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Effects of direct acting antivirals(DAAs)on cryoglobulinemia in patients infected with hepatitis C virus

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ABSTRACT

Background: Hepatitis C virus (HCV) is a global public health problem. There are about 130 to 150 million people suffering from chronic HCV. The highest prevalence of HCV in the world occurs in Egypt with estimates higher than 10% among the general population. Cryoglobulins are proteins found in the blood that precipitate (clump together) in the cold and may cause inflammation and organ damage**.**

Objectives: To evaluate effects of direct acting antivirals on cryoglobulinemia in patients infected with hepatitis C virus and studying the effect of cryoglobulinemia on treatment of HCV by DAAs.

Patients and methods: This cross-sectional study included 130 HCV patients. Patients were treated with sofosbuvir 400 mg plus daclatasvir 60 mg once daily and were evaluated before and after treatment by HCV virus load, detection of cryoglobulin, hematological parameters, liver and kidney function tests,blood glucose and lipid profile.

Results: The efficacy of DAA was significantly lower in cryoglobulin positive patients (88.24%) compared to cryoglobulin negatives (98.23%) ($P < 0.05$).The number of cryoglobulin positive patients (17/130, 13.1%) significantly decreased after treatment of HCV with DAA (6/130, 4.6%) ($P < 0.05$). RBS, cholesterol and triglycerides, ASTand ALT significantly improved after treatment.

Conclusion: Direct acting antivirals were very effective and safe for treating HCV and its associated cryoglobulinemia. Additionally, treatment of HCV patients with DAA lead to improvement of liver function tests, lipid profile and blood glucose.

Keywords: Cryoglobulinemia, Direct acting antiviral drugs, Hepatitis C virus.

INTRODUCTION

As indicated by the World Health Organization (WHO), Egypt is positioned as the country with the world's highest prevalence of Hepatitis C virus (HCV). HCV is transmitted through unexamined blood transfusions, different employments of syringes, and poor cleansing **[1].**

Hepatitis C virus (HCV) is a hepatotropic RNA virus that causes progressive liver damage, which might result in liver cirrhosis and hepatocellular carcinoma. Globally, between 64 and 103 million people are chronically infected. **[2].**

Diagnostic procedures include serum HCV antibody testing, HCV RNA measurement, viral genotype and subtype determination and, lately, assessment of resistance-associated substitutions **[3].**

Unmatched progress in the treatment of chronic HCV infection has been made over the last two decades. Interferon monotherapy was the first approved antiviral treatment. Recently, direct-acting antivirals (DAAs) have replaced interferon-based therapy. Egypt is the leading country in treating HCV patients with DAAs, so, it is important to assess their efficacy and safety **[4].**

Various DAAs have become available, which target three proteins involved in crucial steps of the HCV life cycle: the NS3/4A protease, the NS5A protein and the RNA-dependent RNA polymerase NS5B protein **[5].**

Sofosbuvir is a new drug candidate for hepatitis C treatment, previously known as PS-7977 or GS-7977, that has shown promising results in numerous *in vitro* studies against all the genotypes of HCV. It is a nucleotide analog that is a highly potent inhibitor of the NS5B polymerase in HCV **[6].**

Combination of two or three of these DAAs can cure (defined as a sustained virological response 12 weeks after treatment) HCV infection in >90% of patients, including populations that have been difficult to treat in the past **[7].**

Cryoglobulins are proteins found in the blood that precipitate (clump together) in the cold and may cause inflammation and organ damage. However, these proteins can also be present in low levels in the blood without causing any symptoms. When there are symptoms due to the cryoglobulins, the disease (usually a special rash) is called "cryoglobulinemia**." [8].**

There are three types of cryoglobulins: Type I (also called simple), which is mostly associated with monoclonal gammopathy and/or other hematologic disorders and Type II and Type III (known as mixed cryoglobulins), which are associated with infectious and systemic

diseases **[9].**Treatment of cryoglobulinemia focuses on management of the underlying lymphoproliferative disorder or infectious or systemic causes. Medical management may also include corticosteroids and other immunosuppressive agents and plasmapheresis. Rituximab therapy seems to abrogate the aberrant B cell response **[10].**

So, the aim of this study is tostudy effects of direct acting antivirals on Cryoglobulinemia in patients infected with hepatitis C virus and studying the effects of Cryoglobulinemia on the efficacy ofDAAs for HCV treatment.

