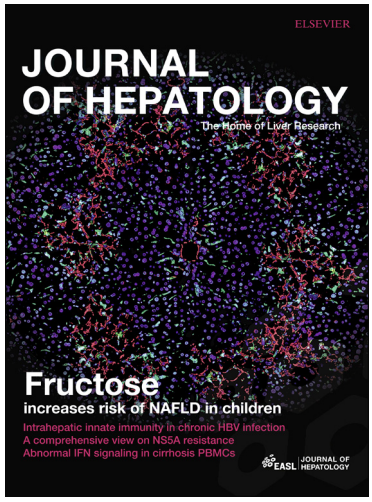

Seminar

Current knowledge in pathophysiology and management of Budd-Chiari syndrome and non-cirrhotic non-tumoral splanchnic vein thrombosis

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Current knowledge in pathophysiology and management of Budd-Chiari syndrome and non-cirrhotic non-tumoral splanchnic vein thrombosis

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Abbreviations: BCS, Budd-Chiari syndrome; CMV, cytomegalovirus; JAK2, Janus kinase 2; MPN, Myeloproliferative neoplasms; NCPVT, portal vein thrombosis

1. Introduction

Budd-Chiari Syndrome (BCS) and non-cirrhotic non-tumoral portal vein thrombosis (NCPVT) are two rare disorders, with several similarities that are categorized under the term splanchnic vein thrombosis. Both disorders are frequently associated with an underlying pro-thrombotic disorder. They can cause severe portal hypertension and usually affect young patients, negatively influencing life expectancy when the diagnosis and treatment is not done at an early stage. Yet, they have specific features that require individual considerations. The current review will focus on the available knowledge on pathophysiology, diagnosis and management of both entities.

BCS is defined as the obstruction of hepatic venous outflow regardless of its causative mechanism or level of obstruction. This obstruction can be traced to the small hepatic venules up to the entrance of the inferior vein cava (IVC) into the right atrium. Hepatic outflow obstruction related to cardiac disease, pericardial disease or sinusoidal obstruction syndrome have different pathophysiological and clinical implications and are excluded from this definition. BCS is classified as primary when the obstruction originates in the vein and thrombosis is the main cause, or secondary when the vein is externally compressed (abscess, tumor). The focus of this review is on primary BCS.

NCPVT refers to the presence of a thrombus in the main portal vein trunk and/or the left or right intrahepatic portal vein branches that may extend to the splenic vein and/or the superior or inferior mesenteric veins. Isolated splenic or mesenteric vein thrombosis are out of the scope of this review.

2. BCS and NCPVT Risk Factors

The estimated incidence of BCS and NCPVT in the absence of cirrhosis and cancer is 1 per million per year and 0.35-2.5 cases per 100 000 per year, respectively [1–3]. Most patients with BCS and NCPVT have identifiable thrombotic risk factors. However, both entities represent only ≈1% of all venous thromboembolic events, implying other local factors besides thrombophilic disorders for developing BCS or NCPVT [4,5]. Although some risk factors are shared by both entities, others are specifically related to one or the other. Indeed, myeloproliferative neoplasm and factor V Leiden mutation are prothrombotic conditions strongly associated with BCS but are less frequently observed in NCPVT [6].

Risk factors for BCS and NCPVT and their prevalence in three large European studies including patients between 2003-2005 and 2013-2014 are presented in **Table 1**. As compared with older multicentric European studies including patients between 2003 and 2005, we observed an overall stability in the prevalence of these risk factors over the last 15 years [7,8]. Work-up for these risk factors is presented in **Table 2**. Multiple prothrombotic conditions are found in 15-20% of patients with BCS or NCPVT suggesting that, when one causal factor is identified, additional factors should be investigated. Conversely, in some patients, no risk factor is found. However, in population-based databases, the reported percentage of patients with no risk factor is variable and has significantly decreased in recent studies, suggesting an improvement in their detection. Indeed, in the European study performed in 2009 analyzing 157 patients with BCS, 16% patients did not show any prothrombotic risk factor. Interestingly, when these patients were re-analyzed during follow-up, additional etiological factors were diagnosed in 12 previously unclassified patients. Nonetheless, recent data from France and Italy describe the absence of a prothrombotic factor in 30% [1] and 61% [2] of patients respectively, maybe due to the intrinsic limitations of population studies. Differences between Eastern and Western countries are found and the prevalence of prothrombotic disorders in

China seems to be very low [9]. However, over the years a higher detection of hypercoagulability conditions has been described [10], reinforcing the need of more studies aimed to uncover the causes of BCS in Asia [11]. Up to 30% of the patients with NCPVT have no identifiable etiological factor.

The next paragraphs discuss the more relevant risk factors for developing BCS or NCPVT.

2.1. Local risk factors

2.1. a. In patients with BCS, abdominal infection or inflammation is more rarely identified than in patients with NCPVT [8]. This suggests that the liver may act as a physical barrier impeding the crossing of thrombus formed in the portal venous system. A complementary hypothesis could be that activated platelets and microvesicles generated at the site of inflammation/infection are cleared within the liver by liver endothelial cells and macrophages [12,13]. However, it is still not fully understood why, even in the setting of a general prothrombotic condition, thrombosis arises at such an unusual site without any inflammatory or mechanical injury. In the European BCS cohort, the presence of local trauma, inflammatory diseases and abdominal infections was only reported in 11% of patients [8], although more recent data from the French survey, it was found to be 25% [1].

2.1. b. In patients with NCPVT, a local cause should be exhaustively investigated, as it may be present in approximately 30% of the cases. Initial imaging studies (CT or MRI) performed during the diagnostic workout should be examined carefully as they may reveal signs of gastrointestinal (appendicitis, diverticulitis, intra-abdominal abscesses or infections) or biliopancreatic pathologies including pancreatic pseudocysts and gallbladder alterations.

2.1.b.1. Abdominal infection and inflammation.

Although thrombosis by itself can induce systemic inflammatory response, abdominal infection is a classical cause for portal vein thrombosis [7]. Together with inflammatory response, activation of coagulation is an important response in the host's defense against infection to prevent the dissemination of microorganisms. This implication of coagulation in infection is illustrated by the improved survival of patients with sepsis carrying heterozygous factor V Leiden compared with those without, a finding confirmed in animal models [14]. Mechanisms by which infection triggers thrombosis have been reviewed recently elsewhere in detail [15]. Briefly, monocytes and neutrophils play an important role: monocytes express tissue factor, the primary initiator of the coagulation cascade, and release tissue factor positive microvesicles; neutrophils release neutrophil extracellular traps (NETs), *i.e.* networks of extracellular fibers, primarily composed of DNA from neutrophils, which bind pathogens and activate coagulation and thrombosis by favoring FVIIa-mediated thrombin generation and activating the intrinsic pathway. Simultaneously, platelets are activated and contribute to clot formation. Endothelial cells lose their physiological antithrombotic phenotype following exposure to inflammatory mediators and to activated neutrophils, platelets, and other cells. In addition to the cellular components, alarmins such as histones, high mobility group box 1, microvesicles and secreted granule proteins, are all important for clot formation [15]. Inflammation without infection, e.g. acute pancreatitis or inflammatory bowel disease, shares with infection many of the above mentioned features and may also contribute to thrombosis [16]. Portal vein thrombosis induced by inflammation or infection can be seen close to the site of infection/inflammation and may extend and or embolise to portal trunk and branches **(Figure 1).**

2.1. b. 2. Abdominal malignancies. Abdominal cancer is another common cause for NCPVT. The pathogenesis of the cancer-associated coagulopathy is complex and multifactorial [17]. Most importantly, tumor cells gain the capacity to activate the host hemostatic system, a phenomenon driven by the same oncogenes responsible for the cellular neoplastic transformation. Indeed, cancer tissues express different procoagulant proteins including tissue factor, factor VII and cancer

procoagulant (a molecule that, unlike tissue factor, directly activates factor X independently of coagulation factor VII), which contribute to the occurrence of the overt symptomatic coagulopathy *in vivo*. The shedding of procoagulant microvesicles is also regulated by oncogenic events and further adds to the pathogenesis of the cancer-associated hypercoagulable state. It is important to note that in one-third of patients with NCPVT exhibiting a recognized local factor an additional general prothrombotic risk factors is found [7,18].

2.2. Myeloproliferative neoplasms

Myeloproliferative neoplasms (MPNs) are chronic clonal hematopoietic stem cell disorders characterized by an overproduction of granulocytes, erythrocytes and/or platelets. Currently, seven subcategories of MPN have been identified, of which Polycythemia Vera (PV), Essential Thrombocythemia (ET) and Primary MyeloFibrosis (PMF) have the highest prevalence. Patients with MPNs are at a high risk of arterial and venous thrombotic complications [19]. A recent meta-analysis revealed that MPN are found in 40% of patients with BCS and 30% of NCPVT [7,8,20–22]. More impressively, NCPVT and BCS are 2000 and 10000 times more common in patients with MPN than in the general population [23]. This high prevalence is not restricted to Western patients, since similar figures have been reported in India, Turkey and Egypt [24–27], although less common in Chinese patients with BCS or NCPVT [9,28].

According to the current WHO 2016 guidelines, the diagnosis of PV is based on several criteria, the main criterion being an increased haemoglobin > 16.5 g/dL in men or > 16.0 g/dL in women, or a hematocrit > 49% in men or > 48% in women [29]. For ET the main criterion is a platelet count >450 x 10e9/l. In addition, typical bone marrow findings including hypercellularity and increased number of mature enlarged, pleomorphic megakaryocytes with hyperlobulated nuclei, are present.

In recent years, several underlying somatic mutations have been identified in MPN. In PV, the *JAK2*^{V617F} (JAK2) or JAK2 exon 12 mutation is found in >95% of patients. In ET and PMF, JAK2 mutations are found in 50%. More recently, mutations in the calreticulin gene (CALR), encoding for a protein present in the endoplasmatic reticulum and involved in regulation of STAT-signaling pathway, have been identified in 80% of MPN patients that are JAK2 negative [30,31]. Based on these findings JAK2, JAK2 exon12 and CALR or thrombopoietin receptor (MPL) mutations have become major diagnostic criteria for MPNs.

Compared to other MPN patients, those with BCS or PVT with underlying MPN are typically younger and more frequently female. In SVT patients who were diagnosed with MPN based on clinical, laboratory and/or morphological features of MPN in the bone marrow, as well as JAK2 mutation status, 80% of BCS and 87% of PVT patients were JAK2 positive [22]. JAK2 mutation, irrespective of other MPN features, was present in 41% in BCS and 28% in PVT patients. Subclassification of MPN in BCS patients reveals 53% PV, 25% ET and 7% PMF. For PVT patients with MPN this is 28% PV, 26% ET and 13% PMF respectively. Other MPN patients could not be classified. However, due to portal hypertension, leading to hypersplenism and hemodilution in patients with BCS or NCPVT, peripheral blood cell counts, haemoglobin or hematocrit can be normal or even reduced, even in the presence of other criteria for MPN. In patients without typical hematologic features, the JAK2 mutation can be found in 17.1% and 15.4% of the patients, respectively [22]. CALR mutations are less frequent in patients with splanchnic vein thrombosis (<5%), however they may be of help to diagnose underlying MPN [32,33]. Due to the low incidence of *CALR* mutations, it has been suggested to screen for CALR

mutations only in patients who are *JAK2*^{V617F} negative and have platelets >200 x 10^9/l with a spleen size of >16 cm [34]. MPL mutations are rare, but they may be included in the diagnostic work-up, together with *JAK2*^{V617F} , JAK2 exon 12 and *CALR* mutations [35–38]. In a small subset of patients with BCS or PVT, peripheral blood counts are normal and molecular markers for MPN are negative, and MPN diagnosis was made by bone marrow biopsy [22]. The role of bone marrow biopsy to diagnose MPN in patients with BCS and NCPVT, when all previous molecular markers are negative, remains challenging. Currently, decisions are made on a case-by-case basis. In the near future, it is possible that the introduction of extensive molecular diagnostic panels, that are able to analyze simultaneously multiple mutations, will change these recommendations.

