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Assessment Association between IFN-β2, AST and Natural Course of Infections with Hepatitis A and C Viruses

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Abstract

Background: Hepatitis A and C viruses are common causing hepatitis (inflammation of liver). Acute and chronic liver infections are characterized by the expression of pro anti-inflammatory cytokines. Human interleukin 6 (IL-6) alliance is interferon beta 2 (designation used in this study) a multifunctional cytokine that interfere in the regulation, maturation and differentiation of immune response.

Objective: The aim of this study is to demonstrate the level of IFN-β2 and correlates with AST level in patient's serum with hepatitis A and C infections.

Methods: We evaluate 46 patients presumably with acute HAV and chronic HCV whom have positive HAV IgM, HCV Ab respectively. AST chemical serum levels were detected using kit of an automated chemical Analyzer. IFN-β2 serum level was demonstrated using ELISA technique. Correlation between parameters was evaluated using SPSS and Tableau statistical software.

Results: IFN-β2 serum level is raised with CHC more than AHA compared with control samples. AST level was elevated with CHC infections more than AHA infections. The correlation coefficient between IFN-β2 level and AST is significant value with CHC patients but is not value with AHA patients. There is a significant correlation between IFN-β2 and AST levels. Negative correlation coefficient emerged between age parameter and groups of hepatitis.

Conclusion: IFN-β2 levels elevated with the increase of AST levels in patients with chronic hepatitis C. The serum levels of IFN-β2, AST varied in different courses of acute hepatitis A and chronic hepatitis C infection. We speculated that measuring levels of IFN-β2 and AST could be used as an indicator to judge the patient's condition with CHC, but not with AHA patients.

Keywords: Acute Hepatitis A patients (AHA); Chronic Hepatitis C patient (CHC); Interferon beta 2 (IFN-β2); AST Aspartate Transaminase (AST); Enzyme-Linked Immunosorbent Assay (ELISA)

Introduction

Hepatitis A and C viruses are common causing hepatitis (inflammation of liver). HCV (+RNA) belongs to *Flaviviridae* family in the Hepacivirus genus [1]. HCV causes chronic liver hepatitis which can result in hepatic fibrosis, liver cirrhosis and hepatocellular carcinoma [2]. HAV (+RNA) is classified under *Picornaviridae* family [3]. HAV is less dangerous than HCV and is typically self-limited to acute liver inflammation and does not result in chronic illness [4]. Although, most chronic cases of HCV lead to high complications, it has a striking capacity to establish persistence and strong association with chronic hepatitis, progressive hepatic fibrosis and liver cancer, clinical outcomes never linked to HAV [3]. Acute and chronic liver infections are characterized by the expression of pro anti-inflammatory cytokines, which lead to many inflammatory diseases of the liver [5]. Inflammation is a protective immune response to ensure the repair of damaged tissue and subtraction of detrimental stimuli by host cells. Immune cells, including macrophages and Dendritic Cells (DCs) play important roles in addition to nonprofessional cells such as epithelial cells, endothelial cells, and fibroblasts also contribute to inflammation induced by microbial infection or tissue damage[1,6]. The immune response against HAV and HCV infections are both B and T-cell derived. Cytokines are important chemical mediators synthesized and secreted from immune cells which described as anti-inflammatory, including (IL-4, IL-6, IL-10, IL-13, IL-17 and TGF-b) [1,7]. The human Interleukin 6 (IL-6) which alliance is interferon beta 2 designated in this study due to the avoidance of repetition in articles and to highlight the lack of suspicion with other types of interferons. IFN-β2 is a multifunctional cytokine that interfere in the regulation, maturation and differentiation of immune response [2,8,9]. It has been produced mainly by kupffer cells [10]. IFN-β2 gene is located on chromosome 7 and is composed of five exons and four introns [8]. IFN-β2 serum levels are correlated with disease severity, so that it may be a useful as indicator of disease activity and therapeutic efficacy in patients with all viruses caused hepatitis [11]. Biochemical tests are used for initial assessment of liver disease such as Alanine and Aspartate aminotransferases ALT (GPT) and AST (GOT) respectively [12]. In this study, we were revealed the AST level in patient's serum. AST serum level is a valuable aid primarily in the diagnosis of such liver diseases [12]. The aim of this study is to determine the cytokine IFNβ-2 and correlates with AST levels of infected patients with HAV and HCV infections. This study was done among populations who were infected or under suspicion infected persons with HAV and HCV virus in Mosul city. Total blood samples (n=61) were collected from August 2018 to December 2018. Informed consent was obtained from every patient prior to sample collection which was performed according to

