

# Portal vein thrombosis risk factors in liver transplant candidates

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## Abstract

**Background and Aim:** Portal vein thrombosis (PVT) is particularly detected in advanced liver cirrhosis patients. We aimed to analyze the risk factors for PVT in liver transplant candidates.

**Materials and Methods:** Dataset for consecutive 165 cirrhotic patients who were evaluated for liver transplantation (LT) were retrospectively analyzed. We sorted patients into two groups: patients with PVT and patients without PVT. Included variables were age, sex, etiology of liver disease, body mass index, MELD-Na score, Child-Pugh score, clinical variables reflecting portal hypertension, and hepatocellular carcinoma. Univariate and multivariate logistic regression analyses were used to identify risk factors of PVT.

**Results:** Of 165 LT candidates, 46 had PVT (27.9%). Ascites, thrombocytopenia, history of variceal bleeding, and band ligation were risk factors for PVT in univariate analysis. In multivariate analysis, only a history of variceal bleeding (OR 3.45, 95% CI 1.02–11.6,  $p=0.046$ ) significantly increased the risk of PVT.

**Conclusion:** The previous history of variceal bleeding predicts PVT development in cirrhosis, suggesting that the severity of portal hypertension is a major predictive factor for PVT in patients with cirrhosis. Future prospective studies are needed to risk stratifying cirrhosis patients prior to LT for future PVT development and to define the prophylactic role of anticoagulation in these patients.

**Keywords:** Cirrhosis; liver transplant; portal vein thrombosis; PVT Risk Index Score.

## Introduction

Portal vein thrombosis (PVT) is a common complication in patients with cirrhosis who are being evaluated for liver transplantation (LT). The prevalence of PVT in LT candidates ranges between 8% and 25%.<sup>[1]</sup> LT recipients with PVT have an inferior survival and more

complications in the posttransplant period.<sup>[2]</sup> Risk factors for PVT in patients with cirrhosis are heterogeneous, and they have not been clearly validated. Major risk factors for PVT in patients with cirrhosis are severity of portal hypertension and liver disease. Obesity, metabolic syndrome, and nonalcoholic steatohepatitis (NASH) cirrhosis are also recognized as independent risk factors for PVT.<sup>[3]</sup> Factor V Leiden and G20210A prothrombin gene mutations may also play a role although available data are conflicting.<sup>[4,5]</sup> Recently, a predictive model for PVT risk has been developed in patients listed for LT in the United States in which NASH etiology, MELD score, moderate-to-severe ascites, age, and African American race were included. This new tool (PVT Risk Index) might be used to identify patients at risk for PVT.<sup>[6]</sup> The recognition of the risk factors for PVT development in LT candidates could modify the management of these patients and consequently improve posttransplant outcomes by starting pretransplant anticoagulation therapy. The aim of this study was to identify the risk factors for predicting PVT development in LT candidates.

## Materials and Methods

Consecutive patients who were evaluated as LT candidates between February 2018 and January 2022 were included. Inclusion criteria were age >18 years and cirrhosis diagnosis based on clinical and radiological findings and laboratory values. Exclusion criteria were age younger than 18 years, previous LT, and myeloproliferative diseases. All patients underwent a workup before LT listing according to the AASLD guidelines.<sup>[7]</sup> Doppler ultrasonography was used to check the portal vein patency, and all patients had a triple-phase computed tomography (CT) or gadolinium magnetic resonance imaging (MRI). PVT diagnosis was confirmed by either CT or MRI. Clinical data regarding age, gender, cirrhosis etiology, body mass index (BMI), diabetes, hepatocellular carcinoma (HCC), nonhepatic malignancy, laboratory values (glucose, bilirubin, international normalized ratio, albumin, sodium, creatinine, and platelets), prior endoscopic banding of varices, history of esophageal variceal bleeding, history of abdominal surgery, history of spontaneous bacterial peritonitis (SBP), presence and grading of ascites, severity of liver disease (MELD-Na and Child-Pugh scores), and Factor V Leiden and G20210A prothrombin gene mutation analyses were recorded retrospectively from the patient files. In addition, PVT Risk Index scores of the patients were calculated (<https://app-phs.hmc.psu.edu/pvtriskindex/>).<sup>[6]</sup> The study was approved by the ethics committee of Health Sciences University Umraniye Training and Research Hospital (date: January 14, 2021 and no.: B.10.1.TKH.4.34.H.GP.0.01/11).

**How to cite this article:** Ak C, Adali G, Sayar S, Agackiran A, Kulali F, Kahraman R, et al. Portal vein thrombosis risk factors in liver transplant candidates. *Hepatology Forum* 2022; 3(3):88–92.

