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Editorial Board Member of *World Journal of Gastroenterology*, Michele Barone, MD, PhD, Adjunct Professor, Research Associate, Section of Gastroenterology, Department of Emergency and Organ Transplantation, University of Bari, Bari 70124, Italy

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## Diagnostic challenges in non-cirrhotic portal hypertension - porto sinusoidal vascular disease

Oana Nicoară-Farcău, Ioana Rusu, Horia Ștefănescu, Marcel Tanțău, Radu Ion Badea, Bogdan Procopet

**ORCID number:** Oana Nicoară-Farcău (0000-0002-4468-2053); Ioana Rusu (0000-0001-9174-6729); Horia Ștefănescu (0000-0002-4034-5471); Marcel Tanțău (0000-0002-7749-0007); Radu Ion Badea (0000-0002-5330-090X); Bogdan Procopet (0000-0001-8118-1760).

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**Oana Nicoară-Farcău, Ioana Rusu, Marcel Tanțău, Radu Ion Badea, Bogdan Procopet**, University of Medicine and Pharmacy “Iuliu Hatieganu”, Cluj-Napoca 400000, Romania

**Oana Nicoară-Farcău, Horia Ștefănescu, Marcel Tanțău, Bogdan Procopet**, Gastroenterology Department, Regional Institute of Gastroenterology and Hepatology “O. Fodor”, Cluj-Napoca 400000, Romania

**Ioana Rusu**, Pathology Department, Regional Institute of Gastroenterology and Hepatology “O. Fodor”, Cluj-Napoca 400000, Romania

**Radu Ion Badea**, Imaging Department, Regional Institute of Gastroenterology and Hepatology “O. Fodor”, Cluj-Napoca 400000, Romania

**Corresponding author:** Bogdan Procopet, MD, PhD, Doctor, Senior Lecturer, Staff Physician, Gastroenterology and Hepatology Department, 3<sup>rd</sup> Medical Clinic, University of Medicine and Pharmacy “Iuliu Hatieganu”, 19-21 Croitorilor Street, Cluj-Napoca 400162, Romania.  
[bogdan.procopet@umfcluj.ro](mailto:bogdan.procopet@umfcluj.ro)

### Abstract

Non-cirrhotic portal hypertension consists of a group of diseases characterized by signs and complications of portal hypertension, which differ from cirrhosis through histological alterations, hemodynamic characterization and, clinical outcome. Because of the similarities in clinical presentation and imaging signs, frequently these patients, and particularly those with porto-sinusoidal vascular disease (PSVD), are misdiagnosed as having liver cirrhosis and thus raising difficulties in their diagnosis. The most challenging differentiation to be considered is between PSVD and cirrhosis and, although not pathognomonic, liver biopsy is still the standard of diagnosis. Although they still require extended validation before being broadly used, new non-invasive methods for the diagnosis of porto-sinusoidal vascular disease, like transient elastography, contrast-enhanced ultrasound or metabolomic profiling, have shown promising results. Another issue is the differentiation between PSVD and chronic extrahepatic portal vein obstruction, especially now when it is known that 40% of patients suffering from PSVD develop portal vein thrombosis. In this particular case, once the portal vein thrombosis occurred, the diagnosis of PSVD is impossible according to the current guidelines. Moreover, so far, the differentiation between PSVD and sinusoidal obstruction syndrome has not been clear so far in particular circumstances. In this review we highlighted the diagnostic challenges regarding the PSVD, as well as the current techniques used in the evaluation of these patients.

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**Core tip:** Non-cirrhotic portal hypertension consists of a group of diseases characterized by signs and complications of portal hypertension. However, their diagnosis is sometimes difficult due to their similarities in clinical presentation, imaging signs and histological modifications despite advances in their understanding. Moreover, these disorders are sometimes misdiagnosed as cirrhosis. This review highlights their diagnostic challenges, especially with regard to porto sinusoidal vascular disease, extrahepatic portal vein obstruction, sinusoidal obstruction syndrome and cirrhosis and discusses the current available diagnostic tools.**Citation:** Nicoară-Farcău O, Rusu I, Ștefănescu H, Tanțău M, Badea RI, Procopeț B.Diagnostic challenges in non-cirrhotic portal hypertension - porto sinusoidal vascular disease. *World J Gastroenterol* 2020; 26(22): 3000-3011**URL:** <https://www.wjgnet.com/1007-9327/full/v26/i22/3000.htm>**DOI:** <https://dx.doi.org/10.3748/wjg.v26.i22.3000>

## INTRODUCTION

Non-cirrhotic portal hypertension is a group of heterogeneous diseases, having in common both the presence of portal hypertension (PHT) as the main clinical feature and the absence of cirrhosis on histology.