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standard protocols approved by the local health authority in Mosul city. A (20) blood samples of acute hepatitis A were collected from Ibn–Alatheer Teaching Hospital and (26) blood samples of chronic hepatitis C collected from hemodialysis patients in Central Health Laboratory. Their ages ranged from (1-74) years at the mean of (38.68) years. We have intended to study the expression of human inflammatory cytokine in acute hepatitis A and chronic hepatitis C patients related to the severity of the infection. Immunoglobulin M (IgM) or IgG antibodies are used to diagnose HAV infections for the viral capsid protein. In general, these capsid antibodies are thought to be protective [13].

Materials and Methods

Current study is an analytical cross-section trial involving two different types of viruses cause inflammation of liver, acute of Hepatitis A Virus (HAV) and chronic Hepatitis C Virus (HCV) with a healthy control group. The ages of patients and healthy control donors were between 1-72 years old which grouped into 5 classes 1=(1-14 years), 2=(15-29 years), 3=(30-44 years), 4=(45-59 years) and 5=(60-74 years). Patients were recruited consecutively, A (20) blood samples of Acute Hepatitis A (AHA) were collected from Ibn–Alatheer Teaching Hospital and (26) blood samples of Chronic Hepatitis C (CHC) from hemodialysis patients in Central Health Laboratory in addition to (15) samples of healthy Control (CL). Five milliliters of blood were withdrawn from each patient under complete aseptic conditions. Sera were separated and stored frozen at -20˚C till tests analysis.

Detect HAV IgM using ELISA

Detection of HAV IgM positive sensitive antibodies were done using Enzyme Linked Immunosorbent Assay (ELISA) commercial kit from (DIALAB-Austria) purchased from according to the manufacturer's instruction.

Detect HCV antibodies using ELISA

Detection of HCV positive sensitive antibodies were done using enzyme linked immunosorbent assay (ELISA) commercial kit from (DIALAB-Austria) purchased from according to the manufacturer's instruction.

Determine AST levels

Biochemical liver test of aspartate aminotransferase AST was demonstrated using an automated chemical analyzer kits form (BIOLABO, France) according to the manufacturer's instruction. The AST concentration (U/L) was detected by velocity method using big biochemistry automatic analyzer (Olympus 2700, Japan).

Detection of IFN-β2 level using ELISA

Serum concentrations of Interferon β2 (IFN-β2) were measured in duplicate using a commercial human platinum enzyme-linked immunosorbent assay kit from (Komabioteh). The OD_{450} were determined using an ELISA reader (Awreness-USA). The cytokine standards were also prepared and the concentration of IFN-β2 (pg/mL) was determined using the standard curve. Samples were divided into 3 groups, healthy control (CL=15), acute hepatitis A (AHA=20) and chronic hepatitis C (CHC=26). ELISA positive results for patients' samples and negative results for the healthy control group samples were confirmed and the results were evaluated. The demographic data and clinical history of patients were gathered based on a questionnaire completed.

Statistical Analysis

The analysis of data was made by using Tableau Desktop 64bit software version (2018) and SPSS Inc. Chicago, IL, USA software version16.0 especially for the calculation of mean values, Standard Deviations (SD) and Standard Error (SE) for serological and biochemical parameters. The homogeneity and correlation efficient r with p value between parameters were used to compare significantly value at $p<0.05,0.01$. Microsoft office excel version 2010 was used to explain the values graphically. The differences between the groups were analyzed by Pearson test with overall correlation between parameters.