PATIENTS AND METHODS

This cross-sectional study was conducted on 130 participants who attended National Liver Institute, Menoufia University during the period from December 2019 to January 2022.

Ethical consideration:the ethical committee of the Faculty of Science, Menoufia University, approved the study. Written informed consent was obtained from the patients after a simple and clear explanation of the research objectives. Patients were selected according to the inclusion and exclusion criteria as follows:

Inclusion Criteria:

- Hepatitis C patients from El-Menoufia governorate.
- Age between 18- 64 years.
- Hepatitis C patients treated by DAAs

Exclusion criteria: -

- Patients who are already on anti-viral therapy.
- Patients who are co-infected with HIV or HBV
- patients who <18 or >64 years old.
- Pregnant female.
- Hepatocellular carcinoma.
- Patients who refuse to participate in the study.
- Other causes of chronic liver diseases (e.g. auto-immune hepatitis, biliary cirrhosis, cardiac cirrhosis etc.).
- Patients suffering from chronic uncontrolled debilitating disease e.g. uncontrolled Diabetes Miletus, Sarcoidosis, SLE, etc.

- Post treatment patients who had one of the major risk factors of HCV reinfection within three months after completing treatment course e.g. dental work up, minor surgery, anorectal surgery, blood transfusion, i.v. drug abusing etc.
- Patients receiving immunosuppressive or cytotoxic medicine.
- Patients present with decompensated hepatic disorders.

Patients were treated withsofosbuvir 400 mg (Gilead Sciences, Inc) once daily plus daclatasvir 60 mg (Bristol Myers Squibb)once daily. Patients were subjected to serial follow-up of hepatitis C ribonucleic acid (viral load).

All patients were subjected to the following:

- Detailed historytaking including personal history (name, age, sex, residence), vaccination history and history of parenteral anti-schistosomal therapy.
- Laboratory investigations including hematological parameters (complete blood count andprothrombin time) using Sysmex KX-21 automatized hematology analyzer (SysmexCorporation, Japan).Biochemical parameters (random blood glucose,liver function tests: included ALT, AST, total and direct bilirubin, albumin and alkaline phosphatase,kidney function tests (creatinine, ureaanduric acid)**,** alpha-fetoprotein,CPKenzyme,lipid profile (cholesterol and triglycerides)using the open system autoanalyzersynchron CX5 (Beckman, PincusandAbraham,USA).
- Virologicalresponse(Quantitative PCR for HCV):serum HCV-RNA levels were quantified by the CobasAmpli Prep/CobasTaqMan HCV-RNA assay (Roche Diagnostics) with a lower detection limit at 15 IU/mL.
- Testing for cryoglobulin: The patient's blood sampleswere kept at 37°C initially to avoid premature precipitation of cryoglobulins and thereby decreasing the yield for subsequent identification. This could cause a false negative result**.** After warm centrifugation or warm cell precipitation, the clear serum was observed at 4°C for formation of cryoprecipitate. The cryoprecipitate was then washed in cold buffer, and the resulting precipitate was warmed to 37°C and subjected to further analysis by immunodiffusion and immunofixation**[8]**.

Statistical analysis:

Statistical Package for the Social Sciences (SPSS) version 23 was used on an IBM compatible personal computer to gather, tabulate, and statistically analyze the data (Armonk, NY: IBM Corp.) There were two sections of statistics; Descriptive statistics: the presentation

of quantitative data as median and range, Analytical statistics: Chi-square test (2), Student t test (t), Mann-Whitney test: it is a nonparametric test (U). P values of ≤0.05 considered significant level.