The difference between them resides in the pathogenetic mechanism and the level where the PHT develops. Amongst these diseases, the most frequent entities are extrahepatic portal vein obstruction (EHPVO), idiopathic portal hypertension (IPH) and Budd Chiari syndrome – all of which are categorized as vascular liver disorders<sup>[1]</sup>. If Budd Chiari syndrome in early stages and EHPVO are recognized relatively easily, IPH may be challenging to diagnose because of the imaging and clinical similarities with cirrhosis.

Moreover, in IPH, there are still many unknown data not only concerning the physio-pathological mechanism<sup>[2-4]</sup>, but also concerning its diagnosis and long-term outcome. It is currently known that portal vein thrombosis (PVT) frequently complicates IPH (up to 40% at 5 years)<sup>[4]</sup>, making the diagnosis of IPH impossible according to the current guidelines, if the patient is evaluated after EHPVO has occurred.

Therefore, as of recently, as a response to the new concepts that define the disease, new terminology for IPH has been proposed: Porto-sinusoidal vascular disease (PSVD)<sup>[5]</sup>. PSVD should be considered in patients with or without PHT, in the absence of histologic cirrhosis but with histological signs suggesting of PSVD<sup>[6]</sup>.

However, despite the significant progress made regarding these conditions, there are still unmet needs and challenges, especially concerning their diagnosis. The purpose of this article is to highlight these challenges and present the way they are currently covered.

## DIAGNOSTIC CHALLENGES

### **Differentiation between PSVD and cirrhosis**

Since PSVD manifests mainly by clinical signs or complications of PHT in the absence of EHPVO, these patients are often misdiagnosed as cryptogenic cirrhosis<sup>[4]</sup>. Indeed, 5.4% of all presumed cryptogenic cirrhosis are, in fact, PSVD<sup>[6]</sup>. If in the case of PSVD the liver function is preserved for a longer time, and the prognosis is relatively good, in the case of cirrhosis, the outcome is entirely different.

PSVD occurs in young patients, mostly under 40 years old in the Western world<sup>[7,8]</sup> or even earlier in the Eastern world<sup>[2]</sup>, by signs or complications of PHT. It should be noted that ascites may develop by a triggering factor, and is usually transient<sup>[9,2]</sup>.

Contrary to PSVD, cirrhosis develops usually later in life, depending on the

etiological factor and the lasting time of the causal factor, while the most frequent complication is ascites<sup>[9]</sup>. In patients with hepatitis C virus infection, there are approximately 30 years from the moment of infection until the development of cirrhosis<sup>[10]</sup>. Therefore, in young patients without apparent etiological factors, the diagnosis of PSVD should not be discarded until performing an extensive workup (including liver biopsy).

If in cirrhosis, the prognosis is mainly related to the liver function and the degree of PHT, in PSVD the liver function remains normal for a more extended period, which will lead to better toleration of complications. The outcome of patients also depends on the associated diseases and varies within different cohorts between 56% and 82% at ten years<sup>[8,11]</sup>. Also, even if 19% of the patients will develop liver impairment (and some of them will require liver transplantation<sup>[7,11]</sup>), the survival rate of patients with PSVD is situated between that of the general population and that of patients who have cirrhosis<sup>[12]</sup>.

Nonetheless, both conditions tend to develop PVT during disease<sup>[4,13]</sup>. Compared to cirrhosis, PSVD patients develop PVT more frequently, up to 40% at five years<sup>[4]</sup>, therefore having a negative impact over life expectancy<sup>[14-17]</sup>. In both conditions, alterations of coagulation factors are present, which may contribute to PVT occurrence. PSVD is frequently associated with thrombotic disorders, as protein C and S deficiency, factor V Leiden mutation, or antiphospholipid syndrome<sup>[4,7,14,15]</sup>. In cirrhosis, protein C, S, and antithrombin III are all decreased whereas factor VIII and von Willebrand factor, strong promoters of coagulation, are increased<sup>[18]</sup>. However, the exact mechanism of PVT development in cirrhosis is unknown.

Therefore, based only on clinical features, it is impossible to distinguish between PSVD and cirrhosis. However, the differentiation between the two conditions is essential for the prognostic and for liver transplantation reference. Consequently, an extensive workup might be necessary to differentiate between the two conditions. If, in the case of liver cirrhosis, the diagnosis can be made based on non-invasive tools, the diagnosis of PSVD demands the exclusion of other causes of PHT<sup>[1]</sup> using a liver biopsy which is the definitive diagnostic tool.

