Review

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Porto-sinusoidal vascular disorder

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Summary

It is well established that portal hypertension can occur in the absence of cirrhosis, as reported in patients with immune disorders, infections and thrombophilia. However, similar histological abnormalities primarily affecting the hepatic sinusoidal and (peri)portal vasculature have also been observed in patients without portal hypertension. Thus, the term porto-sinusoidal vascular disorder (PSVD) has recently been introduced to describe a group of vascular diseases of the liver featuring lesions encompassing the portal venules and sinusoids, irrespective of the presence/absence 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 alcohol-related 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 liver damage should be carefully assessed. In addition to histology and clinical diagnostic criteria, imaging and non-invasive tests such as liver and spleen stiffness measurements could aid in the diagnostic workup. The introduction of PSVD as a novel clinical entity will facilitate collaborative studies and investigations into the underlying molecular pathomechanisms encompassed by this term.

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Key point

Non-cirrhotic portal hypertension eventually results from different histologic intrahepatic vascular alterations.

Background: why PSVD?

Portal hypertension is the main clinical manifestation of advanced chronic liver disease and may be associated with several complications including variceal bleeding, ascites, and hepatic encephalopathy. It usually develops in patients with advanced chronic liver disease due to chronic viral hepatitis, pathological 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 hepatoportal sclerosis, non-cirrhotic portal fibrosis, nodular regenerative hyperplasia (NRH) 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 with the increasing use of immunosuppressive drugs for autoimmune and haematological disorders and the increased prevalence of treated HIV infections, all conditions that have been linked to NCPH.[2]

The complexity and unclear pathogenesis of NCPH has created various controversies and given rise to several questions. With NCPH being the final common pathway of a number of conditions that lead to 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 alcohol-related 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 portal vein thrombosis (PVT) may be one of the causes, as well as a consequence of NCPH, therefore the concomitant presence of 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 micro-anatomy, as observed on liver histology, are located in the lobular branches of the portal vein and in the sinusoidal area, the name porto-sinusoidal vascular disorder (PSVD) has been proposed[5] (Fig. 1).

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 (Fig. 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 characterised 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 patients with PSVD, extrahepatic PVT does not preclude this diagnosis.

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

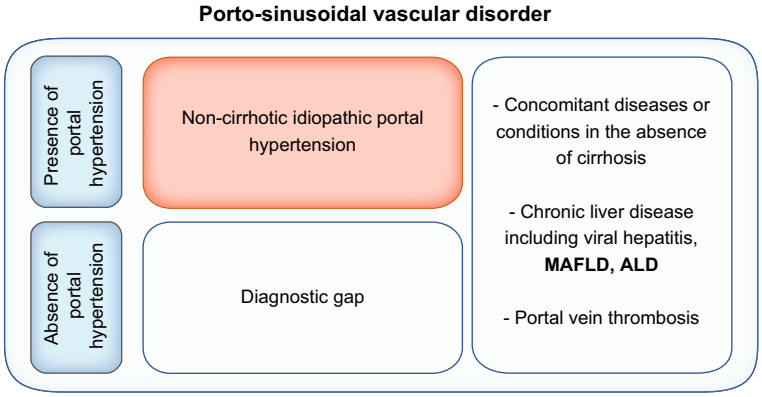
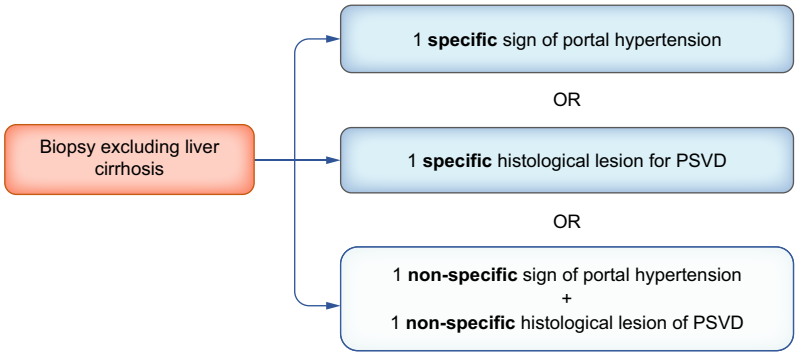


Fig. 1. The term "porto-sinusoidal vascular disorder" is proposed to fill the diagnostic gap represented by patients with histological lesions suggesting porto-sinusoidal vascular disorder without necessarily having portal hypertension. Moreover, this entity includes patients with a diagnosis of portal vein thrombosis and/or chronic liver disease (viral hepatitis, MAFLD, ALD), under the condition that cirrhosis is absent. ALD, alcohol-related liver disease; MAFLD, metabolic dysfunction-associated fatty liver disease.

Liver histology: the different features of PSVD

The diagnosis of PSVD requires, by definition, the examination of a liver biopsy. This biopsy should be



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

* 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).

Fig. 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. PSVD, porto-sinusoidal vascular disorder.

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 sinusoids by an expert liver pathologist.

In a normal liver, a portal tract contains on average 1 portal vein branch, 1 or 2 interlobular bile ducts and 1 or 2 hepatic arterial branches.[6] The portal vein branch, always entirely confined to the portal tract, is commonly 3 or even 4 times larger than the hepatic artery branch and the interlobular bile duct, both of which have the same diameter (Fig. 3A). Portal tracts missing 1 of the 3 components are frequent: while less than 10% contain either no hepatic artery branch or no interlobular bile duct, up to one-third of the portal tracts are missing the portal vein branch.[13]

Three types of histological lesions are recognised as specific for the diagnosis of PSVD. The first is obliterative portal venopathy (Fig. 3B–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 on the terminology for portal and periportal vascular changes associated with idiopathic NCPH, and they propose replacing the term obliterative portal venopathy with 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 enabling the recognition of the portal tract at lower power on the microscope, is not visible anymore (Fig. 3B). In case of difficulties, immunohistochemistry for keratin 7 will enable recognition of the portal tracts by revealing the interlobular bile ducts and/or some ductular reaction (Fig. 3C), whereas the detection of glutamine synthetase will help in locating the centrilobular area (Fig. 3D). Another way to recognise portal vein stenosis, which is 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 (Fig. 3E). Portal vein stenosis has been shown to be the only strong independent histological predictor of NCPH.[8] The second specific lesion is NRH, a diffuse micronodularity of the liver parenchyma in the absence of fibrosis (Fig. 3F–H).[16] NRH is better identified on a reticulin stain, which should always be performed (Fig. 3G). The small nodules of hyperplastic hepatocytes alternate with areas of atrophic plates, which often express keratin 7 on immunohistochemistry (a sign of biliary metaplasia resulting from ischaemia) (Fig. 3H).[9] The third histological lesion considered as specific is so-called incomplete septal fibrosis/cirrhosis. It is described as a liver parenchyma intersected by thin and incomplete fibrotic bands,[10,11] giving rise to incomplete nodules in the vicinity of the portal tracts and the centrilobular areas (Fig. 3I). This is actually a complex entity that is not only difficult to recognise on a liver biopsy, but is also likely to represent one of the features of regressing cirrhosis.[12–14] Currently, it is primarily included in the spectrum of PSVD on clinical grounds.