Over the last ten years, several studies have shed light on the close relationship between MPN and BCS or NCPVT. A pivotal study reported on the existence of *JAK2*^{V617F} in endothelial cells from hepatic veins in two BCS patients [39]. Subsequently, *JAK2*^{V617F} has also been detected in splenic endothelial cells from patients with myelofibrosis [40]. *JAK2*^{V617F} was found in circulating endothelial progenitor cells in 5 out of 17 *JAK2*^{V617F} patients [41]. Interestingly, patients harboring *JAK2*^{V617F} in circulating endothelial progenitor cells were those with a history of thrombosis (splanchnic vein thrombosis, deep vein thrombosis or stroke) [41]. Moreover, *JAK2*^{V617F} mutated circulating endothelial progenitor cells showed significantly higher adhesion proficiency to mononuclear cells than normal circulating endothelial progenitor cells [41]. The exact mechanism of how *JAK2*^{V617F} in the endothelium lead to BCS or NCPVT remains unclear. Recent results from experiments using cultured endothelial cells transduced with a lentivirus expressing JAK2^{V617F} and transgenic mice expressing JAK2^{V617F} in their endothelial cells have filled this gap in knowledge [42]. In this study, James and colleagues demonstrated that JAK2^{V617F} induces the exposure at the surface of endothelial cells of P-Selectin, increasing endothelial adhesion of platelets, of neutrophils and of mononuclear cells and inducing *in vivo* thrombus formation. Interestingly, in mice, small concentrations of TNFα were required to uncover this increased adhesion, suggesting that a low level of inflammation may trigger thrombosis in MPN. Similar results were obtained by an independent group using pluripotent stem cells from patients with MPN redirected towards the endothelial lineage [43].
These results are a step forward into the understanding of the link between BCS or NCPVT and MPN. However, several questions remain unanswered: (a) Is *JAK2*^{V617F} expressed in endothelial cells only in the digestive vascular bed or ubiquitously? If ubiquitous, additional factors are needed and might be inflammatory mediators derived from the gut. (b) Why is the somatic myeloid mutation *JAK2*^{V617F} also found in endothelial cells? It is unlikely that endothelial *JAK2*^{V617F} is due to the occurrence of the mutation in a common cell of origin for endothelial cells and myeloid cells, called hemangioblast. Indeed, hemangioblasts exist in embryos, but not in adults, and *JAK2*^{V617F} related BCS and NCPVT are rare in young children [44]. Younger MPN patients with BCS or NCPVT (≈30 years) compared with those without thrombosis (≈60 years) suggest that the former exhibit hemangioblasts mutations preceding and/or favoring JAK2^{V617F}.
In BCS, *JAK2*^{V617F} is associated with worse prognostic features at presentation and earlier need for hepatic decompression procedures [21]. To determine whether endothelial *JAK2*^{V617F} enhances liver injury and fibrosis induced by hepatic venous outflow obstruction, thus worsening BCS, a surgical model of BCS to mice expressing endothelial *JAK2*^{V617F}was applied. It was observed that the expression of *JAK2*^{V617F} in liver endothelial cells did not affect liver injury or liver fibrosis, meaning that endothelial *JAK2*^{V617F} does not explain the more severe presentation of patients with BCS and *JAK2*^{V617F} [45]. The explanation should therefore be sought mostly in myeloid *JAK2*^{V617F}.

2.3. Other haematological conditions

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare acquired hematological disorder of hematopoietic stem cells which leads to complement-induced hemolysis and is strongly associated

with an increased risk of venous thrombosis [46]. BCS is one of the most common sites of thrombosis in patients with PNH, affecting 7-25%. More than one-fifth of the patients with PNH develop thrombosis in multiple sites [47].

In patients with BCS, PNH has been reported in 9-19% [48], whereas a prevalence of 0-2% has been reported in NCPVT [7]. Patients with a PNH cell population above 60% of the granulocytes have a high risk for thrombosis [49]. Testing for PNH should routinely be performed in all BCS and considered in NCPVT [46].

2.4. Systemic thrombophilic disorders

Factor V Leiden and factor II G20210A gene mutation are other frequently found prothrombotic factors in patients with BCS and NCPVT, respectively, with apparent site specificity. Indeed, prevalence of factor V Leiden is twice as high in European patients with BCS **(Table 1)** than in the general population (≈4-5%), and is commonly associated with other risk factors for thrombosis [6,33]. Similar or even higher figures have been reported in India, Turkey and Egypt, but factor V Leiden is not found in Chinese patients with BCS [27]. The G20210A mutation of the factor II gene is more common in patients with NCPVT **(Table 1)** than in the general Caucasian population (≈2%) [50]. By contrast, the role of factor V Leiden in patients with NCPVT and factor II gene mutation in patients with BCS appears to be negligible. The mechanism underlying this site specificity is unknown.
Antiphospholipid syndrome is a third common risk factor for BCS or NCPVT. However, its diagnosis is difficult due to the poor specificity of antiphospholipid antibodies in chronic liver disease [51]. Primary antiphospholipid syndrome affects males and females, but a large percentage of patients are women with recurrent pregnancy loss, while secondary APS occurs mainly in lupus, and about 90% of lupus patients are female
Precise prevalence of inherited protein C, protein S or antithrombin deficiencies is difficult to estimate since the diagnosis of primary deficiencies is based on determination of plasma levels of these coagulation inhibitors that are synthesized by the liver. In patients with liver dysfunction, a nonspecific decrease in plasma levels of these inhibitors makes interpretation of protein C, protein S or antithrombin levels, quite challenging [52].

2.5. Other Systemic risk factors

2.5.a. Behcet's disease is a rare systemic disorder clinically diagnosed by the presence of recurrent oral aphthous ulcers and genital ulcerations together with eye lesions that may also be associated mainly with the development of BCS [53].

2.5.b. Obesity. In general, obesity is a risk factor for first episode of venous thromboembolism (VTE) with an estimated overall odds ratio for VTE of 2.3 [54]. Obesity is also a risk factor for recurrent VTE with an estimated hazard ratio of 1.6, a degree of risk similar to that of other risk factors for recurrent VTE [54]. In addition to clinical factors such as immobility, obstructive sleep apnea, heart failure, and venous stasis, the major mechanisms proposed to be responsible for obesity-associated thrombosis are impaired fibrinolysis, and chronic inflammation [54]. Adipokines and proinflammatory cytokines secreted by M1 macrophages within adipose tissue contribute to the upregulation of procoagulant factors such as tissue factor and plasminogen activator inhibitor-1 (PAI-1), leading to increased thrombin generation, enhanced platelet activation, reduced fibrinolysis, and an increased risk of thrombosis.
This effect of obesity on venous thrombosis might be even more marked for NCPVT [55]. Indeed, concentrations of inflammatory molecules known to activate endothelial cells rendering them more prothrombotic, including interleukin 6, are higher in the portal vein than in the radial artery of obese patients [56,57].

2.5.c. Acute cytomegalovirus infection. Acute cytomegalovirus (CMV) infection is a cause of NCPVT [58]. Several explanations have been put forward. One plausible mechanism of CMV-induced thrombosis involves formation of antiphospholipid syndrome antibodies observed in patients in response to CMV infection [59], with resulting transient hypercoagulable state. In mice models, the immunological pathways have been studied in greater detail. Through this process, one CMV-derived peptide of particular interest, TIFI, was found to be an analog of human beta-2- glycoprotein I (b2GPI). Mice injected with TIFI developed antiphospholipid antibodies and measurable lupus anticoagulant activity, resulting in more thrombotic events than controls. Translation to humans was postulated by formation of anti-b2GPI antibodies against TIFI which would bind endogenous human b2GPI on the surface of endothelial cells leading to activation of the coagulation cascade[58,60]. The composition of CMV envelop might also contribute to thrombosis. Indeed, the CMV surface contains the necessary procoagulant phospholipid for assembly of coagulation cascade proteins, thus favoring coagulation activation [61]. A third alternative or complementary mechanism relies on the ability of CMV to directly infect endothelial cells and induce endothelial tissue factor expression, and adhesion of monocytes and neutrophils to infected endothelial cells [62,63].

2.6. Portosinusoidal vascular disease/Idiopathic Portal Hypertension. In the absence of an identifiable cause, especially when liver test abnormalities and/or hepatic dysmorphism on imaging are present, further etiologic work up may also include liver biopsy. In fact, idiopathic portal hypertension may be frequently associated with NCPVT. Among patients with idiopathic portal hypertension prevalence of NCPVT is 13-46 % and annual probability of newly developing NCPVT is 9 % [64]. Such a high incidence might be due to reduced blood flow velocity secondary to the increase in intrahepatic resistance, together with portal vein wall abnormalities. Systematic analysis of abdominal imaging of patients with portosinusoidal vascular disease revealed that portal vein abnormalities are 3 times more common than in patients with cirrhosis [65]. More detailed analyses are however lacking.

3. Natural history

3.1. BCS. Clinical manifestations of BCS are extremely heterogeneous and vary from severe forms of acute liver failure to asymptomatic forms incidentally diagnosed when studying mild alterations of liver enzymes. Generally, the diagnosis is made after portal hypertension related complications, mainly ascites. Ascites (83%), hepatomegaly (67%) and abdominal pain (61%) were the most frequent clinical manifestations in a European cohort of 163 BCS patients. In this cohort, 58% of the patients had esophageal varices [8] at diagnosis. Although less common, acute liver failure may be the initial presentation in around 5% of cases [66,67]. This wide range of clinical presentations probably correlates with both, time to establishment and extension of the hepatic vein thrombosis. A slight and gradually-formed thrombosis may be accompanied with the development of hepatic venous collaterals able to decompress at least partially, the portal venous system [68] and maintain the patient asymptomatic; a clinical form described in up to 15% of cases [8,68]. Conversely, an extensive and rapidly constituted thrombosis of the hepatic veins may produce a severe form of liver failure with renal impairment, coagulopathy and death if not adequately treated. However, in many instances, despite the initial form of presentation is acute, signs of chronic liver disease are frequently found (i.e. alterations of liver morphology with atrophy/hypertrophy of different liver segments at imaging studies). This results from hepatic veins (HV) being frequently thrombosed at different time-points in a progressive manner. Obstruction of one hepatic vein can promote the development of intra or extrahepatic collateral circulation aimed to bypass the occluded vein and the patient may remain asymptomatic. However, imaging studies may reveal chronic morphological

changes in the hepatic lobe drained by the occluded vein. If the patient is misdiagnosed and not adequately treated, recurrent thromboses in additional patent veins may happen, promoting severe hepatic congestion and appearance of symptoms, a clinical scenario potentially misdiagnosed as acute disease.

Typical laboratory findings are transaminases elevation reflecting subjacent necrosis and decrease in prothrombin time in severe cases. Biochemical characteristic of ascites are its low cellularity and high protein content [69].

Site of occlusion and clinical presentation seems to be different among patients from Western countries and Asia. In the West, data available suggest that the most frequent site of thrombosis are the hepatic veins [8,70] whereas in most of the reported cases from Asia inferior vena cava (IVC) obstruction (mainly from membrane or web) or combined IVC-HV obstruction prevails [71]. However, recent data from India indicates this is changing [26], and more cases with HV obstruction have been identified in the last decade. Regarding clinical presentation, the most frequent clinical manifestation in the West is ascites and impaired liver function [8,70] compatible with an acute course. In China, it is often diagnosed when complications of portal hypertension arise; the presence of abdominal varices and lower limb edema or ulcers [11] are more frequently described in Eastern patients.

Concomitant splanchnic vein thrombosis and BCS has also being described although incidence varies in epidemiological studies from 3.8-21 % [1].

Another clinical finding in patients with chronic BCS is the presence of benign hepatic regenerative nodules [72,73]. Although pathogenesis remains unclear, coexistence of focal defects of portal perfusion and hypervascularized areas of preserved venous outflow maybe involved in their development. The reported prevalence is highly variable and although in pathology studies has been described in around 60-70% of patients [74,75], in imaging studies is much lower(36%) [76]. Typically, benign nodules are small (under 3-4 cm in diameter), multiple (more than 10 lesions), hypervascularized and disseminated throughout the liver. Benign nodules may not only increase in number during follow-up, but may also increase in size [73]. Histologically, benign nodules have the macro and microscopic alterations of focal nodular hyperplasia (FNH) and they may display a map-like pattern of glutamine synthase expression [77]. However, because the underlying liver is not healthy, these lesions are usually called FNH-like lesions [78]. Similar to traditional FNH, these benign lesions are usually homogeneous and hypervascular at imaging and a presence of a central scar, can be found in nodules larger than 1 cm in diameter [79]. However, other imaging characteristic may be different from those of typical FNH such as hyperintensity on T1-weighted and variable signal T2-weighted MR images. In addition, benign nodules may have washout on contrast-enhanced CT or MR imaging during portal venous and/or delayed phase [79]. Less frequently, patients with chronic BCS may also develop hepatocellular adenomas (HCA) [80] and HCC [81]. Moucari et al reported a 7% five-year cumulative incidence of HCC in a large cohort of BCS patients [81]. A recent systematic review of 16 studies that reported HCC prevalence in BCS highlights the huge difference in the reported rates ranging from 2-46.2%. This is probably due, at least in part, to the heterogeneity of the studies included: geographical differences, dissimilar follow-up time (ranging from 4.5 to 11.6 years), diverse enrolling periods for the studies using different diagnostic tools and treatments and different survivals rates [82]. Risk factors for developing HCC are not well defined, although a higher prevalence has been described in patients with long-term IVC obstruction when compared to

patients with isolated HV involvement [81,83]. Frequently, HCC appears as a hypervascular, heterogeneous at arterial phase and hypoecoic on portal and delayed phase's lesion. However, radiological pattern of HCC in patients with BCS is heterogeneous and differential diagnosis with benign regenerative nodules remains a challenge. As previously mentioned, benign nodules in BCS may present the typical radiological appearance and vascular enhancement pattern of HCC in cirrhosis [81,84,85] and may increase in number and size over time as part of natural history [73]. A recent study specifically evaluating radiological pattern of nodules in BCS, showed that 29% of benign lesions presented washout and up to 18% of benign lesions greater than 1cm showed both washout and arterial phase hyperenhancement [86]. Therefore, HCC diagnosis in BCS is always a challenge and should never rely only on imaging criteria and should require histological confirmation. Although alpha-fetoprotein above a cutoff value of 15 nm/mL has been suggested to be an useful biomarker for HCC in the setting of BCS [81], it needs to be validated in larger cohorts. Surveillance for HCC in patients with chronic BCS is recommended [18], and although specific data are lacking, the same recommendations as in cirrhosis with US every six months remains the most endorsed strategy.

