ejpmr, 2021,8(9), 59-64

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

ESTIMATION OF SERUM INTERLEUKIN-18 IN CHRONIC HEPATITIS C VIRUS-INFECTED PATIENTS

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Article Received on 27/06/2021 **Article Revised on 18/07/2021** **Article Accepted on 08/08/2021**

ABSTRACT

Background: Hepatitis C virus (HCV) infection is a major global health problem and is one of the main causes of chronic liver disease One of the most countries affected by HCV is Egypt. IL-18 plays a crucial role in the inflammatory cascade. The aim was to evaluate Il-18 as a marker for the severity development of hepatic cirrhosis in chronic hepatic C patients. **Methods:** This prospective a case-control study which conducted on 100 patients with post-hepatitis C liver. In addition to 50 healthy subjects served as a control group. IL-18 were measured for all participants **Results:** Serum liver enzymes (ALT and AST) differ significantly ($P < 0.01$) among different groups. The higher ALT and AST level observed in cirrhotic group followed by non-cirrhotic group and the lower ALT and AST level observed in control group.IL-18 protein level differ significantly ($P < 0.01$) among different groups. The higher IL-18 observed in cirrhotic group followed by Non-cirrhotic group and the lower IL-18 observed in the control group. There were significant positive correlations between serum levels of IL-18 and (AFP, INR, ALT, AST, virus number, total bilirubin and direct bilirubin). **Conclusion:** IL-18 levels were elevated in HCV patients than controls. Serum IL-18 is significantly increase in HCV patients and is correlated with liver cirrhosis. So, IL-18 can be used as non-invasive pro inflammatory marker for detection of the chronicity and severity in chronic hepatitis c patients.

KEYWORDS: Il-18- hepatic cirrhosis- chronic hepatic C patients.

INTRODUCTION

Hepatitis C is a serious illness, widely reported particularly in Egypt in many parts of the world .It was once known as a possible viral hepatitis that occurs after blood transfusion or intravenous medication .It is clear that hepatitis C in a high proportion of infected people could lead to continued infection and could lead to chronic illness, cirrhosis, other illnesses and hepatocellular carcinoma (HCC).[1] The measurement of progression of the disease not only offers helpful information on diagnoses and clinical control but also on disease monitoring.[2] In virus infection ,proinflammatory cytokines are two-fold. These cytokines act as an antiviral in acute infection and help to eliminate the infection .However, these cytokines can stimulate chronic infection by inflammatory processes .HCV-mediated activation of IL-18 from macrophages can thus trigger calming hepatical star cells to fibrosis and can serve as potential therapeutic targets.[3] HCV infection is a major health problem in Egypt.[4] Chronic infection with HCV is the leading cause of end stage liver disease, HCC and liver-related death in the country.[5] Functional liver tests are insensitive to disease progression predictions. In patients without severe histological abnormality, serum ALT may be elevated .Standard values also do not preclude progressive hepatitis or cirrhosis.[6] IL-18 is a proinflammatory cytokine with immunomodulatory functions by enhancing T cell responses, regulating IFN-γ production and promoting the development of Th1 immune responses.[7] Hepatic inflammatory activity in chronic hepatitis C was shown to be closely associated with an increased amount of IL-18.[8] The study aimed to evaluate Il-18 as a marker for the severity development of hepatic cirrhosis in chronic hepatic C patients.

MATERIAL AND METHODS

This prospective a case-control study which conducted on 100 patients with post-hepatitis C liver. This study was conducted during the period from November 2018 to February 2019. In addition to 50 healthy subjects served as a control group. The selected participants were subdivided into three groups: Group I: Included 50 healthy subjects (control group), Group II: Included 50

non-cirrhotic patients, Group III: Included 50 cirrhotic patients. The studied groups were related to male sex, with a mean age was 56.55±8.32 years. Samples of studied groups were analyzed at Molecular Biology Unit of Medical Biochemistry Department, Benha Teaching Hospital.