In the absence of a specific histological lesion and a specific sign of portal hypertension, the diagnosis of PSVD requires both a non-specific sign of portal hypertension and a non-specific histological sign of PSVD (Fig. 3K–M). As indicated previously, the names and descriptions of these non-specific histological lesions have been standardised.[7] Herniated portal vein branches, *i.e.* veins not fully embedded in the portal tracts but directly abutting the periportal hepatocytes plates, are one such feature (Fig. 3J). The other ones are the identification of small and thin-walled vascular spaces located either within the portal tracts (called hypervascularised portal tracts) or at the periphery of the portal tracts (called periportal abnormal vessels). These small vessels are either single or numerous and they have different shapes (Fig. 3K, L). Non-specific features of PSVD are also found outside of the portal tracts and correspond to sinusoidal dilatation and mild perisinusoidal fibrosis (Fig. 3M). All these modifications have an uneven distribution and can be very subtle. They may therefore remain under-recognised 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 non-specific, even NRH, have also been described in the absence of portal hypertension.[15,17,18] Therefore, when a liver biopsy is performed for mild liver enzyme abnormalities of unknown aetiology, 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, as the natural history without portal hypertension is still unknown.

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

Key point

The term porto-sinusoidal vascular disorder has been proposed to encompass histological hepatic architectural changes in the presence or absence of portal hypertension.

Clinical manifestations

Patients with PSVD-related portal hypertension are usually asymptomatic until they develop complications of portal hypertension. Transaminases,

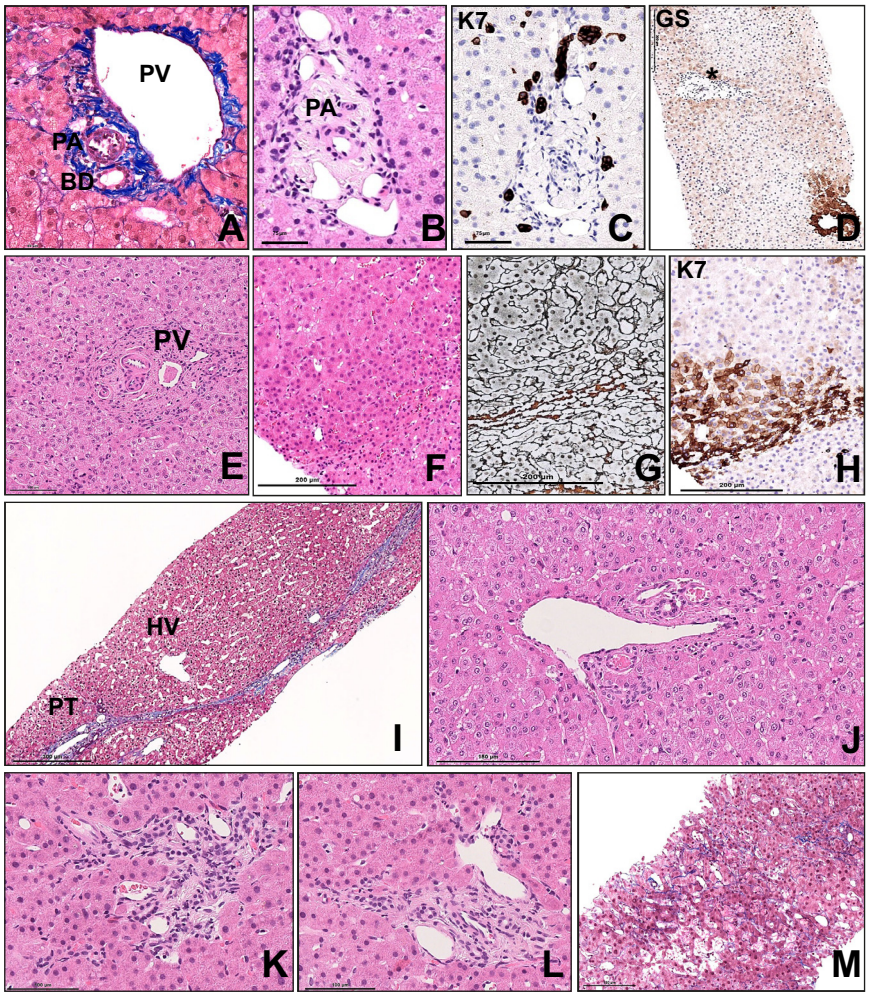


Fig. 3. Features of PSVD on liver histology. (A) Normal portal tract with a triad characterised by a large PV completely embedded in the portal collagen and smaller PA and interlobular BD (Scale bar 50 μm; Masson's trichrome). (B-D) Obliterative portal venopathy/portal vein stenosis. On the H&E stain (B, scale bar 75 μm), this portal tract is characterised by a complete absence of the PV. Immunohistochemistry for K7 acts as a complementary technique to confirm that this structure is a PT by showing the interlobular BD and ductular reaction (C, scale bar 75 μm). Immunohistochemistry for GS enables the recognition of the centrilobular area. The portal tract (*) seen in that figure is therefore also better identified (D, scale bar 300 μm). (E) Obliterative portal venopathy/portal vein stenosis (scale bar 100 μm). On the H&E stain, the PV branch is small, difficult to recognise, with narrowing of its lumen. (F–H) Nodular regenerative hyperplasia (scale bar 200 μm). The small hyperplastic nodules close to atrophic hepatocytes plates seen on the H&E stain (F) are enlightened by the Reticulin stain (G) and by K7 immunohistochemistry, that underlines the atrophic ischaemic plates (H). (I) Incomplete septal fibrosis (scale bar 300 μm; Masson's trichrome). Thin septa are crossing the liver parenchyma creating some nodular architecture, without cirrhosis, but with approximation of the HV to the PTs. 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 hepatocyte plates, (J, H&E, scale bar 150 μm), hypervascularised PT and abnormal periportal vessels (K and L, H&E, scale bar 100 μm), sinusoidal congestion with delicate perisinusoidal fibrosis (M, Masson's Trichrome, scale bar 150 μm). BD, bile duct; GS, glutamine synthetase; HV, hepatic vein; K7, keratin 7; PA, portal arterial branch; PTs, portal tracts; PV, portal vein.

alkaline phosphatase and gamma-glutamyltransferase 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 idiopathic NCPH is characterised by the presence of large varices in two-thirds of patients with PSVD and portal hypertension, and it develops in 20% of patients within an average of 10 years of diagnosis.[24]

Patients with PSVD and portal hypertension develop ascites in 20-50% of cases. Within 5 years of diagnosis, PVT develops in around a third of patients, 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 does not evolve rapidly.[17] However, complications of portal hypertension including portopulmonary hypertension or hepatopulmonary syndrome, as well as hepatic regenerative nodules, may develop 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 liver transplant-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]

In up to 70% of cases, PSVD may occur in the absence of any signs of portal hypertension, such as splenomegaly, gastro-oesophageal varices, porto-systemic collaterals, ascites, or hepatic encephalopathy.[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. However, the precise diagnosis is established by specific findings on liver biopsy in patients presenting with asymptomatic abnormalities of liver laboratory parameters. The natural history and risk factors of PSVD without clinical features of portal hypertension remain largely unknown and only limited data are available.[27,28]

Hypotheses on pathogenesis

Key point

The diagnosis of PSVD requires a liver biopsy.