3.2. Recent NCPVT. Recent NCPVT relates to the new occurrence of a thrombus in the portal venous axis in a patient with a previous patent portal vein. However, it may also occur in patients who exhibit partial portal vein thrombosis, where progression of thrombus is noted. **(Figure 2)**. Various imaging modalities including color Doppler ultrasound, computed tomography and MRI can be used to identify the presence of a thrombus, collateral circulation, or a dilated portal vein with accuracy rates ranging from 88-98%, with sensitivity and specificity of 80–100%. Using grey-scale ultrasound, acute portal vein thrombus typically appears as heterogeneous, mainly hyperechoic material in the vessel lumen. The advantage of CT-scan in this case relates to improved ability to detect possible etiologies or complications. Acute PVT on CT appears with increased attenuation and lack of enhancement, with or without inhomogeneities in portal venous and parenchymal hepatic perfusion. On MRI, the portal vein may appear with edge enhancement because of blood flow surrounding the thrombus or because of an inflammatory response of the venous wall. T1-weighted images may reveal isointense thrombus compared to muscle, while T2 images may show a hyperintense signal [87,88]. The anatomical degree of occlusion of these vessels may be total or partial. While the occlusion by the thrombus may not be complete in imaging studies, the hemodynamic consequence of partial thrombosis may be relevant. Indeed, the portal vein can be compared to a relatively rigid tubular structure [89] in which the Poiseuille's law predicts a decreased blood flow rate proportional to the radius elevated to the fourth power. Thus, a thrombus maintaining 20% of the vessel radius free will result in a >98% decrease of the flow rate (http://hyperphysics.phy-astr.gsu.edu/hbase/ppois2.html). Consequently, partial portal vein thrombosis occupying more than 80% of the lumen corresponds to a nearly complete obstruction **(Figure 3).**

At presentation, NCPVT may involve an extensive obstruction of the portal vein and its right and left branches, superior mesenteric vein, and splenic vein in approximately one third of patients, while obstruction of the portal vein or of its two branches was found in 87% of cases. Moreover, only a single obstructed portal vein branch (with or without splenic or superior mesenteric vein obstruction) was reported in 12% and the splenic or superior mesenteric vein were obstructed in 43% and 58% of patients, respectively [7]. Acute abdominal pain may be the initial manifestation of recent NCPVT. However, the intensity is variable among patients. Recent NCPVT may also be completely asymptomatic, delaying diagnosis for long periods until portal cavernoma develops. Liver function

test abnormalities are usually mild and transient. A systemic inflammatory response syndrome is often present in cases of recent NCPVT due to inflammation related to thrombosis but recognized local or systemic infection is identified in only 20% of these cases. Transient ascites, often of low abundance (hence clinically non relevant unless infection develops) and visible only using ultrasound, CT or MRI, is present in half of the patients [7].

Mesenteric infarction is the most severe and immediate complication of recent NCPVT. Its 60% mortality rate is high in the absence of anticoagulant treatment. Extended resection of small bowel is sometimes necessary and is associated with a significant risk of short bowel syndrome. Early initiation of anticoagulant therapy is associated with a very low incidence of this complication [7]. The diagnosis of venous mesenteric infarction is difficult because the clinical, biological and radiological manifestations are not specific. Severe and persistent abdominal pain, despite full anticoagulant treatment, signs of organ failure (shock, renal failure, metabolic acidosis with elevated arterial lactate), abundant ascites, and/or the presence of blood in stool must evoke the diagnosis of mesenteric infarction. Type 2 diabetes has been identified as a risk factor for mesenteric infarction [90], with a recent study identifying 3 readily available criteria predictive for irreversible intestinal ischemic injury requiring resection in the setting of acute mesenteric ischemia, namely organ failure, serum lactate levels >2 mmol/L and bowel loop dilation on computerized tomography scan. The presence of only one of these criteria was associated with a 40% risk of in irreversible intestinal ischemic injury requiring resection at two- months [91].

The most common manifestations of chronic NCPVT are related to the presence of portal hypertension. Esophageal varices may develop in nearly half of patients [92], whereas other complications, including rectal or ectopic varices, large portosystemic collaterals and splenomegaly, frequently occur during the course of the disease. In general, hepatic function is preserved, in apparent contrast with obvious manifestations of portal hypertension. The most common complications are variceal bleeding, recurrent thrombosis and biliary complications. The risk of variceal bleeding is, as in cirrhosis, higher in medium or large varices and in the presence of red signs. The recurrence or extension of thrombosis may often be asymptomatic and is consequently not only underdiagnosed, but also poorly evaluated. In chronic NCPVT, ascites, hepatic encephalopathy, and bacterial infections are rare and most often transient. They occur preferentially as complications after gastrointestinal bleeding [93]. If specifically looked for, minimal hepatic encephalopathy (MHE) is frequently present among patients with extrahepatic portal vein obstruction [94,95] but their clinical impact is unknown. Hepatic nodules of the "HNF-like" type were found in 21% of adults patients with cavernomatous transformation of the portal vein when studied by MRI [96]. However, the risk of hepatocellular carcinoma is low. Cardiovascular complications such as hepatopulmonary syndrome [97] and pulmonary arterial hypertension [98] have been reported.

Portal cavernoma cholangiopathy is characterized by abnormalities of the intra- and extrahepatic bile ducts. It is the consequence of the extrinsic compression of bile ducts by porto-portal collateral veins (cavernoma) and/or of an ischemic injury of the bile ducts by thrombosis of the venous plexus of the biliary tree [99]. Biliary tract abnormalities may be observed at cholangio-MRI in 77-100% of patients. Portal cavernoma cholangiopathy is most frequently asymptomatic and can be associated with initially mild abnormalities of liver enzymes, particularly cholestatic markers alkaline phosphatase and gamma glutamyl transferase. Severe biliary manifestations including biliary colics, cholecystitis, obstructive jaundice, cholangitis, pancreatitis, are rare, occurring in only 5-30% of cases [99–101].

4. Diagnostic strategy. Staging and prognosis

4.1. BCS: Due to heterogeneous clinical presentation, BCS should be suspected and discarded in any patient with acute or chronic liver disease, especially when its etiology is unknown and/or a prothrombotic condition underlays. The key feature for the diagnosis of BCS is to demonstrate obstruction of the hepatic venous outflow. Non-invasive imaging techniques (Doppler ultrasonography, CT or MRI) are the mainstay for an adequate diagnosis. Doppler ultrasound, performed by an experience operator, has a sensitivity >75% and should be the first choice option [18]. MRI and CT evaluation have a role in diagnostic confirmation or in the absence of an experienced US operator. Both CT and MRI are also useful for mapping intra and extrahepatic collateral networks, identify associated PVT, and planning future treatment. Numerous imaging features have been described in patients with BCS [102,103]. Direct signs included visualization of the occluded veins, presence of endoluminal thrombus in HV, non-visualization of the HV, stagnant or inverted venous flow and collateral networks and are more frequently found in acute BCS. Chronic forms are usually associated with indirect signs such as hypertrophy of the caudate lobe, and a caudate vein >3 mm and concomitant atrophic lobes, dysmorphic liver, parenchymal heterogeneity, heterogeneous enhancement and benign regenerative nodules. CT and MRI can also identify a rapid clearance of contrast from the caudate lobe and patchy hepatic enhancement due to uneven portal perfusion. Acutely occluded veins demonstrate no enhancement following contrast administration on CT scan, whereas in MRI displays hyperintensity on spin echo and signal void on gradient echo sequences. A multidisciplinary approach is essential, as diagnostic efficiency is augmented when the radiologist is aware of the suspected clinical diagnosis.

Liver damage in BCS is variable, and the histological changes (congestion, coagulative necrosis or simple loss of hepatocytes without inflammatory infiltrates and/or fibrosis) are not pathognomonic and do not reflect the severity of the disease. Therefore, liver biopsy is not usually necessary for the diagnosis. The solely scenario when biopsy is necessary is to confirm BCS due to small intrahepatic veins obstruction in the presence of preserved large veins on imaging techniques [18].

Similarly, hepatic venography is only recommended if diagnosis remains uncertain despite the above investigations and classically reveals a spiderweb pattern, formed by a rich collateral circulation.

4.1. a. BCS Staging. Prognostic scores. The prognosis of BCS has dramatically changed in the last decade, with an improvement in survival as a consequence of a better management based on anticoagulation, TIPS and liver transplantation [70]. Better outcomes may also be related to a higher degree of suspicion leading to early stage diagnosis and consequently superior treatment response. Indeed, 3-years mortality in the 60s reached 90% [104], whereas the current expected 5-years survival is above 80%[8,70]. Information regarding prognosis of BCS relies mostly on retrospective studies [68,104–107]. The largest prospective multicenter cohort of consecutive diagnosed patients with BCS comes from the European registry EN-Vie. 157 patients were prospectively diagnosed during a 2 year period and followed up for almost 5 years, reporting a 5-year survival of 85% [70].

As shown in **Table 3**, there are several parameters or combination of them that are used to predict BCS prognosis. Liver function test such as Child-Pugh [108] and MELD score [109] are able to predict outcome in BCS. BCS-specific prognostic scores [67,104,106] are useful for predicting transplant-free survival and invasive therapy-free survival and have been externally validated [70,110]. The BCS-TIPS PI score was developed to identify patients that would not tolerate TIPS. Indeed, this score identifies

patients with poor outcomes despite TIPS, suggesting that liver transplant may be a better alternative. Nevertheless, despite showing a statistically significant association with survival and, permitting comparison among different cohorts, none of the BCS specific PI has excellent discrimination capacity and cannot be used to guide individualized management [70,110].

Histological features and transaminase levels have also been evaluated as prognostic factors. Pathology lesions are not useful to predict outcome in BCS due to heterogeneity of the lesions and the non-homogeneous pattern [67,108]. The largest analysis of western patients with ALF due to BCS included 19 patients registered in the US Acute Liver Failure Study Group and showed poor outcomes. They evaluated patients from 1999-2015 and demonstrated that increased transaminases (AST, ALT) were predictors of bad outcome, marking the severity and/or acuity of the damage. While mortality was high at 58%, cases reported after 2010 had a better outcome due to the improved diagnosis and management [111]. Moreover, in a retrospective study including 96 patients with primary BCS, ALT ≥5 × ULN was associated with more severe clinical presentation, a higher Child-Pugh score, Clichy score, Rotterdam BCS score, and higher mortality. However high levels of ALT that decrease rapidly can be considered as a marker of imminent improvement in liver function, reflecting a good outcome [112].

4.1.b. NCPVT Staging and Prognosis. Following recent thrombosis of the portal vein, and in the absence of recanalization, a network of porto-portal collateral veins, defined as cavernoma, may develop already within a few weeks. The presence of cavernoma is a direct consequence of NCPVT, and this term suggests that thrombosis of the portal vein was not recent. Moreover, the presence of portal vein cavernoma *per se* does not imply chronicity of this condition. Porto-systemic collateral veins may also develop and contribute to the complications of portal hypertension. An accurate diagnosis and staging of NCPVT is important, because it represents the basis for its management. In addition, the purpose of correct classification is to guide therapeutic decisions aimed at obtaining recanalization and at preventing the extension and/or the relapse of portal vein thrombosis and of possible complications. Given the complexity of the clinical picture related to NCPVT, including a high number of possible etiologic factors, and different degrees of obstruction and extension of the thrombosis, the need for an individualized, yet precise approach appears crucial. For these reasons, several classification models have been proposed. One of the most frequently used systems is, however, only based on localization and extension of thrombosis [113]. More recently, Sarin et al. have proposed a new classification [87] , which takes into account not only the location and extension of the thrombus, but also the mode of onset and diagnosis of the thrombosis (recent or chronic), its type of presentation (signs and symptoms), and its possible underlying liver disease (cirrhosis or normal liver). The purpose of this classification **(Table 4)** is to serve as a starting point to report uniformly NCPVT, to better define clinical endpoints, and to compare future studies. The prospective evaluation of this classification should allow a risk stratification to apply therapeutic or preventive strategies.

5. Treatment and Management of complications

5.1. Stepwise Treatment for BCS. Unfortunately, randomized clinical trials comparing different treatment options for BCS are still lacking. Recommendations are based on clinical experience, retrospective studies and expert consensus. Based on these, the current treatment strategy of BCS relies on progressively escalating invasiveness. The first step is based on medical management aimed

at treating portal hypertension related complications and the underlying disease. If no improvement in BCS symptoms or even further deterioration is observed, the next step is devoted to correcting hepatic venous outflow obstruction as described below.

5.1.a. Portal Hypertension complications. Because no specific studies exists in patients with Budd-Chiari, the current recommendation is to treat and prevent portal hypertension related complications as recommended for patients with cirrhosis [18,114].

5.1.b. Treatment of the underlying disease. The underlying disease should be promptly diagnosed and specifically treated. This usually requires a dedicated multidisciplinary team of hepatologist, hematologist and specialists in systemic disorders. As an example, early recognition and adequate treatment of underlying MPN, PNH or Behcet syndrome may markedly influence the outcome of the patients and/or prevent thrombosis progression [115,116].

5.1.c. Correcting hepatic venous outflow obstruction. Stepwise Treatment (Figure 4)

Although there are small retrospective studies showing good outcomes after initial management with surgical shunts [117–119], most recommendations support the gradual escalation of management from least to most invasive. [18,107,114].

