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Porto-sinusoidal vascular disorder in chronic HBV: A significant coexistence not to be overlooked

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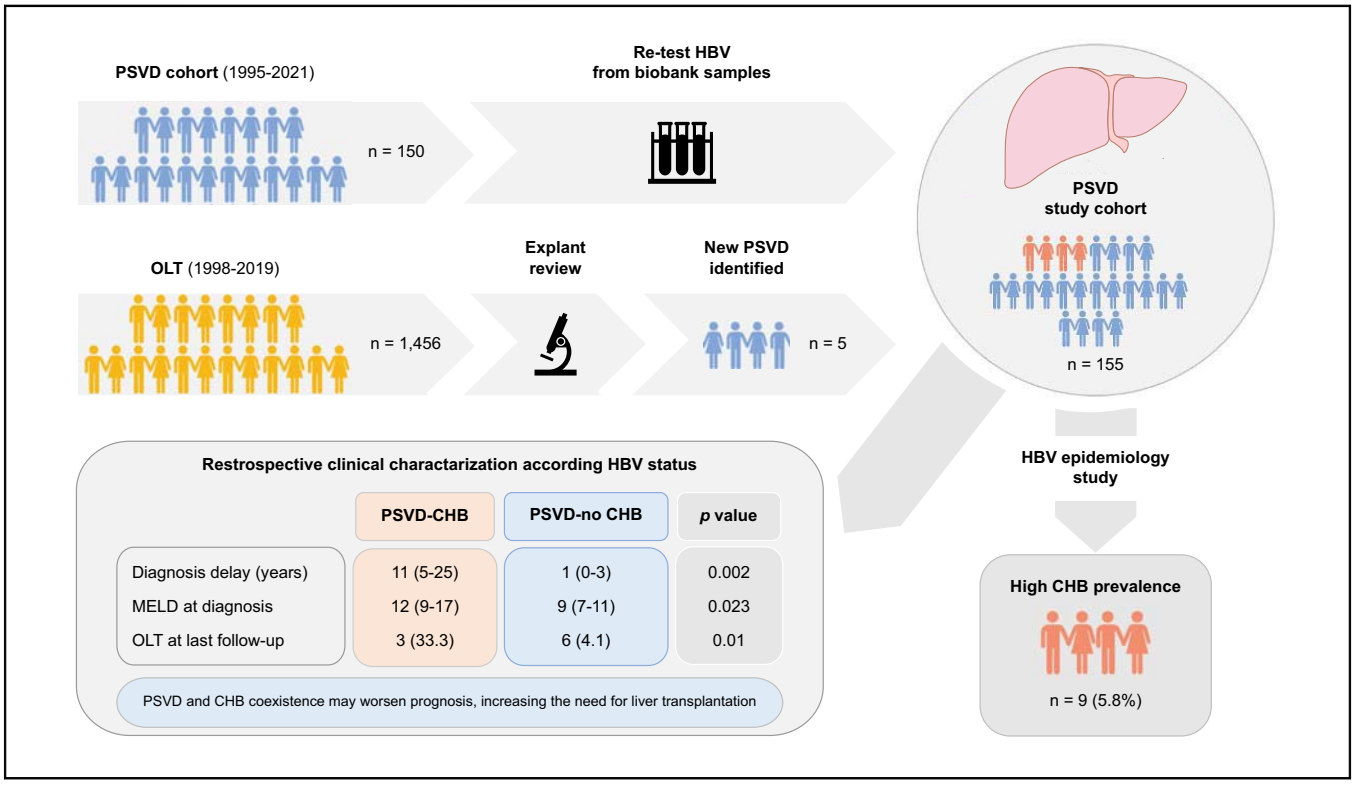
Graphical abstract



Highlights

- We observed a non-negligible prevalence of chronic hepatitis B in the population with PSVD.
- HBV infection may challenge and delay the PSVD diagnosis.
- The coexistence of chronic hepatitis B and PSVD may worsen prognosis, increasing the need for liver transplantation.

Impact and implications

The new diagnostic criteria for porto-sinusoidal vascular disorder (PSVD) allow for coexistence with other liver diseases. The results of the present study highlight, for the first time, a non-negligible prevalence of chronic hepatitis B in the PSVD population that was previously unknown. Coexistence may challenge and delay the PSVD diagnosis and is associated with a more unfavorable clinical course. Our findings will increase awareness of this coexistence and improve PSVD diagnosis and management. Furthermore, the data will encourage new studies to determine the prevalence and clinical behavior of other chronic liver diseases that coexist with PSVD.

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Research article

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Porto-sinusoidal vascular disorder in chronic HBV: A significant coexistence not to be overlooked