Inclusion Criteria: Patients age ≥18 years old, Patients with post-hepatitis C liver which have cirrhosis and non cirrhosis liver and the exclusion Criteria included Patients with liver diseases or cirrhosis due to etiologies other than HCV infection as: (Co-infection with HBV), Patients who have been exposed to antibiotics within two weeks, patients with other medical diseases.

All subjects were subjected to the following: Full history, Clinical examination, Laboratory investigations: Venous blood samples (7.5 ml) were taken using sterile syringes under aseptic conditions. The collected samples were sent immediately to the laboratory of Benha Teaching Hospital and divided as follow: Part 1: (0.5 ml) on EDTA for complete blood count (CBC). CBC including the differential count was done automatically (Symex XS-800i, Japan), Part 2: (0.9 ml) was put on 0.1 ml tri-sodium citrate solution (3.8%) in a ratio of 9:1 for determination of prothrombin time (sec.), concentration and INR (Dade Behring - BFT, Germany) and Part 3: (~ 4 ml) were left to clot for half an hour and then centrifuged for 15 minutes at 1000 ×g. Hyperlipidemic and hemolyzed samples were excluded. Sera were used for the following biochemical investigations: Liver biochemical tests: Including: Serum alanine aminotransferase (ALT) (IU\L), Serum aspartate aminotransferase (AST) (IU\L), Serum bilirubin (total &direct) (mg\dl), Serum albumin (gm\dl) ,anti-HCV tests using enzyme-linked immunosorbent assay (ELISA), HCV-RNA using reverse transcriptase-polymerase chain reaction (RT-PCR) and Estimation of serum IL-18 (pg/ml): by Human Interleukin 18 (IL-18) ELISA Kit Human Interleukin 18 (IL-18) ELISA Kit Catalog Number. CSB-E07450h. For the quantitative determination of human interleukin 18 (IL-18) concentrations.

PRINCIPLE OF THE ASSAY

This assay employs the quantitative sandwich enzyme immunoassay technique. Antibody specific for IL-18 has been pre-coated onto a microplate. Standards and samples are pipetted into the wells and any IL-18 present is bound by the immobilized antibody. After removing any unbound substances, a biotin-conjugated antibody specific for IL-18 is added to the wells. After washing, avidin conjugated Horseradish Peroxidase (HRP) is added to the wells. Following a wash to remove any unbound avidin-enzyme reagent, a substrate solution is added to the wells and color develops in proportion to the amount of IL-18 bound in the initial step. The color development is stopped and the intensity of the color is measured.

Statistical analysis

The data were coded, entered and processed on computer using *Statistical package for social science (SPSS)* (version 24).The results were represented in tabular and diagrammatic forms then interpreted. Mean, standard deviation, range, frequency, and percentage were use as descriptive statistics. The following test was done: Chi-Square test X^2 was used to test the association variables for categorical data. Student's t-test was used to assess the statistical significance of the difference between two population means in a study involving independent samples. ANOVA (F test) for normally quantitative variables, to compare between more than two groups, and Post Hoc test (LSD) for pairwise comparisons. Pearson's correlation coefficient: it evaluates the linear association between 2 quantitative variables (one is the independent var. X, and the other is the dependent var., Y). value of "r" ranges from -1 to 1. P value was considered significant as the following: $P > 0.05$: Non significant, $P \leq 0.05$: Significant.