5.1.c.1. Anticoagulation. The stepped approach starts with medical treatment using anticoagulation, in an attempt to achieve recanalization but mainly to prevent thrombosis progression, together with the treatment or prevention of the complications of portal hypertension. Anticoagulation should be administered to all patients with BCS, even those without an underlying prothrombotic disorders or in those that are initially asymptomatic. Long-term anticoagulation, started as soon as possible after the diagnosis, achieves a five-year intervention free survival with disease-control in 25-30% of patients, particularly in mild/moderate cases. This is observed both in Western and in Asian patients [8,69,99,112]. Either low molecular weight heparin (LMWH) or vitamin K antagonist (VKA) are the treatment of choice to initiate anticoagulation. Therapeutic doses of LMWH should be given together with VKA until the therapeutic range (INR between 2-3) is achieved. It should be noted that long-term LMWH cannot be used in patients with severe renal failure Unfractionated heparin should be avoided due to the high incidence of heparin-induced thrombocytopenia in BCS patients [107]. DOACs are used to treat thrombotic diseases in other vascular areas and, although, there are currently only a few reports [121], this option can also be considered in BCS patients with normal liver function. However, DOACs are not registered for this indication, and therefore, if used, this need to be done with caution, especially in case of additional renal failure.

5.1. c.2. Restoring Hepatic Venous Outflow.

5.1.c.2.a. Thrombolysis. The experience of thrombolysis in BCS is limited. Recombinant tissue plasminogen activator, streptokinase or urokinase have been used. These agents can be instilled through a peripheral vein or locally after catheterization of the thrombosed vein. There are no studies comparing the efficacy of local vs. systemic infusion. No systematic reviews have been published to evaluate the efficacy and risks of thrombolysis in BCS. A narrative review by *Sharma et al.* indicates that the best results are achieved in patients with a recent and incomplete thrombosis who are treated with local and early infusion combined with another interventional procedure (e.g.

angioplasty, stenting) to restore venous outflow [122]. In the published series bleeding complications of thrombolysis were major and can even be fatal [123]. Hence, this therapeutic option is contraindicated in patients with a potentially hemorrhagic condition, or patients who have had an invasive procedure, including paracentesis, in the previous 24 hours. In summary, thrombolysis should only be attempted in select cases with acute or sub-acute BCS, at experienced centers [18].

5.1.c.2.b. Percutaneous angioplasty. In some instances, BCS is due to partial or segmental stenosis in the cranial part of the HV or at the suprahepatic IVC [124]. In these cases, percutaneous transluminal angioplasty with or without stenting restoring the physiological hepatic outflow is effective and safe. This makes mandatory trying to identify such type of patients once the diagnosis of BCS is established. In European patients, segmental stenosis are found in only a low percentage of patients and therefore, this technique only benefits a small proportion of BCS patients (10% in the Envie cohort) [70]. In Asia, where IVC obstruction predominates, the reported applicability is much higher, and combining angioplasty and stenting can achieve patency in >80% at 5 years [125].

Angioplasty is the first step to restore hepatic outflow. However, post-angioplasty re-stenosis may occur necessitating subsequent angioplasties. While stenting may reduce re-stenosis, stent misplacement may make future TIPS or liver transplantation more challenging. In the European cohort, 22 patients underwent angioplasty, 13 patients were treated with angioplasty, 7 with thrombolysis and 2 with both as first invasive treatment. In 6 of these 22 patients, a vascular stent was placed at the time of angioplasty and in total 14 patients (64%) required further treatment (TIPS in 12 and OLT in 2 patients)[70].

A recent retrospective study performed in China suggests higher efficacy and long-term patency of retrievable stents (retrieved after a median of 15 days). However, these results should be taken cautiously due to the short duration of stenting and because of a significant number of retrievable stent patients exhibited acute thrombosis (66.7% vs 2.4%, P= 0.0004) and hence, were additionally treated with thrombolysis [126].

5.1.c.2.c. Derivative techniques. When the above-mentioned treatments are not possible or fail to solve the obstruction of the hepatic blood flow, the portal system can be converted into an outflow tract by derivative techniques.

Before the 90s, surgical shunts were the only derivative technique available. Mesocaval shunt was the most frequent shunt used, preferred to the porto-caval side-to-side shunt since it is easier to perform in the setting of caudate lobe hypertrophy [127]. In the setting of IVC compression, the presence of an infrahepatic caval pressure >20 mmHg or a gradient between it and the right atrium of 15 mmHg, are predictive of inadequate shunt function, unless the stenosis/compression of the IVC is simultaneously corrected [127]. In cases when the obstructed IVC cannot be bypassed, a meso-atrial shunt may be an alternative [128]. Decompressing the cava together with the portal venous system through a Meso-Cavo-Atrial shunt has been proposed as a better alternative to a meso-atrial shunt [129]. Overall, surgical shunts are associated with significant morbidity-mortality, and has not demonstrated a clear survival advantage [104,130]. However, in patients surviving surgery in whom the shunt remains patent, the outcome is excellent [119,131].

Since the 90s, in most places surgical shunts have been replaced by the less invasive transjugular intrahepatic portosystemic shunt (TIPS). TIPS has demonstrated to be more effective in maintaining

patency and is associated with lower morbidity and mortality than surgery in patients with failure to medical treatment or when recanalization has failed [18,114]. However, very good outcomes in selected patients with BCS treated with surgical portal decompression performed early after diagnosis have been reported [132] . Moreover, in cases with HV and concomitant IVC thrombosis or severe compression of the IVC by an enlarged liver, as mentioned, the traditional meso-caval surgical shunt may be ineffective and TIPS becomes a more feasible option [119,133]. TIPS primary patency rate using PTFE-covered stents is 67% at 2 year follow-up [105]. TIPS, however, should be performed in experienced centers due to increased difficulty and morbidity compared with patients with cirrhosis. Indeed, a transcaval approach for the portal vein puncture may be needed in up to 60% of patients given inaccessibility of the hepatic vein [105,134]. In a European prospective cohort of 157 patients with BCS, at 5 year of follow-up, 40% of patients have required TIPS because of failed medical treatment, most of them (73%) during the first 6 months after diagnosis. In this cohort, 5-year survival without liver transplantation was 72% [70]. The use of TIPS at an earlier time point of the recommended stepwise management has been recently suggested [135]. However, there are no direct data supporting this recommendation. In addition, in the study by Seijo et al [70], in the 62 patients receiving TIPS following the stepwise strategy, the median time from BCS diagnosis to TIPS was one month (range 0-38 m). Interestingly, no differences in survival were observed in patients with TIPS received before or after the first months after diagnosis and similar results were observed when the cut-off time was 3 or 6 months after diagnosis. These results suggest that the stepwise strategy is effective and safe provided that patients are followed closely and TIPS is implemented soon after no improvement, hastening further deterioration. In addition, following this strategy, instead of using TIPS to all symptomatic BCS patients; it will prevent a significant number, the potential side effects of TIPS without adding benefits to medical treatment. Evaluation of some criteria two weeks after treatment initiation have been proposed to recognize the optimal time to move along he treatment algorithm in a given patient **(Table 5).** However, this is always a challenge [18]. This is why these patients are best managed in referral centers.

In Asian countries where IVC obstruction prevails, TIPS placement is not as frequent as in Europe. However, the use of TIPS in Asia is increasing, and available reports show similar positive results as in the West [136–140].

Recent data suggest that liver elastography measurements may be a good non-invasive test to evaluate the effectiveness of liver decompression. Currently this has been evaluated after invasive techniques such as balloon angioplasty (with or without stenting) in a small number of patients, showing a reduction of elastography measurement when the liver is adequately decompressed [141]. It is possible that this technology can also be used to monitor the response to medical treatment, although more studies are needed.

5.1.c.2.d. Liver transplantation (LT): indications and post-LT approach. LT represents the last therapeutic option for patients with BCS and failure to other less-invasive therapies. Although it may be a first step in patients with acute hepatic failure as initial presentation [142], TIPS should be considered while waiting for LT as it may foster fast improvement and potentially avoid transplantation. It may be acknowledged that LT in BCS patients represents a technical challenge mainly because of the presence of retroperitoneal fibrosis related to HV thrombosis, liver enlargement and adhesions. In addition, the classical “piggyback” technique for anastomosis

becomes more challenging due to the increased size of the caudate lobe and occlusion of the HV ostia. TIPS did not worsen prognosis after LT in BCS patients [105,143].

Five-year survival rate after LT has improved over the years [144–147]. A large European study showed actuarial overall survivals of 76%, 71% and 68% at 1-year, 5-years and 10-years respectively [145]. Notably, outcome is similar as in patients treated with TIPS (88% and 78% at 1 and 5-year OLT-free survival respectively) [105], reinforcing the benefit of the stepwise approach, selecting patients who undoubtedly require LT and saving the organ for other indications.

Once LT is considered, it will be the cure in cases of inborn errors of metabolism, such as antithrombin deficiency or homozygous factor V Leiden mutation. However, other prothrombotic disorders, such as MP or HPN, can be a contraindication and/or impact post-LT outcome.

MPN is not a contraindication for LT, since optimal treatment of these patients yields excellent long-term survival. Since patients with MPN have mature and well-differentiated granulocytes, the risk of infectious complications after LT is not higher than in LT patients without MPN. Several case series and retrospective studies [142,145,148] did not reveal evidence for accelerate MPN progression (leukemic transformation) after LT in a 10-year follow up period, and survival rate was excellent (71 - >90% over 3 years, comparable to non-MPN patients with BCS).

MPN patients who have undergone liver transplantation for BCS should be treated with anticoagulant drugs and/or aspirin, and with anti-proliferative treatment (hydroxyurea). Several groups report excellent outcomes in MPN patients treated only with hydroxyurea and aspirin after LT, without recurrence of BCS [149,150]. In another study however, recurrence of BCS and other thrombotic complications were reported despite anticoagulant therapy with warfarin [151]. Based on the available data and the severity of thrombotic complications if they occur, it is advised to treat patients with anticoagulants (warfarin), aspirin and hydroxyurea in order to prevent recurrent thrombotic complications after LT. In case of high risk of bleeding or development of bleeding complications, it is suggested to give at least aspirin and anti-proliferative treatment, avoiding vitamin K antagonists.

When the underlying disorder is PNH, LT may be more challenging, as patients may present or develop aplastic anemia, requiring an allogenic stem cell transplant, thereby increasing the risk of infection. Some cases of liver transplantation for BCS in patients with PNH have been reported, sometimes complicated by recurrence of BCS [152,153].

Although evidence comes from small series of cases, living donor liver transplant is a viable choice with acceptable survival rates (>70% at 5 years) [154,155].

5.2. **Treatment of Recent NCPVT**

The aim of therapy for recent NCPVT is to prevent the extension of the thrombus to mesenteric veins and intestinal infarction. In addition, therapy for recent NCPVT must try to achieve portal vein recanalization to prevent the development of portal hypertension.

5.2.a. Anticoagulation. Anticoagulation is the key treatment of recent NCPVT. Although randomized controlled trials are lacking, a landmark European prospective multicenter study reported no thrombus extension to the splenic or mesenteric vein in 95 patients with recent portal vein

thrombosis. They were treated with early administration of low molecular- weight heparin, and rapidly replaced by oral anticoagulation with vitamin K antagonists, targeting an international normalized ratio of 2-3 [7]. Only 2/95 patients developed intestinal infarction. There was no mortality related to NCPVT or its treatment. Full recanalization of the vein was only obtained in one-third of the patients by 6 months of continued anticoagulation therapy. Interestingly, with a prolongation of anticoagulation, there was no further recanalization of the portal vein, but continued recanalization of the splenic and superior mesenteric vein. A year after the onset of NCPVT, 40% of the patients had a permanent obstruction of the portal vein and portal cavernoma [7]. These findings independently validated previous retrospective single center studies [156–159]. Among baseline factors, splenic vein obstruction, ascites [7] and delay in initiating anticoagulation [159] have been associated with the absence of portal vein recanalization. Adverse events on anticoagulation therapy did not obviously differ from those expected from natural history [7]. Mortality rate was 2% after a median follow-up of 8 months after recent NCPVT diagnosis, and was not related to bleeding or NCPVT [7].

Recently, few cases of initial treatment of recent NCPVT with direct oral anticoagulants instead of low molecular weight heparin have been reported [160–162]. The largest study compared 26 patients treated with direct oral anticoagulants with 23 treated with enoxaparin. Although interpretation of the data should be cautious, since more than half these thrombotic events occurred in a cancer setting, recurrence and major bleeding rates were not different between patients treated with direct oral anticoagulants and with enoxaparin [162].

5.2.b. Antibiotics. Antibiotics are given in patients with NCPVT triggered by an abdominal infection. When septic pylephlebitis is diagnosed, prolonged treatment with antibiotics adapted to isolated bacteria or to anaerobic digestive flora is necessary [18]. Recent data suggest that oral antibiotics should be given in patients with acute mesenteric ischemia, since their use is associated with a lower risk of irreversible transmural intestinal necrosis [91].

5.2.c. Treatment of underlying causes. Retrospective studies suggested that rapid identification and treatment of risk factors for NCPVT might favorably influence NCPVT outcome. Indeed, in a retrospective multicenter study including 109 patients with MPN and NCPVT (n=63) or BCS (n=46), cytoreductive therapy was associated with less common severe liver-related events or vascular complications [115]. Although specific data on NCPVT are lacking, etiological treatment in addition to anticoagulation in patients with other vascular liver diseases, such as corticosteroids and/or immunosuppressive therapy in Behcet's disease [116], or eculizumab (a humanized monoclonal antibody directed against the terminal complement protein C5) in paroxysmal nocturnal hemoglobinuria [163], improves patients' outcome.

