Approach to the patient with non-cirrhotic splanchnic venous thrombosis: a brief narrative review

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Abstract

Splanchnic venous thrombosis refers to the obstructive events of the abdominal venous system (portal, splenic, mesenteric, and suprahepatic) present with or without an underlying liver disease. These are rare disorders generally associated with both local risk factors, such as intra-abdominal infections, surgery or abdominal trauma, and systemic risk factors, represented by drugs (notably estrogen therapy) and some types of inherited or acquired thrombophilia, including myeloproliferative neoplasms associated with the V617F mutation of the JAK2 gene. The clinical presentation is heterogeneous, ranging from asymptomatic patients with incidental findings on abdominopelvic imaging to severe systemic compromise in sudden onset cases, with a high morbidity and mortality burden. Anticoagulation therapy is the current recommended treatment based on observational studies, with no consensus on management in the acute and long-term setting for both inmediate complications such as acute liver failure and intestinal ischemia or those arising from secondary portal hypertension over a longer period of time. (Acta gastroenterol. belg., **2023,** 86, **543-554**).

Keywords: Venous thrombosis, splanchnic circulation, thrombophilia, anticoagulation, non-cirrhotic portal hypertension.

Introduction

Splanchnic venous thrombosis (SVT) is an umbrella term that encompasses portal (PVT), splenic (SVT) and mesenteric (MVT) thrombosis, as well as Budd-Chiari syndrome (BCS) which is also known as suprahepatic thrombosis(1). Incidence of SVT is poorly defined, whereas PVT has a prevalence close to 1% with an estimated incidence of 0.7 per 100,000 persons per year to 4 cases per million persons per year; and Budd-Chiari syndrome of 0.5 to 1 per million persons per year (1,2). Cohort studies have documented that splanchnic venous thrombosis predominates in males, with presentation at the age of 50 on average. On the other hand, Budd-Chiari syndrome prevails in young women with an average age of 35 years, additionally, obstruction of the hepatic veins is more frequent than the inferior vena cava (3).

Clinical presentation is highly variable, ranging from incidental findings on imaging in asymptomatic patients to diffuse or localized right hypochondrium pain, as well as massive gastrointestinal bleeding in the setting of concomitant acute liver failure, mesenteric ischemia and, in the long term, portal hypertension, with ascites and secondary liver cirrhosis. A standard management is difficult to establish without randomized clinical trials, so current recommendations are based on observational studies and case series, which highlight anticoagulation therapy as a measure with both impact on survival, prevention of complications, and improvement in quality of life (1,4). The general aspects of clinical presentation, diagnosis, and treatment of patients with splanchnic venous thrombosis are discussed below.

Methodology

A narrative review was conducted, with a literature search of Medline/Pubmed, Cochrane, and Embase. Articles in English and Spanish were included. The search strategy included the following terms (using MeSH descriptors): "Portal Thrombosis", "Mesenteric Thrombosis", "Splanchnic Thrombosis", "Splenic Thrombosis" "Budd-Chiari Syndrome" and "Anticoagulation". These terms where used to retrieve useful grey literature from the references of the articles reviewed by applying a 'snowball' strategy to a Google search. Articles were chosen based on their relevance and the experience/expertise of the authors, obtaining articles from the last ten years in English or Spanish, with the exclusion of experimental studies and case reports.

Definitions

Splanchnic vein thrombosis (SVT) including portal, mesenteric, splenic vein thrombosis, and Budd-Chiari syndrome are considered types of venous thromboembolism of unusual distribution. The operational definition of each entity is set out below (Figure 1):

Portal venous thrombosis (PVT): Portal venous thrombosis (PVT) refers to the blockage of the portal venous system, which includes both the intra- and extrahepatic portions. It can affect the portal vein trunk and its major branches, which can spread to the splenic and superior mesenteric veins in some cases. Depending on the extent of the obstruction, PVT can range from an incidental finding during an abdominal imaging test

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to a serious medical condition associated with clinical manifestations typical of portal hypertension (5,6). It is classified according to its onset as acute (sudden formation of a thrombus in the portal vein) or chronic (portal cavernomatous degeneration), according to medical history as cirrhotic or non-cirrhotic, and finally, according to the degree of obstruction it can be complete or incomplete, associated or not with intra-abdominal infection and/or tumor origin (7).

Mesenteric venous thrombosis (MVT): Mesenteric vein thrombosis (MVT) is now understood to occur in three different subtypes: acute, subacute, and chronic. Acute MVT is characterized by sudden onset symptomatic thrombosis of the superior mesenteric vein (SMV) or its branches, without any collateralization. This type of MVT typically results in abdominal pain and like acute mesenteric ischemia (AMI) caused by arterial types, can lead to intestinal infarction if not diagnosed and treated quickly. On the other hand, subacute and chronic MVT may be asymptomatic, with some patients with the chronic subtype presenting with gastrointestinal bleeding related to portal hypertension (7,8)

Budd-Chiari syndrome (BCS): Budd-Chiari syndrome (BCS) is a condition that manifests itself when there is a blockage at any portion of the hepatic venous outflow tract not caused by cardiac disease, pericardial disease, or veno-occlusive disease, regardless of where or how the blockage occurs. BCS can be classified as primary or secondary, depending on the underlying cause of the blockage. Primary BCS results from a venous process, such as thrombosis or phlebitis, whereas secondary BCS is caused by the compression or invasion of the hepatic veins and/or inferior vena cava by a lesion that originates outside of the vein, such as a malignancy (4,9)

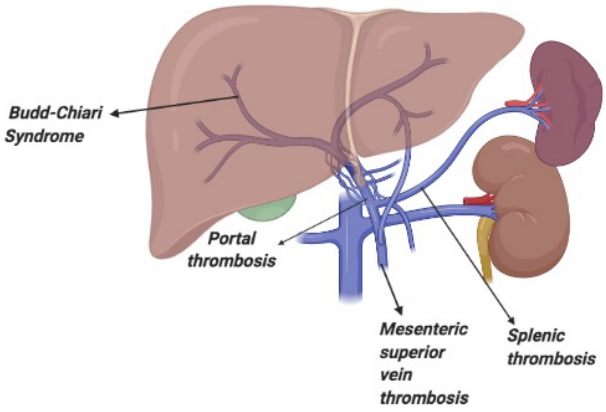

Figure 1. — Splanchnic venous thrombus location (by the authors).

Pathophysiology

Thrombogenesis results from the confluence of the factors described in Virchow's triad: venous stasis, endothelial injury, and hypercoagulability (Figure 2). Some scenarios where thrombogenesis can occur are:

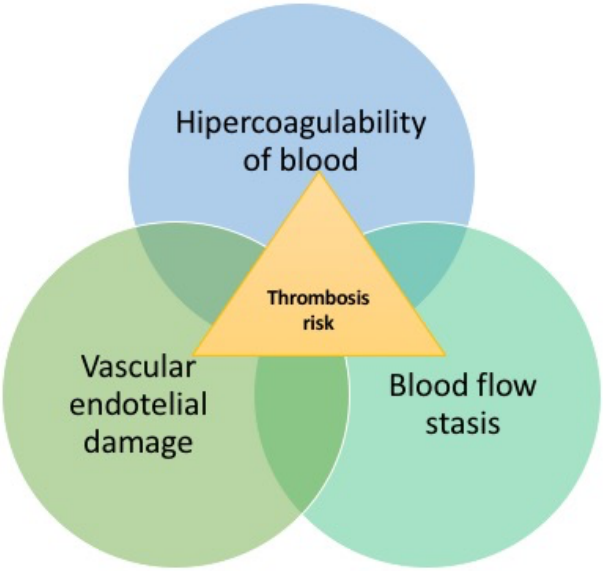

Figure 2. — Virchow's triad: three broad categories of factors that are thought to contribute to thrombosis (by the authors)

visceral organ neoplasms, associated with increased hypercoagulability with direct and indirect vascular invasion, which is favored by infectious complications arising from these processes due to local or distant obstructive effect, as well as any related surgical intervention, favoring venous stasis and/or endothelial injury (10,11). In cirrhotic PVT, reduced outflow velocities from the portal system due to increased capillary hydrostatic pressure and dysfunctional coagulation pathways may contribute to thrombus formation (12).

