The Egyptian Journal of Hospital Medicine (January 2024) Vol. 94, Page 247-254

Serum Protein C and D-Dimer as Predictors of Portal Vein Thrombosis in Cirrhotic Patients without Hepatocellular Carcinoma

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ABSTRACT

Background: Although the exact origin of portal vein thrombosis (PVT) is unknown, many studies have linked it to systemic factors like protein C, protein S as well as antithrombin III deficiencies. Other studies have linked it to the elevation of D-dimer and international normalized ratio (INR).

Aim: To evaluate the role of serum protein C, D-dimer and INR as predictors of portal vein thrombosis among cirrhotic patients without hepatocellular carcinoma (HCC).

Patients and methods: This cross-sectional study was conducted on 60 cirrhotic patients, 30 cirrhotic patients without PVT (Group I) and 30 cirrhotic patients with PVT (Group II), who were collected from patients who attended at the outpatient clinic and inpatient of The Department of Hepatology, Gastroenterology and Infectious Diseases, Faculty of Medicine, University of Benha. Levels of protein C, D dimer and INR were assessed among all participants.

Results: This present study showed that protein C level was lower in group II than in group I. In contrast D-dimer and INR levels were higher in group II than in group I. Positive correlation was found between D-dimer, INR, alanine transaminase (ALT), aspartate transaminase (AST), serum creatinine and total bilirubin with severity of liver disease (Child score) especially with cirrhotic patients with PVT. Negative correlation was found between protein C, platelets and serum albumin with severity of liver disease (Child score) especially with cirrhotic patients with PVT.

Conclusion: Decreased protein C, increased D-dimer and increased INR were considered risk factors for formation of PVT among cases with liver cirrhosis. So, it is important to conduct specific imaging techniques in order to confirm the diagnosis and start treatment early.

Keywords: Protein C, D-dimer, International Normalized Ratio, Portal Vein Thrombosis, Hepatocellular Carcinoma.

INTRODUCTION

There are many different types of chronic liver illnesses, but they all end in cirrhosis. Histologically speaking, it is a widespread hepatic process that transforms normally structured nodules in the liver into fibrous scar tissue. Liver damage can lead to cirrhosis in a matter of weeks or years **(1).**

About 6-8 cm in length, the portal vein branches off from the superior mesenteric vein and the splenic vein at the base of the pancreas. It supplies the liver with roughly 75% of its blood. The portal vein bifurcates in the porta hepatis, with branches going to the right and left lobes of the liver to drain into the sinusoids there **(2)**.

When thrombosis develops in the extrahepatic portal venous system, it can spread upstream to the superior mesenteric and splenic veins or downstream to the intrahepatic portal vein branches**.** Five to twenty-seven percent of cirrhotic patients develop portal vein thrombosis. An increased risk of PVT was revealed in patients with advanced liver cirrhosis, and its occurrence may be linked to sclerotherapy and abdominal surgery, or hepatocellular cancer. Even though protein C, protein S, as well as antithrombin III deficiency conditions have all been linked to portal vein thrombosis, its exact etiology is still unclear **(3).**

Protein C (PC) is a crucial component of a significant natural anticoagulant pathway. It is generated in the liver and circulates in the plasma **(4)**.

Activated protein C (APC) is formed when the trypsin-like protease thrombin reacts with the vitamin K-dependent serine protease enzyme protein C, requiring the cofactor thrombomodulin and the endothelium protein C receptor, the risk of thrombosis is already elevated in people with liver cirrhosis, and vitamin K antagonist medication may further decrease the level of this naturally occurring anticoagulant **(5).**

D-dimer, which is generated when factor XIII cross-links fibrin monomer and plasmin hydrolyzes it, is a sensitive sign of aberrant coagulation and fibrinolysis and a useful early diagnostic marker for thrombosis **(6).**

The international normalized ratio (INR) is a time-tested way to evaluate blood coagulation variables. Fibrinogen (I), prothrombin (II), proaccelerin (V), proconvertin (VI), and X are the specific names of these components (Stuart-Prower factor). In order to achieve hemostasis, the aforementioned components work together as part of the extrinsic coagulation pathway. This metric is frequently utilized in clinical practice by doctors to assess the risk of potentially fatal hemorrhage. This is particularly the case for those on warfarin, have vitamin K insufficiency, or have liver disease **(7).**

We aimed at this work to evaluate the role of protein C, D-dimer and INR as predictors of portal vein thrombosis among cirrhotic patients without hepatocellular carcinoma.

