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Full Length Article

# Natural history and clinical outcomes in patients with portal vein thrombosis by etiology: A retrospective cohort study

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ABSTRACT

*Background:* Portal vein thrombosis (PVT) is an unusual-site thrombosis commonly encountered in patients with malignancies, cirrhosis, and acute abdominal inflammatory conditions (AIC). Current recommendations suggest that anticoagulation may improve recanalization rates but there is limited information on venous thromboembolism (VTE) recurrence rates and whether the etiologies of PVT respond similarly with anticoagulation.
*Objective:* To characterize the natural clinical course and outcomes of patients diagnosed with PVT based on etiology.
*Patients/methods:* Patients with a diagnosis of PVT between 2005 and 2015 who were followed for at least one year and had revised imaging at 12 months ± 3 months were identified. Comorbidities, demographics, anticoagulation choice and clinical outcomes including VTE recurrence, cavernous transformation, PVT recanalization, progression and mortality were obtained.
*Results:* Of 698 patients diagnosed with PVT, 85 patients were evaluable according to criteria: 54 had cirrhosis (63.5%), 15 malignancy (17.6%) and 16 AIC (18.8%). Mean age was 55.6 ± 13.1 years. At presentation, 40% patients were symptomatic and 29.4% received anticoagulation. Patients with AIC were anticoagulated more frequently compared to those with malignancy or cirrhosis (87.5% vs. 33.3% vs. 11.1%). Overall, patients with cirrhosis had lower rates of PVT progression (0% vs. 13.3%, p = 0.02) and patients with AIC had higher rates of cavernous transformation compared to cirrhosis or malignancy-associated PVT (31.3% vs. 7.4% vs. 0%, p = 002). Among untreated patients, those with malignancy had significantly higher rates of VTE recurrence and PVT progression than patients with cirrhosis (20% vs. 4.2% and 20% vs. 0%).
*Conclusions:* The natural course of PVT differs among etiologies. In the absence of anticoagulation, patients with malignancy are more prone to VTE recurrence and PVT progression compared to patients with cirrhosis. Given the high rate of VTE recurrence at 12 months in patients with malignancy-associated PVT, anticoagulation should be considered for this group.

## 1. Introduction

Portal vein thrombosis (PVT) is an unusual-site thrombosis mainly encountered in patients with underlying diseases such as malignancy, cirrhosis, myeloproliferative neoplasms (MPN) and acute inflammatory conditions (AIC). Incidence rates up to 16% have been reported for patients with compensated cirrhosis and 5–26% for decompensated cirrhosis, while the thrombosis incidence rates can be as high as 35% when cirrhosis and hepatocellular carcinoma present concomitantly [1,2]. Patients may be asymptomatic and incidentally diagnosed or they may be symptomatic with abdominal pain as the most commonly associated symptom [2–4].

Because of the PVT patient heterogeneity, decisions about the use and duration of anticoagulation are challenging [5]. There are no randomized clinical studies to guide management and recommendations are extrapolated from observational studies which group different thrombotic etiologies. It is not surprising therefore that there are discordant suggestions regarding anticoagulation from the different

*Abbreviations:* PVT, portal vein thrombosis; MPN, myeloproliferative neoplasms; AIC, acute inflammatory conditions; ACCP, American College of Chest Physicians; VTE, venous thromboembolism; CLG, Clinical Looking Glass

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medical societies: while the American College of Chest Physicians (ACCP) favors anticoagulation only in patients with symptomatic PVT; the American Association for the Study of Liver diseases recommends anticoagulation for all patients with PVT [6,7].

This study is aimed to characterize the natural clinical course and outcomes of patients diagnosed with PVT based on etiology. We examine the venous thromboembolism (VTE) recurrence, cavernous transformation, PVT recanalization, progression and mortality rates at 12 months of initial diagnosis in a cohort from a single institution.

## 2. Methods

### 2.1. Study population

Adult patients diagnosed with PVT by ICD-9 between 2005 and 2015 at Montefiore Medical Center/Albert Einstein College of Medicine (MMC/Einstein) were identified using the institutional data mining software Clinical Looking Glass (CLG). CLG is an interactive software application developed at MMC/Einstein that integrates demographic, clinical and administrative datasets and allows them to be reproduced in a programmable format for statistical access. PVT diagnosis was confirmed by chart review; the date of the first radiologic study showing evidence of PVT was considered the index date. Etiologies associated with PVT were obtained using CLG as follows: a diagnosis of cirrhosis by ICD9 or malignancy using the cancer registry and MPN by ICD9 diagnosed 10 years before the PVT index date. AIC was defined as acute comorbidities (acute appendicitis, diverticulitis, cholecystitis, pancreatitis, peritonitis, cholangitis, hepatic abscess, flares of inflammatory bowel disease, systemic infections with bacteremia or intra-abdominal interventional procedures) by ICD9 codes within 60 days before the index PVT date. Etiologies were confirmed on chart review. Cases that were not linked to any of these diagnoses were considered idiopathic and excluded from the cohort. Cases associated with more than one etiology were also excluded.