In about 50% of patients, PSVD is associated with rare conditions that include specific drug exposure, immune disorders or autoimmune diseases, coagulation disorders, infectious diseases, and congenital or hereditary diseases.[1,5,24] More than one 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, while an overall prevalence of HIV infection in patients with PSVD of 4% was reported 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 NRH, portal sclerosis, and NCPH, while chronic subclinical injury occurs in up to 78% of patients.[33] Moreover, following drug exposure, patients with HIV infection and NRH 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 expected over the next decades.

Thrombophilia

Thickening or occlusion and obliteration of portal venules detected on liver biopsy is generally regarded as indicative of 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 patients with PSVD.[38] Despite the low number of reported cases, factor V Leiden mutations have also been associated with the development of PSVD.[39] PVT is relatively common, further pointing to a procoagulant tendency in these patients.[40] Moreover, it remains unclear whether PVT 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 PVT. 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 recognised as a possible aetiological factor in PSVD.[47]

Hereditary diseases

Familial aggregation and a high rate of HLA-DR3 positivity have been associated with PSVD(48), suggesting the possibility of an immunogenetic basis of non-cirrhotic 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 haematologic and liver abnormalities.[49] In addition to telomere disorders (mutations in *TERT* and *TERC*), developmental disorders (*NOTCH1* and *CTC1*), Turner's syndrome, and *FOPV* (familial obliterative portal venopathy) gene mutations have been reported.[50–53] In patients with HIV and 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 by 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).

Novel insights into the interplay between the 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 NCPH.[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 coeliac disease has also been associated with PSVD. In patients with coeliac 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 or granulomas that cause portal vein or sinusoidal endothelitis. This concept is in line with an overexpression of lymphocyte activation genes in blood samples from patients with PSVD.[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 to a lesser degree than in patients with cirrhosis.[64] These findings suggest that activation of macrophages is 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 so far been insufficiently studied.

Imaging and biomarkers

Ultrasound, CT and MRI

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

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

Key point

Specific and non-specific diagnostic criteria of PSVD include histological features on liver biopsy and clinical features of portal hypertension.

An anatomically dysmorphic liver with atrophy/hypotrophy of the right liver and caudate lobe hypertrophy are more commonly observed in PSVD (Fig. 4), while segment IV atrophy is more common in cirrhosis.[21,65,66] Furthermore, marginal atrophy associated with compensatory central hypertrophy has been described, particularly in patients who have had the disease for a long time.[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 compared to patients with cirrhosis and similar liver function (Fig. 4); furthermore, "ectopic" collaterals and fundal varices are more frequent in PSVD.

As for the appearance of the liver parenchyma, PSVD commonly has a homogenous pattern on ultrasound. On the other hand, PSVD commonly shows a heterogeneous enhancement in the arterial and portal venous phase on CT. On hepatobiliary imaging MRI, liver enhancement, which depends on the uptake of contrast agents from normal hepatocytes,[69] is higher in PSVD than in cirrhosis.

In addition, in PSVD, the liver parenchyma shows a low enhancement area along the portal vein in the delayed phase on contrast-enhanced imaging.[65,70] Interestingly, on ultrasound this

Table 1. Imaging features of PSVD that may differentiate it 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 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			

CEUS, contrast-enhanced ultrasound; PSVD, porto-sinusoidal vascular disorder.

corresponds to an increased thickening of the hyperechogenic tissue surrounding the intrahepatic portal vein branches (Fig. 4). On contrast-enhanced ultrasound using Sonazoid, the enhancement of the portal vein is delayed in PSVD,[71] which 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 calibre, and lack of visibility, as well as non-occlusive and occlusive thrombosis. Sonazoid-enhanced ultrasound using a 3D technique is able 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 (particularly FNH and FNH-like nodules showing arterial hyperenhancement and lack of washout and hyperintensity on the hepatobiliary phase of HBA-MRI) are relatively common in PSVD (12.5–14.0%),[21,65,66] while HCC has been reported very rarely.[73]

It is unclear whether PSVD can be diagnosed by imaging in early stages, before it leads to complications of portal hypertension. A recent study suggests that in specific settings, such 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]

Hepatic vein catheterisation and HVPG measurement

The catheterisation of hepatic veins can be used in patients with suspected PSVD to perform liver biopsy (transjugular route), obtain venography images and measure the hepatic venous pressure gradient (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 pre-sinusoidal 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, which are found in over 50% of cases and prevent adequate occlusion. While histology remains the reference standard to diagnose PSVD, intrahepatic vein-to-vein communicant vessels 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 and thereby better reflecting the heterogeneity of the disease.

Liver and spleen stiffness

Median LSM values are 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), so lower values of LSM in the