RESULTS

- This table showed that the mean of Age (year) in controls, Non- Cirrhotic, Cirrhotic. There was no statistically significant difference between studied groups regarding age and showed that there was no statistically significant difference between studied groups regarding Sex. All patients in the sample are related to male sex **Table (1).**
- This table showed that the mean of HCV viral load in controls, Non- Cirrhotic, Cirrhotic. The mean value of HCV viral load was statistically significant lower among Non- Cirrhotic than Cirrhotic **Table (2)**.
- This table shows that serum liver enzymes (ALT and AST) differ significantly ($P < 0.01$) among different groups. The higher ALT and AST level observed in cirrhotic group followed by non-cirrhotic group and the lower ALT and AST level observed in control group.IL-8 protein level differ significantly ($P < 0.01$) among different groups. The higher IL-18 observed in cirrhotic group followed by Non-cirrhotic group and the lower IL-18 observed in the control group **Table (3)**.
- This table showed that the correlation between IL18 (pg/ml) and other numerical data. There were statistically significant positive correlations between IL18 (pg/ml) and (PCR(IU\L), ALT T(IU\L), AST T(IU\L), BillD (mg/dl), BillT (mg/dl), INR). While there were statistically significant negative correlations between IL18 (pg/ml) and (WBCs (cell/cmm)), Hb (g/dl), Platelets (cell/cmm), Albumin (gm/dl.) **Table (4)**.
- This table showed that the correlation between IL18 and other numerical data. There were statistically significant positive correlations between IL18 and (PCR(IU\L), ALT T(IU\L), BillD (mg/dl), BillT (mg/dl), AFP, ANA). While there were statistically significant negative correlations between IL18 and WBCs (cell/cmm)), Hb (g/dl), Platelets (cell/cmm),

Albumin (gm/dl.). There were no statistically significant correlations between IL18 and other numerical data **Table (5)**.

Table (1): Demographic data among different groups.

Variable	Controls (n.= 50)	Non- Cirrhotic (n.= 50)	Cirrhotic (n.= 50)	F	p
	Mean ± SE (Std. error) (minimum – maximum)				
Age (year)	55.44±4.26 (40.00- 60.00)	56.55±8.32 (40.00- 60.00)	57.62±7.55 (40.00- 60.00)	3.55NS	(P > 0.15)
Sex	Male 50	50	50	1NS	(P > 0.05)
	100%	100%	100%		

Table 2: HCV level among different groups.

Variable	Non- Cirrhotic (n.= 50)	Cirrhotic (n.= 50)	t. test	p
	Mean ± SD (Std. error) (minimum – maximum)			
HCV viral load	436763.49±49648.79 (1000 - 2350000.00)	2125619.18±533166.76 (1100000.00 - 3100000.00)	353.51***	(P < 0.001)

Table 3: Laboratory investigations among different groups.

Variable	Controls (n.= 50)	Non- Cirrhotic (n.= 50)	Cirrhotic (n.= 50)	F	p
	Mean ± SD (Std. error) (**minimum** – maximum)				
ALT (IU/ml)	23.30±6.65 (12 – 43)	84.98±25.24 (30 – 200)	170.72±34.43 (100 – 250)	473.20***	(P < 0.001)
AST(IU/ml)	23.44±6.96 (10 – 38)	72.22±17.23 (33 – 150)	134.24±31.02 (84 – 198)	361.20	(P < 0.001)
Albumin (g/dl)	4.30±0.45 (4.00 – 5.00)	3.2±0.03 (2.90 – 3.70)	2.3±0.02 (2.10 – 3.2)	253.63**	(P < 0.001)
Bill D (mg/dl)	0.13±0.04 (0.09 – 0.25)	0.35±0.12 (0.10 – 0.40)	1.77±0.17 (1.00 – 2.60)	121.12***	(P < 0.001)
Bill T (mg/dl)	0.79±0.14 (0.30 – 1.00)	1.15±0.34 (0.30 – 2.50)	6.79±1.52 (20.00 – 9.00)	175.78***	(P < 0.001)
INR	1.01±0.08 (1.00 – 1.05)	1.13±0.07 (1.00 – 1.24)	2.50±0.37 (1.35 – 3.10)	8.06***	(P < 0.001)
AFP (ng/mL)	3.90±.01 (1.00 – 10.90)	5.90±.01 (1.00 – 10.90)	43.99±25.475 (11 – 125)	84.87***	(P < 0.001)
ANA	5.00±3.46 (3 – 7)	7.00±.3.47 (3 – 9)	55.22±.5.48 (15 – 77)	122.40***	(P < 0.001)
IL-18 (PG/ML)	46.36±14.384 (15 – 73)	328.90±60.158 (235 – 456)	588.03±93.876 (450 – 790)	871.15***	(P < 0.001)

Table 4: Correlations among IL-18 and other variables in non cirrhotic group.

