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MYELOPROLIFERATIVE NEOPLASMS (B STEIN, SECTION EDITOR)

Splanchnic Vein Thrombosis in the Myeloproliferative Neoplasms

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Abstract

Purpose of Review To review the epidemiology, diagnostic challenges, pathogenesis, and treatment strategies for patients with myeloproliferative neoplasm-associated splanchnic vein thrombosis.

Recent Findings The epidemiology of myeloproliferative neoplasm-associated splanchnic vein thrombosis (MPN-SVT) has been well characterized. While typical MPN-associated thrombosis affects older patients and involves the arterial circulation, MPN-SVT mostly impacts younger women. An association with *JAK2* V617F is well-known; recent studies have demonstrated only a weak association with *CALR* mutations. JAK inhibition may represent a novel treatment strategy, complementing anticoagulation, and management of portal hypertension.

Summary While the epidemiology has been well characterized, more work is needed to identify novel contributors to disease pathogenesis, beyond the *JAK2* V617F mutation itself, and endothelial compromise. Testing for MPN mutations in the setting of non-cirrhotic SVT is commonplace; *JAK2* V617F is the most likely to be identified. Testing for *CALR* or *MPL* mutations requires clinical judgement, though not unreasonable. The mainstay of therapy is indefinite anticoagulation; the role of direct oral anticoagulants is unclear. JAK inhibition may play a role in addressing associated splenomegaly and portal hypertension.

Keywords Splanchnic vein thrombosis · *JAK2* V617F mutation · Myeloproliferative neoplasm · Polycythemia vera

Introduction

The classical, *BCR-ABL1*-negative myeloproliferative neoplasms (MPNs) including polycythemia vera (PV), essential thrombocythemia (ET), and myelofibrosis (MF) share overlapping clinical and laboratory features, including an expansion of a mature blood element, a substantial symptom burden, a thrombotic tendency, and the possibility for evolution to MF and/or acute myeloid leukemia (AML). As hypothesized by Dr. Dameshek, these MPNs share a similar underlying disease pathogenesis, characterized by JAK-STAT dysregulation, due to the presence of driver mutations including *JAK2 V617F*, *CALR*, or *MPL* [1]. The identification of such mutations not only has facilitated the diagnostic workup but also has contributed to a better understanding of disease pathogenesis and the development of targeted therapies.

The focus of this review is on the thrombotic tendency observed in MPN patients. Thrombotic rates range from 12 to 39% in PV, from 11 to 25% in ET [2], and 7.2% in patients with MF [3]. Typically, arterial events are more commonly observed, when compared to venous events. Further, thrombotic events are typically observed prior to, or shortly after, an official MPN diagnosis and plateau by the end of the first decade. Traditional risk factors for MPN-associated thrombosis include advanced age and prior thrombosis history. Unfortunately, these risk factors are generic, rather than specific. Regarding cell counts, there is clearly an association between erythrocytosis and vascular events, since lowering hematocrit reduces risk for a cardiovascular event [4]. The presence of leukocytosis, but less so thrombocytosis, is also likely to increase thrombosis risk [5]. With respect to driver mutations, thrombosis risk appears higher in *JAK2* mutant MPN patients, compared to patients with *CALR* mutations,

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particularly, in ET [6, 7]. Beyond mutations, cardiovascular risk factors and inflammatory stress may further contribute. Interestingly, an association between clonal hematopoiesis of indeterminate potential (CHIP) mutations (including *JAK2*, *DNMT3A*, *TET2*, and *ASXL1*) and coronary heart disease has been reported, possibly mediated via inflammation [8••]. There are a number of potential surrogates/biomarkers under investigation. One recent study suggests that increased levels of tissue factor-positive procoagulant microparticles are seen in MPN patients who suffer a thrombotic episode and could potentially serve as a surrogate marker [9•].

Thrombotic events in atypical locations, including the splenic, mesenteric, hepatic, or portal veins, collectively referred to as splanchnic vein thrombosis (SVT), are also classically associated with MPN [10]. While the most common underlying etiology of SVT may be cirrhosis and solid cancers [11••] in the absence of such risk factors, MPNs are a contributing etiology in at least 30–40% of patients [12]. Uniquely, these atypical venous thromboses have a distinct epidemiology, etiology, pathogenesis, and associated clinical challenges compared to more "typical" MPN thrombosis (Table 1). In this review, we discuss such characteristics of MPN-associated SVT.