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Background & Aims: Porto-sinusoidal vascular disorder (PSVD) encompasses a group of liver diseases with vascular abnormalities that can cause portal hypertension in the absence of cirrhosis. The new diagnostic criteria allow for coexistence with other liver diseases, however its relationship with chronic hepatitis B (CHB) remains unclear. This study aimed to assess HBV prevalence in a PSVD cohort and evaluate its clinical impact.
Methods: This retrospective study was conducted on patients with PSVD at Hospital Clínic Barcelona. HBV serology was evaluated, and patients were categorized into HBV chronic infection, past infection, or no HBV exposure. Clinical characteristics and outcomes were compared.
Results: We included 155 patients with PSVD. Prevalence of CHB and past HBV infection in patients with PSVD was higher than in the general population (5.8% *vs.* 0.5%, p <0.0001 and 20% *vs.* 9.1%, p <0.0001, respectively). Patients with CHB had a significant delay in PSVD diagnosis compared to those without CHB (11 [5–25] *vs.* 1 [0–3] years, p = 0.002) and had a more advanced disease (MELD score 12 [9–17] *vs.* 9 [7–11], p = 0.012) at the time of PSVD diagnosis. The clinical evolution of PSVD in patients with CHB was marked by a significantly higher transplantation rate at the last follow-up (33% *vs.* 4.1%, p = 0.001).
Conclusions: Recognizing the coexistence of PSVD and CHB is important for timely diagnosis and optimal management, highlighting the potential benefits of specialized care for potentially improved outcomes.
Impact and implications: The new diagnostic criteria for porto-sinusoidal vascular disorder (PSVD) allow for coexistence with other liver diseases. The results of the present study highlight, for the first time, a non-negligible prevalence of chronic hepatitis B in the PSVD population that was previously unknown. Coexistence may challenge and delay the PSVD diagnosis and is associated with a more unfavorable clinical course. Our findings will increase awareness of this coexistence and improve PSVD diagnosis and management. Furthermore, the data will encourage new studies to determine the prevalence and clinical behavior of other chronic liver diseases that coexist with PSVD.

Introduction

Porto-sinusoidal vascular disorder (PSVD) is a rare entity that encompasses a group of diseases with similar histological abnormalities of the liver (regenerative nodular hyperplasia, incomplete septal cirrhosis and obliterative portal venopathy) in the absence of cirrhosis. The disorder causes portal hypertension (PH) and its related decompensations such as bleeding, ascites, and hepatic encephalopathy, leading to significant morbidity and mortality.[1,2]

Before the introduction of the PSVD nomenclature, which was proposed during an expert conference in 2019 and is now endorsed by both Eastern and Western societies of hepatology, the diagnosis primarily depended on the application of exclusion criteria and the presence of clinical PH.[3,4] Diagnosis required an extensive list of diagnostic tests aimed at excluding other potential causes of PH. However, with the advent of specific diagnostic criteria based on histological and clinical data, PSVD is no longer solely a diagnosis of exclusion. One of the most significant advances is the recognition that a concomitant liver disease, such as viral hepatitis or alcohol-related liver disease, can coexist with vascular alterations in the absence of cirrhosis, and such coexistent liver diseases are no longer considered an exclusion criterion. This realization opens up a new perspective where PSVD and other liver diseases can coexist.

Keywords: Porto-Sinusoidal Vascular Disease; Non-cirrhotic Portal Hypertension; Vascular liver diseases; Idiopathic portal hypertension; Chronic Hepatitis B; Obliterative portal venopathy; Regenerative nodular hyperplasia; Incomplete septal cirrhosis.
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HBV has the potential to progress to chronicity, leading to advanced chronic liver disease and the development of PH.[5] While HBV is commonly associated with cirrhosis, intrahepatic vascular abnormalities typically seen in PSVD have also been observed in patients with chronic HBV (CHB) in the absence of cirrhosis.[6–8] Specifically, a study analyzing 74 consecutive biopsies from treatment-naïve patients with chronic viral hepatitis (HCV and HBV), but without PH, revealed obliterative portal venopathy (a hallmark of PSVD) in up to 25.7% of the patients.[8]

However, it is important to note that previous natural history studies of PSVD excluded patients with positive HBV serology as they were performed based on the previous diagnostic definition of idiopathic PH, where HBV infection was considered an exclusion criterion.[2,9,10] Consequently, the prevalence of HBV exposure among patients with PSVD remains unknown.

Moreover, underlying CHB has been described in isolated cases of PSVD with PH[11] and a recent retrospective study evaluating 91 patients in Austria fulfilling the new PSVD criteria identified two patients with concomitant CHB.[12] These findings raise the following questions, how prevalent is HBV infection in patients with PSVD and what is its potential role in the development or severity of PH.

The aim of our study was to describe the prevalence of HBV in a well characterized PSVD cohort and evaluate the clinical impact of HBV-PSVD coexistence.

Patients and methods

Patient inclusion and data collection

Unicentric retrospective study at Hospital Clínic Barcelona including all the patients fulfilling PSVD criteria according to the VALDIG definition from 1995 to 2021.[3,4] To ensure the inclusion of all patients with PSVD at our Hospital, the vascular liver disease registry was integrated with the orthotopic liver transplant (OLT) registry. HBV serologies were evaluated in all patients with PSVD. For patients with PSVD lacking complete HBV serology (HBsAg, anti-HBc, anti-HBs) data, biobank samples were retrieved, and additional HBV evaluations were performed.

We carefully reviewed liver explant pathology records to identify any misdiagnosed patients. We gathered clinical information on the included patients from the initial diagnosis of liver disease until the most recent follow-up, focusing on three different time points to analyze the clinical evolution: 1) onset of the initial sign of hepatopathy, 2) PSVD diagnosis, and 3) last follow-up visit.

HBV samples and laboratory tests

HBsAg, anti-HBs and anti-HBc were determined by Antellica (Siemens) from biobank serum samples.