PATIENTS AND METHODS

In this cross-sectional study, total 60 cirrhotic patients were included, 30 cirrhotic patients without

Received: 01/09/2023
Accepted: 01/11/2023

PVT and 30 cirrhotic patients with PVT, who were collected from patients who attended at the outpatient clinic and inpatient of The Department of Hepatology, Gastroenterology, and Infectious Diseases, Faculty of Medicine, University of Benha in the period from December 2021 to August 2022. They were 39 male patients and 21 female patients, and their ages ranged from 48 to 63 years, patients were categorized into two groups:

Group I (G I): - included 30 cirrhotic patients without PVT (Non-PVT group).

Group II (G II): - included 30 cirrhotic patients with PVT (PVT group).

Inclusion criteria: Cirrhotic patients ≥18 years old.
Exclusion criteria: 1. Patients < 18 years old. 2. Hepatocellular carcinoma. 3. Patients on anticoagulant therapy.

All the patients who were involved in the study were subjected to the following:

a) Proper history taking including:

I. Symptoms suggesting liver cirrhosis as hepatitis, previous jaundice, alcohol intake and past history of spontaneous bacterial peritonitis.

II. Symptoms suggesting portal vein thrombosis as abdominal pain or distention, nausea, vomiting, diarrhea, gastrointestinal bleeding, anorexia, fever, lactic acidosis, splenomegaly, and sepsis.

b) Complete physical examination including:

I. General examination for jaundice, pallor, cyanosis, petechia, lower limb edema, palmar erythema, and clubbing.

II. Abdominal examination for liver size, consistency, spleen, ascites, dilated abdominal veins and umbilical hernia.

c) Laboratory Investigations:

Complete blood picture, liver profile, INR, kidney function tests, alpha fetoprotein (AFP), random blood glucose, hepatitis viral markers: HCV Ab and HBs Ag, **Level of protein-C:** (ELISA Kits-Sunredbio-Baoshan District, Shanghai, China) and **Level of D- dimer:** (ELISA Kits-Sunredbio-Baoshan District, Shanghai, China).

d) Radiological investigations:

1. Pelvi -Abdominal Ultrasonography and Doppler Ultrasound of portal vein (Siemens 2012 Model) in order to establish diagnosis of cirrhosis of the liver by providing information regarding hepatic echogenicity, abnormalities in the liver's outline, size, presence of nodules, portal vein diameter, and portal vein thrombosis.

2. Triphasic CT of abdomen and pelvis to exclude HCC and to confirm diagnosis of PVT.

Ethical approval: Benha Faculty of Medicine Ethics Committee gave its approval to this study. All participants gave written consents after receiving all information. The Helsinki Declaration was followed throughout the study's conduct.

Statistical Analysis

The Windows SPSS application, version 22, was used for statistical analysis. Qualitative data were represented as frequencies and relative percentages. Quantitative data were expressed as mean ± SD. By creating a receiver operating characteristic (ROC) curve, we were able to ascertain the variables' sensitivity and specificity thresholds for disease existence. A significant p-value was considered when it is equal or less than 0.05.

RESULTS

Table (1) showed no statistically significant differences between the studied groups regarding age, gender, occupation, and special habits (Smoking and alcoholism).

Table (1): Demographic features in the studied groups

Socio-demographic data		Group I No.= 30	Group II No.= 30	Test value	P- value	Sig.
Age (Years)	**Mean±SD**	53.53± 3.10	57.33± 4.40	2.256	0.830	NS
	Range	48-62	50-63			
Gender	**Male**	18(60%)	21(70%)	1.225	0.336	NS
	Female	12(40%)	9(30%)			
Occupation	**Employee**	20(66.7 %)	20(66.7%)	0.000	1.000	NS
	Non employee	10 (33.3%)	10(33.3%)			
Alcoholism	**Alcoholic**	0 (0%)	0(0%)	0.000	1.000	NS
	Non Alcoholic	30 (100%)	30(100%)			
Smoking	**Smoker**	10(33.3%)	8 (26.7%)	1.732	0.653	NS
	Non smoker	20(66.7%)	22 (73.3%)			

Table (2) showed no statistically significant differences between the studied groups regarding abdominal pain, abdominal enlargement, vomiting, diarrhea, fever, jaundice, hematemesis, melena and hepatic encephalopathy.