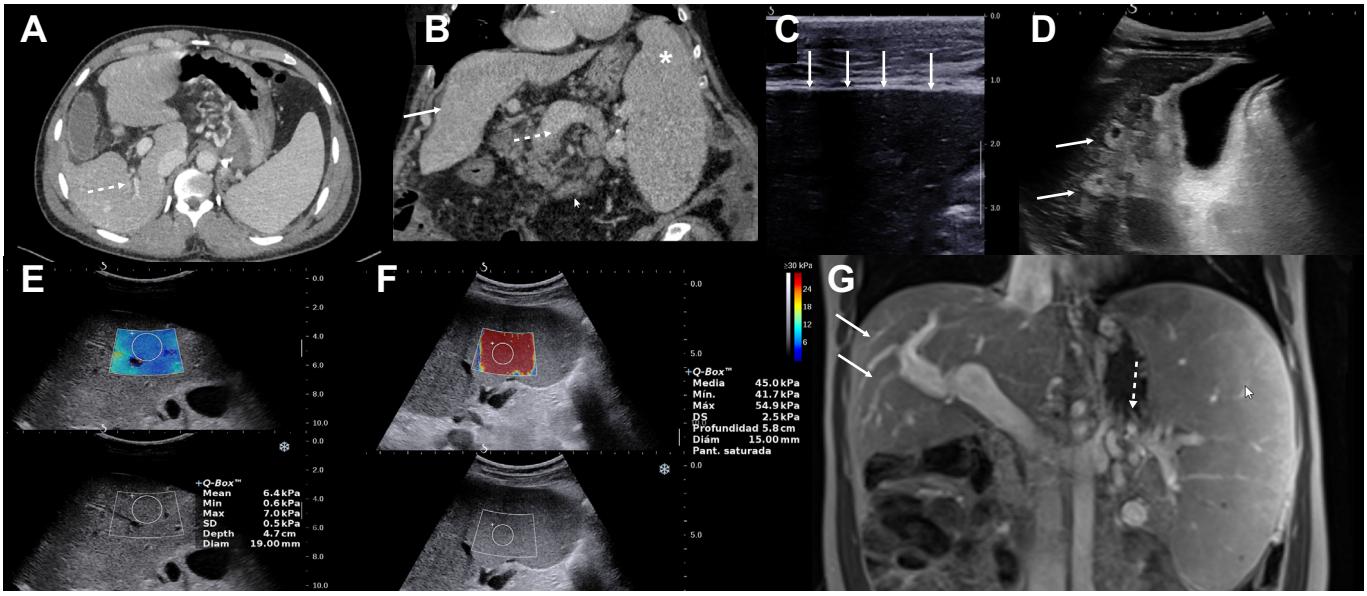


Fig. 4. Imaging features of PSVD (all shown cases had varices on endoscopy and were histologically confirmed). (A) On contrast-enhanced CT the liver is dysmorphic (hypotrophy of the right lobe). The parenchyma around the portal vein branches is poorly enhanced (dotted arrow). (B) On CT, the liver has a smooth surface (arrow); the splenic vein is very enlarged (dotted arrow). There is a large splenomegaly (*). (C) On ultrasound, using a high frequency linear probe, the liver surface looks smooth (arrows). (D) On ultrasound, there is a thickening of the intrahepatic portal vein walls (arrows). (E) Liver stiffness (in this case using 2D-shear wave elastography) is often normal or only slightly elevated. (F) Spleen stiffness is elevated or markedly elevated. (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.

presence of specific or unspecific signs of portal hypertension might raise the suspicion of PSVD.[75] As expected for pre-sinusoidal causes of PH, LSM does not correlate with HVPG in PSVD. Spleen stiffness measurement was markedly increased in PSVD in 2 studies using point shear wave elastography,[78,79] which proposed that in patients with signs of PH the finding of high spleen stiffness measurement and normal or slightly elevated LSM (or the ratio between these 2 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 cell antibodies (AECAs) have been proposed as possible parameters to differentiate PSVD from cirrhosis, since this specific type of autoantibody is more frequent in patients with PSVD.[80] However, 16% of patients with cirrhosis show AECA positivity, and this parameter is unlikely to be sufficient as a single biomarker 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 non-cirrhotic portal fibrosis/idiopathic portal hypertension.[81] Whether this marker of microvascular susceptibility to thrombosis can be used as a potential biomarker is unknown.

Metabolomics

In one study comparing patients with PSVD to those with cirrhosis and healthy individuals, metabolomic analysis of plasma samples showed that 2 models, including 28 and 31 metabolites, respectively, could differentiate PSVD from cirrhosis with high accuracy.[82] The same authors used an untargeted approach to show that a metabolomic signature of 3 specific metabolites can differentiate PSVD from cirrhosis.[83] These results hold promise, but have not been validated, and the cost of the technique limits its applicability.

Transcriptomics

Using a biological network approach (co-expression gene network analysis) to compare 20 PSVD cases, 20 age and sex-matched patients with cirrhosis and 13 healthy individuals, transcriptomics has recently demonstrated that PSVD is characterised 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 haemostasis, coagulation, lipid metabolism and oxidative phosphorylation, and in other areas of medicine they have been associated with vascular remodelling,

Key point

Imaging and non-invasive techniques play an increasingly important role in the diagnosis and management of PSVD.

atherosclerosis and endothelial dysfunction. Whether these pathways result in differential expression of blood proteins that can be used as biomarkers of PSVD has not yet been tested.

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 NCPH from 6 families, and identified a rare homozygous p.N46S mutation in *DGUOK*, a deoxyguanosine kinase required for mitochondrial DNA replication; the mutation impairs ATP binding and reduces catalytic activity, explaining the phenotype in 2 of the studied families. In 4 families with more than 1 member with PSVD, Sarin *et al.* reported an association with HLA-DR 3 positivity.[48] In a family with PSVD (idiopathic NCPH) a mutation in the *KCNN3* gene was identified.[55] This encodes for SK3 channels which are involved in the regulation of vascular tone and blood pressure.

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 under one umbrella term. For these reasons it is important to collect more data 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 ERN RARE-LIVER (European Reference Network for rare liver diseases) for studies to better elucidate the natural history of this condition and its impact.

Abbreviations

AECAs, anti-endothelial cell antibodies; FNH, focal nodular hyperplasia; HVPG, hepatic venous pressure gradient; LSM, liver stiffness measurement; NCPH, non-cirrhotic portal hypertension; NRH, nodular regenerative hyperplasia; PSVD, porto-sinusoidal vascular disorder; PVT, portal vein thrombosis.

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

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Authors' contributions

Manuscript conception and design; literature search; draft manuscript preparation; critical review of the manuscript: ADG, CS, AB.

Supplementary data

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References

[1] Schouten JNL, Verheij J, Seijo S. Idiopathic non-cirrhotic portal hypertension: a review. Orphanet J Rare Dis 2015 May 30;10(1).
[2] Chang PE, Miquel R, Blanco JL, Laguno M, Bruguera M, Abraldes JG, et al. Idiopathic portal hypertension in patients with HIV infection treated with highly active antiretroviral therapy. Am J Gastroenterol [Internet]. 2009 Jul;104(7):1707–1714 [cited 2021 Dec 8]. Available from: https://pubmed.ncbi.nlm.nih.gov/19471257/.
[3] Tublin ME, Towbin AJ, Federle MP, Nalesnik MA. Altered liver morphology after portal vein thrombosis: not always cirrhosis. Dig Dis Sci [Internet]. 2008 Oct;53(10):2784–2788 [cited 2021 Dec 8]. Available from: https://pubmed.ncbi.nlm.nih.gov/18270830/.
[4] Marin D, Galluzzo A, Plessier A, Brancatelli G, Valla D, Vilgrain V. Focal nodular hyperplasia-like lesions in patients with cavernous transformation of the portal vein: prevalence, MR findings and natural history. Eur Radiol [Internet]. 2011 Oct;21(10):2074–2082 [cited 2021 Dec 8]. Available from: https://pubmed.ncbi.nlm.nih.gov/21710271/.
[5] De Gottardi A, Rautou P-E, Schouten J, Rubbia-Brandt L, Leebeek F, Trebicka J, et al. Porto-sinusoidal vascular disease: proposal and description of a novel entity. Lancet Gastroenterol Hepatol 2019;4(5).
[6] Crawford AR, Lin XIZ, Crawford JM. The normal adult human liver biopsy: a quantitative reference standard. Hepatology [Internet]. 1998;28(2):323–331 [cited 2022 Jan 28]. Available from: https://pubmed.ncbi.nlm.nih.gov/9695993/.
[7] Guido M, Alves VAF, Balabaud C, Bathal PS, Bioulac-Sage P, Colombari R, et al. Histology of portal vascular changes associated with idiopathic non-cirrhotic portal hypertension: nomenclature and definition. Histopathology [Internet]. 2019 Jan 1;74(2):219–226 [cited 2022 Jan 28]. Available from: https://pubmed.ncbi.nlm.nih.gov/30129657/.
[8] Liang J, Shi C, Dupont WD, Salaria SN, Huh WJ, Correa H, et al. Key histopathologic features in idiopathic noncirrhotic portal hypertension: an interobserver agreement study and proposal for diagnostic criteria. Mod Pathol [Internet]. 2021 Mar 1;34(3):592–602 [cited 2022 Jan 28]. Available from: https://pubmed.ncbi.nlm.nih.gov/32958831/.
[9] Delladetsima I, Sakellariou S, Kokkori A, Tiniakos D. Atrophic hepatocytes express keratin 7 in ischemia-associated liver lesions. Histol Histopathol [Internet]. 2016 Oct 1;31(10):1089–1094 [cited 2022 Jan 28]. Available from: https://pubmed.ncbi.nlm.nih.gov/26887669/.
[10] Sciot R, Staessen D, Van Damme B, Van Steenbergen W, Fevery J, De Groote J, et al. Incomplete septal cirrhosis: histopathological aspects. Histopathology [Internet]. 1988;13(6):593–603 [cited 2022 Jan 28]. Available from: https://pubmed.ncbi.nlm.nih.gov/2466750/.
[11] Nakanuma Y, Nonomura A, Hayashi M, Doishita K, Takayanagi N, Uchida T, et al. Pathology of the liver in "idiopathic portal hypertension" associated with autoimmune disease. The Ministry of Health and Welfare Disorders of Portal Circulation Research Committee. Acta Pathol Jpn [Internet]. 1989;39(9):586–592 [cited 2021 Dec 26] Available from: https://pubmed.ncbi.nlm.nih.gov/2596298/.
[12] Khan S, Saxena R. Regression of hepatic fibrosis and evolution of cirrhosis: a concise review. Adv Anat Pathol [Internet]. 2021;28(6) [cited 2022 Jan 28] Available from: https://pubmed.ncbi.nlm.nih.gov/34326286/.
[13] Hytiroglou P, Theise ND. Regression of human cirrhosis: an update, 18 years after the pioneering article by Wanless et al. Virchows Arch [Internet]. 2018 Jul 1;473(1):15–22 [cited 2022 Jan 28]. Available from: https://pubmed.ncbi.nlm.nih.gov/29589101/.
[14] Wanless IR, Nakashima E, Sherman M. Regression of human cirrhosis morphologic features and the genesis of incomplete septal cirrhosis. Arch Pathol Lab Med [Internet]. 2000 Nov 1;124(11):1599–1607 [cited 2022 Jan 28] Available from: https://meridian.allenpress.com/aplm/article/124/11/1599/452444/Regression-of-Human-CirrhosisMorphologic-Features.