Definitions

PSVD was diagnosed according to the VALDIG criteria,[3,4] which take into account liver biopsy (>20 mm and minimal fragmentation) and clinical findings: Exclusion of cirrhosis is mandatory with at least one of the following: 1) at least one specific sign of PH (gastroesophageal varices, PH-bleeding, portosystemic collaterals at imaging), 2) at least one histologic lesion specific for PSVD (obliterative portal venopathy, nodular regenerative hyperplasia, incomplete septal fibrosis), 3) at least one feature not specific for PH together with at least one histologic lesion compatible although not specific for PSVD. In addition, the history of bone marrow transplantation, Budd-Chiari syndrome, hepatic venous outflow obstruction, hepatic schistosomiasis diagnosed on liver biopsy, cardiac failure, Fontan surgery, Abernethy syndrome, hereditary hemorrhagic telangiectasia, chronic cholestatic diseases, liver infiltration by tumor cells, sarcoidosis and congenital hepatic fibrosis are considered exclusion criteria.

The onset of the initial sign of hepatopathy was defined as first time detection of liver disease-related laboratory, imaging, or clinical abnormalities.

The following definitions regarding HBV status were used: chronic hepatitis B (CHB): HBsAg positive for more than 6 months; past HBV infection: HBsAg negative, anti-HBc positive, anti-HBs positive or negative; No HBV exposure: HBsAg negative, anti-HBc negative, anti-HBs negative or positive.

Statistical analysis

Quantitative variables were expressed as median (interquartile ranges) and were compared using the Mann-Whitney *U* test. Qualitative variables were expressed as absolute and relative (percentage) frequencies and compared using the Chi-square or the Fisher's test, as appropriate.

Ethical aspects

This study was conducted in accordance with the international guidelines for Ethical Review of Epidemiological Studies and Principles of the Declaration of Helsinki and has the approval of Hospital Clínic Barcelona ethical committee (HCB/2020/0892). All patients included in the study gave signed written informed consent to participate.

Results

Study population

A total of 155 patients who fulfilled the criteria for PSVD were included in the study (Fig. 1); 150 were identified in the vascular liver disease registry and 53 of them had complete HBV serology data, including HBsAg, anti-HBs, and anti-HBc tests. The remaining 97 patients with missing HBV serology data had stored blood samples at our biobank that allowed for HBV testing. Consequently, the entire cohort finally had HBV serology data.

Among the 1,456 liver transplant (OLT) cases performed in our center from 1998 to 2019, five additional patients with PSVD were identified. All five cases were initially misdiagnosed with cirrhosis. However, upon examination of the explanted liver, it was revealed that they actually had PSVD.

HBV epidemiology in PSVD

Out of the total 155 patients with PSVD, 40 (26.49%) patients had a history of exposure to HBV, 9 (5.8%) had CHB and 31 past HBV infection. The analysis of biobank samples in patients lacking HBV data did not reveal any new cases of CHB.

The prevalence of chronic HBV infection in our PSVD cohort was markedly higher than that observed in the Spanish general population (5.8 *vs.* 0.5, p <0.0001),[13] suggesting an intermediate level[14] of HBV prevalence among patients with PSVD.

Past HBV infection was also higher in patients with PSVD than in the general population (20 *vs.* 9.1, p <0.0001)[15] and prevalence increased gradually with patient age, consistent with findings from other epidemiological studies on HBV in Spain (Fig. 2; Table S1).[15,16]

Thirty-eight patients (24.52%) were vaccinated and, in agreement with the historical Spanish vaccination polices, the

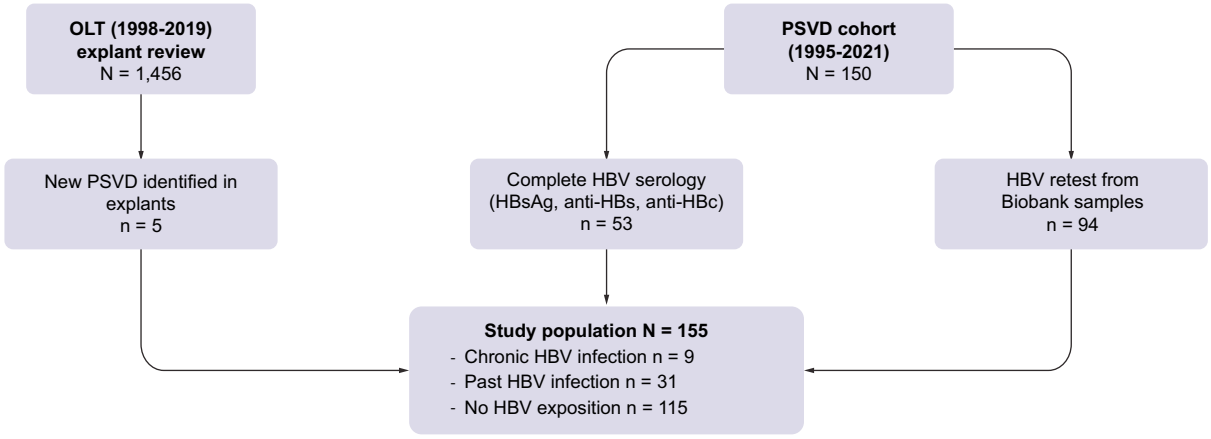

Fig. 1. Flowchart illustrating patient inclusion and methods. OLT, orthotopic liver transplant; PSVD, porto-sinusoidal vascular disorder.

prevalence of vaccination was clearly higher in younger patients (Table S1).[16]

Coinfection of HBV and HIV was observed in only one patient. Given that HIV is associated with both PSVD and HBV[17,18] we examined the prevalence of HIV in our PSVD cohort based on their HBV status and found no significant differences (Table 2).