The first step in evaluating a patient with clinical signs of PHT is by imaging workup. Ultrasound (US) examination is frequently the first examination performed in patients with suspicion of PHT. In PSVD patients, the liver aspect may be either normal or inhomogeneous with an irregular surface (nodular transformation), therefore rendering it very difficult to differentiate it from cirrhosis. In both conditions, the dominating findings are splenomegaly, portal venous axis dilatation, and the presence of spontaneous shunts. Interestingly, in PSVD, the spleen is often larger in comparison with cirrhosis<sup>[19,20]</sup>. In PSVD, the portal vein and its intrahepatic branches may have atypical thickened (> 3 mm) and have hyperechoic walls. This sign could indicate periportal fibrosis manifested as a “layered” pattern. These changes are accompanied by a sudden narrowing or cutoff of intrahepatic second- and third-degree portal vein branches like a “withered tree appearance”<sup>[20]</sup>. Using contrast-enhanced US, in PSVD, the parenchymal enhancement is more heterogeneous due to delayed periportal enhancement<sup>[21]</sup>. Also, the time-intensity curves were different between PSVD and cirrhosis<sup>[22]</sup>.

Cross-sectional imaging methods come in addition to the US and have better performance to assess its extension and duration, mainly if thrombosis of the portal vein is found in the US. Although there is no specific sign for PSDV, the presence of subcapsular atrophy, heterogeneous hepatic enhancement, or paucity of the medium size portal branches may suggest the diagnosis<sup>[23]</sup>.

Liver stiffness measurement (LSM) proved to have excellent results in both the diagnosis of advanced liver diseases and in the usage of identifying and selecting patients at risk to have clinical significant portal hypertension<sup>[24]</sup>. As such, in patients with splenomegaly or low platelet count (high pretest probability of advanced liver disease), an LSM higher than 20 kPa would be a definitive diagnostic for cirrhosis complicated with clinically significant PHT. In patients with PSDV, liver stiffness is normal or slightly elevated in comparison with patients with cirrhosis,  $8.4 \pm 3.3$  kPa *vs*  $40.9 \pm 20.5$  kPa respectively<sup>[25]</sup>, results that were further confirmed by other studies as well<sup>[26]</sup>.

Interestingly, there is a subgroup of patients with PSVD in which the LSM does not help differentiate them from those with cirrhosis. These patients have histological signs of nodular regenerative hyperplasia (NRH), and their LSM ranges from 3.5 kPa to 22.0 kPa<sup>[27,28]</sup> making it difficult to suspect PSVD if the LSM is above 12.5 kPa, which is close to the threshold seen in liver cirrhosis<sup>[29,30]</sup>. Moreover, it seems not to correlate with the degree of liver fibrosis on histological examination<sup>[27]</sup>. According to the new definition, NRH is a specific histological sign of PSVD<sup>[5]</sup>. NRH is a nodular transformation of the hepatic parenchyma without fibrosis surrounding the nodules. Obliterative portal venopathy is the stimulus of this abnormal arrangement of

hepatocytes. These alterations of the portal flow lead to the atrophy of tributary hepatocytes and the hyperplasia of the hepatocytes with normal portal vascularization<sup>[31]</sup>. Moreover, perisinusoidal, centrolobular and some degree of portal and periportal fibrosis may be observed in NRH and this might contribute to the increased LSM<sup>[27]</sup>.

Despite the modest performances for non-cirrhotic PHT diagnosis, LSM has an important role in ruling out cirrhosis. Therefore, in patients with clinical signs of PHT but with low LSM, non-cirrhotic PHT should be strongly suspected.

Hemodynamic studies are used to evaluate the severity of PHT indirectly. The hepatic venous pressure gradient (HVPG) measurement behaves as a risk prediction method in patients with cirrhosis, because it is associated with the development of esophageal varices, variceal bleeding, ascites or hepatocellular carcinoma<sup>[32]</sup>.

Since PSVD patients have a presinusoidal type of PHT, such correlations cannot be made for these patients. Still, hepatic hemodynamic studies are essential for the distinction between the two disorders and cirrhosis.

Compared with cirrhosis, in PSVD patients with signs of PHT, the HVPG is normal or slightly elevated ( $7.8 \pm 3.6$  mmHg in IPH *vs*  $17.0 \pm 3.0$  mmHg in cirrhosis)<sup>[25]</sup>. Although PSVD often has vein-to-vein communications, which might preclude to obtain an adequate wedge hepatic venous pressure, if the balloon is inflated below the vein-to vein shunt, HVPG might be accurately measured<sup>[25]</sup>.

