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Impact of Thrombocytopenia on Bleeding and Thrombosis in Adults with Cancer-associated Splanchnic Vein Thrombosis

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Abstract:
Malignancy is a risk factor for splanchnic vein thrombosis (SpVT). Data on the natural history of cancer-associated SpVT are limited. This was a single-center retrospective cohort study of 581 adult patients with cancer and SpVT. We aimed to characterize the impact of thrombocytopenia on major bleeding and progression or recurrence of SpVT within one year of initial cancer-associated SpVT diagnosis. Baseline thrombocytopenia (platelet < 100,000/uL within 15 days of SpVT diagnosis) was present in 39.5% of patients. A total of 39.2% of patients received therapeutic anticoagulation within two weeks of SpVT diagnosis. The cumulative once-year incidence of major bleeding was 10.7% (95% CI: 8.2-13.2), and for SpVT recurrence/progression was 16.2% (95% CI: 13.2-19.2). In multivariable regression analysis, therapeutic anticoagulation was associated with increased major bleeding (aRR: 1.74, 95% CI: 1.08-2.81) and decreased progression/recurrence of SpVT (aRR: 0.55, 95% CI: 0.35-0.86). Baseline thrombocytopenia was not independently associated with either major bleeding (aRR: 0.76, 95% CI: 0.43-1.34) or progression/recurrence of SpVT (aRR: 1.14, 95% CI: 0.73-1.78). A secondary analysis using inverse probability of treatment weighting with propensity scores for baseline thrombocytopenia corroborated that patients with thrombocytopenia did not have increased bleeding risk (aHR: 0.81, 95% CI: 0.48-1.39). Multivariable analysis treating platelets as a time varying covariate also did not reveal an association with major bleeding (aHR: 0.89, 95% CI: 0.55-1.45). Bleeding and thrombosis progression were frequent in patients with cancer-associated SpVT. Anticoagulation was associated with increased major bleeding and decreased thrombotic progression; thrombocytopenia did not impact outcomes.

Conflict of interest: COI declared - see note

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Impact of Thrombocytopenia on Bleeding and Thrombotic Outcomes in Adults with Cancer-associated Splanchnic Vein Thrombosis

Short title:
Cancer-associated Splanchnic Vein Thrombosis

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Key points

- Major bleeding and recurrent/progressive thrombosis were frequent complications in cancer-associated splanchnic vein thrombosis
- Treatment with anticoagulation was associated with increased major bleeding and decreased thrombotic progression or recurrence

Abstract

Malignancy is a risk factor for splanchnic vein thrombosis (SpVT). Data on the natural history of cancer-associated SpVT are limited. This was a single-center retrospective cohort study of 581 adult patients with cancer and SpVT. We aimed to characterize the impact of thrombocytopenia on major bleeding and progression or recurrence of SpVT within one year of initial cancer-associated SpVT diagnosis. Baseline thrombocytopenia (platelet < 100,000/uL within 15 days of SpVT diagnosis) was present in 39.5% of patients. A total of 39.2% of patients received therapeutic anticoagulation within two weeks of SpVT diagnosis. The cumulative once-year incidence of major bleeding was 10.7% (95% CI: 8.2–13.2), and for SpVT recurrence/progression was 16.2% (95% CI: 13.2–19.2). In multivariable regression analysis, therapeutic anticoagulation was associated with increased major bleeding (aRR: 1.74, 95% CI: 1.08-2.81) and decreased progression/recurrence of SpVT (aRR: 0.55, 95% CI: 0.35-0.86). Baseline thrombocytopenia was not independently associated with either major bleeding (aRR: 0.76, 95% CI: 0.43-1.34) or progression/recurrence of SpVT (aRR: 1.14, 95% CI: 0.73–1.78). A secondary analysis using inverse probability of treatment weighting with propensity scores for baseline thrombocytopenia corroborated that patients with thrombocytopenia did not have increased bleeding risk (aHR: 0.81, 95% CI: 0.48–1.39). Multivariable analysis treating platelets as a time varying covariate also did not reveal an association with major bleeding (aHR: 0.89, 95% CI: 0.55–1.45). Bleeding and thrombosis progression were frequent in patients with cancer-associated SpVT. Anticoagulation was associated with increased major bleeding and decreased thrombotic progression; thrombocytopenia did not impact outcomes.

Introduction

Venous thromboembolism (VTE) is a frequent complication of patients with cancer and is associated with increased morbidity and mortality.[1,2] Splanchnic vein thrombosis (SpVT) refers to thrombosis of the hepatic vein, portal vein, splenic vein, or mesenteric veins.[3] Cancers, especially gastrointestinal (GI) malignancies, are associated with increased risk of SpVT. This risk is especially pronounced in patients with concomitant liver disease or those who have undergone intra-abdominal surgery.[4,5] Although SpVT may be detected incidentally during surveillance imaging, it can present with complications of portal hypertension, GI bleeding, hepatic ischemia, and bowel infarction.[6,7] Moreover, SpVT has been associated with increased mortality in the general population[8] and specifically in patients with localized or metastatic malignancy.[9]

Patients with cancer-associated thrombosis can be particularly challenging to manage due to high risk of VTE recurrence[10] and bleeding complications associated with anticoagulation therapy compared to those without cancer.[11] Optimal management of cancer-associated usual-site VTE (deep vein thrombosis (DVT) or pulmonary embolism (PE)) has now been assessed with several large randomized control trials.[12] However, existing data regarding outcomes cancer-associated SpVT and the impact of anticoagulation on outcomes relies primarily on limited observational data.[13] Current society guidelines reflect this uncertainty surrounding treatment with anticoagulation for patients with cancer-associated SpVT. The American Society of Hematology guidelines suggest either short-term anticoagulation or observation in patients with cancer-associated SpVT,[14] and the American Society of Clinical Oncology recommends treatment of incidental cancer-associated SpVT on a case-by-case

basis.[15] The International Society on Thrombosis and Hemostasis (ISTH) proposes treatment of symptomatic SpVT in both the general population and cancer based on weak quality of evidence.[16]

