Serum Inducible Protein-10 chemokine as a biomarker for clearance of HCV with and without treatment in Egyptian patients

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ABSTRACT

Background: Hepatitis C virus (HCV) is a major health problem worldwide particularly in Egypt. Chemokine IP-10 may be a good prognostic marker for the outcome of HCV treatment

Aim: Assessment the potential predictive value of Serum Inducible Protein-10 chemokine (IP-10) in the clearance of HCV RNA in Egyptian patients with and without treatment

Materials and Methods: Ninety Egyptian individuals were involved in the current study where, 20 (23%) patients were chronic HCV chronic (positive HCV antibodies and positive HCV RNA without treatment, 20 (22%) were healthy individuals (negative for both HCV antibodies and HCV RNA, 20 cases (22%) were natural clearance (positive HCV antibodies and negative for HCV RNA without treatment), 20 (22%) were achieved SVR after treatment (responder group, HCV positive and negative for HCV RNA after treatment) and 10 (11%) were non responder (positive HCV antibodies and still positive HCV RNA after treatment). HCV RNA was quantitated by real time PCR for and serum IP10 level was measured by commercial ELISA kit. All biochemical and hematological examinations included liver function, CBC and alphafeto protein were assessed.

Results: The mean serum levels of IP-10 were significantly higher (p<0.001) in CHC patients (345.4±100) pg/ml than healthy control group (101.5±31.4) and natural clearance group (103.2±40.7). Also serum levels of IP-10 was significantly elevated in non responder group (257.4±52.5) compared with each of SVR group (103.5± 43.5) (p<0.001) and healthy group (101.5±31.4), (p< 0.001). Prediction of a clinical response based on a combination of these chemokines revealed high sensitivity (82%), specificity (85%), negative predictive value (95%), and area under the curve (1.00). Moreover, there is no correlation (R= 0.05), P value p< 0.795) between serum level of IP-10 and HCV viral load.

Conclusion: IP10 is a useful non-invasive biomarker for viral clearance and might be used to apply patients according to the predictable treatment outcome. Accordingly, patients who are unlikely to respond to treatment would avoid unnecessary exposure to medication that is related with high morbidity.
INTRODUCTION

HCV has been exposed to be the most common origin of chronic liver disease and hepatocellular carcinoma all over the world [1]. Hepatitis C virus (HCV) infects more than 185 million people, occurring among individuals of all ages, sexes, races and regions of the world [2]. The brutality of chronic inflammation and the level of liver disease progression differ significantly. Whereas 20–33% of chronic hepatitis C (CHC) patients progress to cirrhosis over 20–30 years, the remains have mild chronic hepatitis that does not progress or developments very slowly [3]. Spontaneous HCV elimination during the acute phase obliges forceful CD4 and CD8 responses against multiple viral epitopes [4]. Egypt has been classified that has highest prevalence rate of HCV in the world (15–20%) [5]. It is broadly putative that the routine of mass parenteral antischistosomal therapy involved application of tartar emetic injections (from 1950s to 1980s) led to extensive infection with (15–20%) of adult patients have HCV antibodies in Egypt [6]. (Makhzangy et al. 2009). Although about 30% of patients may clear the virus spontaneously, the mainstream of patients who develop chronic HCV have been reflected the main health problem [7]. In this patient population, cirrhosis may progress within 20 years of infection. With hepatic decompensation and hepatocellular carcinoma, these longstanding consequences have put more hindrances on resources in an already overstressed Egyptian healthcare system [8]. The four is the most public genotype of HCV in the Middle East and Africa, mostly Egypt which is the reason for more than 90% of HCV infections [9].