Results

HAV IgM ELISA test for all cases with AHA pateints got positive results. Furthermore, HCV Abs ELISA test for patients with CHC got positive results. Relying on the case groups, the number, mean, standard deviations and standard errors for all parameters were revealed in Table 1. According to the age groups, the number, mean, standard deviations and standard errors for all parameters were revealed in Table 2.

Parameters	Case	N	Mean Std. Deviation	Std. Error
IFN-β2 (pg/mL)	CL	15	15.734 ± 23.636	6.102
	AHA	20	18.05 ± 36.128	8.078
	CHC	26	201 ± 187.289	36.73
	Total	61	95.460 ± 153.534	19.658
AST U/L	CL	15	31.880 ± 16.096	4.155
	AHA	20	29.380 ± 17.990	4.022
	CHC	26	49.030 ± 15.125	2.966
	Total	61	38.370 ± 18.573	2.378
Age (years)	CL	15	3.1330 ± 1.187	0.306
	AHA	20	2.900 ± 1.252	0.28
	CHC	26	2.846 ± 1.155	0.226
	Total	61	2.934 ± 1.181	0.151

Note: CL: Control; AHA: Acute Hepatitis A patients; CHC: Chronic Hepatitis C patient.

Table 1: Number, mean, standard deviations and standard errors for all parameters with the case groups.

Parameters		N	Mean Std. Deviation	Std. Error
IFN-β2 (pg/mL)	1-14 y	8	1010E2 ± 155.737	55.061
	15-29 y	14	74.071 ± 118.912	31.78
	30-44 y	19	1.14E2 ± 167.957	38.532
	45-59 y	14	71.537 ± 122.076	32.626
	60-74 y	6	1.34E2 ± 256.446	1.05E+02
	Total	61	95.460 ± 153.534	19.658
Case	1-14 y	8	2.375 ± 0.744	0.263
	15-29 y	14	2.071 ± 0.828	0.221
	30-44 y	19	2.315 ± 0.820	0.188
	45-59 y	14	2.071 ± 0.828	0.221
	60-74 y	6	2.00 ± 0.894	0.365
	Total	61	2.180±0.806	0.103
AST U/L	1-14 y	8	27.650 ± 20.400	7.212
	15-29 y	14	45.121 ± 19.082	5.099
	30-44 y	19	40.463 ± 17.548	4.025
	45-59 y	14	37.307 ± 16.968	4.535
	60-74 y	6	32.766 ± 19.600	8.001
	Total	61	38.375 ± 18.573	2.37814

Table 2: Number, mean, standard deviations and standard errors for all parameters with the age groups.

IFN-β2 serum level

This study is enrolled elevation concentration of IFN-β2 level with the CHC group (mean and standard deviation: 2.010E2 ± 187.289 compared with AHA 18.050 ± 36.128 and for CL 15.734 ± 23.636 groups. These differences are owing to high variation between IFN-β2 concentration samples of CHC group. The correlation coefficient between IFN-β2 level and case groups is significantly related value with p<0.01, r=0.53 with Pearson's test (Figure 1A). Trend line is near the most median gathered samples (Figure 1B).

IFN-β2 level and the age groups is shown elevation of concentration with group 3 and 5 compared with the other groups. The mean, standard deviations and standard errors for each group is in Table 2. The correlation coefficient between IFN-β2 level and age groups is presented no significant value with p>0.01, r=0.031 with Pearson's test (Figure 2A). Trend line is near the most median gathered samples (Figure 2B).

AST serum level

The level of chemical liver test AST is at the same concentration with CL and AHA groups. Most samples are registered with normal concentration compared with CHC group. The mean and standard deviation CL, AHA and CHC groups were 31.880 ± 16.096, 29.380 ± 17.990 and 38.370 ± 18.573 respectively. The correlation coefficient between AST level and case groups is significantly related value with p<0.01, r=0.417 with Pearson's test (Figure 3A). The trending line is nearly at the center of the groups (Figure 3B).

On the other hand, the level of AST measured with age groups is shown no differences levels between age groups. We originated that there is a negative correlation between AST level and age groups at the value with p>0.01, r=0.004. The Pearson's coefficient r is near 0 (Figure 4A). The trending line is nearly at the center of the groups (Figure 4B).