Concurrent thrombocytopenia is frequent in cancer-associated thrombosis, which can be attributed to the malignancy itself, comorbidities, or cancer-directed therapies,[17] and can further complicate decisions surrounding anticoagulation.[18] This is particularly relevant for patients with cancer-associated SpVT as portal hypertension is associated with both lower platelet counts and increased risk of GI bleeding.[19] However, data on how thrombocytopenia modulates thrombotic and hemorrhagic risk in this high risk subpopulation are lacking. This study aimed to describe the clinical characteristics, anticoagulation strategies used, and bleeding and thrombotic outcomes in patients with cancer-associated SpVT. We further aimed to determine the impact of thrombocytopenia at the time of SpVT diagnosis with these outcomes.

Methods

Study Design

This was a single-center retrospective cohort study. Inclusion criteria were age ≥ 18 years, radiographic SpVT diagnosis between 2010 and 2021, and cancer diagnosis made before or up to one month after SpVT diagnosis. Diagnoses of SpVT were confirmed with radiology reports. Exclusion criteria included squamous and basal cell carcinomas of the skin, benign neuroendocrine tumors, in situ neoplasms, neoplasms of uncertain behavior, and myeloproliferative neoplasms (MPNs).

Patients with cancer-associated SpVT were initially identified using billing codes. We subsequently conducted manual chart review for all patients to confirm eligibility and to collect data on patient characteristics, treatment strategies, and outcomes. Cancer status was classified as active if the diagnosis had been made within the preceding six months of the SpVT diagnosis, if the cancer was metastatic, or if the patient was undergoing cancer-directed systemic therapy at the time of SpVT diagnosis. We defined baseline thrombocytopenia as at least one platelet count less than 100,000/uL within 15 days before or after diagnosis of SpVT. The cutoff for thrombocytopenia based on Common Terminology Criteria for Adverse Events (CTCAE v.5.0),[20] which classifies grade 1 thrombocytopenia as less than lower limit of normal (LLN) to 75,000/uL. In keeping with prior work in our group in thrombocytopenia in cancer-associated thrombosis, we defined the LLN as <100,000/uL to discount temporary or clinically inconsequential decreases in platelet count in the range of 100,000-150,000/uL.[17]

Outcomes

All outcomes were defined and measured up to 12 months following the initial diagnosis of SpVT. The primary outcome was major bleeding. Bleeding outcomes were classified according to the ISTH criteria.[21] Secondary outcomes included clinically relevant non-major bleeding (CRNMB) by ISTH criteria;[22] clinically-relevant bleeding, which was defined as a composite of major bleeding and CRNMB; progression or recurrence of SpVT, with progression defined as extension of the thrombus contiguously into a new vein and recurrence defined as a new interval thrombus which was non-contiguous with the initial thrombus; and usual-site VTE, which included DVT and PE.

Analysis

Cumulative incidences of the primary and secondary outcomes were calculated at 12 months from the incident SpVT considering death as a competing risk. We performed Poisson regression with robust variance estimators to identify factors associated with major bleeding including age at thrombosis (continuous), sex, presence of cirrhosis, prior episode of major hemorrhage, abdominal surgery within the last three months, type of SpVT (bland vs tumor thrombus or mixed), thrombocytopenia, therapeutic anticoagulation treatment within two weeks of SpVT diagnosis, baseline creatinine, degree of thrombus occlusion (partially occlusive vs completely occlusive), and vessel involvement (single vessel vs multiple vessels). While we defined thrombocytopenia as a platelet count of less than 100,000/uL as mentioned above, we also tested lower thresholds of thrombocytopenia, 75,000 and 50,000/uL (within 15 days before or after diagnosis of SpVT), as covariates in secondary analyses. In univariable and multivariable regression models, we used age at thrombosis (continuous), sex, prior major bleed, baseline creatinine (continuous), use of antiplatelets, and use of therapeutic anticoagulants within two weeks of diagnosis as covariates. Data is reported using risk ratios (RR) adjusted risk ratios (aRR) and 95% confidence intervals (CI).

In a secondary analysis, we used Cox models with inverse probability of treatment weighting with propensity scores for thrombocytopenia (less than 100,000/uL at baseline) to calculate adjusted hazard ratios (aHR) and 95% CIs for primary and secondary outcomes, including death as a competing risk. Covariates included in the Cox models were the same as the outcome-specific Poisson models. Independent variables used to create the propensity scores included type of cancer (hematologic, solid tumor) and all other variables included in the adjusted regression models. Propensity scores were truncated at the 1st and 99th percentiles. Patients were censored from the analysis at the time of event,

separately by outcome; their last clinical encounter; or at one year after their SpVT diagnosis, whichever was soonest.

Given the dynamic nature of platelet counts that can fluctuate over time, we performed Cox proportional hazards models using the same covariates listed but using thrombocytopenia (<100,000/uL) as a time-varying exposure to assess the impact of thrombocytopenia on major bleeding.

Robust Poisson regression was also performed to assess these same risk factors for association with the secondary outcome of recurrence or progression of SpVT. The model included the same covariates as those included in the model for major bleeding detailed previously, except prior VTE was substituted for prior major bleed.

All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC) and GraphPad Prism (GraphPad Software for Windows, La Jolla, CA).