Table (2): Clinical presentations in the studied groups

		Group I		Group II		Test value	P- value	Sig.
		No.=30	%	No. =30	%			
Abdominal pain	Absent	24	80%	24	80%	0.000	1.000	NS
	Present	6	20%	6	20%			
Abdominal enlargement	Absent	0	33.3%	00	0%	0.000	1.000	NS
	Present	30	100%	30	100%			
Vomiting	Absent	26	86.7%	25	83.3%	0.0900	0.764	NS
	Present	4	13.3%	5	16.7%			
Diarrhea	Absent	29	96.7%	29	96.7%	0.000	1.000	NS
	Present	1	3.3%	1	3.3%			
Fever	Absent	27	90%	27	90%	0.000	1.000	NS
	Present	3	10%	3	10%			
Constipation	Absent	20	66.7	20	66.7	0.000	1.000	NS
	Present	10	33.3	10	33.3			
Jaundice	Absent	26	86.7%	25	83.3%	0.0900	0.764	NS
	Present	4	13.3%	5	16.7%			
Hematemesis	Absent	28	93.3%	27	90%	1.394	0.238	NS
	Present	2	6.7%	3	10%			
Melena	Absent	30	100%	30	100%	0.000	1.000	NS
	Present	0	0%	0	0%			
Hepatic Encephalopathy	Absent	22	73.3%	18	60%	1.813	0.178	NS
	Present	8	26.7%	12	40%			

Table (3) showed no statistically significant differences between the studied groups regarding fever, jaundice, lower limb edema, presence of ascites, hepatomegaly and splenomegaly.

Table (3): Clinical findings in the studied groups

		Group I		Group II		Test value	P-value	Sig.
		No.30	%	No.30	%			
Fever	Absent	27	90%	27	90%	0.000	1.000	NS
	Present	3	10%	3	10%			
Jaundice	Absent	26	86.7%	25	83.3%	0.0900	0.764	NS
	Present	4	13.3%	5	16.7%			
Lower limb edema	Absent	25	83.3%	25	83.3%	0.000	1.000	NS
	Present	5	16.7%	5	16.6%			
Ascites	Absent	0	0%	0	0%	0.000	1.000	NS
	Present	30	100%	30	100%			
Hepatomegaly	Absent	18	60%	21	70%	1.225	0.336	NS
	Present	12	40%	9	30%			
Splenomegaly	Absent	0	0%	0	0%	0.000	1.000	NS
	Present	30	100%	1	100%			

Table (4) showed that there was highly significant differences between the studied groups regarding portal vein thrombosis presence, but there were no statistically significant differences regarding liver, spleen size, GB, presence of ascites and portal vein diameter.

Table (4): Triphasic CT findings in the studied groups

		Group I		Group II		Test value	P- value	Sig.
		No.30	%	No.30	%			
Liver	Cirrhotic	30	100%	30	100%	0.000	1.000	NS
	Not cirrhotic	0	0%	0	0%			
Spleen size	Normal	0	0%	0	0%	0.000	1.000	NS
	Splenomegaly	30	100%	30	100%			
Gall bladder	Normal	26	86.7%	25	83.3%	0.0900	0.764	NS
	Abnormal	4	13.3%	5	16.7%			
Ascites	Absent	0	0%	0	0%	0.000	1.000	NS
	Mild	12	40%	5	16,7%			
	Moderate	11	36.7%	10	33.3%			
	Tense	7	23.3%	15	50%			
Portal vein thrombosis	Absent	30	100%	0	0%	30.00	<0.001	HS
	Present	0	0%	30	100%			
Portal vein diameter (normal 7-13 mm)	Mean ± SD	14.2 ± 1		15.9 ±1.4		0.800	0.669	NS

Table (5) showed that platelets and serum albumin were higher in GI than in GII with statistically significant differences. It also showed that AST, ALT, total bilirubin and serum creatinine were higher in GII than in GI with statistically significant differences.

