Research Article
Cirrhosis and Liver Failure

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Porto-sinusoidal vascular liver disorder with portal hypertension: Natural history and long-term outcome

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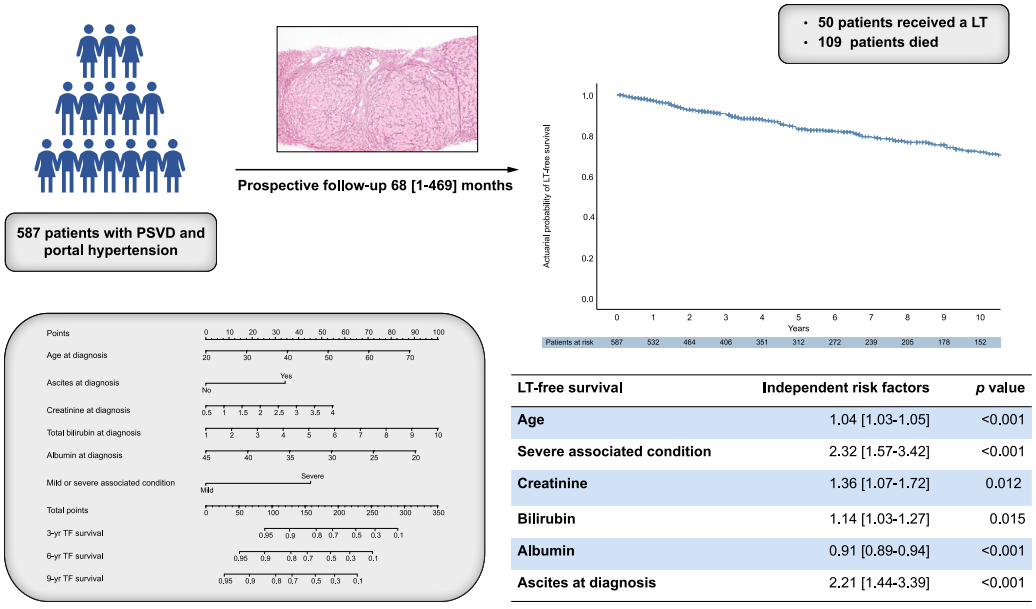
Graphical abstract



LT-free survival	Independent risk factors	*p* value
Age	1.04 [1.03-1.05]	<0.001
Severe associated condition	2.32 [1.57-3.42]	<0.001
Creatinine	1.36 [1.07-1.72]	0.012
Bilirubin	1.14 [1.03-1.27]	0.015
Albumin	0.91 [0.89-0.94]	<0.001
Ascites at diagnosis	2.21 [1.44-3.39]	<0.001

Highlights

- PSVD is a rare entity that causes portal hypertension.
- PSVD must be suspected in patients with portal hypertension and lower liver stiffness and HVPG values than expected in cirrhosis.
- Presence and severity of an associated condition, ascites, age, bilirubin, albumin and creatinine are associated with poor prognosis.

Impact and implications

Porto-sinusoidal vascular liver disorder (PSVD) is a rare entity that usually affects young people, frequently causes severe complications of portal hypertension, and may reduce life expectancy. To date, there is scarce information regarding its clinical manifestations, natural history and prognostic factors. The present study, including the largest number of patients with PSVD reported so far, shows that overall, when managed at centers of expertise, the prognosis of patients with PSVD is good, with LT-free survival rates of 83% and 72% at 5 and 10 years, respectively. Presence and severity of an underlying associated condition, presence of ascites, age and bilirubin, albumin and creatinine levels were associated with poor prognosis. These results are important to know for hepatologists. A final model combining these parameters enabled development of a nomogram that predicts prognosis with good discrimination and calibration capacity and can be easily applied in clinical practice.

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Porto-sinusoidal vascular liver disorder with portal hypertension: Natural history and long-term outcome

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Background & Aims: Current knowledge of the natural history of patients with porto-sinusoidal vascular disorder (PSVD) is derived from small studies. The aim of the present study was to determine the natural history of PSVD and prognostic factors in a large multicenter cohort of patients.

Methods: We performed a retrospective study on patients with PSVD and signs of portal hypertension (PH) prospectively registered in 27 centers.

Results: A total of 587 patients were included, median age of 47 years and 38% were women. Four-hundred and one patients had an associated condition, which was graded as severe in 157. Median follow-up was 68 months. At diagnosis, 64% of patients were asymptomatic while 36% had a PH-related complication: PH-related bleeding in 112 patients, ascites in 117, and hepatic encephalopathy in 11. In those not presenting with bleeding, the incidence of first bleeding was 15% at 5 years, with a 5-year rebleeding rate of 18%. The 5-year cumulative incidence of new or worsening ascites was 18% and of developing PVT was 16%. Fifty (8.5%) patients received a liver transplantation and 109 (19%) died, including 55 non-liver-related deaths. Transplant-free survival was 97% and 83% at 1 and 5 years, respectively. Variables independently associated with transplant-free survival were age, ascites, serum bilirubin, albumin and creatinine levels at diagnosis and severe associated conditions. This allowed for the creation of a nomogram that accurately predicted prognosis.

Conclusions: The prognosis of PSVD is strongly determined by the severity of the associated underlying conditions and parameters of liver and renal function.

Introduction

Porto-sinusoidal vascular liver disorder (PSVD), a term including the condition idiopathic intrahepatic portal hypertension (PH), is a rare vascular liver disorder. Its diagnosis relies on the combination of clinical and histological criteria requiring a good quality liver biopsy demonstrating distinctive histological features with exclusion of cirrhosis.[1,2] Certain laboratory signs,[3] imaging features[4] and liver stiffness measurement results[5] may hint towards the presence of PSVD, but diagnosis is based on histologic and clinical criteria. Patients with PSVD usually have preserved liver function but can develop severe complications of portal hypertension (PH),[6–8] portal vein thrombosis (PVT), and in some cases even require liver transplantation (LT).[9,10] However, data on natural history and identification of factors predicting prognosis are scarce and only based on small

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single-center studies with a relatively limited follow-up duration[11–13]

The aim of this study was to describe the natural history and long-term outcome of a large multicenter cohort of patients with PSVD with PH and to identify factors predicting outcome.

Patients and methods

Patients

All consecutive patients diagnosed with PSVD and signs of PH between January 1990 and January 2020 in 27 centers of the Spanish Hepatic Vascular Diseases Registry (REHEVASC) and/or the EASL endorsed Vascular Liver Disease Group (VALDIG) were considered eligible for inclusion in the study. All these centers have active prospective PSVD registers.