Correlation between IFN-β2 and AST levels

Figure 5 is described the correlation coefficient between IFN-β2 and AST levels significantly related value with p<0.01 and r=0.414. Most samples is observed inside or near the three trending lines specifically those with the median concentration (33.58 U/L) of AST level and under 170 pg/mL level of IFN-β2.

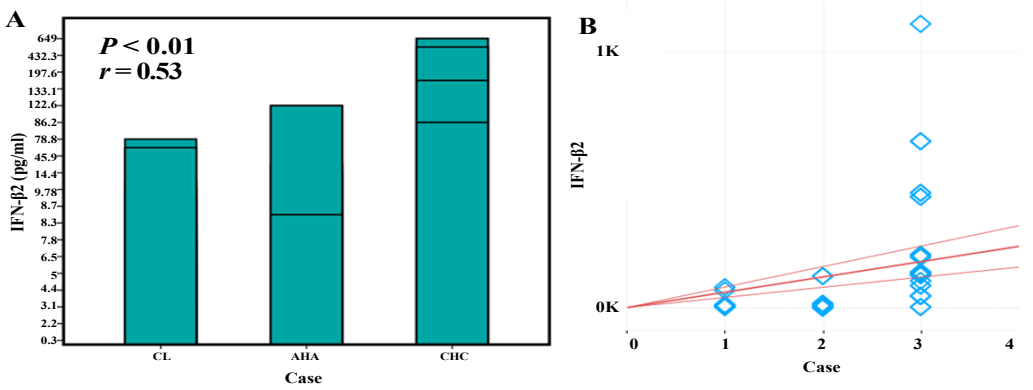

Figure 1A: The correlation coefficient between IFN-β2 level and case groups with Pearson's test. B- Red trend lines: Mid line expresses 0 confidence of samples, upper line is + trend, downer line is - trend.

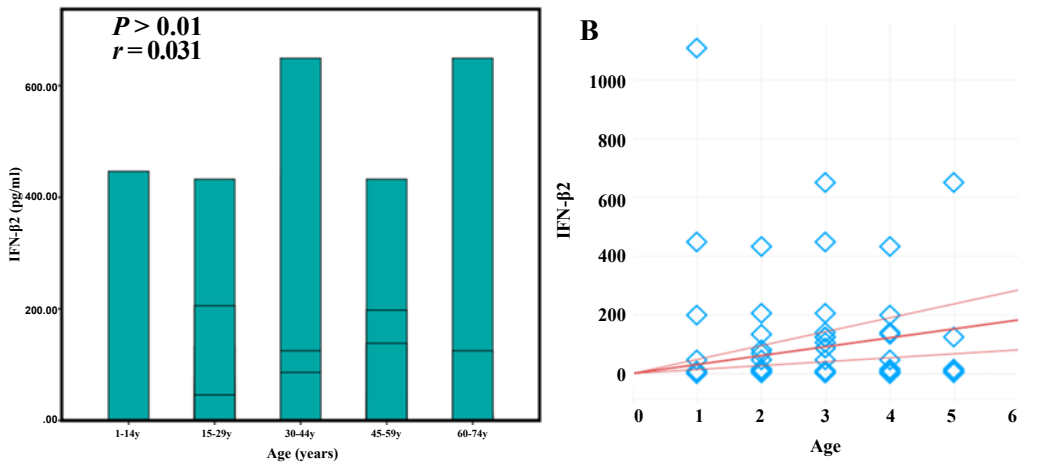

Figure 2B: The correlation coefficient between IFN-β2 level and age groups with Pearson's test. B- Red trend lines: Mid line expresses 0 confidence of samples, upper line is + trend, downer line is – trend.

