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RESEARCH ARTICLE

Portal vein thrombosis in patients with liver cirrhosis: insights to risk factors, clinical presentation and outcome

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Abstract

Background and objectives: Portal vein thrombosis (PVT) is an increasingly recognized complication of liver cirrhosis. It is associated with worsening liver function, ascites and the occurrence of gastroesophageal variceal bleeding. The aim of this work was to clarify the risk factors, clinical presentation and complications of portal vein thrombosis in Egyptian patients with liver cirrhosis and to study the outcome with and without treatment after 6 months follow up period.

Methods: Hospitalized cirrhotic patients (N = 80) were segregated into the PVT and non-PVT groups. PVT was detected by Doppler ultrasonography; each group was divided in two sub groups (A and B) according to presence or absence of HCC respectively. The 2 groups were compared as regards risk factors, clinical presentation and complications. The outcome of treatment with anticoagulation in 6 patients was evaluated.

Result: PVT developed as result of combination of both local and systemic risk factors. HCC, abdominal infection especially spontaneous bacterial peritonitis and abdominal intervention were the most important local risk factors. Abnormalities of coagulation system were among systemic risk factors. Most of cases were asymptomatic and accidentally discovered, others presented with upper GIT bleeding or other complications of liver cell failure. Anticoagulant administration was associated with increased incidence of partial or complete recanalization and less mortality without increased risk of bleeding.

Conclusion and Recommendations: Portal vein thrombosis occurs mostly in cirrhotic patients with advanced liver disease. HCC is the most common local risk factor in our country. Patients with less prolonged coagulation parameters might be at particular risk for developing PVT, so regular monitoring using Doppler-ultrasound should be carried out in these patients. Development of varices is a time dependent phenomenon; it is advisable to screen all PVT patients endoscopically. Owing to decrease complications, early administration of anticoagulation is advised in selected cases.

INTRODUCTION

Portal vein thrombosis (PVT) is defined as an obstruction of the portal vein or its branches which include the splenic, superior mesenteric and inferior mesenteric veins **(1).**

PVT reported incidence in compensated liver disease is between 0.6% and 5% but becomes much higher (up to 25%) in advanced disease **(2).** Hepatocellular carcinoma is the most frequent cause of PVT in cirrhosis, being present in up to 44% of cases and always it has to be searched for when a new diagnosis of PVT is made **(3).** PVT in patients with HCC is associated with worsened survival **(4).**

Clinical presentation always depends on the onset, the extent of the thrombosis and the development of collateral circulation, in acute PVT intestinal congestion and ischemia are typical manifestations **(5).** If the obstruction is not resolved quickly, intestinal perforation, peritonitis, shock and death from multiorgan failure might occur **(6).** On the other hand, chronic PVT can be nearly asymptomatic and incidentally detected following a routine imaging procedures. Patients with chronic PVT present with portal hypertension related complications like esophageal varices, splenomegaly, anemia and thrombocytopenia **(7).**

Although spontaneous resolution of PVT has been reported in the literature **(8)**, a specific therapeutic management may be needed to resolve portal vein obstruction and avoid serious complications. The goal of treatment is correction of causal factors, prevention of thrombosis extension and achievement of portal vein patency **(9).** Anticoagulation is a challenging therapy in individuals with liver cirrhosis because of the well-recognized coagulation abnormalities observed in that setting and because of the increased risk of bleeding, especially from gastrointestinal tract caused by portal hypertension **(10).**

Objectives:

The aim of current study was to clarify the risk factors, clinical presentation and complications of portal vein thrombosis in patients with liver cirrhosis in our country and to study the outcome after 6 months follow up with and without treatment.

Patient and Methods:

3.1. Population study: This study had been conducted at Internal Medicine department in collaboration with Radiology and Microbiology&Immunology departments, Faculty of Medicine, Zagazig University hospitals during the period from January 2013 to June 2015; included 80 patients with liver cirrhosis. Diagnosis of liver cirrhosis was done by clinical examination, laboratory and ultrasound findings and severity of the liver disease was scored according to Child's–Pugh score.

To explore the risk factors associated with PVT, patients were classified into two main groups: the PVT group (n = 50, 31 males and 19 females with a mean age $\pm$ SD 56.4 $\pm$ 7.8 years) and the non-PVT group (n = 30, 17 males and 13 females with a mean age $\pm$ SD 55.7 $\pm$ 6.1years). Each group was classified into two subgroups A and B according to presence or absence of HCC respectively. Group IA (30 patients), group IB (20 patients), Group IIA (10 patients) and group IIB (20 patients).

Patients who had portal vein thrombosis without evidence of liver cirrhosis, myeloproliferative disorders and malignant disease other than liver malignancy were excluded.