Common systemic factors contributing to the development of PVT, MVT, and BCS include hereditary thrombophilias (e.g. Factor V Leiden mutation, protein C or S deficiency, antithrombin deficiency), myeloproliferative disorders and situations of increased hormonal influx (pregnancy and estrogen oral contraceptive use) (13). Some case series have shown that more than 50% of patients with PVT had more than one prothrombotic condition, with myeloproliferative disorders and hereditary thrombophilia being the most common systemic risk factors precipitating the thrombotic event in the venous circulation (14).

Etiology and risk factors

Presence or absence of local and systemic risks factors as underlying triggers for SVT allows for it to be classified as provoked or unprovoked. (9,11). In cohorts of SVT patients who were not selected based on specific risk factors, the most common risk factors identified were liver cirrhosis and solid cancer, each responsible for approximately 25% of cases. Unprovoked SVT on the other hand accounts for 15% to 27% of all cases of SVT (15,16) (Table 1).

Table 1. — **Risk factors associated with splanchnic venous thrombosis (by the authors)**

Etiological factor	Specific condition
Abdominal diseases and interventions	- Acute pancreatitis - Acute cholecystitis and cholangitis - Intrabdominal sepsis - Inflammatory intestinal disease - Diverticulitis - Surgery and trauma abdominal - Splenectomy - Cirrhosis - Gastrointestinal cancer (liver, gallbladder, pancreas, colorectal) - Portal hypertension
Acquired thrombophilias	- JAK/STAT mutation gen (JAK2 V617F) associated: vera polycythemia, essential thrombocytosis, primary myelofibrosis - Paroxysmal nocturnal hemoglobinuria
Congenital thrombophilias	- Antithrombin III, S and C protein deficit - Leiden factor V mutation - Prothrombin gene G20210A mutation - Homocysteinemia
Hormonal influx	- Oral anticonceptives - Hormonal replacement therapy - Pregnancy - Puerperium
Virus	- Cytomegalovirus (CMV)
Autoimmune disorders	- Behçet`s disease - Antiphospholipid syndrome

PVT and MVT are more commonly associated with local risk factors such as cirrhosis, intra-abdominal neoplasms, inflammatory bowel disease, surgical interventions, and abdominal trauma in up to 50% of cases. Whereas BCS is more frequently associated with the V617F mutation of the JAK2 gene and latent or occult myeloproliferative neoplasm, oral contraceptive use, autoimmune disorders (antiphospholipid syndrome and Behçet's disease), and inherited thrombophilias such as factor V Leiden mutation and protein C, S and antithrombin deficiency (17,18).

SVT associated with cirrhosis presents as a unique entity linked to a specific abnormality in the hemostatic system. Individuals with cirrhosis exhibit several variations in their clotting system, as well as changes in the number and functionality of their platelets; the approach to their diagnosis and treatment differs from those without advanced liver disease, the reasoning behind this difference is out of the scope of this review (12,13,19).

Furthermore, in both Europe and Asia, myeloproliferative neoplasms (MPNs) are the most frequent risk factor associated with Budd-Chiari syndrome (BCS) and portal vein thrombosis (PVT). Studies have reported that MPNs are present in 30-57% of BCS cases and 21-25% of PVT cases in Europe (19,20). The prevalence of the V617F mutation of the JAK2 gene is described in up to 32.7% of patients with SVT, 27.7% of patients with PVT, and 41% in cases diagnosed as BCS (21).

Likewise, the utilization of estrogen-based contraceptives and pregnancy has been correlated with an elevated risk of BCS. A significant number of women with BCS, up to 74%, were found to have used oral contraceptives and there has been an observed association between pregnancy and BCS. On the other hand, there is no gender preponderance among PVT patients, unlike BCS, indicating that exposure to female hormones does not appear to cause PVT (22-24).

On the other hand, inherited and acquired thrombophilia is associated with increased risk of thrombosis in unusual sites, Factor V Leiden is a significant risk factor for Budd-Chiari syndrome and portal vein thrombosis, whereas the prothrombin G20210A polymorphism has a smaller role, as stated by Xingshun Qi et al. The presence of the Factor V Leiden mutation increases the risk of both BCS, and PVT in individuals when compared to their counterparts without the mutation, whereas the G20210A prothrombin gene mutation is associated with PVT but not with BCS when compared to healthy individuals (25). Moreover, deficiencies in antithrombin, protein C and protein S are rarely identified as risk factors due to affected synthesis by the relative degree of liver failure underlying chronic splanchnic venous thrombosis(26). Hyperhomocysteinemia, has been proposed as a risk factor for SVT, however, it is challenging to determine the precise role of hyperhomocysteinemia as a risk factor for SVT because homocysteine levels are heavily influenced by diet and vitamin B6, B12, or B9 deficiencies. In contrast, the role of homozygous C677T MTHFR mutations as a risk factor for Budd-Chiari syndrome (BCS) appears to be more significant in Asia than in Europe (27).

Finally, SARS-COV2 has been reported as a risk factor for the development of SVT with the portal vein as the most affected vessel, with a slightly more common presentation in males than females. Several mechanisms have been proposed to explain the pathogenesis of

Table 2. — **Manifestations and complications of splanchnic venous thrombosis**

Thrombosis	Initial manifestation	Portal Hypertension	Liver dysfunction markers	five-year survival	Complications
BCS (acute or chronic presentation)	- Acute abdominal pain acute - Ascites, jaundice - Asymptomatic	Yes	Yes	65%	Ascites, cirrhosis, Liver failure acute (even hyperacute or fulminant)
PVT (acute or chronic presentation)	- Acute abdominal pain - Abdominal symptoms (bloating, dyspepsia) - Asymptomatic	Yes	No	54%	Portal hypertension, cavernoma, esophageal and gastric varices, pancytopenia, hypersplenism, cirrhosis
MVT (acute or chronic presentation)	- Abdominal Pain Sickness, threw up - Diarrhea - Low intestinal bleeding - Asymptomatic	Rare	No	44%	Intestinal ischemia, portal hypertension, esophageal and gastric varices
The spectrum of clinical presentation according to the specific site of the splanchnic venous bed involved by thrombosis is described, including acute and/or chronic onset as well as the estimated five-year survival rate, according to some registries (7, 9-11).					

SVT thrombosis in COVID-19 patients including high levels of proinflammatory cytokines, direct damage to endothelial cells by the virus and increased procoagulant factors (especially VIII-F, vWF, and V-F), and NETs [54, 59, 60]. Additionally, platelets may also play a role in COVID-19-induced thrombosis, as we previously discussed. When occurring in a pre-hypercoagulable state, the life-threatening condition caused by SVT-COVID19 could be catastrophic (28,29).

Less commonly classically described risk factors such as paroxysmal nocturnal hemoglobinuria (PNH) are associated with splanchnic thrombosis (especially BCS) as one of its main manifestations, although there are not sufficient studies yet to support a strong association with this syndrome (10,22,30)

Clinical presentation

Clinical manifestations are highly variable given the diversity of thrombotic involvement and time of onset: 18-29% of cases are asymptomatic and are detected incidentally on imaging studies as part of the diagnostic process for an occult neoplasm or staging of liver cirrhosis (2,3). The most frequent symptoms are abdominal pain, nausea and hyporexia in some cases, ascites, jaundice and fever are described for PVT and BCS (Table 2) (4,7,31). The most related signs and symptoms according to the anatomical segment compromised in the splanchnic circulation are listed below:

BCS: Clinical features depend on the degree of flow obstruction and subsequent recovery of liver function. It is characterized by abdominal pain, hepatomegaly and ascites, with a predominantly hepatocellular biochemical profile, given liver necrosis without collateral formation. It can be classified as fulminant, acute, subacute or chronic. The fulminant forms are rare but cause massive hepatocellular necrosis and severe hepatic encephalopathy and are therefore considered indications for emergent liver transplantation (16,22).