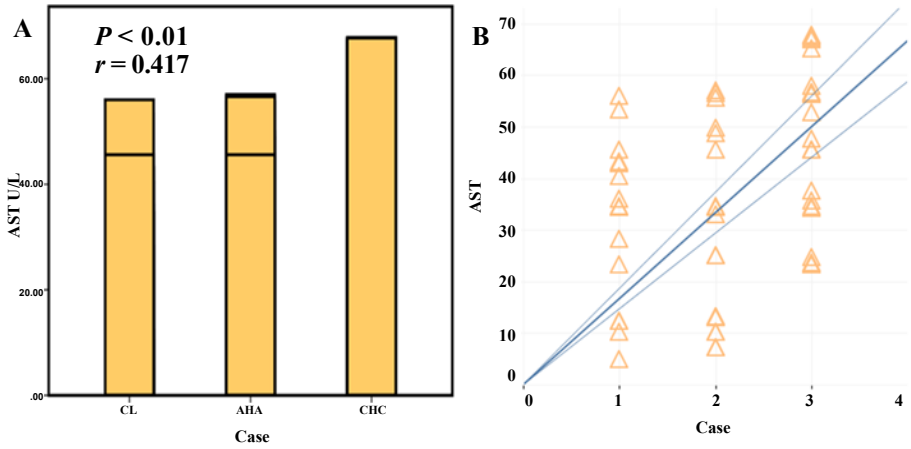

Figure 3A: The correlation coefficient between AST level and case groups with Pearson's test. B- Blue trend lines: Mid line expresses 0 confidence of samples, upper line is + trend, downer line is – trend.

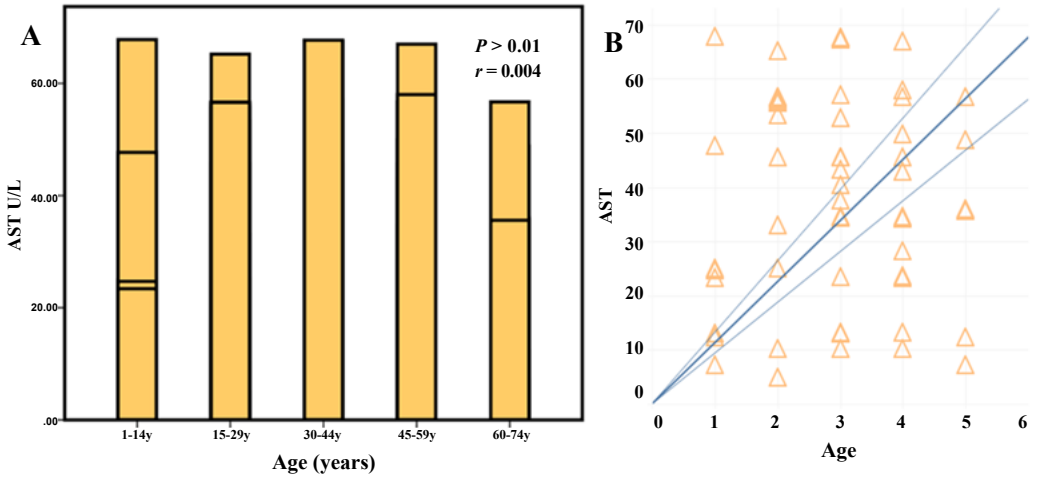

Figure 4A: The correlation coefficient between AST level and age groups with Pearson's test. B- Blue trend lines: Mid line expresses 0 confidence of samples, upper line is + trend, downer line is – trend.

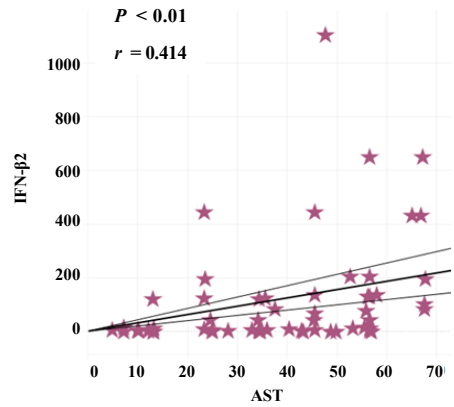

Figure 5: Black trend lines: Mid line expresses 0 confidence of samples, upper line is + trend, down line is – trend.

