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Diagnostic role of Protein Induced by Vitamin K Absence or Antagonist-II (PIVKA-II) and its correlation with serum Lipid Profiles in HCV Iraqi patients

Lubna Hussein Murshed[12a], Athraa Zaidan Hassan[1b] and Jaleel Samanje[1c]

[1]*Department of Medical Laboratory Technique, College of Health and Medical Techniques/ Middle Technical University, Baghdad, Iraq*
[2]*Kirkuk Health Directorate Iraqi Ministry of Health, Kirkuk, Iraq*

[a]E-mail: edc4005@mtu.edu.iq, [b]E-mail: dr.azh.mousawi@mtu.edu.iq
[c*]Corresponding author: jaleel.najah@mtu.edu.iq

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Abstract*— This study aimed to understand the role of serum Protein induced by Vitamin K Absence or Antagonist II (PIVKA-II) and its correlation with lipid profiles as diagnostic biomarkers in patients with different stages of hepatitis C virus infection. A case-control study involved 150 participants aged 5 to ≥81 years, 50 individuals were healthy, and 100 had HCV infection. The mean serum levels of PIVKA-II were significantly increased in acute hepatitis C (AHC), chronic hepatitis C (CHC), Hepatitis C virus-induced liver cirrhosis (HCV-LC) and sustained virologic response (SVR) groups compared to healthy control group. PIVKA-II showed significant negative correlation with Triglycerides (TG) and very low-density lipoprotein (VLDL) in both acute and chronic hepatitis C groups, and negative correlation with low density lipoprotein (LDL) in HCV-LC group. Receiver Operating Characteristic (ROC) curve analysis of PIVKA-II in HCV patients showed higher sensitivity and specificity in all four included HCV stages. Elevated serum PIVKA-II in HCV patients in this study predict its possibility in using as biomarker for diagnosing different HCV stages - acute, chronic, cirrhosis, and sustained virologic response from healthy individuals. However, the small differences in mean serum PIVKA-II levels between HCV groups make it unsuitable biomarker to differentiate between studied stages of HCV infection. The negative correlation between PIVKA-II and serum lipid profiles in treatment naïve HCV patients can be used as a prognostic biomarker for liver disease severity and the risk of Hepatocellular carcinoma (HCC).

Keywords*— *HCV, PIVKA-II, Lipids, serum, Biomarker.

I. INTRODUCTION

Hepatitis C virus (HCV) belongs to the family Flaviviridae of the genus Hepacivirus which is a positive-sense RNA virus [1]. Since HCV is a non-cytopathic virus, immune dysregulation is the primary pathogenesis of HCV-associated liver diseases [2- 4]. Although chronic hepatitis, liver cirrhosis (LC) and hepatocellular carcinoma (HCC) can result from multiple etiologies such as alcohol consumption, non-alcoholic fatty liver disease and chronic viral infections including HCV and HBV, but HCV related cirrhosis and liver cancer caused the deaths of roughly 242,000 people in 2022 and about one million new infections occurring annually [5-6].

Protein induced by vitamin K absence or antagonist-II (PIVKA-II) also known as des-γ-carboxy prothrombin is an aberrant form of prothrombin first identified in patients with cirrhosis and hepatitis and it has been recognized as a promising biomarker useful for diagnosis, monitoring and treatment of HCC [7]. PIVKA-II is produced in the liver and commonly measured for HCC screening in hepatic diseases of different origins, and elevated PIVKA-II values are occasionally observed in patients without HCC. However, PIVKA-II is also present in some benign liver diseases, such as acute and chronic hepatitis when vitamin K is absent or its antagonist is present inhibiting vitamin K-dependent carboxylase activity [8].

Infection with hepatitis C virus significantly affects lipid metabolism, leading to alterations in serum lipid profiles according to disease progression and treatment outcomes, HCV has been revealed to increase lipid biosynthesis and impair lipid catabolism, causing hypocholesterolemia and intracellular accumulation of lipids [9]. Direct acting antivirals (DAAs) also have been reported to affect serum lipid profiles especially low-density lipoprotein (LDL), high-density lipoprotein (HDL) and triglyceride [10]. Finding liver disease in its early stage is one of the most important challenges in HCV research as it enhances the effectiveness of antiviral therapy. This study aimed to assess the levels of serum PIVKA-II and serum lipid profiles for the diagnosis and prediction the stage of HCV disease in HCV patients.