[15] Guido M, Sarcognato S, Sonzogni A, Lucà MG, Senzolo M, Fagiuoli S, et al. Obliterative portal venopathy without portal hypertension: an underestimated condition. Liver Int [Internet]. 2016 Mar 1;36(3):454–460 [cited 2021 Dec 20] Available from: https://pubmed.ncbi.nlm.nih.gov/26264219/.
[16] Krasinskas AM, Goldsmith JD, Burke A, Furth EE. Abnormal intrahepatic portal vasculature in native and allograft liver biopsies: a comparative analysis. Am J Surg Pathol [Internet]. 2005 Oct;29(10):1382–1388 [cited 2022 Jan 29] Available from: https://pubmed.ncbi.nlm.nih.gov/16160482/.
[17] Cazals-Hatem D, Hillaire S, Rudler M, Plessier A, Paradis V, Condat B, et al. Obliterative portal venopathy: portal hypertension is not always present at diagnosis. J Hepatol [Internet]. 2011 Mar;54(3):455–461 [cited 2021 Dec 15] Available from: https://pubmed.ncbi.nlm.nih.gov/21087805/.
[18] Wanless IR. Micronodular transformation (nodular regenerative hyperplasia) of the liver: a report of 64 cases among 2,500 autopsies and a new classification of benign hepatocellular nodules. Hepatology [Internet]. 1990;11(5):787–797 [cited 2022 Jan 28] Available from: https://pubmed.ncbi.nlm.nih.gov/2189821/.
[19] Guido M, Sarcognato S, Sacchi D, Colloredo G. Pathology of idiopathic non-cirrhotic portal hypertension. Virchows Arch [Internet]. 2018 Jul 1;473(1):23–31 [cited 2022 Jan 29] Available from: https://pubmed.ncbi.nlm.nih.gov/29644430/.
[20] Sempoux C, Balabaud C, Paradis V, Bioulac-Sage P. Hepatocellular nodules in vascular liver diseases. Virchows Arch 2018 Jul 1;473(1):33–44.
[21] Glatard AS, Hillaire S, D'Assignies G, Cazals-Hatem D, Plessier A, Valla DC, et al. Obliterative portal venopathy: findings at CT imaging. Radiology [Internet]. 2012;263(3):741–750 [cited 2021 Dec 26] Available from: https://pubmed.ncbi.nlm.nih.gov/22474672/.
[22] Sempoux C, Paradis V, Komuta M, Wee A, Calderaro J, Balabaud C, et al. Hepatocellular nodules expressing markers of hepatocellular adenomas in Budd-Chiari syndrome and other rare hepatic vascular disorders. J Hepatol 2015 Nov 1;63(5):1173–1180.
[23] Montenovo MI, Jalikis FG, Yeh M, Reyes JD. Progression of hepatic adenoma to carcinoma in the setting of hepatoportal sclerosis in HIV patient: case report and review of the literature. Case Rep Hepatol [Internet]. 2016;2016:1732069 [cited 2022 Jan 29] Available from: http://www.ncbi.nlm.nih.gov/pubmed/27812395.
[24] Siramolpiwat S, Seijo S, Miquel R, Berzigotti A, Garcia-Criado A, Darnell A, et al. Idiopathic portal hypertension: natural history and long-term outcome. Hepatology [Internet]. 2014;59(6):2276–2285 [cited 2021 Dec 8] Available from: https://pubmed.ncbi.nlm.nih.gov/24155091/.
[25] Schouten JNL, Van Der Ende ME, Koëter T, Rossing HHM, Komuta M, Verheij J, et al. Risk factors and outcome of HIV-associated idiopathic noncirrhotic portal hypertension. Aliment Pharmacol Ther [Internet]. 2012 Nov;36(9):875–885 [cited 2021 Dec 15] Available from: https://pubmed.ncbi.nlm.nih.gov/22971050/.
[26] Schouten JNL, Nevens F, Hansen B, Laleman W, Van Den Born M, Komuta M, et al. Idiopathic noncirrhotic portal hypertension is associated with poor survival: results of a long-term cohort study. Aliment Pharmacol Ther 2012 Jun;35(12):1424–1433.
[27] Wöran K, Semmler G, Jachs M, Simbrunner B, Bauer DJM, Binter T, et al. Clinical course of porto-sinusoidal vascular disease is distinct from idiopathic noncirrhotic portal hypertension. Clin Gastroenterol Hepatol [Internet]. 2020 [cited 2021 Dec 20]; Available from: https://pubmed.ncbi.nlm.nih.gov/33279774/.
[28] Gioia S, Riggio O, Nardelli S, d'Amati G, Ridola L. Identifying patients at high risk of developing non-cirrhotic portal hypertension. Hepat Med [Internet]. 2021 Nov;13:105–111 [cited 2021 Dec 20] Available from: https://pubmed.ncbi.nlm.nih.gov/34764704/.
[29] Toksvang LN, Schmidt MS, Arup S, Larsen RH, Frandsen TL, Schmiegelow K, et al. Hepatotoxicity during 6-thioguanine treatment in inflammatory bowel disease and childhood acute lymphoblastic leukaemia: a systematic review. PLoS One [Internet]. 2019 May 1;14(5) [cited 2021 Dec 20]. Available from: https://pubmed.ncbi.nlm.nih.gov/31125338/.
[30] Ghabril M, Vuppalanchi R. Drug-induced nodular regenerative hyperplasia. Semin Liver Dis [Internet]. 2014;34(2):240–245 [cited 2021 Dec 20] Available from: https://pubmed.ncbi.nlm.nih.gov/24879987/.
[31] Lee H, Rehman AU, Isabel Fiel M. Idiopathic noncirrhotic portal hypertension: an appraisal. J Pathol Transl Med [Internet]. 2016;50(1):17–25 [cited 2021 Dec 20] Available from: https://pubmed.ncbi.nlm.nih.gov/26563701/.