Table (5): Laboratory findings in the studied groups

		Group I	Group II	Test value	P- value	Sig.
		No.= 30	No.= 30			
Hemoglobin (Hb) (12-16 g/dl)	Mean±SD	13.8±1.6	11.3±2.3	6.325	0.280	NS
Total Leucocytic Count (TLC) (4-11)×1000 cells/L	Mean±SD	5245±139	4950±100	8.625	0.882	NS
Platelets (150-400) ×1000 cells/L	Mean±SD	130.89±17.743	84.500±2.957	9.325	0.043	S
AST (10-40 IU/L)	Mean ±SD	73.4±12.1	87.2±21.6	2.325	0.017	S
ALT (10-40 IU/L)	Mean ±SD	64.2±15.9	77±13.5	2.635	0.025	S
Serum albumin (3.5-5 g/dl)	Mean±SD	3.3±0.38	2.9±0.60	1.635	0.024	S
Total bilirubin (0.7-1.2 mg/dl)	Mean±SD	1.4±0.35	2.73±0.52	6.326	0.001	S
Direct bilirubin (0-0.3 mg/dl)	Mean±SD	0.18±0.03	0.23±.04	0.623	0.651	NS
Alkaline phosphatase (44-147 IU/dl)	Mean±SD	70.7±6.3	91.6±21.3	0.635	0.663	NS
Creatinine (0.7-1.2 mg/dl)	Mean±SD	0.8±0.20	1.6±0.38	2.633	0.012	S
Urea (6-24 mg/dl)	Mean±SD	31.3±5.6	45.4±7.7	0.889	0.163	NS
Alpha-Fetoprotein (Up to 10 ng/ml)	Mean±SD	9.99±4.35	11.4±2.9	6.336	0.601	NS
Random blood glucose (mg/dl)	Mean±SD	111.3±20.3	119.4±9.1	3.626	0.160	NS

Table (6) showed that there was statistically significant increase of INR level in GII more than in GI.

Table (6): Comparing the studied groups regarding INR

		Group I	Group II	Test value	P- value	Sig.
		No.= 30	No.= 30			
INR (Up to 1.1)	Mean±SD	1.22±0.1	1.45±0.34	5.996	0.002	S

Table (7) showed statistically significant difference for both of D-dimer and protein C levels between the studied groups. D-dimer level was significantly higher in GII more than in GI, while protein C was higher in GI than in GII.

Table (7): Comparing the studied groups regarding D-Dimer and protein C

		Group I	Group II	Test value	P- value	Sig.
		No.= 30	No.= 30			
D-DIMER (0-500 ng/ml)	Mean±SD	506.8±54.6	658.5±80.1	5.253	0.001	S
Protein-C (3.9-5.9 ug/ml)	Mean±SD	3.93± 0.28	3.19± 0.54	4.881	0.002	S

Regarding D dimer: (Table 8 & figure 1)

At cut off value of serum D-dimer for GI: GII (501ng/ml): (640ng/ml) respectively:

- Sensitivity in GII (94.3%) was higher than that in GI (89%).
- Specificity in GII (91.2%) was higher than that in GI (88.1%)
- Negative predictive value in GII (95.1%) was higher than that in GI (88.1%)
- Positive predictive value in GII (93.1%) was higher than that in GI (87%).

Regarding Protein C: (Table 8 & figure 1)

At cut off value of serum protein C for GI: GII (3.89 ug/ml): (2.95 ug/ml) respectively:

- Sensitivity in GII (94.7%) was higher than that in GI (90%).
- Specificity in GII (93.5%) was higher than that in GI (88%).
- Negative predictive value in GII (96.1%) was higher than that GI (90.1%).
- Positive predictive value in GII (90.1%) was higher than that in GI (80%).

Table (8): Receiver operator characteristic curve (ROC) analysis of D-dimer and protein C levels in the studied groups

		Group I	Group II
		(No=30)	(No= 30)
D-DIMER N=0-500 ng/ml	**Cut off value (ug/ml)**	**501**	**640**
	SENS%	**89**	**94.3**
	SPEC%	**88.1**	**91.2**
	PPV%	**86.2**	**93.3**
	NPV%	**88.2**	**91.1**
	AUC	**0.845**	**0.983**
Protein C N=3.9-5.9ug/ml	**Cut off value (ug/ml)**	**3.89**	**2.95**
	SENS%	**90**	**94.7**
	SPEC%	**88**	**93.5**
	PPV%	**87**	**93.1**
	NPV%	**88.1**	**95.1**
	AUC	**0.856**	**0.989**