II. PATIENT AND METHODS

Before taking the information and blood samples, approval was obtained from the Medical Ethics Committee on human research of the Middle Technical University, College of Health and Medical Technology (Baghdad, Iraq). In this prospective study, a total collected 150 blood

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samples from five groups of participants who registered during the period from May/2024 to December /2024: Group I included 25 cases of acute hepatitis C whose ages ranged between (5-41) years. Group II comprised 25 patients of chronic hepatitis C with ages ranged between (12-63) years. Group III included 25 cases of (HCV induced cirrhosis) whose ages ranged between (25-81) years and Group IV comprised 25 treated HCV patients known as sustained virologic response (SVR), while Group V (control group) included 50 obviously healthy individuals with ages (5-81) years who were negative for viral screen by ELISA. Results of viral load were obtained from molecular laboratory in gastrointestinal tract Teaching Hospital/Medical city, Baghdad. Inclusion criteria were based on a positive enzyme-linked immunosorbent assay (ELISA) test and a positive PCR viral load test for HCV in groups I,II and III, but a positive HCV antibody test with negative PCR HCV viral load test in group IV (SVR group). The control group included healthy individuals who were negative for viral screen by ELISA. The exclusion criteria in this study include absence of other liver disease, autoimmune, metabolic disorders, co-infection with hepatitis B virus and/or human immunodeficiency virus, malignancies and alcohol abuse, pregnant women and individuals taking warfarin or other blood emulsifying drugs were also excluded.

A. Blood Samples Collection

Five milliliters of venous blood samples were collected from each individual enrolled in this study using disposable syringes and placed into anticoagulant-free gel tubes then were centrifuged at 4000g for 10 minutes and the supernatant serum was collected. Afterwards, serum was divided into two aliquots placed in Eppendorf tubes and frozen at -20 ºC until one of them used for serum PIVKA-II investigation, and the second for lipid profile tests. Serum PIVKA-II levels in all groups were measured by commercially available ELISA kits (Shanghai Ideal Medical Technology Company, LTD., China), according to the operating instructions provided by the manufacturer. Serum levels of Total cholesterol (TC), High density lipoprotein (HDL), Low density lipoprotein (LDL), Very low density lipoprotein (VLDL), and Triglycerides (TG) in patients with HCV and healthy controls were detected using standard automatic biochemistry analyzer (Thermo Fisher 240 V Indiko Plus Clinical Chemistry Analyzer, Kerala, India).

B. Statistical Analysis

Statistical analysis and calculations were performed using Statistical Packages for Social Sciences- version 26, software (SPSS-26) from Chicago, USA. Data were presented in mean, standard deviation, percentage, and standard error of the mean. Normality test was used to determine whether the variables were normally distributed or not. The significance of difference of normally distributed continuous quantitative data was tested with ANOVA test, while the significance of the difference between non-normally distributed continuous quantitative data was tested using the Kruskal-Wallis H test for differences between more than two independent means or the Mann-Whitney U test for differences between two independent means. When the P value was equal to or less than 0.05, statistical significance was taken into account. The correlation between serum lipid profiles and PIVKA-II was computed using Spearman's Rank correlation. The use of PIVKA-II as a disease diagnostic or screening tool and the capacity to identify the "cut-off value" with the best sensitivity and specificity for disease diagnosis were assessed using the ROC curve.

III. RESULTS and DISCUSSION

A. Demographic Distribution of the Studied Groups

Table 1 showed the characteristics of the studied groups according to sex and age with comparison of significance. The table showed that there were 14 male (56%) and 11(44 %) female patients with mean age (14.6) years in the AHC group, while there were 15 male (60%) and 10 female (40 %) patient in both CHC and (HCV-LC) groups with mean age (38.8) and (54.4) years respectively. Moreover, the SVR had 9 male (36 %) and 16 female (64%) and the mean age was (38.9) years, while the control group had 30 male (60 %) and 20 female participants (40%) and the mean age was (35.7) years. It was shown that the highest percentages of the studied groups were male except for SVR group was female. Besides, results in this table demonstrated that there was a highly significant difference between the mean ages of all groups (P=0.001) but there was no statistically significant difference among the sex of these groups (P=0.32). These results were consistent with that of Abdel-Gawad *et al*., [11] and Marzuk *et al*., [12] and Hameed, [13] who found no significant variation in the distribution of HCV antibodies between males and females indicating that the disease may infect both males and females. This is also consistent with Mahran *et al.* [14] who found that there was no significant difference in gender among HCV patients treated with DAAT. Whereas another study by Alsaffar, [15] contradicted the current results showing a significantly higher male-to-female ratio, and a study by Simoes *et al*., [16] who reported that SVR was significantly lower in women than in men. The high rate of HCV infection in men may be explained by the socio-community nature of Iraqis, which forces men to shoulder the burden of employment and exposes them to more pathogens than women. The increased response of women to treatment in Iraq may be attributed to increased women access to care and adherence to therapy, in addition to biological factors such as increased estrogen in women decrease HCV virion production by decreasing virus assembly and secretion [17]. Additionally, enhanced interferon signaling pathways [18] in premenopausal females may be responsible for increased women response than men to antiviral treatment.