Nonetheless, the challenge arises when the hemodynamic studies in patients with PSVD show values similar to the sinusoidal type of PHT. Indeed, 70% of the patients with NRH with clinical signs of PHT (varices/ascites) had HVPG < 10 mmHg suggesting pre-sinusoidal PHT, which was confirmed by a portal vein pressure higher than 12 mm Hg<sup>[33]</sup>. However, 30% of patients had an HVPG > 10 mmHg (WHVP ranged from 16 -34 mmHg), suggesting sinusoidal PHT<sup>[33]</sup>. These findings indicate that both types of PHT may coexist in NRH (pre-sinusoidal and sinusoidal) depending on the predominant mechanism causing the PHT: OPV- pre-sinusoidal or compression of the sinusoids by the regenerative nodules- sinusoidal<sup>[33,34]</sup>. Nevertheless, PSVD is mainly a presinusoidal type of PHT as demonstrated by the increase in the splenic-to-free hepatic pressure gradient<sup>[35]</sup>. However, the treatment with non-selective beta-blockers decreases portal pressure in patients with PSVD as well as EHPVO<sup>[36]</sup>.

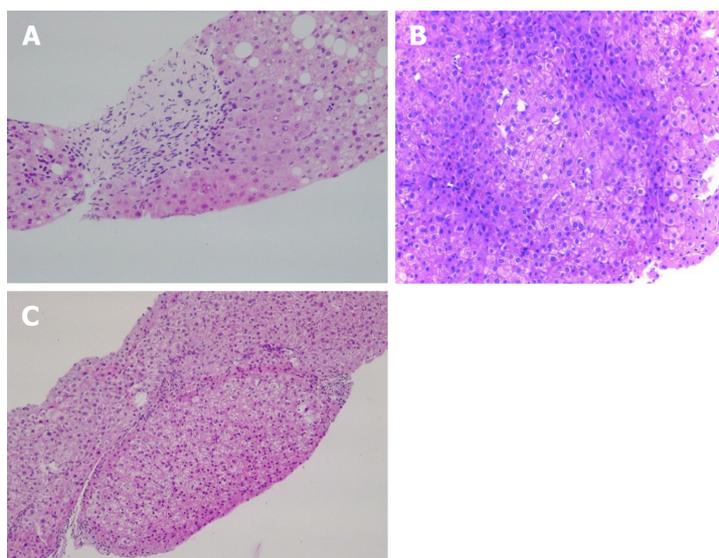
PSVD shows a hyperdynamic circulation comparable with compensated cirrhosis proven by the increased cardiac index and low systemic and pulmonary vascular resistance<sup>[25,37]</sup>.

When performing venography, contrary to cirrhosis, PSVD shows frequent vein-to-vein communications, and the angles between large veins and their tributaries are narrower<sup>[38]</sup>. Also, the middle-sized branches are smooth, but sometimes with irregularities giving a general appearance of “weeping willow”<sup>[38]</sup>.

Transjugular liver biopsy is performed most frequently in PSVD patients because of severe thrombocytopenia. The transjugular route also allows for HVPG measurement. In case of clinical signs of PHT (esophageal varices, splenomegaly and low platelet count) finding an HVPG less than 10 mmHg strongly weights against sinusoidal PHT and should raise the suspicion of non-cirrhotic PHT. Finally, the result of the liver biopsy will lead to a definitive diagnosis. Indeed, the current proposed definition of histological findings clearly states that the diagnosis of PSVD needs the exclusion of liver cirrhosis on a good quality specimen<sup>[5]</sup>.

Classified according to their localization, the most frequent findings are: (1) Portal tracts: Phlebosclerosis or obliterative portal venopathy of the portal veins, characterized by luminal narrowing and sclerosis (Figure 1A); the absence of the portal vein radicle (vanishing); aberrant portal vessels herniated into the periportal parenchyma; abnormal thin shunt vessels adjacent to the portal tracts that open into the sinusoids; various of thin-walled vessels inside the portal tract; portal tracts remnants (hypoplastic portal tract), and incomplete septal fibrosis. Immunohistochemistry analysis may not show pathognomonic features. However, there seems to be differences between the different protein expressions in PSVD and cirrhosis. For example, the connective tissue growth factor is highly expressed in portal mononuclear cells around the bile ducts in PSVD patients. Still, it showed a low expression of matrix metalloproteinase 9 as opposed to what was seen in cirrhotic livers<sup>[39]</sup>. This pattern might explain the periductal and periportal fibrosis in PSVD<sup>[39]</sup>. In PSVD patients, the expression of CD34 (a marker of sinusoidal endothelial cells) was reduced, while pSmad2 was increased in the peripheral portal veins, as opposed to what was seen in cirrhosis<sup>[40]</sup>; (2) Hepatic parenchyma: Parenchymal collapse in the subcapsular region, atrophic hepatocytes with focal nodular regenerative hyperplasia and sinusoidal dilatation with eventually perisinusoidal fibrosis; and (3) Centrolobular vein: Central vein dilatation with or without phlebosclerosis<sup>[3,41,42]</sup>.

