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Full Length Research Paper

Thrombophilic risk factors for non-malignant portal vein thrombosis in HCV related cirrhosis

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The aim of the study to assess occurrence of non-malignant portal vein thrombosis (PVT) in HCV-related cirrhosis in relation to thrombophilic risk factors. This case control study enrolled 42 patients with HCV related cirrhosis subdivided into PVT group (n=20) and non-PVT group (n=22). Laboratory investigations were done to assess liver function as well as thrombophilic profile. Platelet count was statistically significantly lower in PVT group compared to non PVT group (p=0.03). There was no correlation between this low platelet count and presence of antiphospholipid antibodies (IgG or IgM; p=0.71 and 0.85, respectively) or lupus anticoagulant antibodies (p=0.26). Although the level of anti-thrombin III (AT-III) was within the normal range (70-120%) in both groups, it was statistically lower in PVT group (90.65±17.75 vs 114.27±22.51, p<0.001). There was a statistically significant difference in positive D-dimer test result in PVT group when compared to non-PVT group (80% vs 45.5% respectively, X^2=5.301, p=0.021). On logistic regression analysis, risk for PVT increases by 0.95 for every one percent decline in AT-III (B=-.053, p=0.002) and by 4.8 folds in cases with positive D-dimer (B=1.569, p=0.026). On the other hand, INR, APTT, lupus anticoagulant, protein C, protein S, protein C global (PCG) and PCG-FV (protein C global-Factor V) had no statistically significant difference between the two groups (p >0.05). The most important independent predictors for non- malignant PVT in HCV-related cirrhosis seem to be the level of AT III as well as the presence of positive D-dimer.

Keywords: Portal vein thrombosis, liver cirrhosis, antithrombin III, D-dimer, protein S, protein C, protein C global, PCG-FV, antiphospholipid antibodies.

INTRODUCTION

Portal vein thrombosis (PVT); which occurs only in 1% in the general population, is a rather common complication of decompensated cirrhosis with a prevalence of approximately 24.7% in overt PVT and even higher in occult PVT (Mangia et al., 2005; Francoz et al., 2005; Ogren et al., 2006; Fimognari and Violi 2008; Zocco et al., 2009). This prevalence further increases with the development of hepatocellular carcinoma (HCC) (Webster et al., 2005). In addition, evident hepatic vein thrombosis was present in 70% of explanted livers for advanced cirrhosis (Primignani, 2010).

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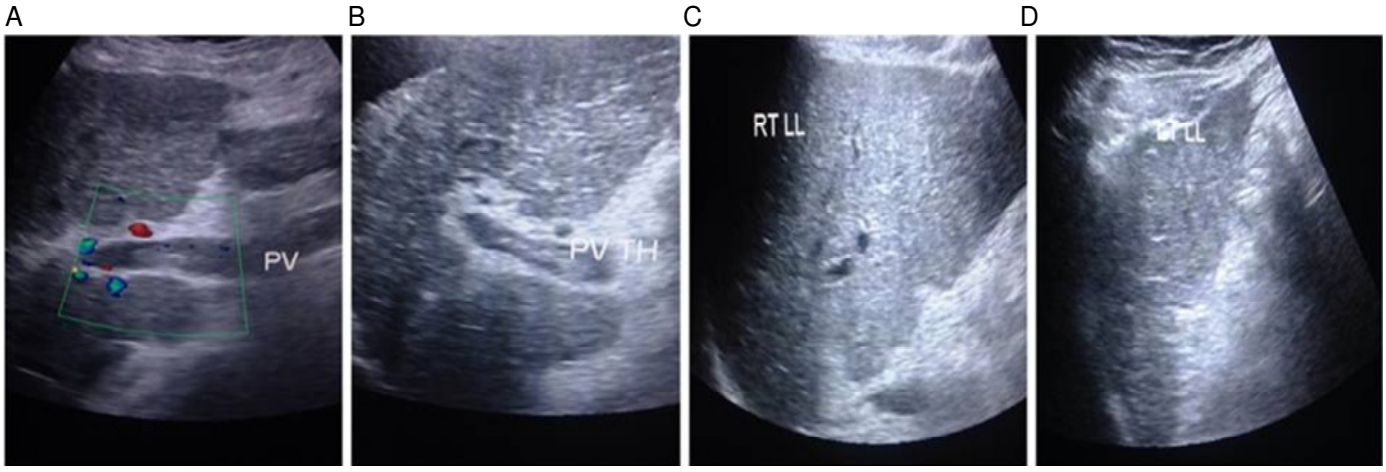

Figure 1. Liver Ultrasonography (US) and Color Doppler US of portal system. A: Dilated main portal vein with echogenic thrombus occluded near totally its lumen with no detected color flow or Doppler signals inside; B: Thrombus occluded near totally the lumen of portal vein; C: Right lobe of the liver lobe shows cirrhotic changes with no detectable focal lesions; D: Left lobe of the liver shows cirrhotic changes with no detectable focal lesions.