Correlation between case groups with IFN-β2 levels

The serum IFN-β2 in CHC patient group (median:1.331 pg/mL) was significantly decreased compared to control group (median: 7.800 pg/mL) while it was no significant less decreased AHA group (median : 6.800) the On the other hand, which suggesting the potential relationship between IFN-β2 and HCV infection but not with HAV infection. When compared with the mean differences, It has been observed that there is a significant value between CL and CHC groups with IFN-β2 level (MD: 185.269; $p \leq 0.05$) (Table 3). We found that there is a significant correlation between AHA and CHC groups with IFN-β2 level (MD: 182.953; $p \leq 0.05$) but on the contrary, there is no significant correlation between CL and AHA groups with IFN-β2 (MD: 2.316; $p>0.05$) (Table 3). The description of relationships between case groups and IFN-β2 level is summarized in Figure 6.

Correlation between case groups with AST levels

From the data analysis, there is a significant correlation value between CL and CHC groups with AST (MD: 17.150; $p \leq 0.05$) (Table 3). Furthermore, there is a significant correlation between AHA and CHC groups with AST level (MD: 19.650; $p \leq 0.05$) while this relation is difference between CL and AHA groups with AST level so there is no association between them (MD: 2.500; $p>0.05$) (Table 3). The description of relationships between case groups and AST level is summarized in Figure 7.

Correlation between case groups with age groups

Our study revealed that there is no connotation and no significant value between case groups (CL-CHC, AHA-CL and CHC-AHA) with age groups (MD: 0.287; 0.233 and 0.053) respectively with $p>0.05$ (Table 3). The description of relationships between case groups and age groups is summarized in Figure 8.

The distribution of data cohorts (IFN-β2, AST and age groups) under the dependent factors (AHA s16-35 and CHC s36-61) groups compared with CL (s1-15) group is showed there is no differences

Dependent Variable	Case	Mean Difference	Std. Error	Sig.
IFN-β2	CL CHC	185.269*	40.603	0
	AHA CL	2.316	42.773	0.999
	CHC AHA	182.953*	37.245	0
AST	CL CHC	17.150*	5.299	0.008
	AHA CL	2.5	5.583	0.905
	CHC AHA	19.650*	4.861	0.001
Age	CL CHC	0.287	0.387	0.761
	AHA CL	0.233	0.408	0.85
	CHC AHA	0.053	0.355	0.989

Note: *The mean difference is significant at the $p \leq 0.05$ level.

Table 3: Correlation between case groups with dependent parameters.

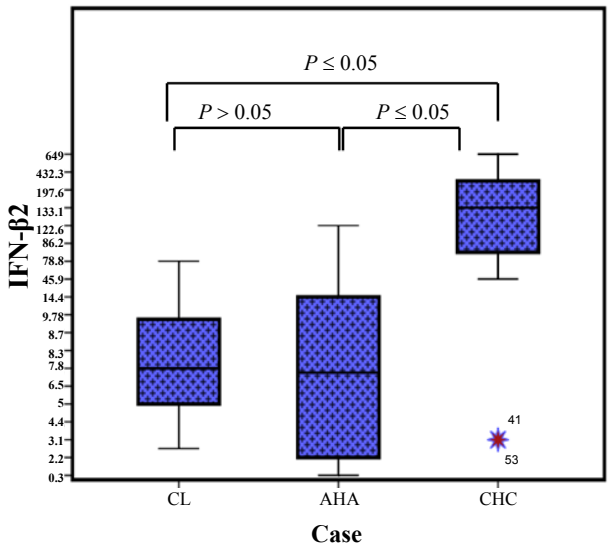

Figure 6: Correlation coefficient between CL, AHA and CHC with frequencies of IFN-β2. 41 and 53 samples show lower concentration of IFN-β2.

