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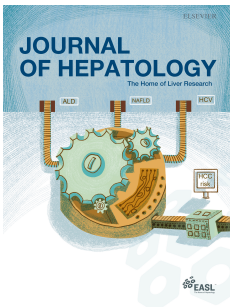

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Porto-sinusoidal vascular disorder

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The authors declare no conflicts of interest.

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KEY POINTS:

- Non-cirrhotic portal hypertension eventually results from different histologic intrahepatic vascular alterations
- The term *porto-sinusoidal vascular disorder* has been proposed to encompass histological hepatic architectural changes in the presence or absence of portal hypertension
- The diagnosis of PSVD requires a liver biopsy
- Specific and non-specific diagnostic criteria of PSVD include include histological features on liver biopsy and clinical features of portal hypertension
- Imaging and non-invasive techniques play an increasingly important role in the diagnosis and management of PSVD

SUMMARY

It is well established that portal hypertension (PH) can occur in the absence of cirrhosis, as reported in patients with immune disorders, infections and thrombophilia. However, similar histological abnormalities affecting primarly the hepatic sinusoidal and the (peri)portal vasculature have also been observed in patients without PH. Thus, the term porto-sinusoidal vascular disorder (PSVD) has been recently introduced to describe a group of vascular diseases of the liver featuring lesions encompassing the portal venules and sinusoids, irrespective of the absence or presence of portal hypertension.

Liver biopsy is fundamental for PSVD diagnosis. Specific histology findings include nodular regenerative hyperplasia, obliterative portal venopathy/portal vein stenosis and incomplete septal fibrosis/cirrhosis. Since other conditions including alcoholic and non-alcoholic fatty liver disease, or viral hepatitis, or the presence of portal vein thrombosis may occur in patients with PSVD, their relative contribution to the liver damage should be carefully assessed. In addition to histology and clinical diagnostic criteria, imaging and noninvasive tests such as liver and spleen stiffness measurements seem to aid in the diagnostic workup. The introduction of PSVD as a novel clinical entity will facilitate collaborative studies and investigations of the underlying molecular pathomechanisms.

1) Background: why porto-sinusoidal vascular disorder?

Portal hypertension is the main clinical manifestation of advanced chronic liver disease and may be associated with several complications including variceal bleeding, ascites, hepatic encephalopathy and others. It usually develops in patients with advanced chronic liver disease due to chronic viral hepatitis, pathologic alcohol consumption, obesity or other metabolic disorders. However, in a small number of patients, portal hypertension is observed in the absence of cirrhosis and in the absence of portal vein or hepatic vein obstruction, e.g. by thrombosis.

This condition has been called non-cirrhotic portal hypertension (NCPH) and it derives from a variety of histopathologic entities that have been referred to as various terms such as hepatoportal sclerosis, non-cirrhotic portal fibrosis, nodular regenerative hyperplasia or incomplete septal fibrosis/cirrhosis (1). The mechanisms of NCPH are poorly understood and current therapy is restricted to the management of portal hypertension. This disorder has gained increased attention over the last decades in parallel to the frequent use of immunosuppressive drugs for autoimmune and hematological disorders and the increased prevalence of treated Human Immunodeficiency Virus infections, all conditions that have been linked to NCPH (2).

The complexity and unclear pathogenesis of NCPH opened various controversies and gave rise to several questions. With NCPH being the final common pathway of different conditions leading to a number of heterogeneous histologic changes in the liver, the first question was about the nature of NCPH before the development of portal hypertension, that is, in patients without any signs or complications related to portal hypertension. Moreover, according to the definition of NCPH, patients with other chronic liver diseases, including viral hepatitis, metabolic dysfunction-associated fatty liver disease and alcoholic liver disease, independently of their severity, were *a priori* excluded from the diagnosis of NCPH. Knowing that early stages of these liver diseases may coexist with the presence of portal sinusoidal alterations on liver biopsy, it seemed incorrect to consider them as exclusion criteria. Finally, it is currently known that PVT may be one of the causes, as well as a consequence of NCPH, therefore the concomitant presence of portal vein thrombosis (PVT) should not exclude the presence of any form of NCPH (3,4).

For these reasons, and based on the observation that the changes occurring in the hepatic microanatomy, as observed on liver histology, are located in the lobular branches of the portal vein and in the sinusoid area, the name *porto-sinusoidal vascular disorder* (PSVD) has been proposed (5) (Figure 1).

2) Diagnostic criteria

The main features of the definition of PSVD include the absence of cirrhosis in a liver biopsy and the detection of specific or non-specific histological findings with or without portal hypertension (Figure 2). The concomitant presence of causes for liver disease such as alcohol misuse, metabolic syndrome, or viral hepatitis, does not exclude PSVD, if liver biopsy shows specific findings indicative of PSVD. In these overlapping cases, the respective contribution of PSVD and parenchymal liver disease to the development or degree of severity of portal hypertension remains an open issue. Conditions affecting the hepatic veins (e.g. Budd-Chiari syndrome) or specific liver diseases that have been well characterized as causing microvascular damage such as sarcoidosis, congenital hepatic fibrosis or sinusoidal obstruction syndrome are a priori excluded from the diagnosis of PSVD. Due to its most frequent secondary occurrence in PSVD patients, extrahepatic portal vein thrombosis does not preclude this diagnosis.

This definition intends to uniform the diagnosis of this disorder that may comprise several histological features and vascular abnormalities that occur in the presence/absence of portal hypertension and of concomitant parenchymal liver disease.

3) Liver histology: the different features of PSVD

The diagnosis of porto-sinusoidal vascular disorder requires, by definition, the examination of a liver biopsy. This biopsy should be longer than 20 mm and should contain at least 10 portal tracts (5). These requirements are linked to the fact that the aim of the biopsy is first to exclude cirrhosis, and second, to assess the specific diagnostic features of the disease that can be subtle, unevenly distributed, and found only by a careful examination of the portal tracts and of the sinusoids by an expert liver pathologist.