Epidemiology

While advanced age is a traditional risk factor for MPN thrombosis, SVT is more commonly identified in younger patients, especially women. A retrospective study of 120 younger (< 45 years) patients with PV compared to 84 PV patients older than 65 observed a statistically similar prevalence of thrombosis. This was an interesting finding, since younger patients also had lower leukocyte counts and lower *JAK2* allelic burdens. However, when looking at the involved vasculature, there were significant differences, since venous events were more commonly identified in younger patients, compared to older patients. Specifically, SVT occurrence was more frequent in the younger patients compared to 84 older patients (> 65 years) (13 vs. 2%, $P < 0.0056$) and the younger patients were mainly female (76%) [13]. Another retrospective study of 270 patients with *JAK2* V617F-positive MPN which included 164 women and 106 men also observed higher rates of abdominal vascular thrombotic events in women compared to men [14]. Other studies have also observed a higher likelihood for venous thrombosis in younger patients and in women. A study of 1545 patients with PV showed that venous thrombosis was more frequent in women than in men (9.3 vs. 5.4%, $P < 0.01$) [15]. Also, a recent study of patients with MPN showed a higher venous thrombotic risk 1 year after MPN diagnosis in the younger patients with MPN [ages 18–49, 50–59 (HR 14.6, HR 9 respectively)] compared to the older patients [ages 60–69, 70–79, ≥ 80 (HR 5.4, HR 4.3, HR 3.1 respectively)] [16••]. The trend for the venous thrombotic risk was similar at 3 months and 5 years after MPN diagnosis [16••]. Among the MPNs, SVT appears most commonly identified in PV, compared to ET or MF. In a 2012 meta-analysis, the distribution of MPN subtypes revealed that PV is most common at 52.9% in Budd-Chiari syndrome (BCS) and 27.5% in portal vein thrombosis (PVT), followed by ET with 24.6% in BCS and 26.2% in PVT and finally by MF with 6.7% in BCS and 12.8% in PVT [12]. In a more recent study of 51 patients with MPN complicated by portal hypertension (HTN), SVT was found in 76% of patients with PV compared to the other MPNs at 26%, $P = 0.0007$ [17]. MPN-associated SVT can present with an entirely latent MPN, but emergence of a phenotype usually occurs. Of the MPNs, the most common phenotype to emerge is also PV (for

Table 1 Risk factors, pathogenesis, diagnostic challenges, and treatments of SVT in MPN

Characteristic	Response
Demographics	• Younger, female patients; PV > ET > MF
Pathogenesis	• Site-specific endothelial compromise? ▪ *JAK2* V617F identified in splanchnic vascular endothelium • Predisposition? ▪ *JAK2* 46/1 haplotype associated with MPN and SVT
Molecular features	• *JAK2* V617F >> *CALR*, *MPL*, *JAK2* exon 12
Diagnostic challenges	• Phenotype often masked by hypersplenism, GI bleeding, hemodilution • Or, MPN can be entirely latent at thrombosis diagnosis
Progression: rate of overt MPN development	• ~13–41% at 0.7 – 10 yrs., depending on site (Budd-Chiari syndrome > portal vein thrombosis)
Treatment	• Experts' consensus: anticoagulation (VKA; DOACs (small studies)); aspirin; cytoreduction (usually hydroxyurea) • Other therapeutic options when indicated: TIPS procedure, liver transplant (BCS leading to cirrhosis) • Ruxolitnib (small studies)

VKA vitamin K antagonists, *DOAC* direct-acting oral anticoagulant, *TIPS* transjugular intrahepatic portosystemic shunt

both BCS and PVT) [12]. As mentioned, driver mutations in the MPN include in order of prevalence *JAK2* V617F, *CALR*, and *MPL*. A study of 241 SVT patients (104 BCS, 137 PVT) detected *JAK2* V617F in 45% of patients with BCS and 34% with PVT [18]. Subsequently, a 2012 meta-analysis confirmed an association between BCS, PVT, *JAK2* mutations, and MPNs. Among 1062 BCS and 855 PVT patients, the prevalence of MPNs and *JAK2* V617F was 40.9 and 41.1% in BCS patients, respectively; in patients with PVT, the prevalence of MPNs and *JAK2* V617F was 31.5 and 27.7%. Of the 40.9% of BCS patients with MPN, 80.3% were *JAK2 V617F*-positive, and of the 31.5% PVT patients with MPN patients, 86.6% were *JAK2* V617F-positive [12]. In another study, the *JAK2* V617F mutation was found in 21.4% of patients with idiopathic PVT or BCS [19].