Apart from these lesions, two other important findings represent major diagnostic



**Figure 1 Pathological image.** A: Obliterative portal venopathy. Portal tract with round fibrous enlargement and vanishing of the portal vein radicle [Hematoxylin-eosin (HE) staining, 200×]; B: Liver biopsy showing nodular regenerative hyperplasia with vague nodularity of the parenchyma and compression of the adjacent hepatic (HE staining, 200×); C: Incomplete septal cirrhosis with delicate fibrous septa and no cirrhotic-type nodule formation is seen (HE staining, 200×).

arguments for PSVD: Nodular regenerative hyperplasia and incomplete septal fibrosis<sup>[43]</sup>.

Nodular regenerative hyperplasia is a nodular transformation of the hepatic parenchyma characterized by hyperplastic hepatocytes arranged in few cell-thick plates and surrounded by zones of atrophic hepatocytes without fibrosis (Figure 1B).

Compared with PSVD, in cirrhosis, aside from the presence of regenerative nodules with fibrosis, there is a reduction in the portal vascular bed with a compensatory increase of the hepatic arteries and intrahepatic shunt formation between the portal veins and hepatic veins or hepatic arteries and hepatic veins or portal veins. In PSVD, the hepatic arterial flow fails to compensate for the reduction of the portal venous index leading to atrophy - especially in the subcapsular area<sup>[3,44]</sup>. These histological modifications have been distributed into different stages according to the severity of the disease: Stage I, with the absence of peripheral parenchymal atrophy, stage II, with the presence of peripheral parenchymal atrophy in a non-atrophic liver, stage III with the presence of peripheral parenchymal atrophy in an atrophic liver and stage IV with the presence of obstructive thrombosis in intrahepatic large branches or trunk of portal vein<sup>[45]</sup>.

Incomplete septal fibrosis is characterized by thin fibrous septa that originate from the portal tract and end blindly inside the hepatic parenchyma without bridging with other septa (Figure 1C)<sup>[43]</sup>. Recently, increasing evidence of cirrhosis regression emerged, and one of the most challenging tasks is to differentiate cirrhosis regression<sup>[46]</sup> from incomplete septal fibrosis (related to PSVD)<sup>[47]</sup>. Following the regression of cirrhosis, vasculature anomalies can persist for many years, which is probably the reason for PHT findings in these patients. "Hepatic repair complex" represents histological prove of cirrhosis regression. It includes isolated thick fibrous septa, periportal fibrous spikes, portal tracts remnants, aberrant parenchymal vessels or regenerative nodules<sup>[46]</sup>. Together with a very well documented clinical history and etiological workup it is essential to differentiate between the two pathological entities<sup>[43]</sup>.

It should be noted that esophageal varices or variceal bleeding is the most frequent symptom in patients with PSVD. It has been proven that in cirrhosis, HVPG  $\geq 10$  mmHg, which defines clinically significant PHT (CSPH), increases the risk of esophageal varices that need treatment. Consequently, in compensated cirrhosis, all efforts should be made to identify those patients with CSPH, preferably using non-invasive means. Thus, according to the last Baveno consensus, in the case of cirrhotic patients if platelets are above 150000/mm<sup>3</sup> and liver stiffness measured by transient elastography is less than 20 kPa<sup>[48]</sup>, then screening endoscopies can be avoided. However, these recommendations cannot be made for non-cirrhotic portal hypertensive patients.

Even so, it is worth noting that while in PSVD the esophageal varices are often

large and gastric varices are more common than in the case of cirrhosis<sup>[7,49,50]</sup> the course of esophageal varices development and variceal growth is very similar between patients with PSDV and cirrhosis<sup>[7,12]</sup>. Recent studies have shown that patients with PSVD without varices develop them at rates of 10%, 20%, and 65%, and those with small ones show progression at rates of 13%, 35%, and 44% at 1, 2, and 5 years, respectively<sup>[11,12]</sup>.

Recently, plasma global metabolic profiling in patients with PSVD was able to distinguish between PSVD and cirrhosis based on 28 metabolites with an AUROC of 0.99<sup>[51]</sup>. Using targeted analysis, the same group identified three lipid metabolites (fatty acid, lysophosphatidylethanolamine, and triacylglycerol) to differentiate PSVD from cirrhosis. Two lipid metabolites (bile acid and lysophosphatidylethanolamine) would discriminate PSDV from healthy volunteers<sup>[52]</sup>. New biomarkers of PSVD may offer opportunities for diagnosis of PSVD in preclinical stages.