Results

Patient characteristics

A total of 581 patients met inclusion criteria. (**Table 1)**. Overall, 63.6% (n=368) were male, 44.2% (n=257) of patients had a prior diagnosis of cirrhosis, 5.2% (n=30) had a history of a prior VTE, and 6.0% (n=35) had abdominal surgery in the last three months. The most common cancer types were hepatobiliary (55.2%, n=321), pancreatic (22.0%, n=128), and colorectal (5.3%, n=31). Hematologic malignancies accounted for 6.2% (n=36) of cancers. Most (92.8%, n=525) cancers were classified as

active at the time of index SpVT. The most common presenting symptom of SpVT was abdominal pain (42.3%, n=246), while 32.7% (n=190) were diagnosed incidentally. The most commonly involved site in the splanchnic bed was the portal vein (89.3%, n=519). Based on radiographic characteristics, 70.6% (n=408) of patients had bland SpVT, whereas 19.9% (n=115) had tumor SpVT, and 5.5% (n=32) were mixed type. Of cases in which data was available, the majority of SpVT (68.2%, n=264) were radiologically classified as partially occlusive.

Of 512 patients with available baseline platelet count data, 39.5% (n=202) of patients had platelet count <100,000/uL; overall, 12.7% (n=65) had platelet counts 75,000-99,000/uL, 14.1% (n=72) had counts 50,000-74,000/uL, and 12.7% (n=65) had counts <50,000/uL. A total of 5.5% (n=32) of patients were on anticoagulation at baseline at the time of SpVT diagnosis, and 19.4% (n=113) were on antiplatelet therapy. Less than half (39.2%, n=228) of patients received therapeutic anticoagulation within two weeks of diagnosis, and 4.0% (n=23) of patients received a mechanical thrombectomy. Most common anticoagulants used were low-molecular-weight heparin (43.0% n=98), direct oral anticoagulants (24.1%, n=55), and warfarin (18.4%, n=42). Median duration of anticoagulation treatment was 3.0 months (IQR 0.5-6.0). Survival at one year was 54.4%, and median follow-up time was 5.3 months (interquartile range: 1.3–12.0).

Bleeding outcomes

The cumulative incidence of major bleeding events within one year of SpVT diagnosis was 10.7% (95% CI: 8.2–13.2) (**Table 2, Figure 1a)**. Of these major bleeding episodes, 69.4% (n=43) were upper GI bleeds. The cumulative incidence of CRNMB at one year was 6.2% (95% CI: 4.2–8.2) (**Figure 1b**), and cumulative incidence of clinically relevant bleeding was 16.9% (95% CI: 13.8–19.9).

Among the 62 patients who had major bleeding, 31 (50%) had been started on therapeutic anticoagulation for their SpVT; of patients started on anticoagulation, 29 (93.5%) remained on anticoagulation up until their bleeding event. Among the 36 patients who had CRNMB, 17 (47.2%) had been started on anticoagulation; of patients started on anticoagulation, all remained on anticoagulation at the time of the bleeding event. Outcomes were further stratified by tumor type, stage, presence of symptoms, and treatment with therapeutic anticoagulation (**Supplemental Table 1**).

Multivariable Poisson regression analysis identified male sex and therapeutic anticoagulation within two weeks of diagnosis as independent predictors of major bleeding (aRR: 2.42, 95% CI: 1.27–4.59; and aRR: 1.74, 95% CI: 1.08-2.81, respectively) (**Table 3)**. Baseline thrombocytopenia (< 100,000/uL) was not associated with major bleeding (aRR: 0.76, 95% CI: 0.43–1.34). Notably, antiplatelet use at baseline (aRR: 1.46, 95% CI: 0.85–2.52) was not significantly associated with major bleeding at 12 months.

In the secondary Cox models with inverse probability of treatment weighting with propensity scores for thrombocytopenia, baseline thrombocytopenia (<100,000/uL) was not associated with a significant risk of major bleeding within one year (aHR: 0.81, 95% CI: 0.48–1.39). Similarly, in the multivariable Cox model with platelet count as a time-varying covariate over the course of the follow-up period, thrombocytopenia was not associated with major bleeding (aHR: 0.89, 95% CI: 0.55–1.45) (**Supplemental Table 2**).

Thrombotic outcomes

The cumulative incidence of progression or recurrence of SpVT at one year was 16.2% (95% CI: 13.2–19.2) (**Figure 2a**) and usual-site VTE at one year was 5.2% (95% CI: 3.4–7.0) (**Figure 2b**). Of the 99 patients who had progression or recurrence, 27 (27.3%) had been treated with therapeutic anticoagulation at the time of their initial SpVT; of patients treated, 19 (70.3%) were still on anticoagulation at the time of their thrombotic event. Of the 30 patients who had usual-site VTE, 18 (60.0%) had been treated with therapeutic anticoagulation for their SpVT; of these patients, only 10 (55.6%) were still on anticoagulation at the time of their usual-site VTE. In the multivariable regression model therapeutic anticoagulation within two weeks of diagnosis was associated with a lower incidence of progression or recurrence of SpVT (aRR: 0.55, 95% CI: 0.35-0.86) (**Table 4**). Of note, baseline thrombocytopenia (aRR: 1.14, 95% CI: 0.73–1.78) was not associated with progression/recurrence of SpVT.

In the Cox models with inverse probability of treatment weighting with propensity scores for thrombocytopenia, patients with thrombocytopenia did not have significantly increased risk of progression or recurrence of SpVT (aHR: 1.14, 95% CI: 0.70–1.84).

Discussion

In our cohort of patients with cancer-associated SpVT, both major bleeding and thrombosis progression/recurrence were frequent complications of SpVT. Treatment with therapeutic anticoagulation within two weeks of diagnosis was associated with increased major bleeding and decreased progression or recurrence or SpVT within one year. Thrombocytopenia (<100,000/uL) at baseline or analyzed as a time-varying covariate was not an independent risk factor for major bleeding or recurrent/progressive thrombosis at one year from SpVT diagnosis.