Most studies associating *JAK2* V617F with SVT come from Western Hemispheric populations. It is possible that the association between *JAK2* mutations and SVT varies by race/ethnicity. A study including Korean patients reported a lower prevalence of *JAK2* V617F in those with SVT [20]. Of the 26 patients with SVT that were studied, the *JAK2* V617F mutation was detected in three patients (11.5%) with overt MPN. The prevalence of the *JAK2* V617F mutation was only 4.2% (1/24) in the subset of patients with SVT without an overt MPN [20]. This study was comparatively small, and in general, the literature otherwise supports an association between *JAK2* V617F and myeloproliferative neoplasm-associated splanchnic vein thrombosis (MPN-SVT) [12, 19].

Associations between SVT and other driver mutations, including *MPL* or *CALR*, are weaker in comparison. In a study of 241 SVT patients, neither *JAK2* exon 12 nor *MPL*515 mutations were detected [18]. A retrospective study of 29 patients with MPN-related SVT detected *JAK2* V617F mutations in 27 patients; only one patient had an *MPL* W515K mutation, and *CALR* was not found in the other *JAK2*-negative patient [21]. Haslam et al. investigated 144 patients with SVT; 59 of the patients were previously screened for *MPL* mutations, which were found in only 2 patients and *CALR* mutations were not detected in any of the 144 patients [22]. In the Smalberg et al.'s 2012 meta-analysis, 268 SVT patients were tested for *JAK2* exon 12 and 305 for *MPL*515 mutations [12]; the *MPL*W515K mutation was detected in three patients but the *JAK2* exon 12 mutation was not present in any case [12]. In another study, *CALR* mutations were rarely identified, only seen in 2% (4 of 209) patients with SVT [23]. Recently, Poisson et. al. (2017) looked at *JAK2* V617F, *MPL*, and *CALR* mutations in 312 patients with SVT; *JAK2* V617F was detected in 59 patients, 5 patients had *CALR* mutations, and *MPL* was not detected in anyone [24•]. *CALR* mutations were detected in patients with a spleen height ≥ 16 cm and platelet count > 200×10^9/L [24•]. With a positive predictive value of 56% and a negative predictive value of 100%, the investigators conclude that the above criteria be employed for selective testing of *CALR* mutation in patients with SVT [24•].

Pathogenesis

The prevalence of *JAK2* V617F mutations in MPN-SVT, compared to other driver mutations, suggests a contribution toward disease pathogenesis. There may also be contributions from altered endothelium. Local endothelial cells (ECs) and circulating endothelial colony forming cells (ECFCs) in MPN patients have been implicated in promoting thrombotic events in the splanchnic vasculature. Sozer et al. studied three BCS patients with PV, and while the patients' hepatocytes contained WT JAK2, the ECs from two of the three PV patients with BCS harbored the *JAK2* V617F mutation [25]. Rosti et al. measured ECFCs in SVT patients with MPNs compared to those without MPN and found that SVT was associated with elevated ECFC frequency in MPN patients [26]. A significantly lower frequency of ECFCs in SVT patients without MPN was observed, compared to SVT patients with MPN ($P = 0.01$), and none of the SVT patients without MPN had elevated ECFC frequency [26]. While there was a clear association between SVT and ECFC frequency in MPN patients, the authors did however highlight a need for standardization of ECFC assessment [26].

A unique genetic predisposition may also play a role. Studies have shown that the *JAK2* 46/1 haplotype is associated with MPN and SVT. Villani et al. argued that the *JAK2* 46/1 haplotype is a susceptibility factor for MPN patients presenting with SVT in a study where they showed that MPN patients with SVT had a higher frequency of *JAK2 46/1* haplotype compared to controls [27]. Another study of 199 SVT patients detected an association between the 46/1 haplotype and JAK2 V617F-positive SVT patients compared with controls ($P < 0.01$). They also found an association between this haplotype and *JAK2* V617F-negative SVT patients with MPN as there was an increased frequency ($P = 0$ .06) compared to the controls [28]. In addition, a retrospective study of 180 SVT patients reported that the *JAK2* 46/1 haplotype was significantly associated with the frequency of the somatic V617F mutation among women (OR 4.1; 95% CI 1.1–14.9) but not in men [29]. The authors suggested this may account for the higher incidence of the *JAK2* V617F mutation in women with SVT [29]. These authors speculated upon sex-related factors that might contribute to mutation development via the 46/1 haplotype [29].