Variables	IL18 (pg/ml)	P value
WBCs (cell/cmm))	-0.763-**	0.011
Hb (g/dl)	-0.384-**	0.013
Platelets (cell/cmm)	-0.242*	0.023
PCR	0.666**	0.011
ALT T(IU\L)	0.569**	0.012
AST T(IU\L)	0.495**	0.011
Albumin (gm/dl.)	-0.693-**	0.016
BillD (mg/dl)	0.676**	0.015
BillT (mg/dl)	0.732**	0.00018
INR	0.404**	0.0012

Table 5: Correlations among IL-18 and other variables in cirrotic group.

	IL18	P value
WBCs (cell/cmm))	-0.659-**	0.008
Hb (g/dl)	-0.625-**	0.014
Platelets (cell/cmm)	-0.577-**	0.0023
PCR(IU\L)	0.865**	0.0061
ALT T(IU\L)	0.483**	0.019
AST T(IU\L)	0.146NS	0.11
Albumin (gm/dl.)	-0.930-**	0.016
BillD (mg/dl)	0.577**	0.015
BillT (mg/dl)	0.697**	0.009
INR	-0.251NS	0.14
AFP	0.950**	0.0016
ANA	0.813**	0.0017

DISCUSSION

In our study, there were no statistically significant differences between the three studied groups as regards gender and age.

Our results cleared that, HCV virus level cleared that, the virus level differ significantly (P < 0.05) among different groups. The higher virus number observed in cirrhotic group as it reached to (2125619.18±533166.76) followed by its level in non-cirrhotic group and its level in control group as its level reached to (0.00).

This result was comparable to result documented by **El-Amin et al.,**[2] who found there was statistical significant increase in viral load by PCR in Group III compared to Group II (p value<0.05).

Our results observed the serum liver enzymes (ALT and AST) differ significantly (P < 0.01) among different groups. The higher ALT level observed in cirrhotic group 170.72±34.43 IU/ml followed by non-cirrhotic group as its level reached to 84.98±25.24 IU/ml. And the lower ALT level was observed in control group as its level reached to 23.30±6.65 IU/ml. While, the higher AST level observed in cirrhotic group 134.24±31.02 IU/ml followed by non-cirrhotic group as its level reached to 72.22±17.23 IU/ml. Lower AST level was observed in control group as its level reached to 23.44±6.96 IU/ml.

This finding is in agreement with **Li et al.,**[9] who revealed that the group of patients with cirrhosis had higher aspartate aminotransferase (AST) compared with the group of patients with CHC-only. Compared with the control group, the AST, ALT values in the group of patients with cirrhosis were significantly higher (*P* < .001). This is in agreement with **Zechini et al.,**[10] who suggested that serum aminotransferases, especially the AST level, were associated with liver damage explaining more release of AST from liver cell.

In our study, the bilirubin (D and T) level differ significantly (P < 0.01) among different groups. The higher Bill D observed in cirrhotic group as its value reached to 1.77±0.17 mg/dl, followed by non-cirrhotic group as its level reached to 0.35±0.12 mg/dl and the lower Bill D was observed in the control group 0.13±0.04 mg/dl. The higher Bill T observed in cirrhotic group as its value reached to 6.79±1.52 mg/dl, followed by non-cirrhotic group as its level reached to 1.15±0.34 mg/dl and the lower Bill T was observed in the control group 0.79±0.14 mg/dl.In harmony with the present study, **Sharma et al.,**[11] who found that, the mean levels of bilirubin were significantly elevated in patients with cirrhotic group followed by non-cirrhotic group and the lower was observed in the control group.

Our results observed AFP differ significantly (P < 0.01) among different groups. The higher AFP level observed in cirrhotic group 43.99±25.475 followed by non-cirrhotic group as its level reached to 5.90±0.01. And the lower AFP level was observed in control group as its level reached to 3.90±0.00. Current results were consistent with that of **Barakat et al.,**[12]

This study showed that, IL-8 protein level differ significantly (P < 0.01) among different groups. The higher IL-18 observed in cirrhotic group as its value reached to 588.03±93.876, followed by non-cirrhotic group as its level reached to 328.90±60.158 and the lower IL-18 was observed in the control group 46.36±14.384. This finding was in accordance with the study of **Sharma et al.,**[11] who reported that IL-18 levels reflect the severity and activity of HCV infection, and may contribute to the pathogenesis and progression of liver disease associated with HCV.