Our results were consistent with those of Hetta *et al*., who showed that mean age in HCV induced liver cirrhosis patients was highly significantly higher than mean age of chronic hepatitis C virus group [19]. However, the observation of our study disagrees with study by Alazzawy *et al*., who showed that the studied groups were age matched (P > 0.05) and that the highest rate of patients with acute and chronic hepatitis C virus was within the age group 40-49 years [20]. The results of our study indicates that HCV is

slowly progress disease and doesn't cause morbidity for many years, in addition, complications from HCV increase with increased age being remained undiagnosed. The response to treatment is higher at younger age with the mean age 38.9 years in this study, especially those who are diagnosed early.

TABLE 1. Demographic distribution of the studied groups

Variable		Patients				control	P-value
		AHC	*CHC*	*HCV-LC*	*SVR*		
Age year	Range	5 - 41	12- 63	25-81	17-72	5 - 81	0.001 HS
	Mean ± SD	14.6 ±10.5	38.8 ±11.8	54.4 ±14.5	38.9 ±12.5	35.7 ±18.9	
Sex	Male No. (%)	14 (56.0)	15 (60.0)	15 (60.0)	9 (36.0)	30 (60.0)	0.32 NS
	Female No. (%)	11 (44.0)	10 (40.0)	10 (40.0)	16 (64.0)	20 (40.0)	
	Total No.	25	25	25	25	50	

HS=Highly significant, NS=Not significant, SD=Standard deviation, No=Number, P=Probability, AHC= acute hepatitis C, CHC= chronic hepatitis C, HCV-LC= hepatitis C virus induced liver cirrhosis, SVR= sustained virologic response.

B. Serum levels of PIVKA-II among the studied groups

Results listed in Table 2 reveals that the mean serum concentration of PIVKA-II in acute, chronic, HCV induced LC, SVR and control groups were (67.55±25.97, 68.25±25.5, 77.17±26.48, 64.3±27.31, 25.6±5.4) respectively, and these means showed highly significant difference among the studied groups (P value =0.0001). Also, showed highly significant difference in the mean level of PIVKA-II at level (P< 0.01) between each of disease groups compared to control group (AHC, CHC, HCV-LC and SVR vs. control) respectively. The results revealed that the highest circulating PIVKA-II levels were noticed in (HCV-LC) patients' group. This data confirm the results obtained from numerous studies which found that PIVKA-II plays a crucial role in the hepatocellular carcinoma and cirrhosis [8, 21]. Additionally, the current study is consistent with study by Ji *et al*., who demonstrated that high serum PIVKA-II levels were present in cirrhotic patients [22]. Present results observed that serum levels of PIVKA-II in HCV patients with SVR were significantly higher than those found in healthy control, this improves that HCV patients with sustained virological response remain at risk of developing HCC as elevated serum PIVKA-II has demonstrated as a biomarker for HCC prediction [23]. Furthermore, several hypotheses have been suggested to augment the formation of PIVKA-II by HCV-infected cells. It would seem that the HCV causes decreased serum lipids concentration as it uses it in replication process [24], also hepatic cells damage and biliary obstruction due to HCV infection and cirrhosis leads to decreased hepatic synthesis function which characterized by low bile salts and serum lipids concentration, all of these factors lead to malabsorption of fat soluble vitamins such as vitamin K absorption, thus increased abnormal prothrombin production [25].

