Splanchnic vein thrombosis is a condition in which the veins in the abdomen are affected by a blood clot. This condition can be asymptomatic or may present with symptoms such as abdominal pain, gastrointestinal bleeding, and ascites. The main risk factors include abdominal disorders, such as mesenteric, portal, splenic, and supra-hepatic vein thrombosis, which is an underdiagnosed disease, with heterogeneous clinical presentations and a non-negligible rate of incidental findings.

The main risk factors include abdominal diseases or interventions (e.g., infections, cirrhosis, abdominal cancer or surgical procedures), haematological disorders (mainly myeloproliferative neoplasms), inherited thrombophilic states and hormonal imbalances. New biological markers of subclinical disorders have recently been identified: JAK2 mutation and flow cytometry for CD55 and CD59. Clinical manifestations are generally aspecific. During the acute phase, main symptoms can be abdominal pain, gastrointestinal bleeding and ascites; while long-term consequences include liver cirrhosis and portal hypertension.

Advances in non-invasive vascular imaging (Doppler ultrasound, angio-computed tomography and magnetic resonance imaging), have improved the diagnosis of SVT. Alterations in blood tests may suggest an underlying haematological or hepatic disorder.

The optimal treatment of SVT remains an open issue, since large clinical trials are lacking. Expert consensus recommend to treat acute symptomatic non-cirrhotic portal vein thrombosis with parenteral anticoagulation during the acute phase, followed by oral anticoagulants for at least 3 months, though lifelong treatment is recommended in case of persistent prothrombotic factors. In Budd-Chiari syndrome, anticoagulation is recommended for all patients in the absence of major contraindications. However, the risk to benefit-ratio of anticoagulant therapy, both in the acute phase and for the long-term secondary prevention, still needs to be better assessed.

**Keywords**

Splanchnic vein thrombosis, risk factors, treatment, clinical history

**Summary**

Splanchnic vein thrombosis (SVT) — including mesenteric, portal, splenic and supra-hepatic veins thrombosis — is an underdiagnosed disease, with heterogeneous clinical presentations and a non-negligible rate of incidental findings.

The main risk factors include abdominal diseases or interventions (e.g., infections, cirrhosis, abdominal cancer or surgical procedures), haematological disorders (mainly myeloproliferative neoplasms), inherited thrombophilic states and hormonal imbalances. New biological markers of subclinical disorders have recently been identified: JAK2 mutation and flow cytometry for CD55 and CD59. Clinical manifestations are generally aspecific. During the acute phase, main symptoms can be abdominal pain, gastrointestinal bleeding and ascites; while long-term consequences include liver cirrhosis and portal hypertension.

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**Schlüsselwörter**

Splanchnicus-Venenthrombose, Risikofaktoren, Behandlung, Klinische Historie

**Zusammenfassung**


Fortschritte bei der nicht invasiven Gefäßdarstellung (Doppler-Ultraschall, Gefäß-Computertomografie und Magnetresonanztomografie) haben die Diagnostik der splanchnischen Venenthrombose verbessert. Auffällige Blutbefunde können auf eine zugrunde liegende hämatologische oder hepatische Störung hinweisen.

Die optimale Behandlung der splanchnischen Venenthrombose ist noch eine offene Frage, da große klinische Studien fehlen. Experten empfehlen übereinstimmend, die akute, symptomatische, nicht zirrhotische Pfortaderthrombose im akuten Stadium mittels parenteraler Antikoagulation zu behandeln und anschließend über mindestens 3 Monate orale Antikoagulanzien zu geben; bei persistierenden prothrombotischen Faktoren wird jedoch eine lebenslange Behandlung empfohlen. Bei einem Budd-Chiari-Syndrom wird für alle Patienten ohne größere Kontraindikationen eine Antikoagulation empfohlen. Allerdings muss das Nutzen-/Risikoverhältnis einer gerinnungshemmenden Therapie sowohl für die Akutbehandlung als auch für die langfristige Sekundärprävention noch besser untersucht werden.

Splanchnic vein thrombosis (SVT) is defined by the formation of a thrombus in one or more abdominal veins draining from different organs, including small and large bowel, liver, spleen and pancreas, which may be associated with a rather heterogeneous spectrum of underlying disorders, either local or systemic, and which results in variable clinical presentations. Not uncommonly, SVT represents a clinical challenge both for diagnosis and for treatment decisions, which may be requested in patients with extensive thrombi and concomitant gastrointestinal bleeding. Unfortunately, well designed clinical trials are substantially lacking, and most information is derived from observational studies with a high risk of selection biases.
Epidemiology

The epidemiology of SVT is poorly defined and shows significant variation depending on single clinical entity and on the data sources. Furthermore, the incidence of SVT is likely underestimated, given the heterogeneity of clinical presentations and the non-negligible rate of asymptomatic or at least unsuspected events.

