Original Article

Natural Course of Nonmalignant Partial Portal Vein Thrombosis in Cirrhotic Patients

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ABSTRACT

Background/Aim: Portal vein thrombosis (PVT) has a high incidence in patients with liver cirrhosis and determines a poor prognosis of hepatic disease. The aim of our study was to define the natural course of partial PVT in cirrhotic patients, including survival and decompensation rates. **Patients and Methods:** We performed a prospective, cohort study, in a tertiary referral center. There were 22 cirrhotic patients with partial nonmalignant PVT, without anticoagulant treatment, who were followed-up between January 2011 and October 2013. All patients were evaluated by Doppler abdominal ultrasound and computed tomography. Kaplan–Meier method was used to determine the difference in clinical events between the study subgroups. **Results:** After a mean follow-up period of 20.22 months, partial PVT improved in 5 (22.73%), was stable in 11 (50%), and worsened in 6 (27.27%) patients. Hepatic decompensation rate at 6 and 18 months was higher in patients with worsened PVT than in those with stable/improved PVT (50% vs. 25%, $P < 0.0001$ and 100% vs. 56.25%, $P < 0.0001$, respectively). The survival rate at 6 months was 66.66% in worsened PVT group vs. 81.25% ($P = 0.005$) in stable/improved group, and 16.66% vs. 81.25% ($P < 0.0001$) at 18 months, respectively. Multivariate analysis showed that Model of End-Life Disease was the independent predictor of hepatic decompensation [hazard ratio (HR) 1.42; 95% confidence interval (CI): 1.08–1.87, $P = 0.012$] and survival (HR 1.76; 95% CI: 1.06–2.92, $P = 0.028$). **Conclusions:** Nonmalignant partial PVT remained stable/improved in over half of cirrhotic patients and aggravated in more than one fourth in whom it negatively influenced the survival and decompensation rates.

Key Words: Liver cirrhosis, natural course, portal vein thrombosis, survival

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The liver plays a central role in maintaining the critical balance between bleeding and thrombotic events. Liver cirrhosis (LC) is characterized by a complex picture of impaired coagulation, thrombocytopenia, decreased pro- and anticoagulant factors produced by the liver, increased von Willebrand factor, factor VIII, and decreased pro- and antifibrinolytic factors, with a low tendency to hyperfibrinolysis.[1,2] Despite clear evidence of an increased tendency for bleeding in patients with liver cirrhosis, in some circumstances these patients are characterized by a hypercoagulable state.[3]

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The incidence of portal vein thrombosis (PVT) in compensated LC was reported between 0.6% and 5%, and much higher (15%–25%) in decompensated disease.[4-6] There are no data regarding the difference in the prevalence between partial and total PVT in cirrhotic patients. PVT is a serious complication of cirrhosis due to further increase in portal venous pressure and decreased blood flow to the liver, with the risk of variceal bleeding and worsening of the liver function.[7,8] However, the impact of PVT on the natural history of cirrhosis remains unclear.[9,10] Also, the natural course of PVT in patients with LC is not well known. Moreover, there are many asymptomatic cirrhotic patients in whom PVT is detected incidentally on abdominal ultrasound, and it is not established whether such

patients need anticoagulant therapy.[9] At present, there is neither consensus nor are there guidelines regarding the anticoagulant drugs to be used, duration of treatment, and monitoring methods of cirrhotic patients with PVT.

To establish the indication for anticoagulant treatment and to evaluate its efficacy, it is important to define the natural course of PVT in LC. Several studies have reported that spontaneous recanalization of the portal vein in the absence of any specific therapy is unusual, especially in total PVT,[11-13] but the results are controversial, depending on the study design.[7,14] Subsequently, there are some unanswered questions regarding PVT and the progression of LC, the impact on LC natural history, or the rate of spontaneous recanalization.

The aim of this study was to evaluate the natural history of nonmalign partial portal vein thrombosis and its impact on the long-term outcomes in cirrhotic patients.