The etiology of non-neoplastic cirrhotic PVT is multifactorial (Leebeek et al., 2012; Shetty and Ghosh, 2011). Sluggish blood flow within portal system secondary to increased hepatic resistance plays an important role (Lebrec et al., 1983; Ponziani et al., 2010), in addition to inherited or acquired prothrombotic disorders which are less frequent but should not be neglected (Thompson and Sherlock, 1964; Montalto et al., 2002). Other risk factors include infection, male gender, surgical trauma (eg. splenectomy, porto-caval shunts), variceal hemorrhage (±sclerotherapy), thrombocytopenia and Child–-Turcott-Pugh (CTP) Class C (van'tRiet et al., 2002; Amitrano et al., 2000; Yerdel et al., 2014; Chen et al., 2014).

Since PVT is significantly associated with increased morbidity and mortality in cirrhotic patients (Englesbe et al., 2010), early detection and appropriate management of de novo thrombosis is of paramount importance, particularly for those awaiting liver transplantation. Unfortunately, its recurrence after transplantation adversely affects both patient and graft survival (Francoz et al., 2005; Duffy et al., 2009).

Non-malignant PVT is not an uncommon condition in Egyptian cirrhotic patients. It can affect patients' survival especially those who are waiting for liver transplantation. In Egypt, the only permissible technique used is living related liver transplantation (LRLT) leading to a long waiting list. So, we are facing many problems such as changing MELD score or development of complications including PVT along the course of the disease. Also, there is a possibility of recurrence of PVT after surgical procedure that can affect the graft survival. So, early detection and recognition of the possible cause (s) of PVT can avoid the inevitable fate of increasing morbidity and mortality among those patients.

To the best of our knowledge there is no enough data about the natural history and thrombophilic risk factors for development of PVT in Egyptian patients with HCV related cirrhosis. Therefore, this study was conducted to assess thrombophilic risk factors in cirrhotic patients without HCC, and presence of other possible risk factors.

PATIENTS and METHODS

Patients

This case control study recruited 42 patients with HCV related cirrhosis (31 men, 11 women), selected from Hepatology outpatient clinic at Mansoura Specialized Medical University Hospital, Egypt. An informed written consent that was approved by our local ethical scientific committee in Faculty of Medicine, Mansura University, obtained from all patients after explanation of the aim of the study and the study details.

Chronic liver disease was diagnosed based on the clinical, laboratory and radiological findings and its severity was scored according to the Child-Turcott-Pugh (Pugh et al., 1973) and Model for End stage liver disease (MELD) scores (Freeman et al., 2002; Huo et al., 2006). To explore PVT risk factors, patients were divided into two groups: PVT (n =20) and non-PVT (n=22) groups. All patients underwent abdominal ultrasonography (US), Color Doppler US (Figure 1), and multiphasic helical computed tomography to rule out underlying hepatocellular carcinoma and to confirm PVT.

Patients with non-HCV chronic liver disease, patients with malignant diseases including hepatocellular carcinoma, non-hepatic hemostatic disorders, bacterial sepsis, renal dysfunction, peripheral or hepatic venous thrombosis, recent splenectomy, liver transplantation, anticoagulation therapy were excluded.

