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Correlation between Liver Function Tests and Polymerase Chain Reaction in Chronic Hepatitis C Patients

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Abstract

Background: Hepatitis C virus infection is currently the most significant public health problem globally and particularly in Egypt. The outcomes of HCV infection range from asymptomatic chronic infection, with normal or nearly normal liver functions, to severe chronic hepatitis, evolving rapidly to cirrhosis and hepatocellular carcinoma. Our objective is to asses and evaluates the relationship between liver function tests, serum HCV-RNA positivity and the severity of liver damage in chronic HCV patients.

Method: We studied 329 patients with chronic HCV, they were categorized into two groups according to the PCR results: first group were positive PCR (86 %), and second group were negative PCR (14 %). Liver transaminases, total and direct bilirubin, serum albumin, HCV RNA detection and viral load by real time PCR, and liver biopsy were done to all patients. Results: This study showed that the liver transaminases were significantly higher in HCV positive patients than in HCV negative patients (p value <0.0001). We also observed that the comparison between positive PCR group with negative PCR group revealed that, there were no statistically significant difference regarding albumin, alkaline phosphate, total bilirubin , direct bilirubin and prothrombin (p=0.35, p=0.80, p=0.26, p=0.86 and p=0.99 respectively).

Conclusions: high results of liver function tests may be indicator for the severity of liver damage in chronic HCV patients but also PCR should be done as some cases show normal results while its PCR was high. There is no relationship between liver function tests and the grade of activity or fibrosis.

Keywords HCV; PCR; AST; ALT; liver biopsy

Introduction

Hepatitis C virus (HCV) infection is a serious global health threat, despite considerable reduction of the incidence of new infection; the prevalence of HCV is predicted to remain constant in the near future [1]. HCV is a major cause of chronic liver disease, affecting 170 million (3%) of the world's population and approximately 2.7 million Americans [2], where cirrhosis can occur in 20% of these patients [3]. Egypt has the highest prevalence of HCV worldwide (15%) [4] and the highest prevalence of HCV genotype 4, which are responsible for almost 90% of HCV infections [5]. 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 [6], hence the need for suitable and reliable investigations to predict the severity of liver injury caused by HCV infection [7].

Non-invasive assessment of liver fibrosis is a challenging area. Several methods have been proposed in patients with chronic hepatitis C such as aminotransferase, Gamma glutamyl transferase, Bilirubin, Albumin / Total Protein ratio, Prothrombin time, AST /ALT ratio, AST to platelet ratio index, transient elastography, Fibrotest and Magnetic resonance elastography [8].

PCR is an expensive technique and liver biopsy is an invasive method while liver function tests is less expensive and less invasive, so our study was carried out to assess and evaluate the relationship between liver function tests, serum HCV-RNA positivity and the severity of liver damage in chronic HCV patients. If the liver function tests including serum albumin, AST and ALT have high results, they may be used as indicator for the severity of liver damage in chronic HCV patients.

Study design and Patients

The study included 329 chronic HCV patients. The participants were recruited from Gastroenterology department of Elhelal health insurance hospital, Sohag, Egypt. They were diagnosed as chronic HCV patients depending on clinical and laboratory basis. The study was approved by Scientific and Ethical committees at Sohag Faculty of Medicine, Sohag University. Written informed consents were obtained from the participants.

The participants were subjected to the following:

1- Full history taking and thorough clinical examination.

2- Abdominal ultrasonography.

3- Ultrasonographic guided liver biopsy: Liver biopsy was performed for all studied patients as a part of pre-treatment evaluation for HCV infection. The degree of hepatic fibrosis and portal

inflammation was evaluated according to the METAVIR scoring system. 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 necro-inflammatory grade and another for the stage of fibrosis. The stage of fibrosis varied from 0 to 4 (F0 = no fibrosis; F1 = portal fibrosis without septa; F2 = portal fibrosis with few septa; F3 = septal fibrosis, without cirrhosis; F4 = cirrhosis). The grade of inflammatory activity (the intensity of necro-inflammatory lesions) classified into; none, mild, moderate and severe. The activity is graded on a 4-point scale from A0 to A3 [9].

Fibrosis score

F0 = no fibrosis

F1 = portal fibrosis without septa

F2 = portal fibrosis with few septa

F3 = numerous septa without cirrhosis

F4 = cirrhosis

Activity score

A0 = no activity

A1 = mild activity

A2 = moderate activity

A3 = severe activity

4- Peripheral venous blood samples were collected under complete aseptic conditions from each patient for the following laboratory tests:

a) Liver function tests were performed on Autoanalyzer ERMA AE 600N (Biochmical, Japan). Aspartate aminotransferase (AST\GOT), alanine aminotransferase (ALT\GPT), albumin and alkaline phosphatase (ALP) were measured by kits supplied by Spectrum, Egypt. Gamma-Glutamyltransferase (GGT) was measured by photometric method according to the manufacturers' instructions (Biosystems, Spain). Total and direct bilirubin was measured by photometric method according to the manufacturers' instructions (Human-Germany).

b) Sero-diagnosis of HCV:

Detection of anti-HCV was performed by using ELISA technique according to the manufacturers' instructions (Biokit, Spain).

c) Detection of HCV RNA by real time PCR:

HCV RNA was extracted from patients' serum samples by QIAamp viral RNA Mini Kit (Qiagen, USA) according to the manufacturer's instructions. HCV-RNA was determined quantitatively by real-time PCR assay using Rotor-Gene Q instrument (Qiagen, Germany).