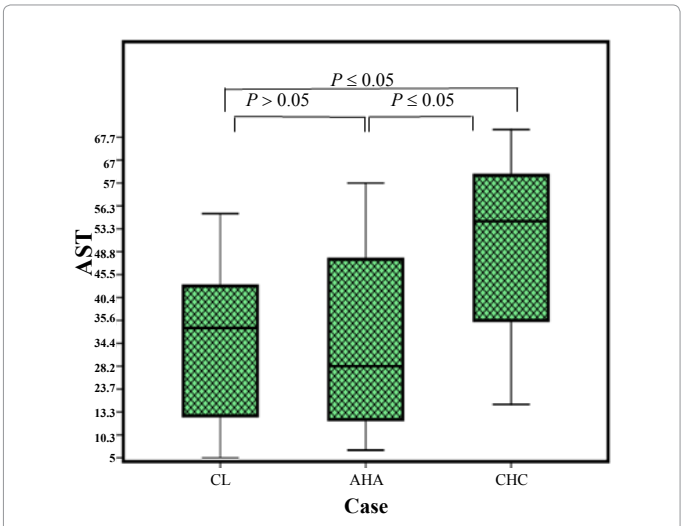

Figure 7: Association between CL, AHA and CHC with frequencies of AST.

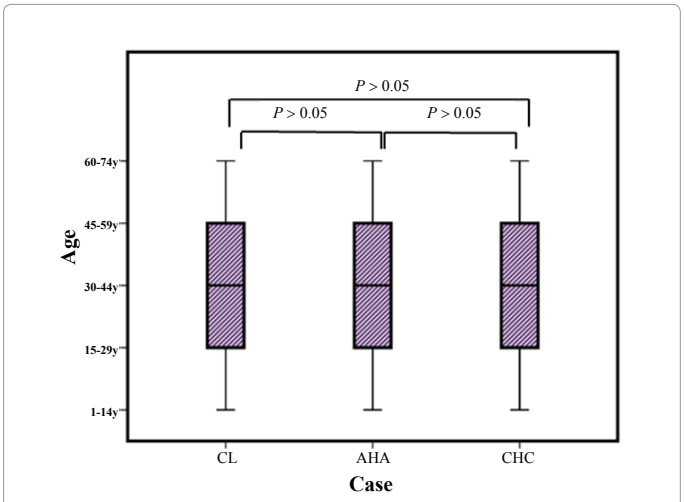

Figure 8: Association between CL, AHA and CHC with frequencies of age groups.

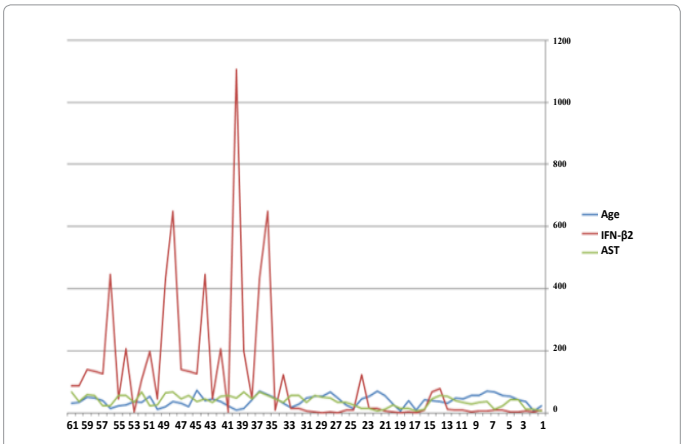

Figure 9: Distribution frequencies between factors and samples (1-61).

between them excepting with IFN-β2. The distribution of this variable had showed high frequencies between samples (Figure 9).

Discussion

Inflammation of liver infections caused by hepatitis A and C viruses are still a major health problem worldwide [14]. Cytokines play a dual important role in virus infection. In acute infection, these cytokines act as an antiviral and help to clear acute infection; they may stimulate inflammatory processes in chronic infection [10]. It has been found that HAV evokes a minimal intrahepatic type I IFN response in chimpanzees, less quantitatively than that observed in acute HCV infections. This finding is attributed of the RNA viral which is about 100-1000 fold more abundant in acute HAV versus HCV infection [11,15]. Since interleukin IL-6 has its alliance name is interferon β2, we have exceeded to use IFN-β2 instead of IL-6 in this study. This is the first time, we found association between acute hepatitis A and chronic hepatitis C infections according to cytokines and chemical parameters.