Table 1. Clinical, laboratory, radiological characteristics in patients with or without portal vein thrombosis

Parameter	PVT group (n= 20) Mean±SD or No.(%)	non-PVT group (n= 22) Mean±SD or No.(%)	p value
Age (years)	49.85±6.46	49.09±6.77	0.71
Sex			
Male	16(80%)	15(68.18%)	
Female	4(20%)	7(31.82%)	0.38
S. albumin (g/dl)	2.60±0.85	3.16±0.52	0.01
S. bilirubin (mg/dl)	1.71±0.62	1.76±1.66	0.90
ALT (IU/L)	38.13±26.45	42.26±22.08	0.58
AST (IU/L)	49.67±16.09	49.68±32.78	0.99
S. creatinine (mg/dl)	1.03±0.25	1.27±.69	0.17
Hemoglobin (g/dl)	8.87±1.73	10.28±1.74	0.01
WBCs (cell/cm^3)	5.610±4.14	1.081±1.94	0.02
Child – Pugh class			
A	5(25%)	13(59.1%)	
B	6(30%)	5(22.72%)	0.06
C	9(45%)	4(18.18%)	
MELD score	12.51±3	11.41±4.82	0.87
AFP (ng/ml)	9.95±6.93	8.20±4.29	0.32
Portal vein diameter (mm)	16.40±0.57	13±0.17	0.37
Portal flow velocity (cm/sec) in patent vessel	17.3±6.2	17.8±4.8	0.30

Methods

Laboratory tests

5 ml of venous blood was withdrawn from each patient for complete blood count (CBC), liver function tests, and serological markers of viral hepatitis.

Thrombophilic profile

5 ml of venous blood sample was collected using 3.8% sodium citrate (blood to anticoagulant ratio of 9:1) and centrifuged. Immediate preparation of platelet-poor plasma was done together with coagulation screening tests. Prothrombin time (PT) and Activated partial thromboplastin time (APTT) were performed using SIEMENS (Germany) Thromborel S and pathromtin SL, respectively. Aliquots of platelet-poor plasma were stored at -70° C and thawed before doing specific thrombophilic tests. Protein C and AT-III activity were done using chromogenic assay (SIEMENS, Germany). Free protein S was measured by ELISA technique (REAADS, USA). PCG assay was measured using coagulation assay (SIEMENS, Germany). D-dimer semi-quantitative assay was performed using latex (Remel, Europe). Antiphospholipid antibodies (lupus anticoagulant and antiphospholipid antibodies) were diagnosed according to previously described methods (Brandt et al., 1995).

Statistical Analysis

Collected Data were entered and analyzed using an SPSS software version 17. Categorical (qualitative) data were expressed as numbers and percentages while quantitative (metric) data were expressed as mean +/- SD if normally distributed or median if not. Categorical (qualitative) data were compared by Chi-square or Fisher's exact test. Continuous (metric) data were compared by independent samples t-test for two groups or one way ANOVA test for more than two groups if normally distributed or using nonparametric tests if not. Univariate logistic regression models were used to examine the associations between outcomes and different variables. Multivariate analysis was done for the associations between outcomes and significant variables on Univariate analysis. A p value <0.05 was considered statistically significant.

RESULTS

Table 1 demonstrated the clinical, and laboratory features of the two groups. Levels of serum albumin and hemoglobin were significantly lower in PVT group (P=<0.01). Also, there was statistically significant increased white blood cell count (P=<0.02) in PVT group in spite of being within normal range. No statistically

Table 2. Coagulation, anticoagulation and fibrolytic factors in patients with and without PVT

Parameter	PVT group (n= 20)	Non-PVT group (n= 22)	P value
	Mean±SD or No.(%)		
Platelets count (cell/cm^3)	76.45±44.24	103±35.73	0.03
INR	1.36±0.32	1.258±0.28	0.23
APTT	44.50±14.81	41.27±11.82	0.43
Lupus anticoagulant	36.14±5.08	37±5.72	0.61
Antiphospholipid			
IgM	3.97±2.13	6.14±3.66	0.06
IgG	6.03±2.62	3.51±1.08	0.01
Anti-thrombin III (%)	90.65±17.75	114.27±22.51	0.001
Protein C	57.75±20.16	63.31±19.80	0.37
Protein S	67.60±14.26	70±17.88	0.63
Positive D-dimer	16/20(80%)	10/22(45.45%)	0.02
P.C.G	12/20(60%)	12/22(54.55%)	0.45
P.C.G .V	6/20(30%)	5/22(22.73%)	0.69