Partial or complete thrombosis of the portal vein or one of its branches or tributaries in all 50 patients was diagnosed with Doppler ultrasound and contrast enhanced triphasic CT.

PVT was classified as complete or partial if Doppler ultrasound determined absence or reduction of blood flow in the main portal trunk, left or right lobar branches, superior mesenteric vein or splenic vein. PVT was defined asymptomatic if thrombosis was occasionally revealed during a routine ultrasound examination and symptomatic when the patient was admitted because of one or more of PVT complications either acute or chronic.

A written consent was taken from all patients and control subjects according to Helsinki guidelines. Results and possible adverse effects of the anticoagulation therapy were also explored.

3.2. Methods:

All subjects of the study were subjected to:

A)Thorough history taking, full clinical examination and routine investigations according to the methods applied in the laboratories of Zagazig University hospitals and included: complete blood picture, serum bilirubin (total and direct), albumin, ALT, AST, creatinine, urea, PT, PTT, INR and viral hepatitis markers; HCV antibodies and HBsAg.

Diagnosis of the case with primary biliary cirrhosis included in the study was done by positive antimitochondrial antibody (AMA) and liver biopsy whereas autoimmune hepatitis case was diagnosed by positive serology (ANA and hyperglobulinemia).

B) Special investigations included:

1-Measurment of protein C and S by ELISA: blood was collected by venipuncture, plasma collected with either 3.2% or 3.8% sodium citrate anticoagulant as the sample matrix and the sample centrifuged immediately. The plasma was removed and stored at 2 - 8°C until testing can be performed. If not tested within 8 hours of collection, the sample was stored at - 70°C and tested within 1 month.

2- Diagnosis of hepatocellularr carcinoma was done by abdominal ultrasound, contrast enhanced triphasic CT and alpha feto protein. Staging was done according to the Barcelona-Clinic Liver Cancer (BCLC) staging system.

3-Diagnosis of portal hypertensive gastropathy and grading of esophageal and gastric varices were made by upper GIT endoscopy.

3.3: Treatment: Six (12%) patients without HCC were selected for anticoagulation therapy according to certain criteria as: acute onset of PVT (less than 1 month), absence of varices by upper GIT endoscope, absence of portal cavernoma by Doppler ultrasound, platelet count >50000/ml, accepted coagulation profile with INR less than 1.7 and class A or B Child's–Pugh classification.

These patients received anticoagulation therapy in the form of low molecular weight heparin, Fondaparinux (Arixtra) 7.5 mg subcutaneously once daily followed by oral anticoagulant (warfarin) started with 3mg daily in a gradually increased dose for INR adjustment to 2-2.5 for duration of at least 6 months.

3.4. Follow up: started from the time of diagnosis and lasted for 6 months later. Patients were followed as regards mortality, morbidity (defined as new onset or recurrence of upper GIT bleeding, encephalopathy or aggravation of ascitis) as well as extension of PVT by Doppler ultrasound and grading of varices and gastropathy by upper GIT endoscopy.

Primary prophylaxis using non-selective b-blockers was done for patients with esophageal varices. For secondary prophylaxis of re-bleeding, combined sclerotherapy and non-selective b-blockers had been used.

3.5. Statistical analysis:

Data were analyzed with SPSS version 15.0 (statistical package for the Social Science, Chicago, IL). Quantitative data were expressed as mean ± standard deviation (SD) or standard error (SE). SE=SD/square root of patients number which was used in case of big SD. Data were analyzed by independent sample, paired t test and one way analysis of variance (ANOVA). Qualitative data were expressed as number and percentage and were analyzed by Chi square (X2) test. Correlation was done using Pearson correlation test. The receiver operating characteristic (ROC) curve and 95% confidence interval (CI) was performed to determine cutoff values for the studied biomarkers. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were determined. P-value was considered significant if <0.05 and highly significant if <0.001.

Results:

PVT occurred in 50 cirrhotic patients (group I) in 6 patients with HBV, 40 patients with HCV infection, in two patients with combined HCV&HBV, in one patient with autoimmune hepatitis and another one with primary biliary cirrhosis ***(table I)*****.** Viral hepatitis was therefore the etiological factor in 96 percent of the cirrhotic patients demonstrating PVT; the percentages of patients with these etiological factors did not significantly differ between the two groups. Analysis of our results showed that male patients percentage was significantly higher in group I than group II (P<0.05). The percentages of patients who smoke, consuming contraceptive pills, have hypertension or diabetes mellitus differ significantly between the two groups being higher in PVT group, also advanced Child's class was associated with higher incidence of PVT development in cirrhotic patients as shown in ***table I*****.**