PATIENTS AND METHODS

Study population

We conducted a prospective cohort study on cirrhotic patients admitted in a tertiary referral center. Patients diagnosed with partial PVT between January 1, 2011, and December 31, 2011, were followed up until October 30, 2013, or death.

We excluded patients who received anticoagulant treatment, patients with malignant disease including hepatocellular carcinoma, known thrombofilia, patients with a history of transjugular intrahepatic portosystemic shunt (TIPS), and those with portal cavernoma.

A written consent was obtained from all the patients. The study was performed in accordance with the Declaration of Helsinki and approved by our local Ethics Committee.

Data collection

From each patient we collected the following information: Age, gender, international normalized ratio, serum bilirubin and albumin, platelet counts, and etiology of LC.

The diagnosis of liver cirrhosis was established based on clinical manifestations and biological, endoscopical, and ultrasound changes suggestive for advanced liver disease and portal hypertension. LC severity was evaluated using the Model of End-Life Disease (MELD) score and Child–Pugh class.

Patency of the portal vein was assessed by abdominal ultrasonography and Doppler ultrasonography in all screened patients at the time of enrollment. All patients diagnosed with PVT based on Doppler ultrasonography had contrast-enhanced computed tomography to confirm the presence and extension of PVT. Partial PVT was defined as the presence of a hyperecogenic material in portal lumen without complete obstruction.

Events definition

PVT was considered improved when complete recanalization or a reduction of more than 50% of the thrombus was achieved, stable when the thrombus maintained the same dimensions or there was a reduction less than 50%, and worsened when the thrombus was extended to superior mesenteric vein (SMV), splenic vein, or complete PVT.[14]

The patients were evaluated every 3 months by abdominal ultrasound combined with Doppler examination, and at 6 months by computed tomography, for a mean observational period of 20.22 ± 8.6 months.

Statistical analysis

Data were analyzed with the SPSS Software Version 17.0 for Windows (SPSS Inc., Chicago, IL, USA). Continuous variables were presented as mean ± standard deviation and categorical variables as frequency and percentage. Student's *t* test was used to compare normally distributed continuous variables and the Mann–Whitney *U* test for variables without normal distribution. The χ^2 test was used to compare categorical variables. Kaplan–Meier method was used to determine if there was a significant difference in clinical events between the study subgroups. Independent predictors for survival and decompensation were assessed by using a Cox proportional hazards model. A two-tailed P value < 0.05 was considered as statistically significant.

RESULTS

General characteristics

There were 1580 patients with cirrhosis over the screening interval, out of them 121 were associated PVT. Among cirrhotic patients with PVT, 99 patients were considered to be not eligible according to the inclusion/exclusion criteria (79 with concomitant/history of hepatocellular carcinoma, 4 with insufficient laboratory data, 12 with other malignant diseases, 3 with anticoagulant treatment for cardiac diseases, and 1 with TIPS). Thus, the study included 22 patients (12 males, 10 females, mean age 61.45 ± 9.63 years; range, 29–80 years). Chronic viral hepatitis was the main cause of LC in half of the patients. Nine patients (40.9%) were asymptomatic, 10 patients (45.5%) were admitted with abdominal pain, and in 3 patients (13.6%) PVT diagnosis was associated with variceal bleeding. The majority of the patients had thrombosis of a single vessel (81.1%) and PVT involved the right portal vein in 3 patients and left portal

vein in 4 patients. The overall mean observation period was 20.22 ± 8.61 months, ranging from 4 to 31 months. Baseline characteristics of the cirrhotic patients with partial PVT are summarized in Table 1.

