlate elastometry with METAVIR scoring system are the followings: < 7.1 Kpa for F0-1, 7.1-9.4 kpa for F2, 9.5-12.5 Kpa for F3 and > 12.5 Kpa for F4 [11].
- 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 histologic lesions in chronic hepatitis C using two separate scores, one for 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.
  Grade for activity (A): A0: no histologic necroinflammatory activity; A1: minimal activity, A2: moderate activity, A3: severe activity.
  The intra- and interobserver variations of this METAVIR scoring system are lower than those of the widely used Knodell scoring system. For METAVIR fibrosis stages there is an almost perfect concordance [11].
- **Exclusion Criteria:**

1. Patients with decompensated cirrhosis.
2. Patients with hepatocellular carcinoma.
3. Patients with diabetes mellitus.
4. Prior or current anti viral therapies.
5. Current or past history of regular or excessive alcohol consumption.
6. Other liver diseases as alcoholic liver disease, non alcoholic fatty liver disease (NAFLD), drug-induced hepatitis, other viral hepatitis, hereditary haemochromatosis, Wilson's disease, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis and α1 antitrypsin deficiency.
7. Current intravenous drug abuse.
8. HIV infection.
9. Obese patients.
10. Patients refusing to be entitled in the study.

- This study was approved by the local ethical committee and a written consent was obtained from each individual before participation in the study.

Statistical methods:

The data was 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 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 ≤ 0.05: significant (S).
P-value < 0.01: highly significant (HS).

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.

80 patients underwent ultrasonography guided liver biopsy; the remaining 58 patients were examined using Fibroscan.

On correlating stages of fibrosis to other studied parameters, the followings were 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).

A highly significant higher percentage of cases with high level of HCV viraemia was found among

patients with fibrosis stage 3 as compared to other stages of fibrosis (P = 0.000) (table 2).

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 cases with fibrosis stages 3 and 4 as compared to other stages of fibrosis (P = 0.01) (table 1).

On correlating the grade of activity (among the 80 patients who under went liver biopsy) to other studied parameters, the only significant correlation was found between the grade of activity and the stage of fibrosis (p = 0.000) (table 3, 4 &5).

Table (1) Correlation between stage of fibrosis and other studied parameters

Fibrosis score	Mean	SD	F	P
Age				
FS 0 N=10	39.3	9.1	3.2	0.01
FS 1 N=29	41.3	9.2		
FS2 N=56	37.3	8.2		
FS3 N=29	43.6	9.1		
FS4 N=14	44.0	10.6		
Body mass index				
FS 0 N=10	23.5	1.3	4.2	0.003
FS 1 N=29	28.6	4.9		
FS2 N=56	26.3	3.6		
FS3 N=29	28.0	4.1		
FS4 N=14	28.3	3.5		
ALT				
FS 0 N=10	39.0	32.3	4.0	0.004
FS 1 N=29	82.6	63.5		
FS2 N=56	50.9	24.1		
FS3 N=29	62.0	38.0		
FS4 N=14	74.3	41.9		
Albumin				
FS 0 N=10	4.2	0.2	3.1	0.01
FS 1 N=29	4.0	0.3		
FS2 N=56	4.0	0.2		
FS3 N=29	3.9	0.3		
FS4 N=14	3.9	0.3		
Direct bilirubin				
FS 0 N=10	0.18	0.2	1.4	0.2
FS 1 N=29	0.20	0.1		
FS2 N=56	0.23	0.2		
FS3 N=29	0.29	0.2		
FS4 N=14	0.26	0.2		

Table (2) Correlation between stage of fibrosis and level of HCV viraemia

	Low viraemia No. %	Mid viraemia No. %	High viraemia No. %	X2	P
FS 0 N=10	7 70.0	3 30.0	0		
FS1 N=29	10 34.5	12 41.4	7 24.1		
FS2 N=56	19 33.9	32 57.1	5 8.9	29.1	0.000
FS3 N=29	10 34.5	8 27.6	11 37.9		
FS4 N=14	11 78.6	3 21.4	0		