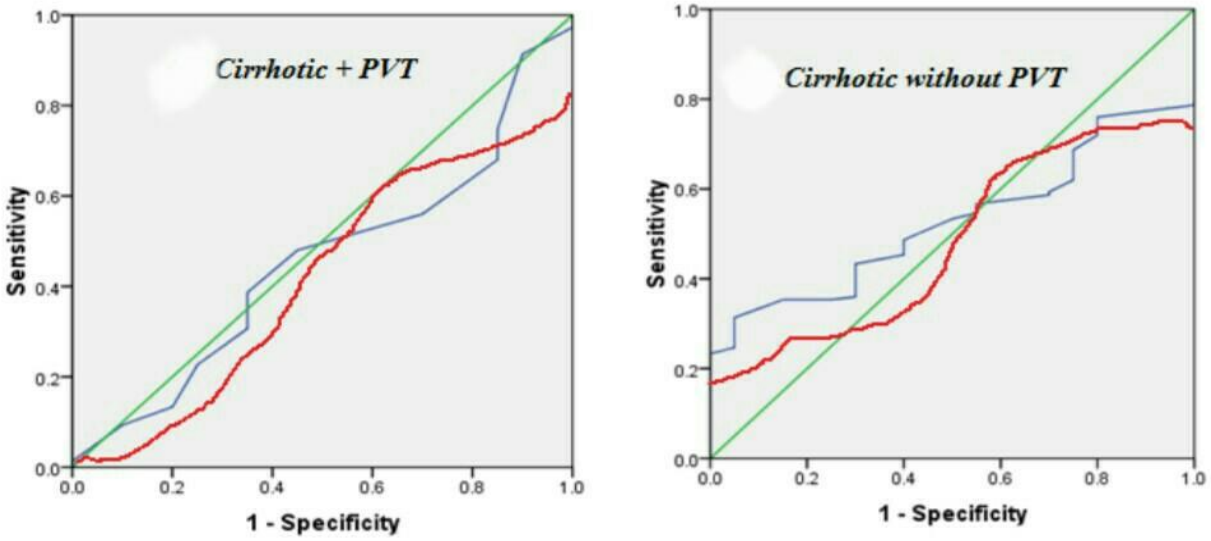

Figure (1): ROC curves of D-Dimer and protein C of the studied groups. Reference: Green line, Protein C: Red line, D-Dimer: Blue line.

Table (9) showed positive correlation between D-dimer, INR, ALT, AST, serum creatinine and total bilirubin with the studied groups especially GII. However, negative correlation was found between protein C, platelets and serum albumin with the studied groups especially GII.

Table (9): Comparison of different parameters in detection of portal vein thrombosis (by r. = Linear Correlation Coefficient)

	Group I		Group II	
	r.	P	r.	P
D-dimer (N=0-500 ng/ml)	**0.241**	**0.049**	**0.335**	**0.001**
Protein C (N=3.9-5.9ug/ml)	**-0.453**	**0.048**	**-0.239**	**0.002**
Platelets (150-400) ×1000 cells/L	**-0.456**	**0.047**	**-0.141**	**0.030**
ALT and AST (10-40 IU/L)	**0.134**	**0.036**	**0.248**	**0.017**
INR (Up to 1.1)	**0.135**	**0.047**	**0.254**	**0.002**
S. creatinine (3.5-5 g/dl)	**0.072**	**0.049**	**0.241**	**0.025**
Total bilirubin (0.7-1.2 mg/dl)	**0.085**	**0.048**	**0.205**	**0.031**
S. albumin (3.5-5 g/dl)	**-0.172**	**0.046**	**-0.161**	**0.028**

Table (10) showed that D-dimer, INR, ALT, AST, total bilirubin and serum creatinine were increasing with the increase of severity of liver disease (Child score) in the studied groups especially GII. In contrast, protein C, platelets and serum albumin were decreasing with the increase of severity of liver disease (Child score) in the studied groups especially in GII.

Table (10): Comparison of different parameters with Child–Pugh classification in the studied groups

	Child A			Child B			Child C		
	Group I	Group II	P-value	Group I	Group II	P-value	Group I	Group II	P-value
D-dimer	495.3±30.5	605.4±40.6	0.044	498±39.8	660.2±48.4	0.005	525.3±25.2	710±50.8	0.001
Protein C	4.1±0.28	3.65± 0.30	. 038	3.9±0.26	3.12± 0.2	0.009	3.88±0.1	2.8±0.15	.002
Platelets	141.1±29.8	87.1±1.5	0.068	130.2±12.3	85.2±3.7	0.059	120±10.5	81.2±1.91	0.04
ALT	52±6.2	64±10.5	0.035	60.4±13.5	75±9.8	0.026	80.2±4.3	92± 21.91	0.020
AST	60±8.3	70±8.3	0.033	75±15.6	88±20.3	0.020	85.2±7.8	103.6±11.4	0.013
INR	1.15±0.3	1.33±0.32	0.008	1.2±0.21	1.4±0.31	0.005	1.27±0.30	1.48±0.33	0.002
S. creatinine	0.5±0.1	0.9±0.19	0.066	0.95±0.21	1.48±0.34	0.035	1.25±0.02	2±0.48	0.011
Total bilirubin	0.9±0.2	1.6±0.4	0.025	1.4±0.3	2.1±0.51	0.012	1.7±0.41	2.19±0.53	0.001
S. albumin	3.55±0.03	3.2±0.3	0.052	3.35±0.32	2.9±0.6	0.035	2.95±0.25	2.6±0.46	0.023