Course of partial PVT

During the follow-up period, PVT remained stable in 11 (50%) patients, improved in 5 (22.73%), and worsened in 6 (27.27%) patients. In 2 patients complete portal vein recanalization was obtained after a mean follow-up period of 10.5 months. At the time of enrollment, there were 4 patients with PVT extension to SMV (one of them with splenic vein involvement), all remaining stable during follow-up. None of the patients received anticoagulant treatment. The patients ($n = 18$) with thrombus limited to portal vein had not developed extension to SMV or splenic vein during the study period.

Clinical outcomes

The correlation between the natural course of PVT and clinical evolution is summarized in Table 2.

The Kaplan–Meier probability of episodic hepatic decompensation at 6 and 18 months was 0.95 [95% confidence interval (CI) 0.41–0.99], and 0.70 (95% CI 0.05–0.80) [Figure 1]. The rate of 6 months decompensation was 31.8%, and 68.1% at 18 months. There was a clear association between progression or regression of partial PVT and clinical outcome ($\chi^2 = 27.677$, $P < 0.0001$) [Figure 2]. Eleven (68.7%) patients with stable/improved PVT and three (50%) of those with worsened PVT remained free of decompensation at 6 months ($P = 0.006$). At 18 months, seven (43.7%) patients from those with stable/improved PVT and none of the patients with worsened PVT remained free of decompensation ($P < 0.0001$).

The Kaplan–Meier probability of survival at 6 and 18 months was 0.95 (95% CI 0.52–0.99), and 0.74 (95% CI 0.21–0.78) [Figure 3]. There was a clear association between progression or regression of partial PVT and survival ($\chi^2 = 6.347$, $P < 0.0001$) [Figure 4]. The rate of survival at 6 and 18 months in the first group (PVT stable/improved) was higher compared with the second group (worsened PVT) (81.2% vs. 66.6%, $P = 0.005$; 81.2% vs. 16.6%, $P < 0.0001$). At the end of the study, the mortality rate was 56.2% in the first group and 100% in the second group of patients ($P < 0.0001$). Medium survival time was 19.22 months in the first group and 8.6 months in the second group of patients ($P < 0.0001$).

Multivariate analysis showed that the MELD score at diagnosis of PVT in cirrhotic patients was the only independent predictor of survival [hazard ratio (HR) 1.76; 95% CI: 1.06–2.92, $P = 0.028$] and hepatic decompensation (HR 1.42; 95% CI: 1.08–1.87, $P = 0.012$).

Table 1: Baseline characteristics of the patients with LC and partial PVT

Characteristics	PVT (*n*=22)
Age, years (mean±SD)	61.45±9.63
Male *n*, %	12 (54.54%)
Diabetes *n*, %	3 (13.63%)
Smoking *n*, %	10 (45.45%)
Etiology (alcoholic/viral/other)	6/11/5
MELD score (mean±SD)	12.73±4.34
Child-Pugh score (mean±SD)	7.7±1.82
Child-Pugh class (A/B/C)	7/9/6
Blood glucose, mg/dL (mean±SD)	117.08±46.79
WBC count, per mL (mean±SD)	6129.54±2552.44
Hemoglobin, g/dl (mean±SD)	11.26±1.85
INR, % (mean±SD)	1.23±0.16
Platelet count, $\times 10^9$ per L (mean±SD)	112±74.86
Ascites	
Absent	10
Mild	3
Moderate	8
Severe	1
Esophageal varices	
Small	2
Medium	6
Large	14
Vessels with thrombosis	
PVT	18
PVT, SMV	3
PVT, SMV, and splenic vein	1

MELD: Model of end-life disease, SD: Standard deviation, WBC: White blood count, INR: International normalized ratio, PVT: Portal vein thrombosis, SMV: Superior mesenteric vein

Table 2: Correlation between the natural course of partial portal vein thrombosis and clinical evolution

Parameter	Stable/improved (*n*=16) (%)	Worsened (*n*=6) (%)	*P* value
Esophageal varices (size)			
Small	2 (12.5)	1 (16.6)	0.230
Medium	8 (50.0)	1 (16.6)	<0.0001
Large	6 (37.5)	4 (66.6)	<0.0001
Variceal bleeding	5 (31.2)	5 (83.3)	<0.0001
Refractory ascites	6 (37.5)	4 (66.6)	<0.0001