Evaluation of PSVD evolution according to HBV status

To characterize PSVD evolution according to HBV status we retrospectively analyzed the clinical characteristics at three different time points: 1) onset of the initial sign of hepatopathy, 2) PSVD diagnosis and 3) last follow-up visit.

Clinical evolution in patients with past HBV infection

First, we evaluated the clinical evolution of patients with PSVD and a history of past HBV infection (n = 31), comparing them with those who had not been exposed to HBV (n = 115).

At the onset of the initial sign of hepatopathy, patients with past HBV were significantly older (47 [28–55] years *vs.* 40 [28–55] years, $p = 0.044$)[15,16] but despite the age differences, no differences in hepatic function, signs of PH and hepatic decompensation were observed (Table S3).

The median time from the onset of the initial sign of hepatopathy to the diagnosis of PSVD in patients with past HBV infection was not significantly different to that in the group with no prior HBV exposure (1 [0–2] years *vs.* 0 [0–4] years, $p = 0.734$). In addition, at the time of PSVD diagnosis, no clinical differences or differences in PSVD-associated conditions were observed between the two groups (Table S4).

Finally, at the time of last follow-up (median years of follow-up (7 [3–14] years *vs.* 8 [5–16] years, $p = 0.120$), both study groups had a comparable progression with no differences in liver function, liver decompensation, death or OLT (Table S6). Based on this data, both cohorts were thereafter grouped together as PSVD-No CHB.

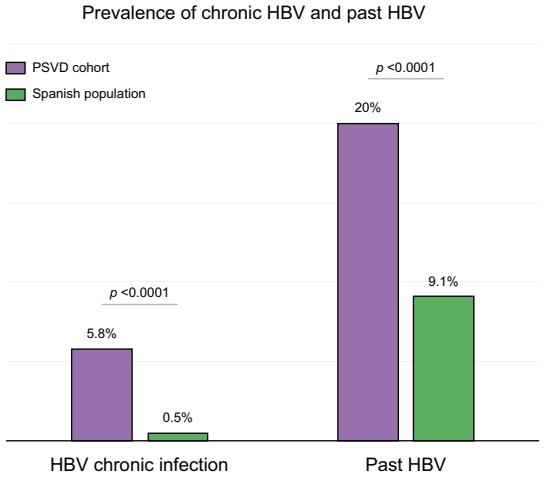

Fig. 2. Prevalence of chronic HBV and past HBV. PSVD cohort *vs.* Spanish population. Chi-square goodness of fit test. Levels of significance: p <0.0001, p <0.0001. PSVD, porto-sinusoidal vascular disorder.

Clinical evolution in patients with chronic HBV

To assess whether the coexistence of PSVD and CHB (PSVD-CHB) exhibited different clinical characteristics, we compared the PSVD-CHB group with PSVD patients with no CHB (PSVD-No CHB, including patients with past HBV infection and with no HBV exposure).

At the onset of the initial sign of hepatopathy, no significant differences were observed between the PSVD-CHB and PSVD-No CHB groups. Patients in both groups exhibited similar ages and similar liver disease stages (Table 1). In all cases HBV was diagnosed prior to PSVD. However, the median time to PSVD diagnosis was significantly higher in patients with PSVD-CHB (11 [5–25] years *vs.* 1 [0–3] year; $p = 0.002$), indicating an important diagnostic delay. This delay was often due to misdiagnosis as advanced HBV-related chronic liver disease. Furthermore, the misdiagnosis was also illustrated by a significantly higher proportion of patients with a PSVD diagnosis after OLT in the CHB group (2 [22.2%] *vs.* 3 [2.1%], $p = 0.027$) (Table 2). Fig. S1 shows how the diagnostic delay in our cohort has improved over the years due to greater awareness of PSVD. However, despite the improvement, a more pronounced diagnostic delay persisted in the PSVD-CHB compared to the PSVD-No CHB group.

At the time of PSVD diagnosis, patients with PSVD-CHB were older (56 [52–68] years *vs.* 45 [34–57] years, $p = 0.0024$) had worse hepatic function (MELD score 12 [9–17] *vs.* 9 [7–11], $p = 0.023$) and higher prevalence of large varices (100% *vs.* 58.6%, $p = 0.012$). Five (55.6%) PSVD-CHB patients developed variceal

Table 1. Clinical characteristics at the onset of initial sign of hepatopathy.