DISCUSSION

Development of PVT in patients with liver cirrhosis is strange and complex as they display disruption of both anti- and pro- coagulant hemostatic mechanisms, so they are at risk of both bleeding and thromboembolism [8].

No optimal monitoring techniques for PVT have been identified yet. There is conflicting evidence from studies that suggest hypercoagulability, decreased blood flow, endothelial cell damage, and cirrhosis sequelae as predictors of PVT development in cirrhosis [9].

In the present study comparing the demographic data between the cirrhotic groups with and without PVT showed that there was no statistically significant differences between studied groups regarding age, gender, residence, occupation and special habits. In consistency with the present study **Serag *et al.*** [10] reported that PVT and non- PVT cases with cirrhosis and no HCC did not differ significantly in terms of age, gender, occupation, smoking status, or alcohol consumption. However, **Atty *et al.*** [11] reported that PVT was strongly linked with age in individuals with cirrhosis, but not with gender. Our findings may not be consistent with those of other studies because of these variables. In the present study comparing clinical presentations, clinical findings and medical history between the studied groups showed that there was non-significant difference regarding abdominal pain, abdominal enlargement, vomiting, diarrhea, constipation, fever, Jaundice, hepatomegaly, splenomegaly, lower limb edema, ascites, and hepatic encephalopathy. In harmony with the present study **Atty *et al.*** [11] revealed that ascites, encephalopathy, and GIT bleeding were not significantly associated with the incidence of PVT in patients with cirrhosis. In contrast to the present study **Metawea *et al.*** [12] revealed that significant differences were found between PVT and non-PVT groups as regards esophageal varices, hepatic encephalopathy, and ascites. But variceal hemorrhage was non-significantly higher in PVT group. The disagreement with the present study may be due to the difference in sample size and cirrhosis severity.

In the present study the comparison of the groups' triphasic CT scans revealed a statistically significant difference in the existence of portal vein thrombosis, but no such difference in the size of the liver or spleen, GB, ascites presence or portal vein diameter. In agreement with the present study **Atty *et al.*** [11] reported that triphasic CT results, such as liver and spleen size, GB, ascites and portal vein diameter did not show significant difference between the PVT and non-PVT groups. The only exception was the existence of portal vein thrombosis. In contrast to the present study **Kinjo *et al.*** [13] reported that PVT patients had larger spleens than those who did not have the condition.

In the present study the comparison of laboratory data between the studied groups showed that platelets and serum albumin were higher in non-PVT than in PVT group with statistically significant difference. We also found that AST, ALT, total bilirubin, and serum creatinine were significantly higher in PVT group than in non-PVT group. While, there was no statistically significant difference between the studied groups regarding HB, TLC, urea, direct bilirubin, alkaline phosphatase, hepatitis viral markers, AFP and random blood sugar. In agreement with the present study **Metawea *et al.*** [12] revealed that PVT was strongly linked to elevated levels of ALT, AST, total bilirubin and serum creatinine, and decreased levels of serum albumin and platelets in patients with cirrhosis. However, there was no correlation between the prevalence of PVT and any of the following: HB, TLC, AST, urea, direct bilirubin, or random blood glucose. In contrast to the present study, **Serag *et al.*** [10] revealed that there was no statistically significant difference between the studied groups as regards ALT, AST, albumin, total bilirubin and platelets. The disagreement may be due to the difference in sample size and inclusion criteria.