Notable characteristics of our cohort include the high prevalence of cirrhosis (44.2%) and non-luminal intra-abdominal tumors (77.3%). The proportion of SpVT patients with cirrhosis at our institution is higher than previously published cohorts of SpVT in the general population: 17.6% of patients in an individual-patient meta-analysis,[23] 11.3% in a national Danish registry,[8] and 2.9% of a retrospective cohort of 1561 patients.[9] It is uncertain whether this reflects a higher prevalence of cirrhosis in patients with cancer-associated SpVT compared to patients with SpVT in the general population, or whether this reflects unique characteristics of the population at our institution, a major liver transplant referral center. Similarly, the proportion of patients with hepatobiliary tumors is higher in our study (55.2%) compared to other cohorts of cancer-associated SpVT: 18.8% with hepatobiliary in a recent cohort,[24] and 57.6% with hepatobiliary and pancreatic combined in a separate study.[13] This may relate to the high prevalence of cirrhosis in our population. Coincident thrombocytopenia at the time of SpVT diagnosis was also frequent in our study. A retrospective cohort study of patients at our institution noted that VTE was associated with thrombocytopenia (<100,000/uL) in 22% of patients with solid tumors.[17] Data presented here suggests that thrombocytopenia may be more prevalent in cancer patients with SpVT than with usual-site VTE.

Uncertainty regarding optimal treatment of SpVT is reflected in the fact that a minority of patients in our cohort were treated with anticoagulation within two weeks of diagnosis. Reports of rates of treatment of SpVT with anticoagulation vary in the literature. A prospective cohort study of 132 patients with SpVT with or without cancer found that 68.9% were treated with anticoagulation, compared to 99.2% of patients in a control group with usual-site VTE.[13] In an individual patient meta-analysis of prospective trials of patients with SpVT, 85% of patients overall received anticoagulation,

and 73.6% of those with solid cancers were treated.[23] In contrast, a retrospective cohort study of SpVT in the general population found that only 23.9% of patients age > 65 years received anticoagulation within one month.[9] Notably, in a recent cohort study of 298 patients with cancer associated SpVT, of which 49% were hepatocellular carcinoma, approximately 15% were treated with anticoagulation.[25] We postulate that reasons for relatively low rates of anticoagulation in our cohort may reflect institutional practice as well as the significant proportion of patients with of thrombocytopenia (39.5%), tumor thrombi (19.9%), and incidentally diagnosed thrombi (32.7%), which could be interpreted as more likely to be chronic in the appropriate clinical setting.

The existing literature on the association between treatment with anticoagulation and clinical outcomes in patients with cancer-associated SpVT is unsettled. In our cohort, treatment with anticoagulation was associated with increased major bleeding and decreased recurrence or progression of thrombosis in the regression models. Our findings regarding thrombotic outcomes are generally in agreement with prospective data in the general population (including patients without cancer) which has also suggested a lower incidence of recurrent thrombosis in patients treated with anticoagulation.[23,26] The data regarding anticoagulation and its association with bleeding in patients with SpVT is more mixed. Smaller retrospective studies have demonstrated increased rates of hemorrhage in patients with SpVT treated with anticoagulation.[27] On the other hand, some prospective analyses of SpVT patients in the general population have reported that anticoagulation is correlated with lower risk of bleeding.[6,23] This association has been proposed to be due to increased recanalization in patients receiving anticoagulation, in turn leading to lower portal venous pressures and reduced variceal bleeding risk.[23] A retrospective cohort of 298 patients with cancer-associated SpVT found that anticoagulation was not associated with major bleeding but was associated with

increased rates of recanalization on re-imaging.[25] Taken together, these data highlight the clinical challenge of cancer-associated SpVT and the relative equipoise regarding anticoagulation strategies facing clinicians in many instances.

Existing data on the relationship between thrombocytopenia and bleeding in cancer-associated SpVT are limited. A 2021 single-center retrospective cohort of 1,561 patients with SPVT included 1,056 (71.0%) with cancer, although bleeding and thrombotic outcomes were not reported separately.[9] A 2022 individual-patient meta-analysis of prospective studies included 1635 patients with SpVT, of whom 523 had solid cancer, 118 had MPNs, and 20 had other hematologic cancers.[23] In this meta-analysis, patients with thrombocytopenia were underrepresented, with only 3.7% of all patients with platelet count of less than 50,000/uL. Our study, with 581 patients with cancer-associated SpVT, including 39.5% of patients with platelet < 100,000/uL and 12.7% with < 50,000/uL, is one of the largest cohorts of cancer patients with SpVT and aims to fill a gap in the literature by characterizing outcomes of those with concomitant thrombocytopenia. Our finding that thrombocytopenia was not associated with bleeding risk has several possible explanations. First, the data are retrospective, and the possibility of an untested confounder cannot be excluded. Certain characteristics of our patient population, such as the high incidence of cirrhosis, could affect the relationship between platelet count and bleeding: the relationship between liver dysfunction and bleeding is complex, and thrombocytopenia does not necessarily predict spontaneous major bleeding in patients with cirrhosis.[28,29] Moreover, platelet count was measured as a baseline variable, which may not accurately reflect the platelet count at the time of the bleeding episode. While we attempted to address this by testing thrombocytopenia as a time-dependent covariate in the multivariable regression, due to the retrospective nature of the study, platelet count data was not necessarily collected at regular and

frequent intervals, and thus the degree of thrombocytopenia immediately preceding a bleeding event for any individual patient may be over- or underestimated based on the data available. Additionally, we defined thrombocytopenia as 100,000/uL, which is higher than what may be conventionally considered to be the threshold at which risk of bleeding substantially increases. We specifically chose 100,000/uL as our threshold based on recent data suggesting that thrombocytopenia of this degree may confer increased bleeding risk in patients with cancer-associated VTE receiving anticoagulation.[30] Similar data exists showing increased bleeding risk with this threshold in patients with hepatitis C-related chronic liver disease[31] and with atrial fibrillation on anticoagulation.[32] Furthermore, we tested a platelet count threshold of 50,000/uL in our regression model and did not find an association with major bleeding.