Diagnostic Challenges

Above studies support *JAK2* V617F testing when a patient is diagnosed with SVT in the absence of cirrhosis. Testing

should be initiated even when overt myeloproliferation is absent (normal blood counts, as an example). Hypersplenism, hemodilution, and bleeding may mask the underlying MPN phenotype in patients with SVT, which can result in significant delay in MPN diagnosis, with therapeutic implications as well. However, MPN can remain occult for years without evidence of a laboratory abnormality. In a meta-analysis, *JAK2* V617F screening was positive in 17.1 and 15.4% of the BCS and PVT patients, respectively, in patients without hallmark hematological features of MPN [12]. The study revealed that in some cases, the typical laboratory or morphological features of MPN did not manifest until even 10 years after diagnosis [12]. PV is the most common MPN that emerges in latent cases that present with SVT [12]. In some cases of unexplained cirrhosis/portal HTN, it may also be useful to test for *JAK2* V617F, as this may lead to unrecognized chronic BCS or PVT. Given the association between BCS, PVT, and MPN, it is still reasonable to test for *CALR* or *MPL* mutations, noting that the prevalence of these mutations is much lower.

Given that the molecular mutation may not be present in all MPN cases, a bone marrow biopsy is also a consideration for diagnostic purposes. A 2015 study evaluated the bone marrow morphology of 29 MPN patients with SVT and described clinical and molecular features based on the morphological phenotype [30]. They found a complete diagnostic match between the clinical and morphological features of the PMF patients; however, discrepancies between clinical and laboratory (morphological) features were frequent in the patients with an ET-like morphology [30]. The most discrepancies were found in 11 patients with PV-like marrow morphology; only three of whom showed a typical PV clinical phenotype [30]. This highlights the importance of employing both molecular studies and bone marrow biopsies in establishing a diagnosis in patients suspected to have underlying MPN in the setting of an SVT.

Recurrence

Patients with MPN-associated SVT have a high risk of thrombotic recurrence compared to SVT patients without MPN. Ageno et al. led a prospective study of 604 patients with SVT in which 49 patients had underlying MPN and ultimately were found to have a 5.9 per 100 patient-year risk of thrombotic recurrence compared to 3.2 per 100 patient-year in patients with transient risk factors including recent surgery, intra-abdominal infection, use of hormone therapy, pregnancy/puerperium, and abdominal trauma [11••]. A retrospective study of 181 MPN patients who presented with SVT reported 31 new thrombotic events over 3.2 years, with an estimated rate of 4.2 per 100 patient-years [31••]. Factors associated with a significantly higher risk of recurrence were BCS, splenomegaly, and leukocytosis [31••]. Riva et al.'s 2015 study looked at the risk of recurrent thrombotic event in patients with SVT who had received at least 3 months of vitamin K antagonist treatment before discontinuing the anticoagulation [32]. The study revealed recurrence rate of 2.4 (95% CI 0.6–9.6) per 100 patient-years in patients with unprovoked SVT and 10.2 (95% CI 4.2–24.4) per 100 patient-years in patients with a permanent risk factor (solid cancer, myeloproliferative neoplasm, liver cirrhosis, and inflammatory bowel disease), while no thrombotic event occurred in patients with transient risk factors [32]. Authors note caveats of the study which include small sample size, selection bias, and the fact that thrombotic risk factors such as the *JAK2* mutation were not checked in all the patients [32]. To the contrary, a more recent study has been unable to establish consistent markers that predict SVT recurrence in patients with MPN [33].