The accomplishment of a Sustained virological response (SVR) is the purpose of giving treatment to chronic HCV patients to overcome hepatitis C Virus with undetectable HCV RNA at 12 weeks after finalising treatment course [10]. Many direct acting antiviral agents have been developed in this era showing vigorous activity with higher rates of sustained virological response [11]. The dose of both sofosbuvir and daclatasvir is taken orally once per day, in a dose of 400 mg and 60 mg, correspondingly and this is according to the protocol of Egyptian National Committee for Controlling HCV (NCCVH) and the guidelines of European Association for the Study of the Liver [12]. Also SOF-DCV in patients with chronic HCV-G4 was verified to be safe and related with a high SVR12 rate (95.1%), in patients with different stages of fibrosis [13]. Thus, recognizing factors that predict SVR become fundamental option which will improve clinical decision making, from the economic point of view to economize treatment cost and increase its efficacy [14]. It has been noticed the immune factors other than antibodies may play a defensive role in HCV infection. T cells have been confirmed to be important in the control of many viral infections. Vigorous and polyfunctional HCV-specific T cell responses have been related with the spontaneous clearance of infection [15]. Chemokines and cytokines regulate inflammation and immunity in HCV infection they are considered engaging biomarker for treatment and play vital role in clearance of the virus [16]. Chemokines (CKs) are considered a family of small
proteins secreted by the cells. Their name (derivative from chemoattractant cytokines) is due to their capacity to induce directed chemotaxis in close responsive cells. Some CKs are involved during an immune response to recruit cells of the immune system cells to a site of infection, so they can target and destroy invading bodies such as microbes. While others are considered homeostatic and are implicated in controlling the migration of cells during normal processes of tissue maintenance or development, so they are assumed to be attractive biomarkers for treatment consequence. Many chemokine are influenced by exogenous interferon and play important roles in clearance of the virus. The immune system of responders inclines to have a lower baseline activation before starting treatment that is markedly induced in response to treatment by IFN. Interferon-gamma inducible protein 10 kDa (IP-10); also known as chemokine (c-x-c) motif ligand 10 (CXCL10) which formed in its mature form of 77 amino acids. CXCL10 has been assigned to various roles, for instance chemoattraction for monocytes/macrophages, T cells, NK cells, and dendritic cells, promotion of T cell adhesion to endothelial cells, antitumor activity, and inhibition of bone marrow colony development and angiogenesis.

IP-10 is interferon stimulating gene produced by different cells, including hepatocytes and non parenchymal liver cells during CHC. The Intrahepatic production of IP10 and other non-ELR chemokines recruits a pro-inflammatory, anti-viral immune response to the liver by binding chemokine receptor CXCR3 on CD4+ TH1, CD8+ Tc, and natural killer cells. And this in turn stimulate the innate and adaptive immune response, So the non-ELR CXC chemokines specifically CXCL10, assistance in coordinate the hepatic inflammatory response of chronic hepatitis C. It has been proposed that CXCL10 in the serum of chronic HCV patients may not denote the biologically active form. Because it was found as truncated form, resulting from the N-terminal cleavage of two aminoacids by the protease dipeptidylpeptidase 4 (DPP4, orCD26). So, the truncated form of CXCL10 retains CXCR3 binding, but does not induce signaling. As such, it acts as antagonist effect and this shows that, presence of high level of IP10 in chronic patients and decrease in individuals whose clear the virus. Also IP10 decreased with DAA therapy until they reached levels similar to healthy donors obviously suggesting a re-orchestration of innate and adaptive immune cells with prospective consequences for inflammatory processes. Therefore, assessment of pre-treatment IP-10 may be useful in response prediction in chronic HCV infection. And become good prognostic marker for the outcome of HCV treatment. The current study aimed at evaluation of the value of pre-treatment serum IP level in the prediction of the likelihood of SVR in Egyptian chronic HCV patients receiving SOF-DCV combination therapy.

Materials and methods:
The present study recruited 90 Cases (48 males, 42 females) and their ages ranged from 23 to 65 years. The study excluded the patients who met the following criteria (pregnancy, liver cirrhosis, liver
transplantation, heart disease, renal failure, autoimmune disease or co-infection with HBV or HIV). The study protocol was approved by Local Ethics Committee. An informed written consent was taken from each patient before inclusion in this study. The study involved five cohorts as the following: 1st cohort (control): twenty healthy volunteers had negative HCV Ab by Elisa and negative HCV RNA by PCR. 2nd cohort (Natural Clearance): Twenty patients had positive HCV Ab and negative HCV RNA and they didn't receive any anti-HCV treatment. 3rd cohort (Chronic Hepatitis C) Twenty patients had a positive HCV Ab and positive HCV RNA. 4th cohort (sustained virological responders after treatment; Twenty patients had a negative HCV RNA after 12 weeks of treatment. 5th cohort (Non-responders after treatment); ten patients had a positive HCV RNA after 12 weeks of treatment.

**Antiviral regimen**

The antiviral treatment regimen consisted of one tablet containing 400 mg of SOF (Sovaldi®; Gilead Sciences Inc., Foster City, CA, USA) once daily and one tablet containing 60 mg of DCV (Daklinza®; Bristol-Myers Squibb, New York, NY, USA) once daily. The treatment period was 12 weeks. Other contraindications included in the Standard Product Characteristics of SOF and DCV, especially drug–drug interactions, were respected. Sustained virological response (SVR) was assessed as HCV RNA negativity 12 weeks post treatment.