The reason for male sex being independently associated with higher major bleeding incidence in the adjusted multivariable analysis is not clear. Such an effect is not consistent with the existing literature. In one large retrospective study, the rate of bleeding in patients in the general population treated with anticoagulation for VTE was higher in women, but there was no significant association between sex and major bleeding in a multivariable regression model.[33] The difference in bleeding rates by sex in our cohort could suggest an unidentified confounder associated with male sex. Given that this finding is incongruous with existing literature and lacks a clear mechanistic explanation, the clinical significance of this finding should be interpreted with caution.

We report one of the largest cohorts of patients with cancer-associated SpVT to date. However, we acknowledge certain limitations. Because patients were included based on imaging criteria, there may be a selection bias in the sample towards those receiving more frequent imaging or those with greater access to healthcare. Although we attempted to adjust for several covariates, the retrospective nature of the study introduces the possibility of unmeasured confounders. Being a single-center study

could influence the generalizability of the findings; for example, a relatively high proportion of patients in our sample had a prior diagnosis of cirrhosis. Moreover, the high incidence of cirrhosis indicates that malignancy may not have been the sole etiology of the thrombosis in a significant proportion of patients. Data on major clinical outcomes and key covariates were collected by manual chart extraction by trained clinicians. But retrospective data collection may miss relatively minor clinical events which were not documented in the medical record and thus be undercounted, which may explain why rates of CRNMB in our cohort were lower than major bleeding rates. An additional limitation is the reliance of baseline clinical characteristics at the time of diagnosis of SpVT; certain variables, in particular laboratory data, may fluctuate significantly over the course of the study period, and baseline data does not reflect this variability. Further, while patients with thrombocytopenia were well-represented in this cohort, our analysis of patients with severe thrombocytopenia (<50,000/uL) was still limited by sample size. Finally, certain characteristics of the SpVT at time of diagnosis, such as its chronicity and the extent to which it is composed of bland or tumor thrombus, are not always clear based on radiographic characteristics, especially with certain modalities such as ultrasound. As a result, features of the thrombus with the potential to affect outcomes could have been underappreciated in our analysis.

In this retrospective cohort study, we found that in patients with cancer-associated SpVT, both bleeding and thrombotic complications were frequent. Less than half of patients were treated with therapeutic anticoagulation, highlighting the challenges of management in this high-risk population. Anticoagulation was associated with increased major bleeding and decreased SpVT progression or recurrence. While thrombocytopenia was a frequent comorbidity, it was not independently associated with a higher risk of bleeding. Prospective studies of patients with cancer-associated SpVT with

adequate representation of patients with thrombocytopenia are needed to better characterize outcomes of these patients and to define optimal treatment strategies.

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Authorship Contributions

MA, JZ, and RP designed the study. MA and MJFT collected the data. LD performed statistical analyses. MA, MJFT, LD, and RP drafted the manuscript. All other authors critically reviewed and approved the final manuscript.

Conflict of Interest Disclosure

Dr. Zwicker reports personal fees from Calyx, personal fees from CSL Berhing, personal fees from Sanofi, grants from Incyte, and grants from Quercegen outside the submitted work. Dr. Patell reports personal fees from Merck Research outside the submitted work. No other disclosures were reported.

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Tables

Table 1: Patient characteristics

Characteristic	**N=581 n (%)**
Age at thrombosis (years)- mean ± SD	64.2 ± 11.4
Sex	
Female	211 (36.4)
Male	368 (63.6)
Comorbidities	
Cirrhosis	257 (44.2)
Prior major hemorrhage	67 (11.5)
Abdominal surgery in past 3 months	35 (6.0)
Prior VTE	30 (5.2)
Cancer diagnosis*	
Hepatobiliary	321 (55.2)
Pancreatic	128 (22.0)
Colorectal	31 (5.3)
Lymphoma	23 (4.0)
Stomach	17 (2.9)
Breast	15 (2.6)
Leukemia	13 (2.2)
Kidney	11 (1.9)
Prostate	8 (1.4)
Esophageal	5 (0.9)
Lung	5 (0.9)
Small intestine	5 (0.9)
Endometrial	4 (0.7)
Melanoma	4 (0.7)
Ovarian	4 (0.7)
Sarcoma	4 (0.7)
Bladder	3 (0.5)
Head and neck	3 (0.5)
Myeloma	2 (0.3)
Non-melanoma skin	1 (0.2)
Thyroid	1 (0.2)
Other	23 (4.0)
Cancer stage (n=560)	
Local	133 (23.8)
Locally advanced	199 (35.5)
Metastatic	228 (40.7)
Cancer status	
Active (diagnosed or treated within last 6 months)	525 (92.8)
In remission	41 (7.2)
Medications at time of SpVT	
Antiplatelet	113 (19.4)
Anticoagulant	32 (5.5)
Systemic cancer therapy	116 (20.0)
Thrombosis Location*	
Portal vein	519 (89.3)
Hepatic vein	35 (6.0)
Splenic vein	66 (11.4)
Superior mesenteric vein	119 (20.5)
Inferior mesenteric vein	6 (1.0)
Extent of SpVT (n=387)	
Completely occlusive	123 (31.8)