In our patients, PVT occurred in the PV trunk causing complete obstruction in 9 (18%) patients, in superior mesenteric vein in 2 (4%) patients, in both the PV trunk and a branch in 14 (28%) patients. In five (10%) patients, thrombosis was found in a branch of the PV only. Partial PVT obstruction occurred in the PV trunk in 12 (24%) patients, in both the PV trunk and a branch in 6 (12%) patients and in 2 (4%) patients, thrombosis was found in a branch of the PV ***(table I)*****.**

As regards local risk factors for PVT, we found that HCC is the most common cause associated with increased incidence of PVT. Abdominal intervention (as splenctomy, chemoemboliezation or radiofrequency ablation for HCC, cholycystectomy, appendectomy and one case admitted for drainage of complicated liver abscess) as well as intra abdominal infection

(spontaneous bacterial peritonitis and liver abscesses) were other risk factors for PVT development. On other hand, abdominal inflammation and previous sclerotherapy were not associated with increased risk for PVT development ***(table II)*.**

Regarding the thrombotic risk factors and biochemical characteristics of patients with and without PVT, the levels of protein C&S showed significant reduction in PVT group than non-PVT group in Child's B and C classes only ***(table III)*.** Increase in PTT and INR levels with increased severity of liver disease was found in both groups, however in Child's B and C classes there was less increase in PTT and INR levels in PVT group than non-PVT group with statistically significant difference (p value was 0.001& 0.04 in Child's class B & C respectively for INR and 0.05&0.000 for PTT) but in Child's A, no significant difference between both groups was found. There were also decrease in platelets count with increased severity of liver disease in both groups; in patients with Child's C the decrease in platelets count in PVT group was significantly less than that of non-PVT group but in patients with Child's A and B classes , no significant difference between groups was found ***(table IV)*.**

As regard clinical presentation, (30%) of cases were asymptomatic and discovered accidently during ultrasound examination whereas (30%) presented with deterioration of liver condition as hepatic encephalopathy and aggravation of ascitis, (28%) presented with upper GIT bleeding and (12%) with abdominal pain and lower GIT bleeding ***(table V)*.**

Careful examination of the clinical characteristics of the PVT patients indicated no differences between the characteristics of patients with isolated PV trunk thrombosis and those with PV trunk and a branch or involvement of a branch alone, however SMV involvement was never asymptomatic; ischemic manifestations as acute abdominal pain or lower GIT bleeding were predominant symptoms ***(table VI)*.**

As regards endoscopic findings of patients with PVT at presentation and after 6 months follow up period, presence of PVT was associated with higher grade of gastropathy and esophageal varices after 6 months despite regular endotherapy. On the other hand, in non-PVT group improvement of gastropathy and esophageal varices had been occurred after 6 months following regular endotherapy ***(table VII)*.**

Follow up of the 6 patients after starting anticoagulation therapy with low molecular weight heparin and warfrin showed that a partial or complete canalization of portal vein as detected with Doppler ultrasound was achieved in majority of cases as well as no progression of the thrombosis or death had been occurred. On contrary in patients didn't receive treatment recanalization of portal vein was less with more progression of the thrombosis and death occurred in 65.9% of the patients ***(table VIII).***

Additionally, 23 of the 50 PVT patients (46%) who were not treated were re-admitted due to gastrointestinal bleeding within 6 months following their initial presentation, this was versus 5 patients only (16.6)% in non-PVT group with a statistically significant difference (p value was 0.005).

29 of the 50 patients in PVT group (58%) versus (13.3%) in non-PVT group died during period of follow up ***(table IX)***; 11 patients due to upper GIT bleeding, 6 patients from renal failure, 3 patients from liver cell failure, 3 patients from sepsis, one patient from combined renal and hepatic failure and rest of patients due to DIC or chest infection.

Table I. Clinical characteristics of cirrhotic patients (n=80) with and without portal vein thrombosis.

History	**PVT** (N= 50)		**Non-PVT** (N=30)		*p*
Smoking	Number	%	Number	%	
Yes	29	58.0	8	26.7	0.01
Contraceptive users	Female (N=19)		Female (N=13)		
Yes	13		2		0.000
Co-morbid factors					
DM	21	42.0	7	23.3	0.04
DM &hypertension	6	12.0	0	0.0	
Hypertension	8	16.0	5	16.7	

Etiology of cirrhosis					
1ry billiary cirrhosis	1	2.0	0	0.0	
Autoimmune Hepatitis	1	2.0	0	0.0	
HBV	6	12.0	3	10.0	
HCV	40	80.0	26	86.66	0.1
HCV&HBV	2	4.0	1	3.33	
Child's-pough class					
Child's class A	7		5		
Child's class B	10		5		
Child's class C	33		20		
Site of thrombosis	**Complete**	**Partial**			
Main stem	9	12	0		
Main stem and right branch	7	4	0		
Main stem and left branch	7	2	0		
Right branch	2	1	0		
Left branch	3	1	0		
Extension to SMV	2	0	0		

Table II. Prevalence of local risk factors in both groups.