**Sampling:**

Venous blood samples of about 10 ml were collected from each patient, required volumes were put into sterile vaccutainer tube contained EDTA for complete blood count, sodium citrate for prothrombin time and gel for assessment of Hepatitis B surface Antigen (HBsAg), Hepatitis C Virus Antibody (HCVAb), Human immunodeficiency virus (Anti – HIV), ALT, AST, Bilirubin), Alkaline phosphatase, Albumin, Tumor marker Alpha Fetoprotein (AFP), CXCL 10 and HCV RNA PCR.

**HCV-RNA Quantification:**

HCV RNA was assessed by the Roche COBAS® AmpliPrep/COBAS TaqMan® HCV Quantitative Test v2.0 (Roche Molecular Systems Inc., Branchburg, NJ, USA). The lower detection limit was 15 IU/ml. HCV-RNA levels were assessed in all cohorts

**IP-10 Quantification:**

Serum IP-10 level was measured in all cohorts by the commercially enzyme-linked immunosorbent assay according to manual procedures (Human CXCL10/ IP-10; Quantikine ® ELISA R&D Systems, Minneapolis, USA). The minimum detectable level is 1.67 pg/mL.

**Measurement of serum Liver function tests:**

Serum ALT, AST, albumin and alkaline Phospahtase were measured by spectrophotometer using kits supplied by SPINREA CT,S.A.U. -Ctra. Santa Coloma, Girona Spain. Serum total and direct bilirubin were measured by spectrophotometer using kits (Diamond, Cairo, Egypt).

**Tumor marker alpha feto protein:**

Was measured in all cohorts by the commercially available enzyme-linked immunosorbent assay (Invitrogen, USA).

**Complete blood count:**

For all cohorts were done by automated cell counter alpha SWE Lab, Sweden.

**Statistical analysis:**

All parametric values are expressed as means (SD). Different groups were compared using the student’s t test. The spearman coefficient was used to evaluate correlations between variables. Variables included in the analyses were age, sex, aspartate transaminase (AST), alanine aminotransferase (ALT), alpha fetoprotein (AFP), hematological tests, baseline serum IP-10 level, and viral load. Statistical
analyses were performed by SPSS 15.0 for Windows (SPSS Inc., Chicago, Illinois, USA); p values lower than 0.05 were considered significant. Moreover, The sensitivity and specificity, Efficiency, Positive Predictive Value, Negative Predictive Value of IP-10 in the positive and negative HCV RNA was measured as shown in the table (1).

Results:

Ninety Egyptian individuals were involved in the current study where, 20 (23%) patients were chronic HCV chronic (positive HCV antibodies and positive HCV RNA without treatment, 20 (22%) were healthy individuals (negative for both HCV antibodies and HCV RNA, 20 cases (22%) were natural clearance (positive HCV antibodies and negative for HCV RNA without treatment), 20 (22%) were achieved SVR after treatment (responders group, HCV positive and negative for HCV RNA after treatment) and 10 (11%) were non responders (positive HCV antibodies and still positive HCV RNA after treatment figure (1).

The mean serum levels of IP-10 chronic HCV, natural clearance, responders and no responders groups

The mean serum levels of IP-10 were significantly higher (p< 0.001) in CHC patients (345.4±100) pg/ml than healthy control group (101.5±31.4) and natural clearance group (103.2±40.7). Also serum levels of IP-10 was significantly elevated in non responder group (257.4±52.5) compared with each of SVR group (103.5±43.5) (p< 0.001) and healthy group (101.5±31.4), (p< 0.001) as shown in figure (2).

The sensitivity and specificity of IP -10 in the positive and negative HCV RNA with and without treatment

Assessment of serum level of IP-10 by using ELISA has showed discrimination between chronic HCV infection and HCV spontaneous clearance also between responders and non responders patients to new DAAs. Prediction of a clinical response based on serum level of IP-10 chemokine demonstrated high sensitivity (82%), specificity (85%), negative predictive value (95%), table 1. The ROC curve of IP10 showed an AUC of 1.00 (95% confidence interval 1.00-1.00). At a cut off value 194.565pg/ml for predicting SVR, at point the sensitivity was 100% and specificity was 100% as shown in figure (3). However, there is no correlation ((R= 0.05), P value p< 0.795) between serum level of IP-10 and HCV viral load as shown in figure (4).