### **Differentiation between PSVD and EHPVO**

The EHPVO is considered to be a childhood disease in the developing countries, whereas in the Western world, it is the second most frequent cause of PHT in adults, and a prothrombotic state frequently causes it<sup>[53]</sup>.

Similar to PSVD, liver structure and function remain preserved until late in the course of the disease, and the most important clinical presentation is recurrent episodes of gastroesophageal variceal bleeding, which are often well controlled. The hallmark of chronic EHPVO is the cavernous transformation of the portal vein, which is easily detectable on different imaging methods. As previously mentioned, up to 40% of PSVD patients will develop PVT during the disease<sup>[4]</sup>, and thus, some patients may become symptomatic only after PVT occurrence. According to the current guidelines, these patients cannot be correctly diagnosed. However, the most recent definition does not exclude the diagnosis of PSVD in the context of PVT<sup>[5]</sup>. Still, when a cavernoma reveals the signs of PHT, the diagnosis of PSVD cannot be made<sup>[5]</sup>. This is a diagnostic challenge, nonetheless, because the cavernous transformation can occur soon after the acute thrombosis<sup>[54]</sup>. Thus, it cannot exclude the presence of a PVT lying on a PSVD. When PVT develops in PSVD, it is mostly restricted in the main trunk or the intrahepatic branches of the portal vein. However, the extension to the superior mesenteric vein (SMV) or splenic vein (SV) is possible and might lead to the progression of the disease<sup>[8-15]</sup>. Isolated SV and SMV thrombosis are excluded from the definition of EHPVO. However, the extension to these vessels is possible as well in this setting. At presentation, one-third of the patients may already have an extended PV obstruction<sup>[55]</sup>. Indeed, apart from the possible thrombophilia factors associated with PSVD and EHPVO, alike in cirrhosis, the splenic vein endothelium suffers anomalies due to the increase in portal hypertension. These injuries could be a reason for splenic thrombosis<sup>[56]</sup>.

Because in both conditions prothrombotic abnormalities are frequently associated and because both have similar clinical features, for the moment, it is impossible to differentiate between PSVD complicated with PVT and EHPVO.

In reality, the situation is even more complicated because chronic EHPVO may lead to a dysmorphic liver and a mosaic pattern of parenchymal enhancement in the arterial phase<sup>[57]</sup> and, therefore, in some cases it is impossible to be differentiated from cirrhosis or PSDV. These morphological abnormalities have a histological correspondence, which is similar in EHPVO and PSDV.

Probably the most relevant question to be answered is whether the distinction of these disorders has an impact on the clinical practice. At the moment, both diseases are managed similarly as cirrhosis, namely, to control PHT related complications<sup>[1]</sup>. As previously stated, the diagnosis of EHPVO is based on imaging findings. The hallmark of the US is the cavernous transformation of the portal vein defined by serpiginous vascular channels replacing the portal vein. Despite the patency of these collaterals, they are not able to maintain an efficient portal inflow and thus determining the development of PHT. Similar to PSVD and cirrhosis, there are signs of PHT as splenomegaly and portosystemic collaterals. Usually, the liver surface is smooth, but with the progression of the disease, it may become irregular – therefore simulating cirrhosis.

Sometimes signs of portal biliopathy may be seen<sup>[5,58]</sup>, and using the contrast-enhanced US the diagnosis is more accurate<sup>[59]</sup>. There is no imaging technique or sign that may be used to distinguish PSVD complicated with PVT from EHPVO.

LSM by transient elastography shows lower values than those observed in cirrhosis and interestingly, lower also than those found in PSVD<sup>[30]</sup>. As in most cases of PSVD, in pure EHPVO, the HVPG is also below 10 mmHg<sup>[16,25]</sup>.

In EHPVO, as in PSVD, 71% of the patients are already diagnosed with large varices at the first presentation. If no varices are found at initial endoscopy, the esophageal varices development rate is 2%, 22% and 22% at 1, 3 and 5 years,

respectively. Also, small varices grow at a rate of 13%, 40%, and 54% at 1, 3 and 5 years, respectively<sup>[60]</sup>. This similar natural history between these conditions led to the same management<sup>[1]</sup>, although the level of evidence for PSDV and EHPVO is quite low.

The liver histology is not characteristic in EHPVO. As such, portal fibrosis can be found in about 40% of the cases. Compared with EHPVO, PSDV showed phlebosclerosis, portal tract remnants, and nodular regeneration more frequently<sup>[42]</sup>. **Table 1** resumes the comparison between different histological findings in PSDV, EHPVO, and cirrhosis. A summary of the most relevant diagnostic tools differentiating PSVD from EHPVO and cirrhosis is presented in **Table 2**.