Local risk factors	PVT group (50)	Non-PVT group (30)	*p*
Cancer (HCC)	30 (60%)	10 (33.3%)	0.02
Abdominal intervention	20 (40%)	4 (13.3%)	0.01
Intra abdominal infection	21 (42%)	3 (10%)	.0100
Abdominal inflammation	9 (18%)	4 (13.3%)	0.7
Previous sclerotherapy	13 (26%)	5 (16.6%)	0.3

Table III. Protein C&S levels in both groups according to Child's class.

		Group I	Group II	t-test	*p*
Protein C	Child's class A	3.3±.2	3.6±0.1	-1.2	0.2
	Child's class B	2.5±0.7	2.9±0.1	-2.0	0.03
	Child's class C	1.9±0.2	2.5±0.3	-9.7	0.000
Protein S	Child's class A	19.4±1.8	20.5±0.6	-1.4	0.2
	Child's class B	17.1±1.5	19.5±0.4	-3.5	0.004
	Child's class C	15.2±1.3	18.2±1.0	-8.9	0.001

Table IV. Platelet levels & Coagulation profile between both groups according to Child's class.

	Group I	Group II	*p*
Platelet			
Child's class A	148.7±23.7	146.2±27.0	0.22
Child's class B	132.2±25.3	102.8±12.9	0.4
Child's class C	97.1±45.5	80.7±18.6	0.000

PTT			
Child's score A	28.6±0.9	29.1±1.2	0.4
Child's score B	43.0±6.0	48.9±0.9	0.05
Child's score C	46.5±6.1	58.1±2.9	0.000
INR			
Child's score A	1.1±0.04	1.1±0.1	0.7
Child's score B	1.5±0.2	1.8±0.1	0.001
Child's score C	1.7±0.3	2.0±0.3	0..04

Table V. Clinical presentation of the PVT group.

No	**%**	
Asymptomatic	15	30.0
Upper GIT bleeding	14	28.0
Deterioration of liver functions	15	30.0
-Hepatic encephalopathy	9	18.0
-Aggravation of ascitis	6	12.0
Lower GIT bleeding	1	2
Acute Abdominal pain	5	10

Table VI. Correlation between the extension of PVT and clinical presentation.

PVT presentation	**Asymptomatic**	**Ischemic manifestations (acute abdominal pain or lower GIT bleeding)**	**(upper GIT bleeding)**	*p*
Site of thrombosis				
Main stem	6	3	6	0.5
Main stem and right branch	3	0	4	0.5
Main stem and left branch	2	1	2	0.8
Right branch	2	0	1	0.1
Left branch	2	0	1	0.2
Extension to SMV	0	2	0	0.0

Table VII. Endoscopic findings of patients in both groups at presentation and after 6 months.

PVT group	**At presentation (N=21)**		**After 6 months (N=21)**		*P*
	No	%	**No**	%	
Gastropathy					
Gastropathy grade I	8	38.0	4	19.0	
Gastropathy grade II	4	19.04	7	33.3	0.03
Gastropathy grade III	6	28.57	10	47.6	
Esophageal varices					
OV I	5	23.8	0	0	0.04
OV II	4	19.04	2	9.52	
OV III	3	14.2	6	28.5	
OV IV	3	14.2	7	33.3	

Non- PVT group	**At presentation (N=26)**		**After 6 months (N=26)**		*p*
	No	%	**No**	%	
Gastropathy					
Gastropathy grade I	3	11.53	4	15.3	0.6
Gastropathy grade II	4	15.38	3	11.5	
Gastropathy grade III	3	11.53	0	0	
Esophageal varices					
OV I	2	7.69	3	11.5	
OV II	3	11.53	3	11.5	0.09
OV III	5	19.23	2	7.6	
OV IV	4	15.38	1	3.8	

Table VIII. Follow up Doppler ultrasound for patients with PVT group with anticoagulant therapy and without treatment.