Biochemical parameters (liver functions, Alphafetoprotein) of the studied groups and serum level of IP-10

There is significant difference (P value < 0.001) among five groups for biochemical parameter where the chronic HCV Patients and Non responders patients had high level of ALT, AST, ALP and AFP more than responders, natural clearance as shown in table 2. Moreover, there is non positive correlation between IP10 level with alkaline phosphatase, and albumin as shown in Figure (5). There is positive correlation between IP10 level and each of hemoglobin and RBCs and negative correlation between IP10 level and each of HCT and platelets as shown in Figure (6).

Discussion

HCV infection is characterized by an enlarged production of chemokines and cytokines[22]. Chemokines, moreover being inflammatory mediators, may as well be useful as markers of treatment consequence. Furthermore, IP10 is a chemokine that targets T lymphocytes and monocytes . IP10 has a chemotactic function on different cell types
(monocytes, macrophages, natural killer cells, activated T lymphocytes and dendritic cells) by binding with specific receptor CXCR3 \(^{[27]}\). High pre-treatment IP10 levels reflect the therapeutic non-response. This outcome be unique for IP10 because the other non-ELR CXC or CC chemokines studied haven’t prognostic value for treatment response in HCV infection \(^{[19]}\). This study was designed to assess the role of chemokine IP10 for stratifying the patients who go to HCV spontaneous clearance without treatment and who are expected to be responder to the treatment of HCV Egyptian patients. In this study, the mean age of chronic HCV patients and Non responder to treatment is 49±12 and 47±13 respectively. This is agreement with the result of \(^{[28]}\), where the mean age of hepatitis C infected patients was 49.19±11.50. And the lower mean ages were found in healthy (38±11), spontaneous clearance (41±10) and responder to treatment (42± 11). In this study healthy individuals, natural clearance and responders had BMI less than chronic patients and Non responders which agree with \(^{[27]}\) which reported that patients with SVR were younger and had lower BMI.

The main finding of this study is significant association of serum IP10 levels in spontaneous clearance compared with HCV chronic patients without treatment and IP10 levels in non responders (NR) to treatment compared with treatment responders. The results show higher IP 10 level in chronic patients (345.4±100) pg/ml) compared with spontaneous clearance (103±40.7pg/ml) and compared with healthy controls (101±31.4pg/ml) and IP10 levels were higher in non responders (257.4±52.5 pg/ml) compared with responders (103.5± 43.5 pg/ml) which is agreement with results of \(^{[29]}\) which 586 and 392 pg/ml respectively. It has been reported that plasma CXCL10 is treated by dipeptidylpeptidase DPP4; also known as CD26) thus leading to the generation of an antagonist form. \(^{[30]}\) supported the NH₂-truncation of CXCL10 (short form ) which is capable of binding CXCR3 but does not induce signaling \(^{[25]}\). Confirming that CXCL10 levels are increased in chronic and non responder patients to treatment of HCV \(^{[31]}\).

The current results showed a positive correlation between IP10 levels with AST & ALT and this is consistent with \(^{[20]}\) who mention that the elevated IP10 level was positively related with liver damage as indicated by high liver fibrosis score and high liver enzymes level. Moreover, this disagree with \(^{[27]}\) which reported that the correlation of serum IP10 level with AST and ALT levels didn’t reach to significant levels and this may be attributed to small sample size. In the current study, there wasn’t a significant correlation between IP10 level and HCV RNA levels which may be due to low sample size, and most patients have almost nearly viral load and this is consistent with \(^{[27]}\) and \(^{[32]}\), and disagree with \(^{[16]}\) who reported that IP10 levels significantly decrease in patients reaching SVR compared with non responders suggesting that decline of this chemokine could be an indicator of disruption of interahepatic virus –host interaction and this attributed to DAAs persuade rapid decrease in HCV replication with a consequent reduction of IP10 plasma level. Moreover, the present data showed negative correlation between IP1 0 plasma level and AFP. And this disagree with \(^{[28]}\) and this attributed to his patients grade were cirrhosis and our patients are chronic and non responder and didn’t reach to cirrhosis state where (AFP) is a tumor marker of hepatocellular carcinoma (HCC) \(^{[33]}\). Also slight raises of AFP can be seen in benign liver diseases such as virus related acute and chronic hepatitis \(^{[34]}\).