Portal Hypertension

Portal hypertension (pHTN), and its consequences, including esophageal varices and fluid retention, is a known complication of MPN and can develop as a longstanding consequence of SVT [17, 34, 35]. A 2015 multicenter retrospective study looked at 51 with pHTN as a result of underlying MPN [17]. PV was the most frequent underlying MPN and splanchnic thrombosis was more prevalent in PV patients compared to the other MPNs (76 vs. 26%, $P = 0.0007$) [17]. The authors suggest that the thrombosis is a cause of portal HTN in PV patients and that perhaps MPN patients with SVT should be screened for portal HTN [17]. Some other causes of portal HTN include intrahepatic obstruction due to extramedullary hematopoiesis within the sinusoids, and/or increased portal blood flow secondary to splenomegaly.

Treatment

The management of SVT often requires a multidisciplinary approach, including a hematologist and gastroenterologist/hematologist. Treatments include anticoagulation, cytoreduction, management of portal hypertension, and, in some cases, liver transplant.

Anticoagulation

Current guidelines which are based on observational studies and consensus from experts recommend indefinite anticoagulation in patients with SVT and underlying MPN as these patients harbor a permanent risk of thrombosis [36].

However, a survey of 73 physicians regarding anticoagulation or antiplatelet therapy duration for MPN revealed a lack of consensus in actual practice and the need for a clinical studies to inform an evidence-based set of guidelines [37]. Anticoagulation using warfarin appears to be the primary method of preventative therapy; however, there is always a concern for bleeding especially when SVT is complicated by portal HTN. Further, if there is hepatic insult from SVT (BCS), a prolonged prothrombin time may make it difficult to monitor warfarin. Not surprisingly, a retrospective study that looked at 120 non-cirrhotic PVT patients on anticoagulation found that anticoagulation appeared to prevent thrombotic recurrence while significantly increasing risk of GI bleed [38].

As with management of thromboses in other sites, failures can occur. In a study by Potthoff et al. (2015), in which MPN patients with SVT received orthotopic liver transplantation (OLT) as well as anticoagulation, the study revealed that anticoagulation did not completely prevent thrombosis recurrent as two of the 29 remaining patients with MPN (after at least 3 years of OLT) developed BCS recurrence [39•]. In an observational study of 181 MPN-SVT patients, 85% were on vitamin K antagonists, and 15% were not; the recurrence rate was lower in anticoagulated patients (3.9 per 100 patient-years compared to 7.2 per 100 patient-years), but still present [31••]. The authors concluded that the high recurrence rate despite VKA suggests the need for new forms of secondary prophylaxis, such as with new antithrombotics and/or JAK inhibitors [31••]. The authors acknowledged that limitations of this study included selection bias as perhaps patients with high bleeding risk did not receive anticoagulation [31••].

There is scant information regarding use of direct-acting oral anticoagulants (DOACs). A prospective study looked at outcomes with DOACs (Xa inhibitors) for treatment of venous thromboembolism (VTE) in atypical locations (VTE-ALs, which included SVT) compared to patients with VTE in typical locations (VTE-TLs) such as deep vein thrombosis or pulmonary embolism. This study also included patients with VTE-AL on enoxaparin [40]. The authors reported that VTE recurrence and major hemorrhage rates were not different among the groups [40]. They observed a higher mortality rate among the VTE-AL group compared to the VTE-TL group but also cautioned that the VTE-AL patients with events had a malignancy [40]. This study did not include MPN patients, but is included here because of the use of DOACs in patients with SVT. Another study looked at 25 patients with MPN receiving DOACs for atrial fibrillation (13 patients) and thrombotic events (12 patients) then followed for a median of 2.1 years [41]. These patients were compared to other MPN patients who received low-dose aspirin, and overall, there was no significant difference between bleeding and thrombotic events between the two groups [41]. None of the 12 patients with thrombotic events had SVT, however.

A more recent study of 84 MPN patients with SVT in which at least 65% received systemic anticoagulation ± aspirin ± cytoreduction (in addition to some surgical intervention if required) did not show a benefit of anticoagulation [33]. At baseline, 46% percent of the 84 patients had recurrent SVT [33]. At a median of 2.7-year follow-up, 10% of the patients developed a recurrent SVT which did not appear to be related to the type of SVT or management and the authors questioned the value of systemic anticoagulation or the need for alternate forms of anticoagulation such as direct oral anticoagulants [33].