### 2.2. Data collection and definitions

Patients who were followed for at least one year and had revised imaging at 12 ± 3 months after the index date were selected and assessed by individual medical chart review. Imaging reports were accessed to identify VTE recurrence and PVT recanalization, progression and cavernous transformation. VTE recurrence was defined as any noncontiguous venous thrombosis encountered after the index event while PVT progression was defined as new thrombosis extending from the original clot to contiguous vessels. The PVT was considered recanalized when patency of the portal vein system was described on follow-up imaging report. Cavernous transformation was diagnosed when there was a description of collateral vessel formation or mention of a cavernoma or cavernous transformation in the follow-up report. Data was censored at 12 months. Demographic information obtained from the medical record included age, sex, race and BMI. Decisions regarding anticoagulation treatment, including choice and duration, were documented from chart review. Mortality data included death records within our institution as well as those reported by social security records. Approval was obtained from the Montefiore Medical Center/Albert Einstein College of Medicine Institutional Review Board.

### 2.3. Statistical analysis

Baseline demographic characteristics were analyzed using descriptive statistics. Patients were analyzed by PVT etiology and by anticoagulation choice. Continuous variables were calculated as means (SD) or medians (IQ range) depending on normality of distribution. Continuous variables were compared using *t*-tests or anova test where appropriate. Categorical variables were compared using chi-squares or Fisher's exact test as required.

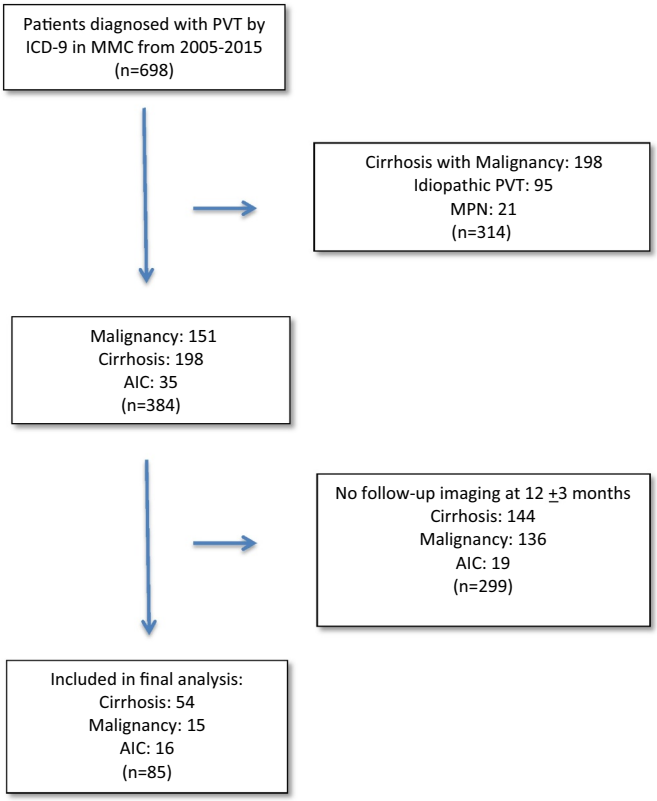


**Fig. 1.** Study flow diagram.

## 3. Results

A total of 698 patients with a diagnosis of PVT were identified. As seen in Fig. 1, 198 (28.4%) had cirrhosis, 151 (21.6%) had malignancy, 198 (28.4%) had concomitant cirrhosis and malignancy, 95 (13.6%) were idiopathic, 21 (3%) had MPN and 35 (5%) had AIC. The medical charts of patients with cirrhosis, malignancy and AIC were reviewed (n = 384). Of these, 85 had documented imaging follow-up at 12 ± 3 months and were included in the analysis. The most common reason for follow-up imaging within the first year of diagnosis was PVT follow-up (33.7%) followed by symptoms or signs (25.3%) which included abdominal pain, abdominal distention, encephalopathy, fever or abnormal laboratory values. Among these 85 patients, 54 patients (63.5%) had cirrhosis, 15 (17.6%) had malignancy and 16 (18.8%) had AIC (Fig. 1).

The mean age for the general cohort was 55.6 ± 13.1 years, with the AIC subgroup being the youngest at 48.1 ± 18.4 years (Table 1). 42% were Hispanic and 25% were African-American. The average BMI was 28.2 ± 6.6. At initial presentation, 60% of the patients were asymptomatic. Anticoagulation treatment was given to 29.4% of patients (25/85).