ROC curve analysis showed a suitable IP10 cutoff level in predicting the SVR to DAAs treatment the best sensitivity and specificity for identifying SVR was 194 pg/ml while all the responder to treatment in this study had IP10 level less than 194.
pg/ml (specificity 100%) and all Non responders had IP10 level more than 194pg/ml with (sensitivity 100%) [35], reported that the pretreatment IP10 level for predicting SVR was 499.02pg/ml with specificity 100% and sensitivity 82.6% And[36] reported that pretreatment threshold IP10 level with the best settlement sensitivity and specificity to identify non-responder was 359 pg/ml, 81.8% of non responders (NR) were identified by IP10 more than 359 pg/ml and 45.2% of SVR had IP10 level less than 359pg/ml. One of the several factors causative to virological response in chronic hepatitis C (CHC) is interferon-gamma-inducible protein-10 (IP-10). Its level reflects the status of interferon-stimulated genes, which in turn is related with virological response to antiviral therapy as reported by[37].

**Conclusion**

IP10 is a useful non-invasive biomarker for viral clearance and it became beneficial for predicting the promising virological response before beginning the treatment. Subsequently, patients who are unlikely to respond to the treatment would avoid need exposure to medication that is related with high morbidity.

**References**


33. Taura, Naota, Sachiko Fukuda, Tatsuki Ichikawa, Hisamitsu Miyaaki, Hidetaka Shibata, Takuya Honda, Tohei Yamaguchi, Yoko Kubota, Shinjiro Uchida, Yasuhiro Kamo, Emi Yoshimura, Hajime Isomoto, Takehiro Matsumoto, Fuminao Takeshima,


TABLES

Table (1): The sensitivity and specificity of IP -10 in the positive and negative HCV RNA

<table>
<thead>
<tr>
<th>Reference test</th>
<th>Evaluated test</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+ve</td>
<td>-ve</td>
</tr>
<tr>
<td>+ve</td>
<td>True +ve (a)</td>
<td>False-ve (c)</td>
</tr>
<tr>
<td>-ve</td>
<td>False +ve (b)</td>
<td>True –ve (d)</td>
</tr>
</tbody>
</table>

Sensitivity: \( \frac{a}{a+c} \times 100 = \frac{28}{28+2} \times 100 = 93\% \)
Specificity : \( \frac{d}{d+b} \times 100 = \frac{58}{58+2} \times 100 = 96\% \)

Efficiency: \( \frac{(a+c)}{(a+b+c+d)} \times 100 = 95.5\% \)
Positive Predictive Value : \( \frac{a}{a+b} \times 100 = \frac{28}{28+2} = 93\% \)
Negative Predictive Value : \( \frac{d}{d+c} \times 100 = \frac{58}{58+2} = 96\% \)