RESULTS

A flowchart of the study population is shown in **Figure 1.** Of the 145 patients,15 patients were excluded from the study (9 patients declined consent and 6 patients did not meet the inclusion criteria, 130 patients were willing to participate in the study.

In our study, a total of 130 patients, their age ranges from 22-62 years with a mean of (39.79±10.59) years. Moreover, 80 patients (61.54%) were males and 50 (38.46%) were females**(Table 1).**126/130 patients (96.9%) were cured by DAA and 4/130 patients(3.1%) were positive PCR after treatment (P <0.001)**(Table 2).**The efficacy of DAA was significantly lower in cryoglobulin positive patients (88.24%) compared to cryoglobulin negatives (98.23%) (P < 0.05),**(seeTable3).**

The number of cryoglobulin positive patients (17/130, 13.1%) significantly decreased after treatment of HCV with DAA (6/130, 4.6%) (P < 0.05) **(Table4).** The age was significantly older among positive cryoglobulin(52.82±8.30 years) than negative cryoglobulin(37.83±9.48 years) (P <0.05) **(Table 5).**

In the positive cryoglobulin group, RBS, cholesterol and triglycerides were significantly decreased after treatment (130.83±73.40, 196.33±26.11, 112.00±18.88) than pretreatment (188.41±76.62, 256.12±48.21, 137.00±27.32), respectively (P<0.05), **(Table 6).**

Moreover,ASTandALT were significantly decreased after treatment (36.67±6.83, 35.50±5.72) than pretreatment (62.29±24.63, 73.59±29.481), respectively (P<0.05) **(Table 6).**

DISCUSSION

A total of 130 patients participated in this study, their age ranges from (22-62) years with mean age (39.79±10.59) years. Moreover, 80 patients (61.54%) were males and 50 patients (38.46%) were females. **Naga *et al.,***reported that the mean age of 640 patients at diagnosis of chronic HCV infection was 49.89 ± 11.22**[11]**. Also,**Mohamoud*etal.,***reported that HCV prevalence increases significantly with age with the highest rates observed among patients aged greater than 40 years**[12]**.

In this study, 126/130 patients (96.9%) were cured by DAA and the prevalence of cryoglobulinemia (17/130, 13.1%) significantly decreased after treatment of HCV with DAA (6/130, 4.6%) (P < 0.05).

Because the activity of mixed cryoglobulinemia (MC) usually correlates with viremia, therapy should be directed toward the potential causal agent**[13]**.The efficacy and safety of all oral direct-acting antivirals (DAAs) therapy in HCV-MC are largely unknown**[14]**and very few studies investigate the efficacy of sofosbuvir-based DAA regimens for HCV patients generally and for HCV-MC patients specifically. The results of the study by **Hassan*et al.,*** pertaining to the therapeutic efficacy of the combined use of sofosbuvir and daclatasvir as oral DAAs revealed 100% SVR12 and clearance of cryoglobulins, with significant improvements in Child-Pugh score, liver FibroScan status, hemoglobin levels, platelet counts, liver functions, and eGFR and creatinine levels, with 87% of the included patients showing a complete response and 13% a partial response without any side effects (apparent clinical or laboratory abnormalities). This indicates the higher therapeutic efficacy and safety of sofosbuvir and daclatasvir in managing HCV-MC **[15]**.