**Received:** March 01, 2022; **Accepted:** July 04, 2022; **Available online:** September 23, 2022

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## Statistical Analysis

Categorical variables were given as frequencies with percentages, and continuous variables were presented as median (min–max) based on the distribution of variables. Normality was confirmed with the Shapiro–Wilk test. Pearson’s Chi-squared test was used for categorical variables, and the Mann–Whitney U test was used to determine nonnormally distributed variables. Multivariable logistic regression was performed to determine risk factors for PVT. Multivariate models included variables significantly associated with the presence of PVT in univariate analysis at a level of significance of  $p < 0.20$ . The data were analyzed using the Statistical Package for Social Sciences (SPSS, v. 25.0) at a significance level of 0.05.

## Results

In total, 165 patients were included; the median age of the patients was 59 years (18–74), and 124 (75.2%) of them were males. Baseline characteristics of all patients are shown in Table 1. PVT was detected in 46 (27.9%) patients, and most of the patients (77%) had an intermediate PVT Risk Index score. Hepatitis B virus infection was the most common etiology of cirrhosis (32.1%), followed by NAFLD (30.9%). Seventy-one (43%) patients were diagnosed with HCC. Additionally, 7 (4.2%) patients were diagnosed with non-HCC malignancies.

The univariate and multivariate analysis results of the risk factors predicting PVT are shown in Table 2. There were no significant differences in age between patients with or without PVT. PVT Risk Index scores, factor V Leiden mutation, and prothrombin G20210A mutation were not associated with PVT risk. The proportion of patients with PVT was significantly lower in Child-Pugh A patients than in Child-Pugh B and Child-Pugh C patients. Ascites, history of variceal bleeding and history of esophageal variceal band ligation, and platelet count below  $150 \times 10^9$  were significantly more common in patients with PVT than in those without PVT. In multivariable logistic regression analysis, only the history of variceal bleeding significantly increased the risk of PVT (OR 3.45,  $p = 0.046$ ).

## Discussion

PVT in the setting of cirrhosis poses an increased risk for intestinal ischemia in acute cases, as well as hepatic decompensation, increased difficulty with liver transplant surgery, and higher posttransplant mortality for chronic PVT.<sup>[8]</sup> As noted in the Baveno VII consensus report, PVT screening is recommended at the time of HCC screening in all patients who are potential liver transplant candidates.<sup>[9]</sup> The relative risk of developing PVT in the presence of cirrhosis is increased more than sevenfold above the risk observed in the general population.<sup>[10]</sup> PVT prevalence increases with the degree of liver failure and in the setting of HCC, being as low as 1% in patients with the compensated disease and rising to 8%–25% in candidates for LT and 40% in the presence of HCC.<sup>[11]</sup> In our study, PVT was detected in 27.8% of cirrhosis patients who were LT candidates.

Emerging information from large transplant registries suggests that NASH may be an independent risk factor for the development of nontumoral PVT in patients with decompensated cirrhosis as it is associated with increased plasminogen activator inhibitor and reduced protein C levels.<sup>[12,13]</sup> In our study, NAFLD was proportionally higher in patients with PVT than in patients without PVT (39.1% vs 27.7%), but there was no statistical difference ( $p = 0.157$ ). Additionally, patients with cryptogenic cirrhosis also had higher PVT rates than those without PVT (15.2% vs 9.2%,  $p = 0.203$ ).

**Table 1.** Baseline characteristics of all patients

Variables	n=165
Age (years)	59 (18–74)
Age >60 years	72 (43.6)
Gender, male	124 (75.2)
BMI (kg/m <sup>2</sup> )	28.4 (16.3–50.4)
BMI $\geq 30$	65 (39.4)
Cirrhosis etiology	
HBV	53 (32.1)
NAFLD	51 (30.9)
Cryptogenic	18 (10.9)
HCV	16 (9.7)
Alcohol	14 (8.5)
Other	13 (7.9)
Cirrhosis duration (months)	21 (0.3–240)
Child-Pugh score	
A	45 (27.3)
B	71 (43)
C	49 (29.7)
MELD score	15 (5–45)
MELD >25	17 (10.3)
Ascites	116 (70.3)
Ascites grade 2/3	79 (47.9)
Portal vein thrombosis	46 (27.9)
History of variceal bleeding	40 (24.2)
History of band ligation	45 (27.3)
History of SBP	16 (9.7)
History of abdominal surgery	42 (25.5)
HCC	71 (43)
Non-HCC malignancy	7 (4.2)
Diabetes	81 (49.1)
Duration of diabetes (years)	6.5 (0.1–20)
Platelet count <150 X10 <sup>9</sup>	134 (81.2)
Factor V Leiden mutation (heterozygote)	10 (6.1)
PT G20210A mutation (heterozygote)	5 (3)
PVT Risk Index	3.16 (2.01–5.92)
Low	29 (17.6)
Intermediate	127 (77)
High	9 (5.5)