In the present study the comparison of INR between the studied groups showed that it was significantly increased in the PVT group more than the non-PVT group. In agreement with the present study, **Prakash *et al.*** [14] revealed that INR was significantly higher in the PVT group than in the non-PVT group. So, it could be strongly linked to the prevalence of portal vein thrombosis. In harmony with the present study **Metawea *et al.*** [12] revealed that PVT was strongly associated with increased level of INR. **Atty *et al.*** [11] also revealed there was significantly higher INR level in the PVT group than the non-PVT group. In contrast to the present study **Serag *et al.*** [10], reported that INR level showed no statistically significant difference between the PVT group and the non-PVT group.

In the present study, regarding levels of D-dimer and protein C, it was found that D-dimer level was significantly higher in PVT group than in non-PVT group, while protein C was higher in non-PVT group than in PVT group. In harmony with the present study, **Metawea *et al.*** [12] revealed that compared to cirrhotic patients without PVT, those with PVT had much lower levels of protein C and protein S, and significantly higher amounts of D-dimer. In disagreement with the present study, **Xu *et al.*** [15] revealed that there was no difference in protein C levels between the PVT and non-PVT groups, although they reported that D-dimer levels were considerably greater in the PVT group. In disagreement with the present study **Turon *et al.*** [16] revealed that mean D-dimer level was not significantly different between PVT and non-PVT groups (466.8±225.8 ng/mL versus 0.460.9±221.2 ng/mL, P=0.95). In disagreement with the present study **Cagin *et al.*** [17] revealed that there was no significant difference between patients with and without portal vein thrombosis as regards protein C and protein S. In the present study D-dimer and INR blood levels were positively correlated with severity of liver disease (Child score), particularly in the PVT group. There was

a negative correlation between protein C and severity of liver disease (Child score), particularly in the PVT group. In agreement with the present study, **Then *et al.*** [7] revealed a positive correlation between INR and severity of liver disease. In disagreement with the present study **Serag *et al.*** [10] revealed that there was no correlation between INR and deterioration and severity of liver disease. In agreement with the present study **Xu *et al.*** [15] revealed a positive correlation between D-dimer and severity of liver disease. In agreement with the present study **Atty *et al.*** [11] revealed a negative correlation between protein C and severity of liver disease. In harmony with the present study **Metawea *et al.*** [12] revealed a negative relationship between liver disease severity and levels of protein C and protein S, but no relationship between D-dimer and liver disease severity in the PVT group or the non-PVT group. In disagreement with the present study **Xu *et al.*** [15] found that blood levels of protein C were not associated with liver disease severity. It's possible that varying sample sizes are to blame for the discrepancy. To test the diagnostic accuracy of D-dimer and protein C, ROC curve analysis was performed. It was found that the cut off value of D-dimer for non-PVT group was 501 ng/ml and in PVT group was 640 ng/ml. Sensitivity in PVT group (94.3%) was higher than non-PVT group (89%). Specificity in PVT group (91.2%) was higher than non-PVT group (88.1%). Negative predictive value in PVT group (91.1%) was higher than non-PVT group (88.2%). Positive predictive value in PVT group (93.3%) was higher than PVT group (86.2%).

The present study showed that the cut off value of protein C for non-PVT group was (3.89 ug/ml) and PVT group (2.95 ug/ml). Sensitivity in PVT group (94.7%) was higher than that in non-PVT group (88%). Specificity in PVT group (93.5%) was higher than in non-PVT group (87%). Negative predictive value in PVT group (95.1%) was higher than non-PVT group (88.1%). Positive predictive value in PVT group (93.1%) was higher than non-PVT group (87%). The present study was in line with **Metawea *et al.*** [12] who revealed that with a protein C cutoff value of 2.87 ug/ml, they were able to predict PVT in cirrhotic people with a diagnostic accuracy of 94%, sensitivity of 88%, and specificity of 100% (AUC = 0.974, p 0.001). On this cutoff, the NPV was 100% and the PPV was 89.3%. There was a strong correlation between a D-dimer level greater than 600 ng/ml with PVT in cirrhotic people, with a diagnostic accuracy of 92%, sensitivity of 88%, and specificity of 96% (AUC = 0.982, p 0.001). With this cutoff, the net present value was 95.7% and the present value was 88.9%.

CONCLUSION

Risk factors for PVT formation in individuals with liver cirrhosis were identified in this study as decreased protein C, increased D-dimer, and increased INR levels. Thus, they can have a suspicion of PVT, and then specialized imaging techniques are used to confirm the diagnosis. Then, treatment can be started early on to prevent major complications.

- **Financial support and sponsorship:** Nil
- **Conflict of Interest:** Nil.

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