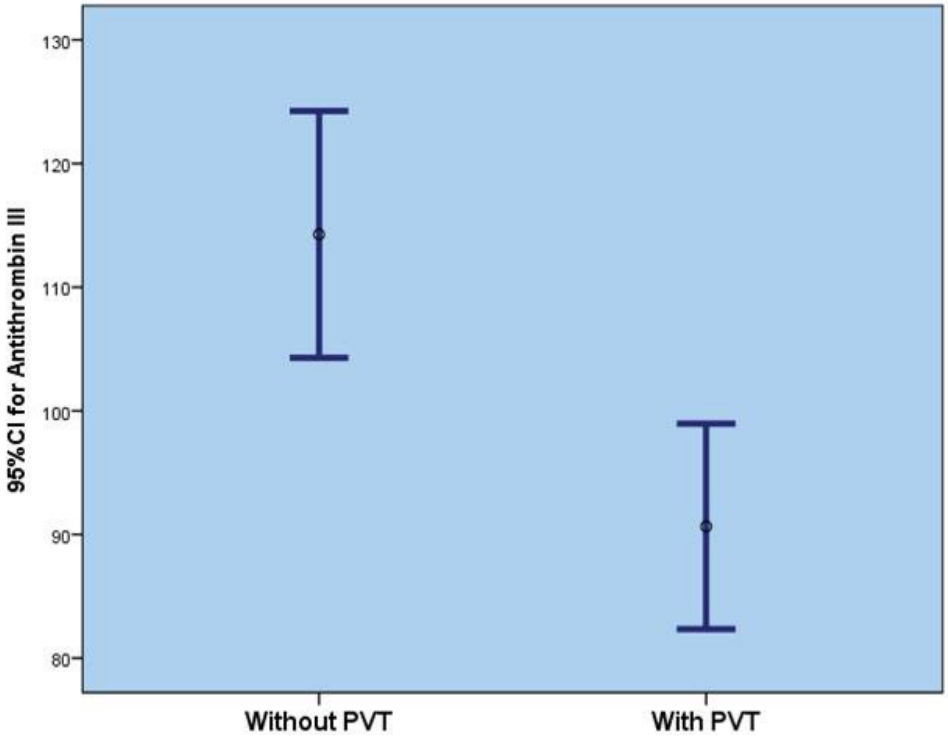

Figure 2. Error Bar shows significant difference in antithrombin-III % in both groups

significant difference was detected for other parameters. Among patients with PVT, five (25%) were in Child-Pugh class A, 6 (30%) in Class B, and 9 (45%) in class C. Child-Pugh classes were not significantly different between patients with or without PVT. Portal vein diameter was increased in PVT group compared to the group without PVT with no statistically significant difference (p=0.37).

Table 2: As regards risk factors for development of PVT, platelets count was statistically significantly low in PVT group (p=0.03). There was no correlation between this low platelets count and presence of antiphospholipid antibodies (IgG or IgM; p=0.71 and 0.85, respectively) or lupus anticoagulant antibodies (p=0.26). Although the level of anti-thrombin III (AT-III) was within the normal range (70-120%) in both groups, it was statistically lower in PVT group (90.65±17.75 vs 114.27±22.51, p<0.001) (Figure 2). AT-III cutoff value of <113.50% is found to be