DISCUSSION

To date insufficient data are available on the natural evolution of PVT.[9,10] The aim of this study was to establish the natural history of nonmalignant partial PVT and the influence of PVT on the outcomes in patients with cirrhosis, in order to identify subgroups of patients who could benefit from PVT treatment. Our study found that more than half of cirrhotic patients diagnosed with partial PVT improved or remained stable without treatment, whereas worsened

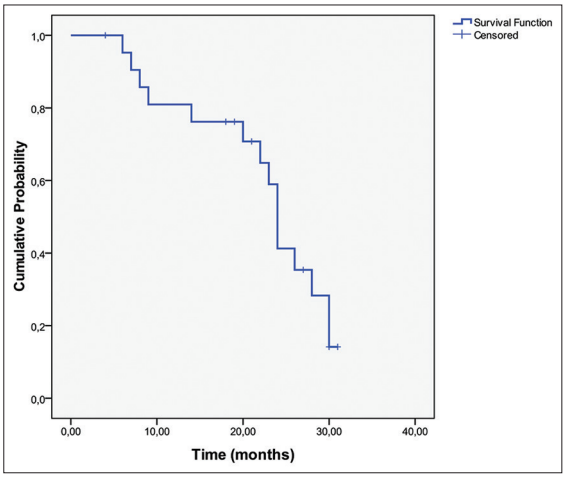

Figure 1: Kaplan–Meier plot showing the probability of patients with partial portal vein thrombosis remaining without decompensation over the follow-up period

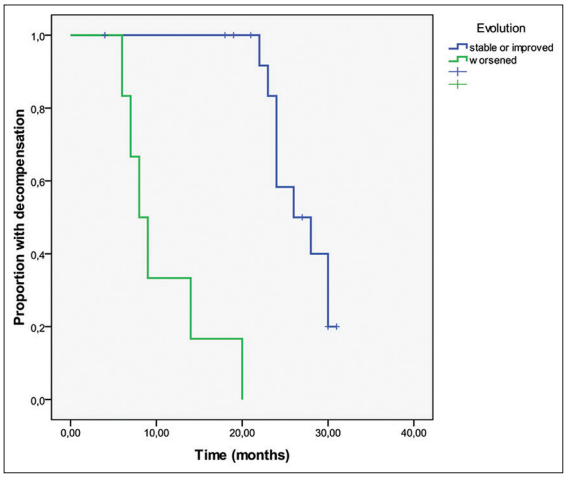

Figure 2: Kaplan–Meier plots showing the probability to remain without decompensation in patients with stable/improved partial portal vein thrombosis (PVT) compared with those with worsened partial PVT

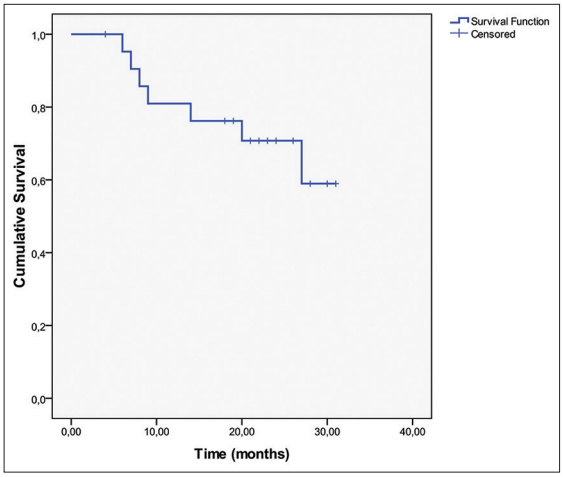

Figure 3: Kaplan–Meier plot showing the probability of survival in patients with partial portal vein thrombosis over the follow-up period