Table (3) Correlation between grade of activity and other studied parameters

Grade of activity	Mean	SD	F	P
Age				
Grade 1 N=21	37.7	9.4	1.5	0.2
Grade 2 N=36	38.0	8.6		
Grade 3 N=20	40.1	8.1		
Grade 4 N=3	48.3	11.1		
Body mass index				
Grade 1 N=21	25.3	3.2	1.1	0.3
Grade 2 N=36	26.8	4.0		
Grade 3 N=20	27.3	3.7		
Grade 4 N=3	28.0	4.2		
ALT				
Grade 1 N=21	43.5	33.7	2.4	0.07
Grade 2 N=36	59.0	44.1		
Grade 3 N=20	73.9	33.9		
Grade 4 N=3	37.3	17.9		
Albumin				
Grade 1 N=21	4.2	0.2	2.4	0.06
Grade 2 N=36	4.0	0.3		
Grade 3 N=20	4.0	0.3		
Grade 4 N=3	3.8	0.2		
Direct bilirubin				
Grade 1 N=21	0.14	0.1	1.2	0.2
Grade 2 N=36	0.19	0.2		
Grade 3 N=20	0.19	0.1		
Grade 4 N=3	0.33	0.4		

Table (4) Correlation between grade of activity and level of HCV viraemia

	Low level viraemia No. %	Mid viraemia No. %	High viraemia No. %	X2	P
Grade 1 N=21	14 66.7	5 23.8	2 9.5	0.1	0.7
Grade 2 N=36	20 55.6	10 27.8	6 16.7		
Grade 3 N=20	13 65.0	0	7 35.0		
Grade 4 N=3	3 100.0	0	0		

Table (5) correlation between grade of activity and stage of fibrosis

Activity / fibrosis	1 No. %	2 No. %	3 No. %	4 No. %	X2	P
FS 0 N=10	9 90.0	1 10.0			57.3	0.000
FS1 N=21	8 38.1	10 47.6	3 14.3			
FS2 N=21	4 19.0	12 57.1	5 23.8			
FS3 N=17		11 64.7	6 35.3			
FS4 N=11		2 18.2	6 54.4	3 27.3		

Discussion:

Ever since hepatitis C virus was discovered approximately 20 years ago, HCV infections have become the leading cause of chronic liver disease worldwide [12].

Patients infected with HCV have different clinical features and outcomes; some are undetected and

progress into chronic liver diseases slowly over several decades, while others develop into liver cirrhosis, end-stage liver diseases or hepatocellular carcinoma within a few years [13], hence the need for suitable and reliable clinical examinations to predict the severity of liver injury caused by HCV infection.

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 [14-18]. 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 [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 [15], Puoti and colleagues argued such a correlation[16].

The current study revealed an insignificant correlation between ALT level and grade of necroinflammation ($p = 0.07$). Strikingly, patients with stage 1and 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 Pei Liu and colleagues [13] who found that, level of serum ALT was not markedly related with 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 studied. Also these findings suggest that serum ALT level cannot serve as a parameter to assess liver damage in 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 [13]. 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.[19], 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 presented in patients with a normal ALT level [20].

As for the relationship between serum HCV-RNA titer and liver histological damage, studies have shown different and conflicting results. Some showed no relationship [21, 22] while others revealed significant correlations between serum HCV-RNA titer and liver damage [23]. The current study showed a highly significant higher levels of HCV RNA titer among 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 [13].

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 age is a well known factor that is associated with responsiveness to Pegylated interferon α/ribavirin therapy in chronic HCV infection. Generally, it is believed that younger individuals (usually < 40 years of age) respond better to IFN-α treatment than older persons [24, 25]. The obvious 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) [26].

Cross sectional studies have indicated that age at acquisition of HCV infection is positively associated with the rate of fibrosis progression [27].

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 [28] 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 age at infection [29].

In accordance with these reports, the current study revealed a significant correlation between age and stage of fibrosis as patients with stage 3, 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 a viral disease but also a special type of metabolic disease [26]. Insulin resistance, obesity, and steatosis are associated with a higher risk of fibrosis progression in chronic HCV infection [30, 31].

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 grade of necroinflammation activity and stage 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 [29, 32].Also, G W McCaughan and J George suggested that progressive inflammation may underlies the observed non-linear rates of fibrosis progression in chronic HCV infected patients [32].

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 non invasive procedures that measures liver stiffness (transient elastography "Fibroscan") remain essential for accurate staging of liver fibrosis in patient with chronic HCV (genotype 4) infection.

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Corresponding Author:
Reham Ezzat Al Swaff, MD, MRCP (UK), Internal Medicine Department, Faculty of Medicine, Ain Shams University ,E mail: drrehamalswaff@yahoo.com , Tel: 01005624487.
Address: 30 Manshiet Al Bakry st, Heliopolis, Cairo, Egypt

Author responsible for reprint requests:
Reham Ezzat Al Swaff, MD, MRCP (UK), Internal Medicine Department, Faculty of Medicine, Ain Shams University ,E mail: drrehamalswaff@yahoo.com , Tel: 01005624487.
Address: 30 Manshiet Al Bakry st, Heliopolis, Cairo, Egypt

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