On the other hand, chronic BCS presents with portal hypertension and liver cirrhosis resulting from centrilobular fibrosis that develops over weeks and periportal nodular regeneration and progressive fibrosis that progresses over months, up to 15% are asymptomatic. Clinical features such as hepatomegaly, splenomegaly, right upper quadrant pain and ascites are frequently observed while jaundice and elevated transaminases are less commonly found (11,32).

PVT: Clinical presentation and severity of symptoms are variable and depend on the degree and rate of thrombus formation, and whether collateral circulation is present. As with BCS, it may present acutely or chronically depending on the speed of onset of venous flow obstruction. Thrombosis of the splenoportal axis not associated with liver cirrhosis or tumor disease is the second leading cause of portal hypertension in the Western world (33).

For chronic PVT, cavernomatous transformation (dilatation of the paracoledochal and epicoledochal veins, usually secondary to portal thrombosis, leading to the replacement of the single tubular structure of the portal vein by an area of multiple, tortuous collaterals) usually occurs with clinical manifestations variable in presentation and intensity: esophageal varices, gastric varices and hypersplenism resulting from variable portal hypertension, with a cumulative risk for hepatic encephalopathy (31,34)

Portal cholangiopathy with mild cholestasis or more severe biliary complications (such as acute cholangitis) may occur in chronic PVT, with symptoms such as jaundice, pruritus, abdominal pain of varying intensity and fever (35). Chronic PVT is usually asymptomatic but should be investigated in cases of variceal hemorrhage without documented liver cirrhosis, as well as in cases of cirrhotic in the setting of abrupt progression of ascites, severe hepatic encephalopathy and severe hypersplenism with secondary pancytopenia (34)

There are two classification systems for PVT: the Baveno VI system, which uses an anatomical-based classification, regardless of clinical or functional characteristics and incorporates features such as chronicity of thrombus, type of underlying disease and involvement of portal

Table 3. — **General anatomic-functional Classification of PVT**

Baveno VI Classification				
Type 1 (65-80%)	**Type II (10-15%)**	**Type III (0.3-7%)**	**Type IV (0.6-2.7%)**	**Type V (1.3-2.4%)**
RPV is divided into an anterior branch (supplying segments V and VIII) and a posterior branch (supplying segments VI and VII). LVP runs horizontally to the left and then turns medially (supplying segments I, II, III, and IV).	Trifurcation of MVP, dividing into the right anterior and posterior branches and the LPV.	The right posterior portal branch arises directly from the MPV as its first branch and the LPV is the terminal branch, arising after the origin of the right anterior portal vein.	Trifurcation of the RPV, in which the branch of segment VII is the first branch of the RPV.	Trifurcation of the RPV, in which the branch of segment VI arises early as a separate branch of the RPV.
Sarin System				
Site of PVT (Type 1, 2a, 2b, 3)	**Degree of portal venous system occlusion (O, NO)**	**Duration and Presentation (R, C)**	**Extent of PV system occlusion (S, M, SM)**	**Type and presence of underlying liver disease**
Type 1: Only trunk Type 2: Only branch: 2a, one branch; 2b, both branches Type 3: Trunk and branches	O: Occlusive: No flow visible in PV lumen on imaging/Doppler study NO: Nonocclusive: Flow visible in PV lumen through imaging/ Doppler study	R: Recent (first time detected in previously patent PV, presence of hyperdense thrombus on imaging, absent or limited collateral circulation, dilated PV at the site of occlusion) *Asymptomatic: (As)*Symptomatic: (S), Acute PVT features (with or without ABI) Ch: Chronic (no hyperdense thrombus; previously diagnosed PVT on follow-up, portal cavernoma and clinical features of PHT) Asymptomatic Symptomatic: features of portal hypertension (with or without PHT)	Splenic vein, mesenteric vein or both	Cirrhotic, noncirrhotic liver disease, post-liver transplant, HCC, local malignancies, and associated conditions

Both classifications have been proposed in cirrhotic patients. The Baveno VI classification includes portal venous thrombosis, together with splenic thrombosis, as causes of pre-hepatic portal hypertension, with increased pressure in the segment upstream of the lesion; for more than 6 months is considered chronic thrombosis. Cheng et al. further divide it into the 5 types listed, as mentioned according to the thrombosed anatomical segment, considering that after its entry through the hilium, the main portal vein (MPV) divides into a larger right portal vein (RPV) and a smaller left portal vein (LPV). ABI, acute bowel ischemia; HCC, hepatocellular carcinoma; IMV, inferior mesenteric vein; PHT, portal hypertension; PVT, portal vein thrombosis; PV, portal vein; SV, splenic vein. Modified from (39).

vein branches; and the Sarin system, which addresses the functional relevance of PVT to clearly define the duration and presentation of the disease, without having an established prognostic and therapeutic goal that places it above traditional anatomical classifications (36,37) (Table 3).

MVT: It can present as an acute, subacute, or chronic disease. In the acute form, it may be associated with diarrhea, nausea, vomiting and gastrointestinal bleeding, as well as severe abdominal pain radiating to the back and paralytic ileus secondary to intestinal ischemia due to the involvement of proximal mesenteric venous arches. Intestinal ischemia should be suspected in the case of hematochezia with or without ascites and in the setting of progressive acute kidney injury with metabolic acidosis and hyperlactatemia. Mortality rates are high. In its chronic presentation abdominal pain varies in intensity according to the degree of venous collateral circulation (38-40).

Complications

The range of complications is determined by the short or long-term consequences of bleeding and thrombosis. Thrombosis leads to the development of liver cirrhosis and portal hypertension with the risk of hemorrhage associated to personal history, presence of esophageal or gastric varices, use of antiplatelet and anticoagulant drugs, platelet count and splanchnic venous pressure induced by residual venous obstruction. Depending on the site of thrombosis a person affected may develop subacute or late-onset liver failure, portal hypertension and long-term intestinal ischemia (13,31,32,41).

Reports show major bleeding rates in splenic thrombosis of 6.9% and for PVT gastrointestinal bleeding rates of 12.5%; however, these rates may vary up to 46% in the presence of active neoplasm or liver cirrhosis (42).

Likewise, recurrence of thrombosis is associated with delayed initiation of anticoagulation therapy and the underlying prothrombotic condition, resulting in a 10-year risk of 24% for PVT with or without cirrhosis and/or malignancy, describing a cumulative annual risk of 5.5%. The annual recanalisation rate after PVT has been described to be around 38% (43).

Diagnosis

The diagnosis of SVT relies on imaging techniques, where angiography was once the gold standard it has now been replaced by Doppler-ultrasound (DUS), computed tomography (CT) and magnetic resonance (MR) (44-46). The usefulness of D-dimer, a biomarker commonly used for detecting deep vein thrombosis and pulmonary embolism, is limited in this situation (47).

DUS is the first-line diagnostic test for PVT and BCS with high sensitivity (89-93%) and specificity (92-99%) but can be affected by interoperator variability and anthropometric characteristics of the patient. It can also identify the degree of thrombosis by detecting partial or complete obstruction of the portal and intrahepatic veins. However, it has a low diagnostic yield in mesenteric thrombosis (4,44,48). BCS ultrasound findings include hepatic vein occlusion, caudate lobe hypertrophy, focal hepatic enhancement, hypervascular nodules (nodular regenerative hyperplasia), and intrahepatic collateral vessels. In cases of PVT hyperechoic material within the portal vein, distension, absence of flow in these vessels, presence of cavernoma, and reduced portal vein distension are observed. Portal vein velocity of less than 15 cm/s measured by color Doppler can significantly predict the development of PVT in up to 91.7% of cases. Contrast Doppler ultrasound has a sensitivity of up to 88% - 100% and specificity of 94%-96% for PVT and BCS respectively (11,13,49).