[32] Cotte L, Bénet T, Billioud C, Miailhes P, Scoazec JY, Ferry T, et al. The role of nucleoside and nucleotide analogues in nodular regenerative hyperplasia in HIV-infected patients: a case control study. J Hepatol [Internet]. 2011 Mar;54(3):489–496 [cited 2021 Dec 20] Available from: https://pubmed.ncbi.nlm.nih.gov/21056493/.
[33] Kim HP, Navarro V, Zacks S, Odin J, Kleiner DE, Hayashi PH. The clinical spectrum and diagnosis of oxaliplatin liver injury in the era of nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol [Internet]. 2021 Oct 1;19(10):2199–2201 [cited 2021 Dec 20] Available from: https://pubmed.ncbi.nlm.nih.gov/33007507/.
[34] Mallet VO, Varthaman A, Lasne D, Viard JP, Gouya H, Borgel D, et al. Acquired protein S deficiency leads to obliterative portal venopathy and to compensatory nodular regenerative hyperplasia in HIV-infected patients. AIDS [Internet]. 2009 Jul;23(12):1511–1518 [cited 2021 Dec 20] Available from: https://pubmed.ncbi.nlm.nih.gov/19512859/.
[35] Nayak NC. Idiopathic portal hypertension (noncirrhotic portal fibrosis), thrombosis in portal venous system and protein C deficiency. Hepatology [Internet]. 1989;10(5). 902–902. [cited 2021 Dec 25] Available from: https://pubmed.ncbi.nlm.nih.gov/2807175/.
[36] Hwang S, Kim DY, Kim M, Chon YE, Lee HJ, Park YN, et al. Deficiencies in proteins C and S in a patient with idiopathic portal hypertension accompanied by portal vein thrombosis. Korean J Hepatol [Internet]. 2010;16(2):176–181 [cited 2021 Dec 25] Available from: https://pubmed.ncbi.nlm.nih.gov/20606502/.
[37] Okuda K, Orozco H, Garcia-Tsao G, Takahashi T. Idiopathic portal hypertension and protein C deficiency. Hepatology [Internet]. 1989;10(5). 903–903. [cited 2021 Dec 26] Available from: https://pubmed.ncbi.nlm.nih.gov/2807176/.
[38] Murai Y, Ohfuji S, Fukushima W, Tamakoshi A, Yamaguchi S, Hashizume M, et al. Prognostic factors in patients with idiopathic portal hypertension: two Japanese nationwide epidemiological surveys in 1999 and 2005. Hepatol Res [Internet]. 2012 Dec;42(12):1211–1220 [cited 2021 Dec 25] Available from: https://pubmed.ncbi.nlm.nih.gov/22583903/.
[39] Ishii M, Katada Y. Idiopathic portal hypertension in a systemic sclerosis patient heterozygous for factor V Leiden mutation. Rheumatol Int [Internet]. 2003;23(1):44–46 [cited 2021 Dec 25]. Available from: https://pubmed.ncbi.nlm.nih.gov/12548441/.
[40] Matsutani S, Maruyama H, Akiike T, Kobayashi S, Yoshizumi H, Okugawa H, et al. Study of portal vein thrombosis in patients with idiopathic portal hypertension in Japan. Liver Int [Internet]. 2005 Oct;25(5):978–983 [cited 2021 Dec 25] Available from: https://pubmed.ncbi.nlm.nih.gov/16162156/.
[41] Kline K, Al Hanayneh M, Bilal M, Stevenson-Lerner H. Portal vein thrombosis leading to pre-sinusoidal non-cirrhotic portal hypertension resulting in decreased synthetic function of the liver. Gastroenterol Hepatol Bed Bench [Internet]. 2019;12(2):174–177 [cited 2021 Dec 26] Available from: https://pubmed.ncbi.nlm.nih.gov/31191844/.
[42] Goel A, Ramakrishna B, Zachariah U, Sajith KG, Burad DK, Kodiatte TA, et al. What makes non-cirrhotic portal hypertension a common disease in India? Analysis for environmental factors. Indian J Med Res [Internet]. 2019 Apr 1;149(4):468–478 [cited 2021 Dec 26] Available from: https://pubmed.ncbi.nlm.nih.gov/31411170/.
[43] Guha Mazumder DN. Effect of chronic intake of arsenic-contaminated water on liver. Toxicol Appl Pharmacol 2005 Aug 15;206(2):169–175.
[44] Kono K, Ohnishi K, Omata M, Saito M, Nakayama T, Hatano H, et al. Experimental portal fibrosis produced by intraportal injection of killed nonpathogenic Escherichia coli in rabbits. Gastroenterology [Internet]. 1988;94(3):787–796 [cited 2021 Dec 26] Available from: https://pubmed.ncbi.nlm.nih.gov/3276575/.
[45] Harmanci O, Bayraktar Y. Clinical characteristics of idiopathic portal hypertension. World J Gastroenterol [Internet]. 2007 Apr 7;13(13):1906 [cited 2021 Dec 26] Available from: pmc/articles/PMC4146965/.
[46] Sarin SK. Non-cirrhotic portal fibrosis. J Gastroenterol Hepatol [Internet]. 2002;17(Suppl 3) [cited 2021 Dec 26] Available from: https://pubmed.ncbi.nlm.nih.gov/12472939/.
[47] Vispo E, Morello J, Rodriguez-Novoa S, Soriano V. Noncirrhotic portal hypertension in HIV infection. Curr Opin Infect Dis [Internet]. 2011 Feb;24(1):12–18 [cited 2021 Dec 26] Available from: https://pubmed.ncbi.nlm.nih.gov/21157331/.
[48] Sarin SK, Mehra NK, Agarwal A, Malhotra V, Anand BS, Taneja V. Familial aggregation in noncirrhotic portal fibrosis: a report of four families. Am J Gastroenterol [Internet]. 1987;82(11):1130–1133 [cited 2021 Dec 26] Available from: https://pubmed.ncbi.nlm.nih.gov/3499813/.