In harmony with the present study, **Ahmed et al.,**[13] who found Serum IL-18 levels were significantly higher in chronic HCV patients compared to controls. The same findings were observed by **Niu et al.,**[14] who demonstrated a positive association between CHC and plasma IL-18 levels.

El-Hendawy et al.,[15] found that, serum levels of IL-18 in hepatitis C patients were significantly higher with a mean value of 592.96 ± 112.68 when compared with the control group.

The same finding was observed by **Ludwiczek et al.,**[16] who found that disease progression from noncirrhotic to cirrhotic disease was accompagnied by an increase in plasma IL-18 level.

Our results cleared that, the albumin level differ significantly (P < 0.01) among different groups.The higher albumin level observed in control group 4.30±0.45 g/dl followed by its level in non-cirrhotic group 3.2±0.03 g/dl and the lower albumin level was observed in cirrhotic group as its level reached to 2.3±0.02 g/dl.

Hall and Cash,[17] stated that the liver function tests usually indicate the type and severity of liver injury.

In the current study, the positive correlation (Increasing of IL-18 associated with increasing of the other parameter) of IL-18 observed with AFP (0.950), INR (0.813). This finding was in accordance with the study of **Mohran et al.,**[18] who found there was a statistically significant correlation between IL-18 level and INR in case group patients.

Current results were consistent with that of **El-Hendawy et al.,**[15] who showed that, there were significant positive correlations between serum levels of IL-18 and INR (*P* < 0.02).

This was in agreement with the results of **Kronenberger *et al.*,**[19]

Our results cleared that, there is a negative correlation (Increasing of IL-18 decrease the other parameters) between IL-18 with Albumin.

Current results were consistent with that of **Mohran *et al.*,**[20] found that a negative correlation with albumin in HCV patients.

In the present study there was positive significant correlation between IL-18 level and (ALT, AST).

This finding is in agreement with **El-Amin et al.,**[2] who found there was positive high significant correlation between IL-18 level and AST (r=0.33, p value 0.03).

Similarly, **Wang *et al.*,**[21] showed that the concentrations of serum IL-18 in CHC patients were positively correlated with the levels of serum ALT and AST (r = 0.388, $P < 0.001$; r = 0.400, $P < 0.001$, respectively).

In the current study, there was positive significant correlation between IL-18 level and virus number.

This finding is in agreement with **El-Amin et al.,**[2] who found there was positive high significant correlation between IL-18 level and viral load (r=0.55, p value<0.01).

Current results were consistent with that of **El-Hendawy et al.,**[15] showed that the concentrations of serum IL-18 in CHC patients were positively correlates with the level of HCV RNA (r = 0.90, $P < 0.001$).

In the present study there was positive significant correlation between IL-18 level and (total bilirubin, direct bilirubin).

This result was comparable to result documented by **Tangkijvanich et al.,**[22] who found that patients with high serum IL-18 levels had significantly higher mean total bilirubin and direct bilirubin.

CONCLUSION

IL-18 levels were elevated in HCV patients than controls. Serum IL-18 is significantly increase in HCV patients and is correlated with liver cirrhosis. So, IL-18 can be used as non-invasive pro inflammatory marker for detection of the chronicity and severity in chronic hepatitis c patients. Thus, the present study attempts to gain a better understanding of the involvement of IL-18 in HCV infection. The magnitude of its production with regard to cirrhosis. Our data confirm the proinflammatory role of IL-18 in HCV infection, and IL-18 levels were found to reflect HCV-induced inflammation and hepatic injury. It is possible that up-regulation of IL-18 production has a role in the development of chronicity and accelerates the evolution of chronic hepatitis towards cirrhosis.

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