1.patients received anticoagulant:							
Site	At presentation		After 6 months		Cavernoma	Resolution (partial or complete)	Progression
	Complete	**Partial**	**Complete**	**Partial**			
Main stem	2	1	1	1	1	2	0
Main stem and left branch	1	0	0	1	0	1	0
Extension to SMV	2	0	0	0	0	2	0
2.Patients didn't receive anticoagulant:							
Main stem	3	6	7	2	4	0	4
Main stem and right branch	1	1	2	0	2	0	1
Main stem and left branch	1	1	1	0	1	1	0
Right branch	0	1	1	0	0	0	1
Left branch	1	0	1	0	0	0	0

Table IX. Mortality among both groups.

Mortality	**Group I (N=50)**		**Group II (N=30)**		*p*
	With HCC	Without HCC	With HCC	Without HCC	
	30	20	10	20	
Living	5(16.6%)	16(80%)	7(70%)	19(85%)	0.001
Dead	25(83.3%)	4(20%)	3(30%)	1(5%)	

Discussion:

Liver has many haemostatic functions including the synthesis of most coagulation factors and inhibitors as well as fibrinolytic factors. The balance between procoagulant and anticoagulant factors is essential to prevent excessive blood loss from injured vessels and to prevent spontaneous thrombosis **(11).**The global effect of liver disease with regard to hemostasis is therefore complex, so that patients with advanced liver disease can experience severe bleeding or even thrombotic complications **(12).**

In our study as regards presence of co- morbid factors namely DM and hypertension, the prevalence of DM and hypertension was higher in PVT group than non-PVT group, these results match the findings reported by **Martinelli et al. (13)** who clarified that hypertension and DM were associated with increased risk of PVT. That finding may be attributed to the association of dyslipidemia with diabetes and increased risk of atherosclerosis, so patients with liver cirrhosis and associated diabetes or hypertension carry the risk for PVT more than cirrhotic patients without them.

The number of patients who were smokers and users of contraceptive pills were also statistically higher in PVT group than non-PVT group indicating that these factors may increase the risk for PVT development in cirrhotic patients which goes in agreement with **Shetty and Ghosh study (14).** These results may be attributed to the hypercoagulability caused by hormonal pills and increased risk of atherosclerosis with smoking.

Risk factors:

PVT in patients with liver disease is the result of concomitant local and systemic thrombophilic factors **(15).** In current study as shown in ***table (II)*** malignancy specially (HCC) was the most common local risk factor for PVT followed by abdominal infection specially SBP then abdominal intervention especially splenectomy**.** Similar results were also reported by other studies as **Sogaard et al.(6)** in which abdominal inflammation especially pancreatitis was the most common risk factor (19%) followed by cancer (13%) then abdominal intervention (8%).This difference was due to higher prevalence of HCC due to chronic hepatitis C in our country and higher prevalence of pancreatitis abroad secondary to alcoholism.

As regards HCC characteristics in our patients, 25 patients had multiple focal lesions and 5 had single lesion, most of them were larger than 3cm. 15 patients were classified as stage D, 8 were stage C, 2 were stage B and 5 were stage A according to BCLC staging for HCC. As regards CTP classification system, 21 patients were Child's class C, 5 were Child's B and 4 were Child's A. From these findings we confirmed that HCC was one of the most important local risk factors of PVT development especially when the tumor is multifocal or large unifocal and associated with advanced liver stage. These results came with agreement with the results reported by **Connolly et al. (4)** who demonstrated that advanced tumor stage, higher CTP classification and multifocal tumor were associated with increased risk of PVT.

Previous endoscopic sclerotherapy even if it was found to be more frequent in patients with PVT than in those without, was not considered a risk factor for thrombosis as already shown by current study, **Mangia et al. (16)** and **Francoz et al. (17)** studies but this was opposite to the results reported by **Amitrano et al. (18)** who demonstrated that endoscopic sclerotherapy of esophageal varices may represent a trigger factor for portal vein thrombosis in cirrhotic patients. The role of sclerotherapy as a trigger factor of PVT was not supported by our data may be due to the smaller number of the studied patients and the inclusion of HCC which was not included in the other study. Band ligation may be an alternative advisable choice without documented adverse effects as regards PVT incidence but it needs further studies.

As regards protein C and S levels, current study showed that in early stage of liver cirrhosis there were no significant differences between both groups but with increasing severity of liver disease, protein C and S levels were significantly lower in PVT group in comparison to non-PVT group. The same results were also reported by **Tacke et al. (20)** and **Donglei et al. (21).**That finding may be explained by failure of hepatocytes to synthesize adequate amounts of PC and PS under ischemic and hypoxic conditions. Also, the decrease in PC and PS may be attributed to the endothelial cell damage caused by portal hypertension which leads to the activation and subsequent consumption of PC and PS.