Characteristic	PSVD-CHB n = 9	PSVD-No CHB* n = 146	*p* value
Age at first sign of hepatopathy (years)	47 (27–56)	42 (32–55)	0.711
Laboratory test			
AST (U/L)	23 (17–34)	34 (24–46)	0.143
ALT (U/L)	19 (15–26)	34 (21–47)	0.061
Total bilirubin (mg/dl)	0.95 (0.66–1.15)	0.9 (0.6–1.3)	0.909
Indirect bilirubin (mg/dl)	0.8	0.75 (4–1)	0.945
Albumin (g/L)	43.5 (42–45)	41.5 (38–44)	0.186
Prothrombin time (%)	89.6 (77–100)	80.5 (69–94)	0.419
INR	0.99 (0.93–1.1)	1.1 (1–1.2)	0.149
Creatinine (mg/dl)	1.15 (1–1.39)	0.81 (0.7–0.98)	**0.017**
Platelets*10^9	110 (74–205)	109 (69–139)	0.808
Hemoglobin (g/dl)	12.5 (10.9–12.7)	13.5 (11.5–14.3)	0.315
Hepatic function			
Child-Pugh score	5 (5–5)	5 (5–6)	0.219
MELD score	9 (7.5–10)	8 (7–10)	0.567
Portal hypertension signs			
Specific signs** n (%)	7 (77.8)	86 (58.9)	0.317
Thrombocytopenia (<150)	4 (66.7)	93 (78.8)	0.61
Splenomegaly (>13 cm), n (%)	5 (83.3)	82.5 (113)	1
Spleen size (cm)	14.5 (14–16)	16 (14–18)	0.418
LSM (kPa)	8.55(5.4–12.4)	7.9 (6–10.25)	0.761
Esophageal varices, n (%)	7 (77.8)	86 (58.9)	0.317
Large varices, n (%)	6 (66.7)	69 (47.3)	0.316
Clinical features			
Decompensation, n (%)	2 (22.2)	43(29.5)	1
Variceal bleeding, n (%)	2 (22.2)	26 (17.8)	0.666
Ascites, n (%)	1 (11.1)	20 (13.7)	1
Hepatic encephalopathy, n (%)	0	0	1
Portal vein thrombosis, n (%)	0	19 (13.1)	0.602

Quantitative variables expressed as median and IQ (25–75), qualitative variables expressed as n and (%).
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CHB, chronic hepatitis B; INR, international normalized ratio; LSM, liver stiffness measurement; OLT, orthotopic liver transplant; PSVD, porto-sinusoidal vascular disorder.
* PSVD-No CHB = Past HBV + no HBV exposure.
** Specific signs of portal hypertension: esophageal varices and portal hypertension-related bleeding.

bleeding associated with a second decompensation (ascites and/or hepatic encephalopathy (55.6% *vs.* 20.1% p 0.101) (Table 2). No differences in PSVD-associated conditions were observed between the two groups (Table 3).

During follow-up (median years of follow-up 11 [5–25] *vs.* 8 [5–15], p = 0.420), disease progression was more severe in the PSVD-CHB group, leading to a higher necessity for OLT (3 [33%] *vs.* 6 [4.1%] p = 0.001). In the PSVD-CHB group, the OLT indication was hepatopulmonary syndrome in one case and impaired liver function plus ascites in the other cases. In the PSVD-No CHB group, OLT was indicated for hepatopulmonary syndrome, refractory ascites and impaired liver function, with two patients in each category. No differences in hepatocellular carcinoma or portal vein thrombosis development were observed between the two groups (Table 4).

Chronic HBV in PSVD

Upon detecting indications of a potential distinct behavior in patients with PSVD-CHB coexistence, we conducted a more comprehensive analysis to provide a detailed description of this population.

Out of the total number of patients with PSVD, nine were diagnosed with CHB. For confirmation of the diagnosis, biopsy samples were meticulously reviewed by an expert pathologist who verified the presence of vascular alterations without cirrhosis and ensured that the criteria for PSVD were met.

All patients with PSVD-CHB were HBeAg negative. The median follow-up was 16 years, ranging from 5 to 21 years. Among them, five patients (55.56%) met criteria for treatment and were under antiviral treatment (4 tenofovir, 1 entecavir). During the course of their infection, three untreated patients achieved functional cure after 19, 12 and 23 years of infection (Table 5), with the diagnosis of PSVD made after CHB cure in all three. Anti-hepatitis D antibodies were tested in seven of the nine patients and were negative in all of them. One of the two HDV-non-tested patients had HBV seroconversion during follow-up and so HDV was clinically discarded. The other HDV-non-tested patient was HIV+HBV (HBsAg+) under tenofovir treatment and although definitive data to rule out HDV infection was not available, the transaminase values were within normal ranges, supporting the absence of viral activity.

PSVD diagnosis was delayed, with the diagnosis made a median of 11 (5–25) years after the initial identification of signs of PH (Table 6). In seven cases the biopsy that gave the diagnosis was performed due to decompensation and/or signs of PH progression despite long term adequate virologic control and low liver stiffness values (7.7 [5–12.2] kPa) and/or hepatic venous pressure gradient (6 [3.5–10] mmHg). Two patients misdiagnosed with cirrhosis were correctly identified as having PSVD at the time of OLT after evaluation of the explanted liver.

Five (55.6%) patients had an identifiable PSVD-associated condition, with 33.3% having immune disorders, 22.2% related to drug exposure and 11.1% associated with HIV infection. At the time of PSVD diagnosis, hepatic function was moderately impaired (MELD score 12 [9–17] and Child-Pugh score 5 [5–8]), with 5 (55.6%) experiencing hepatic decompensation (55.6% PH-bleeding, 33.3% ascites, 22.2% hepatic encephalopathy). All of them had large varices and 4 (44.4%) had portal vein thrombosis.

Table 2. Clinical characteristics at PSVD diagnosis.