Statistical analysis

Data was analyzed using STATA intercooled version 9.2. Quantitative data was analyzed using student t-test to compare means of two groups. Mann-Whitney test was used for uneven distributed data. Qualitative data were compared using Chi square test. Person correlation analysis was used to calculate correlation co-efficient and p value. p value was considered significant if it was less than 0.05.

Results

The study group comprised of 329 patients with chronic HCV, 309 males and 20 females. The median age of the participants was 49 years and a range from 18-85 years. Out of 329 chronic HCV patients included in the study, 285(86%) patients were positive PCR and 44(14%) patients were negative PCR.

Table (1) presents the age of studied population and it show that most of the patients were in the age between 40-60 year (86.02%) followed by the age of <40 year (10.03%) and the smallest group were >60 year (3.95%). It also presents the residence of the studied groups and it showed that Sohag city were the highest percent of HCV (23.4%) followed by Elmaragha city (19.45%).

Characteristics	Summary statistics
Age	
Mean (SD)	48.98 (7.82)
Median (range)	49 (18-85)
Age group	
<40 year	33 (10.03%)
40-60 year	283 (86.02%)
>60 year	13 (3.95%)
Individual Ages	
Akhmeem	28 (8.51%)
Paliana	23 (6.99%)
Maragha	64 (19.45%)
Almonsha	26 (7.9%)
Grga	29 (8.81%)
Gehena	7 (2.13%)
Daresalam	31 (9.42%)
Sakolta	6 (1.55%)
Sohag	77 (23.4%)
Tema	12 (3.65%)
Tahta	26 (7.9%)

Table 1: The age and residence of the studied population

Liver functions of study population

Table (2) presents the liver functions of studied population and it showed that:

Albumin was normal in 36.17% but decreased in 32.83% and increased in 31% of patients.

Alkaline phosphatase was normal in 89.67% of the patients and increased in 10.33% of them.

AST 22.49% of the patients were with normal results but 52.28% of them had results up to the double of the normal and 25.23% of them had results more than the double of the normal (>24 -100). Figure (1)

show that most of the patients 52.28% had results up to the double of the normal of AST.

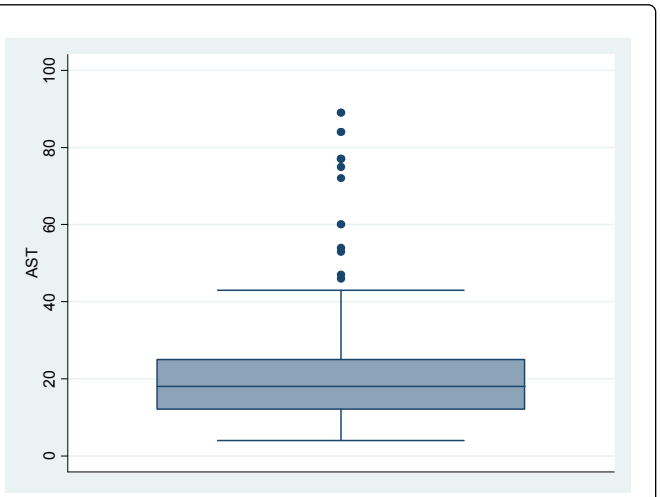

Figure 1: 52.28% of the patients had results up to the double of the normal of AST.

ALT 23.40 % of the patients were with normal results but 52.58% of them had results up to the double of the normal and 24.01% of them had results more than the double of the normal (>24 -100). Figure (2) show that most of the patients 52.58% had results up to the double of the normal results of ALT.

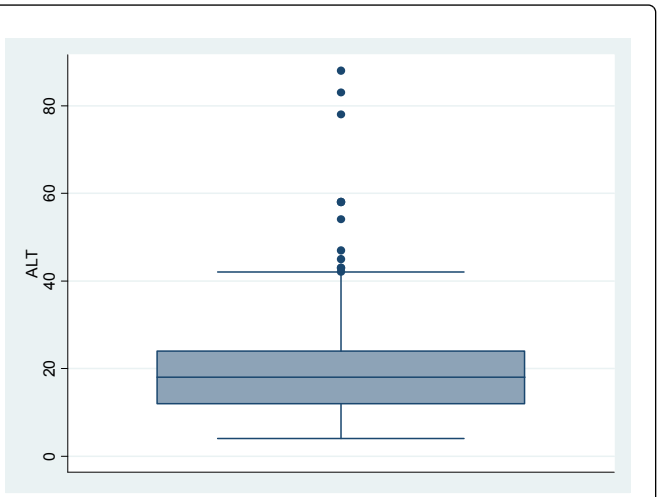

Figure 2: 52.58% of the patients had results up to the double of the normal of ALT

GGT 69.6 % of the patients were with normal results but 22.49 % of them had results up to the double of the normal and 7.9 % of them had results more than double of the normal result (>100).

Total bilirubin 94.22% of the patients were with normal results.

Prothrombin concentration in 95.44% of the patients was with normal.