In a normal liver, a portal tract contains on average one portal vein branch, one or two interlobular bile ducts and one or two hepatic arterial branches (6). The portal vein branch, always entirely confined to the portal tract, is commonly three or even four times larger than the hepatic artery branch and the interlobular bile duct, both of them having the same diameter (Figure 3 A). Portal tracts missing one of the three components are frequent, with less than 10% containing either no hepatic artery branch or no interlobular bile duct, but up to one third of the portal tracts missing the portal vein branch (13).

Three types of histological lesions are recognized as specific for the diagnosis of PSVD. The first one is obliterative portal venopathy (Figures 3 B-E). This lesion has been reported

previously under different names, hepatoportal sclerosis, phlebosclerosis or portal vein obliteration. Efforts have been made by a group of expert liver pathologists to reach a consensus for defining standardized names for portal and periportal vascular changes associated with INCPH, and they propose to replace the term obliterative portal venopathy by *portal vein stenosis* (7). Portal vein stenosis means any narrowing of the portal vein branch lumen, ranging from incomplete to complete disappearance of the vein and replacement by fibrosis. Consequently, the portal tracts look small, rounded and fibrotic, and can be difficult to identify because the lumen of the vein, commonly the main visible structure allowing the recognition of the portal tract at lower power on the microscope, is not visible anymore (Figure 3 B). In case of difficulties, immunohistochemistry for keratin 7 (K7) will allow the recognition of the portal tracts by showing the interlobular bile ducts and/or some ductular reaction (Figure 3 C), whereas the detection of Glutamine synthetase (GS) will help to localize the centrolobular area (Figure 3 D). Another way to recognize portal vein stenosis, sometimes very subtle, is that the diameter of the vein branch becomes smaller than the one of the arterial branch and of the interlobular bile duct (Figure 3 E). Portal vein stenosis has been shown as the only strong independent histological predictor for non-cirrhotic portal hypertension (8). The second specific lesion is nodular regenerative hyperplasia (NRH), a diffuse micronodularity of the liver parenchyma without fibrosis (Figures 3 F-H) (16). NRH is better identified on a reticulin stain that should always be performed (Figure 3 G). The small nodules of hyperplastic hepatocytes are alternating with areas of atrophic plates often expressing K7 by immunohistochemistry as a sign of biliary metaplasia, resulting from ischemia (Figure 3 H) (9). The third histological lesion considered as specific is the so-called incomplete septal fibrosis/cirrhosis. It is described as a liver parenchyma crossed by thin and incomplete fibrotic bands (10,11), giving rise to some sort of incomplete nodules with approximation of the portal tracts and the centrolobular areas (Figure 3 I). This is actually a complex entity, not only difficult to recognize on a liver biopsy, but also considered to represent most probably one of the features of a regressing cirrhosis (12–14). Its inclusion in the spectrum of PSVD relies so far mostly on clinical grounds.

In the absence of one specific histological lesion and of one specific sign of portal hypertension, the diagnosis of PSVD requires to find both one nonspecific sign of portal hypertension and one nonspecific histological sign of PSVD (Figure 3 K-M). As indicated previously, the names and descriptions of these nonspecific histological lesions have been standardized (7). Finding herniated portal vein branches, veins not fully embedded in the portal tracts but directly abutting the periportal hepatocytes plates, is one of these features

(Figure 3 J). The other ones are the identification of small and thin-walled vascular spaces located either within the portal tracts and called hypervascularized portal tracts, or at the periphery of the portal tracts and called periportal abnormal vessels. These small vessels are either single or numerous and they have different shapes (Figures 3 K and 3 L). Nonspecific features of PSVD are also found outside of the portal tracts and correspond to sinusoidal dilatation and mild perisinusoidal fibrosis (Figure 3 M). All these modifications have an uneven distribution and can be very subtle. They may therefore remain underrecognized if the pathologist is not aware of them. On the contrary, they can also be found in other liver diseases and in other clinical contexts such as liver transplantation (15,16). These histological lesions, specific and nonspecific, even NRH, have also been described in the absence of portal hypertension (15,17,18). Therefore, when a liver biopsy is performed for mild abnormalities of the liver enzymes of unknown etiology, with no portal hypertension and no underlining causal factor identified, the presence of them should be recorded as they may potentially represent a preclinical situation (15,17,19). Longitudinal studies are needed to evaluate this specific situation, the natural history without portal hypertension being still unknown.

A last point that deserves attention is the possibility for development of liver nodules, mainly focal nodular hyperplasia (FNH), and FNH-like nodules, that are hyperplastic reactive lesions resulting from the imbalance between the portal and arterial flows. Monoclonal lesions, hepatocellular adenomas (HCA) and hepatocellular carcinomas (HCC) have also been reported, as for other vascular liver diseases (20–23).

4) Clinical manifestations

Patients with PSVD-related portal hypertension are usually asymptomatic until they develop complications of portal hypertension. Transaminases, alkaline phosphatase and gamma-glutamyl transferase may be increased, but generally only moderately. The liver function is generally maintained with most patients showing normal serum albumin and bilirubin levels. Some patients develop complications of portal hypertension, mostly variceal bleeding, which is the initial manifestation in around 20-40% of cases, whereas ascites and encephalopathy are uncommon presenting symptoms. Indeed, the natural history of patients with INCPH is characterized by the presence of large varices presentation in two-thirds of the patients with PSVD and portal hypertension and develops in 20% of patients within an average of 10 years of diagnosis (24).