Partially occlusive	264 (68.2)
Type of SpVT	
Bland	408 (70.6)
Tumor	115 (19.9)
Mixed	32 (5.5)
Uncertain	23 (4.0)
Presenting signs/symptoms of SpVT*	
Abdominal pain	246 (42.3)
Nausea/vomiting	49 (8.4)
Ascites	57 (9.8)
Jaundice	46 (7.9)
Abnormal liver function tests	66 (11.4)
GI bleed	27 (4.6)
Ischemic bowel	4 (0.7)
Incidental finding	190 (32.7)
Other	147 (25.3)
Concurrently diagnosed usual-site VTE	
DVT	15 (2.6)
PE	14 (2.4)
Baseline laboratory results- mean ± SD	
Hemoglobin (g/dL)	10.8 ± 2.1
Platelets (K/uL)	194 ± 137
Creatinine (mg/dL)	1.1 ± 0.8
Prothrombin time (seconds)	18.3 ± 13.2
Partial thromboplastin time (seconds)	47.7 ± 32.3
Treatment within two weeks of diagnosis	
Therapeutic anticoagulation	228 (39.2)
Unfractionated heparin	33 (14.5)
Warfarin	42 (18.4)
LMWH	98 (43.0)
DOAC	55 (24.1)
Fondaparinux	0 (0.0)
Mechanical thrombectomy	23 (4.0)
Baseline platelet count	
≥100,000/ uL	310 (60.6)
75,000-99,000/uL	65 (12.7)
50,000-74,000/uL	72 (14.1)
<50,000/uL	65 (12.7)

SD=standard deviation, GI=gastrointestinal, SpVT=splanchnic vein thrombosis, VTE=venous thromboembolism, DVT=deep vein thrombosis, PE=pulmonary embolism, LMWH=low molecular weight heparin, DOAC=direct oral anticoagulant, CT=computed tomography.

*Patients can have multiple attributes, and thus totals may sum to more than 100%

Table 2: Cumulative incidence of primary and secondary outcomes by thrombocytopenia status

	Overall cohort N=581			Platelet <100,000 uL n=202			Platelet ≥100,000 uL n=310		
Outcome (within one year of SpVT diagnosis)	**n**	**Incidence (95% CI)**	**Time to Event in Days (Median, IQR)**	**n**	**Incidence (95% CI)**	**Time to Event in Days (Median, IQR)**	**n**	**Incidence (95% CI)**	**Time to Event in Days (Median, IQR)**
Major Bleeding	62	10.7% (8.2–13.2)	70.0 (17.0–146)	21	10.4% (6.2–14.6)	23.0 (12.0–146)	34	11.0% (7.5–14.5)	77.0 (23.0–144)
Upper GI	43	7.4% (5.3–9.5)	75.0 (14.0–160)	13	6.4% (3.1–9.8)	13.0 (3.0–146)	24	7.7% (4.8–10.7)	82.0 (22.5–152)
Lower GI	4	0.7% (0.02–1.4)	55.5 (37.0–83.0)	1	0.5% (0.00–1.5)	46.0 (46.0–46.0)	3	1.0% (0.00–2.1)	65.0 (28.0–101)
Intracranial	5	0.9% (0.01–1.6)	129 (110–244)	2	1.0% (0.00–2.4)	187 (129–244)	2	0.7% (0.00–1.5)	141 (21.0–261)
Retroperitoneal	2	0.3% (0.00–0.08)	23.5 (6.0–41.0)	0	0.0%	--	2	0.7% (0.00–1.5)	23.5 (6.0–41.0)
Intraarticular/intramuscular	3	0.5% (0.00–1.1)	23.0 (16.0–54.0)	3	1.5% (0.00–3.2)	23.0 (16.0–54.0)	0	0.0%	--
Mucocutaneous	0	0.0%	--	0	0.0%	--	0	0.0%	--
Pericardial	0	0.0%	--	0	0.0%	--	0	0.0%	--
Clinically relevant non-major bleeding	36	6.2% (4.2–8.2)	56.0 (19.0–117)	13	6.4% (3.1–9.8)	97.0 (55.0–220)	18	5.8% (3.2–8.4)	21.5 (5.0–90.0)
Clinically relevant bleeding	98	16.9% (13.8–19.9)	60.5 (18.0–141)	34	16.8% (11.7–22.0)	55.5 (16.0–154)	52	16.8% (12.6–20.9)	56.0 (20.5–101)
Progression and/or recurrence of SpVT*	94	16.2% (13.2–19.2)	87.0 (51.0–146)	29	14.4% (9.5–19.2)	82.0 (37.0–161)	40	12.9% (9.2–16.6)	73.0 (44.5–125)
Progression	79	13.6% (10.8–16.4)	89.0 (56.0–151)	24	11.9% (7.4–16.3)	81.0 (37.5–159)	33	10.7% (7.2–14.1)	87.0 (56.0–130)
Recurrence	20	3.4% (2.0–4.9)	110 (24.5–195)	6	3.0% (0.6–5.3)	174 (17.0–224)	8	2.6% (0.8–4.4)	53.0 (15.5–95.5)
Usual-site VTE (DVT or PE)	30	5.2% (3.4–7.0)	80.5 (43.0–137)	5	2.5% (0.3–4.6)	134 (92.0–174)	21	6.8% (4.0–9.6)	71.0 (43.0–137)
DVT	16	2.8% (1.4–4.1)	81.0 (35.5–185)	5	2.5% (0.3–4.6)	134 (92.0–174)	9	2.9% (1.0–4.8)	66.0 (43.0–196)
PE	14	2.4% (1.2–4.0)	80.5 (54.0–100)	0	0.0%	--	12	3.9% (1.7–6.0)	77.0 (48.0–119)

*For patients with progression and recurrence, time to event is time to the earlier event

CI=confidence interval, IQR=interquartile range, SpVT=splanchnic vein thrombosis, GI=gastrointestinal, VTE=venous thromboembolism, DVT=deep vein thrombosis, PE=pulmonary embolism