The incidence of Budd-Chiari syndrome (BCS) has been estimated to be about 0.5–1 case per million people (1–2), representing the least frequent manifestation in the SVT spectrum.

The epidemiological data regarding portal vein thrombosis (PVT) vary from a reported incidence of less than 4 cases per million people, according to hospital registry data (3), to a population prevalence of 1% found in a large study based on autopsies (4).

The incidence of mesenteric vein thrombosis (MVT) was found to be 2.7/100,000 person-years in a recent study (5), whereas no accurate data are available on the incidence of splenic vein thrombosis (spVT) in the general population.

With regards to asymptomatic SVT events, in a recent retrospective review of 2,591 computed tomography (CT) scans of the abdomen performed in a single hospital over 6 months for reasons other than the search of suspected SVT, the prevalence of unsuspected abdominal vein thrombosis was 1.74% (95% confidence intervals (CI) 1.29–2.34), with the majority of events occurring in the splanchnic veins (6).

Risk factors

Splanchnic vein thrombosis risk factors can be classified as:

- abdominal (local) or systemic
- temporary or permanent
- congenital or acquired

Recently, new biological markers of systemic risk factors have been added to this list (Box).

Overall, the number of risk factors that have been reported to be associated with splanchnic vein thrombosis is increasing, and, consequently, an increasing number of patients with two or more concomitant risk factors have been described both in Western and Eastern countries.

Even if the relative incidence of risk factors varies according to age, economic status, geographical area, and thrombosis location, myeloproliferative neoplasms (MPNs), cancer, intra-abdominal inflammatory conditions, surgery, cirrhosis, and portal hypertension are the most common identified acquired risk factors. The use of oral contraceptives was reported in about 10–15% of young women with a mesenteric venous thrombosis in Western countries, while pregnancy and puerperium are not uncommon in young women patients in Asian countries (7). Peculiar risk factors of the Mediterranean area include Behçet’s disease and hydatidosis, while membranous webs of the inferior vena cava are typically found in Asian patients (8).

Among the inherited thrombophilia, Factor V Leiden mutation has shown stronger association with BCS than with PVT, while the converse has been reported for prothrombin G20210A mutation (9–11). Most of patients resulted to have a minor inherited thrombophilic defect associated with a concomitant major local or systemic acquired provoking risk factor (Box). A local precipitating factor is rarely reported in BCS patients, while it is common in patients with portal vein thrombosis. Chronic MPNs are the leading systemic cause of splanchnic vein thrombosis, and are diagnosed in half BCS patients and one-third of extra-hepatic PVT (8).

Janus kinase 2 (JAK2) mutation is, together with flow cytometry for CD55 and CD59, the main new biological marker of subclinical risk factors. JAK2 is a tyrosin kinase involved in a cytokine-induced intracellular signaling pathway. The somatic mutation JAK2 V617F, a valine-to-phenyl-
alanine substitution at position 617 resulting in a gain-of-function of JAK2 (12), is detectable in a large majority of patients with overt MPN, and up to 40% of patients without overt MPN (8). The results of a recent meta-analysis have shown that the prevalence of JAK2 V617F mutation in patients with objectively diagnosed SVT is as high as 32.7% (95% CI 25.5–35.9%) (13), as compared to a prevalence of about 1% amongst patients with VTE in other sites and in patients with arterial thrombosis.

The analysis of case-control studies, in which cases were patients with SVT and controls were healthy subjects or patients with non-thrombotic liver or pancreatic diseases, found an odds ratio (OR) for the association between JAK2 mutation and SVT of 54 (95% confidence intervals (CI) 13–222) (13). To explain the increased risk of venous thrombosis in patients carriers of the JAK2 mutation, a link has been hypothesized between the mutation, elevation in blood cells count, in particular leukocytosis, and the hemostatic system activation. Flow cytometry for CD55 and CD59 may identify paroxysmal nocturnal hemoglobinuria (PNH) in a subclinical state when clinical and laboratory signs of hemolysis are still lacking (14).

Even if splanchnic vein thrombosis can be theoretically classified as ‘primary’ or ‘secondary’ depending on the underlying cause, such a distinction is not always possible in clinical practice. The increasing number of new possible minor risk factors, such as cytomegalovirus infectious (15), decrease the number of truly unprovoked events. Moreover, multiple factors are already present in approximately one-third of patients with BCS and two-thirds of patients with PVT.