Outcomes at 12 months of index PVT date showed significant differences in PVT progression and cavernous transformation by etiologic groups. Patients with cirrhosis had lower rates of PVT progression compared to malignancy and AIC (0% vs.13.3% vs. 6.3%, p = 0.02) while patients with AIC had higher rates of cavernous transformation compared to cirrhosis and malignancy (31.3% vs. 7.4% vs. 0%, p = 0.02). The PVT recurrence rate in patients with malignancy was 20% while it was 3.7% and 6.3% for those with cirrhosis and AIC, respectively (Table 1).

When those who were left untreated were separately analyzed (Table 2), PVT outcome was different with different etiologies: patients with cirrhosis had significantly lower rates of VTE recurrence and PVT progression than patients with malignancy (4.2% vs 20%; 0% vs 20%,

**Table 1**
Characteristics and outcomes of patients with PVT by etiologic subgroup.

| | Total | Cirrhosis | Malignancy | AIC | P |
|---|---|---|---|---|---|
| N (%) | 85 (100) | 54 (63.5) | 15 (17.6) | 16 (18.8) | |
| Age (y), mean (SD) | 55.6 (13.1) | 56.3 (10.6) | 61 (11.9) | 48.1 (18.4) | 0.09 |
| BMI, mean (SD) | 28.2 (6.6) | 28.4 (5.9) | 24.8 (5.3) | 30.2 (8.4) | 0.15 |
| Male gender, n (%) | 42 (49.4) | 28 (51.9) | 8 (53.3) | 6 (37.5) | 0.61 |
| Anticoagulation, n (%) | 25 (29.4) | 6 (11.1) | 5 (33.3) | 14 (87.5) | < **0.01** |
| Outcomes at 12 months | | | | | |
| Cavernous transformation, n(%) | 9 (10.5) | 4 (7.4) | 0 (0) | 5 (31.3) | **0.02** |
| PVT recanalization, n(%) | 36 (42.4) | 27 (50) | 3 (20) | 6 (37.5) | 0.11 |
| PVT progression, n(%) | 3 (3.5) | 0 (0) | 2 (13.3) | 1 (6.3) | **0.02** |
| VTE recurrence, n(%) | 6 (7.1) | 2 (3.7) | 3 (20) | 1 (6.3) | 0.06 |
| Mortality, n(%) | 7 (8.2) | 5 (9.3) | 2 (13.3) | 0 (0) | 0.38 |

Abbreviations: AIC: abdominal inflammatory conditions; IQR: interquartile range; BMI: body mass index.
Bold data indicates significance at $p < 0.05$.

respectively).

### 3.1. AIC

The most common PVT predisposing factors in this subgroup were pancreatitis and post-surgical. Compared to other subgroups, the anticoagulation rate was significantly higher (87.5% vs. 33.3% vs. 11.1%, $p < 0.01$) (Table 1). The rate of cavernous transformation was higher than that of patients with cirrhosis or malignancy (31.3% vs 7.4% vs 0%, $p = 0.02$). None of the patients in this subgroup died within 12 months of diagnosis.

### 3.2. Cirrhosis

Patients with cirrhosis were the least likely to receive anticoagulation (11.1%); however, the PVT progression rate was significantly lower in this group compared to patients with AIC or malignancy (0% vs. 6.3% vs. 13.3%, $p = 0.02$). As noted, even in the absence of anticoagulation, cirrhotic patients had lower PVT progression and VTE recurrence rates compared to those with malignancy (0% vs. 20%, $p = 0.04$ for progression; 4.2% vs. 20% for recurrence, $p = 0.03$).

### 3.3. Malignancy

Within this subgroup, 40% of the patients had pancreatic cancer, followed by colon cancer in 20%. Patients with malignancy-related PVT had worse outcomes compared to the other groups: higher rates of PVT progression (20%) which decreased to 0% in anticoagulated participants and the highest VTE recurrence rate (20%) which did not improve in the group of patients that received anticoagulation; however, the patient number was small.

## 4. Discussion

PVT is a complication resulting from many morbidities, some of which are more prothrombotic than others. Our data demonstrate that the underlying morbidity has a major effect on the natural course and outcomes of PVT; hence, the associated etiology should be a factor to consider when deciding whether to anticoagulate. Prior studies have described patients with PVT but they report outcomes without examining the different etiologies of PVT and/or by combining all splanchnic vein thrombosis [5,8,9]. We examined only PVT and, in an effort to better delineate the disease process, we did not include patients with combined etiologies nor did we include MPN-associated PVT since the very prothrombotic nature of this disease is well-known.