PSVD patients with portal hypertension can develop ascites in 20-50% of cases. Within five years of diagnosis, portal vein thrombosis develops in around a third of subjects, but is completely obstructive (i.e. occupying more than 80% of the vessel lumen) in only a third of patients (17,24,25). The incidence of thrombosis is increased in patients with a history of bleeding and with associated conditions, in particular HIV infection. There is a substantial lack of data concerning the evolution of PSVD over time, although some authors have reported a low level of progression of liver function tests suggesting that PSVD is not evolving rapidly (17). However, complications of portal hypertension including porto-pulmonary hypertension or hepatopulmonary syndrome may develop, as well as hepatic regenerative nodules, but the precise risk factors leading to these complications are currently unknown. The outcome of PSVD depends on the complications of portal hypertension and in published series mortality can reach 15-20% after an 8-year follow-up period. The risk of progression of PSVD to advanced liver disease is highly variable and determines the referral rate for liver transplantation. A Dutch study reported low overall and LT-free survival of 78% and 72% at 5 years, respectively. Nevertheless, it should be noted that a small proportion of patients (13%) died from liver-related causes. The presence of ascites or mostly of a concomitant immunological or haemato-oncological disease represented a poor prognostic factor (17,24–26).

PSVD may, however, occur in the absence of any signs of portal hypertension, such as splenomegaly, gastro-esophageal varices, portosystemic collaterals, ascites, or hepatic encephalopathy, in up to 70% of cases (27). In such cases, altered liver tests may be the only laboratory features hinting towards the diagnosis of PSVD (15,17). Slightly impaired liver function tests, a higher rate of prothrombotic conditions, and immune diseases are likely to contribute to the progression to portal hypertension in these cases. The precise diagnosis, however, is established by specific findings at liver biopsy performed in patients presenting with asymptomatic abnormalities of liver laboratory parameters. The natural history and risk factors of PSVD without clinical features of portal hypertension remains largely unknown and only few data are available (27,28).

5) Hypotheses on pathogenesis

In about 50% of patients PSVD is associated with rare conditions that include specific drug exposure, immune disorders or autoimmune diseases, coagulation disorders, infectious and congenital or hereditary diseases (1,5,24). several of these conditions may be simultaneously present in patients with PSVD.

Drug exposure

PSVD has been related to prior exposure to immunosuppressive or antineoplastic agents (in particular azathioprine and oxaliplatin) as well as to numerous other drugs (29–31). Older age and cumulative exposure to didanosine and stavudine were shown to be independent predictors for the development of NRH in patients with HIV infection and the overall prevalence of HIV infection in PSVD patients has been reported 4% in a Dutch study (25,32). Therapy with oxaliplatin, an alkylating agent given with fluorouracil and leucovorin as a mainstay adjuvant chemotherapy for colorectal cancer has been associated with several degrees of liver injury ranging from frequent mild liver enzyme increases to rare severe injury leading to acute liver failure. Chronic injury from endothelial cell damage and architectural distortion may manifest years later with nodular regenerative hyperplasia, portal sclerosis, and noncirrhotic portal hypertension, while chronic subclinical injury occurs in up to 78% of patients (33). Moreover, following drug exposure, patients with HIV infection and nodular regenerative hyperplasia developed secondary protein S deficiency (34). Since didanosine and stavudine are no longer in use for antiretroviral therapy against HIV, a decrease in the prevalence of PSVD among HIV infected patients is to be expected over the next decades.

Thrombophilia

Thickening or occlusion and obliteration of portal venules detected on liver biopsy, are generally regarded as indicative for previous thrombosis. Indeed, prothrombotic conditions such as protein C deficiency have been associated with a higher incidence of PSVD (35–37) suggesting a procoagulant imbalance in PSVD patients (38). Despite the low number of reported cases, also factor V Leiden mutations have been associated to the development of PSVD (39). Portal vein thrombosis is relatively common further pointing at a procoagulant tendency in these patients (40). Moreover, it remains unclear whether portal vein thrombosis represents a complication of PSVD or rather contributes to its pathogenesis (41) or whether both possibilities should be considered. In fact, the presence of a thrombophilic factor *per se*, and/or a decreased portal flow velocity induced by PSVD may contribute to the pathogenesis of portal vein thrombosis. On the other hand, the imbalance between portal and arterial hepatic inflow induced by PVT may, in turn, induce sinusoidal vascular abnormalities. Future studies shall elucidate the prevalence and impact of prothrombotic risk factors and the role of PVT in PSVD.

Infections

Epidemiological findings suggest a relationship between low hygienic living conditions, low socioeconomic status and the development of PSVD, possibly related to the presence of

arsenic in ground drinking water (42,43). However, another important factor related to the environment is the prevalence of infections. Experimental evidence indicates that the translocation of intestinal bacteria into the portal vein may result in histologic alterations similar to PSVD (44). Chronic or recurrent infections leading to antigenemia of intestinal origin may end in mild portal inflammation resulting in pathological changes compatible with PSVD (45,46). Also long-lasting HIV infection has been recognized as possible etiological factors in PSVD (47).

Hereditary diseases

Familial aggregation has been found regarding PSVD and HLA-DR3 (48) suggesting the possibility of an immunogenetic basis of noncirrhotic portal fibrosis. Moreover, mutations in the telomerase gene complex have been described in patients with PSVD, indicating that heterozygous telomerase loss-of-function mutations may play a role in a large spectrum of hematologic and liver abnormalities (49). In addition to telomer disorders (mutations TERT and TERC), also developmental disorders (NOTCH1 and CTC 1), Turner's syndrome, and FOPV (familial obliterative portal venopathy gene) mutations have been reported (50–53). In HIV patients with PSVD, single nucleotide polymorphisms of genes involved in the purine metabolic pathway have been identified, suggesting a genetic link with their previous exposure to didanosine (54).