Diagnosis of PSVD was based on the following diagnostic criteria: 1) A good quality liver biopsy to rule out cirrhosis plus one specific sign of PH (gastric, esophageal, or ectopic varices; portal hypertensive bleeding; porto-systemic collaterals at imaging); 2) A good quality liver biopsy to rule out cirrhosis plus one histological lesion specific for PSVD (obliterative portal venopathy or nodular regenerative hyperplasia or incomplete septal fibrosis or cirrhosis [ISC]) and 3) A good quality liver biopsy to rule out cirrhosis plus one sign not specific for PH (ascites, platelet count below 150.000 per μl or spleen size >13 cm) plus one histological lesion not specific for PSVD (portal tract abnormalities; irregular distribution of the portal tracts and central veins, non-zonal sinusoidal dilation or mild perisinusoidal fibrosis)[14,15](16). Although the current PSVD criteria did not exclude PVT, patients with PVT were only included if there was clear data in clinical records showing that PH was present before PVT development or when specific histological signs of PSVD were seen at liver biopsy examination.[16] Liver biopsies were performed via the transjugular or percutaneous route[17] and were evaluated by pathologists with an interest in liver disease. In addition to H&E, liver biopsies were stained with reticulin in more than 90% of patients. Liver histology data were captured from the pathological reports of each participating hospital. The liver biopsy specimen was considered of adequate size if it was ≥20 mm in length together with minimal fragmentation or was otherwise considered adequate for interpretation by an expert pathologist.[14] The cut-off used to define splenomegaly was >13 cm in the largest axis. The worsening of ascites and further decompensation were defined according to the Baveno VII consensus criteria.[14] The presence of ascites (due to the high percentage of associated pathologies in this entity) was studied to rule out other causes, such as malignancy or renal causes.

All patients registered at REHEVASC (Spanish) or VALDIG (international) registries gave specific written informed consent to use their clinical data for research studies approved by the Ethical Committee (number registration: HCB/2019/0361). After reapproval by each institution, the corresponding data transfer agreements were signed by their respective legal departments.

Patients with PSVD without an underlying associated condition or with an underlying condition that, according to its natural history, is associated with a life expectancy similar to that of healthy individuals (*e.g.* autoimmune hypothyroidism or Graves disease) were classified as having no or a mild associated condition, as previously reported.[18] The remaining patients with persistent underlying conditions that are known to be potentially associated with reduced life expectancy, such as severe lupus with kidney involvement, were classified as having a persistent severe associated condition[18] (Table S1). A complete thrombophilia study was performed (antithrombin deficiency, protein C deficiency, protein S deficiency, mutation of factor II (F2, G20210A mutation), factor V-Leiden (F5, G1691A mutation), lupus anticoagulant, anti-β-2-glycoprotein-1 antibodies, anti-cardiolipin antibodies, paroxysmal hemoglobinuria, *JAK2* and calreticulin mutations. The thrombophilia study was performed after suspension of oral anticoagulants and outside the acute episode.

Mortality attributed to liver-related events (LREs) was recoded based on the International Statistical Classification of Diseases and Related Health Problems (ICD-10) causes.[19] If PVT was detected by ultrasound, an abdominal CT scan was performed to confirm and evaluate extension. High-risk varices were defined as large esophageal varices (EVs), small EVs with red signs, gastric varices, or ectopic varices. In a subgroup of patients, measurements of the hepatic venous pressure gradient (HVPG) and/or liver stiffness measurements (LSM) by transient elastography (TE) were available. LSM was performed by experienced hepatology nurses or hepatologists trained for TE (more than 100 exams), using FibroScan™ (Echosens, Paris, France). TE-LSM was considered reliable when meeting the manufacturer's recommendations, *i.e.* IQR/TE-LSM ≤0.30, and ≥10 valid measurements.[20]

Patients were followed up until January 2020, liver transplantation or death. All patients underwent routine blood analyses and abdominal ultrasound every 6-12 months during follow-up to evaluate the possible development of nodules or PVT, among other conditions. Clinical records of all patients were retrospectively reviewed, and the data were entered into specifically designed clinical record forms. One investigator per center reviewed all clinical record forms before their inclusion in the database.

Statistical analysis

Continuous variables were reported as median [IQR] or mean ± SD, as required. Categorical variables were shown as n (%) of patients. Comparisons of continuous variables were performed using Student's *t* test or Mann-Whitney *U* test, as applicable. The main endpoints of the study were evaluated using a time-dependent analysis.

Time zero for analyzing time-event curves was the date of the first sign or manifestation of PH.

We investigated the association of potential prognostic factors with the different endpoints using a predefined set of variables (specified for each analysis). We chose this strategy to minimize the chances of spurious findings due to the multiplicity of analyzed events. We used either Cox regression or a competing risk framework (Fine and Gray model) as described in,[21] depending on the specific endpoint.

For predicting transplant-free survival, we developed a risk prediction model with Cox regression. We considered nine parameters (eight variables, one of them with two categories) for inclusion in the model, which would meet the sample size criteria provided a pre-estimated R2 of the model of 0.2.[22] We performed a backward selection, with six variables (seven parameters) retained in the model, with subsequent bootstrap to assess for the stability of the variable selection process. Due to

the three different criteria used for PSVD diagnosis, we considered a model stratified by the variable "diagnostic criteria", which did not relevantly change the coefficients of the model. Therefore, for simplicity, the final presented model was the non-stratified one (further details are provided in Table S10). We applied uniform shrinking with bootstrapping. Performance was assessed with discrimination and calibration. Discrimination, which reflects how predictions separate high-risk from low-risk patients (patients with an earlier LRE time should exhibit a higher risk and those with no LRE/later LRE time a lower risk) was assessed with the bootstrap-corrected C-statistic, that was derived from the Somers' Dxy rank correlation (for a censored response variable) computed at each resample with formula C-statistic= Dxy/2+0.5. Calibration was tested graphically by plotting a smooth calibration curve of the observed event rates against the predicted risks at 5 years, and numerically with a) the integrated calibration index (mean absolute difference between smoothed observed proportions and predicted probabilities and b) the E50 and E90 (median and 90th percentile absolute difference between observed and predicted probabilities of the outcome).[23] Analysis was conducted in using the IBM SPSS Statistics 22 IBM SPSS and R, using the rms survival and tidy cmprsk packages.

Results

Study population

Six hundred and twenty-five patients were initially identified. Thirty-eight patients were excluded due to inadequate liver biopsy (n = 15), key missing data (n = 13), and age less than 14 years (n = 10). Thus, finally, 587 well-characterized patients with PSVD were included, fulfilling the following diagnostic criteria: 445 (75.8%) had no cirrhosis at liver biopsy together with the presence of at least one sign specific for PH, 62 (10.5%) had no cirrhosis at liver biopsy plus at least one histological lesion specific for PSVD, and finally 80 (13.7%) had no cirrhosis plus at least one sign not specific for PH and at least one histological lesion not specific for PSVD.

The median duration of follow-up from the first laboratory, clinical or radiological manifestation showing PH to the end of follow-up was 68 (range 1-469) months and from liver biopsy confirming PSVD was 41 (range 1-428) months. The median time between the first manifestation of PH and confirmatory liver biopsy was 6 (range 0-357) months. In 223 patients (38%), the confirmatory biopsy was delayed for more than 1 year and in 171 of them (29% of the whole cohort) for more than 2 years. Fig. S1 shows the delay between first PH manifestation (time "0") and the confirmatory diagnosis by liver biopsy according to the year of first manifestation. As shown, before the year 2000, the delay in diagnosis was clearly greater; awareness of the disorder markedly reduced the diagnostic delay, especially during the last 10 years. Of the 587 patients, 39 (6.6%) were lost to follow-up after a median follow-up of 64 (range 20-108) months.