In agreement with these findings, **Sise*et al.,*** reported that 83% of HCV-MC patients showed SVR12 rates for sofosbuvir-based DAA regimens**[14]**. Also, our findings were in line with **Saadoun*et al.,*** who reported an abrupt decay of HCV-RNA with DAAs with a rapid improvement of the clinical manifestations of MC that may allow the reduction or even cessation of the traditional immunosuppressive therapy **[16]**. **Gragnani*et al.,***reported that IFN-free DAAs therapy was highly effective and safe for HCV-MC, with an overall 100% rate of clinical response of vasculitis**[17]**. Furthermore, **Emery *et al.,*** concludes in their study that DAAs resulted in high rates of SVR in HCV-MC with excellent safety. However, some of their patients did not have complete clinical or immunological response, suggesting a delay to clinical response, particularly in those with severe vasculitis**[18]**.

On the other hand, the study by **Ghaleb*et al.,*** revealed that, the prevalence of cryoglobulin was (72%)**[19]**. Also, **Okuse*et al.,*** found that, the prevalence of cryoglobulin was 70% in a Japanese study of 232 HCV-infected patients using diffusion method for detection of cryoglobulin**[20]**. Additionally, the two studies by **Ferri*et al.,* [21]** and **Landau *et al.,* [22]** found that 50% to 60% of HCV infected patients produce a mixed cryoglobulin that will lead to a cryoglobulinemicvasculitis in 15% of cases. In another study by **Akriviadis*et al.,*** who studied 81 patients with HCV, a prevalence of 45.7% was reported**[23]**.The discrepancy of the prevalence of cryoglobulins reported in the present study may be attributed to the different methods used for the diagnosis, different genetic backgrounds and relatively small number of the patients in the different studies.

The efficacy of DAA was significantly lower in cryoglobulin positive patients (88.24%) compared to cryoglobulin negatives (98.23%). In relation to this, Gragnanietal.[17] reported

that MC is a negative predictor factor of virologic response and clearance of HCV led to resolution of symptomatic MCS in IFN based therapy of HCV patients. However, Elshazly [24] and Boglione et al. **[25]**reported that SVR12 showed no significant difference between MCS-positive and MCS-negative groups.

As HCV infection has various extrahepatic presentations such as metabolic dysfunctions **[26],** patients with CHC are more likely to develop prediabetes and diabetes **[27, 28].**HCV eradication using antiviral therapy significantly reduces hepatic complications and ameliorates metabolic disarrangement **[29,30].** Insulin resistance and beta cell function may improve **[30–32]** and the incidence of diabetes might decrease after HCV eradication **[33].** However, the results remain inconsistent among different studies **[34].**

This study showed that AST, ALT and direct bilirubin, total bilirubin and alkaline phosphatase were significantly increased in positive cryoglobulinthan negative cryoglobulin patients. In the same line, the study by **Ghaleb*et al.,*** revealed that, patients who were positive for cryoglobulin had a significantly higher liver function (ALT, AST, direct bilirubin, total bilirubin and alkaline phosphatase), (P< 0.05)**[19]**. Also, the study by **Sansonno*etal.,***reportedthatAST, ALT and total bilirubin in HCV patients who were positive for cryoglobulin were significantly higher than those negative cryoglobulin (P < 0.05)**[35]**. Furthermore, the study by **Lee *et al.,* [36]** found that, there was a significant relation between cryoglobulin and liver function in positive cryoglobulin (p< 0.05).

In the positive cryoglobulin group, RBS, cholesterol, triglycerides, ASTand ALT were significantly improved after treatment. In agreement with this, cohort studies suggest that successful treatment of chronic HCV infection with currently available direct acting antiviral agents (DAAs) improves glycemic control in these diabetics **[37–42].Matsui *et al*.,** demonstrated in vitro that hepatitis C viral replication suppresses GLUT2 expression and hence cellular glucose uptake, doing so by degrading and downregulating hepatocyte nuclear factor 1α **[43]**.Furthermore,**Mada*et al*.,** demonstrated that treatment of chronic hepatitis C with DAAs results in statistically significant and meaningful reductions in hemoglobin A1C levels in patients with coexisting diabetic mellitus if a SVR is achieved **[44].** However, some authorsreported improvement in HbA1C with DAA treatment and no significant change in the HbA1C level with DAA treatment for HCV **[45, 46].**