Finally, whole exome sequencing studies in patients and families affected with PSVD led to the discovery of various mutations related to the development of this disorder (53,55,56), corroborating the hypothesis that mutations may play a pathogenic role (see also below).

6) Novel insights into the interplay between immune system and PSVD

Disorders of the immune system, including both immune deficiencies, acquired or congenital, and autoimmune diseases, have been diagnosed in up to 10% of patients suffering from PSVD (57,58). In immune deficiencies, PSVD has been found in patients with common variable immune deficiency (57), hyper-IgM syndrome, primary antibody-deficiency syndromes such as Bruton's disease (58), and in Felty's syndrome (59).

As far as autoimmune disorders are concerned, anti-DNA antibodies have been reported in 69.2% of female patients, antinuclear antibodies in 24%, and anti-microsomal antibodies in 21.5%, in association with idiopathic non-cirrhotic portal hypertension (11).

In patients with inflammatory bowel disease, the prevalence of PSVD was reported to be 6% (60). However, it is difficult to decipher whether PSVD is mainly linked to the underlying inflammatory bowel disease or to azathioprine exposure.

Adult celiac disease has also been associated with PSVD. In patients with celiac disease, gluten-induced apoptosis of enterocytes may contribute to micro-thrombotic events in the small portal vein radicles through elevated serum cardiolipin IgA antibodies (61).

It has been proposed that the sinusoidal changes found in patients with conditions of disordered immunity, are related to intrasinusoidal cytotoxic T lymphocytes, granulomas, causing portal vein or sinusoidal endothelitis. This concept is in line with an overexpression of lymphocyte activation genes in blood samples from PSVD patients (62,63).

Macrophages play a significant role in the development and progression of chronic liver disease. Their activation markers soluble CD163 and soluble mannose receptor have been found to be elevated in patients with NCPH, although at a lesser degree than in patients with cirrhosis (64). These findings suggest that activation processes of macrophages are also involved in the pathogenesis of PSVD.

However, the mechanisms by which immunological abnormalities are associated with the development of PSVD are very heterogeneous and have been so far insufficiently studied.

7) Imaging and biomarkers

Ultrasound, CT and MRI

PSVD is often misdiagnosed as liver cirrhosis. However, in patients with portal hypertension, some morphological and functional imaging features can support the correct diagnosis of PSVD. These are summarized in Table 1.

Liver surface nodularity, which is a typical finding in cirrhosis, is lacking in most of the PSVD cases. In a recent CT/MR study, only 16% of patients with proven PSVD showed a nodular liver surface (65) (Figure 4).

An anatomically dysmorphic liver with atrophy/hypotrophy of the right liver and caudate lobe hypertrophy are more commonly observed in PSVD (Figure 4), while segment IV atrophy is more common in cirrhosis (21,65,66). Furthermore, a marginal atrophy associated with compensatory central hypertrophy has been described, particularly in patients with long duration of the disease (67,68).

In addition, signs of portal hypertension (large splenomegaly, porto-systemic collaterals, dilatation of the portal vein, splenic vein and mesenteric vein) are more severe in patients with PSVD as compared to patients with cirrhosis and similar liver function (Figure 4); furthermore, “ectopic” collaterals and fundal varices are more frequent in PSVD.

As for the appearance of the liver parenchyma, PSVD has commonly a homogenous pattern on US. On the other hand, PSVD commonly shows a heterogeneous enhancement in the

arterial and portal venous phase on CT. On hepato-biliary imaging MRI, liver enhancement, which depends on the uptake of contrast agents from normal hepatocytes (69), is higher in PSVD as compared to cirrhosis.

In addition, in PSVD the liver parenchyma shows a low enhancement area along the portal vein in the delayed phase in contrast-enhanced imaging (65,70). Interestingly, on ultrasound this corresponds to an increased thickening of the hyperechogenic tissue surrounding the intrahepatic portal vein branches (Figure 4). On contrast-enhanced ultrasound (CEUS) using Sonazoid, the enhancement of the portal vein is delayed in PSVD (71), and this might be due to the abnormalities of the portal veins observed in this disorder. Abnormalities of the intra- and extrahepatic portal venous system are also more commonly observed in PSVD, and include portal vein wall thickening, reduced caliber, and lack of visibility, non-occlusive and occlusive thrombosis. CEUS using Sonazoid with 3D technique, is able to provide a non-invasive portography and to depict the anatomic abnormalities of the intrahepatic portal vein structure and may have the potential to discriminate PSVD from cirrhosis (72).

As for focal liver lesions, benign lesions and in particular FNH and FNH-like nodules showing arterial hyperenhancement and lack of washout and hyperintensity on the HBP of HBA-MRI, and are relatively common in PSVD (12.5–14.0%) (21,65,66). HCC has been very rarely reported (73).

Whether PSVD can be diagnosed by imaging in early stages, before it leads to complications of portal hypertension is unclear. A recent study suggests that in the specific settings as oxaliplatin-induced PSVD, splenomegaly and porto-systemic collaterals develop in 23% of cases during treatment, and resolve in the vast majority of cases after its completion; the lack of improvement of splenomegaly, predicts the development of chronic portal hypertension (74).

<u>Hepatic vein catheterization and hepatic venous pressure gradient (HVPG) measurement</u>

The catheterization of hepatic veins can be used in patients with suspected PSVD to perform liver biopsy (transjugular route), obtain venography images and measure the HVPG. Patients with PSVD and evident clinical signs of portal hypertension show a normal or mildly elevated HVPG (usually below 10 mmHg) (72), which obviously underestimates portal pressure. This mismatch is partly due to a presinusoidal component of portal hypertension, which is not reflected by the wedged hepatic venous pressure, and by the presence of intrahepatic vein-to-vein communicant vessels (HVVC), which are found in over 50% of

cases and prevent an adequate occlusion. While histology remain the reference standard to diagnose PSVD, HVVC should raise the suspicion of PSVD, since they are much less frequent in cirrhosis (10% of cases) (72). Transjugular liver biopsy can be obtained in the same procedure, with the possible advantage of sampling different areas of the parenchyma better reflecting the heterogeneity of the disease.