Table 1 shows the main clinical and laboratory characteristics at diagnosis. Median age was 47 (IQR 33-59) years. Two-hundred and ten patients (35.8%) were symptomatic at diagnosis; the main clinical manifestations were variceal bleeding in 112 patients (53.3%), and ascites in 117 (55.7%). The remaining 377 patients (64.2%) had radiological, laboratory, and/or endoscopic signs associated with PH but not PH-related symptoms. As shown in Table S2, there were no major differences in the form of presentation according to the underlying associated condition. As expected, and probably due to the inclusion of family members of index cases, the number of familial cases that were asymptomatic at diagnosis was slightly higher.

Among the 13 patients with dyspnea, eight had hepato-pulmonary syndrome and three patients had porto-pulmonary hypertension; in the other two patients, the respiratory symptoms were due to the presence of severe ascites. Three additional patients had hepato-pulmonary syndrome diagnosed through dedicated screening, and 11 additional patients had porto-pulmonary hypertension identified at cardiopulmonary catheterization. The latter patients were asymptomatic.

The most common laboratory abnormality was thrombocytopenia, as 60% of the patients had platelet counts <150 ($x10^9$/L) (Table 1); 10 patients had a previous splenectomy. Median spleen size, available in 397 (67.6%) patients, was 16 cm (IQR 14-19). Aspartate aminotransferase and alanine aminotransferase were altered in 86 (14.6%) of the patients, and only 62 patients (10.6%) had values >2x the upper limit of normal (ULN). Gamma-glutamyl transferase (>1.5x ULN in 48% and >3x ULN in 30%) and alkaline phosphatase (>1.5x ULN in 17% and >3x ULN in 4%) were mildly elevated.

In 186 patients (31.7%), no associated condition was identified. By contrast, as shown in Table 1 and Table S1, in 401 patients, one or more associated conditions were found, immunological disorders being the most frequent. Thirty-six patients (6.1%) had coexistence of an immunological and hematological or prothrombotic disorder. In 157 patients (26.7%), the associated condition was severe/life-threatening. The thrombophilia study was performed in 537 (91.5%) patients, and a prothrombotic disorder was only detected in 46 (7.8%). Interestingly, the number of patients with HIV-associated PSVD decreased over time. Most patients with HIV had a diagnosis of PSVD before 2010 (67.5%) and only 16 (37.5%) after the year 2010, when inosine analogues for HIV treatment were mostly abandoned. The last patient who had been exposed to didanosine was diagnosed in 2016. In 14 (28.6%) patients with HIV-associated PSVD, no history of treatment with an inosine analogue was identified. Twenty patients had a history of previous solid organ transplantation (5 lung and 15 kidney) and 23 had familial aggregation (Table 1).

Liver histology

Table S3 summarizes the histological findings on liver biopsy. The length of the liver biopsies was available in 439 (75%) patients and was a median of 20 mm (IQR 18-26 mm); 151 (25.7%) patients had a liver biopsy >20 mm. The median number of portal tracts, described in 262 (45%) patients, was 8 (IQR 5-20). Cirrhosis was excluded by the liver histopathology expert. Three-hundred twenty-two patients (55%) had at least one specific histological lesion. Of those, nodular regenerative hyperplasia (NRH) was the most frequent, followed by obliterative portal venopathy (OPV). Incomplete septal fibrosis/cirrhosis was identified in 97 patients (in 56 of these patients either in association with NRH or OPV). ISC was diagnosed on liver explant in only 9 of the 41 patients with ICS as a sole specific histological lesion. There is a debate as to whether ICS can only be assessed at liver explant and for that reason, we

Table 1. Baseline charecteristics and associated disorders.

	n (%)/median; IQR
Men	367 (62.5%)
Age at first manifestation	47 (33; 59)
Asymptomatic at diagnosis	377 (64.2%)
Thrombocytopenia and splenomegaly	291 (77.2%)
Abnormal imaging other than splenomegaly*/elevated liver enzymes	86 (22.8%)
Symptomatic at diagnosis	210 (35.8%)
Only variceal bleeding	87 (41.4%)
Only ascites	92 (43.8%)
Variceal bleeding and ascites	25 (12%)
Hepatic encephalopathy	11 (4.7%) (**)
Dyspnea	13 (6.3%) (***)
Duration between first manifestation of portal hypertension and liver biopsy (months)	6 (0; 34)
Splenomegaly	478 (81.4%)
Spleen size in the largest axis (cm)	16 (14; 19)
Esophageal varices at diagnosis	
No/small/large/bleeding varices at diagnosis	142/107/226/112
Serum total bilirubin (mg/dl)	1 (0.6; 1.4)
Serum direct/indirect bilirubin (mg/dl)	0.3 (0.2; 0.6)/0.6 (0.3; 0.9)
Serum AST/ALT (U/L)	32 (22; 48)/31(20; 48)
Serum GGT/ALP (U/L) (normal range: <40 U/L/<116 U/L)	56 (32; 96)/156 (83; 258)
Serum albumin (mg/dl)	39 (35; 43)
Serum sodium (mEq/L)	140 (138; 142)
Serum creatinine (mg/dl)	0.8 (0.7; 1)
Hemoglobin (g/L)	12.5 (10.8; 14.1)
Platelet count (x10^9/L)†	101 (64; 146)
Leucocytes (x10^9/L)	4.4 (3.1; 5.9)
INR	1.1 (1; 1.2)
Child-Pugh score	5 (5; 6)
A/B/C/n.a.	434 (73.9%)/93 (15.8%)/8 (1.4%)/52 (8.9%)
MELD	8 (7; 11)
Associated disorders‡	
No associated condition identified	186 (31.7%)
Immunological disorder	190 (32.4%)
Common variable immunodeficiency syndrome	40 (6.8%)
Inflammatory bowel disease	33 (5.6%)
26/33 received azathioprine (78.8%)	
Celiac disease	14 (2.4%)
Hypothyroidism	8 (1.4%)
Systemic lupus erythematosus	8 (1.4%)
Vasculitis	7 (1.2%)
Sjögren	6 (1%)
Rheumatoid arthritis	6 (1%)
Psoriasis	5 (0.8%)
Graves disease	5 (0.8%)
Myasthenia gravis	4 (0.6%)
Sarcoidosis (****)	3 (0.5%)
Autoimmune nephropathy	2 (0.3%)
POEMS	2 (0.3%)
Others (Behçet, dermatomyositis, sacroiliitis, Stills disease…)	47 (8%)
Hematological disorders	**54 (9.2%)**
Myeloproliferative neoplasm	19 (3.2%)
Idiopathic thrombocytopenic purpura	9 (1.5%)
Aplastic anemia	7 (1.2%)
Hodgkin's lymphoma	5 (0.8%)
Marginal B cell lymphoma	4 (0.6%)
Multiple myeloma	4 (0.6%)
Others (monoclonal gammopathy of uncertain significance, Castleman, chronic lymphoid leukemia…)	6 (1%)
Prothrombotic disorders (evaluated in 537 patients)	**51 (8.7%)**, 5 ≥2 coexisting prothrombotic factors
Antithrombin deficiency	12 (2%)
Antiphospholipid syndrome	11 (1.8%)
Protein C deficiency	9 (1.5%)
Protein S deficiency	8 (1.4%)
Prothrombin gene mutation	4 (0.6%)
Factor V Leiden mutation	3 (0.5%)
Paroxysmal hemoglobinuria	1 (0.1%)
Others prothrombotic disorders (FVIII elevation, *MTHFR* mutation)	3 (0.5%)
Other associated disorders	147 (25%)
HIV infection	49 (8.3%)
(Didanosine/zidovudine/stavudine/lamivudine)	(31/3/2/5/8)
Other associated disorders	98 (15.2%)
Associated medications:	
Azathioprine (in addition to those with IBD)	21 (3.4%)
Oxaliplatin	42 (7.2%)
Familiar aggregation (*****)	23 (3.9%)
Recurrent abdominal infections	5 (0.8%)
Others (Cystic fibrosis, Turner syndrome...)	7 (1.2%)