Data are shown as median (interquartile range) or n (%). BMI was available for 159 patients. Factor V Leiden and PT G20210A mutation analyses were available for 85 patients. PVT: Portal vein thrombosis; BMI: Body mass index; HBV: Hepatitis B virus; NAFLD: Nonalcoholic fatty liver disease; HCV: Hepatitis C virus; SBP: Spontaneous bacterial peritonitis; HCC: Hepatocellular carcinoma; MELD: Model for end-stage liver disease.

The reason for these results could be the small number of patients, as there were only 51 patients with NAFLD cirrhosis in this study.

In general, the predisposing factors of PVT are categorized into local and systemic factors. The portal venous system in cirrhosis represents a local environmental factor particularly prone to thrombus formation by reduced blood flow from portal hypertension and the inflammatory milieu secondary to hepatic injury and gut transloca-

**Table 2.** Comparison of patients with and without portal vein thrombosis

Variables	Patients without PVT n=119 (72.1)	Patients with PVT n=46 (27.9)	Univariate analysis			Multivariate analysis		
			OR	95% CI	p	OR	95% CI	p
Age (years)	59 (18–74)	59 (29–72)	0.99	0.96–1.03	0.866			
Age >60 years	52 (43.7)	20 (43.5)	0.99	0.49–1.96	0.991			
Gender, male	33 (27.7)	8 (17.4)	0.54	0.23–1.29	0.172	0.57	0.13–2.41	0.448
BMI (kg/m <sup>2</sup> )	28.1 (16.3–50.4)	28.7 (19.1–47.3)	1.03	0.98–1.09	0.215			
BMI ≥30	45 (38.1)	20 (43.5)	1.24	0.62–2.49	0.530			
Cirrhosis etiology								
HBV	41 (34.5)	12 (26.1)	0.67	0.31–1.43	0.304			
NAFLD	33 (27.7)	18 (39.1)	1.67	0.81–3.42	0.157	1.10	0.35–3.55	0.863
Cryptogenic	11 (9.2)	7 (15.2)	1.95	0.69–5.49	0.203			
HCV	12 (10.1)	4 (8.7)	0.84	0.25–2.78	0.787			
Alcohol	11 (9.2)	3 (6.5)	0.68	0.18–2.57	0.576			
Other	11 (9.2)	2 (4.3)	0.55	0.11–2.67	0.464			
Cirrhosis duration, months	12 (0.3–240)	27 (1–180)	1.00	0.99–1.01	0.126	1.00	0.99–1.01	0.415
Child-Pugh score								
A	37 (31.1)	8 (17.4)	0.41	0.16–1.01	<b>0.049</b>	1.65	0.15–17.4	0.676
B	47 (39.5)	24 (52.2)	1.88	0.95–3.75	0.068	1.14	0.30–4.29	0.849
C	35 (29.4)	14 (30.4)	0.97	0.46–2.02	0.935			
MELD score								
MELD >25	13 (10.9)	4 (8.7)	0.77	0.24–2.51	0.673			
Presence of ascites								
Ascites grade 2/3	52 (43.7)	27 (58.7)	1.83	0.91–3.64	0.086	1.28	0.32–5.18	0.727
History of variceal bleeding								
History of band ligation	26 (21.8)	19 (41.3)	2.51	1.21–5.22	<b>0.013</b>			
History of SBP	10 (8.4)	6 (13)	1.63	0.55–4.79	0.370			
History of abdominal surgery	29 (24.4)	13 (28.3)	1.22	0.56–2.63	0.607			
HCC								
Non-HCC malignancy	5 (4.2)	2 (4.3)	1.03	0.19–5.54	0.967			
Presence of diabetes								
Duration of diabetes (years)	7 (0.1–20)	6 (0.1–20)	1.01	0.93–1.10	0.743			
Platelet count <150 X 10 <sup>9</sup>								
Factor V Leiden heterozygote	5 (8.3)	5 (20)	1.65	0.84–3.24	0.139	3.84	0.83–17.7	0.084
PT G20210A heterozygote	4 (6.7)	1 (4)	0.76	0.24–2.34	0.638			
PVT risk index								
Low	22 (18.5)	7 (15.2)	0.75	0.29–1.88	0.540			
Intermediate	91 (76.5)	36 (78.3)	1.10	0.48–2.51	0.807			
High	6 (5)	3 (6.5)	1.31	0.31–5.48	0.708			