Contrast abdominal CT and abdominal MRI are the gold standard for the diagnosis of SVT, with a sensitivity of 100% and specificity of 98%, respectively. They assess the extent of thrombosis and help determine other differential diagnoses. They are the gold standard for the diagnosis of MVT in which case filling defect in the mesenteric vein can be observed in addition to bowel wall thickening, intestinal pneumatosis and portal vein gas. Contrast-enhanced magnetic resonance angiography is a complementary diagnostic option to define the degree of tumour invasion and the presence of gastric varices in cases of PVT (11,13).

Differentiating acute or recent PVT from chronic PVT can be challenging, but it is important for treatment decisions. Acute PVT appears as a hyperechoic material in an enlarged vein with no or limited blood flow on DUS or as hyperattenuating material without luminal contrast enhancement on CT. On the other hand, portal cavernoma is the primary finding of chronic thrombosis and can be easily detected by both DUS and CT, it is characterized by the presence of multiple small collaterals around the PVT. In cases where the diagnosis timeline is unclear, clinical presentation, absence of collateral circulation and previous exam results may be useful in determining if presentation of SVT is acute or recent (48,49). Liver biopsy is only used in rare cases to confirm forms of BCS involving small intrahepatic veins or to exclude other hepatic disorders (45).

In cases of non-cirrhotic SVT without precipitating factors, several genetic and biochemical tests to diagnose and manage thrombotic disorders should be made. Genetic testing for the V617F mutation of the JAK2 gene is recommended for all patients. If the test is negative further testing for the CALR gene is suggested if the platelet count is greater than -200 x 10^9/L or the spleen length is greater than 16 cm. Next-generation sequencing and bone marrow biopsy should be considered if necessary (4,21).

Additionally, genetic testing for the prothrombin G20210A and Factor V Leiden mutations is advised, along with testing for Protein S, Protein C and antithrombin activities in the absence of vitamin K antagonists. Careful interpretation of impaired liver function is recommended (45,46).

Furthermore, to evaluate the possibility of an autoimmune disorder causing thrombosis, lupus anticoagulant, anti-cardiolipin and anti-beta2 glycoprotein 1 antibody testing should be conducted. If the initial test results are positive, repeat testing should be conducted after 12 weeks to confirm the results. These tests are crucial in determining the presence of antiphospholipid syndrome (4,42,50).

The presence of SVT in male sex, mediterranean origin or genital/oral ulcers should alert the clinician to the possibility of Behçet`s disease. On the other hand, a younger age, bicytopenia (anemia, thrombocytopenia) or pancytopenia, hypersplenism or signs of hemolysis should raise suspicion for paroxysmal nocturnal hemoglobinuria. The determination of other diseases such as hyperhomocysteinemia should be individualized (45,46).

Treatment

Treatment of SVT poses a particular clinical challenge given the risk of bleeding and thrombosis in the same clinical setting, requiring multidisciplinary management. Furthermore, the low quality of evidence based on observational studies may require in many cases a stepwise management that includes interventional radiology procedures such as balloon and stent application and the insertion of transjugular intrahepatic portosystemic shunts (TIPS), surgical procedures for vascular decompression and finally liver transplantation (2,6,51)

Anticoagulation (AC) therapy is the cornerstone of SVT treatment and aims to prevent thrombus extension or recurrence, establish vessel patency and prevent complications such as portal hypertension or intestinal infarction (3). Valeriani et al. conducted a systematic review regarding AC in the SVT scenario. This study found that compared to no treatment, the use of anticoagulant therapy led to higher rates of SVT recanalization and lower rates of thrombosis progression, major bleeding and overall mortality. Specifically, the risk of recanalization was 2.39 times higher and the risk of thrombosis progression was 0.24 times lower

with anticoagulant therapy. In addition, the risk of major bleeding was reduced by 0.73 times and the risk of overall mortality was reduced by 0.45 times. These findings suggest that anticoagulant therapy is an effective treatment option for improving SVT recanalization and reducing the risk of thrombosis progression, without increasing the risk of major bleeding (52). Nevertheless, management in these patients should be individualized according to the severity, presentation, site and extent of the thrombus, as well as its characteristics, always taking into consideration the risk/benefit ratio.

Anticoagulants which have demonstrated benefit are low molecular weight heparins (LMWH), unfractionated heparin (UFH) and vitamin K antagonists (VKA). The use of direct oral anticoagulants (DOACs) for the treatment of SVT is still a matter of debate due to the absence of patients with SVT in the registration trials for DOACs (46).

However, retrospective and limited prospective data have demonstrated the safety and effectiveness of DOACs compared to VKAs and LMWH in this cohort of patients (53). For example, Naymagon et al. conducted a study comparing the use of DOACs with LMWH and Warfarin for the treatment of non-cirrhotic acute PVT. The study found that the patients treated with DOACs were found to have recanalization rates similar to those treated with enoxaparin and greater than those treated with Warfarin. Additionally, the rate of major bleeding was reduced with DOACs compared to Warfarin (54). On the other hand, Janczak et al. assessed the outcome of rivaroxaban and apixaban for the treatment of venous thromboembolism (VTE) of atypical location (VTE-AL) such as SVT; they found that rates of VTE recurrence and bleeding in patients treated with rivaroxaban and apixaban for VTE-AL were comparable to those observed in patients with VTE of typical location and similar to those treated with enoxaparin (54). Finally, The RIVA-SVT 100 study was a prospective cohort study that was conducted internationally with a single group assignment and an open-label design. It did not include patients with cirrhosis but included those with unprovoked SVT, solid cancer and hematologic malignancies. According to the study results, the use of rivaroxaban was safer than heparin and VKAs in terms of bleeding for patients with acute SVT. Additionally, the study found that the use of rivaroxaban was effective in terms of recanalization of splanchnic veins within three months of treatment (55).

All these data suggest that DOACs may be a safer and more effective alternatives to traditional anticoagulants for the treatment of portal vein thrombosis in patients without cirrhosis. However, it is important to note that more research is needed to fully evaluate the safety and effectiveness of DOACs for the treatment of SVT. Overall, DOACs represent an effective and safe alternative to VKAs for the treatment of SVT. For this reason, 2020 ISTH guidelines suggest the possibility of using DOACs in acute and some selected cases of chronic SVT (56).

When the objective diagnosis of SVT is made, the following stepwise clinical approach is proposed (Figure 4):

- Generative risk factor: When making the diagnosis, the search for the underlying risk factor should begin, bearing in mind that in up to 60% of cases it is possible to identify an underlying systemic prothrombotic disorder as the etiological factor (Table 1). This is crucial for defining prognosis of SVT, designing strategies to control reversible factors and to institute appropriate treatment. Additional prognostic factors to consider include the site and extent of SVT as well as the severity of presentation. This was depicted in greater detail above (1-3,56).
- Bleeding risk factors: These need to be assessed for any therapeutic approach and include: age older than 75 years, previous cerebrovascular disease, chronic kidney disease, use of antiplatelet agents, under-lying liver disease, previous gastrointestinal bleeding (variceal or not), esophageal varices and low platelet count. Bleeding risk scores are not validated for SVT (12).
- Anticoagulation therapy: Recommendations in SVT have been associated with improved survival, low risk of recurrence and higher recanalization rate, with an apparent increase in bleeding risk; for example, initiation of early anticoagulation in the acute phase of PVT will significantly impact the likelihood of recanalization and thus the prognosis of these patients. In the chronic phase of PVT (or portal carcinomatosis) symptomatology and morbidity are driven by the complications of portal hypertension that have developed so far. To date, anticoagulation in these cases is reserved for patients in whom an underlying prothrombotic disorder has been demonstrated (52). There are no clinical trials to support the quality of evidence for anticoagulation therapy. Recommendations are summarised in Table 4.