[49] Calado RT, Regal JA, Kleiner DE, Schrump DS, Peterson NR, Pons V, et al. A spectrum of severe familial liver disorders associate with telomerase mutations. PLoS One [Internet]. 2009 Nov 20;4(11) [cited 2021 Dec 26] Available from: https://pubmed.ncbi.nlm.nih.gov/19936245/.
[50] Majumdar A, Delatycki MB, Crowley P, Lokan J, Tharian B, Angus PW, et al. An autosomal dominant form of non-cirrhotic portal hypertension. J Hepatol [Internet]. 2015;63(2):525–527 [cited 2022 Jan 3] Available from: https://pubmed.ncbi.nlm.nih.gov/25796481/.
[51] Girard M, Amiel J, Fabre M, Pariente D, Lyonnet S, Jacquemin E. Adams-Oliver syndrome and hepatoportal sclerosis: occasional association or common mechanism? Am J Med Genet A [Internet]. 2005 Jun 1;135(2):186–189 [cited 2022 Jan 3] Available from: https://pubmed.ncbi.nlm.nih.gov/15832360/.
[52] Croquelois A, Blindenbacher A, Terracciano L, Wang X, Langer I, Radtke F, et al. Inducible inactivation of Notch1 causes nodular regenerative hyperplasia in mice. Hepatology [Internet]. 2005 Mar;41(3):487–496 [cited 2022 Jan 3] Available from: https://pubmed.ncbi.nlm.nih.gov/15723439/.
[53] Besmond C, Valla D, Hubert L, Poirier K, Grosse B, Guettier C, et al. Mutations in the novel gene FOPV are associated with familial autosomal dominant and non-familial obliterative portal venopathy. Liver Int [Internet]. 2018 Feb 1;38(2):358–364 [cited 2021 Dec 26] Available from: https://pubmed.ncbi.nlm.nih.gov/28792652/.
[54] Vispo E, Cevik M, Rockstroh JK, Barreiro P, Nelson M, Scourfield A, et al. Genetic determinants of idiopathic noncirrhotic portal hypertension in HIV-infected patients. Clin Infect Dis [Internet]. 2013 Apr 15;56(8):1117–1122 [cited 2021 Dec 26] Available from: https://pubmed.ncbi.nlm.nih.gov/23315321/.
[55] Koot BGP, Alders M, Verheij J, Beuers U, Cobben JM. A de novo mutation in KCNN3 associated with autosomal dominant idiopathic non-cirrhotic portal hypertension. J Hepatol [Internet]. 2016 Apr 1;64(4):974–977 [cited 2021 Dec 26] Available from: https://pubmed.ncbi.nlm.nih.gov/26658685/.
[56] Vilarinho S, Sari S, Yilmaz G, Stiegler AL, Boggon TJ, Jain D, et al. Recurrent recessive mutation in deoxyguanosine kinase causes idiopathic non-cirrhotic portal hypertension. Hepatology [Internet]. 2016;63(6):1977–1986 [cited 2021 Dec 26] Available from: https://pubmed.ncbi.nlm.nih.gov/26874653/.
[57] Pulvirenti F, Pentassuglio I, Milito C, Valente M, De Santis A, Conti V, et al. Idiopathic non cirrhotic portal hypertension and spleno-portal axis abnormalities in patients with severe primary antibody deficiencies. J Immunol Res [Internet]. 2014;2014 [cited 2021 Dec 26] Available from: https://pubmed.ncbi.nlm.nih.gov/24741616/.
[58] Malamut G, Ziol M, Suarez F, Beaugrand M, Viallard JF, Lascaux AS, et al. Nodular regenerative hyperplasia: the main liver disease in patients with primary hypogammaglobulinemia and hepatic abnormalities. J Hepatol [Internet]. 2008 Jan;48(1):74–82 [cited 2021 Dec 26] Available from: https://pubmed.ncbi.nlm.nih.gov/17998147/.
[59] Stock H, Kadry Z, Smith JP. Surgical management of portal hypertension in Felty's syndrome: a case report and literature review. J Hepatol [Internet]. 2009 Apr;50(4):831–835 [cited 2021 Dec 26] Available from: https://pubmed.ncbi.nlm.nih.gov/19231014/.
[60] Seinen ML, Van Asseldonk DP, De Boer NK, Bouma G, Van Nieuwkerk CM, Mulder CJ, et al. Nodular regenerative hyperplasia of the liver in patients with IBD treated with allopurinol-thiopurine combination therapy. Inflamm Bowel Dis [Internet]. 2017 Mar 1;23(3):448–452 [cited 2021 Dec 26] Available from: https://pubmed.ncbi.nlm.nih.gov/28151736/.
[61] Eapen CE, Nightingale P, Hubscher SG, Lane PJ, Plant T, Velissaris D, et al. Non-cirrhotic intrahepatic portal hypertension: associated gut diseases and prognostic factors. Dig Dis Sci [Internet]. 2011 Jan;56(1):227–235 [cited 2021 Dec 26] Available from: https://pubmed.ncbi.nlm.nih.gov/20499175/.
[62] Yamaguchi N, Tokushige K, Haruta I, Yamauchi K, Hayashi N. Analysis of adhesion molecules in patients with idiopathic portal hypertension. J Gastroenterol Hepatol [Internet]. 1999;14(4):364–369 [cited 2021 Dec 26] Available from: https://pubmed.ncbi.nlm.nih.gov/10207787/.
[63] Kotani K, Kawabe J, Morikawa H, Akahoshi T, Hashizume M, Shiomi S. Comprehensive screening of gene function and networks by DNA microarray analysis in Japanese patients with idiopathic portal hypertension. Mediators Inflamm [Internet]. 2015;2015 [cited 2021 Dec 26] Available from: https://pubmed.ncbi.nlm.nih.gov/26549939/.
[64] Ørntoft NW, Blé M, Baiges A, Ferrusquia J, Hernández-Gea V, Turon F, et al. Divergences in macrophage activation markers soluble CD163 and mannose receptor in patients with non-cirrhotic and cirrhotic portal hypertension. Front Physiol [Internet]. 2021 Jun 11;12 [cited 2021 Dec 25] Available from: https://pubmed.ncbi.nlm.nih.gov/34177608/.
[65] Kang JH, Kim DH, Kim SY, Kang HJ, Lee JB, Kim KW, et al. Porto-sinusoidal vascular disease with portal hypertension versus liver cirrhosis: differences in imaging features on CT and hepatobiliary contrast-enhanced MRI. Abdom Radiol (New York) [Internet]. 2021 May 1;46(5):1891–1903 [cited 2021 Dec 26] Available from: https://pubmed.ncbi.nlm.nih.gov/33095310/.
[66] Krishnan P, Fiel MI, Rosenkrantz AB, Hajdu CH, Schiano TD, Oyfe I, et al. Hepatoportal sclerosis: CT and MRI appearance with histopathologic correlation. AJR Am J Roentgenol [Internet]. 2012 Feb;198(2):370–376 [cited 2021 Dec 26] Available from: https://pubmed.ncbi.nlm.nih.gov/22268180/.
[67] Waguri N, Suda T, Kamura T, Aoyagi Y. Heterogeneous hepatic enhancement on CT angiography in idiopathic portal hypertension. Liver [Internet]. 2002;22(3):276–280 [cited 2021 Dec 26] Available from: https://pubmed.ncbi.nlm.nih.gov/12100579/.
[68] Matsui O, Takashima T, Kadoya M, Kitagawa K. Computed tomography during arterial portography in idiopathic portal hypertension. Radiat Med [Internet]. 1984;2(3):189–193 [cited 2021 Dec 26] Available from: https://pubmed.ncbi.nlm.nih.gov/6543969/.
[69] Verloh N, Haimerl M, Zeman F, Schlabeck M, Barreiros A, Loss M, et al. Assessing liver function by liver enhancement during the hepatobiliary phase with Gd-EOB-DTPA-enhanced MRI at 3 Tesla. Eur Radiol [Internet]. 2014;24(5):1013–1019 [cited 2021 Dec 26] Available from: https://pubmed.ncbi.nlm.nih.gov/24531844/.
[70] Maruyama H, Ishibashi H, Takahashi M, Imazeki F, Yokosuka O. Effect of signal intensity from the accumulated microbubbles in the liver for differentiation of idiopathic portal hypertension from liver cirrhosis. Radiology [Internet]. 2009 Aug;252(2):587–594 [cited 2021 Dec 26] Available from: https://pubmed.ncbi.nlm.nih.gov/19508988/.
[71] Maruyama H, Shimada T, Ishibashi H, Takahashi M, Kamesaki H, Yokosuka O. Delayed periportal enhancement: a characteristic finding on contrast ultrasound in idiopathic portal hypertension. Hepatol Int [Internet]. 2012 Apr;6(2):511–519 [cited 2021 Dec 26] Available from: https://pubmed.ncbi.nlm.nih.gov/21710291/.
[72] Maruyama H, Okugawa H, Kobayashi S, Yoshizumi H, Takahashi M, Ishibashi H, et al. Non-invasive portography: a microbubble-induced three-dimensional sonogram for discriminating idiopathic portal hypertension from cirrhosis. Br J Radiol [Internet]. 2012 May;85(1013):587–595 [cited 2021 Dec 26] Available from: https://pubmed.ncbi.nlm.nih.gov/21343319/.
[73] Okuda K, Nakashima T, Kojiro M, Kondo Y, Wada K. Hepatocellular carcinoma without cirrhosis in Japanese patients. Gastroenterology [Internet]. 1989;97(1):140–146 [cited 2022 Jan 3] Available from: https://pubmed.ncbi.nlm.nih.gov/2542116/.
[74] Cha DI, Song KD, Ha SY, Hong JY, Hwang JA, Ko SE. Long-term follow-up of oxaliplatin-induced liver damage in patients with colorectal cancer. Br J Radiol [Internet]. 2021 Jul 1;94(1123) [cited 2022 Jan 3] Available from: https://pubmed.ncbi.nlm.nih.gov/34133224/.
[75] Seijo S, Reverter E, Miquel R, Berzigotti A, Abraldes JG, Bosch J, et al. Role of hepatic vein catheterisation and transient elastography in the diagnosis of idiopathic portal hypertension. Dig Liver Dis [Internet]. 2012 Oct;44(10):855–860 [cited 2022 Jan 3] Available from: https://pubmed.ncbi.nlm.nih.gov/22721839/.
[76] Elkrief L, Lazareth M, Chevret S, Paradis V, Magaz M, Blaise L, et al. Liver stiffness by transient elastography to detect porto-sinusoidal vascular liver disease with portal hypertension. Hepatology [Internet]. 2021 Jul 1;74(1):364–378 [cited 2022 Jan 3] Available from: https://pubmed.ncbi.nlm.nih.gov/33345307/.
[77] Sharma P, Agarwal R, Dhawan S, Bansal N, Singla V, Kumar A, et al. Transient elastography (Fibroscan) in patients with non-cirrhotic portal fibrosis. J Clin Exp Hepatol [Internet]. 2017 Sep 1;7(3):230–234 [cited 2022 Jan 3] Available from: https://pubmed.ncbi.nlm.nih.gov/28970710/.
[78] Furuichi Y, Moriyasu F, Taira J, Sugimoto K, Sano T, Ichimura S, et al. Noninvasive diagnostic method for idiopathic portal hypertension based on measurements of liver and spleen stiffness by ARFI elastography. J Gastroenterol [Internet]. 2013 Sep 1;48(9):1061–1068 [cited 2022 Jan 3] Available from: https://pubmed.ncbi.nlm.nih.gov/23142969/.