Characteristics	Summary statistics
Albumin	
Mean (SD)	4.22 (0.68)
Median (range)	4.1 (2.3-6.2)
Albumin	
<3.8	108 (32.83%)
3.8-4.5	119(36.17%)
>4.5	102 (31.00%)
Alkaline phosphatase	
Mean (SD)	186.89 (63.67)
Median (range)	179 (12-531)
Alkaline phosphatase	
<=258	295 (89.67%)
>258	34 (10.33%)
AST	
Mean (SD)	20.17 (13.89)
Median (range)	18 (4-89)
AST	
<12	74 (22.49%)
24-Dec	172 (52.28%)
>24 -100	83 (25.23%)
ALT	
Mean (SD)	19.28 (11.45)
Median (range)	18 (4-88)
ALT	
<12	77 (23.40%)
24-Dec	173 (52.58%)
>24 -100	79 (24.01%)
GGT	
Mean (SD)	46.09 (38.56)
Median (range)	38 (2.3-414)
GGT	
≤52	229 (69.6%)
>52-100	74 (22.49%)
>100	26 (7.9%)
Total bilirubin	
Mean (SD)	0.69 (0.29)
Median (range)	0.66 (0.14-2.5)
Total bilirubin	

<=1	310 (94.22%)
>1	19 (5.78%)
Prothrombin	
Mean (SD)	86.17 (12.79)
Median (range)	87 (18-182)
Prothrombin	
<70	12 (3.65%)
70-100	314 (95.44%)
>100	3 (0.91%)

Table 2: Presents the liver functions of studied population

Comparison between Positive and Negative PCR patients as regard age

Table (3) show no significant statistical difference in age between positive and negative PCR patients and it showed that the patients in the age group between 40-60 year 86.21 % of them were positive PCR and13.87%of them were negative PCR and patients in the age group <40 year 90.90 % of them were positive PCR and 9.09%of them were negative PCR and patients in the age group >60 years 84.61 %of them were positive PCR and 15.38% of them were negative PCR. Figure (3) shows comparison between positive and negative PCR persons as regard age. Figure (4) shows that there is no statistically significant difference regarding age (r=0.09-p=0.15).

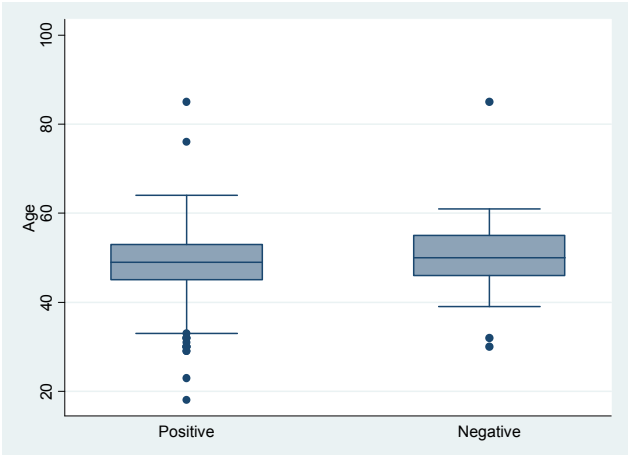

Figure 3: Comparison between positive and negative PCR persons as regard age

	Positive PCR (285)	Negative PCR (44)	p value
Age			
Mean (SD)	48.75 (7.68)	50.43 (8.65)	0.19
Median (range)	49 (18-85)	50 (30-85)	NS
Age group			
<40 year	30 (90.90%)	3 (9.09%)	0.74
40-60 year	244 (86.21%)	39 (13.87%)	NS
>60 year	11 (84.61%)	2 (15.38%)	

Table 3: Show no significant statistical difference in age between positive and negative PCR patients

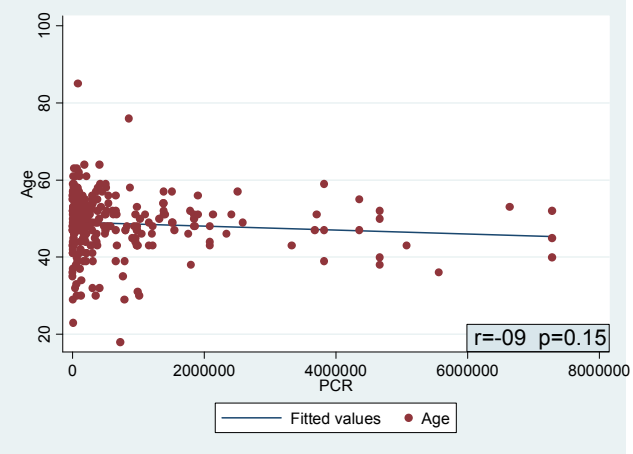

Figure 4: Show that there is no statistically significant difference regarding age (r=-0.9, p=0.15).