Characteristic	PSVD-CHB n = 9	PSVD-No CHB* n = 146	*p* value
Sex (male), n (%)	9 (100)	92 (63)	**0.028**
Age at diagnosis	56 (52–68)	45(34–57)	**0.024**
Diagnosis delay** (years)	11 (5–25)	1 (0–3)	**0.002**
PSVD-associated condition, n (%)	5 (55.6)	91 (62.3)	0.732
Laboratory test			
AST (U/L)	41 (26–55)	34 (25–46)	0.649
ALT (U/L)	29 (11–42)	32 (21–47)	0.720
Bilirubin (mg/dl)	1.46 (1.05–2.7)	1 (0.7–1.5)	0.059
Indirect bilirubin (mg/dl)	1 (0.9–3.6)	0.8 (0.4–1.1)	0.127
Albumin (g/L)	40.1 (35–42.5)	39.5 (36–43)	0.935
Prothrombin time (%)	54 (32–79)	79 (67–92)	0.053
INR	1.32 (1.33–1.73)	1.13 (1.03–1.24)	0.069
Creatinine (mg/dl)	0.92 (0.64–1.08)	0.8 (0.69–0.97)	0.463
Platelets*10^9	67 (44–109)	98 (68–137)	0.188
Hemoglobin (g/dl)	11.7 (9.9–12.9)	12.8 (10.9–14.1)	0.269
Hepatic function			
Child-Pugh score	5 (5–8)	5 (5–6)	0.781
MELD score	12 (9–17)	9 (7–11)	**0.023**
Portal hypertension signs			
Specific signs,*** n (%)	9 (100)	112 (77.2)	0.206
Thrombocytopenia (<150), n (%)	7 (77.8)	116 (84.6)	1
Splenomegaly (>13 cm), n (%)	7 (77.8)	112 (77.2)	0.635
Spleen size (cm)	14.5 (14–21)	16 (14–18)	0.980
LSM (kPa)	7.7 (5.05–12.2)	7.9 (5.9–10.3)	0.953
HVPG mmHg	6 (3.5–10)	8.5 (5–11)	0.455
Esophageal varices, n (%)	9 (100)	112 (77.2)	0.206
Large varices, n (%)	9 (100)	85 (58.2)	**0.012**
Clinical features			
Decompensation, n (%)	5 (55.6)	61 (43.9)	0.513
Second decompensation, n (%)	5 (55.6)	29 (20.1)	0.101
Variceal bleeding, n (%)	5 (55.6)	40 (27.8)	0.127
Ascites, n (%)	3 (33.3)	28 (19.2)	0.385
Hepatic encephalopathy, n (%)	2 (22.2)	0	**0.012**
Portal vein thrombosis, n (%)	4 (44.4)	45 (30.8)	0.465
OLT, n (%)	2 (22.2)	3 (2.1)	**0.027**
TIPS, n (%)	1 (11.1)	9 (6.2)	0.460
Surgical shunt, n (%)	0	8 (5.5)	1

Quantitative variables expressed as median (IQR) and qualitative variables expressed as n (%).
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CHB, chronic hepatitis B; INR, international normalized ratio; LSM, liver stiffness measurement; OLT, orthotopic liver transplant; PSVD, porto-sinusoidal vascular disorder; TIPS, transjugular intrahepatic portosystemic shunt.
* PSVD-No CHB = Past HBV + no HBV exposure.
** Diagnosis delay: Time between detection of first sign of hepatopathy and PSVD diagnosis with biopsy.
*** PSVD-No CHB = Past HBV + no HBV exposure.

Starting from the moment when the first sign of hepatopathy was identified, the median follow-up time was 11 (5–25) years. At the time of the last follow-up, three patients were transplanted. Additionally, one patient died of a liver-related cause 28 months after the PSVD diagnosis. None of the patients developed hepatocellular carcinoma.

Discussion

The revised definition of PSVD allows for its coexistence with other chronic liver diseases in the absence of cirrhosis.[3,4]

Existing data and our own clinical experience indicate that CHB may be present in a subset of patients with PSVD.[1,8,11,12] Our findings revealed a significant prevalence of CHB (5.8%) and past HBV infection (20%) among patients with PSVD, confirming the coexistence of PSVD and HBV infection. Importantly, the prevalence of CHB in PSVD was higher than that observed in the general Spanish population, reaching levels of intermediate prevalence.[13–15] The high prevalence of HBV exposure among patients with PSVD is complex and probably multifactorial. Direct vascular damage by the HBV could play a role in this relationship. Previous pathology reports have described damage in the intrahepatic vasculature at early stages of HBV infection, suggesting a direct damaging effect of the virus on the vasculature regardless of the parenchymal alterations. Obliterative portal venopathy has been linked to histological activity index, suggesting that inflammation at the small portal veins could cause their obliteration and contribute to PSVD development in the absence of cirrhosis.[8] Although our study also suggests that HBV may directly target the intrahepatic vessels, which may explain why PH can progress and even lead to decompensation after viral control and improvement of liver function, specifically designed studies are needed to address this hypothesis. Geographical origin could also explain part of the relationship, we compared how well our PSVD cohort reflected the global Spanish population (Data obtained from INE: Spanish National institute of statistics)[19] and we did observe that our PSVD cohort had and increased proportion of individuals from African origin (7.7 *vs.* 2.7%, p <0.001). In addition, exposure to HBV (CHB or Past HBV) was higher in the African population (17.5 *vs.* 4.3% p = 0.013). Although this might slightly contribute to the increased prevalence of HBV exposure, we did repeat the analysis

Table 3. PSVD-associated conditions according to presence of chronic HBV.

Associated condition	PSVD-CHB n = 9	PSVD-No CHB* n = 146	*p* value
Idiopathic, n (%)	4 (44.4)	55 (37.7)	0.732
Immune disorder, n (%)	3 (33.3)	34 (23.3)	0.446
HIV, n (%)	1 (11.1)	30 (20.5)	0.688
Hematological disorder, n (%)	0	8 (5.5)	1
Drug, n (%)	(2) 22.2	32 (21.9)	1
Azathioprine (n)	2	13	
Oxaliplatin (n)	0	7	
Didanosine (n)	0	12	

CHB, chronic hepatitis B; PSVD, porto-sinusoidal vascular disorder.
* PSVD-No CHB = Past HBV + No HBV exposure.