### **Differentiation between PSVD and healthy population**

Recently, increased attention has focused on the ability to discern between the healthy population and those with histological signs of PSVD but no clinical signs of PHT. Indeed, 20% of the patients with obliterative portal venopathy without signs of PHT, present initially alterations in liver enzymes without any other etiology<sup>[17]</sup>. This is important since 40% of the these patients will developed PHT during the follow up<sup>[61]</sup>. Until present, no laboratory findings (either serum tests, autoantibody, or pro-thrombotic conditions) may predict which patient will develop PHT<sup>[61]</sup>. Naturally, this raised the question whether obliterative portal venopathy can be considered an early stage of PSDV and whether the diagnostic could be made sooner (before the development of PHT)<sup>[17,61]</sup>. Indeed, the new definition of PSVD includes patients with histological signs of PSVD but without clinical signs of PHT<sup>[5]</sup>.

However, currently there are not enough data regarding either the natural history or what should be the appropriate management of these patients.

### **PSVD and sinusoidal obstruction syndrome**

The definition of PSVD excludes patients with sinusoidal obstruction syndrome (SOS) and those following bone marrow transplantation. However, so far, data regarding the distinction between the two entities is scarce, and sometimes these two conditions are confounded. Indeed, the diagnosis of SOS is simple, according to the clinical Seattle and Baltimore criteria<sup>[62]</sup>. SOS is defined by hepatomegaly, fluid retention and weight gain, with elevated serum bilirubin that follows cytoreductive therapy, in the absence of other explanations for these signs and symptoms. It occurs between 0 and 20 d following the administration of the toxic drug<sup>[62]</sup>. The challenge arises when SOS become evident long after the administration of the causative agent<sup>[63,64]</sup>, especially after oxaliplatin or azathioprine, which are two drugs that could contribute to the development of PSVD<sup>[62]</sup>.

Histologically, SOS is characterized by sinusoidal destruction and microscopic hemorrhage; however, this pattern is present in 51% of cases in one series<sup>[63]</sup>. Nevertheless, 15%-33% of patients will also develop NRH induced-oxaliplatin, which might be related to the severity of sinusoidal injury<sup>[65-67]</sup>.

In patients treated with oxaliplatin, the depletion of glutathione transferase could be the initial mechanism of SOS<sup>[63,68]</sup>. This depletion leads to toxic insult to sinusoidal endothelial cells and it compromises the integrity of the vascular wall, followed by activation of the hepatic stellate cells and the deposition of matrix in the sinusoids. Obstruction is caused by erythrocytes sloughing, and blebs, characterized by free fragments of cytoplasmic processes, occasionally containing cellular organelles. Finally, oxaliplatin may cause fibrotic obliteration of the small vessels, hepatocyte plate disruption, and parenchymal extinction lesions along with hyperperfused regenerative areas<sup>[65,69,70]</sup>. Chronic hypoxia of the centrilobular areas caused by intrahepatic blood flow impairment may lead to NRH<sup>[63]</sup>. However, signs of HNR can be found outside of the spectrum of SOS<sup>[65]</sup>.

Some patients treated with azathioprine will also develop signs of SOS/NRH. However, the pathophysiological mechanisms are not very clear<sup>[62,71]</sup>.

As both SOS and NRH can appear after treatment with oxaliplatin and azathioprine, the distinction between the two is very important. This is relevant because, although in patients with SOS most cases (70%-90%) will resolve spontaneously, a few may progress to NRH<sup>[62]</sup>.

Moreover, it is important since a significant feature of NRH is that it can become clinically evident long after the finalization of chemotherapy<sup>[63,72]</sup>.

### **PSVD in the pediatric population**

In the pediatric population, EHPVO is the most frequent cause of portal hypertension. It is caused mostly by phlebitis after umbilical catheterization or omphalitis, previous surgery, dehydration or a prothrombotic state<sup>[73]</sup>. Rarely, it is caused by non-cirrhotic portal fibrosis which accounts for 4.6% of all causes of non-cirrhotic PHT in children<sup>[74]</sup>. This entity is compatible with what is described in adults as PSVD<sup>[50,75,76]</sup>.