Although the general approach depicted above would apply to all cases of SVT, there are some nuances regarding specific subtype of SVT.

Budd Chiari Syndrome

The management of BCS requires specialized centers with access to interventional radiology and liver transplantation, and a multidisciplinary team including specialists in hematology, interventional radiology and hepatology. A stepwise treatment strategy, guided by the previous therapy has been proposed, it involves medical therapy alone, interventional radiology and liver transplantation (46).

Anticoagulation therapy helps prevent the formation of new clots and helps to dissolve existing clots in BCS. The decision to initiate anticoagulation should be made as soon as possible in most patients, provided there are no contraindications. It is also recommended to perform an upper endoscopy to screen for esophageal varices prior to initiating anticoagulation therapy. Long-term anticoagulation therapy is currently recommended for all patients with BCS based on survival data compared to historical controls, even in the absence of an identified

prothrombotic disorder. LMWH is usually the preferred anticoagulant but may be substituted with VKA in patients with stable disease and a target INR between two and three. Although direct oral anticoagulants (DOACs) seem safe and effective in patients with BCS, there are no clear recommendations regarding their use in this situation, therefore they should be considered in a case-by-case basis (22,32).

Furthermore, some methods for restoring the patency of thrombosed veins include: thrombolytic therapy, angioplasty or stenting and trans jugular Porto hepatic systemic shunt (TIPS). Thrombolytic therapy is mainly used in patients with acute BCS and a well-defined clot. On the other hand, for patients with chronic or acute symptomatic BCS or with cirrhosis, it is recommended to perform a percutaneous transluminal angioplasty to establish a short hepatic vein stenosis, which has shown to be highly effective in restoring the normal drainage of the portal and sinusoidal blood and has a low risk of complications. In patients with chronic Budd-Chiari syndrome that does not respond to the previous management, TIPS placement should be considered, if the latter does not work liver transplantation should be performed (22,32) (Figure 3).

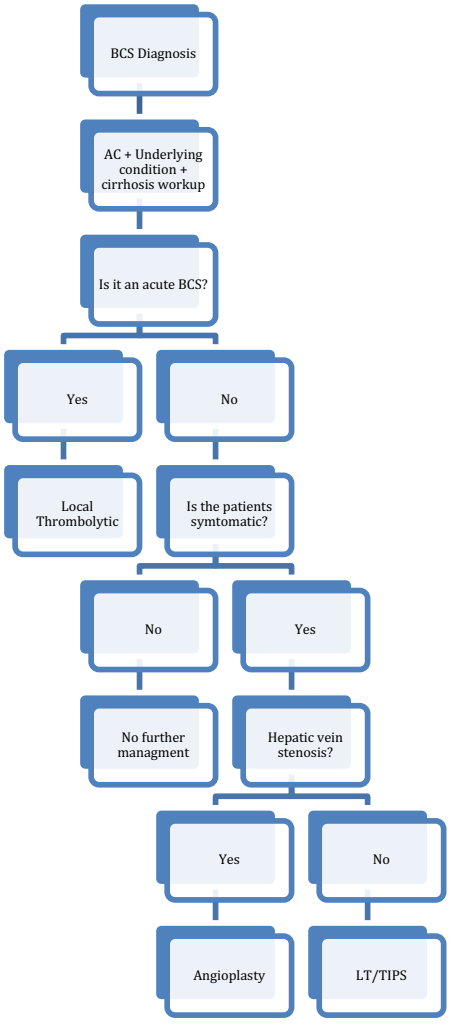

Figure 3. — Proposed algorithm for patients with Budd-Chiari syndrome

MVT: mesenteric venous thrombosis, AC: anticoagulation, LV: variceal ligation, BB: beta-blocker, TIPS: transjugular intrahepatic portosystemic, SMV: superior mesenteric vein, IVC: inferior vena cava, LT: liver transplantation, UGB: upper gastrointestinal bleeding.

Portal Vein Thrombosis

The management approach in patients with PVT varies greatly depending on degree of liver fibrosis and onset of presentation (acute vs chronic). In the case of acute PVT, the vessel is completely occluded leading to splanchnic congestion and secondary ischaemia, presenting with sudden onset colic abdominal pain radiating to the lumbar region, with or without fever, as well as nausea, vomiting and diarrhea. In the presence of known liver cirrhosis, the patient usually presents with gastrointestinal bleeding (variceal or not), ileus and infectious complications, especially spontaneous bacterial peritonitis according to the clinical stage scored by the Child-Pugh scale. Physical examination reveals splenomegaly and hepatomegaly as well as tension ascites and the presence of collateral circulation in the abdominal wall. If PVT is partially occlusive, symptoms may be minimal or absent (35,51).

Patients who have acute PVT should promptly begin anticoagulation treatment, as studies have shown that it reduces the risk of clot enlargement and minimizes the chances of developing intestinal infarction, which is a severe complication that can occur in up to 30% of untreated patients but only 2% of the treated patients (30). The recommended treatment approach for patients with acute PVT is to administer anticoagulation therapy for six months unless there are indications for long-term treatment due to an uncorrectable thrombotic risk factor or a thrombus extending into the mesenteric veins. To achieve prompt anticoagulation patients should begin treatment with low molecular weight heparin. Once their condition stabilizes and there are no scheduled invasive procedures, they can switch to an oral anticoagulant such as VKA or DOACs (9,11).

Conversely, patients with chronic PVT are at a high risk of portal hypertension complications and therefore should be screened for esophageal varices. Regarding medical management for patients with a higher likelihood of recurring thrombosis based on their medical history or lab results, anticoagulation is typically recommended. For these patients, long-term anticoagulation is suggested, with special consideration given to the risk of adverse events like bleeding. In case of presenting with a history of gastrointestinal bleeding or large varices who are at a heightened risk for bleeding, anticoagulation is only administered if adequate measures to prevent recurrent bleeding can be put in place, especially in patients with cirrhosis (57). For patients without significant or long-lasting risk factors for thrombosis, the RIPORT randomized controlled trial discovered that rivaroxaban at a dosage of 15 mg per day decreased the rate of recurring thrombosis from 19/100 patient-years to 0/100 patient-years. Additionally,

Table 4. — **Anticoagulation therapy in splanchnic venous thrombosis (SVT)**

Conditions	Treatment
	PVT not cirrhotic
SVT, not cirrhotic, symptomatic, no bleeding	Start of LWHM 1 mg/kg/12 hours and start vitamin K antagonist in 48 to 72 hours, INR goal: 2-3
SVT in cancer	LWHM 1 mg/Kg/12 hours during 3 to 6 months
GFR <30 mL/min	LWHM reduced dose by 50%, monitoring with Xa anti-factor, considered start vitamin K antagonist
Platelets >30.000 or < 50.000	Reduced the dose of LWHM by 50% and don't start vitamin K antagonist until thrombocytopenia improve
Platelets < 30.000	Refrain from the use of anticoagulants until thrombocytopenia improve
	PVT cirrhotic
Symptomatic cirrhotic	Start of LWHM 1 mg/kg/12 hours and start vitamin K antagonist in 48 to 72 hours, INR goal: 2-3
Chronic kidney disease or acute kidney injury	LWHM reduced dose by 50%, monitoring with Xa anti-factor, considered start vitamin K antagonist. Considered refrain use anticoagulant if there is coagulopathy or poor short-term prognosis
Platelets < 50.000	Refrain from the use of anticoagulants until thrombocytopenia improve or if its present prolonged thrombosis and occlusive reduced LWHM by 50%
Incidental SVT	Apply the same proposed treatment regimens for the symptomatic patient, except: thrombosis is inconclusive, probably not recent, and limited to single vein segment; no permanent or no recent removable risk factors (1 month) for thrombosis identified; the risk of bleeding is moderate to high or poor prognosis of underlying disease
The different clinical scenarios in the context of the patient with splanchnic venous bed thrombosis, including the patient with active cancer, are outlined (26-29).	