TABLE 2. Srum levels of PIVKA-II in the studied groups

PIVKA-II (ng/ml)		Study Groups				
		AHC	*CHC*	*HCV-LC*	*SVR*	*HC*
Mean ± SD		67.55 ±25.97	68.25 ±25.5	77.17 ±26.48	64.3 ±27.31	25.6 ±5.4
Mean Rank		95.04	90.76	105.84	88.28	36.54
P- value	P.value comparing all	0.0001 (HS)				
	AHC vs. CHC	0.720 (NS)				
	AHC vs. LC	0.123 (NS)				
	AHC vs. SVR	0.567 (NS)				
	AHC vs. HC	0.0001 (HS)				
	CHC vs. LC	0.091 (NS)				
	CHC vs. SVR	0.907 (NS)				
	CHC vs. HC	0.0001 (HS)				
	LC vs. SVR	0.057 (NS)				
	LC vs. HC	0.0001 (HS)				
	SVR vs. HC	0.0001 (HS)				

C. Levels of serum lipid profile tests in the studied groups

Table 3 reveals that the maximum serum total cholesterol, TG, LDL and VLDL levels (271.5±91.7, 169.5±67.4, 200.9±90.5 and 33.9±13.5 mg/dl) respectively were in the SVR group, and the minimum levels were found in HCV-LC and CHC groups, while maximum serum HDL level was in control group (41.1±8.2 mg/dl) followed by SVR group (36.5±15.4 mg/dl) with minimum levels in CHC group (24.4±10.97 mg/dl). The current study observed a highly significant difference in mean levels of LDL between all groups and between (AHC vs. SVR), (CHC vs. SVR), (LC vs. SVR) and (SVR vs. HC) at p-value < 0.01. While there were significant statistical differences in VLDL cholesterol at p-value ≤ 0.05 between (AHC vs. HC), (CHC vs. HC) and (LC vs. HC) groups, but this difference was not statically significant when comparing across all groups. The differences in mean total cholesterol were statistically highly significant at level P<0.000 between AHC, CHC and LC groups respectively comparing SVR and HC groups respectively, and highly significant difference in SVR vs. HC group. The differences in mean TG were significant between (AHC vs. HC), (CHC vs. HC) and (HCV-LC vs. HC) at the P<0.05 level. Moreover, serum concentration of HDL-C showed highly significant difference among the studied groups (P value <0.01). Also, there was highly significant difference in the Mean level of HDL-C when comparing AHC, CHC, HCV-LC and SVR groups respectively to HC, but significant difference at P<0.05 levels when comparing AHC vs. CHC groups. These results were in consistent with a study by Peschel *et al*., [26] who reported a significant increase in serum total cholesterol, LDL, VLDL, HDL and triglycerides. However, our results disagreed with a study by AbdEl-maksoud *et al*., [27] who found that serum levels of total cholesterol, TG, LDL and VLDL significantly decreased in HCV patients who achieved SVR, but it agreed with our study in increasing serum HDL cholesterol in these patients. HCV circulates in the blood as lipoviral particles by association with LDL and VLDL evading immune system and facilitating its entry to hepatocytes by binding to LDL receptors in hepatocytes [28] and is responsible for decreased serum lipids because it inhibits the protein (microsomal triglycerides transfer) which is responsible for VLDL assembly and secretion, HCV also uses lipid metabolism pathways in the liver to

TABLE 3. Serum levels of Lipid profiles in the studied groups.