Data are shown as median (interquartile range) or n (%). BMI was available for 159 patients. Factor V and factor 2 mutation analyses were available for 85 patients. PVT: Portal vein thrombosis; BMI: Body mass index; HBV: Hepatitis B virus; NAFLD: Nonalcoholic fatty liver disease; HCV: Hepatitis C virus; SBP: Spontaneous bacterial peritonitis; HCC: Hepatocellular carcinoma; OR: Odd ratios; CI: Confidence interval; MELD: Model for end-stage liver disease.

tion of bacteria or their by-products. A wide variety of systemic factors are described, including inherited and acquired thrombophilia, extraabdominal cancer, hormonal therapy, and autoimmune disorder.<sup>[14–16]</sup> In our study, the factors reflecting the degree of portal hypertension were associated with the presence of PVT. In univariate analysis, ascites ( $p=0.014$ ), history of variceal bleeding ( $p=0.020$ ), and history of band ligation for variceal bleeding ( $p=0.013$ ) predicted the development of PVT. However, when the multivariable analysis was

performed, only the history of variceal bleeding was a significant risk factor for PVT (OR: 3.45,  $p=0.046$ ).

There are conflicting data in the literature regarding the association between factor V Leiden mutation, PT G20210A mutation, presence of HCC, previous abdominal surgery, and PVT in cirrhotic patients.<sup>[4–6,17,18]</sup> In a meta-analysis comprising 1929 subjects with cirrhosis, factor V Leiden and PT G20210A mutations were associated with increased PVT risk in patients with cirrhosis.<sup>[4]</sup> However, in a prospective study,

which included 1243 adults with cirrhosis, there was no relationship between factor V Leiden and PT G20210A mutations and the development of PVT.<sup>[5]</sup> We also did not find an association between factor V Leiden and PT G20210A mutations and PVT. The presence of HCC appears to be a risk factor for PVT.<sup>[19,20]</sup> Although our cohort included 71 (43%) patients with HCC, there was no association between the presence of HCC and the presence of PVT. A study showed that only splenectomy caused the development of PVT, and other abdominal surgical interventions were not associated with PVT.<sup>[21]</sup> Compatible with this study, in our study, none of the patients had splenectomy, and there was no association between previous abdominal surgery and PVT.

Another independent risk factor for PVT is the degree of thrombocytopenia, and this is also emphasized in the Baveno VII consensus report as patients with low platelet counts are at a higher risk of PVT.<sup>[19,22,23]</sup> This seems paradoxical since a low platelet count should logically predispose to bleeding. As cirrhosis and portal hypertension progress, the resultant decrease in portal flow outweighs the protective effect of low platelet count against thrombosis, and the paradoxical finding of increased PVT with lower platelet counts may thus be related to decreased portal flows that occur with the progression of portal hypertension.<sup>[24]</sup> In our study, thrombocytopenia was more common in patients who developed PVT ( $p=0.039$ ), but it was not significant in the multivariable analysis.

A new predictive model for PVT (PVT Risk Index score), which included 66 568 liver transplant candidates, was proposed recently. This model included NASH etiology, MELD score, moderate-to-severe ascites, and age as predictors of PVT and African American race as protective from PVT.<sup>[6]</sup> In our study, the majority of patients (77%) fell into the intermediate risk category, and there was no association between the PVT Risk Index score and the presence of PVT. This might be due to the small sample size and lack of African American race in our cohort. This new PVT prediction score has not been prospectively validated. Additionally, the PVT Risk Index score included only moderate-to-severe ascites as a predictor of PVT; however, the history of variceal bleeding could be added to the model as it is known that the severity of portal hypertension is a major contributor to the development of PVT. Furthermore, thromboelastography could be another variable to add as a measure to evaluate the risk for bleeding or clotting in patients with cirrhosis.

Limitations of this study are that it was a small cohort, retrospective study and conducted in a single center.

## Conclusion

In our study, in patients with cirrhosis, only the history of variceal bleeding independently predicted an increased risk of development of PVT. New predictive models and prevention strategies need to be developed in the future to prevent complications of PVT and reduce the mortality of LT patients.

**Ethics Committee Approval:** The Umraniye Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 14.01.2021, number: B.10.1.TKH.4.34.H.GP.0.01/11).

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept – CA, GA; Design – SS, GA; Supervision – GA, SS; Fundings – KO; Materials – AA, FK; Data Collection and/or Processing – CA, GA; Analysis and/or Interpretation – GA, CA; Literature Search – RK, OO; Writing – CA, GA; Critical Reviews – GA, KO.

**Conflict of Interest:** The authors have no conflict of interest to declare.

**Financial Disclosure:** The authors declared that this study has received no financial support.

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