Liver and spleen stiffness

Values of LSM are in median 7.8-8 kPa in the reported studies; however, up to 50% of patients show values of LSM above 10 kPa, which could suggest cirrhosis (75–77). However, cirrhotic portal hypertension is usually associated with higher LSM values (>20-25 kPa), and lower values of LSM in the presence of specific or unspecific signs of portal hypertension might raise the suspicion of PSVD (75). As expected in pre-sinusoidal causes of PH, LSM does not correlate with HVPG in PSVD. Spleen stiffness measurement (SSM) was markedly increased in PSVD in two studies using point shear wave elastography (78,79), which proposed that in patients with signs of PH the finding of high SSM and normal or slightly elevated LSM (or the ration between these two parameters) should prompt further investigations to rule out PSVD.

Laboratory tests

Thrombocytopenia is the most common laboratory abnormality in PSVD, but no studies regarding its possible prognostic value in this disorder are available. As for diagnostic biomarkers, recently, anti-endothelial cells antibodies (AECA) have been proposed as possible parameter to differentiate PSVD from cirrhosis, since this specific type of autoantibodies is more frequent in patients with PSVD (80). However, 16% of patients with cirrhosis show AECA, and this parameter is unlikely to be sufficient as a single biomarker to be used in an individual patient to diagnose PSVD. However, AECA may raise the suspicion for PSVD. The activity of ADAMTS13 (disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13), a zinc-containing metalloprotease, which cleaves the von Willebrand factor, is significantly reduced in patients with NCPF/IPH (81). Whether this marker of microvascular susceptibility to thrombosis can be used as potential biomarker is unknown.

Metabolomics

In one study comparing PSVD with cirrhosis and healthy subjects, metabolomic analysis of plasma samples showed that two models, respectively including 28 and 31 metabolites could differentiate PSVD from cirrhosis with high accuracy (82). The same authors reported that using an untargeted approach analysis, a metabolomic signature of three specific metabolites can differentiate PSVD from cirrhosis (83). These results hold promise, but have not been validated yet, and the cost of the technique limits its applicability.

Transcriptomics

Using a biological network approach (co-expression gene network analysis) from 20 PSVD cases, 20 age and gender matched patients with cirrhosis and 13 healthy subjects, transcriptomics has recently demonstrated that PSVD is characterized by a deregulation of pathways involved in vascular homeostasis (84). Specifically, the study identified genes of the Serpin family (SERPINC1), the apolipoproteins (APOA, APOB, APOC), ATP synthases (ATP5G1, ATP5B), fibrinogen genes (FGB, FGA) and alpha-2-macroglobulin as differentially expressed in PSVD. These genes are involved in vascular hemostasis, coagulation, lipid metabolism and oxidative phosphorylation, and in other areas of medicine they have been associated with vascular remodeling, atherosclerosis and endothelial dysfunction. Whether these pathways result in differential expression of blood proteins that can be used in biomarkers of PSVD has not been tested so far.

Genomics

A genetic cause for PSVD has been identified in some family clusters and cases using whole genome sequencing. Vilarinho et al. (56) studied 8 children with idiopathic non cirrhotic portal hypertension from 6 families, and identified a rare homozygous p.N46S mutation in DGUOK, a deoxyguanosine kinase required for mitochondrial DNA replication; the mutation impairs adenosine triphosphate binding and reduces catalytic activity and explained the phenotype in 2 of the studied families. In four families with more than one member with PSVD, Sarin et al. reported an association with HLA-DR 3 positive (48). In a family with PSVD (idiopathic non cirrhotic portal hypertension) a mutation in the KCNN3 gene was identified (55). This encodes for SK3 channels which are involved in the regulation of the vascular tone and blood pressure.

8) Research agenda

While the introduction of PSVD as a novel clinical entity is expected to facilitate collaborative studies by providing uniform diagnostic criteria, it may appear as an oversimplification to combine several distinct features and potentially underlying pathophysiologic mechanisms into one umbrella term. For these reasons it is important to collect further experience and refine the definition accordingly. Efforts are ongoing to collect data on patients with PSVD in a registry that will serve as a coordination platform at the European Reference Network Rare Liver for studies to better elucidate the natural history of this condition and its impact.

FIGURE LEGENDS

Figure 1: The term “porto-sinusoidal vascular disorder” is proposed to fill the diagnostic gap represented by patients with histological lesions suggesting PSVD without necessarily having portal hypertension. Moreover, this entity includes patients with the diagnosis of portal vein thrombosis and/or chronic liver disease (viral hepatits, MAFLD, alcoholic liver disease), under the condition that cirrhosis is absent.

Figure 2: The criteria to define porto-sinusoidal vascular disorder require liver biopsy and include the presence of specific or non-specific signs of portal hypertension. Importantly, the absence of portal hypertension and the presence of portal vein thrombosis or of concomitant chronic liver disease are possible in the absence of cirrhosis.

Figure 3:

A. Normal portal tract with a triad characterized by a large portal vein (PV) completely embedded in the portal collagen and smaller portal arterial branch (PA) and interlobular bile duct (BD). (Scale bar 50 um; Masson’s Trichrome).