5.2.d. Thrombolysis and/or interventional radiology. Pharmacological thrombolysis (local or systemic) has been proposed as an adjunct to anticoagulation. However, severe procedure-related morbidity and fatalities have been reported with recannalization rates similar to those achieved with anticoagulation alone [123,164,165].

Recent reports suggest better results with a combination of transjugular thrombectomy, local fibrinolysis and/or transjugular intrahepatic portosystemic shunt, as summarized in **Table 6**. Interestingly, patients treated with this approach rarely developed portal cavernoma and signs of portal hypertension. This invasive strategy does not fit to all patients with acute NCPVT, but might be useful in patients with progressive thrombosis, clinical deterioration despite anticoagulation, or

with a low likelihood of recanalization following therapeutic anticoagulation. This strategy might also be considered in patients with superior mesenteric vein thrombosis and features predictive of irreversible intestinal ischemic injury, as detailed above [91].

5.2.e. Surgery. Surgical thrombectomy is currently not an option for NCPVT given the invasiveness of the procedure, the low rate of recanalization achieved, and the favorable outcome yielded using only anticoagulation [18].

Surgery has two main indications in patients with acute NCPVT: (a) treatment of a local factor responsible for NCPVT; (b) suspicion of mesenteric infarction [166].

5.3. Treatment of Chronic NCPVT

5.3.a Management of complications of portal hypertension.

In general, the current recommendation is to treat and prevent portal hypertension related complications as it is recommended for patients with cirrhosis [18,114].

5.3.a.1 Esophageal varices. In a recent study that included 178 non-cirrhotic patients with NCPVT, the natural history of esophageal varices appeared similar to that observed in patients with cirrhosis [92]. In patients without varices at inclusion, the risk of developing them was 2% at 1 year and 22% at 3 years. Progression from small to medium or large varices was 13% at 1 year, and 54% at 5 years. In patients with medium or large varices, who received adequate prophylaxis, the risk of bleeding was 9% at 1 year and 32% at 5 years. Studies comparing head to head different therapeutic strategies are lacking, small sized or with mixed different portal hypertension etiologies. Therefore, there are not strong data on the real impact of those treatments in the natural history of the disease [18]. However, it has been suggested that the use of non-selective beta-blockers was associated with a decreased risk of bleeding [167] and improved survival [168], and that incidence of bleeding was similar using beta-blockers or endoscopic band ligation (32% and 25%, respectively) [92,169]. Currently, the same principles related to the use of beta-blockers and endoscopic therapy in patients with cirrhosis should also be applied in patients with extrahepatic portal vein obstruction [114].

In patients treated with anticoagulants for extrahepatic portal vein obstruction, the incidence (7.4%) and severity of bleeding after endoscopic band ligation were not significantly different compared to that observed in non-anticoagulated patients [170] . Similarly, one study in cirrhotic patients suggesting that LMWH during prophylactic endoscopic band ligation does not increase the risk of bleeding and death [171]. Although more results in the issue are needed, these studies seem to challenge the current accepted concept that anticoagulation should be delayed until adequate treatment of variceal bleeding has been established.

5.3.a.2 Anticoagulation. The indications for the administration of long-term anticoagulant therapy in patients with chronic NCPVT remain in part controversial and are based on retrospective series in adults[172]. Anticoagulants have been associated with decreased risk of thrombosis extension or recurrence in three studies and improved survival. Recurrence of thrombosis was associated with the presence of a pro-thrombotic condition. In patients with a history of intestinal infarction, long-term anticoagulation therapy was associated with a decreased risk of recurrent thrombosis [167,168,173,174]. No change [167], or a mild increased risk of gastrointestinal bleedings [175], in patients under anticoagulation treatment, has been reported, however without

increasing bleeding severity [167,175]. The most commonly used anticoagulants are unfractionated heparin as initial anticoagulant treatment, low molecular weight and vitamin K antagonists. One significant drawback of unfractionated heparin is the occurrence of heparin-induced thrombocytopenia that has been reported in up to 20% of patients with NCPVT associated with a myeloproliferative disorder [176].

5.3.a.3 Derivative techniques. The insertion of a TIPS in patients with cavernoma may be indicated in case of recurrent bleeding and of refractory ascites not manageable medically or endoscopically. TIPS in patients with chronic portal vein thrombosis is usually technically difficult or impossible to perform. Although this has more extensively been evaluated in patients with cirrhosis with associated portal vein thrombosis, risk factors for failure in TIPS procedure is the lack of identification of the intrahepatic portal vein branches, presence of portal cavernoma without identification of the portal vein trunk, and lack of a clear "landing" zone at mesenteric or splenic territories [177]. Long-term outcome of TIPS in patients with chronic portal vein thrombosis is unknown. In some patients with chronic portal vein thrombosis, recanalization of the portal vein restoring physiological portal blood flow without the need of TIPS could be a better therapeutic strategy **(Figure 5)**. Contemporary imaging techniques now make recanalization of the portal vein more possible.

5.3.a.4. Management of NCPVT in the pediatric population. Chronic NCPVT in children, in spite of good tolerance of symptoms in case of portal hypertension and variceal bleeding, is not a harmless condition. Medical care and hospitalizations may be often required due to a number of possible complications including neurological or cognitive deficits, somatic growth retardation, progressive portal cavernoma cholangiopathy, resulting in an impaired quality of life [178]. In the pediatric population, the meso-Rex shunt or the mesenterico-left portal vein bypass, in contrast to porto-systemic shunts which divert portal blood flow into the systemic circulation, may restore blood flow in a closest possible physiological manner and has been associated with resolution of portal hypertension. In addition, other complications such as coagulopathy, neurocognitive defects from hepatic encephalopathy, growth retardation and portal cavernoma cholangiopathy, may be partially or completely corrected after this procedure [179,180] . As a consequence, the meso-Rex bypass should be considered the treatment of choice in children with chronic PVT, and its feasibility should be evaluated in tertiary hospitals. In children presenting with intra-hepatic cavernoma, or with poor quality splanchnic veins, surgical options are limited, but since portal cavernoma is not a contraindication to liver transplantation, children with severe clinical manifestations of chronic NVPVT should be evaluated for liver transplantation, including living donor related procedures. While the preferred non-surgical options for the treatment of varices remain endoscopic band ligation and non-selective betablockers, no consensus is currently available [181].

5.3.b. Invasive treatment: Surgery/Portal Vein recanalization. Portal vein recanalization followed by TIPS (PVR-TIPS) was initially developed in liver transplant candidates to allow a physiological anastomosis between the graft and the recipient portal vein [182,183]. The transplenic approach to access the thrombosed portal vein was shown to be superior to the transhepatic approach with a high success getting PVR and fewer side-effects [183]. The technique has been described in detail describing long-term patency of the recanalized vein in the most recent report [183,184]. The technique for PVR-TIPS has now become perfected and it is easily reproducible. In brief, the films of a potential PVR-TIPS patient are reviewed and cavernoma and chronic NCPVT identified **(Figure 6a)**. In

the coronal plane, an intraparenchymal splenic vein that flow in-line to the main splenic vein is identified and punctured. A 5-French system is advanced to the junction of the splenic and portal vein, with subsequent splenoportography, demonstrating confirming cavernomatous transformation **(Figure 6b)**. The diminutive portal "chord" is identified, with retrograde accessing through this chord into the right portal vein. A 10 mm snare is deployed and used as a target for standard TIPS puncture. An exchange length glide wire is used for through-and-through access out the spleen. From there, proper measurement from the hepatic vein to 1 cm into the main PV is made followed by stent placement. Angioplasty of the chronically thrombosed PV will immediately reestablish flow **(Figure 7a)**. With time, the vein will remodel and behave normally **(Figure 7b)**. Most patients treated with PVR with TIPS has been done in patients with cirrhosis. However, some patients without cirrhosis has also been treated. Indeed, a recent study shows good results performing PVR without the need of TIPS provided the portal vein thrombosis does not occlude distal intrahepatic portal vein branches [185,186]. However, the potential role of PVR-TIPS in this scenario should be further investigated.

5.3.c. Management of Portal cavernoma cholangiopathy .

The recommendations for the treatment of portal cavernoma cholangiopathy are based on expert opinions [99]. Specific treatment should only be considered in cases of jaundice, pruritus, or cholangitis [18,99]. Endoscopic treatment is indicated for main bile duct stones or biliary stenosis, however, the risk of bleeding is increased when varices are present around the bile ducts. After endoscopic treatment, the use of ursodeoxycholic acid may decrease the risk of recurrence of symptoms [100,101,187]. There are no data evaluating the efficacy of endoscopic treatment versus ursodeoxycholic acid in these groups of patients. Shunt surgery may also be required in some selected cases of failure of other treatment modalities, while bilio-digestive anastomoses are associated with a high risk of severe complications (cholangitis and intraoperative bleeding) and recurrence of biliopathy in 30% and 70% of cases respectively, according with a systematic review [188]. Overall, management of severe complications of portal cavernoma cholangiopathy are usually challenging and require individualized and multidisciplinary approach.

6 . Specific considerations on the treatment of the associated condition

6.1. MPN. Diagnosing the underlying etiological factor for developing NCPVT is important, since it may have therapeutic or prognostic implications. According to current MPN guidelines, patients diagnosed with MPN are treated prophylactically with low-dose aspirin. However, in many patients with MPN-associated NCPVT, the thrombotic event is the presenting symptom of the MPN. In case of NCPVT and underlying MPN, anticoagulant treatment with unfractionated heparin or low molecular weight heparin should be started immediately. Long-term treatment with VKA should be given long-term for NCPVT in MPN patients, because of the high risk of recurrence [18,189]. The risk of recurrent thrombotic complications is associated with several factors, including history of previous thrombosis, splenomegaly and leukocytosis [190]. It is unknown whether aspirin should be added to treatment with VKA in NCPVT patients with MPN in order to reduce the high recurrence rate. In a retrospective study in 44 patients with NCPVT and MPN, the prevalence of recurrent thrombosis was higher in individuals treated with VKA than in patients treated with aspirin or with combination therapy of VKA and aspirin [191]. In a more recent study, these findings could not be confirmed, and recurrent thrombosis was not dependent upon the type of anticoagulant treatment [190,192].

Therefore, prospective studies are urgently needed to assess the benefit of combination anticoagulant therapy. MPN patients should be also treated with anti-proliferative therapy and/or phlebotomy in case of elevated blood cell counts in order to normalize peripheral blood cell counts [193]. In general, in patients with polycythemia vera, hematocrit <45% and platelet count <400 x10e9/l and WBC count <10 x 10e9/l should be the therapeutic target [194,195]. In ET patients, the aim is to maintain platelet counts <400 x10e9/l [196]. It is unclear whether these target values are also optimal in patients with NCPVT.

6.2. PNH: The diagnosis of underlying PNH in patients with NCPVT may have important implications for treatment. PNH patients with thrombotic events, who are known to have a high risk of recurrence even despite VKA treatment, can be treated more effectively with eculizumab, an antibody directed to complement factor C5, which strongly reduces the risk of thrombotic events [197].

7. Direct oral Anticoagulants in patients with BCS and NCPVT

Direct Oral Anti-Coagulants (DOACs) are direct acting oral anticoagulant drugs, which target factor IIa (thrombin) (e.g,. Dabigatran) or factor Xa (e.g. Rivaroxaban, Apixaban and Edoxaban). The advantages of DOACs compared to VKA include reduced risk of major bleeding, fixed dose once or twice daily, fast action within 2-3 hours, short half-life, limited interaction with food and drugs , and no need for monitoring[198]. Possible disadvantages of DOACs are the lack of an antidote in Europe in case of bleeding associated with the use of factor Xa inhibitors, inability to routinely monitor these drugs, and the high costs [198]. The incidence of gastrointestinal bleeding may be slightly higher with DOACs compared to VKA treated patients, especially with dabigatran and rivaroxaban [199–201]. This is of importance because patients with BCS or PVT may even be at a higher risk of gastro-intestinal bleeding.

No randomized clinical trials have been performed in patients with vascular liver disorders, including NCPVT or BCS. In addition, it is also still debated whether DOACs can be safely used in patients with liver disease, since these patients were not included in the large trials on venous thrombosis and atrial fibrillation. The label advice for using DOACs in patients with hepatic dysfunction suggests not to use DOACs in moderate to severe cirrhosis. Several cases or case series reported the use of DOACs in these patients [160,202–205]. The VALDIG study group recently reported 60 patients with NCPVT and 9 with BCS, some of whom also had cirrhosis, who were treated with DOACs [206]. They found a low rate of recurrent thrombosis and bleeding in 5% of patients, and concluded that DOACs seemed safe and effective for individuals with NCPVT. Prospective randomized clinical trials are urgently needed to investigate the efficacy and safety of DOACs in comparison to current treatment in patients with BCS and NCPVT, before DOACs can be recommended for these patients.

8. Pregnancy and splanchnic vein thrombosis.

BCS and NCPVT frequently affect women of childbearing age who might desire pregnancy. In general, pregnancy and the postpartum are prothrombotic states. Moreover, hemodynamic changes occurring during pregnancy are reminiscent of the circulatory changes classically associated with portal hypertension and might thus further augment them. Pregnancy in women with BCS and NCPVT theoretically favors splanchnic vein thrombosis and complications of portal hypertension.