Since these two factors are mechanistically connected, PC is a major physiological anticoagulant. The thrombin–thrombomodulin complex activates PC which inhibits the blood coagulation cascade by selective degradation of the procoagulant factors Va and VIIIa. PS acts as a cofactor in the PC-catalyzed inactivation of Factor Va and enhances the activity of PC **(22).** Besides our findings, the roles of PC and PS in other diseases had long been established. For example, the occurrence of PC and PS deficiency is relatively high in patients with deep venous thrombosis in the lower extremities. Also, the decline of PC and PS was found to be related to cerebrovascular ischemia **(21).**

Liver cirrhosis is generally associated with profound alterations of the coagulation and anticoagulation systems. For example, INR and PTT are important parameters indicating coagulation functions were significantly prolonged in severe liver cirrhosis. Our study showed that in patients with advanced liver cirrhosis, the increase in PTT and

INR levels were less in PVT group than control group but in patients with early stages of liver cirrhosis, no differences in their levels was found between the 2 groups. Therefore, patients with advanced liver cirrhosis and less prolonged coagulation parameters appear to carry a higher risk of PVT compared with patients with advanced liver cirrhosis and markedly prolonged coagulation parameters. These findings were also reported by **Weber et al. (19)** in their study on cirrhotic patients with PVT.

The platelet levels were also lower with advanced stages of liver disease possibly from hypersplenism, immune mechanisms and/or decreased production of thrombopoietin synthesis in the liver **(23).** Our study demonstrated that platelet count inversely proportionate with degree of liver decompensation. In patients with Child's class C, the decrease in platelet count in PVT group was less than that of control group. These results were in agreement with **Francoz et al. (24)** and **Donglei et al. (21)** who reported that cirrhotic patients with PVT had higher platelet level in comparison with cirrhotic patients without PVT and advanced stages of liver disease.

From the previous results we can conclude that, in cirrhotic patients the impact of portal hypertension and deficiency of natural anticoagulants (PC and PS) overcomes the proper effect of low platelet count and prolonged PTT and INR in preventing PVT occurrence. Furthermore, an important role was played by an advanced disease staging as well as by the reduction of portal flow velocity and changes of portal hemodynamic as reported by **Francoz et al. (24).**

Clinical presentation:

Clinical presentation always depends on the onset, the extent of the thrombosis and the development of collateral circulation **(5).** Our results as shown in ***table (V)*** were near results reported by **Amitrano et al.(15)** in their study on 79 cirrhotic patients with PVT who demonstrated that (43%) were asymptomatic , (39%) presented with upper GIT bleeding, (17%) presented with abdominal pain and (7.9 %) presented with symptoms of intestinal infarction.

The presence of complete occlusion of superior mesenteric vein was never asymptomatic and presented with the clinical features of intestinal ischemia or infarction. It depends mostly on the absence of an efficient collateral circulation in the mesenteric bed. Conversely a complete thrombosis of main portal trunk or in right or left branches was symptomless in many patients and we couldn't find a relationship between the site of portal thrombosis and clinical presentation. Similar findings were supported by **Amitrano et al. (15).** Further studies need to be done to show whether the site of PVT affects the clinical characteristics of the disease in cirrhotic patients.

Follow up:

The grades of esophageal varices and gastropathy were higher in PVT group than non-PVT group after 6 months follow up as shown in ***table (VII)***, so presence of PVT was associated with increasing the grade of esophageal varices and gastropathy and also associated with poor eradication of esophageal varices despite regular endotherapy.

Six patients were selected for anticoagulation therapy according to criteria reported by **Qi et al. (25).** Our results shown in ***table (VIII)*** were near to results reported by **Amitrano et al. (26)** in their study on 28 cirrhotic patients with PVT in which complete recanalization of portal vein occurred in 33.3%, partial recanalization in 50% and no response in 16.7% of patients and were higher than results reported by **Senzolo et al. (27)** in which recanalization of 16 patients (41%) had occurred in comparison with no recanalization in patients not given anticoagulant. Also **Butera et al. (28)** on their study on 16 cirrhotic patients with PVT reported complete recanalization in 5 patients (31.25%) and reduction of size of thrombosis in 15 patients (93.7%).

In remaining of cirrhotic patients with PVT not received anticoagulation therapy, spontaneous resolution of only one patient with partial PVT had occurred while 6 patients had progression of PVT from partial to complete obstruction, so the rate of recanalization was higher with anticoagulation therapy than without treatment.

In spite of anticoagulation therapy given to these cirrhotic patients, there were no bleeding episodes during the follow up period. This finding matches the results of **Butera et al. (28)** who gave anticoagulant therapy to sixteen cirrhotic patients with PVT and esophageal varices with no evidence of bleeding episode had occurred.