B-D. Obliterative portal venopathy/portal vein stenosis. On the Hematoxylin-Eosin stain (B, scale bar 75 um), this portal tract is characterized by a complete absence of the portal vein (PA: portal arterial branch). Immunohistochemistry for Keratin 7 (K7) acts as a complementary technique to confirm that this structure is a portal tract by showing the interlobular bile duct and ductular reaction (C, scale bar 75 um). Immunohistochemistry for Glutamine Synthetase (GS) allows the recognition of the centrolobular area. The portal tract (*) seen in that figure is therefore also better identified (D, scale bar 300 um).

E. Obliterative portal venopathy/portal vein stenosis (scale bar 100 um). On the Hematoxylin-Eosin stain, the portal vein (PV) branch is small, difficult to recognize, with narrowing of its lumen.

F-H. Nodular regenerative hyperplasia (scale bar 200 □m). The small hyperplastic nodules close to atrophic hepatocytes plates seen on the Hematoxylin-Eosin stain (F) are enlighten by the Reticulin stain (G) and by Keratin 7 (K7) immunohistochemistry, that underlines the atrophic ischemic plates (H).

I. Incomplete septal fibrosis (scale bar 300 um; Masson’s Trichrome). Thin septa are crossing the liver parenchyma creating some nodular architecture, without cirrhosis, but with

approximation of the hepatic vein (HV) to the portal tracts (PT). This lesion is part of the spectrum of alterations observed in regressing cirrhosis.
J-M. Non-specific histological signs of PSVD: herniated portal vein, a vein in direct contact with the hepatocytes plates, (J, Hematoxylin-Eosin, scale bar 150 um), hypervascularized portal tract and abnormal periportal vessels (K and L, Hematoxylin-Eosin, scale bar 100 um), sinusoidal congestion with delicate perisinusoidal fibrosis (M, Masson's Trichrome, scale bar 150 um).

Figure 4. Imaging features of PSVD (all shown cases had varices on endoscopy, and were histologically confirmed). Panel A. On contrast-enhanced CT the liver is dysmorphic (hypotrophy of the right lobe). The parenchyma around the portal vein branches is poorly enhanced (dotted arrow). Panel B. On CT The liver has a smooth surface (arrow); the splenic vein is very enlarged (dotted arrow). There is a large splenomegaly (*). Panel C. On ultrasound, using a high frequency linear probe, the liver surface looks smooth (arrows). Panel D. On ultrasound, there is a thickening of the intrahepatic portal vein walls (arrows). Panel E. Liver stiffness (in this case using 2D-Shear wave elastography) is often normal or only slightly elevated. Panel F. Spleen stiffness is elevated or markedly elevated. Panel G. On MR angiography, the right liver is hypotrophic. The intrahepatic portal vein has an abnormal morphology (willow-like; arrows), the extrahepatic portal vein is very dilated, and there are porto-systemic collaterals arising from the splenic vein (dotted arrow). The spleen is very enlarged.

Table 1. Imaging features of PSVD that may allow discrimination from cirrhosis.

Imaging (ultrasound, CT, MRI)	Contrast-enhanced imaging	Elastography	Invasive imaging
Smooth liver surface in the majority of patients; in some cases shows a general wave-like pattern with large elevations and depressions (67,68).	Abnormalities of the morphology of the portal vein (intra- and extrahepatic)	Mild-moderate increase of liver stiffness	Portography (portal phase on mesenteric arteriography): abnormal course and branching of intrahepatic peripheral portal branches, poorly contrast-enhanced.
Marginal atrophy and compensatory central hypertrophy (more marked in patients with long progression of the disease) (67,68)	Low enhancement area along the portal vein in the delayed phase	Marked increase of spleen stiffness	Hepatic venography: hepatic vein-to-vein communicant vessels; “willow-like” aspect of the hepatic veins
Atrophy/hypotrophy of the right liver + caudate lobe hypertrophy	Heterogeneous enhancement in the arterial and portal venous phase on CT.		Hepatic venous pressure measurement: usually normal or mildly increased (<10 mmHg)
Presence of benign focal liver lesions (nodular regenerative hyperplasia and focal nodular hyperplasia) (78)	On hepato-biliary imaging MRI, liver enhancement, which depends on the uptake of contrast agents from normal hepatocytes		
Splenomegaly associated with marked dilatation of the splenic artery and vein	Possible occlusive or non-occlusive thrombosis of the portal venous system		
Marked signs of portal hypertension, disproportionate to a conserved liver function	CEUS using Sonazoid: delayed enhancement of the portal vein		
On ultrasound: thickening of the hyperechogenic tissue surrounding the intrahepatic portal vein branches			

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Figure 1: Why PSVD?