Table 4. Clinical characteristics at last follow-up.

Characteristics	PSVD-CHB n = 9	PSVD-No CHB* n = 146	*p* value
Age at last follow-up (years)	57 (53–70)	54 (43–65)	0.313
Total time of follow-up (years)	11 (5–25)	8 (5–15)	0.420
Laboratory test			
Total bilirubin (mg/dl)	1.4 (1.1–2)	1.2 (0.8–1.9)	0.564
Albumin (g/L)	41 (33–41)	39 (35–43)	0.758
Prothrombin time (%)	70 (45–94.5)	70 (51.6–80)	0.906
INR	1.2 (1–1.67)	1.2 (1.1–1.5)	0.970
Creatinine (mg/dl)	1 (0.7–1.4)	0.84 (0.66–1.1)	0.341
Platelets*10^9	64 (41–160)	96 (60–134)	0.452
Hemoglobin (g/dl)	13.4 (12.8–14.3)	13.5 (11.6–14.9)	0.374
Hepatic function			
Child score	7 (5–8)	6 (5–7)	0.684
MELD score	15 (10–16)	11 (8–17)	0.497
Portal hypertension signs			
Specific signs,** n (%)	9 (100)	124 (84.9)	0.364
Thrombocytopenia (<150), n (%)	7 (77.8)	122 (85.9)	0.620
Splenomegaly (>13 cm), n (%)	7 (77.8)	111 (78.7)	1
Esophageal varices, n (%)	9 (100)	124 (85.5)	0.611
Large varices, n (%)	9 (100)	110 (75.9)	0.210
Clinical features			
Decompensation, n (%)	6 (66.7)	6 (59.3)	0.741
Second decompensation, n (%)	6 (66.7)	58 (40.3)	0.166
Variceal bleeding, n (%)	5 (55.6)	63 (43.2)	0.507
Variceal re-bleeding, n (%)	2 (22.2)	30 (20.8)	1
Ascites, n (%)	5 (55.6)	48 (33.1)	0.276
SBP, n (%)	1 (11.1)	6 (4.2)	0.352
Hepatic encephalopathy, n (%)	4 (44.4)	25 (17.4)	0.066
Hepatocarcinoma, n (%)	0	2 (1.4) (2)	1
Portal vein thrombosis, n (%)	4 (44.4)	63 (44.4)	1
TIPS, n (%)	1 (11.1)	23 (15.8)	1
Surgical shunt, n (%)	0	8 (5.5)	1
Death, n (%)	1 (11.1)	36 (24.7)	0.687
Liver-related death, n (%)	1 (11.1)	19 (13)	1
OLT, n (%)	3 (33.3)	6 (4.1)	**0.01**

Quantitative variables expressed as median (IQR) and qualitative variables expressed as n (%).
CHB, chronic hepatitis B; INR, international normalized ratio; OLT, orthotopic liver transplant; PSVD, porto-sinusoidal vascular disorder; SBP, spontaneous bacterial peritonitis; TIPS, transjugular intrahepatic portosystemic shunt.
* PSVD-No CHB = Past HBV + no HBV exposure.
** Specific signs of portal hypertension: esophageal varices, portal hypertension-related bleeding.

Table 5. Virus characterization in patients with PSVD and chronic HBV.

ID	HBV biology	Treatment	Functional cure
1	HBeAg-negative chronic infection	No	No
2	HBeAg-negative chronic infection	No	Yes
3	HBeAg-negative chronic infection	No	Yes
4	HBeAg-negative chronic infection	Tenofovir	No
5	HBeAg-negative chronic infection	Tenofovir	No
6	HBeAg-negative chronic infection	Entecavir	No
7	HBeAg-negative chronic infection	Tenofovir	No
8	HBeAg-negative chronic infection	Tenofovir	No
9	HBeAg-negative chronic infection	No	Yes

PSVD, porto-sinusoidal vascular disorder.

Table 6. PSVD with chronic HBV clinical characteristics.*

	Features at PSVD diagnosis							Features at last follow-up					
ID	Age	Diagnostic delay (years)	Associated condition	LSM (kPa)	MELD	Decompensation	PVT	Time of follow-up (months)	MELD	Decompensation	PVT	OLT	Death
1	77	0	No	12.4	11	No	No	28	16	A, HE	No	No	Yes
2	68	12	No	26.6	8	A, VB	No	29	14	A, SBP, VB, HE	No	No	No
3	54	28	No	12	17	No	Yes	33	15	No	Yes	No	No
4	52	5	HIV & CD	5.6	7	A, VB	No	1	7	A, VB	No	No	No
5	56	0	UC	3.8	9	No	No	6	9	A, VB	No	No	No
6	69	11	UC & AZA	4.5	20	A, VB	Yes	Diagnosis after OLT (Explant revision)				Yes	No
7	57	29	No	9.1	14	VB, HE, HPS	Yes	5	15	VB, HE, HPS	Yes	Yes	No
8	50	8	Crohn & AZA	6.3	12	No	Yes	34	10	No	Yes	No	No
9	36	25	No	NA	20	A, VB, HE	No	Diagnosis after OLT (Explant revision)				Yes	No

* A, ascites; AZA, azathioprine; CD, coeliac disease; HE, hepatic encephalopathy; HPS, hepatopulmonary syndrome; OLT, orthotopic liver transplant; PSVD, porto-sinusoidal vascular disorder; UC, ulcerative colitis; VB, variceal bleeding.

after excluding African patients and the differences in prevalence remained clearly significant: CHB 5.6% *vs.* 0.5%, p <0.001; past HBV 18.1% *vs.* 9.1%, p <0.001. Low socioeconomic status and poor living conditions could also impact HBV exposure and PSVD prevalence.[1,2] Regrettably information on socioeconomic status was not available, but recurrent abdominal infections were present in only one patient who had no history of HBV exposure.