However, data obtained by the VALDIG network were favorable and demonstrated that pregnancy should not be contraindicated in these women when the liver disease was stabilized, including, if needed, by the use of portal decompressive procedure [207,208]. Outcomes of pregnancy in women with vascular diseases of the liver and the management of pregnancy and delivery has been reviewed elsewhere in detail [209]. Briefly, the presence of esophageal varices should be screened and adequate prophylaxis of bleeding applied in a manner similar to what is recommended for patients with cirrhosis. Portopulmonary hypertension should be searched for prior to conception, since pregnancy can worsen lung disease [210]. The risk of miscarriage and premature birth is heightened, particularly in women with BCS. Current management of these diseases makes it very likely to see the child carried to full term once the pregnancy reaches 20 weeks. Assisted vaginal delivery is the preferred mode of delivery. Caesarean section should be restricted to gynecological indications. Indeed, cesarean section is known to carry a substantially increased risk of thromboembolic complications and may be hazardous in patients with portal hypertension due to large pelvic venous collaterals and postoperative ascites [211,212]. Most women likely benefit from anticoagulation during the postpartum and some during pregnancy. These women should be managed by a multidisciplinary team of hepatologists and obstetricians well-versed in high-risk pregnancies.

9. **Future perspective**

Improvement in the quality of imaging studies and awareness of the BCS and NCPVT has increased the number of patients that are currently diagnosed with these conditions. Initiatives from the last decades joining efforts in especially dedicated groups comprised of hepatologist, hematologist, radiologist, surgeons and basic scientists has resulted in huge advances in knowledge on these disorders and an exponential increase in the number of publications on splanchnic vein thrombosis. Nevertheless, there are still a number of questions that remain to be answered in relation to identification of the underlying causes promoting SVT, prognosis of a given patient, and the choice of the best treatment for each individual patient. Development of new molecular diagnostic tools, prognostic models and the development of pre-clinical models mimicking these disorders that could be used to test new therapies are unmet needs that are warranted to help in the better management of these patients.

Figure Legends:

Figure 1. 58 year old male patient with a perforated sigmoid diverticulitis with abscess formation (lower green arrow), complicated with an inferior mesenteric vein thrombus (upper green arrow) with extension into intrahepatic portal branches (red arrow). (Courtesy of Dr Onorina Bruno, Hôpital Beaujon, Clichy, France)

Figure 2: Evolution of portal pressure in portal vein thrombosis. In recent portal vein thrombosis, the rapid raise in portal pressure (red line) may be associated with clinically relevant consequences including bowel infarction and ascites. However, when portal pressure is already increased due to cirrhotic or non-cirrhotic portal hypertension (violet line), the hemodynamic consequences of portal vein thrombosis are attenuated due to the presence of collateral vessels. When complete recanalization occurs, portal pressure returns to baseline levels (dashed lines).

Figure 3: According to Poiseuille's law, and assuming that the portal vein is a rigid tube, following portal vein thrombosis, blood flow decreases proportionally to the fourth power of the vessel radius. For example, in the presence of a thrombus occupying 80% of the lumen, the blood flow is decreased by 98.4%.

Figure 4: Minimal Invasiveness therapeutic strategy for BCS

Figure 5: Patient with NCPV a) before and b) after angioplasty restoring physiological portal blood flow.

Figure 6: a. Coronal contrast-enhanced CT demonstrates cirrhotic liver, cavernomatous transformation and patent splenic vein (arrow), **b.** trans-splenic splenoportography confirms absent main portal vein with cavernomas.

Figure 7: a. Completion TIPS demonstrates flow and 4 cm of unstented main portal vein, ready for transplantation; **b.**TIPS venography after 2 months shows continued expansion of the main portal vein while the patient awaits for liver availability.

Table 1. Prevalence of acquired and inherited risk factors for BCS, NCPVT in 3 recent European cohort studies [32,34,55]

Underlying disorders	**NCPVT N=432**		**BCS** N=168	
	N tested	% positive	N tested	% positive
Systemic				
Acquired conditions				
Myeloproliferative neoplasms	432	21%	168	41%
JAK2 ^{V617F}	432	16%	168	35%
Antiphospholipid syndrome	429	6%	165	10%
PNH	386	0.3%	152	7%
Inherited conditions				
Factor V Leiden	429	3%	165	8%
Factor II gene mutation	432	6%	168	3%
Protein C deficiency	404	5%	150	5%
Protein S deficiency	407	5%	147	4%
Antithrombin deficiency	416	1%	153	1%
External factors				
Recent pregnancy	353	2%	168	1%
Recent oral contraceptive use	353	14%	168	22%
Systemic disease*	432	3%	168	6%
Local factor**				
Inflammatory intra-abdominal lesions**	432	11%	168	2%
Intra-abdominal surgery	432	10%	168	1%
Abdominal trauma	292	4%	168	2%
> 1 risk factor	432	14%	168	19%
No cause***	219	42%	168	24%

* including connective tissue disease, celiac disease, Behçet's disease, mastocytosis, inflammatory bowel disease, human immunodeficiency virus infection, sarcoidosis, myeloma,

** Acute pancreatitis, biliary or intestinal infection or inflammation.

Abbreviations: BCS, Budd-Chiari syndrome; PNH, Paroxysmal nocturnal hemoglobinuria; NCPVT, portal vein thrombosis.

*** Oral contraception and pregnancy were not considered risk factors for NCPVT in all studies.

Table 2. Investigations for thrombotic risk factors in patients with BCS or NCPVT

Underlying disorders	Suggestive signs*	Work-up
Systemic		
Acquired conditions		
MPN	Normal platelet count Large spleen	1. In all patients, test first *JAK2*^{V617F} in peripheral granulocyte DNA. 2. In patients without *JAK2*^{V617F}, but with spleen height ≥ 16 cm and platelet count > 200 x10^9/L, test for *CALR* mutations. Propose a bone marrow biopsy in patients without *CALR* mutations. 3. In the remaining patients, *i.e.* those without *JAK2*^{V617F} when spleen height is < 16 cm and platelet count ≤ 200 x10^9/L, MPNs are extremely uncommon. *MPL* and *JAK2* exon 12 mutations are very rare. MPN diagnosis relies on bone marrow biopsy performed on a case-by-case basis.
Antiphospholipid syndrome		Diagnosis based on repeatedly detectable anticardiolipin antibodies at high level, or lupus anticoagulant, or antibeta2 glycoprotein 1 antibodies. Many patients with vascular liver disease have nonspecific fluctuating, low titer antiphospholipid antibodies in the absence of antiphospholipid syndrome.
PNH	Small hepatic vein involvement	CD55 and CD59 deficient clone at flow-cytometry of peripheral blood cells.
Inherited conditions		
Factor V Leiden		Activated protein C resistance. To be confirmed in patients with positive results, by molecular testing for factor V Leiden mutation
Factor II gene mutation		Molecular testing for G20210A mutation
Protein C deficiency		Results can be interpreted only in patients with normal coagulation factor levels. Diagnosis based on decreased protein C activity levels. Inherited deficiency can be established only with a positive test in first degree relatives.
Protein S deficiency		Results can be interpreted only in patients with normal coagulation factor levels. Diagnosis based on decreased free protein S levels. Inherited deficiency can be established only with a positive test in first degree relatives.
Antithrombin deficiency		Results can be interpreted only in patients with normal coagulation factor levels.

		Diagnosis based on decreased antithrombin activity levels. Inherited deficiency can be established only with a positive test in first degree relatives.
Hyperhomocysteinemia.		Increased serum homocysteine level prior to disease. Uncertain value of C677T homozygous polymorphism. In many patients, a definite diagnosis for underlying hyperhomocysteinemia will not be possible. Blood folate and serum vitamin B12 levels may be useful.
External factors		
Recent pregnancy		Medical history
Recent oral contraceptive use		Medical history
Systemic disease		
Behcet disease	Involvement of inferior vena cava	Diagnosis based on a set of conventional criteria. To be routinely considered in patients with inferior vena cava thrombosis, or originating from endemic areas, or having extrahepatic features suggestive for the disease.
HIV infection		Anti-human immunodeficiency virus antibodies
Celiac disease		Anti-transglutaminase antibodies
Sarcoidosis	Black patients; respiratory symptoms	Serum angiotensin-converting–enzyme level; Biopsy
Cytomegalovirus infection		Anti-CMV IgM
Local factor		
Inflammatory intra-abdominal lesions		Medical history. CT-scan. Increased circulating levels of C reactive protein and/or of fibrinogen and/or increased platelet count, although recent thrombosis can by itself induce systemic inflammation.
Abdominal surgery		Medical history
Abdominal trauma		Medical history

* all causes should be tested in all patients. Do not restrict testing to patients displaying these signs.
Abbreviations: BCS, Budd-Chiari syndrome; NCPVT, portal vein thrombosis; PNH, Paroxysmal Nocturnal Hemoglobinuria, MPN; Myeloproliferative neoplasms.

Table 3: BCS specific prognostic index

Score	Formula	Cut-off	Predicted survival rate	Reference
Score	Formula	Cut-off	Predicted survival rate	Reference
Clichy PI	ascites score[a]×0.75)+(Pugh score×0.28)+(age× 0.037) + (creatinine × 0.0036)	5.4 (range from 3.4 to 9.1)	At 5y ≤5.4: 95% > 5.4: 65%	[104]
New Clichy PI	0.95×ascites score+0.35×Pugh score+0.0 47×age+0.0045×serum creatinine+2.2×type III[b]—2.6	5.1 (range from 2.0 to 9.7)	At 5y <5.1: 100% ≥ 5.1: 65%	[67]
Rotterdam BCS index	1.27×encephalopathy+1.04×ascites + 0.72 × prothrombin time + 0.004 × bilirubin	class I: 0 - 1.1 class II: 1.1-1.5 class	At 5y class I 89% class II 74% class III 42%	[106]

		III: ≥1.5 (range from 0.02 to 4.03)		
TIPS-BCS PI	age ((years) x 0.08 + bilirubin (mg/dL) x 0.16 + international normalized ratio (INR) x 0.63	7	1-year OLT-free survival ≤7 95% >7 12%	[105]
BCS-intervention-free survival prognostic score	ascites [yes = 1, no = 0]*1.675 + ln creatinine [umol/L]*0.613 + ln bilirubin [umol/ L]*0.440)	Interval I: ≤5 Interval 2: 5-6 Interval 3: ≥ 6	Intervention-Free Survival Interval I 78.3% Interval 2 27.8% Interval 3 6.8%	[70]
BCSurvival score	age/10*0.370 + ln creatinine [umol/L]*0.809 + ln bilirubin [umol/L]*0.496)	Interval I: ≤7 Interval 2: 7-8 Interval 3 ≥ 8	Probability survival 87.5% 63.3% 42.9%	[70]

[a:]ascites score: 1, absent with free sodium intake and no diuretic agents; 2, easy to control with sodium restriction or diuretic agents; and 3, resistant to this

treatment because of hyponatremia or functional renal failure

[b]: type III' is a binary variable coded as 1 for patients with clinicopathological findings of acute injury superimposed on chronic lesions, and 0 for the other patients.

Table 4. Morphological, functional, and clinical classification of NCPVT [87]

Site of NCPVT - **Type 1**: trunk only - **Type 2**: branch only: 2a, one branch; 2b, both branches - **Type 3**: trunk and branches
Degree of portal venous system occlusion **O**: Occlusive: no flow visible in PV lumen on imaging/Doppler study **NO**: Non-occlusive: flow visible in PV lumen through imaging/Doppler study
Duration and Presentation **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) **Ch**: Chronic (no hyperdense thrombus; previously diagnosed NCPVT on follow-up, portal cavernoma and clinical features of PHT) **As**: Asymptomatic **S**: Symptomatic: features of acute NCPVT (with or without acute bowel ischemia) or features of portal hypertension
Extent of PV system occlusion (S, M, SM) **S**: Splenic vein, **M**: mesenteric vein or **SM**: both
Type and presence of underlying liver disease Cirrhotic, non-cirrhotic liver disease, post-liver transplant, HCC, local malignancies, and associated

conditions

Table 5. Evaluation of the response to treatment (Adapted from Plessier A et al. [107]**)**

		Ongoing treatment response (2 weeks)	Complete treatment response
Ascites		**Yes**	**No clinically detectable ***
	creatinine	**Normal or decreasing**	**normal**
	sodium	**Normal or increasing**	**normal**
	Balance (water-Na)	**negative**	
	NaCl intake	**moderate**	**moderate**
Factor V level		**increasing**	**above 40% of normal value**
Serum conjugated bilirrubin		**Decreasing**	**below 15 µmol/L**
PHT related bleeding			**No**
SB Infections			**No**

BMI		**>20kg/m2**

* without diuretic treatment or low dose (spironolactone 75mg/d or furosemide 40 mg/d)

Table 6. Interventional radiology treatment of acute extensive portal vein thrombosis without cirrhosis