Moreover,**Mohey El-Din *et al.,***showed that eradication of HCV by DAAs will result in a parallel decrease in lipid parameters including cholesterol, triglycerides, HDL and LDL and that may improve clinical outcomes in patients with stablished T2DM **[47]**. However, the

results of the different studies are, conversely, quite often contradictory,regarding lipid profile, since some show increases in HDL cholesterol levels **[48–51],** but this is not reported in other studies **[52–54]** or even a decrease is observed **[54].** In the case of triglycerides, disparate results have also been reported, with minimal or absent changes **[50,55]** or even decreases **[56,57].**

The main limitations of the present study were the limited number of patients participating and the single center study nature of the study and this was attributed to the financial limitations.

CONCLUSION

Direct acting antivirals were very effective and safe for treating HCV and its associated cryoglobulinemia and so it helped in eliminating HCV burden in Egypt. Additionally, treatment of HCV patients with DAA lead to improvement of liver function tests, lipid profile and blood glucose which might improve the quality of life of the patients.

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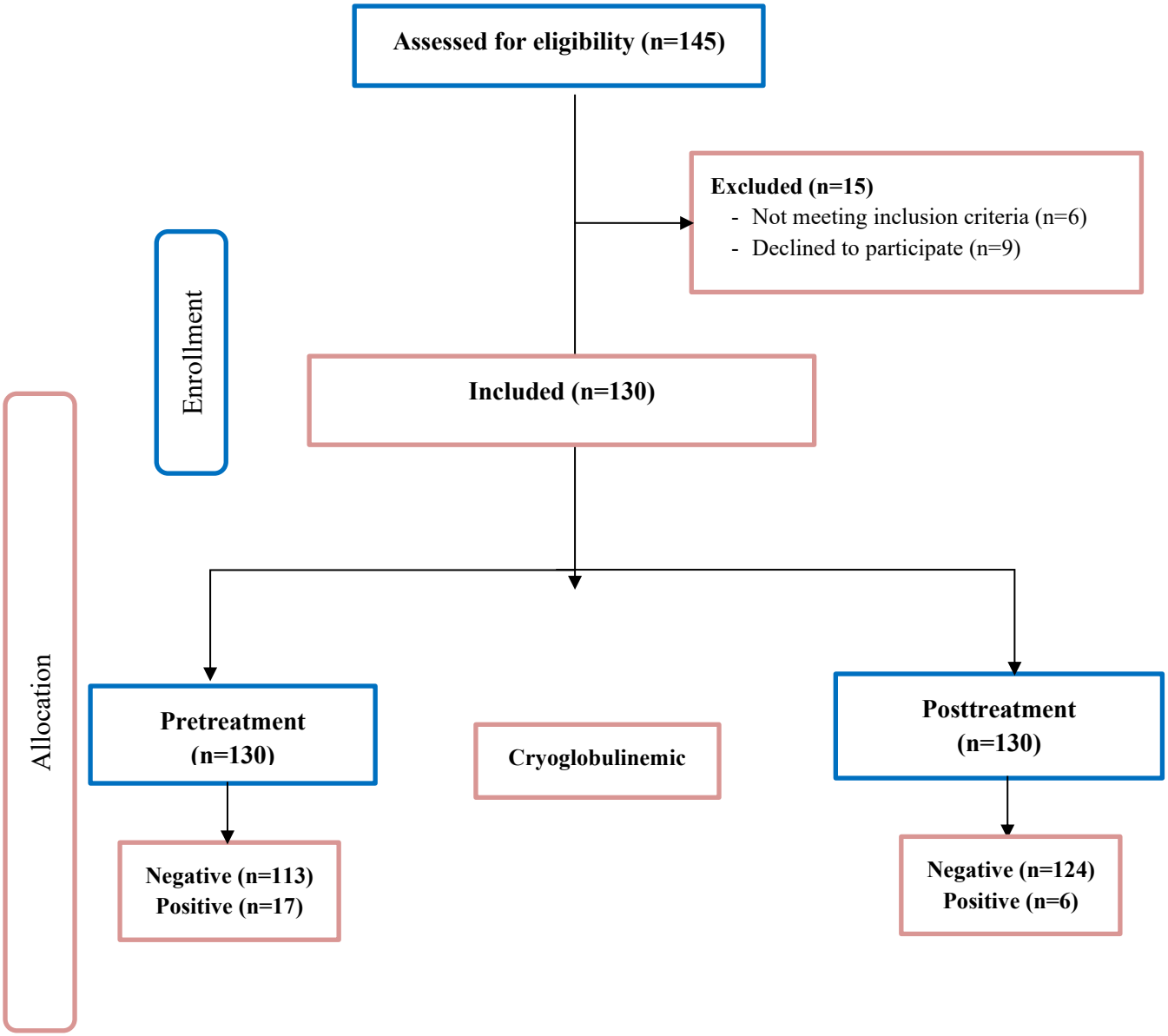