**Table 1** Histological differences between porto-sinusoidal vascular disease, extrahepatic portal vein obstruction and cirrhosis

	PSVD	EHPVO	Cirrhosis
<b>Portal and periportal zone</b>			
Small portal vein obliteration ("hepato-portal sclerosis", phlebosclerosis)	++	+/-	-
Periportal shunt vessel	++	+	-
Fibrous septa	+/-; without bridging <sup>1</sup>	-	++; with bridging delimitating nodules
Inflammation	-	-	++
Portal biliopathy	-	+/-	-
<b>Liver lobule (parenchyma)</b>			
Perisinusoidal fibrosis	+	-	+/-
Sinusoidal dilatation	++	++	-
Nodular regenerative hyperplasia	+	+	-
Hepatocyte atrophy	+	+	-
<b>Centrilobular zone</b>			
Central vein dilatation	++	+	-
Perivenular fibrosis	++	+	-

<sup>1</sup>Incomplete septal fibrosis. ++: Almost always present; +: Usually present; +/-: Occasionally present; -: Usually absent; PSVD: Porto-sinusoidal vascular disease; EHPVO: Extrahepatic portal vein obstruction.

However, it is important to notice some clinical differences. It occurs secondary to malignancy or after chemotherapy<sup>[50]</sup> or may have a genetic component<sup>[77]</sup>. The clinical presentation occurs by the age of 13 years and is found predominantly in males. Frequently, the diagnosis is revealed by splenomegaly, symptomatic hypersplenism, or variceal bleeding<sup>[11]</sup>. Unlike the adult population, the growth retardation is seen in 73% of children<sup>[74]</sup>, although this feature has been described in EHPVO as well<sup>[78]</sup>. Due to the low number of patients, little is known so far about the long term prognosis or these patients, but in the mid-term, it seems to be favorable<sup>[74]</sup>.

## CONCLUSION

In conclusion, with all available diagnostic tools, the diagnosis of PSVD with or without PH remains challenging, and liver biopsy is still indispensable. PSVD frequently complicates with PVT and, if the diagnosis is not previously done, the diagnosis is currently virtually impossible. This is because there are no pathognomonic features for PSVD on liver biopsy and, moreover, PSVD and EHPVO share many histological findings. To overcome these drawbacks, evidence from the metabolomics field are promising, yet require further studies.

**Table 2** Main invasive/non invasive characteristics found in porto-sinusoidal vascular disease, extrahepatic portal vein obstruction and cirrhosis

Diagnostic tools	PSVD	EHPVO	Cirrhosis
<b>Invasive tools</b>			
Liver biopsy	Predominant vascular anomalies	Predominant vascular anomalies	Predominant architectural changes and fibrosis
Hepatic hemodynamics	FHVP N	FHVP N	FHVP N
	WHVP ↓	WHVP ↓	WHVP ↑
	HVPG N or slightly ↑	HVPG N	HVPG ↑
	Frequent vein-to-vein communications	Infrequent vein-to-vein communications	Infrequent vein-to-vein communications
Endoscopic findings	Hyperdynamic circulatory state	Hyperdynamic circulatory state	Hyperdynamic circulatory state
	Esophageal varices	Esophageal varices	Esophageal varices
	Gastric varices (GOV1, GOV2) more common	Gastric varices more common (especially IGV1, IGV2)	Gastric varices less common
	Portal hypertensive gastropathy less common	Portal hypertensive gastropathy less common	Portal hypertensive gastropathy more common
<b>Non invasive tools</b>			
Ultrasound examination			
Liver	Normal/irregular surface	Normal/irregular surface	Irregular surface
	Homogeneous/innhomogenous parenchima	Homogeneous/innhomogenous parenchima	Innhomogenous
Portal veins	Dilatated, hyperechoic with thickened walls	Chronic thrombosis	Dilatated
	+/- spontaneous shunts	+/- cavernomatous transformation	+/- thrombosis
	+/- thrombosis	+/- portal biliopathy	
Spleen	Often giant splenomegaly	Often giant splenomegaly	Splenomegaly
Porto systemic collaterals, +/- ascites			
CEUS examination	Delayed periportal enhancement		Homogenous/heterogenous/delayed periportal enhancement
Cross-sectional imaging	Heterogeneous hepatic enhancement or paucity of the medium size portal branches	(1) Better characterization of the level and extension of thrombus; and (2) Better characterization of the portal biliopathy	Better characterization of the focal liver lesions
Elastography			
Liver stiffness	N or slightly ↑	N or slightly ↑ (less then in the PSVD)	↑ (has prognostic value)
Spleen stiffness	↑	↑	↑ (less then in PSVD or EHPVO)

PSVD: Porto-sinusoidal vascular disease; EHPVO: Extrahepatic portal vein obstruction; CEUS: Contrast-enhanced ultrasound; HVPG: Hepatic venous pressure gradient; WHVP: Wedged hepatic venous pressure; FHVP: Free hepatic vein press.

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