Comparison between Positive and Negative PCR patients as regard Liver functions

Table (4) presents comparison between positive and negative PCR patients as regard liver functions and it revealed that, there were no statistically significant difference regarding Albumin, Alkaline phosphatase, total bilirubin , direct bilirubin (p=0.35, p=0.8, p=0.26, p=0.86 respectively) and it also showed that:

	Positive PCR (285)	Negative PCR (44)	p value
Albumin			
Mean (SD)	4.22 (0.66)	4.32 (0.80)	0.35
Median (range)	4.1 (2.3-6.2)	4.15 (2.6-6.2)	
Albumin			
<3.8	92 (32.28)	16 (36.36)	0.41
3.8-4.5	107 (37.54)	12 (27.27)	
>4.5	86 (30.18)	16 (36.36)	
Alkaline phosphatase			
Mean (SD)	186.55 (62.58)	189.14 (71.03)	0.8
Median (range)	180 (12-531)	178 (22-400)	
Alkaline phosphatase			
<=258	257 (90.18)	38 (86.36)	0.44

>258	28 (9.82)	6 (13.64)	
AST			
Mean (SD)	21.51 (14.38)	11.47 (4.10)	
Median (range)	19 (4-89)	11 (6-21)	<0.0001
AST			
12-Feb	50 (17.54)	24 (54.55)	
>12 -24	152 (53.33)	20 (45.45)	<0.0001
>24-100	83 (29.12)	0 (0.00)	
ALT			
Mean (SD)	20.30 (11.76)	12.68 (5.92)	
Median (range)	18 (4-88)	12 (4-25)	<0.0001
ALT			
12-Feb	57 (20)	20 (45.45)	
>12 -24	150 (52.63)	23 (52.27)	<0.0001
>24-100	78 (27.37)	1 (2.27)	
GGT			
Mean (SD)	47.58 (39.83)	36.48 (27.48)	
Median (range)	39 (2.3-414)	28 (3.2-129)	0.03
GGT			
≤52	194 (68.07)	35 (79.54)	
>52-100	67 (23.51)	7 (15.91)	0.29
>100	24 (8.42)	2 (4.55)	
Total bilirubin			
Mean (SD)	0.69 (0.27)	0.71 (0.43)	
Median (range)	0.7 (0.14-2.5)	0.6 (0.17-2.5)	0.26
Total bilirubin			
<=1	270 (94.74)	40 (90.91)	0.31
>1	15 (5.26)	4 (9.09)	
Direct bilirubin			
Mean (SD)	0.22 (0.13)	0.26 (0.25)	
Median (range)	0.2 (0.1 - 1.7)	0.19 (0.1-1.7)	0.86
Prothrombin			
Mean (SD)	86.17 (13.43)	86.18 (7.52)	0.99
Median (range)	87 (18-182)	85 (72-100)	
Prothrombin			
<70	12 (4.21)	0 (0.00)	
70-100	270 (94.74)	44 (100.00)	0.3
>100	3 (1.05)	0 (0.00)	

Table 4: Presents comparison between Positive and Negative PCR patients as regard Liver functions

Albumin 37.54% of positive PCR patients were with normal results and 27.27 % of negative PCR patients were with normal results.

Alkaline phosphatase 90.18% of positive PCR patients were with normal results and 86.36 % of negative PCR patients were with normal results.

Total bilirubin 94.74% of positive PCR patients were with normal results and 90.91 % of negative PCR patients were with normal results.

On the other hand, there was statistically significant difference in AST, ALT (p<0.0001) and GGT (p=0.03). As regarding AST 17.54 % of positive PCR patients were with normal results and 53.33 % of them had results up to the double of the normal and 29.12 % of them had results more than the double of the normal (>24 -100), but for the negative PCR patients 54.55% of them were with normal results and 45.45% of them had results up to the double of the normal and none of them had results more than the double of the normal (>24 -100). Figure (5) show that AST 53.33% of positive PCR patients had results up to the double of the normal but for the negative PCR patients 54.55% of them were with normal results.

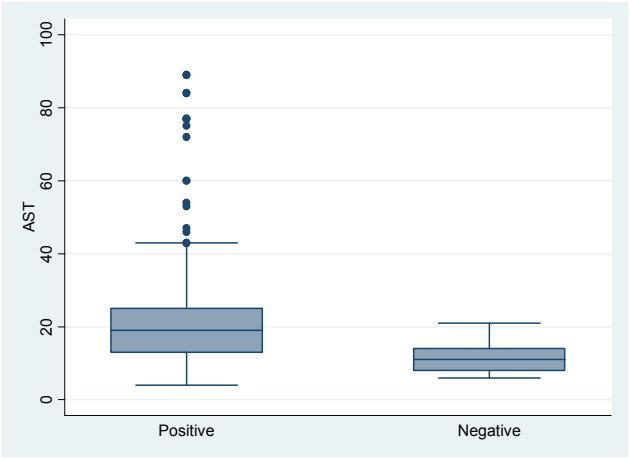

Figure (5): Show that about AST 53.33% of positive PCR patients had results up to the double of the normal but for the negative PCR patients 54.55% of them were with normal results.

Figure (6) show that there is statistically significant difference regarding AST and PCR (r=0.12-p=0.051). For ALT 20% of positive PCR patients were with normal results and 52.63 % of them had results up to the double of the normal and 27.37 % of them had results more than the double of the normal (24 -100), but for the negative PCR patients 45.45% of them were with normal results and 52.27% of them had results up to the double of the normal and 2.27% of them had results more than the double of the normal (24 -100).