Correct identification and classification of these risk factors help in evaluating and planning patient therapy, and in screening family members to evaluate an individual risk. Based on available evidences, it seems wise to advise physicians to systematically search for any possible underlying risk factor, including in particular thrombophilia screening and search for JAK2 mutation.

**Clinical history**

In the acute phase of SVT, clinical manifestations and short-term prognosis are associated with the underlying disorder and/or represent the consequence of the acute thrombosis. These include acute abdomen, that may be present in up to 50% of patients with MVT and is associated with intestinal infarction (5, 16), gastrointestinal bleeding, which is found in as many as one fourth of patients and is mainly associated with the presence of gastrœsophageal varices, and ascites, which is common in BCS and PVT patients and is caused by portal hypertension.

With regard to long-term prognosis, SVT may lead to serious consequences, which include liver cirrhosis in patients with BCS and portal hypertension in patients with BCS and PVT, with all their sequelae. Moreover, as for any VTE event, patients who experience an episode of SVT show also an increased risk of recurrences. The incidence of recurrent venous thrombosis after a mean follow up of 27 months was found to be 3.5/100 patient-years in a large cohort study (16). Importantly, half of the recurrent events involved the splanchnic veins, while the other half involved limb veins or pulmonary arteries (16). In the spectrum of SVT, spVT showed the highest recurrence-free survival at 10 years (97%) and MVT the lowest (60%) (16).

Another important aspect of the long-term course of SVT is represented by the recanalization rate of the splanchnic veins, which may greatly contribute to splanchnic venous hemodynamics and, thus, to the risk of recurrence. In a recent follow-up study of patients with SVT, the one year recanalization rate was found to be 38%, 54% and 61% in patients with PVT, spVT, and MVT, respectively (17). Anticoagulant treatment has been associated with higher rates of recanalization (18–19).

Finally, the risk of bleeding needs also to be considered in the short and long-term history of SVT, as it may be related with underlying diseases, portal hypertension and anticoagulant treatment. In the study by Thatipelli et al. major bleeding rates were 6.9/100 patient-years, most commonly involving the gastrointestinal tract (16). In another cohort of patients with PVT, the incidence of gastrointestinal bleeding was 12.5/100 patient-years (20).

In this and other studies, the presence and size of varices was associated with recurrent bleeding, independently of anticoagulant therapy (18–19). Interestingly, in a multicenter, retrospective study on patients with MVT, we found that the case-fatality rate of thrombosis was significantly higher than that of gastrointestinal bleeding (21).

**Diagnosis**

Advances in non-invasive vascular imaging, such as Doppler ultrasound, angio-computed tomography (CT) and magnetic resonance imaging (MRI), have improved the diagnosis of splanchnic vein thrombosis (22).
Liver function tests are typically normal or only mildly altered in patients with PVT who do not have concomitant cirrhosis or other hepatic diseases (23). Patients with BCS may have non-specific alterations of liver function tests (24). In case of polycythemia or thrombocytosis, a search for an underlying myeloproliferative disorder should be performed.

The presence of BCS should be suspected in case of acute onset of ascites and painful hepatomegaly or when refractory ascites is present. Due to its high sensitivity and specificity, Doppler ultrasonography is frequently used when BCS is suspected (25). Ultrasound with color Doppler imaging has a 98% negative predictive value and is the imaging modality of choice also in diagnosing portal vein thrombosis (26), conversely overlying bowel gas often limits the ultrasound diagnosis of isolated MVT.

Findings, that support the diagnosis of BCS, include absence of flow or retrograde flow in the hepatic veins, visualisation of a thrombus within the hepatic veins or failure to visualise the hepatic veins (27–28). In acute portal vein thrombosis, ultrasound examination demonstrates a hyperchoic material within the portal vein and sometimes in its tributaries with inverted direction of blood flow in these vessels (29) (Fig. 1). Conversely, chronic portal vein thrombosis is diagnosed when a portal cavernoma, a network of veins around porta hepatis, is demonstrated (30).

Angio-CT or MRI are required if the diagnosis of SVT remains uncertain after ultrasound. With these techniques the liver parenchyma itself is usually better visualised, as they show perfusion details or necrotic areas, and underlying causes of splanchnic vein thrombosis may be identified (31). Angiography is reserved to patients undergoing endovascular invasive procedures or to patients undergoing preoperative assessment if surgical intervention is planned.

A liver biopsy is not required to confirm the diagnosis of splanchnic vein thrombosis and it is seldom performed to rule out other unknown underlying causes of thrombosis, especially in patients with BCS.

### Treatment

The optimal treatment of SVT remains an open issue, since there are no randomized controlled trials and current recommendations are based only on cohort studies and expert opinion (32).