Given the available data, there is no clear explanation for the higher observed prevalence of HBV within the PSVD population in our cohort. The single-center and retrospective design of our study limits our capacity to fully elucidate this phenomenon. To validate our findings, we examined the available published data and it has come to our attention that most of the existing series were published prior to the introduction of the new PSVD terminology and consequently, these earlier studies may not have accounted for the possibility of coexisting causes of liver disease in cases labelled as idiopathic PH. Recently, the VALDIG group conducted an extensive assessment of the natural history of PSVD in an international multicenter study.[20] We analyzed this cohort consisting of 587 patients with PSVD and found that 10 patients (1.7%) had chronic HBV (CHB), and 15 had a history of past HBV infection (2.55%). Although these data also reveal the coexistence of CHB and PSVD, it is important to acknowledge that not all these patients were comprehensively evaluated. In fact, a significant proportion of patients, 285 (48.5%), lacked serological data and, as a result, we cannot definitively rule out past HBV exposure in a significant number of patients.

The findings from our present study not only provide a rationale for screening for HBV infection in patients with suspected PSVD but also prompt consideration of the possibility of PSVD in patients with HBV infection.

Interestingly, our study showed that patients with PSVD-CHB experienced a delayed diagnosis and presented with more advanced stages of the disease. At the time of PSVD diagnosis, patients with PSVD-CHB had worse liver function and higher prevalence of signs of PH compared to non-infected patients. These findings suggest that there may be difficulties in diagnosing PSVD in patients with CHB, potentially due to the misdiagnosis of advanced HBV-related chronic liver disease. The presence of signs of PH and liver decompensation in patients with well-controlled chronic HBV infection, as indicated by low liver stiffness values and hepatic venous pressure gradient below 10 mmHg, should prompt consideration of liver biopsy to rule out PSVD. Furthermore, the notable disparity in liver transplantation rates between the PSVD-CHB and PSVD-No CHB groups at the end of follow-up indicates that patients with PSVD-CHB may have an unfavorable prognosis.

It is true that distinguishing between incomplete or regressive cirrhosis and PSVD remains challenging since there is no specific diagnostic tool able to differentiate the two entities. Instead, a comprehensive clinical and pathological history is often the primary means of differentiation, although obtaining complete information can be challenging. In our study an expert pathologist meticulously evaluated the liver specimens of patients with HBV exposure to verify the absence of cirrhosis and the presence of vascular alterations. Notably, septal incomplete cirrhosis, which might be the most ambiguous pathological finding in the context of regressed cirrhosis, was observed in only two patients and it was consistently accompanied by other vascular alterations. In addition, in all patients except one, liver decompensation always occurred after a prolonged period of well-controlled viral activity either with drugs or spontaneous seroconversion. This pattern leads support to a PSVD diagnosis, where the disease progressed independently of good viral control rather than a regression and decompensation of HBV-related cirrhosis following viral control.

The strengths of our study include the analysis of the largest cohort of patients with PSVD for whom the presence of HBV was characterized, with reevaluation of liver specimens by an expert pathologist to reconfirm the coexistence of PSVD and CHB. However, there are limitations to consider, including the unicentric and retrospective nature of the study and the rarity of PSVD, which resulted in a relatively small sample size.

In conclusion, our study highlights the non-negligible prevalence of CHB in the PSVD population for first time and the challenges associated with diagnosing PSVD in the presence of HBV infection. Coexistence of CHB and PSVD may be associated with a more unfavorable clinical course, characterized by a higher requirement for liver transplantation. These findings not only provide a rationale for screening for HBV infection in patients with suspected PSVD but also prompt consideration of the possibility of PSVD in patients with HBV infection. Furthermore, the findings underscore the importance of referring these patients to specialized centers for optimal management. Future multicenter studies with larger sample sizes are needed to further investigate the impact of HBV infection in PSVD. Additionally, exploring the prevalence and impact of other chronic liver diseases, such as viral hepatitis C, steatotic liver disease, and alcohol-related liver disease in PSVD, warrants further investigation.

Abbreviations

CHB, chronic hepatitis B; OLT, orthotopic liver transplant; PH, portal hypertension; PSVD, porto-sinusoidal vascular disorder.

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Conflict of interest

The authors who have taken part in this study declare they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Conceptualization: VHG, PO. Methodology: VHG, PO, SL, AO. Investigation: PO, VPC, LO, CM, SL, MM, PRu, SS, PRo, FT, AO. Formal analysis: PO, AB. Project administration: VHG. Supervision: VHG, JCGP. Writing original draft: PO, VHG, JCGP, SL.

Data availability statement

The raw/processed data required to reproduce the above findings cannot be shared at this time for legal/ethical reasons.

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Supplementary data

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