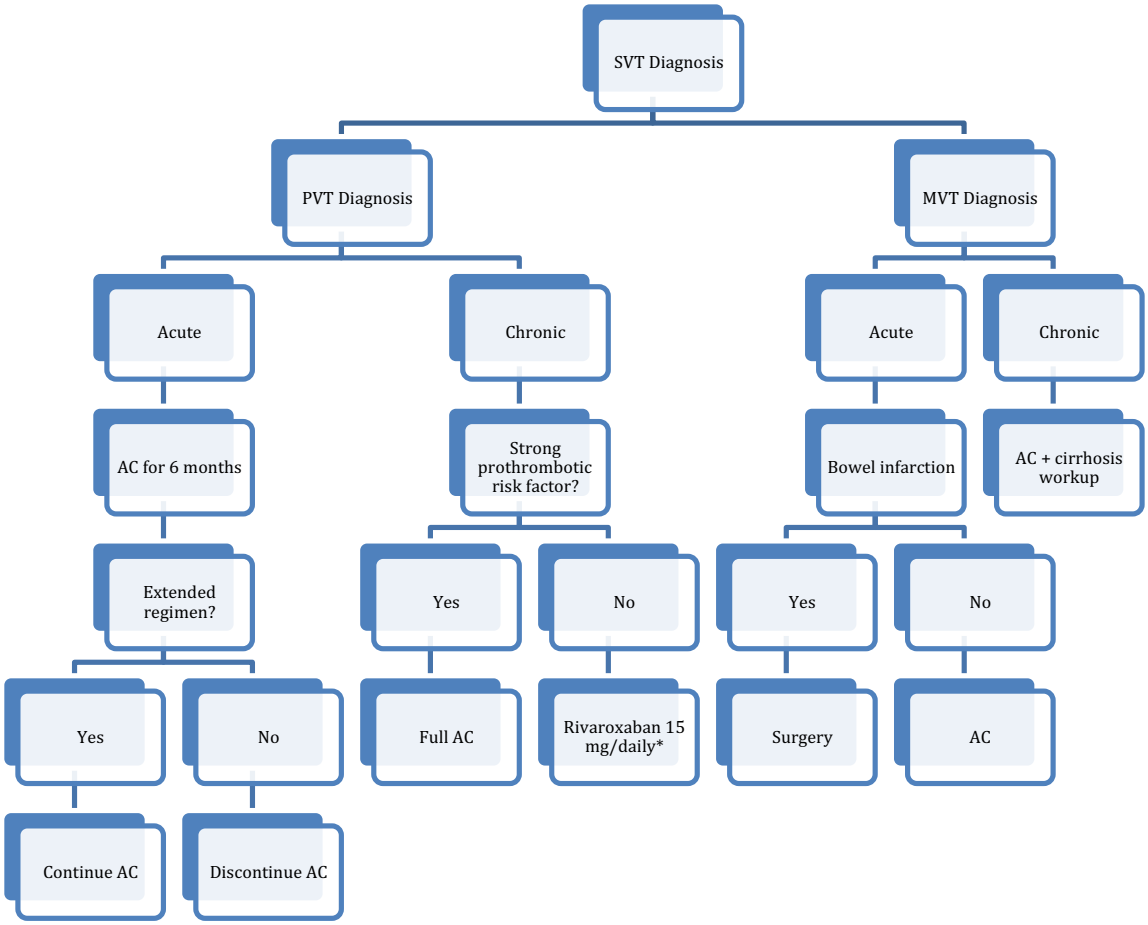

Figure 4. — Proposed management algorithm for splanchnic venous thrombosis with emphasis on the non-cirrhotic patient. A management strategy is proposed, taking into account the frequency of portal hypertension according to each segment of the splanchnic venous circulation involved, as well as the time of onset over time (acute, chronic); it includes pharmacological and non-pharmacological strategies.
SVT: Splanchnic venous thrombosis, MVT: mesenteric venous thrombosis, PVT: Portal venous thrombosis, BCS: Budd-Chiari syndrome, AC: anticoagulation, LV: variceal ligation, BB: beta-blocker, TIPS: transjugular intrahepatic portosystemic, SMV: superior mesenteric vein, IVC: inferior vena cava, LT: liver transplantation, UGB: upper gastrointestinal bleeding.

plasma D-dimer concentrations under 500 ng/ml one month after the conclusion of anticoagulation therapy were predictive of a low risk of recurrence. Moreover, the occurrence of thrombosis was rare in patients with an isolated transient local factor for PVT (58). Therefore, for patients without general thrombosis risk factors and only one transient local factor, anticoagulation may be stopped with D-dimer monitoring one month later to determine if resuming therapy is necessary (57).

Further investigations are required to establish clear guidelines and evaluate patient outcomes regarding the implementation of invasive strategies in individuals with recent PVT extending to the superior mesenteric vein, including trans jugular or transhepatic thrombus aspiration, local fibrinolysis and TIPS. This is especially crucial in the presence of indicators suggesting an increased likelihood of intestinal necrosis (59).

Mesenteric Vein Thrombosis

For acute and subacute mesenteric venous thrombosis, the main treatment approach is conservative and involves systemic anticoagulation to prevent further extension of the clot, bowel rest and close monitoring for any signs of clinical deterioration. AC strategy should be established with low molecular weight heparin (38). Once patient condition stabilizes and there are no scheduled invasive procedures, they can switch to an oral anticoagulant such as VKA or DOACs. Surgical intervention is reserved for patients who show clear evidence of bowel infarction. In some cases, thrombolytic therapy or other endovascular treatments may be used as adjuncts to anticoagulation for patients who do not respond to conventional therapy (8,17).

On the contrary, patients with chronic MVT should be screened for esophageal varices and portal hypertensive cholangiopathy, and managed as a patient with cirrhosis. Anticoagulation is advised for these patients, particularly if they have prothrombotic states. However, there is limited evidence on the effectiveness of anticoagulants in this scenario (8,38,39).

Prognosis

Prognostic variables depend on the anatomical site involved, the extent of thrombosis and the patient's own disease burden. In available studies, the annual 10-year overall survival rate for SVT was 60%, with advanced age, active cancer and myeloproliferative neoplasms being independent predictors for mortality (12,28). There are differences according to the presentation profile: for example, patients with BCS have a better survival rate than those with PVT, with overall survival at 1 year between 81%-85% and 62% at 10 years (13,27).

For BCS overall survival at 1 year, 5 years and 10 years was 82%, 69% and 62% respectively. Encephalopathy, ascites, prolonged prothrombin time and elevated bilirubin have been independently associated with poor prognosis (26,27). For PVT overall survival was 69% at 1 year and 54% at 5 years, with age, total bilirubin levels, clinical stage of liver cirrhosis and presence of malignancy being significant predictors of mortality. Finally, MVT has a lower mortality rate than its arterial counterpart, with 44% compared to 66%-89%.

The overall recurrence of SVT lowers from 0-25% to less than 3% with initiation of anticoagulation therapy (1,12).

Conclusions

– SVT is a complex clinical entity involving the compromise of several vascular anatomical segments, with great clinical heterogeneity in its presentation associated with multiple mediate (portal hypertension, liver cirrhosis) and immediate complications (acute liver failure and intestinal ischemia). Additionally, this is a potentially life-threatening disease associated with a substantial risk of recurrence and gastrointestinal bleeding.

– The most common predisposing factors for SVT in the absence of cirrhosis can be local or systemic, highlighting the following: solid abdominal cancer, abdominal surgery (in the previous 3 months) and intraabdominal infection or inflammatory diseases (inflammatory bowel disease, pancreatitis, diverticulitis, appendicitis, cholecystitis, cholangitis, abdominal abscess). PVT and MVT are more commonly associated with the aforementioned conditions, while BCS is more frequently associated with the V617F mutation of the JAK2 gene (latent or occult myeloproliferative neoplasm), irrespective of oral contraceptives use, autoimmune disorders or inherited thrombophilias (such as factor V Leiden mutation and protein C, S). Additionally, up to 20% of cases are idiopathic. Therefore, studies to identify underlying causes should be individualized.