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; IBD, inflammatory bowel disease; INR, international normalized ratio; POEMS, polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes; PVT, non-cirrhotic portal vein thrombosis; SLE, systemic lupus erythematosus.

*Morphological alterations of the liver, presence of portal-systemic collaterals.

**Four of the eleven patients presented in the context of variceal bleeding at diagnosis and in seven of them the HE coexisted as a symptom together with ascites.

***Seven of these patients that presented dyspnea at diagnosis, coexisted with ascites.

****They only had extrahepatic sarcoidosis.

*****Twenty-three patients (3.9%); father and son: n = 2; father and brother/s: n = 8; father and one sister: n = 1; mother and brother: n = 1; sister: n = 3; one or more brothers: n = 6; cousin: n = 1; nephew: n = 1).

†10 patients with splenectomy.

‡41 patients had coexistence of an immunological and hematological disorder.

wanted to further analyze the subgroup pf patients with PSVD and ICS. As shown in Table S4, the LSM and HVPG values as well as clinical characteristics of these patients were like those of the overall population of patients with PSVD included in the study, supporting the diagnosis of PSVD in those patients with ISC on liver histology.

One-hundred sixty-six (28%) had only non-specific lesions, while 99 (16.8%) patients did not have specific or unspecific signs of PSVD and were considered as "normal".

In addition, as a quality control measure, we requested scanned images of the liver biopsies for central reading by our experienced pathologist (AD) from centers providing less than 15 patients (a total of 106 of the 567 [18%] included patients). We received those from 67 of these patients (63%). In 59 of the 67 scanned biopsies (88%) cirrhosis was completely ruled out after review. In the remaining eight patients, review of the scanned images sent did not provide evidence of cirrhosis, but the number of portal tracts included was low. However, the clinical review of these eight patients showed either a LSM below 10 kPa and/or an HVPG below 10 mmHg despite these eight patients exhibiting clear specific signs of PH, supporting the diagnosis of PSVD. Altogether we think that the probability of a false diagnosis of PSVD in the current cohort is extremely low.

Splanchnic hemodynamics

Four hundred and twenty-eight patients (73%) had HVPG measurements. One hundred-eight patients (25.2%) had hepatic vein-to-vein communications, but it was possible to occlude the hepatic vein distally to the communication in 32 of them. Median HVPG in the 352 patients with adequate vein occlusion was 8 (IQR 5-11) mmHg, 127 patients (36.1%) and 34 patients (9.7%) had an HVPG >10 mmHg and >16 mmHg, respectively. Seventy-four of the 127 patients with an HVPG >10 mmHg, in whom it is especially relevant to rule out cirrhosis, had LSM measurements. LSM was <10 kPa (a value rarely, if ever, found in patients with cirrhosis[5]) in 44 of them (59.5%) and >20 kPa (a value more frequently found in cirrhosis) in only three patients (4%).[5] In addition, none of these 127 patients had positivity for HBsAg or for anti-HCV antibodies and only three of them had alcohol intake above levels that can potentially produce liver damage. Moreover, in 84/127 (66%), liver biopsy not only excluded cirrhosis, but also identified at least one specific histological finding of PSVD. All these data reasonably allow us to rule out cirrhosis despite HVPG >10 mmHg. In the 76 patients without adequate vein occlusion, the median HVPG was 5 (IQR 3-8.5) mmHg, only eight patients (10.5%) had an HVPG ≥10, and only one had an HVPG ≥16 mmHg.

Liver stiffness measurement

LSM was available in 393 (67%) patients, with a median value of 7.8 kPa (IQR 5.6-10.6). LSM was <10 kPa in 274 (70%) patients, between 10 and 20 kPa in 106 (27%), and >20 kPa in only 13 (3%). Controlled attenuation parameter was only available in 104 patients with a median value of 192 (IQR 148-232) dB/m. Only one patient had a controlled attenuation parameter >248 dB/m,[24] a value associated with the presence of steatosis.[20]

Gastroesophageal varices and variceal bleeding

In 112 patients (19.1%), variceal bleeding was the first clinical manifestation. Of the remaining 475 patients, at first screening esophagogastroduodenoscopy (EGD), 333 patients had gastro-esophageal varices (226 large and 107 small varices; 280 of these 333 patients were considered to have high-risk varices while no varices were observed in the remaining 142 [29.7%]) (Fig. S2).

Sixty-six patients of the 142 without varices (46.8%) had follow-up EGD, and 26 of them developed gastro-esophageal varices. Cumulative incidence of remaining free of new gastro-esophageal varices was 93%, 91% and 81.5% at 1, 2 and 5 years, respectively. The remaining 76 patients did not have further EGD, mostly because of short follow-up since the previous one (Fig. S2). There were no significant differences in clinical and laboratory characteristics in patients with or without follow-up endoscopies (data not shown).

In 62 of the 107 patients (57.9%) with small varices, a follow-up endoscopy was performed (Fig. S2), showing progression to high-risk varices in 38 patients and stability in 22.

Overall, in addition to the 112 patients with PH-related bleeding at diagnosis, 97 patients had a PH-related first bleeding during follow-up with cumulative incidences, considering LT and death as competing events, of 3%, 8%, and 15% at 1, 2, and 5 years, respectively (Fig. 1A). Only age and presence of high-risk varices was associated with a higher risk of first PH-related bleeding during follow-up (Table S5).

Of the 280 patients who had high-risk varices (230 large EVs, 20 gastro-esophageal varices type 1, 12 gastro-esophageal varices type 2, 12 isolated gastric varices type 1, one isolated gastric varices type 2 and 5 ectopic varices) 205 (73.2%) received primary prophylaxis with non-selective beta-blockers (NSBBs), 21 (7.5%) with endoscopic variceal ligation (EVL), and 15 (5.4%) with combined NSBBs plus EVL. Thirty-nine (13.9%) patients did not receive primary prophylaxis due to side effects, patient refusal, or unknown reasons.

A total of 209 patients had an acute PH-related bleeding (173 patients were treated with vasoactive drugs plus endoscopic treatment, 16 with vasoactive drugs alone, 13 with endoscopic treatment alone and in 7 this information was not available). The acute bleeding episode was initially controlled in 174 patients (83%), but 35 patients required salvage therapy. Overall, 6-week mortality after a PH-related bleeding was 5.5%. Seventy-three patients of the 209 (34.9%) rebled during follow-up. The cumulative probability of PH-related rebleeding, with LT and death as competing events, was 12%, 14%, and 18% at 1, 2, and 5 years respectively (Fig. 1B).