Groups	Parameters in (mg/dl)				
	TC Mean ± SD	*TG Mean ± SD*	*HDL Mean ± SD*	*LDL Mean ± SD*	*VLDL Mean ± SD*
AHC	163.6 ±70.6	149.9 ±90.4	29.96 ±11.8	103.7 ±66.9	30 ±18.1
CHC	158.8 ±57.1	136.1 ±64.6	24.4 ±10.97	105.6 ±56.9	27.2 ±12.9
HCV-LC	155.2 ±69.3	136.8 ±51.5	30.2 ±8.01	97.5 ±68.8	27.7 ±10.3
SVR	271.5 ±91.7	169.5 ±67.4	36.5 ±15.4	200.9 ±90.5	33.9 ±13.5
HC	196.8±49.1	165.4±44.5	41.1±8.2	122.5±48.1	33.1±8.9
P-value among all	0.000 (HS)	0.041 (S)	0.000 (HS)	0.000 (HS)	0.051 (NS)
AHC v CHC	0.839 (NS)	0.946 (NS)	0.036 (S)	0.946 (NS)	0.930 (NS)
AHC vs. LC	0.648 (NS)	0.793 (NS)	0.900 (NS)	0.567 (NS)	0.778 (NS)
AHC vs. SVR	0.000 (HS)	0.065 (NS)	0.438 (NS)	0.000 (HS)	0.071 (NS)
AHC vs. HC	0.009 (HS)	0.020 (S)	0.000 (HS)	0.076 (NS)	0.020 (S)
CHC vs. LC	0.969 (NS)	0.869 (NS)	0.009 (HS)	0.648 (NS)	0.801 (NS)
CHC vs. SVR	0.000 (HS)	0.133 (NS)	0.001 (HS)	0.000 (HS)	0.133 (NS)
CHC vs. HC	0.004 (HS)	0.043 (S)	0.000 (HS)	0.078 (NS)	0.043(S)
LC vs.SVR	0.000 (HS)	0.128 (NS)	0.290 (NS)	0.000 (HS)	0.157 (NS)
LC vs. HC	0.007 (HS)	0.028 (S)	0.000 (HS)	0.037 (S)	0.044 (S)
SVR vs. HC	0.001 (HS)	0.719 (NS)	0.007 (HS)	0.000 (HS)	0.723 (NS)

facilitate its replication and secretion [29]. Another cause of decreased serum lipids during HCV infection is increased triglycerides accumulation in the liver and reducing its secretion leading to hepatic steatosis by upregulation of *SREBP-1c* (a lipid uptake gene) and downregulation of lipids clearance by beta-oxidation process [30]. In addition, increased expression of LDL receptor in hepatocytes by HCV leads to increased LDL uptake by hepatocytes, thus contributing to reduced circulating LDL cholesterol [31]. Finally, chronic inflammation resulting from HCV infection induces cytokine secretion like (TNF-α and IL-6), these cytokines impair lipoprotein synthesis and lipid transport [32]. The decreased serum HDL level during HCV infection is mostly due to altered HDL-cholesterol synthesis and catabolism [33]. The mechanism of increased serum lipid profiles after achieving sustained virologic response in HCV patients is still unknown but evidence suggested that it may belong to the lack of virus direct interaction with host's lipid metabolism and most of these patients may have a metabolic syndrome especially those who had liver fibrosis [34].

D. Estimation Spearman's Rank Correlation between studied parameters in the HCV patients groups

Spearman's rank correlation showed highly significant negative and moderate correlation between serum PIVKA-II and serum TG and VLDL levels respectively in both acute and chronic HCV groups. A significant weak negative correlation was observed between PIVKA-II and serum LDL levels in HCV induced liver cirrhosis group, PIVKA-II tends to increase with increased degree of hepatic function insufficiency [35]. A low serum lipid profile is also associated with liver dysfunction, since the liver plays a key role in lipid metabolism. A negative correlation suggests as liver function worsens, the PIVKA-II levels increase and serum lipid levels (Total cholesterol, LDL, Triglycerides and VLDL) tend to decrease [36]. Both high PIVKA-II levels and low lipid levels are associated with HCC [37]. Monitoring this inverse correlation in HCV patients may aid in the detection or prediction of early-stage HCC.

Table 4: Spearman's Rank correlation between the Levels of PIVKA-II and Lipid profile among studied groups.

Parameters		PIVKA-II (ng/ml) level in studied groups				
		AHC (N=25)	*CHC (N=25)*	*HCV-LC (N=25)*	*SVR (N=25)*	*HC (N=50)*
Age (years)	R	-0.173	-0.035	-0.005	0.174	0.066
	P	0.407	0.866	0.980	0.407	0.651
Viral load (IU/ml)	R	0.072	0.329	0.616	.....	…….
	P	0.731	0.353	0.102	……..	…….
TC (mg/dl)	R	-0.324	-0.133	-0.295	0.388	0.155
	P	0.114	0.526	0.153	0.055	0.282
TG (mg/dl)	R	-0.676**	-0.614**	0.095	0.317	-0.103
	P	0.000	0.001	0.653	0.123	0.476
HDL (mg/dl)	R	-0.066	0.321	0.142	0.002	0.072
	P	0.753	0.118	0.500	0.991	0.618
LDL (mg/dl)	R	-0.094	-0.073	-0.407*	0.022	0.181
	P	0.655	0.727	0.044	0.918	0.208
VLDL (mg/dl)	R	-0.670**	-0.619**	0.134	0.317	-0.101
	P	0.000	0.001	0.523	0.123	0.485