Table (2): The biochemical parameters profile among cohort study

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Healthy controls 20</th>
<th>Chronic 20</th>
<th>Natural clearance 20</th>
<th>Responders 20</th>
<th>Non-Responders 10</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFP (ng/ml)</td>
<td>1.64 ±0.91</td>
<td>4.95±4.86</td>
<td>4.86 ±1.02</td>
<td>2.67 ±2.82</td>
<td>8.22 ±3.22</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Direct Bilirubin(mg/dl)</td>
<td>0.18 ±0.03</td>
<td>0.23±0.13</td>
<td>0.13 ±0.02</td>
<td>0.18 ±0.05</td>
<td>0.28 ±0.13</td>
<td>0.007</td>
</tr>
<tr>
<td>Total Bilirubin (mg/dl)</td>
<td>0.53 ±0.11</td>
<td>1.28±0.76</td>
<td>0.57 ±0.10</td>
<td>0.59 ±0.16</td>
<td>0.91 ±0.26</td>
<td>0.333</td>
</tr>
<tr>
<td>PT (seconds)</td>
<td>12.1 ±0.2</td>
<td>12.6±0.4</td>
<td>12.3 ±0.2</td>
<td>12.2 ±0.3</td>
<td>13.0 ±0.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>4.41 ±0.26</td>
<td>4.19±0.24</td>
<td>4.31 ±0.30</td>
<td>4.35 ±0.21</td>
<td>3.79 ±0.44</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ALP (U/L)</td>
<td>73 ±13</td>
<td>88±14</td>
<td>14 ±12</td>
<td>70 ±13</td>
<td>93 ±9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>25 ± 6</td>
<td>45 ± 18</td>
<td>29 ± 7</td>
<td>30 ± 13</td>
<td>49 ± 13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>24 ±6</td>
<td>47±20</td>
<td>20 ±8</td>
<td>31 ±17</td>
<td>53 ±12</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Where AFP (ng/ml) :Alpha Feto protein : up to 10, Direct Bilirubin(mg/dl) : Up to 0.25, Total Bilirubin (mg/dl) : Up to 1.0, PT (seconds) : prothrombine time : 11.5 – 12.0, Albumin (g/L) : 3.5 – 5.2 , ALP (U/L): Alkaline Phosphatase : Up to 127, ALT (U/L) : Glutamate pyruvate transaminase : Up to 40, AST (U/L): Glutamate Oxaloacetete transaminase : Up to 40
Table (3): The hematological parameters profile among cohort study:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Healthy control (n=20)</th>
<th>Chronic group (n=20)</th>
<th>Natural clearance group (n=20)</th>
<th>Responders group (n=20)</th>
<th>Non-Responders group (n=10)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>38±11</td>
<td>49±12</td>
<td>42±11</td>
<td>41±10</td>
<td>47±13</td>
<td>0.027</td>
</tr>
<tr>
<td>Sex (M) (F)</td>
<td>10 (50.0%)</td>
<td>14 (70.0%)</td>
<td>11 (55.0%)</td>
<td>6 (30.0%)</td>
<td>7 (70.0%)</td>
<td>0.098</td>
</tr>
<tr>
<td>BMI (kg/m)</td>
<td>23.0 ±3.49</td>
<td>27.1 ±4.40</td>
<td>24.6 ±4.38</td>
<td>24.9±4.69</td>
<td>28.2 ±2.60</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RBCs (10⁶/mm³)</td>
<td>4.61 ±0.61</td>
<td>4.81 ±0.41</td>
<td>4.74 ±0.54</td>
<td>4.47 ±0.45</td>
<td>4.66 ±0.40</td>
<td>0.262</td>
</tr>
<tr>
<td>Hb (g/L)</td>
<td>12.56 ±1.80</td>
<td>13.07 ± 1.39</td>
<td>12.61 ±1.77</td>
<td>11.79 ±1.25</td>
<td>12.49 ±1.36</td>
<td>0.145</td>
</tr>
<tr>
<td>HCT (%)</td>
<td>37.71 ±5.42</td>
<td>39.27 ± 3.97</td>
<td>38.07 ±5.53</td>
<td>35.58 ±4.13</td>
<td>38.00 ±4.27</td>
<td>0.187</td>
</tr>
<tr>
<td>TLC (10³/mm³)</td>
<td>7.16 ±1.50</td>
<td>7.16 ±1.98</td>
<td>7.91 ±1.53</td>
<td>8.42 ±1.75</td>
<td>5.26 ±0.86</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Neutrophils (%)</td>
<td>54.40 ±7.26</td>
<td>47.12 ±14.90</td>
<td>54.15±6.75</td>
<td>55.20 ±6.54</td>
<td>48.50 ±7.53</td>
<td>0.027</td>
</tr>
<tr>
<td>Lymphocytes (%)</td>
<td>38 ±8</td>
<td>44 ±9</td>
<td>38 ±7</td>
<td>37 ±6</td>
<td>44 ±8</td>
<td>0.023</td>
</tr>
<tr>
<td>Monocytes (%)</td>
<td>7 ±3</td>
<td>6 ±2</td>
<td>6 ±2</td>
<td>6 ±3</td>
<td>6 ±2</td>
<td>0.836</td>
</tr>
<tr>
<td>PLT (10³/mm³)</td>
<td>241 ±44</td>
<td>170 ±59</td>
<td>199 ±44</td>
<td>212 ±38</td>
<td>108 ± 37</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Where RBCs (10⁶/mm³) : red blood cells : Male 4.5–5.6 & Female 3.8–5.0, Hb (g/L) : Hemoglobin : Male 13.0–17.0 & Female 12.0–16.0, HCT (%) : Hematocrite : Male 40.0–52.0 & Female 36.0–42.0, TLC (10³/mm³) : Total Leukocyte count : 4.0–11.0, Neutrophils (%) : 40–60, Lymphocytes (%) : 20–40, Monocytes (%) : 2.0–8.0, PLT (10³/mm³) : Platelets count : 150–400
FIGURES

Figure (1): Distribution of the enrolled patients in the present study.

Figure (2): serum level of IP-10 in chronic HCV, natural clearance and responders and non-responders patients as measured by ELISA
Figure (3): ROC analysis of serum level of IP-10 in responders and non-responders HCV patients to DAA treatment.

Figure (4): The correlation of serum level of IP-10 and HCV HCV viral load
Figure (5): Correlation among IP-10 level, liver function parameters.
Figure (6): Correlation among IP-10 level, Hematological parameters.