Development of other clinical decompensations

Ascites (radiological and/or clinically evident) was present at diagnosis in 124 (21.1%) patients (as the only PH complication in 92 patients, associated with PH-bleeding in 25 additional patients and with hepatic encephalopathy [HE] in 7). Patients with ascites at diagnosis were older, had more severe associated diseases, worse kidney function, and a higher HVPG and LSM (Table S6) than those without. Ascites appeared during follow-up in 148 additional patients. In 143 of the 272 (52.6%) patients with ascites at some point, ascites was totally controlled after the resolution of a trigger event (bleeding), while it was controlled with small doses of diuretics in 50 patients. However, in 30 patients, ascites persisted despite the use of diuretics, and in 49 ascites became recurrent/refractory (23 received a transjugular intrahepatic portosystemic shunt [TIPS], 14 a LT, and 12 had contraindications for LT and were managed with large volume paracentesis). The cumulative incidences of development (in patients without ascites at diagnosis) and of worsening of ascites (in those with previous ascites), considering LT and death as competing events, was 3%, 6%, 14% and 28%, and of 5.1%, 8.9%, 18% and 32% at 1, 2, 5 and 10 years, respectively (Fig. S3A,B).

HE was present at diagnosis in 11/587 (1.9%) patients and appeared during follow-up in 61 additional patients (in 26 after a TIPS). HE was graded (per West Haven criteria[25]) I, II, III, and IV in 8%, 31%, 33%, and 18% respectively. In 21 patients, HE was recurrent (9 after TIPS): 13 of them received a LT, while the remaining eight patients (4 after TIPS) were treated conservatively (4 died).

Development of portal vein thrombosis

One hundred and seventy-three patients (29.5%) presented with PVT at some point during the clinical course (in 35 patients PVT was present at PSVD diagnosis, and in 138 patients, PVT appeared during follow-up); no patient was receiving anticoagulation at diagnosis of PVT. When PVT was present at diagnosis, in 24 of 35 (69%) patients, it was associated with

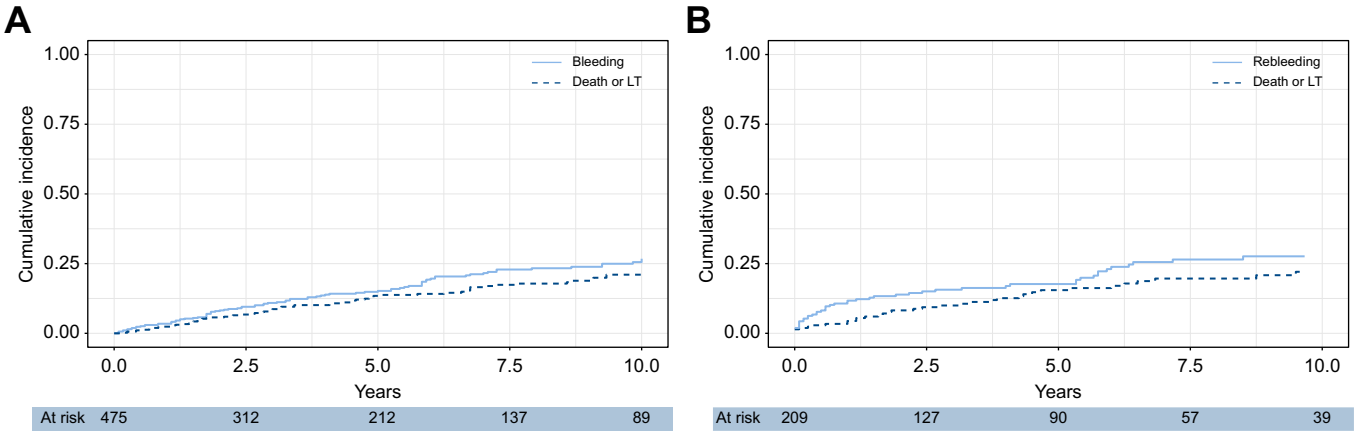

Fig. 1. Cumulative probability of having PH-related first bleeding or rebleeding, considering LT and death as competing events. (A) Cumulative probability of having PH-related first bleeding considering LT and death as a competing events. (B) Cumulative probability of having PH-related rebleeding considering LT and death as a competing event. LT, liver transplant; PH, portal hypertension.

symptoms (15 ascites and 9 variceal bleeding). By contrast, when thrombosis was detected during follow-up, only 36/138 (26%) patients were symptomatic (variceal bleeding in 21, ascites in 11, abdominal pain in 3, and fever in 1), whereas thrombosis was detected at routine imaging in the remaining 102 patients. Table S7 shows the extension of PVT. The cumulative incidence of developing PVT in the 552 patients without PVT at diagnosis, considering death and LT as competing events, was 5%, 7%, 16%, and 30% at 1, 2, 5, and 10 years, respectively (Fig. S4). As shown in Table S8A, HIV-associated PSVD, ascites at diagnosis, and presence of high-risk varices, but not the presence of a prothrombotic disorder, were associated with PVT risk. We conducted additional regression analysis to test the association between liver stiffness, HVPG, spleen size or histopathology parameters. To keep the integrity of our approach of *a priori* selection of variables, these were additional individual regression analyses in which we adjusted the effects of the given variable by high-risk varices, ascites, and HIV etiology. Among the new tested variables, only HVPG was (inversely) associated with the rate of PVT (Table S8B). Though this finding might be related to chance and must be taken with great caution, especially considering that only a subset of patients had HVPG measurements.

In 108 patients, anticoagulation was started once thrombosis was documented. PVT outcome in patients receiving or not anticoagulation is shown in Fig. S5. The recanalization rate was higher among anticoagulated *vs*. non-anticoagulated patients (56/108 [51.9%] *vs.* 6/65 [9.2%], respectively). No other clinical or analytical characteristics predicted the probability of recanalization[26] (data not shown).

Liver transplant-free survival

Fifty patients (8.5%) were transplanted, and 109 (18.6%) died. In 50 (45.9%) patients who died, death was directly or indirectly related to PSVD complications, while in 59, death was non-liver related. Table S9 summarizes the different causes of death. Actuarial probability of LT-free survival was 97%, 93%, 83%, and 72% at 1, 2, 5, and 10 years, respectively (Fig. 2). Table 2 shows variables associated with LT-free survival at univariable analysis. Age, severity of the underlying associated condition, ascites at diagnosis, serum creatinine, bilirubin, and albumin levels were independently associated with LT-free survival on multivariable Cox regression analyses. A final model including these variables is represented by the nomogram in Fig. 3. This model showed good discrimination and calibration (Table S10). Table S10 also shows the formula to calculate the model. Fig. S6 shows the calibration plots of the model. In the 352 patients who presented an HVPG measurement with an adequate hepatic vein occlusion, there was a strong association (p = 0.0002) between HVPG and the probability of transplant or death during follow-up (Fig. S7A). However, the addition of HVPG to the above-shown predictive model did not result in improved predictions as compared to the clinical model alone (C-statistic of the clinical model in this subset of patients 0.838 *vs.* 0.837 for the model adding HVPG) (Fig. S7B).