The role of anticoagulation in patients with PVT has been explored in retrospective studies but remains controversial. Although the clinician's reasons to not anticoagulate were not available for most of our cases, the lack of anticoagulation particularly in the cirrhotic group might be attributed to concerns of a higher bleeding risk [10,11] or of a lack of benefit with regards to rethrombosis or recanalization. A recent systematic review by Loffredo et al. reported higher PVT recanalization rates without higher bleeding complications in patients with cirrhosis in those who received anticoagulation [12]. In our study, however, only 3.7% of patients with cirrhosis had VTE recurrence and none of them had PVT progression which suggests that anticoagulation might be spared in this group. Our institution is a referral center for liver transplant with physicians who have a great deal of experience in this area and our data, gathered without their knowledge or input, appears to support what seems to be a reluctance to anticoagulate these patients. Further efforts should be directed at delineating which characteristics of these cirrhotic patients would favor anticoagulation and which might favor withholding treatment.

In patients with AIC, Choudry et al. [4] reported what he considered

**Table 2**
Outcomes in patients with PVT by anticoagulation subgroup.

| | Total (n = 85) | Cirrhosis (n = 54) | Malignancy (n = 15) | AIC (n = 16) | |
|---|---|---|---|---|---|
| Not anticoagulated, n (%) | 60 (70.6) | 48 (88.9) | 10 (66.7) | 2 (12.5) | p |
| Cavernous transformation, n (%) | 5 (8.3) | 4 (8.3) | 0 (0) | 1 (50) | 0.19 |
| PVT recanalization, n (%) | 29 (48.3) | 26 (54.2) | 2 (20) | 1 (50) | 0.09 |
| PVT progression, n (%) | 2 (3.3) | 0 (0) | 2 (20) | 0 | **0.04** |
| VTE recurrence, n (%) | 5 (8.3) | 2 (4.2) | 2 (20) | 1 (50) | **0.03** |
| Mortality, n (%) | 6 (10) | 4 (8.3) | 2 (20) | 0 | 0.41 |
| Anticoagulated, n (%) | 25 (29.4) | 6 (11.1) | 5 (33.3) | 14 (87.5) | p |
| Cavernous transformation, n (%) | 4 (16) | 0 (0) | 0 (0) | 4 (28.6) | 0.28 |
| PVT recanalization, n (%) | 7 (28) | 1 (16.7) | 1 (20) | 5 (35.7) | 0.84 |
| PVT progression, n (%) | 1 (4) | 0 (0) | 0 (0) | 1 (7.1) | 1 |
| VTE recurrence, n (%) | 1 (4) | 0 (0) | 1 (20) | 0 (0) | 0.2 |
| Mortality, n (%) | 1 (4) | 1(16.7) | 0 (0) | 0 (0) | 0.4 |

Bold data indicates significance at $p < 0.05$.

to be a low mortality rate of 11% and which he attributed to higher rates of anticoagulation and/or antibiotic use. Kanellopoulu [13] also reported more recanalization and lower mortality rates in those AIC patients who were anticoagulated with acute PVT. Our results support these data in that, for the acute AIC state without underlying morbidities, anticoagulation may be preferred therapy.

Our data suggest that patients with malignancy-associated PVT have a high rate of VTE recurrence and PVT progression after a year of PVT diagnosis. In our cohort, rates of anticoagulation were lower than previously reported for patients with malignancies. This is not readily explained by the number of asymptomatic patients since over 50% of our symptomatic patients were not anticoagulated. Moreover, when outcomes in the malignancy group were compared by anticoagulation status, PVT progression rates were more favorable for the anticoagulated group. Based on this, clinicians should consider anticoagulation in patients with malignancy-associated PVT.

The decision to anticoagulate patients with PVT remains a major challenge for the clinician. To our knowledge, outcomes of patients with PVT by etiologic groups have never been compared before [3,8,9]. Etiology and morbidity are important issues to consider since we demonstrate that patients with cirrhosis have high recanalization rates compared to other subgroups, despite having lower anticoagulation rates. Further studies are needed to confirm these results and to determine why the disparities in outcome exist and whether fibrinolysis or associated decreases in liver-produced coagulation factors play a role [14].

As in all the prior publications, ours is not a randomized controlled study. Only patients with follow-up imaging were included in the analysis which could introduce a selection bias. As most of the outcomes (cavernous transformation, VTE recurrence and PVT progression or recanalization) can only be established by imaging and can present without any clinical manifestation, we determined that follow-up imaging would be a requirement for the study, understanding that this could result in a higher number of adverse events.

In conclusion, PVT is a heterogeneous condition and its natural history differs depending on the underlying associated etiology. In the absence of anticoagulation, patients with malignancy are more prone to VTE recurrence and PVT progression compared to patients with cirrhosis. Given the high rate of VTE recurrence at 12 months in patients with malignancy-associated PVT, anticoagulation should be recommended for this group. Patients with cirrhosis had lower rates of VTE recurrence and PVT progression in the absence of anticoagulation which suggests that anticoagulation could possibly be spared in this group or in a subgroup. More studies are needed that will allow better delineation of the causes and appropriate tailored therapies for portal vein thrombosis.

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