Table 3: Univariable and multivariable analysis for major bleeding within one year of cancer associated splanchnic vein thrombosis diagnosis

Characteristic	**Major bleeding n (%)**	**Unadjusted RR (95% CI)**	**Adjusted* RR (95% CI)**
Age at thrombosis			
≤65 years	39 (12.7)	Ref	Ref
>65 years	23 (8.4)	0.67 (0.41–1.08)	0.67 (0.30–1.51)
Sex			
Female	11 (5.2)	Ref	Ref
Male	51 (13.9)	2.66 (1.42–4.99)	2.42 (1.27–4.59)
Cirrhosis			
Absent	35 (10.8)	Ref	Ref
Present	27 (10.5)	0.97 (0.61–1.56)	0.73 (0.41–1.31)
Abdominal surgery within past 3 months			
Absent	58 (10.6)	Ref	Ref
Present	4 (11.4)	1.08 (0.41–2.79)	1.03 (0.37–2.83)
Prior major bleed			
Absent	52 (10.1)	Ref	Ref
Present	10 (14.9)	1.48 (0.79–2.76)	1.50 (0.79–2.84)
Baseline creatinine			
≤1.0	43 (9.5)	Ref	Ref
>1.0	19 (14.6)	1.53 (0.93–2.54)	1.44 (0.83–2.49)
Recent systemic chemotherapy			
Absent	51 (11.0)	Ref	Ref
Present	11 (9.5)	0.86 (0.47–1.61)	1.13 (0.60–2.11)
Use of antiplatelets at baseline			
Absent	45 (9.6)	Ref	Ref
Present	17 (15.0)	1.56 (0.93–2.63)	1.46 (0.85–2.52)
Type of thrombus			
Bland/mixed	46 (10.5)	Ref	Ref
Tumor	14 (12.2)	1.16 (0.66–2.04)	1.24 (0.71–2.18)
Thrombus occlusion			
Partial	20 (16.3)	Ref	Ref
Complete	27 (10.2)	0.63 (0.37–1.08)	0.69 (0.40–1.17)
Anticoagulation within two weeks			
Absent	31 (8.8)	Ref	Ref
Present	31 (13.6)	1.55 (0.97–2.48)	1.74 (1.08–2.81)
Thrombocytopenia			
None	34 (11.0)	Ref	Ref
*Platelets 75,000-99,000/*uL	8 (12.3)	1.12 (0.55–2.31)	0.86 (0.39–1.90)
*Platelets 50,000-74,000/*uL	3 (4.2)	0.38 (0.12–1.20)	0.33 (0.10–1.03)
*Platelets <50,000/*uL	10 (15.4)	1.40 (0.73–2.69)	1.21 (0.60–2.44)
Thrombocytopenia at baseline			
None	34 (11.0)	Ref	Ref
*Platelets <100,000/*uL	21 (10.4)	0.95 (0.57–1.59)	0.76 (0.43–1.34)
Vessel involvement			
Single	49 (10.8)	Ref	Ref
Multiple	13 (10.3)	0.96 (0.54–1.71)	0.89 (0.48–1.65)
Type of cancer			
Hepatobiliary	37 (11.5)	Ref	Ref
Pancreatic	16 (12.7)	1.10 (0.64–1.91)	1.15 (0.66–2.02)
Luminal gastrointestinal	4 (8.2)	0.71 (0.26–1.90)	0.70 (0.27–1.82)
Other	5 (5.9)	0.51 (0.21–1.26)	0.57 (0.23–1.46)

*Adjusted for age at thrombosis (continuous), sex, prior major bleed, baseline creatinine (continuous), use of antiplatelets, use of therapeutic anticoagulants within two weeks of diagnosis, and type of cancer
RR=relative risk, CI=confidence interval

Table 4: Univariable and multivariable regression for progression or recurrence of cancer associated splanchnic vein thrombosis within one year of splanchnic vein thrombosis diagnosis

Characteristic	**Progression or recurrence, n (%)**	**Unadjusted RR (95% CI)**	**Adjusted* RR (95% CI)**
Age at thrombosis			
≤65 years	50 (16.2)	Ref	Ref
>65 years	44 (16.1)	0.99 (0.69–1.44)	0.78 (0.45–1.37)
Sex			
Female	32 (15.2)	Ref	Ref
Male	62 (16.9)	1.11 (0.75–1.64)	1.13 (0.74–1.73)
Cirrhosis			
Absent	46 (14.2)	Ref	Ref
Present	48 (18.7)	1.32 (0.91–1.90)	1.48 (0.83–2.64)
Abdominal surgery within past 3 months			
Absent	92 (16.9)	Ref	Ref
Present	2 (5.7)	0.34 (0.09–1.32)	0.43 (0.11–1.65)
Prior VTE			
Absent	88 (16.0)	Ref	Ref
Present	6 (20.0)	1.25 (0.60–2.63)	1.34 (0.64–2.78)
Baseline creatinine			
≤1.0	82 (18.2)	Ref	Ref
>1.0	12 (9.2)	0.51 (0.29–0.90)	0.51 (0.25–1.04)
Recent systemic chemotherapy			
Absent	75 (16.1)	Ref	Ref
Present	19 (16.4)	1.02 (0.64–1.61)	1.11 (0.68–1.81)
Use of antiplatelets at baseline			
Absent	77 (16.5)	Ref	Ref
Present	17 (15.0)	0.91 (0.56–1.48)	0.93 (0.56–1.52)
Type of thrombus			
Bland/mixed	68 (15.5)	Ref	Ref
Tumor	24 (20.9)	1.35 (0.89–2.05)	1.16 (0.76–1.79)
Thrombus occlusion			
Partial	16 (13.0)	Ref	Ref
Complete	42 (15.9)	1.22 (0.72–2.09)	1.37 (0.79–2.37)
Anticoagulation within two weeks			
Absent	69 (19.6)	Ref	Ref
Present	25 (11.0)	0.56 (0.37–0.86)	0.55 (0.35–0.86)
Thrombocytopenia at baseline			
None	40 (12.9)	Ref	Ref
*Platelets 75,000-99,000/*uL	8 (12.3)	0.95 (0.47–1.94)	0.89 (0.44–1.83)
*Platelets 50,000-74,000/*uL	15 (20.8)	1.61 (0.95–2.76)	1.67 (0.97–2.88)
*Platelets <50,000/*uL	6 (9.2)	0.72 (0.32–1.62)	0.76 (0.33–1.73)
Thrombocytopenia			
None	40 (12.9)	Ref	Ref
*Platelets <100,000/*uL	29 (14.4)	1.11 (0.71–1.73)	1.14 (0.73–1.78)
Vessel involvement			
Single	77 (16.9)	Ref	Ref
Multiple	17 (13.5)	0.80 (0.49–1.30)	0.79 (0.47–1.32)
Type of cancer			
Hepatobiliary	55 (17.1)	Ref	Ref
Pancreatic	24 (19.1)	1.11 (0.72–1.71)	1.36 (0.85–2.19)
Luminal gastrointestinal	5 (10.2)	0.60 (0.25–1.41)	0.67 (0.27–1.66)
Other	10 (11.8)	0.69 (0.37–1.29)	0.84 (0.44–1.61)