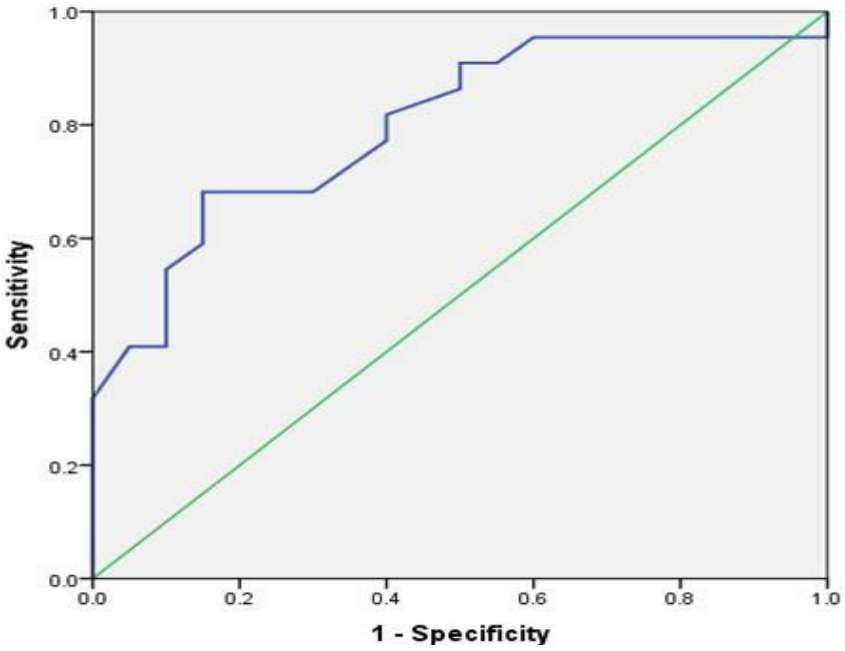

Figure 3. Receiver Operating Characteristics ROC curve for antithrombin-III%

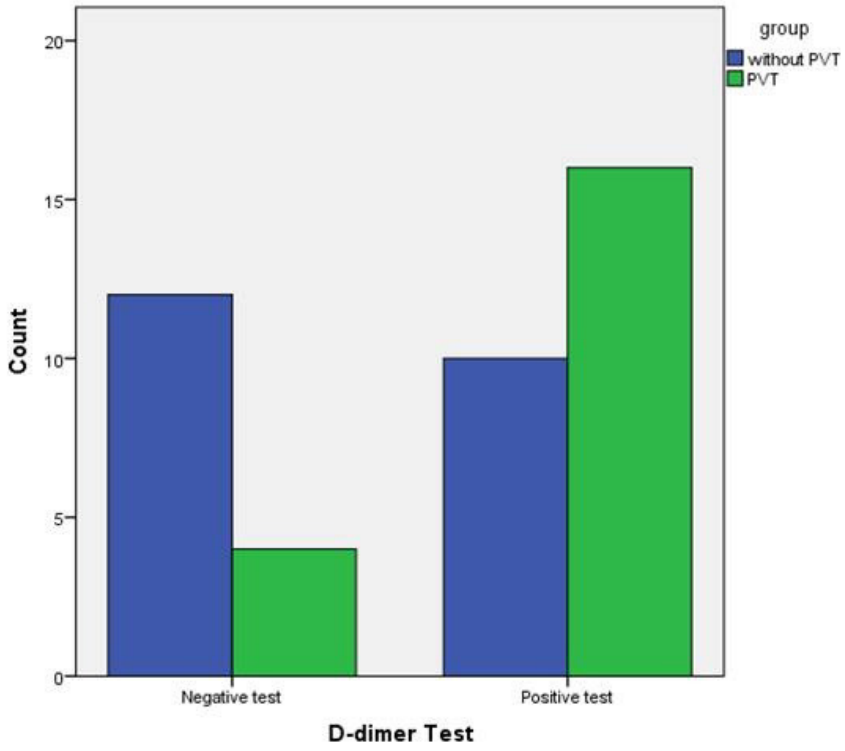

Figure 4. Error Bar shows significant difference in positive D-dimer in both groups

associated with PVT (sensitivity 68% and specificity 85%) (Figure 3). There was a statistically significant difference in positive D-dimer test result in PVT group when compared to non-PVT group (80% vs 45.5% respectively, X^2=5.301, p=0.021) (Figure 4). There was no statistically significant difference as regards other parameters; INR (P=0.23), APTT (P=0.43), lupus anticoagulant (P=0.61), protein C (P=0.37) and S (P=0.63), PCG (P=0.45) and PCG-FV (P=0.69).

Table 3. Correlation between PVT and other parameters

Parameter	Correlation coefficient	P value
Age	0.059	0.71
sex	-.134	0.39
Platelets count	0.27	0.08
INR	0.186	0.23
APTT	0.123	0.43
Lupus anticoagulant	0.01	0.94
Antiphospholipid		
IgM	-0.364	0.06
IgG	0.48	0.71
AT- III%	-0.510	<0.001
Protein C	-0.141	0.37
Protein S	-.075	0.63
D-dimer	0.355	0.02
PCG	-.118	0.45
PCG-FV	0.063	0.69

Table 3: There was positive correlation between PVT and positivity of D-dimer (P=0.02). Also, there was negative correlation between development of PVT and antithrombin III level (p<0.001). On logistic regression analysis, risk for PVT increases by 0.95 for every one percent decline in AT-III (B=-.053, p=0.002) and increases by 12 folds in cases with AT-III level < 113.5% as well as by 4.8 folds in cases with positive D-dimer (B=1.569, p=0.026).

DISCUSSION

There was old false concept that patients with liver cirrhosis were auto-anticoagulated and thus protected from any thrombotic episodes based on prolonged PT, and APTT. This belief greatly changed based on a population based study done in Denmark, that reported slightly higher relative risk of venous thrombosis (Søgaard et al., 2009) among cirrhotics even those on pharmacological thrombo-prophylaxis (Gulley et al., 2008; García-Fuster et al., 2008). In addition, Warnaar et al. (2008) reported occurrence of pulmonary embolism alone in 32 patients (43%) from total 74, a combination of PE and intracardiac thrombosis in 42 patients (57%) during liver transplantation despite their marked prolonged coagulation profile.