Frequent complications during follow-up period in non treated patients were detected as new onset of varices, recurrent upper GIT bleeding and aggravation of liver decompensation. A larger part of patients with chronic PVT

developed esophageal varices in comparison with patients with acute PVT. These results came with agreement with the results reported by **Janssen et al. (29).** Thus, the development of varices is a time dependent phenomenon.

The recurrence of upper GIT bleeding was higher in PVT group (46%) than in control group (16.6%) despite regular sclerotherapy and use of B-blockers, these results were near to **Sogaard et al. (6)** in which the recurrence rate was (43%) and was higher than recurrence rate of **Zargar et al. (30)** who reported a recurrence rate in PVT group of (19.4%). The results were higher in our study may be due to inclusion of patients with HCC in current study that were not included in study of **Zargar et al.**

As regards mortality , it was higher in PVT patients without HCC (20%) in comparison to non-PVT patients without HCC ***(table IX)***, these results were near to the results reported by **Soggard et al.(6)** in which mortality rate were (27%) and **Ferreira et al.(31)** in which mortality rate was (24%). Also mortality was 83.3 % in PVT patients with HCC in comparison to 30% in non-PVT patients with HCC. **Connolly et al. (4)** demonstrated that the median survival duration in patients with PVT and HCC was 2.3 months compared to 17.4 months in HCC patients without PVT.

The overall mortality rate of non-PVT group was (13.3%) only, one case died from renal failure, the second one died from recurrent upper GIT bleeding, the third one died from liver cell failure and the last one from sepsis. So we concluded that patients with liver cirrhosis and PVT were associated with increased rate of mortality than cirrhotics without PVT especially when associated with HCC.

Finally to conclude, Portal vein thrombosis occurs mostly in a cirrhotic patient with advanced liver disease due to combination of local and systemic risk factors. It is completely asymptomatic in many cases but when symptomatic it presents with life-threatening complications as gastrointestinal bleeding or intestinal infarction. Partial/complete recanalization was more frequent in patients treated with anticoagulation therapy than without treatment. Anticoagulation therapy in cirrhotic patients with PVT was not associated with increased risk of GIT bleeding.

Recommendations:

1- Regular monitoring using Doppler-ultrasound should be carried out in cirrhotic patients with advanced stages and less prolonged coagulation parameters.
2- Regular screening of all chronic PVT patients endoscopically for detection of varices and prophylactic measures.
3- Early administration of anticoagulation is advised in selected cases especially acute PVT to avoid serious complications**.**
4- HCC has to be searched for in new cases presented with PVT**.**

References:

1. **Kinjo N, Kawanaka H, Akahoshi T, et al.** Portal vein thrombosis in liver cirrhosis. *World J Hepatol 2014; 6:* 64-71[PMID:24575165 DOI: 10.4254/wjh. v6.i2.64]
2. **Garcia JC, Hernandez M, Bosch J, et al.** Extra hepatic portal vein thrombosis. *Semin Liver Dis 2008; 28:*282–92.
3. **Alkim H, Ayaz S, Sasmaz N, et al.** Haemostatic Abnormalities in Cirrhosis and Tumor-Related Portal Vein Thrombosis. *Clin Appl Thromb Hemost2012; 18:*10.1177/1076029611427900.
4. **Connolly G, Chen R, Hyrien O, et al.** Incidence, risk factors and consequences of portal vein and systemic thromboses in hepatocellular carcinoma. *Thromb Res2008; 122:* 299–306.
5. **Northup PG, Sundaram V, Fallon MB, et al.** Hyper coagulation and thrombophilia in liver disease. *J Thromb Haemost 2008; 6:* 2-9.
6. **Sogaard KK, Astrup LB, Vilstrup H, et al.** Portal vein thrombosis; risk factors, clinical presentation and treatment. *BMC Gastroenterol 2007; 7:* 34.
7. **Hoekstra J and Janssen H. Vascular liver disorders (II):** portal vein thrombosis. *Neth J Med 2009; 67:* 46-53.
8. **Condat B, Pessione F, Helene DM, et al.** Recent portal or mesenteric venous thrombosis: increased recognition and frequent recanalization on anticoagulant therapy. *Hepatology 2000; 32:* 466-470.
9. **De Leve LD, Valla DC and Garcia-T, et al.** Vascular disorders of the liver. *Hepatology 2009; 49:* 1729-1764.