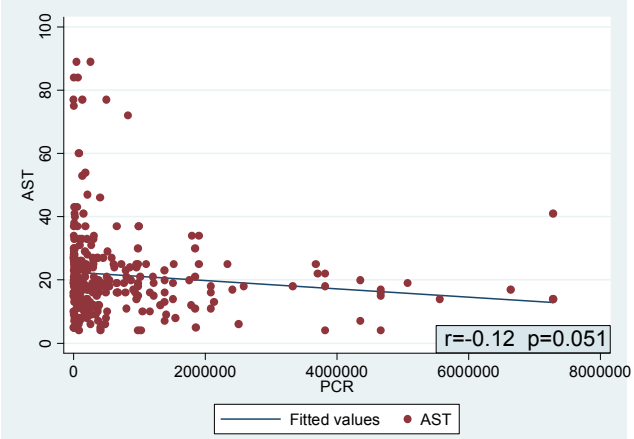

Figure 6: Show that there is statistically significant difference regarding AST and PCR (r=-0.12, p=0.051).

Figure (7) shows that 52.63 % of positive PCR patients had ALT results up to the double of the normal, but for the negative PCR patients 45.45% of them were within normal.

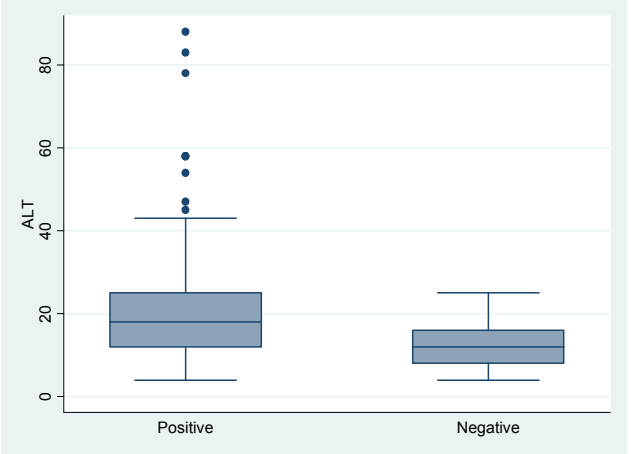

Figure 7: For ALT 52.63 % of positive PCR patients had results up to the double of the normal but for the negative PCR patients 45.45% of them were within normal.

Figure (8) show that there is statistically significant difference regarding ALT and PCR (r=0.14-p=0.02). Regarding GGT 68.07 % of positive PCR patients were with normal results and 23.51 % of them had results up to the double of the normal and 8.42 % of them had results more than the double of the normal (>100), but for the negative PCR patients 79.54% of them were with normal results and 15.91% of them had results up to the double of the normal and 4.55% of them had results more than the double of the (>100).

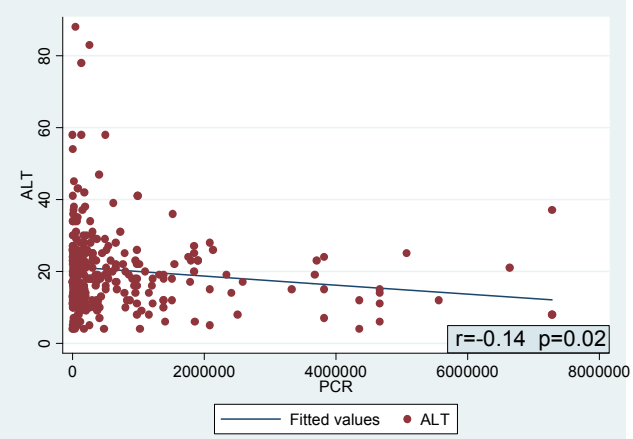

Figure 8: Show that there is statistically significant difference regarding ALT and PCR (r=-0.14, p=0.02).

For total bilirubin 94.74% of positive PCR patients were with normal results and 90.91 % of negative PCR patients had also normal results.

Prothrombin concentration 94.74 % of positive PCR patients were with normal results and 100% of negative PCR patients were with normal results.

Correlation between PCR with activity and fibrosis

The range of PCR of patients is 459-7282883. A1F1 and A2F2 had the highest percent 29.68%. Table (5) presents correlation between PCR with activity and fibrosis in liver biopsy of patients.

Variable	Number (%)
PCR	
Mean (SD)	716139.2 (1269488)
Median (range)	200587 (459-7282883)
Liver biopsy	
A0F1	4 (1.41)
A1F1	84 (29.68)
A1F2	9 (3.18)
A2 F1	2 (0.71)
A2 F2	2 (0.71)
A2F0	1 (0.35)
A2F1	48 (16.96)
A2F2	84 (29.68)
A2F3	29 (10.25)
A2F4	5 (1.77)
A3F1	2 (0.71)

A3F2	7 (2.47)
A3F3	2 (0.71)
A3F4	2 (0.71)
A4F3	2 (0.71)

Table 5: Correlation between PCR with activity and fibrosis

Table (6) presents that the correlation between PCR with activity and fibrosis revealed that there were no statistically significant difference regarding activity and fibrosis (p=0.37, p=0.22 respectively).

	Correlation co-efficient	p value
Activity	0.05	0.37
Fibrosis	0.07	0.22

Table 6: Correlation between PCR with activity and fibrosis

Correlation between AST, ALT and GGT with activity and fibrosis

Our study showed that there is no statistically significant difference (r=0.002, r=0.02, p=0.96, p=0.78 respectively). Table (7) presents correlation between AST with activity and fibrosis.

	Correlation co-efficient	p value
Activity	0.002	0.96
Fibrosis	0.02	0.78

Table 7: Correlation between AST with activity and fibrosis

Figure (9) show that there is no statistically significant difference regarding AST with activity (r=0.002, p=0.96).