We explored the dichotomous variables ascites at diagnosis or the presence/severity of the associated condition. LT-free survival of the 124 patients with ascites at diagnosis was significantly lower than that of those without (91.1%, 79.4%, 60%, and 46.1% *vs.* 98.5%, 95.8%, 88.7%, and 78.1% at 1, 2, 5, and 10 years, respectively). Similarly, patients with a severe associated condition presented a significantly worse LT-free survival (91.1%, 69%, and 46.1% LT-free survival at 1, 5, and 10 years) than those with mild or no associated condition (98.9%, 88.7%, and 78.1%, respectively) (Fig. S8). Fig. S9A,B show cumulative LT-free survival in the most frequent PSVD-associated conditions.

Composite endpoint risk

The actuarial probability of remaining free of developing the composite endpoint: first decompensation or further decompensation, death or LT was 93.8%, 89.2%, 77.8%, and 61.9% at 1, 2, 5, and 10 years, respectively (Fig. 4). The same composite endpoint but considering only liver-related death is shown in Fig. S10.

The actuarial probability of remaining free of this composite endpoint and of PVT was 92.4%, 86.7%, 72.8%, and 54.9 % at 1, 2, 5, and 10 years, respectively (Fig. S11). The actuarial probability of remaining free of this composite endpoint, but

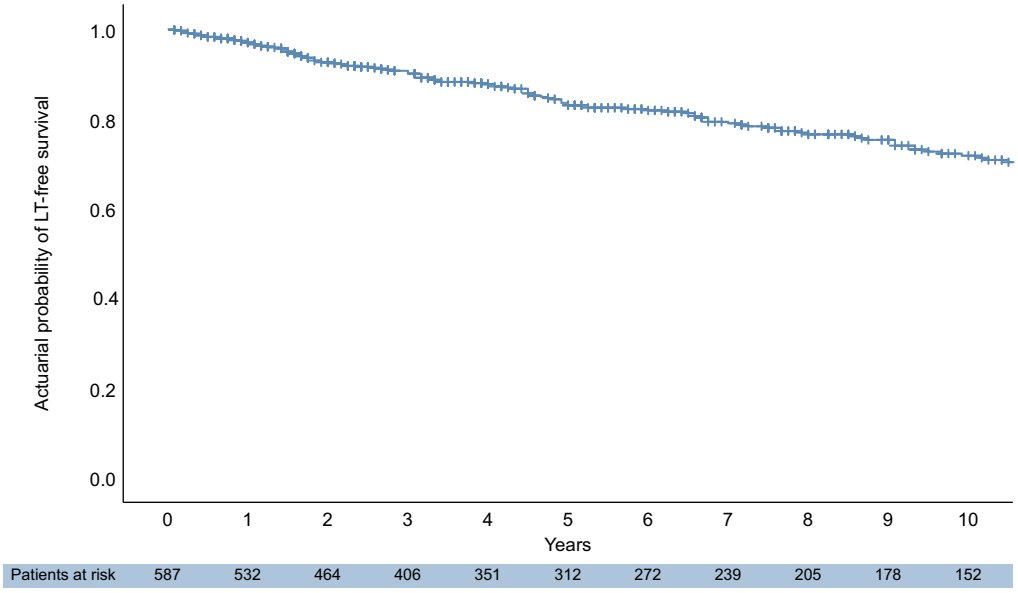

Fig. 2. Actuarial probability of LT-free survival. LT, liver transplant.

Table 2. Univariate and multivariate analysis for trasplant-free survival.

	Univariate		Multivariate	
All patients (N = 587)	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**
Age	1.04 (1.03-1.05)	**<0.001**	1.04 (1.03-1.05)	**<0.001**
Severe associated disease	2.55 (1.83-3.56)	**<0.001**	2.32 (1.57-3.42)	**<0.001**
MELD score	1.14 (1.10-1.18)	**<0.001**		
CHILD-Pugh score	1.51 (1.37-1.66)	**<0.001**		
Creatinine (mg/dl)	1.64 (1.3-2.06)	**<0.001**	1.36 (1.07-1.72)	**<0.001**
Bilirrubin (mg/dl)	1.16 (1.03-1.31)	**0.016**	1.14 (1.03-1.27)	**0.015**
AST (U/L)	1 (0.99-1.01)	0.8		
ALT (U/L)	1 (1-1)	0.9		
Albumin (g/L)	0.9 (0.87-0.92)	**<0.001**	0.91 (0.89-0.94)	**<0.001**
Platelets (x10^9/L)	1 (1-1)	0.5		
INR	1.02 (0.59-1.77)	0.9		
Ascites at diagnosis	3.31 (2.36-4.64)	**<0.001**	2.21 (1.44-3.39)	**<0.001**
Encephalopathy at diagnosis	2.77 (1.22-6.28)	**0.015**		
Variceal bleeding at diagnosis	1.11 (0.76-1.62)	0.6		
Portal vein thrombosis at diagnosis	0.94 (0.5-1.74)	0.8		
Nodular regenerative hyperplasia	1.404 (0.644-3.065)	0.383		
Obliterative venopathy	1.117 (0.501-2.761)	0.639		
Incomplete septal fibrosis	1.171 (0.521-2.603)	0.705		
HVPG (+)	1.06 (1.04-1.09)	**<0.01**		
Liver stiffness (++)	0.99 (0.96-1.02)	0.5		

(+) Only available in 352 patients. (++) Only available in 393 patients.
Values in bold denote statistical significance.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; HVPG, hepatic venous pressure gradient; INR, international normalized ratio.

only considering liver-related death and adding PVT, is depicted in Fig. S12.

Finally, the risk of being free of the first decompensation in patients asymptomatic at diagnosis is represented in Fig. S13A and the actuarial probability of further decompensation-free survival in asymptomatic patients at diagnosis is represented in Fig. S13B.

Hepatic nodules

Seventy-one (12%) patients had or developed liver nodules during follow-up. Twenty-nine patients had exclusively a single nodule (38%), 20 (27%) had two nodules, 8 (11%) had three nodules, and 14 (20%) patients had four or more nodules. The median size of the maximum diameter of the nodule was 11 mm (2;22). In 22 patients, nodules were biopsied: 16 lesions resulted in focal nodular hyperplasia, three in hepatocellular carcinoma (HCC: 3/587 [0.5%]), and the other three in liver metastases from a previously resected colorectal carcinoma. No cholangiocarcinoma was found.

The remaining nodules were considered benign since they did not grow or show significant radiological changes during imaging follow-up after a median of 58 (25–105) months.