TIPS

The transjugular intrahepatic portosystemic shunt (TIPS) procedure has been employed for management of portal HTN in patients with SVT. A retrospective analysis of 29 MPN patients who underwent the TIPS procedure evaluated the efficacy and long-term outcomes of in MPN-associated pHTN [42••]. The authors found that while most patients experienced complete clinical resolution of pHTN, 31.0% of patients experienced in-stent thrombosis and required subsequent intervention [42••]. In the Yan et al.'s 2015 study, three out of five patients with pHTN and MPN who received TIPS no longer had portal HTN by follow-up [17]. Survival post-TIPS has also been reported. A retrospective study of 27 patients with BCS in whom 17 had MPN received anticoagulation with or without the TIPs procedure [43]. In 18 of the patients who had a TIPS intervention, the overall survival was 96% at 1 year and 81% at 5 years [43]. In Reilly's retrospective study, 1-, 2-, 3-, and 4-year overall survivals post-TIPS were 96.4, 92.3, 84.6, and 71.4%, respectively [42••].

Liver Transplant

Some patients with SVT (BCS) require liver transplant. A retrospective study investigated the long-term prognosis of patients with MPN-associated BCS after OLT [39•]. Out of 78 patients with BCS, 41 of those patients had MPN [39•]. After 3 years, 29/41 patients with MPN (71%) had survived; also, the 5- and 10-year survivals were not significantly different in these patients compared to those without MPN ($P = 0.81$ and $P = 0.66$ respectively) [39•].

Cytoreduction

Because thrombosis history traditionally indicates a high-risk MPN, cytoreductive therapy is recommended. However, some patients have a normal complete count, and a cytoreductive is added after myeloproliferation presents itself.

Of the cytoreductives, hydroxyurea is typically utilized, based on expert consensus. However, the benefits are not always very clear. DeStefano et al. suggested that hydroxyurea did not decrease recurrent thrombosis in patients with MPN-associated SVT [31••]. Interferons are also a consideration for younger patients with MPN-SVT in need of cytoreduction.

Ruxolitinib

As splenomegaly may be a risk factor for thrombotic recurrence in MPN-associated SVT, it has been suggested that there is a possible role for JAK inhibition in the management of MPN-SVT [31••]. Additionally, since splenomegaly can increase portal hypertension, perhaps reducing spleen size could impact this parameter. Pieri et al. recently showed that ruxolitinib is safe in MPN-associated SVT [44••]. Twenty-one patients with MPN-SVT were treated with Ruxolitnib for 24 weeks [44••]. The patients experienced a spleen volume reduction of ≥ 35% in six of the 21 (29%) patients at 24 weeks and a > 50% spleen length reduction by palpation at any time up to week 24 was observed in 62% patients. There was no bleeding and hematological toxicities were similar to those in patients without SVT [44••]. In addition, 4 of the patients who were able to have spleen stiffness checked were found to have a decrease in this parameter with ruxolitinib use [44••]. While spleen stiffness has not been studied in MPN-SVT patients, a decrease in spleen/liver stiffness is associated with improvement in pHTN in patients with cirrhosis. A subsequent case reported on the use of ruxolitinib in a 26-month-old with Budd-Chiari due to *JAK2*+ PV [45]. The patient's disease had been controlled on pegylated IFN for 2 years, until development of nephrotic syndrome [45]. That treatment was stopped and hematological control was maintained on hydroxyurea [45]. The therapy was then switched to ruxolitinib and the patient remained stable on this for 20 months with improvement including reduction in spleen size and without side effects [45].

Conclusion

Thrombosis is a well-known complication of MPNs, typically affecting older patients, and involving the arterial circulation. MPN-SVT is unique in that it more commonly occurs in younger women with MPN, even in the setting of an entirely normal blood count. Of the MPN driver mutations, *JAK2* V617F is most commonly identified, suggesting its contribution to pathogenesis. Otherwise, mechanisms for SVT occurrence in MPN are less characterized, though endothelial injury and genetic predisposition may play a role. The main diagnostic challenge is that the MPN may be entirely occult, delaying recognition. The management of MPN-SVT most commonly includes anticoagulation and cytoreduction but, in some cases, there is a requirement for TIPS or liver transplant. Duration of anticoagulation is based largely on expert consensus. Emerging therapy includes JAK inhibitor therapy, but more long-term studies are required to understand if it indeed decreases SVT recurrence.

Compliance with Ethical Standards

Conflict of Interest Brady Stein reports other from Incyte Corporation, outside the submitted work. Imo J. Akpan has no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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