Figure (10) show that there is no statistically significant difference regarding AST with fibrosis (r=0.02, p=0.78).

Our study showed that there is no statistically significant difference between ALT with activity and fibrosis. Table (8) presents correlation between ALT with activity and fibrosis (r=0.001, r=0.03, p=0.99, p=0.67).

	Correlation co-efficient	p value
Activity	-0.001	0.99
Fibrosis	0.03	0.67

Table 8: Correlation between ALT with activity and fibrosis

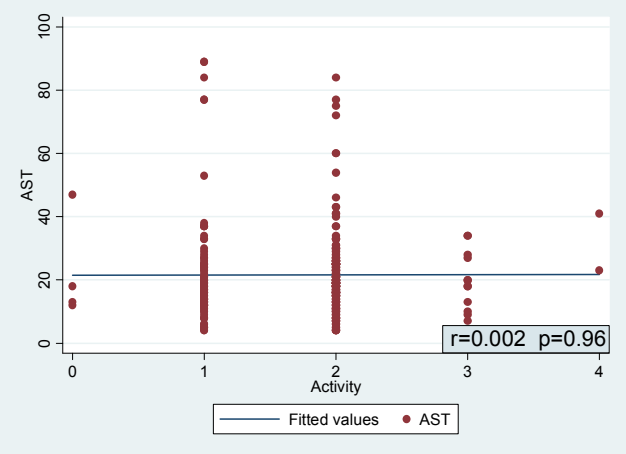

Figure 9: Show that there is no statistically significant difference regarding AST with activity (r=0.002, p=0.96).

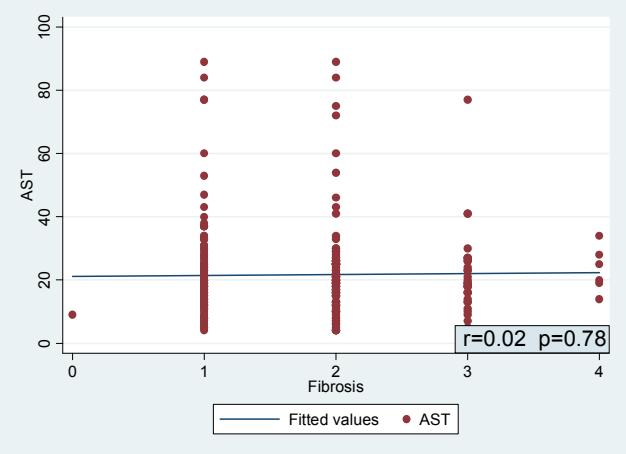

Figure 10: Show that there is no statistically significant difference regarding AST with fibrosis (r=0.02, p=0.78).

Figure (11) show that there is no statistically significant difference regarding ALT with activity (r=0.001, p=0.99).

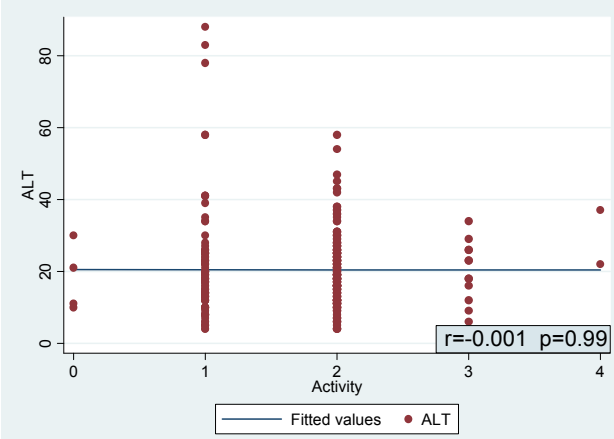

Figure 11: Show that there is no statistically significant difference regarding ALT with activity (r=-0.001, p=0.99).

Figure (12) show that there is no statistically significant difference regarding ALT with fibrosis (r=0.03, p=0.67).

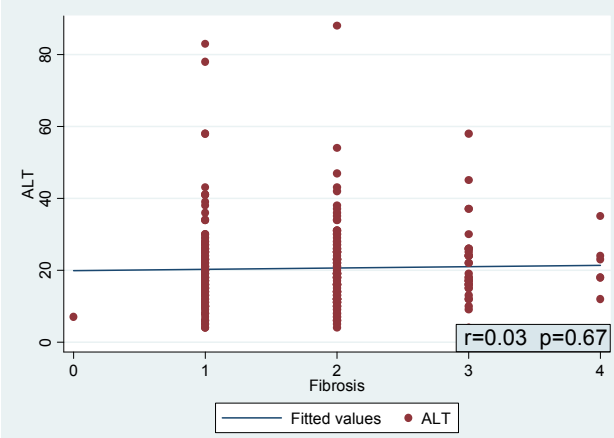

Figure 12: Show that there is no statistically significant difference regarding ALT with fibrosis (r=0.03-p=0.67).

Our study showed that there is no statistically significant difference between GGT with activity and fibrosis. Table (9) presents correlation between GGT with activity and fibrosis (r=0.01, r=0.007, p=0.83, p=0.91).

	Correlation co-efficient	p value
Activity	0.01	0.83
Fibrosis	0.007	0.91

Table 9: Correlation between GGT with activity and fibrosis

Figure (13) show that there is no statistically significant difference regarding GGT with activity (r=0.01, p=0.83).