Natural history and prognosis of PSVD

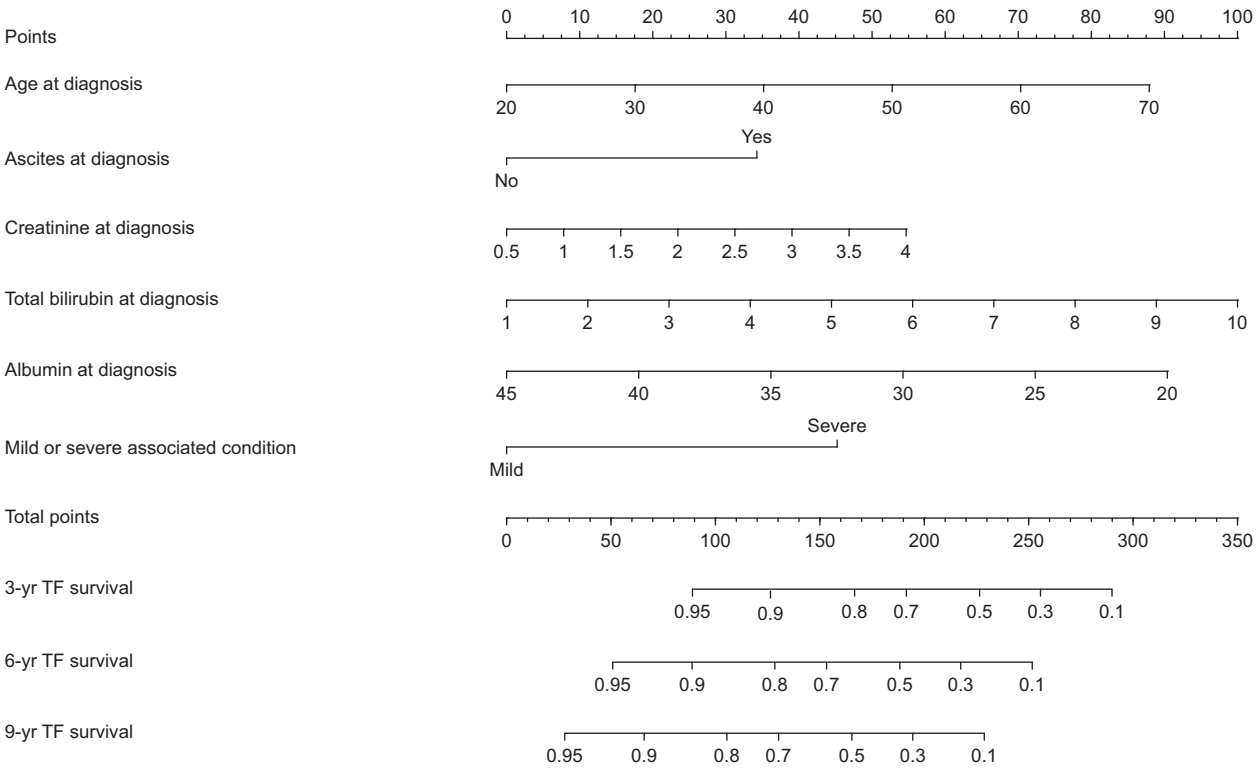

Fig. 3. Nomogram predicting prognosis of patients with PSVD. PSVD, porto-sinusoidal vascular disease.

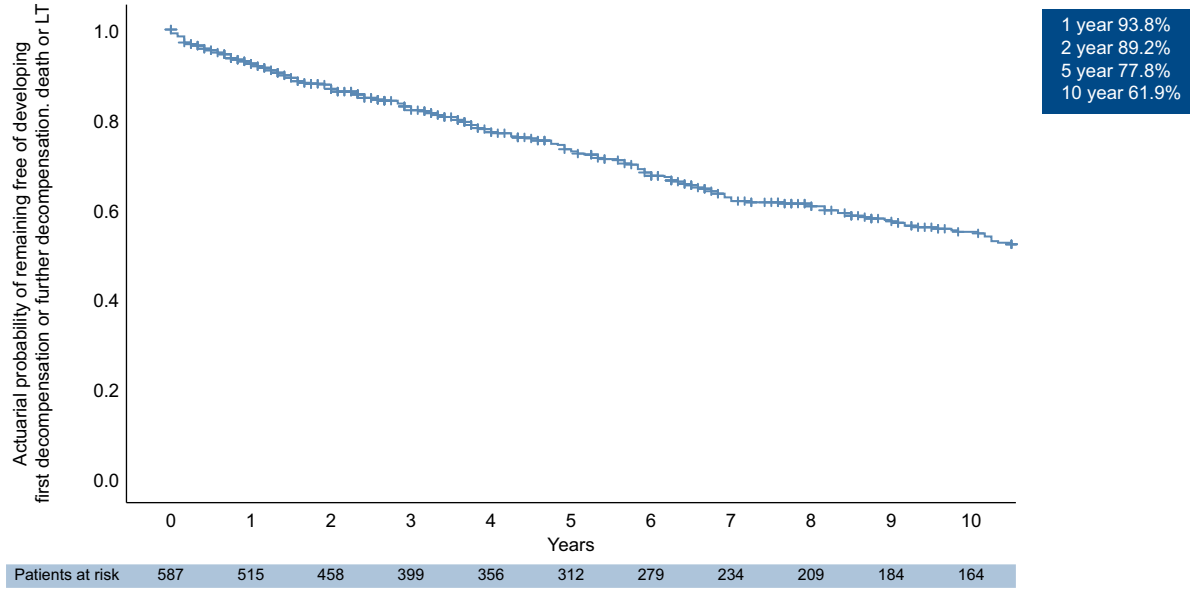

Fig. 4. Composite endpoint (first bleeding or ascites or HE in asymptomatic patients at diagnosis or rebleeding or worsen ascites in those who had already presented it, further decompensation, death, or liver transplant). HE, hepatic encephalopathy.

In all three HCC cases, liver non-HCC tissue confirmed the diagnosis of PSVD (two with obliterative venopathy and one with NRH). Two of these patients had pure-idiopathic PSVD, and one was a didanosine-associated PSVD. Table S11 describes the details of those patients. HCC was diagnosed a median of 52 months [13-52] after diagnosis.

Liver transplant indication

One hundred and twenty-four patients developed liver decompensations (complications of ascites and development of HE, being the most frequent), severe enough to be considered potential candidates for LT. However, only 50 (8.5%) patients were transplanted, and 10 (1.4%) additional patients are still on

the waiting list or in evaluation. The main reasons for not transplanting the remaining 64 (10.9%) patients were the severity of the associated condition and age older than 70 years. Of those 64 patients, 46 (72%) died, mostly due to liver disease 39/46 (85%).

Discussion

PSVD is a rare condition[27,28] and, as a consequence, knowledge about its natural history, prognosis, and predictive factors is scarce. Indeed, to date, only small single-center cohorts of patients with PSVD have been reported.[6,29–31] The current international multicenter study is the largest and most detailed long-term follow-up study of well-characterized patients with PSVD and PH[32] and thus, instrumental for defining its natural history.