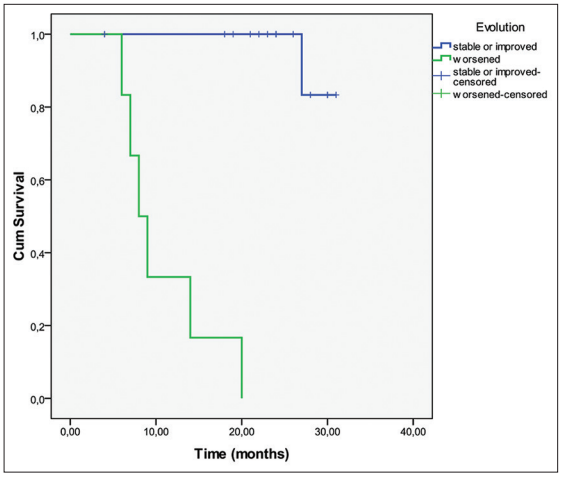

Figure 4: Kaplan–Meier plots showing the survival probability of patients with stable/improved partial portal vein thrombosis (PVT) compared with those with worsened partial PVT

PVT negatively influenced the patient's clinical outcomes. The findings provided evidence that anticoagulant treatment may not be necessary for the majority of cirrhotic patients with partial PVT.

The published data on the natural course of partial PVT are few and contradictory.[9-11,15-17] Several studies reported that spontaneous recanalization of PVT is rare.[12-14] In the study by Francoz *et al*., no patient achieved recanalization of partial and total PVT in the absence of anticoagulation, whereas 42% achieved recanalization on anticoagulant therapy.[11] Senzolo *et al*[14] reported thrombus progression in 75% patients who did not receive anticoagulation treatment, compared with only 15% of treated patients. However, Maruyama *et al*. reported spontaneous improvement in 47.6%, unchanged appearance in 45.2%, and progression in only 7.2%, and found no difference in the natural course of PVT based on the degree of obstruction or the location of the thrombus.[10] In another study aimed to define the natural course of nonmalignant partial PVT in cirrhotic patients, Luca *et al*. confirmed that in 45% patients partial PVT improved, and thrombus progression did not influence patients' clinical outcome.[9]

The difference between these studies could be explained at least partially by their design, the primary outcome, small sample size, and short-term follow-up. Definitive diagnosis of PVT can be obtained by CT and magnetic resonance imaging, both methods providing information about the extent of the thrombosis and the development of collateral circulation. Previously, data regarding natural history of partial PVT were extracted from studies evaluating the efficacy of anticoagulant treatment in

cirrhotic patients. All these studies[7,10-14] included a heterogeneous population, mostly formed by partial PVT, but with no consensus regarding partial/total PVT definition, which may explain the large range in prevalence of PVT in cirrhotic patients.

Our study confirmed the findings reported by Luca *et al*[9] although we found that worsened PVT was associated with patients' poor clinical outcome, including mortality.

Our study has some strengths: It is a prospective cohort study, excluded patients with hepatocellular carcinoma where the incidence of PVT is higher and the mechanism of thrombus formation is different (invasive of portal vein by hepatoma cells in addition to abnormalities of coagulation and fibrinolysis systems),[18] and all patients had imaging evaluation at the time of screening and every 3–6 months in the follow-up period. However, this study has also several limitations: Small number of patients included, a single center study, and absence of routine testing for a hypercoagulable state.

Finally, as our study shows that worsened partial PVT has a prognostic value, this variable may be included in the future studies aimed to identify predictor factors of mortality in cirrhotic patients.

CONCLUSION

Our study shows that more than half of cirrhotic patients with partial PVT had a stable or improved thrombus evolution without anticoagulant therapy, although worsened PVT negatively influenced outcomes. Prospective randomized controlled clinical trials are needed, but until then clinicians should carefully consider the risk of anticoagulant treatment in cirrhotic patients with partial PVT.

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