*Adjusted for age at thrombosis (continuous), sex, prior venous thromboembolism, baseline creatinine (continuous), use of antiplatelets, use of therapeutic anticoagulants within two weeks of diagnosis, and type of cancer
RR=relative risk, CI=confidence interval

Figure Legends:

Figure 1: Cumulative incidence of (a) major bleeding and (b) clinically relevant non major bleeding using the Kaplan-Meier method with death as a competing risk within one year of diagnosis of cancer-associated splanchnic vein thrombosis.

Figure 2: Cumulative incidence of (a) progression/recurrence of splanchnic vein thrombosis and (b) usual-site venous thromboembolism using the Kaplan-Meier method with death as a competing risk within one year of diagnosis of cancer-associated splanchnic vein thrombosis

Figure 1

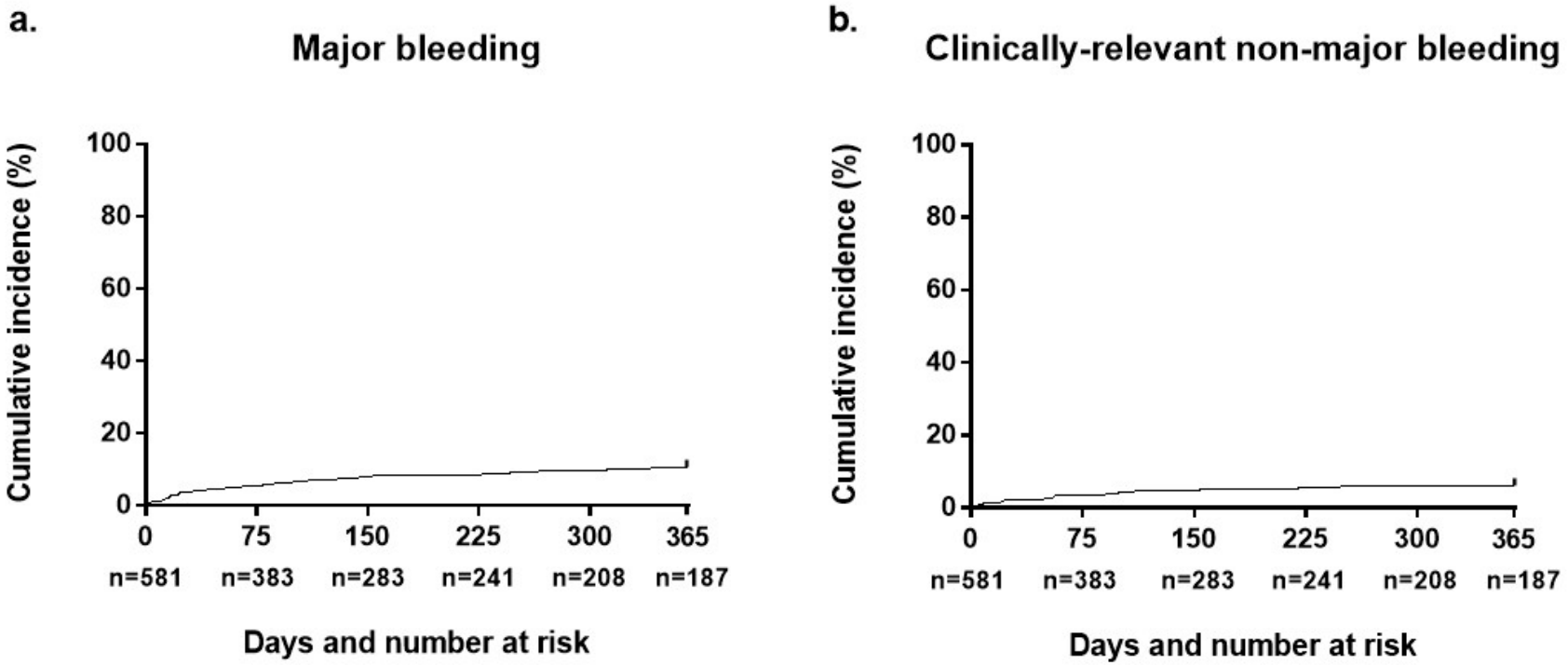

Figure 2