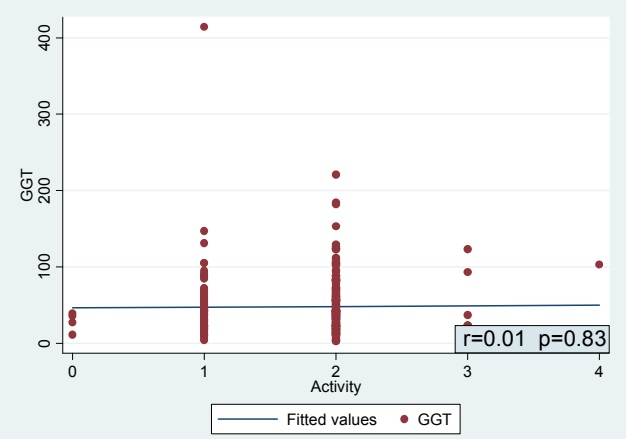

Figure 13: Show that there is no statistically significant difference regarding GGT with activity (r=0.01-p=0.83).

Figure (14) show that there is no statistically significant difference regarding GGT with fibrosis (r=0.007, p=0.91).

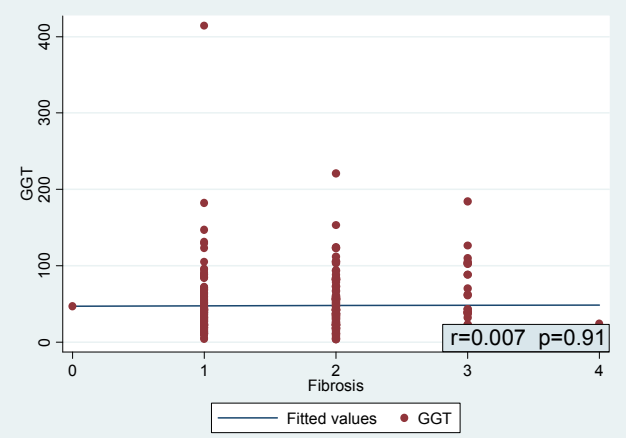

Figure 14: Show that there is no statistically significant difference regarding GGT with fibrosis (r=0.007, p=0.91).

Discussion

Hepatitis C virus (HCV) is a blood borne pathogen that is endemic in most parts of the world, with an estimated overall prevalence of nearly 3% [2]. Approximately 80% of patients with hepatitis C virus develop chronic infection, and progression to cirrhosis occurs in nearly 20% of these subjects [3]. 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 [6]. In most individuals, liver disease progresses slowly over several decades, but the rate of progression is highly variable. Ever since hepatitis C virus was discovered approximately 20 years ago, HCV infections have become the leading cause of chronic liver disease worldwide [10-12]. Egypt has the highest

prevalence of HCV worldwide (15%) [4] and the highest prevalence of HCV genotype 4, which are responsible for almost 90% of HCV infections [5]. Studies assessing the relationship between serum viral titers and the severity of biochemical and histological abnormalities have produced conflicting results. Some found no correlation between HCV viral loads, and serum ALT values and the extent of histological damage [13- 17], and others found significant correlation between HCV RNA titers and both serum ALT and degree of hepatic inflammation [18, 19].

PCR is an expensive technique and liver biopsy is an invasive method while liver function tests is less expensive and less invasive, so our study was carried out to assess and evaluate the relationship between liver function tests, serum HCV-RNA positivity and the severity of liver damage in chronic HCV patients.

Our patients were categorized into two groups according to the PCR results: first group were positive PCR 285/329 patients (86%), and second group were negative PCR 44/329 patients (14%). We observed that our patient's data showed no significant statistical difference in age between positive and negative PCR patients (p=0.19) and most of the patients were in the age group between 40-60 year (86.02%). It is widely believed that the parenteral anti-schistosomiasis therapy (PAT) campaigns to control schistosomiasis are the major drivers of the HCV epidemic in Egypt [20]. During the early twentieth century, schistosomiasis was highly prevalent in Egypt, especially in rural areas [21]. From the 1950s to the early 1980s, the Egyptian Ministry of Health led large-scale campaigns to control the disease [21]. Millions of people were treated with intravenous injections of tartar emetic, before an oral drug replaced this standard of care across the country in the 1980s [20]. Reuse of glass syringes and lax sterilization practices during PAT campaigns appear to have caused widespread infection with HCV, which by the 1990s had replaced schistosomiasis as the primary cause of liver disease in Egypt [21]. Different studies have shown a dramatic increase in HCV prevalence with age; a cohort effect that may be explained, at least in part, by the early association between PAT and HCV transmission [22-24].

We found that there is high prevalence of HCV infection in males compared to female gender (309 males and 20 females). These differences may also be in part attributed to the PAT campaigns, as males were more affected by the schistosomiasis disease burden and hence were main targets of these campaigns. This result is agree with other one which done in Egypt by Mohamed MK. Et al. [25]

We observed that there were significant statistical difference in residence (p=0.03) and Sohag city were the highest percent of HCV (23.4%) it may be due to the more educational degree in the capital cities as so they may be diagnosed early more than in the other cities followed by Elmaragha city (19.45%) and this also may be due to schistosomiasis that were common in this city.