The present study is underscored the baseline IFN-β2 level. There was significantly higher in the CHC patients than in AHA patients compared with control group. This finding is in agreement with Neculoiu and his colleagues. He identified the presence of increased levels of IL-6 and IL-6R in patients with CHC [8,15]. Recently, there were no explicit reports perceiving the relationship between IFN-β2 level and AHA patients and basing on this, we didn't record connotation between them. The baseline of IL6 > 3 pg/mL is a decent indicator of deprived treatment outcomes of hepatitis therapy [9]. Previous study revealed that IL 33 overexpression is allied with the development of HCV related live CHC patients [16].

AST serum level is one of the important pointers for liver injury. The current study is enrolled elevation of AST level for CHC patients compared with control group with high significant value. On the contrary, the AST level were decrease with AHA patients compared with the control group with no significant value. Our findings explain that there is independent relation between AST level with case groups. Our data is agreed with other study found trends are expressed through the significant increases in AST, ALT, and ALP activities in all patients greatest extent in those with HCV [16]. Furthermore, these data indicated that serum levels of IFN-β2 elevated with the increase of AST levels in patients with chronic hepatitis C infections. In contrast, the IFN-β2 and AST might indicate liver damage of patients with CHC.

The outcomes of our records revealed that there is negative association between the hepatitis infection conditions and the age fundamental in accordance of the main factors used in this study Figures (2B, 4B).

Our data provided evidence that concomitant between IFN-β2 level and chemical parameter AST level which is disclosed correlated significant value with $p<0.01$.This finding is disagreed with previous study presented the low level of IFN-β2 lack of correlation with biochemical and histopathological parameters of the chronic hepatitis [5]. Earlier study emerged correlation between the frequency and liver injury as reflected by increases in serum Alanine Aminotransferase (ALT) [3].

Association between variable factors were described using the Pearson correlation coefficient and confirmed after linear regression. To test for differences between groups, we used One way ANOVA for continuous variables. Parameters considered significant in univariate analysis were introduced into multivariate analysis, using logistic (Tableau) regression analysis for categorical data and multiple regressions for continuous data. Multiple regression analysis and trending lines showed that AST levels, independent IFN-β2 levels for acute hepatitis A infections while these analysis is dependent with chronic hepatitis C. This fact supports the theory that IL-6/sIL-6R complex system is set off in chronic HCV infections [7,15]. Here we would like to clarify, till now there is no imperative information about association between IFN-β2 in patients with acute hepatitis A infections. Prior study exposed new findings summarized to demand relationships between innate and adaptive immune responses and acute liver injury, despite its major fecal-oral route of transmission, the role of the gut as a site for HAV replication and perhaps as a regulator of immune responses so that the HAV has received insufficient attention [13,17]. Our findings are in agreement with the results of Abd El Salama et al., who occurred positive correlation between increase level of IFN-β2 with elevated with AST serum level. On the contrary, our results disagreed with the same study which is found positive significant relation between IFN-β2 level with age ranks [10].

The recent study had only a small number of cases with short follow up, therefore it is recommended to evaluate the dynamic changes in IFN-β2 and other liver function parameters. Future studies with a larger number of samples and extended follow up are warranted to keep up the fundamental association.

In summary, the current study is resulted a sign association between IFN-β and AST levels with the chronic hepatitis C infection. Furthermore, we didn't detect connotation between IFN-β and AST levels with the acute hepatitis A infections. Besides that, it has been reported negative correlation between IFN-β2 and AST levels with age groups. The novel findings might provide new insights into open way to find correlations between different cytokines and biochemical parameters in accordance with all types of viruses that cause liver inflammation.

Conclusion

We can conclude that IFN-β2 levels elevated with the increase of AST levels in patients with chronic hepatitis C. The serum levels of IFN-β2, AST varied in different courses of acute hepatitis A and chronic hepatitis C infection. We speculated that measuring levels of IFN-β2 and AST could be used as an indicator to judge the patient's condition with CHC, but not with AHA patients.

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