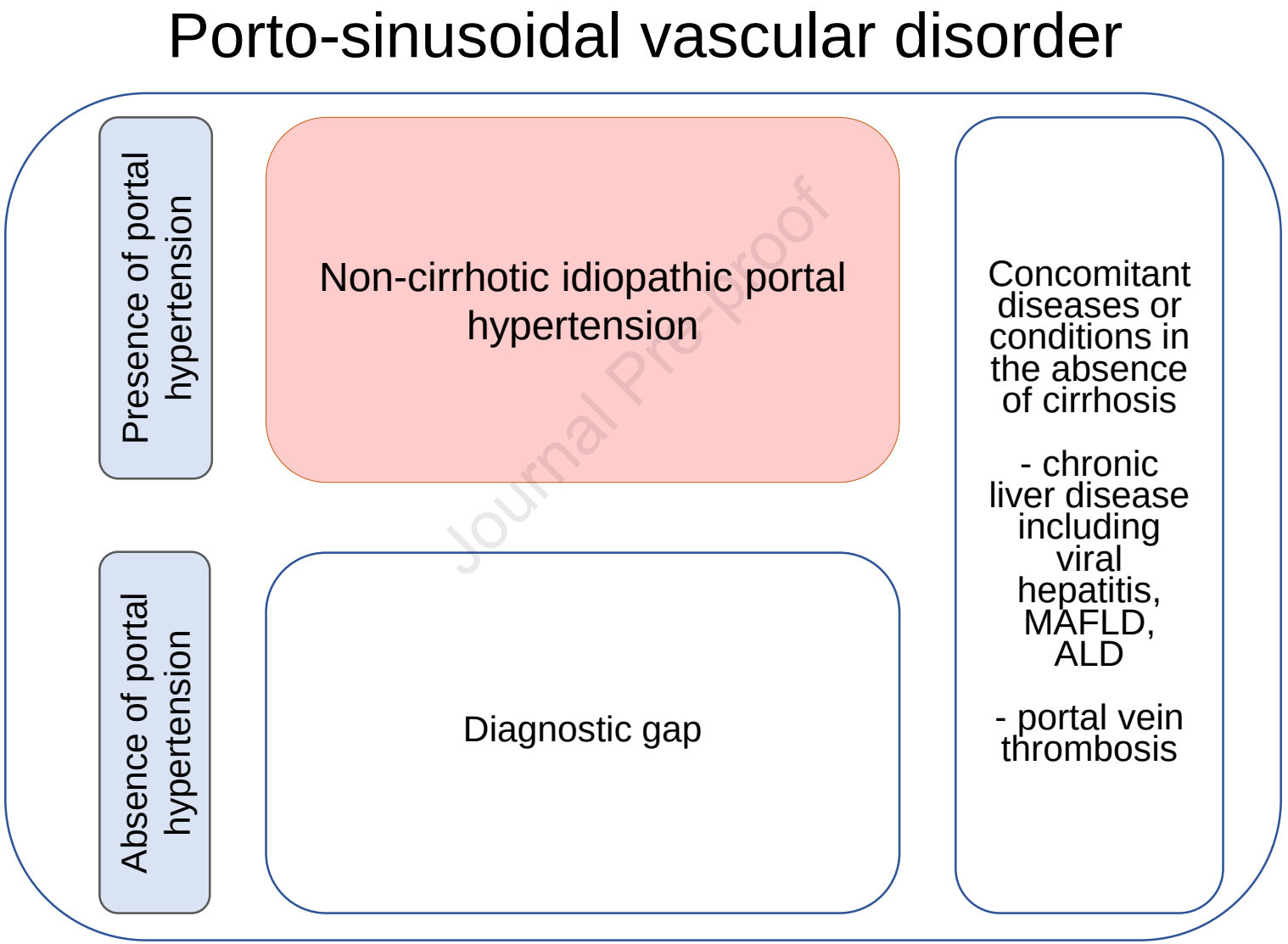


Figure 2: definition of PSVD

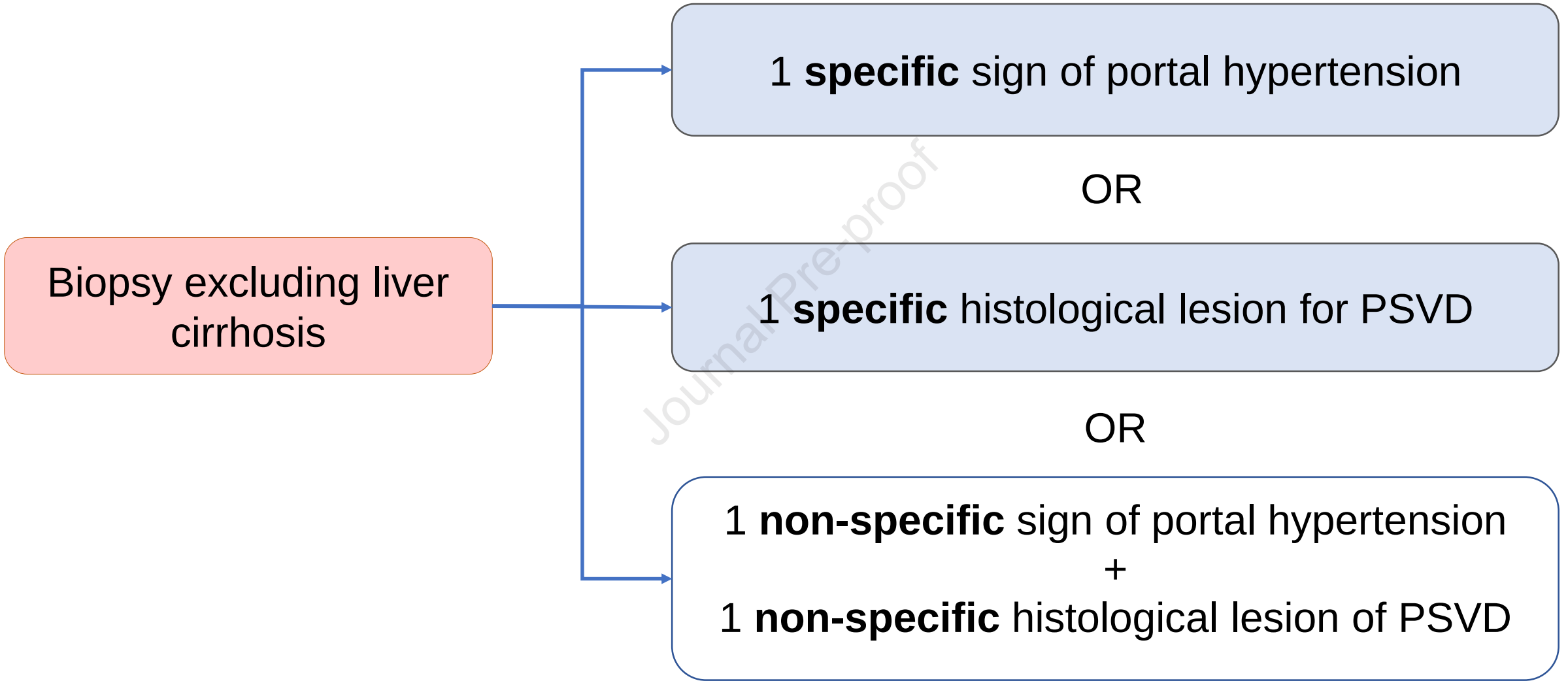
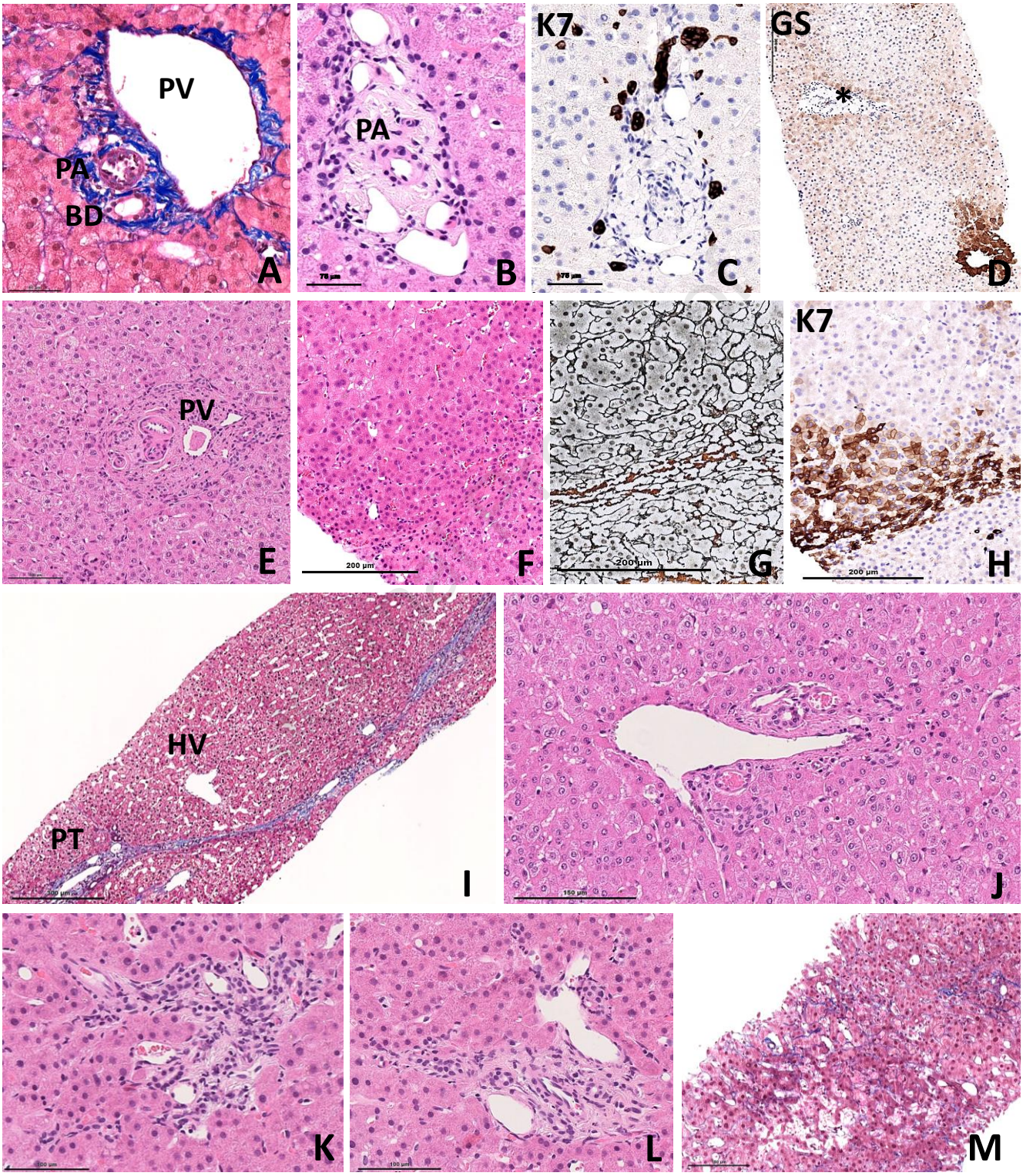


Figure 2 (continued): definition of PSVD

	Signs of portal hypertension	Histological lesions suggestive of PSVD assessed by an expert pathologist	Remarks*
Specific	Gastric, esophageal or ectopic varices Portal hypertensive bleeding Porto-systemic collaterals at imaging	Obliterative portal venopathy (thickening of portal vein branch wall, occlusion of the lumen, vanishing of portal veins) Nodular regenerative hyperplasia Incomplete septal fibrosis (also called incomplete septal cirrhosis); this latter feature can only be assessed on liver explants and not on liver biopsies	The term *portal vein stenosis* is proposed to replace *obliterative portal venopathy*
Not specific	Ascites Platelet count < 150'000/mm^3 Spleen size ≥ 13 cm in the largest axis	Portal tract abnormalities (multiplication, increased number of arteries, periportal vascular channels, aberrant vessels) Architectural disturbance: irregular distribution of the portal tracts and central veins Non-zonal sinusoidal dilatation Mild perisinusoidal fibrosis	The terms: *herniated portal vein branches, hypervascularized portal tracts, and periportal abnormal vessels* are proposed to standardize the nomenclature

* According to Guido et al., Histology of portal vascular changes associated with idiopathic non-cirrhotic portal hypertension: nomenclature and definition. Histopathology, 2019

The diagnosis of PSVD excludes conditions affecting the hepatic veins (Budd-Chiari syndrome) and liver diseases causing microvascular damage (sarcoidosis, congenital hepatic fibrosis, sinusoidal obstruction syndrome)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