– Anticoagulation therapy is indicated in the setting of the symptomatic patient, preferably in the acute stage, always assessing the risk-benefit ratio over the risk of major bleeding; early initiation of this measure may favor partial or complete recanalization of portal flow, thus avoiding the development of portal hypertension and its complications. Whereas spontaneous recanalization is rare in cases of portal vein thrombosis without underlying liver disease, it can occur in about 40% of patients with cirrhosis.

– According to current evidence, rivaroxaban appears to be a reasonable alternative to standard anticoagulation for the treatment of SVT in patients without cirrhosis, taking into account low rates of major bleeding and recurrent SVT at 3 months. Additional data from interventional and observational studies are needed to confirm findings of studies available to date and provide information on the long-term risks (eg, after 3 months) of anticoagulation therapy in this patient population, including those with oncological diagnosis.

– Thrombolytic therapy should be reserved for cases of severe disease (acute course with high thrombotic

burden) or those who do not respond to anticoagulation within a time frame ranging from one week to six months. Thrombectomy by catheter aspiration has been tried successfully as documented in some case reports; however, its widespread use is not recommended. Surgical thrombectomy is associated with increased recurrence of thrombosis, increased morbidity and mortality, and should not be indicated in the management of these patients.

References

1. AGENO W., DENTALI F., SQUIZZATO A. How I treat splanchnic vein thrombosis. *Blood*, 2014, **124**(25):3685-3691.
2. AGENO W. Managing unusual presentations of venous thromboembolism. *J Thromb Thrombolysis*, 2015, **39**(3):304-310.
3. AGENO W., BEYER-WESTENDORF J., GARCIA D., LAZO-LANGNER A., MCBANE R., PACIARONI M. Guidance for the management of venous thrombosis in unusual sites. *J Thromb Thrombolysis*, 2016,**41**(1):129-143.
4. VALERIANI E., RIVA N., DI NISIO M., AGENO W. Splanchnic Vein Thrombosis: Current Perspectives. *Vasc Health Risk Manag*, 2019, **15**:449-461
5. GALANTE A., DE GOTTARDI A. Portal vein thrombosis: an overview of current treatment options. *Acta Gastroenterol Belg*., 2021, **84**(2):327-332.
6. BASIT SA, STONE CD, GISH R. Portal vein thrombosis. *Clin Liver Dis*. 2015;**19**(1):199-221.
7. CARNEIRO C, BRITO J, BILREIRO C, BARROS M, BAHIA C, SANTIAGO I, et al. All about portal vein: a pictorial display to anatomy, variants and physiopathology. *Insights Imaging*, 2019,**10**(1):1-18.
8. DEMELO-RODRÍGUEZ P, ORDIERES-ORTEGA L, OBLITAS CM. Mesenteric venous thrombosis. *Med Clin* (Barc), 2023, **160**(9):400-406.
9. ELKRIEF L, PAYANCÉ A, PLESSIER A, RONOT M, PARADIS V, VALLA D, et al. Management of splanchnic vein thrombosis. *JHEP Rep*., 2023,**5**(4):100667.
10. TREBICKA J, STRASSBURG CP. Etiology and Complications of Portal Vein Thrombosis. *Viszeralmedizin*, 2014,**30**(6):375-380.
11. CAMERLO S, LIGATO J, ROSATI G, CARRÀ G, RUSSO I, DE GOBBI M, et al. Shedding Light on the Pathogenesis of Splanchnic Vein Thrombosis. *Int J Mol Sci*., 2023, **24**(3):2262
12. STINE JG, NORTHUP PG. Management of non-tumoral portal vein thrombosis in patients with cirrhosis. *Dig Dis Sci*.,2019, **64**(3):619-626.
13. GADANI S, PARTOVI S, LEVITIN A, ZERONA N, SENGUPTA S, AMICO GD, et al. Narrative review of portal vein thrombosis in cirrhosis: pathophysiology, diagnosis, and management from an interventional radiology perspective. *Cardiovasc Diagn Ther*., 2022,**12**(1):135-146.
14. ALZUBAIDI S, PATEL I, SAINI A, KNUTTINEN G, NAIDU S, KRIEGSHUASER S, et al. Current concepts in portal vein thrombosis: etiology, clinical presentation and management. *Abdominal Radiology*, 2019, **44**(10):3453-3462.
15. AGENO W, RIVA N, SCHULMAN S, BEYER-WESTENDORF J, BANG SM, SENZOLO M, et al. Long-term Clinical Outcomes of Splanchnic Vein Thrombosis: Results of an International Registry. *JAMA Intern Med*.,2015,**175**(9):1474-1480.
16. RAJANI R, MELIN T, BJÖRNSSON E, BROOMÉ U, SANGFELT P, DANIELSSON Å, et al. Budd-Chiari syndrome in Sweden: epidemiology, clinical characteristics and survival - an 18-year experience. *Liver International*, 2009,**29**(2):253-259.
17. HMOUD B, SINGAL AK, KAMATH PS. Mesenteric venous thrombosis. *J Clin Exp Hepatol*., 2014,**4**(3):257-263.
18. LUSSANA F, DENTALI F, AGENO W, KAMPHUISEN PW. Venous thrombosis at unusual sites and the role of thrombophilia. *Semin Thromb Hemost*., 2007,**33**(6):582-587.
19. MANGIA A, VILLANI MR, CAPPUCCI G, SANTORO R, RICCIARDI R, FACCIORUSSO D, et al. Causes of portal venous thrombosis in cirrhotic patients: the role of genetic and acquired factors. *Eur J Gastroenterol Hepatol*., 2005,**17**(7):745-751.
20. TURON F, CERVANTES F, COLOMER D, BAIGES A, HERNÁNDEZ-GEA V, GARCIA-PAGÁN JC. Role of calreticulin mutations in the aetiological diagnosis of splanchnic vein thrombosis. *J Hepatol.*, 2015,**62**(1):72-74.
21. SEKHAR M, MCVINNIE K, BURROUGHS AK. Splanchnic vein thrombosis in myeloproliferative neoplasms. *Br J Haematol*., 2013,**162**(6):730-747.
22. MURAD SD, PLESSIER A, HERNANDEZ-GUERRA M, FABRIS F, EAPEN CE, BAHR MJ, et al. Etiology, management, and outcome of the Budd-Chiari syndrome. *Ann Intern Med.*, 2009, **151**(3):167-175.
23. BISSONNETTE J, DURAND F, DE RAUCOURT E, CECCALDI PF, PLESSIER A, VALLA D, et al. Pregnancy and vascular liver disease. *J Clin Exp Hepatol*., 2015,**5**(1):41-50.
24. DENNINGER MH, CHAÏT Y, CASADEVALL N, HILLAIRE S, GUILLIN MC, BEZEAUD A, et al. Cause of portal or hepatic venous thrombosis in adults: The role of multiple concurrent factors. *Hepatology*, 2000,**31**(3):587-591.
25. QI X, REN W, DE STEFANO V, FAN D. Associations of coagulation factor V Leiden and prothrombin G20210A mutations with Budd-Chiari syndrome and portal vein thrombosis: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol*., 2014,**12**(11):1801-1812.
26. FISHER NC, WILDE JT, ROPER J, ELIAS E. Deficiency of natural anticoagulant proteins C, S, and antithrombin in portal vein thrombosis: a secondary phenomenon? *Gut*, 2000,**46**(4):534-539.
27. QI X, YANG Z, DE STEFANO V, FAN D. Methylenetetrahydrofolate reductase C677T gene mutation and hyperhomocysteinemia in Budd-Chiari syndrome and portal vein thrombosis: A systematic review and meta-analysis of observational studies. *Hepatol Res*., 2014,**44**(14):480-498.
28. SINGH B, KAUR P, MAROULES M. Splanchnic vein thrombosis in COVID-19: A review of literature. *Digestive and Liver Disease*, 2020, **52**(12):1407-1409.
29. TRIPOLINO C, PIZZINI AM, ZACCARONI S, CICOGNANI C, DAPPORTO S, CIPOLLINI ML, et al. Is SARS-CoV-2 infection an emerging risk factor for splanchnic venous thrombosis? *Clin Hemorheol Microcirc*., 2021,**79**(2):347-355.
30. PLESSIER A, DARWISH-MURAD S, HERNANDEZ-GUERRA M, CONSIGNY Y, FABRIS F, TREBICKA J, et al. Acute portal vein thrombosis unrelated to cirrhosis: a prospective multicenter follow-up study. *Hepatology*, 2010,**51**(1):210-218.
31. SHATZEL JJ, O'DONNELL M, OLSON SR, KEARNEY MR, DAUGHETY MM, HUM J, et al. Venous thrombosis in unusual sites: A practical review for the hematologist. *Eur J Haematol*.,2019, **102**(1):53-62.
32. SHUKLA A, SHRESHTHA A, MUKUND A, CHHAGAN B, EAPEN C, HAN G, et al. Budd-Chiari syndrome: consensus guidance of the Asian Pacific Association for the study of the liver (APASL). *Hepatol Int.*, 2021,**15**(3):531-567
33. HANDA P, CROWTHER M, DOUKETIS JD. Portal vein thrombosis: a clinician-oriented and practical review. *Clin Appl Thromb Hemost*., 2014,**20**(5):498-506.
34. LOUDIN M, AHN J. Portal Vein Thrombosis in Cirrhosis. *J Clin Gastroenterol*., 2017,**51**(7):579-585.
35. THOMPSON A. Portal vein thrombosis - a primer for the general physician. *Clin Med* (Lond). 2017,**17**(5):479
36. PUENTE A, FORTEA JI, HUELIN P, CRESPO J. Portal hypertension. *Medicine* (Spain), 2020,**13**(6):308-315.
37. SARIN SK, PHILIPS CA, KAMATH PS, CHOUDHURY A, MARUYAMA H, NERY FG, et al. Toward a Comprehensive New Classification of Portal Vein Thrombosis in Patients With Cirrhosis. *Gastroenterology*, 2016, **151**(4):574-577.
38. RUSSELL CE, WADHERA RK, PIAZZA G. Mesenteric venous thrombosis. *Circulation*, 2015,**131**(18):1599-1603.
39. KUMAR S, SARR MG, KAMATH PS. Mesenteric venous thrombosis. *N Engl J Med*., 2001;**345**(23):1683-1688.
40. BLUMBERG SN, MALDONADO TS. Mesenteric venous thrombosis. *J Vasc Surg Venous Lymphat Disord*., 2016,**4**(4):501-507.
41. SHARMA AM, ZHU D, HENRY Z. Portal vein thrombosis: When to treat and how?. *Vascular Medicine* (United Kingdom), 2016,**21**(1):61-69.
42. RIVA N, AGENO W. Approach to thrombosis at unusual sites: Splanchnic and cerebral vein thrombosis. *Vascular Medicine* (United Kingdom), 2017,**22**(6):529-540.
43. RIVA N, DONADINI MP, DENTALI F, SQUIZZATO A, AGENO W. Clinical approach to splanchnic vein thrombosis: risk factors and treatment. *Thromb Res*., 2012;**130** Suppl 1:S1-S3.
44. RIVA N, AGENO W. Clinical manifestations and imaging tools in the diagnosis of splanchnic and cerebral vein thromboses. *Thromb Res*., 2018,**163**:252-259.
45. DELEVE LD, VALLA DC, GARCIA-TSAO G. Vascular disorders of the liver. *Hepatology*, 2009,**49**(5):1729-1764.
46. GARCIA-PAGÁN JC, BUSCARINI E, JANSSEN HLA, LEEBEEK FWG, PLESSIER A, RUBBIA-BRANDT L, et al. EASL Clinical Practice Guidelines: Vascular diseases of the liver. *J Hepatol.*, 2016,**64**(1):179-202.
47. RIVA N, ATTARD LM, VELLA K, SQUIZZATO A, GATT A, CALLEJA-AGIUS J. Diagnostic accuracy of D-dimer in patients at high-risk for splanchnic vein thrombosis: A systematic review and meta-analysis. *Thromb Res*., 2021,**207**:102-112.
48. MANTAKA A, AUGOUSTAKI A, KOUROUMALIS EA, SAMONAKIS DN. Portal vein thrombosis in cirrhosis: diagnosis, natural history, and *therapeutic challenges. Ann Gastroenterol*.,2018, **31**(3):315-29.