Both coagulation factors and their inhibitors formed in the liver, and their synthesis were reduced equally in the patients with liver cirrhosis. Consequently, the hemostasis balance is obtained. However, this balance is less stable than normal individuals, sometimes there is a tendency to either hypo or hypercoagulation state (Amitrano et al., 2007; Monroe and Hoffman, 2009; Erkan et al., 2005).

On analysis of the prothrombotic risk in cirrhotic patients who developed PVT in our study, the platelets count was statistically significantly low in this group compared to cirrhotic patients with patent portal system (p=0.03). Also, this low platelets count was not associated with presence of antiphospholipid antibodies. This result in accordance with many studies (Ushitora et al., 2001; Zhang et al., 2010). The possible explanations for low platelets may be hypersplenism, immune mediated thrombocytopenia and/or decrease level of thrombopoietin by cirrhotic liver. In addition, qualitative changes in platelets contribute to the formation of PVT and considered more important than quantitative changes during development of PVT (Bajaj et al., 2001).

As regards D-dimer, it was positive in both groups with or without PVT (80% and 45.45% respectively), but it was much higher in PVT group (p<0.02).This is in agreement with study done by Zhang et al. (2010).

D-dimer is a fibrin degradation product resulting from degradation of blood clot by fibrinolytic system. It is useful and reliable diagnostic marker for both coagulation and fibrinolysis in thrombotic disorder (eg. Deep venous thrombosis and pulmonary embolism). D-dimer is considered a feature of fibrinolysis in patient with liver cirrhosis. In addition, it is related to progression of the disease that assessed by Child-Pugh score (Violi et al., 1995).

In contrary, Violi et al. (1989) postulated that the association between D-dimer and hemostasis in patients with liver cirrhosis could not be established.

Currently, AT-III; a serine protease inhibitor, is considered the most important physiological inhibitors of coagulation. AT-III has an inherited activity to inhibit the activation of coagulation factors, also heparin potentiate this ability as much as 1000 folds (Blajchman, 1994; Luxembourg et al., 2011). The current study revealed that AT-III has lower concentrations in cirrhotic patients with PVT compared to patient without PVT despite being within the normal range, this findings is similar to

previous published studies (Zocco et al., 2009; Ushitora et al., 2011).

The relation of antiphospholipid antibodies with portal vein thrombosis in liver cirrhosis is still controversial. In one series, anticardiolipin antibody titers were significantly higher among cirrhotic patients with PVT (Oksüzoglu et al., 2003). On the other hand, Harada et al. (2000) concluded that despite the higher frequency of anticardiolipin antibodies in association with chronic HCV infection, they do not exhibit any clinical significance. Antibodies produced against different cardiolipin-binding proteins and phospholipids might be triggered by HCV per se or by prolonged tissue damage as a feature of extrahepatic manifestations of HCV.

The current study cannot establish any association between occurrence of PVT and presence of antiphospholipid antibodies or lupus anticoagulant.

The current study revealed presence of thrombophilic gene mutations by using PCG and PCG V in both groups with or without PVT (30% vs 22.73%, p=0.69). There was no correlation between occurrence of these mutation and development of PVT. Mangia et al. (2005) postulate that presence of prothrombotic mutations in cirrhotic patients did not play a causative role in PVT formation, but two-thirds of cases were explained in this study by previous sclerotherapy and/or abdominal surgery; with pathogenesis of the other cases remained to be elusive (Erkan et al., 2005).

Regarding the other laboratory findings, low serum albumin level was observed in our study, it was related to the progression of the liver disease. Hemoglobin level was significantly low in PVT group. This is low hemoglobin level can be explained by hypersplenism which become more evident with the development of PVT that once developed, it aggravates the portal hypertension (Lisman et al., 2010; Erkan et al., 2014).

CONCLUSION

The most important thrombophilic risk factors for non-malignant PVT in our Egyptian patients with HCV-related cirrhosis seems to be the level of AT III which increases the risk by 0.95 for every unit decrease as well as positive D-dimer (increase the risk by 4.8 folds). Thrombocytopenia in those patients cannot always be explained by anti-phospholipid syndrome.

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