Figure 1. Flowchart of the studied cases.

Table (1): Demographic data of the studied patients

Variable	All studied patients N=130

Age (Years)		
Mean ±SD	39.79±10.59	
Range	22-62	
Sex	**N**	**%**
Male	80	61.54
Female	50	38.46

Table (2**):** Virological response among the studied groups

Variable	All studied groups				X^2	*P value*
	Pre-N=130		Post N=130			
PCR	**N**	**%**	**N**	**%**		
Negative	0	0	126	96.9	260.00	**<0.001***
Positive	130	100	4	3.1		

X²: Chi-Square Tests, ***:** Significant, **PCR:**Polymerase Chain Reaction.

Table (3): Virological responses of DAAs in positive and negative cryoglobulin patients

PCR	Cryoglobulin				X^2	*P value*
	Negative		Positive			
	N	**%**	**N**	**%**		
Before						
Negative	0	0.0	0	0.0	---	---
Positive	113	100.0	17	100.0		
After						
Negative	111	98.23	15	88.24	6.03	0.0452
Positive	2	1.76	2	11.76		
% Improvement						
%	98.23%		88.24%		6.03	**0.0452***
X^2	246.5		80.12			
P value	**<0.001***		**<0.001***			

***:** Significant, **PCR:**Polymerase Chain Reaction.

Table (4**):** Cryoglobulin measurement among the studied groups

Variable	Count				X^2	*P value*
	Pre		Post			
	N=130	**%**	**N=130**	**%**		
Cryoglobulin(mg/L)						
Negative	113	86.9	124	95.4	5.771	**0.016***
Positive	17	13.1	6	4.6		

X²: Chi-Square Tests, ***:** Significant.

Table (5): Comparison between cryoglobulinnegative and positive regarding age

Variable	Cryoglobulin		*U*	*P value*	95% CI	
	Negative N=113	Positive N=17			Lower	Upper
Age (Years)						
Mean ±SD	37.83±9.48	52.82±8.30	6.809	**<0.001**	-19.55	-10.43

***:** significant, **U:** Mann-Whitney U test.

Table (6): Comparison between laboratory values of positive and negative cryoglobulinpatients before and after treatment.