10. **Geneviève H and Marc B.** Management of anticoagulation for portal vein thrombosis in individuals with cirrhosis: A Systematic Review. *International Journal of Hepatology 2012; Article ID 672986*:1-6.
11. **Tripodi A, Salerno F, Chantarangkul V, et al.** Evidence of normal thrombin generation in cirrhosis despite abnormal conventional coagulation tests. *Hepatology2005; 41(3):*553-558.
12. **Lisman T, Leebeek FW, de Groot PG, et al.** Haemostatic abnormalities in patients with liver disease. *J Hepatol 2002; 37(2):*280-287.
13. **Martinelli I, Bucciarelli P, Mannucci PM, et al.** Thrombotic risk factors: basic pathophysiology. *Crit Care Med. 2010 Feb; 38 (2 Suppl):* S3-9.
14. **Shetty S and Ghosh K.** Thrombophilic dimension of Budd chiari syndrome and portal venous thrombosis, a concise review. *Thrombosis Research 2011; 127:* 505-12.
15. **Amitrano L, Guardascione MA, Brancaccio V, et al.** Risk factors and clinical presentation of portal vein thrombosis in patients with liver cirrhosis. *J Hepatol 2004; 40:* 736-741.
16. **Mangia A, Villani MR, Cappucci G, et al.** Causes of portal venous thrombosis in cirrhotic patients: the role of genetic and acquired factors. *Eur J Gastroenterol Hepatol 2005; 17:*745e51.
17. **Francoz C, Durand F, Sommacale D, et al.** Incidence of splanchnic vein thrombosis in candidates for liver transplantation and usefulness of anticoagulant therapy while waiting for liver transplantation. *Hepatology 2002; 36:*191A.
18. **Amitrano L, Brancaccio V, Guardascione M, et al.** Portal vein thrombosis after variceal endoscopic sclerotherapy in cirrhotic patients: role of genetic thrombophilia. *Endoscopy 2002; 34:*535–537.
19. **Weber A, Krebs S, Lenhardt L, et al.** Correlation of routinely used coagulation parameters and presence of portal vein thrombosis in patients with liver cirrhosis. *Hepatology Research2009; 39:* 882–887.
20. **Tacke F, Schöffski P, Trautwein C, et al.** Tissue factor and thrombomodulin levels are correlated with stage of cirrhosis in patients with liver disease. *Blood Coagul. Fibrinolysis 2001; 12:* 539–45.
21. **Donglei Z, Jianyu H, Nin Y, et al.** Protein C and D-dimer are related to portal vein thrombosis in patients with liver cirrhosis. *Journal of Gastroenterology and Hepatology2010; 25:* 116–121.
22. **Shen MC, Lin JS and Tsay W.** Protein C and protein S deficiencies are the most important risk factors associated with thrombosis in Chinese venous thrombophilic patients in Taiwan. *Thromb. Res. 2000; 99:* 447–52.
23. **Zarbock A, Polanowska Grabowska RK and Ley K.** Platelet–neutrophil-interactions: linking hemostasis and inflammation. *Blood Rev 2007; 21(2):*99–111.
24. **Francoz C, Belghiti J, Vilgrain V, et al.** Splanchnic vein thrombosis in candidates for liver transplantation: usefulness of screening and anticoagulation. *Gut 2005; 54:* 691-697.
25. **Qi X, Han G, Wu K, et al.** Anticoagulation for Portal Vein Thrombosis in Cirrhosis .*The American Journal of Medicine 2010; 123 (9):*S19-20.
26. **Amitrano L, Guardascione MA, Menchise A, et al.** Safety and efficacy of anticoagulation therapy with low molecular weight heparin for portal vein thrombosis in patients with liver cirrhosis. *J Clin Gastroenterol 2010; 44:*448–451.
27. **Senzolo M , Sartori MT , Gasparini D, et al.** Algorithm for the treatment of PVT and splanchnic vein thrombosis in patients with liver cirrhosis. *Digestive and Liver Disease 2010; 42:*S1–S51.
28. **Butera G, Simone1 F, Iaco A et al.** Anticoagulant treatment for non neoplastic portal vein thrombosis in patients with liver cirrhosis and esophageal varices. *Digestive and Liver Disease 2010; 42* Suppl. (1) S1–S51.
29. **Janssen HL, Wijnhoud A, Haagsma EB, et al.** Extra hepatic portal vein thrombosis: etiology and determinants of survival. *Gut2001; 49:* 720-724.
30. **Zargar S, Javid G, Khan B, et al.** Endoscopic ligation vs. sclerotherapy in adults with extra hepatic portal venous obstruction: a prospective randomized study. *J of gastrointestinal endoscopy 2005; 61(1):*58-67.
31. **Ferreira C, Alexandrino P, Ramalho F,et al.** Portal vein thrombosis in cirrhotic patients is associated with advanced liver disease and predicts poor long term prognosis. *Hepatology2010; 52:* 1072A.