Reference Number of patients	Procedure	Long-term anticoagulation	Recanalization	Complications	Recurrence of thrombosis
Hollingshead, 2005 [164] N=20	Local thrombolysis alone	Yes	-Complete: 3/20 -Partial: 12/20 -No: 5/20	- 1 death 2 weeks after thrombolytic therapy. - 11 major complications (bleeding) - 2 liver transplantation	Not mentioned
Smalberg JH, 2008 [123] N=4	Local thrombolysis, combined -in 1 out of the 4 patients- with TIPS	Yes	-Complete: 1/4 -Partial: 1/4 -No: 2/4	2 major bleeding	Not mentioned
Cao, 2013 [213] N=12	Percutaneous transhepatic balloon angioplasty and/or stent placement without thrombolysis or thrombectomy	No	11/12	1 death from acute respiratory distress syndrome 8 days after the procedure	5/12
Rosenqvist, 2016 [214] N=4	Local thrombolysis, combined -in 3 out of the 4 patients- with TIPS	Not available	Limited data. "Three recovered and have survived more than 6 years."		
Klinger, 2017 (64) N=17	Combination of transjugular thrombectomy, local fibrinolysis and – depending on thrombus resolution – TIPS	Yes (≥ 12 months after recanalization)	-Complete: 9/17 -Partial: 7/17 -No: 1/17	-2 HIT, including 1 leading to segmental bowel resection) -1 additional bowel resection -1 hepatic artery pseudoaneurysm with spontaneous occlusion	-2/17 recurrence of NCPVT at 28 months (1 recanalized) -3 TIPS obstructions, all recanalized -1 portal cavernoma
Wolter, 2018 (65) N=9	Thrombectomy, local fibrinolysis and/or TIPS	Not available	-Partial or complete: 7/9 -No: 2/9 (due to failure to access	None	3 TIPS obstructions (1 recanalized)

			portal vein)		

Abbreviations: HIT, heparin induced thrombocytopenia; TIPS, transjugular intrahepatic portosystemic shunt

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Figure 1

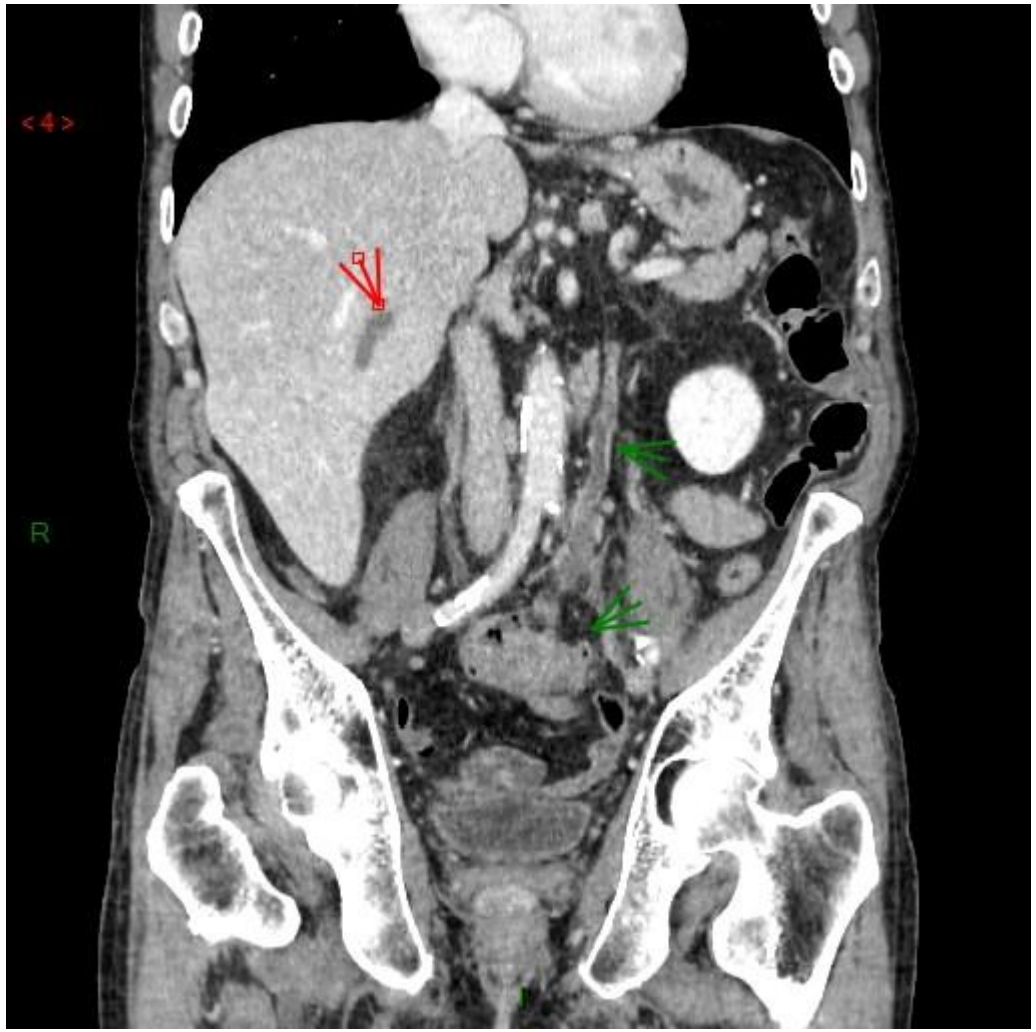
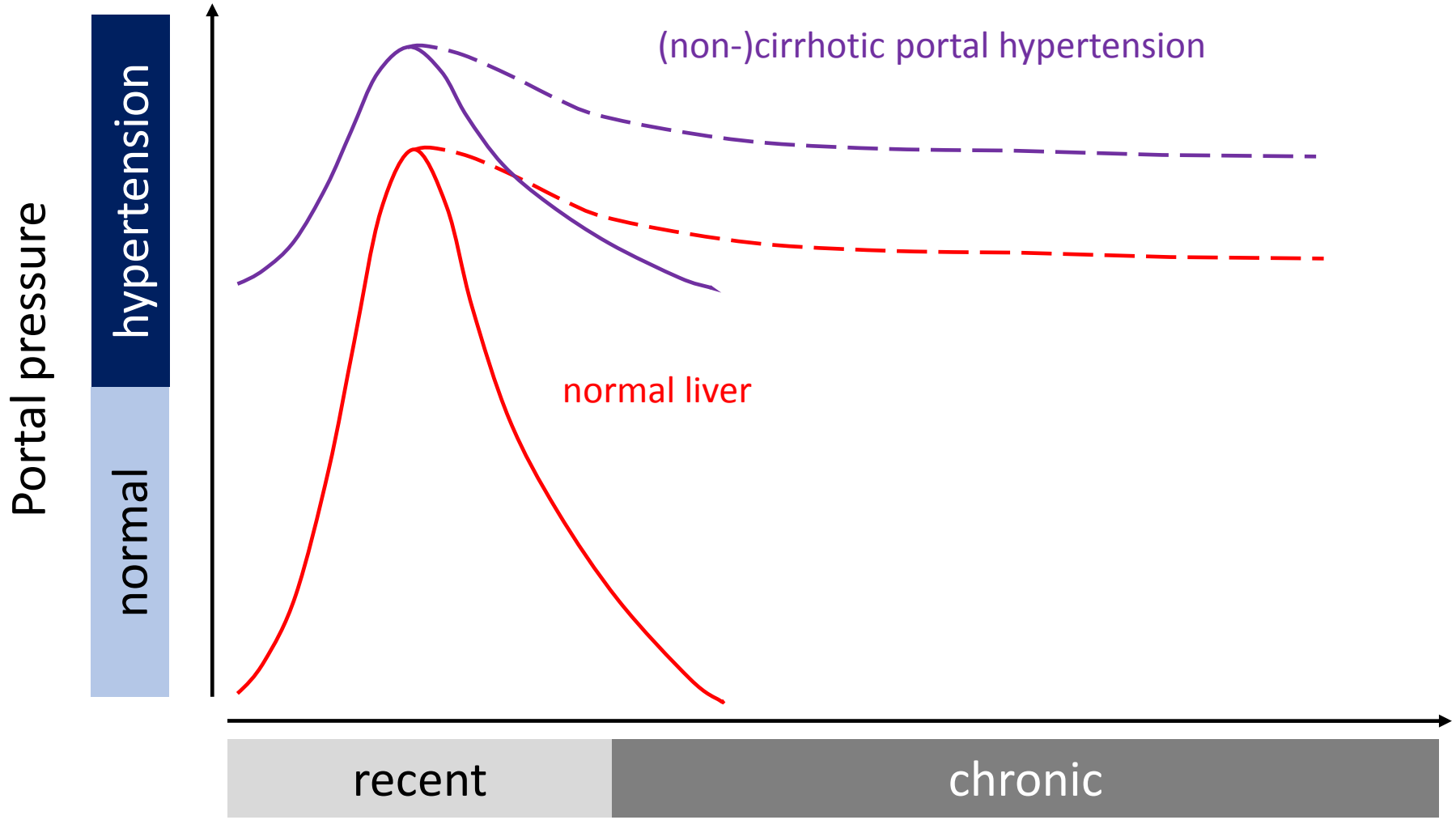


Figure 1

Figure 2



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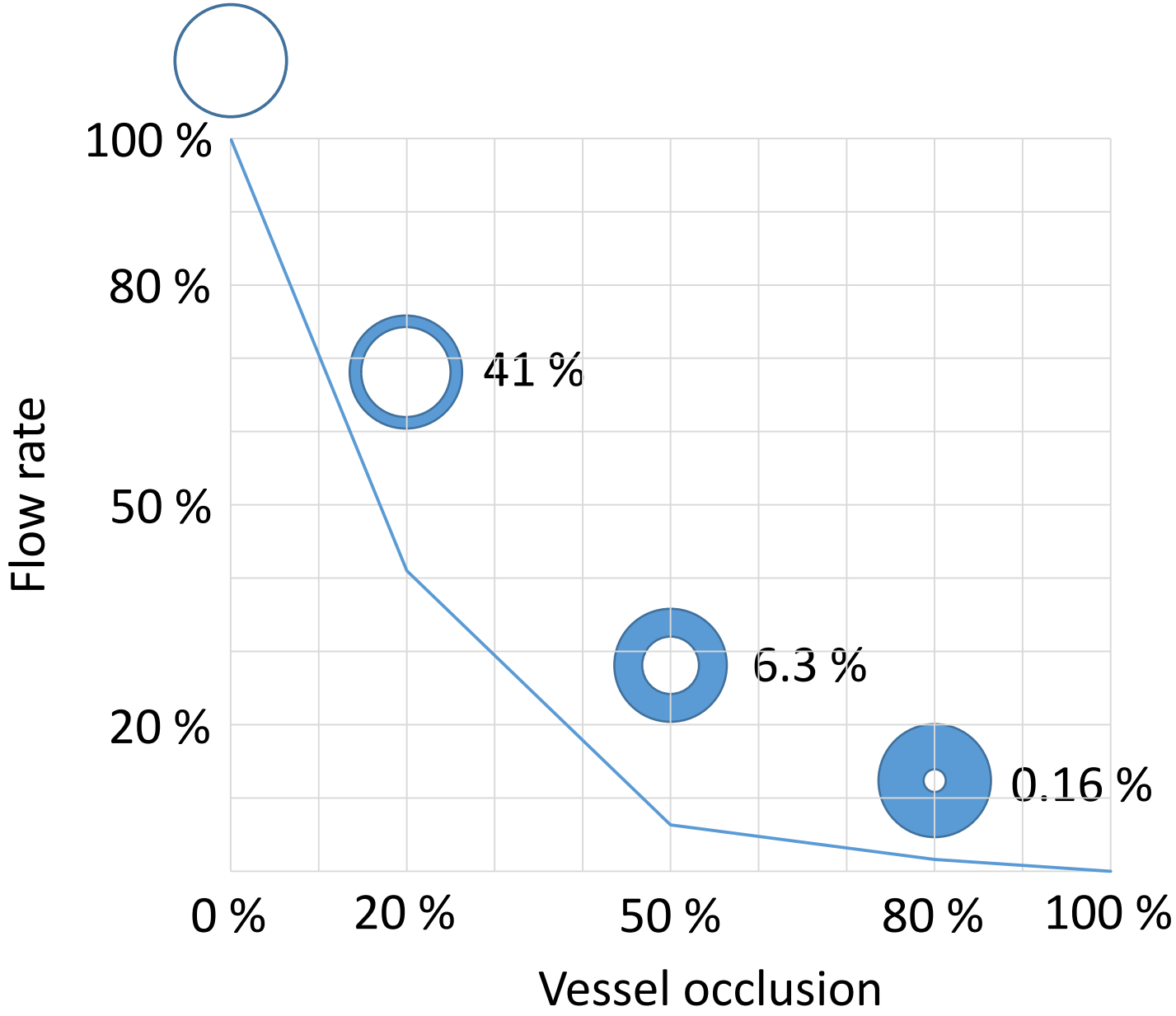