Our study showed that AST and ALT were significantly higher in HCV positive patients than in HCV negative patients (p<0.0001); for AST 82.45% of the patients had elevated values, and for ALT 80% of the patients had elevated results. While in HCV negative PCR patients, for AST 54.55% of the patients were with normal results but 45.45% were elevated and for ALT 45.45% of the patients were with normal results but 54.54% were elevated. Other studies had got similar results; Bozdayia et al. had got similar results in their study and they had suggested that hepatitis C patients with higher ALT levels have more active immune response to chronic viral infection [26]. Kurasaki et al. showed that the ALT in the HCV PCR positive group was much higher than that in the HCV PCR negative group and indicated that HCV replication is related to the progress of chronic liver disease, and supported the theory that HCV may have cytopathogenic effect, moreover, they showed that the ALT in the HCV RNA high level group was much higher than that in the HCV RNA low level group [27]. Ghany et al. found in their investigation significant correlation between serum HCV RNA and ALT levels in the patients who received therapy (interferon), but no correlation was observed in the untreated and immune-suppressed patients [28]. Ahmed et al. observed elevated ALT and AST levels in PCR positive patients compared to normal range. However other investigators have reported findings different from ours on the correlations between ALT levels and HCV RNA. Their results indicate that the severity of liver disease is independent from serum levels of hepatitis C virus and that HCV RNA viral load significantly correlates inversely with ALT levels [29]. Dincer et al. observed that there was no significant difference in viral load between patients with abnormal ALT levels and those with normal ALT levels [30]. Abraham et al also showed that the viral load was independent of ALT level in HCV [31]. Lee et al, in their study found that serum ALT levels were not positively correlated with HCV RNA titers [6]. Delic et al. found that viral load showed significant inverse correlation with ALT levels. In addition, viral load was significantly higher in patients with normal ALT levels than in those with a high level of ALT. Also, at the same time they observed no significant correlation between HCV RNA viral load and AST levels, while these two aminotransferase (ALT/ AST) levels were in positive correlation in the study group. So they suggested that viral load in chronically infected individuals is the most sensitive marker of disease activity and all patients with high HCV RNA viral load must be treated including patients with low or normal ALT levels [32].

In our study we also observed that the comparison between positive PCR group with negative PCR group revealed that, there were no statistically significant difference regarding Albumin, Alkaline phosphatase, total bilirubin, direct bilirubin, and prothrombin (p=0.35, p=0.80, p=0.26, p=0.86, p=0.99 respectively) as most of the patients were within normal results for both positive and negative PCR patients. However, some investigators have reported findings different from ours Ahmad et al. showed that serum Alkaline phosphatase levels were not considered valuable markers during HCV diagnosis but he showed that change in Alkaline phosphatase levels greater than 120 U/L can be indicative of advanced disease progression. Their data showed significant increase in bilirubin levels in patients with genotype 4. They showed that high bilirubin level is usually associated with hepatocellular carcinoma and liver cirrhosis by active or non-active HCV [29]. Wahib et al. showed that 35% of the HCV PCR positive patients had elevated results of bilirubin levels but serum albumin was normal in all patients [33].

In this study our observation of the correlation between PCR with activity and fibrosis revealed that there were no statistically significant difference between PCR with activity and fibrosis (p=0.37, p=0.22 respectively) and there is also no statistically significant difference regarding AST, ALT and GGT with both activity and fibrosis. Our results agreed with the studies conducted by Lee et al., Saleem et al. and Fouad et al. who found no significant correlation between HCV RNA load as measured by quantitative PCR and both the grade of activity and fibrosis stage [6,34,35].

This could be attributed to the fact that serum HCV RNA load is not a stable parameter because it fluctuates. In addition, a high amount of circulating HCV does not always imply a more active state of viral

replication in the liver nor does it indicate a more severe degree of liver disease. HCV is known to replicate both within the liver as well as in extra-hepatic sites [35].

On the other hand, Kato et al. observed significantly higher HCV RNA titers in patients with chronic active hepatitis and cirrhosis compared to those with milder histological abnormalities such as persistent chronic hepatitis [18]. Similarly, Fanning et al. in a study on Irish women who acquired their HCV infection through the administration of contaminated anti-D immunoglobulin obtained a significant correlation between serum HCV viral loads and the degree of hepatic inflammation in liver biopsy specimens [19]. Anand et al., showed that none of the laboratory tests showed any correlation with HCV viral count [36]. Zechini et al. demonstrated a statistically significant correlation of aminotransferase levels with the histological parameters, and an even stronger correlation with the AST levels and suggested that aminotransferase values, especially AST, may correlate with the degree of liver damage [37]. Puoti and colleagues argued such a correlation [38]. Liu and colleagues [39] 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. Al Swaff R in her study showed highly significant higher levels of HCV RNA titer among patients with stage 3 hepatic fibrosis. In contrast, grades of activity were independent of serum HCV-RNA titer. Also she found that patients with stages 1 and 4 hepatic fibrosis had significantly higher levels of ALT than patients with other stages of hepatic fibrosis [7]. 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 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 [39]. 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 [40-41]. 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 [42].

Conclusions

In conclusion high results of liver function tests may be indicator for the severity of liver damage in chronic HCV patients but also PCR should be done as some cases show normal results while its PCR was high. Our study showed there is no relationship between liver function tests and the grade of activity or fibrosis stage of liver biopsy in chronic HCV patients so liver biopsy is important to know the severity of liver damage. 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.

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