Variables	Positive		*P value*	Negative		*P value*
	Pre	Post		Pre	Post	
	Mean ±SD	Mean ±SD		Mean ±SD	Mean ±SD	
Hb (g/dl)	12.84±1.60	11.72±1.09	0.080	12.64±1.50	11.99±1.47	0.067
RBCS (cells/mcL)	4.52±0.72	3.85±0.38	**0.010***	4.30±0.56	4.22±0.56	0.283
HCT	39.56±5.99	34.97±4.33	0.067	37.86±4.98	36.88±4.75	0.121
MCV (fL)	84.18±4.72	84.17±2.32	0.995	83.82±5.71	79.90±4.51	0.058
MCH (pg)	26.70±1.77	27.57±1.07	0.177	27.65±1.15	27.25±1.63	0.128
MCHC (g/dL)	32.54±0.89	32.10±0.92	0.342	32.85±0.90	31.96±3.78	0.112
WBC (10^9/L)	7.11±2.60	6.57±3.02	0.704	7.80±2.51	7.13±2.20	0.132
PLT (10^9/L)	181.94±46.44	153.00±43.41	0.200	204.45±62.75	190.96±54.11	0.079
Lymph (K/µL)	40.15±5.67	38.80±5.63	0.627	37.67±11.91	36.50±10.34	0.425
Mon	6.99±1.70	5.65±1.17	0.056	6.87±2.04	6.86±1.75	0.964
GRA	51.95±5.25	52.75±6.44	0.791	54.78±11.87	56.90±10.14	0.142
PT (Sec)	13.59±0.80	12.80±0.11	**0.001***	13.32±0.48	13.13±0.45	0.320
Conc	89.06±10.42	98.50±1.64	**0.002***	93.55±15.21	93.75±6.98	0.898
INR	1.12±0.14	1.01±0.01	**0.005***	1.09±0.07	1.07±0.13	0.158
RBS	188.41±76.62	130.83±73.40	**0.006***	104.91±33.04	106.92±36.90	0.659
CPK (mcg/L)	65.12±26.89	53.00±24.88	0.340	41.23±17.79	46.63±19.25	**0.026***
AFP (ng/mL)	6.44±2.73	4.77±2.67	0.224	3.59±1.65	3.98±2.06	0.110
Cholesterol (mg/dL)	256.12±48.21	196.33±26.11	**0.002***	186.88±49.06	177.46±35.62	0.095
Triglycerides (mg/dL)	137.00±27.32	112.00±18.88	**0.029***	79.62±29.03	81.44±29.95	0.636
Urea (mg/dL)	43.18±9.17	36.33±4.89	**0.035**	33.43±6.86	35.41±7.98	**0.041**
Creatinine (mg/dL)	1.18±0.16	1.13±0.19	0.582	0.97±0.20	1.05±0.21	**0.001**
uric Acid (mg/dL)	5.61±1.52	6.17±1.38	0.424	4.39±0.74	4.42±0.52	0.740
AST (U/L)	62.29±24.63	36.67±6.83	**0.001**	44.47±23.10	34.56±15.17	**<0.001***
ALT (U/L)	73.59±29.48	35.50±5.72	**<0.001***	47.81±26.64	35.81±15.98	**<0.001***
ALB (g/dL)	3.51±0.29	3.88±0.50	0.134	3.84±0.57	4.01±0.76	**0.047**
Direct bilirubin (mg/dL)	0.53±0.26	0.23±0.08	**<0.001***	0.30±0.15	0.19±0.06	**<0.001***
Total bilirubin (mg/dL)	1.39±0.45	1.03±0.26	**0.032**	1.13±0.25	0.97±0.25	**<0.001***
Alkaline Phosphatase (IU/L)	118.24±60.73	60.67±15.86	**0.002**	65.59±31.63	53.25±23.30	**0.001**

Hb: Hemoglobin, **RBCs:** Red blood cells, **HCT:**hematocrit, **MCV:** Mean corpuscular volume, **MCH:**Mean Corpuscular Hemoglobin, **MCHC:**Mean corpuscular hemoglobin concentration, **WBC:** White blood cell, **PLT:**Platelet, **Mon:**Monocytes**, GRA:** Granulocyte, **PT:** Prothrombin time**, INR:** international randomized ratio**, RBS:** Random blood sugar, **CPK:**Creatine Phosphokinase, **AFP:**Alpha-fetoprotein, **ALT:** Alanine aminotransferase, **AST:**aspartate aminotransferase, **ALB:** Albumin***:** Significant