Figure 3

Figure 4

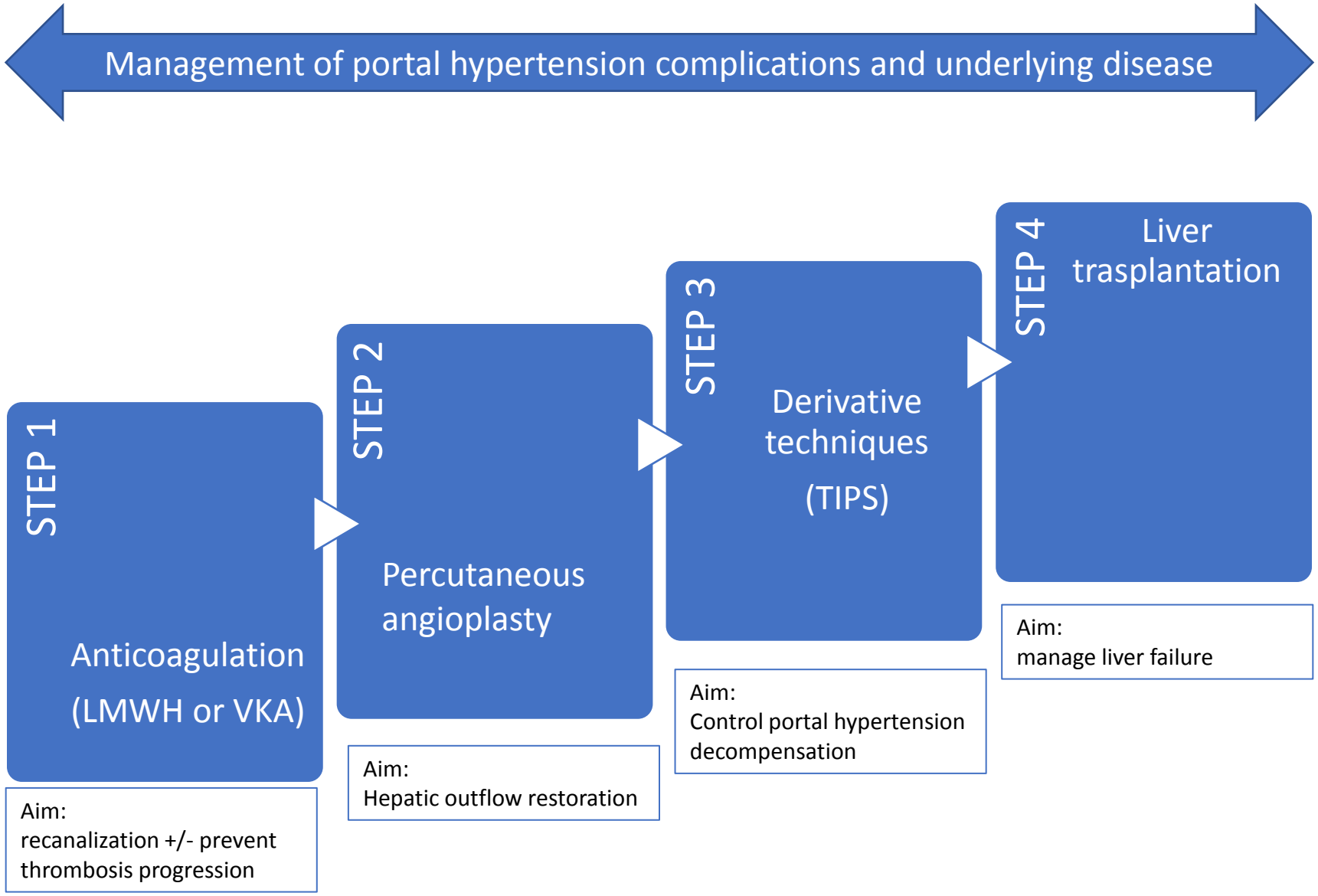
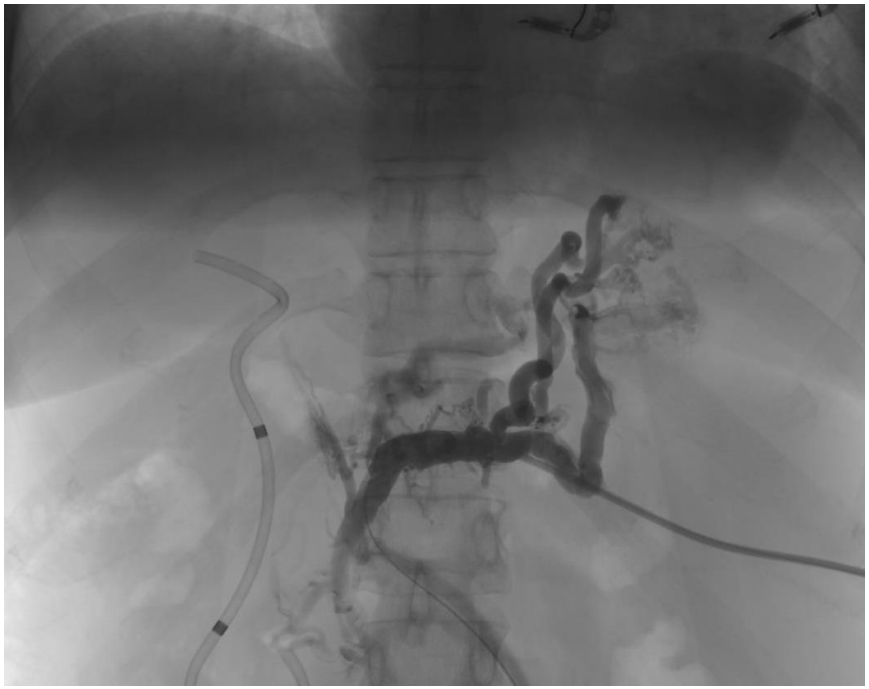


Fig 4

a



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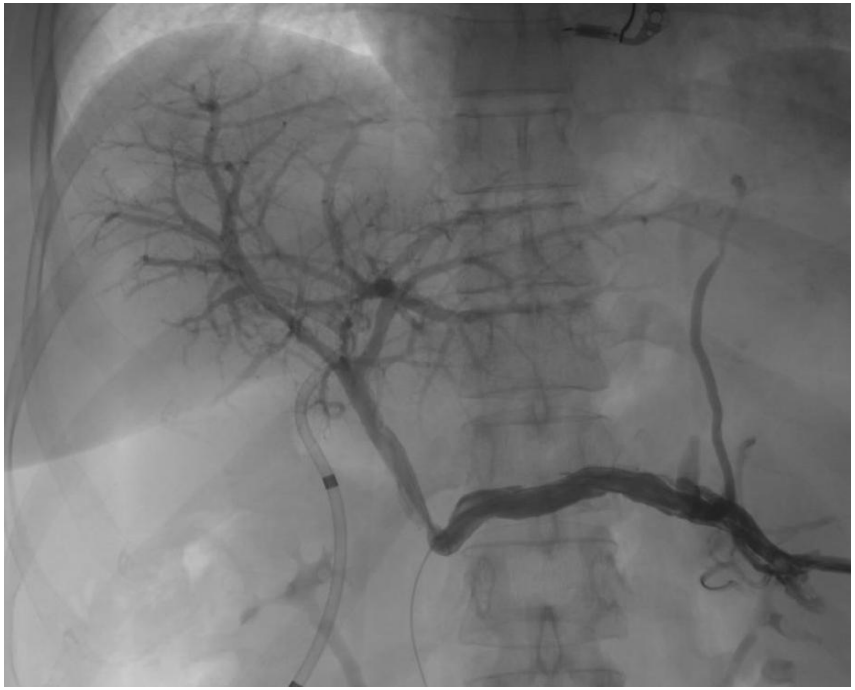
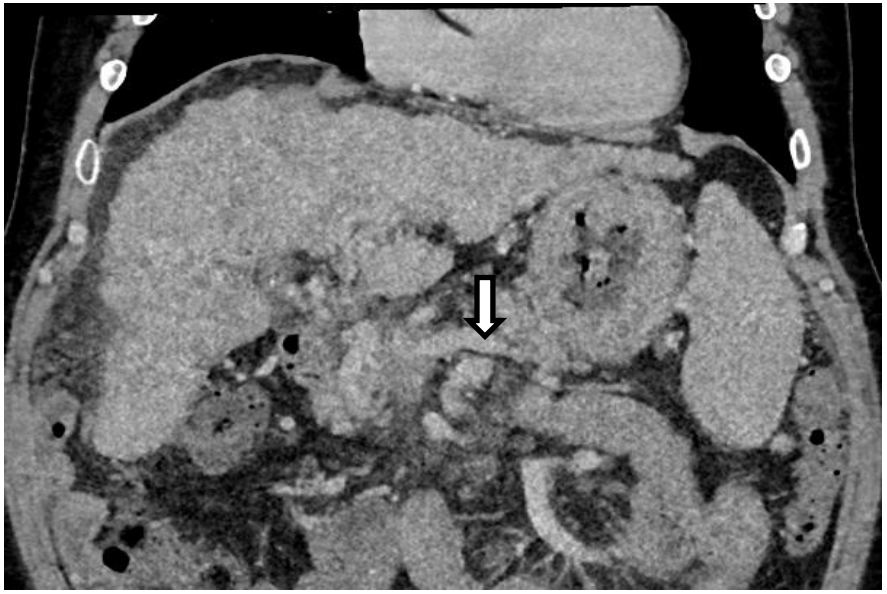


Figure 5.

a



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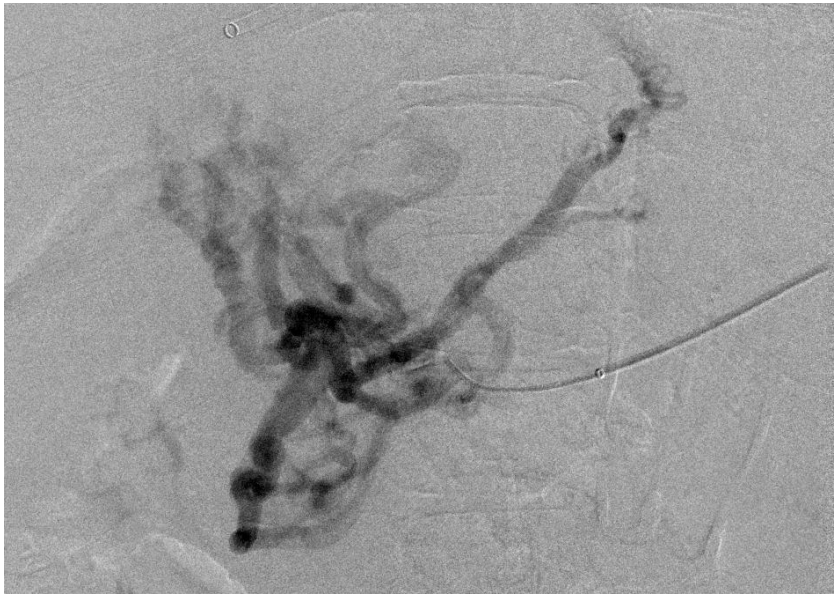

Figure 6

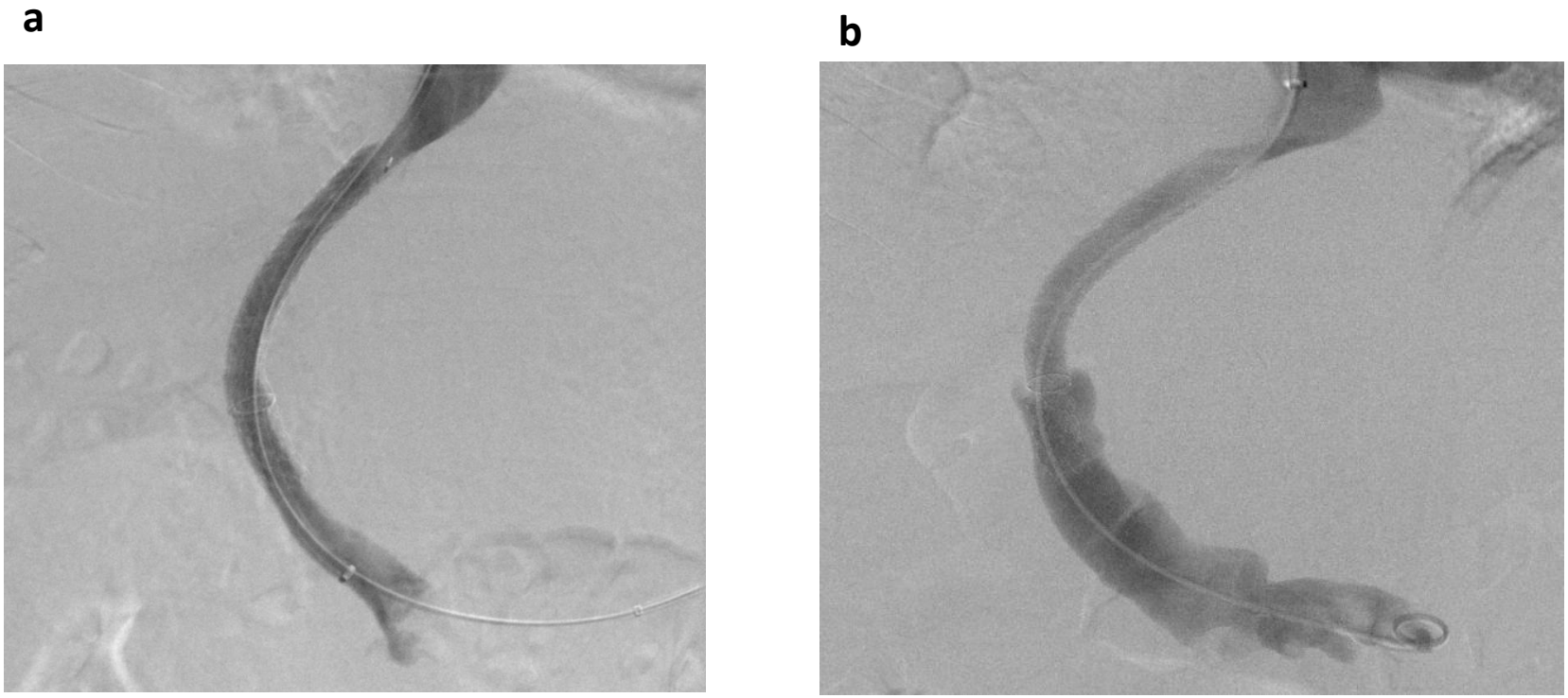

Figure 7