** Highly significant at P<0.01 levels, * Significant at P<0.05 levels.

E. Estimation the ROC curve analysis for serum PIVKA-II level among the studied groups

ROC curve analysis for PIVKA-II showed that in AHC patients' group, the area under the curve (AUC) was 0.916, and optimal cut-off value was 35.945ng/ml with sensitivity and specificity 84%, 100% respectively, 95% confidence interval equal to 0.826-1.006 as in Fig. 1-A. While in CHC patients the AUC for PIVKA-II was 0.885 and optimal cut-off value was 47.06ng/ml with sensitivity and specificity 80%, 100% respectively, 95% confidence interval was equal to 0.773-0.996 as in Fig. 1-B. Moreover, In HCV-LC group (Fig. 1-C) the AUC of PIVKA-II was 0.895 and optimal cut-off value was 51.475 ng/ml with sensitivity and specificity 84%, 100% respectively, 95% confidence interval equal to 0.793-0.958. Finally in sustained virologic response group (SVR), the AUC for PIVKA-II was 0.862 and optimal cut-off value was 49.635ng/ml with sensitivity and specificity 68%, 100% respectively, 95% confidence interval equal to 0.767-0.958 as in Fig. 1-D. These results indicate that serum PIVKA-II can be used as an excellent biomarker with higher sensitivity and specificity for diagnosing different stages of HCV (acute, chronic, HCV induced liver cirrhosis, and sustained virologic response) from healthy individuals, as the area under the curve (AURC) was above 80% in all

included hepatitis C groups as shown in (Fig. 1). However, due to the minimal differences in AURC value between studied HCV groups, this makes PIVKA-II unsuitable biomarker to determine the stage of HCV infection. This is the first study performing ROC curve analysis for PIVKA-II alone in HCV patients free of HCC, also this study is the first only study performing correlation between PIVKA-II and serum lipid profiles in HCV patients without HCC, therefore there is a need for further studies with larger sample size confirming these results.

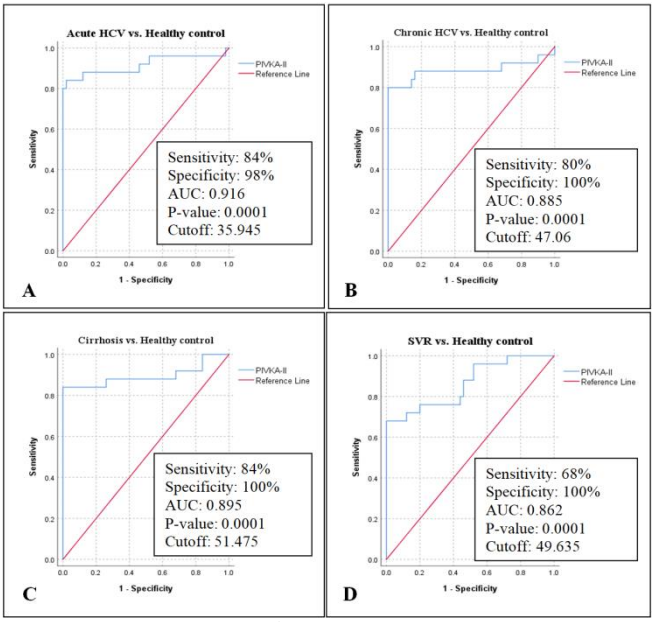

Fig. 1: ROC curves estimation for PIVKA-II in (A): Acute hepatitis C vs. Healthy control group. (B): Chronic hepatitis C vs. Healthy control group. (C): HCV induced liver cirrhosis vs. Healthy control group. (D): Sustained virologic response vs. Healthy control group.

IV. CONCLUSION

Elevated serum PIVKA-II has been reported in HCV patients in this study predicting its possibility in using as biomarker for diagnosing different HCV stages as acute, chronic, cirrhosis, and sustained virologic response from healthy individuals. However, the small differences in mean serum PIVKA-II levels between HCV groups makes it unsuitable for use as a biomarker to differentiate between studied different stages of the HCV infection. The negative correlation between PIVKA-II and serum lipid profiles in treatment naïve HCV patients can be used as a prognostic biomarker for liver disease severity and the risk of HCC.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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