[79] Ahmad AK, Atzori S, Taylor-Robinson SD, Maurice JB, Cooke GS, Garvey L. Spleen stiffness measurements using point shear wave elastography detects noncirrhotic portal hypertension in human immunodeficiency virus. Medicine (Baltimore) [Internet]. 2019 Nov 1;98(47) [cited 2022 Jan 3] Available from: https://pubmed.ncbi.nlm.nih.gov/31764798/.

[80] Cerda Reyes E, González-Navarro EA, Magaz M, Muñoz-Sánchez G, Diaz A, Silva-Junior G, et al. Autoimmune biomarkers in porto-sinusoidal vascular disease: potential role in its diagnosis and pathophysiology. Liver Int [Internet]. 2021 Sep 1;41(9):2171–2178 [cited 2022 Jan 3] Available from: https://pubmed.ncbi.nlm.nih.gov/34173316/.

[81] Mackie I, Eapen CE, Neil D, Lawrie AS, Chitolie A, Shaw JC, et al. Idiopathic noncirrhotic intrahepatic portal hypertension is associated with sustained ADAMTS13 Deficiency. Dig Dis Sci [Internet]. 2011 Aug;56(8):2456–2465 [cited 2022 Jan 3] Available from: https://pubmed.ncbi.nlm.nih.gov/21573942/.

[82] Seijo S, Lozano JJ, Alonso C, Reverter E, Miquel R, Abraldes JG, et al. Metabolomics discloses potential biomarkers for the noninvasive diagnosis of idiopathic portal hypertension. Am J Gastroenterol [Internet]. 2013 Jun;108(6):926–932 [cited 2022 Jan 3] Available from: https://pubmed.ncbi.nlm.nih.gov/23419380/.

[83] Seijo S, Lozano JJ, Alonso C, Miquel R, Berzigotti A, Reverter E, et al. Metabolomics as a diagnostic tool for idiopathic non-cirrhotic portal hypertension. Liver Int [Internet]. 2016 Jul 1;36(7):1051–1058 [cited 2022 Jan 3] Available from: https://pubmed.ncbi.nlm.nih.gov/26394550/.

[84] Hernández-Gea V, Campreciós G, Betancourt F, Pérez-Campuzano V, Seijo S, Díaz A, et al. Co-expression gene network analysis reveals novel regulatory pathways involved in porto-sinusoidal vascular disease. J Hepatol [Internet]. 2021 Oct 1;75(4):924–934 [cited 2022 Jan 3] Available from: https://pubmed.ncbi.nlm.nih.gov/34052252/.