49. RIVA N, AGENO W, SCHULMAN S, BEYER-WESTENDORF J, DUCE R, MALATO A, et al. Clinical history and antithrombotic treatment of incidentally detected splanchnic vein thrombosis: a multicentre, international prospective registry. *Lancet Haematol.*, 2016,**3**(6):267-275.
50. HARNIK IG, BRANDT LJ. Mesenteric venous thrombosis. *Vasc Med*., 2010,**15**(5):407-418.
51. MANZANO-ROBLEDA M DEL C, BARRANCO-FRAGOSO B, URIBE M, MÉNDEZ-SÁNCHEZ N. Portal vein thrombosis: What is new? *Ann Hepatol*., 2015, **14**(1):20-27.
52. VALERIANI E, DI NISIO M, RIVA N, COHEN O, GARCIA-PAGAN JC, MAGAZ M, et al. Anticoagulant therapy for splanchnic vein thrombosis: a systematic review and meta-analysis. *Blood*, 2021, **137**(9):1233-1240.
53. MATHEW C, ZUMBERG M. Evidence-Based Minireview: Should warfarin or a direct oral anticoagulant be used in patients presenting with thrombosis in the splanchnic or cerebral veins? *Hematology*, 2021, **2021**(1):100-105.
54. NAYMAGON L, TREMBLAY D, ZUBIZARRETA N, MOSHIER E, TROY K, SCHIANO T, et al. The efficacy and safety of direct oral anticoagulants in noncirrhotic portal vein thrombosis. *Blood Adv*., 2020,**4**(4):655-666.
55. AGENO W, WESTENDORF JB, CONTINO L, BUCHERINI E, SARTORI MT, SENZOLO M, et al. Rivaroxaban for the treatment of noncirrhotic splanchnic vein thrombosis: an interventional prospective cohort study. *Blood Adv*., 2022, **6**(12):3569-3578.
56. DI NISIO M, VALERIANI E, RIVA N, SCHULMAN S, BEYER-WESTENDORF J, AGENO W. Anticoagulant therapy for splanchnic vein thrombosis: ISTH SSC Subcommittee Control of Anticoagulation. *Journal of Thrombosis and Haemostasis*, 2020,**18**(7):1562-1568.
57. NORTHUP PG, GARCIA-PAGAN JC, GARCIA-TSAO G, INTAGLIATA NM, SUPERINA RA, ROBERTS LN, et al. Vascular Liver Disorders, Portal Vein Thrombosis, and Procedural Bleeding in Patients With Liver Disease: 2020 Practice Guidance by the American Association for the Study of Liver Diseases. *Hepatology*, 2021,**73**(1):366-413.
58. ELIE PLESSIER A, GORIA O, CERVONI JP, OLLIVIER I, BUREAU C, POUJOL-ROBERT A, et al. Rivaroxaban Prophylaxis in Noncirrhotic Portal Vein Thrombosis. *NEJM Evid*., 2022;**1**(12)
59. BENMASSAOUD A, ALRUBAIY L, YU D, CHOWDARY P, SEKHAR M, PARIKH P, et al. A stepwise thrombolysis regimen in the management of acute portal vein thrombosis in patients with evidence of intestinal ischaemia. *Aliment Pharmacol Ther*., 2019,**50**(9):1049-1058.