The management of acute PVT and MVT requires prompt anticoagulation with the aim of prevent the intestinal infarction and the long-term complications of chronic portal hypertension (33).

The basis for the anticoagulant treatment of PVT dates back to the study of Condat et al. (20). This retrospective survey involved 136 patients, of whom 84 were treated with heparin or vitamin K antagonists. After a median follow up of almost 4 years, the benefit-risk ratio favored anticoagulant therapy. No significant association was found between anticoagulant therapy and the risk or the severity of gastrointestinal bleeding events, while the absence of anticoagulant therapy was an independent predictor for recurrence of thrombosis.

More recently, Plessier et al. (17) prospectively assessed the outcome of early anticoagulation in acute PVT. In a European multicenter study, 95 patients were treated within 30 days from diagnosis (83% within 5 days). The therapeutic regimen consisted mainly of heparin followed by oral anticoagulation, for at least 6 months. Anticoagulation successfully prevented thrombus extension and was associated with a favorable 1-year recanalization rate. Major bleeding occurred in 5% and intestinal infarction in 3%, although no death resulted from thrombosis or hemorrhage.

Long-term safety and efficacy of oral anticoagulants has also been demonstrated in a cohort of 77 patients with MVT (21). Therapeutic options in BCS include medical management (anticoagulant and diuretics) and invasive techniques (thrombolysis, percutaneous transluminal angioplasty, surgical or transjugular intrahepatic portosystemic shunting (TIPS) and orthotopic liver transplantation (OLT)) (33–34).

Darwich-Murad et al. (35) prospectively assessed a cohort of 163 cases of BCS in a European multicenter study. Many patients were safely managed with non-invasive treatments (86% anticoagulation and 61% diuretics), but 51% required invasive procedures. TIPS was associated with a good outcome, thus emerging as the treatment of choice for patients without response to medical management and with refractory ascites or progressive liver dysfunction. OLT arose as a salvage procedure, in case of fulminant liver failure or unsuccessful previous interventions. Survival rate was 87% at 1 year and 82% at 2 years, due to the high percentage of patients receiving anticoagulation and the use of minimally invasive procedures (such as TIPS). Only 8% of the anticoagulated patients developed variceal bleeding, without any fatality.

Divergent conclusions resulted from the largest retrospective cohort of SVT, recently published by Thatipelli et al. (16). The authors enrolled 832 patients with thrombosis of different splanchnic veins (including hepatic, splenic, portal or mesenteric). Several etiologies were involved, mostly malignancy and cirrhosis (27% and 24% respectively), which were excluded from previous studies (17, 20, 35). Only 235 patients (28%) were anticoagulated with warfarin, of whom 175 lifelong, but no information is provided on the use of alternative anticoagulant drugs such as heparins. The authors concluded that anticoagulant treatment did not improve recurrence-free survival and was rather found to be an independent predictor of bleeding events.

In the absence of strong evidences, current recommendations derive from the Baveno V consensus workshop (32). In non-cirrhotic patients with acute symptomatic PVT, anticoagulation with low molecular weight heparin should be started immediately and followed by oral anticoagulant for at least 3 months. Life-long therapy is recommended in case of underlying persistent prothrombotic factors. There is insufficient evidence in favor of interventional therapy and no consensus on management of chronic portal vein obstruction.

In the treatment of BCS, anticoagulation is recommended for all patients, in the absence of major contraindications. In case of worsening with medical treatment, patients should be considered for invasive procedures as angioplasty/stenting, TIPS and lastly liver transplantation (32). It is
furthermore important to establish appropriate prophylaxis of bleeding with beta-blockers or with endoscopic treatment of oesophageal varices (33–34). The optimal management of cirrhotic patients still needs to be elucidated.

Conclusions

SVT is a probably underdiagnosed disease requiring important clinical decisions under a diagnostic and therapeutic point of view. A timely diagnosis and treatment may prevent thrombus extension and in particular reduce the burden of local vascular and non-vascular complications, which may result in subsequent bleeding events. Although clinical signs and symptoms are generally non-specific, SVT should be suspected in the concomitant presence of known risk factors, and future diagnostic algorithms including pre-test probability, laboratory evaluation and instrumental investigation is warranted.

The risk to benefit-ratio of anticoagulant therapy, both in the acute phase and for the long-term secondary prevention, needs to be better assessed starting with large multicenter prospective cohort studies and, possibly, with subsequent randomized controlled trials. These studies should also identify prognostic markers with the aim to stratify patients for their individual risk of both recurrences and bleeding complications.

Literatur


N. Riva et al.: Splanchnic vein thrombosis