Our study, as it happens in other rare diseases, confirms the frequent delay in PSVD diagnosis. Indeed, in 38% of patients, the diagnosis was delayed more than 1 year, and in 29%, more than 2 years. In many of these cases, patients were previously misdiagnosed with cirrhosis or did not have a diagnosis at all with the consequent fear and anxiety. Fortunately, the increased awareness of PSVD, based on an increase in its dissemination at scientific and educational levels, has markedly reduced diagnostic delay. A better understanding of the clinical manifestations of the disease may further increase PSVD awareness and early diagnosis. In that regard, our study found that in almost 65% of patients, the first manifestation of the disease was clinical or laboratory abnormalities suggestive of PH, but patients were completely asymptomatic. In those who were symptomatic, variceal bleeding and ascites were the most frequent PH complications, either isolated or in combination. Most patients were middle-aged and had only mild alterations or normal liver parameters. The combination of this clinical scenario, together with the presence of an associated condition (present in two-thirds of patients in our study) would increase clinical suspicion of PSVD, corroborated by LSM and HVPG values lower than expected in patients with cirrhosis and similar signs of PH. Patients with PSVD may also have pulmonary manifestations of PH such as hepatopulmonary syndrome or porto-pulmonary hypertension. However, although not specifically assessed in all patients, it seems that the prevalence of these pulmonary alterations was low but probably similar to that found in patients with cirrhosis and good liver function.[33]

A strong association between PSVD and the presence of inherited or acquired prothrombotic disorders has previously been suggested. However, in the present cohort of patients with PSVD, despite an extensive work-up for risk factors for thrombosis in more than 90% of patients, a prothrombotic abnormality was found in less than 10% of patients and, individually, the prevalence of these abnormalities was similar to or only slightly greater than that of the general population.[34–36] These data suggest that the theory of prothrombotic conditions inducing obstruction of sinusoids and portal venules only accounts for a minority of PSVD cases, if any.[37] In addition, this data does not support routine performance of a comprenhensive thrombophilic study in these patients.

NRH and obliterative OPV were the most frequent "specific" lesions, identified at liver biopsy (33.4% and 22% of cases, respectively). These two histological lesions frequently coexisted. Thus, 25% of patients with NRH also had OPV and 38% of those with OPV also had NRH. The most common "nonspecific" sign was sinusoidal dilatation, observed in almost half of patients (48.4%). The combination of typical and atypical signs most frequently seen was NRH with sinusoidal dilatation (16.5%). Obliterative venopathy appeared to be more prevalent in patients with more advanced disease (those with ascites), though the association was not statistically significant. It is important to note that our study merely identified the presence or absence of lesions on liver histology, without distinguishing between the severity or quantity of portal tracts affected. This limitation leaves open the possibility that discrepancies in severity or the number of affected portal tracts could contribute to a more pronounced degree of PH. Future research could explore this intriguing avenue further, offering valuable insights into the mechanisms underlying PH.

It is important to remark that 45% of the patients with PSVD in this cohort did not have any specific histological signs and almost 17% of the patients also did not have any unspecific histological sign of PSVD. However, these data must be interpreted with caution because, although biopsies were performed and reviewed in referral centers, no central reading of the liver biopsies was performed. These results demonstrated that the histological diagnosis of PSVD remains challenging and always requires high-clinical suspicion and expert pathologists.

The current study confirms previous observations in smaller cohorts of patients[6] that the risk of developing high-risk varices in patients with PSVD is similar to that in patients with cirrhosis,[38,39] supporting a similar screening approach. We could not identify factors able to predict the development of high-risk varices. In addition, the lack of granular data including the exact time of follow-up endoscopies, the different timing of endoscopies, and the lack of universal follow-up endoscopies among other factors precluded evaluating factors that predict progression of varices. Future prospective studies will shed more light on this issue.

The cumulative incidence of first PH-related bleeding in those patients without it at admission was relatively low (15% at 5 years), and only age and the presence of high-risk varices were predictors of it. Most patients with high-risk varices received treatment with NSBBs, and only a few of them received EVL or no treatment for primary prophylaxis. Thus, it is not possible to compare the efficacy of these different strategies. However, the 5-year probability of first PH-related bleeding of 19% is consistent with that previously reported and suggests that NSBBs are a good treatment option for these patients.[6]

Acute variceal bleeding was controlled in more than 80% of patients using a similar treatment strategy and achieving a similar bleeding control rate as in patients with cirrhosis. However, in our cohort, 6-week mortality was very low (3.4%), probably reflecting the good liver reserve that most patients with PSVD maintain and comparable to that observed in patients with Child-Pugh class A cirrhosis. Secondary prophylaxis, performed in most patients with NSBBs plus EVL, was very successful with a very low rebleeding rate (less than 20% at 5 years) that compares favorably with that observed in patients with cirrhosis.[40] These data suggest that the therapeutic strategies used in patients with cirrhosis may also be as effective in PSVD.

Our study confirms that patients with PSVD have a high risk of developing PVT, which is even higher in those patients with HIV-associated PSVD,[6] while the contribution of a proven thrombophilia was just marginal in this large cohort. In addition, our study demonstrated that ascites at diagnosis and the presence of high-risk varices were also independent risk factors for PVT development. Variceal bleeding at diagnosis, shown to predict PVT in a previous study with 69 patients,[12] was replaced by high-risk varices in the current study. Altogether, this suggests that the severity of PH is a major driver of PVT development. Interestingly, the recanalization rate obtained with anticoagulation (51.9%) was similar to that observed in patients with cirrhosis and PVT,[41,42] and no factors predicted this possibility. This suggests that a procoagulant imbalance may represent a pathogenic mechanism and a therapeutic target.

The severity of the underlying associated condition and parameters of liver and renal function (ascites as first manifestation, bilirubin, albumin, and creatinine levels) and age were all shown to be independent predictors of prognosis. Determining whether a given patient has a severe associated condition must be based on clinical criteria and knowledge on the natural history of the specific associated disease.

The presence and severity of the associated condition has a strong predictive value for survival, either as a direct cause of non-liver-related death (the cause of death was non-liver-related in >50% of patients who died), or by precluding transplantation in the case of progressive liver failure. Indeed, in the current cohort, there were 64 patients with a clinical indication where LT was contraindicated because of severe associated conditions, and most of these patients died from a liver-related cause. It is worth mentioning the poor outcome of common variable immunodeficiency-associated PSVD, which was associated with a 25% mortality rate, with 90% of deaths being liver-related. These patients probably have a more aggressive clinical course[43] and thus warrant specific consideration (46,47). On the contrary, survival of patients with HIV-associated PSVD seems to be better than that observed in other PSVD groups, a fact that suggests that stopping didanosine and/or stavudine, drugs that have been pathophysiologically involved in PSVD development in these patients, has a favorable impact on PSVD course. Unfortunately, despite being the largest cohort of patients with PSVD, the absolute number of other specific associated entities was too small to draw definitive conclusions about their specific impact on mortality.

Ascites at diagnosis, as previously described,[30] was associated with poor LT-free survival. Although multivariable analysis showed that ascites was an independent factor, it is worth noting that patients with ascites at diagnosis, in comparison to those who were asymptomatic at the time of diagnosis or experienced variceal bleeding, also had a higher frequency of other factors independently associated with LT-free survival such as older age, poorer liver function, severe associated conditions, and higher HVPG. Thus, ascites in patients with PSVD might reflect a more advanced disease involving the hepatic sinusoidal area that can lead to severe PH complications, liver deterioration, and death. Bilirubin, albumin, and creatinine parameters – frequently found to have prognostic value in patients with cirrhosis – although usually mildly altered, also have prognostic value in patients with PSVD. Using all of these parameters that were independently associated with prognosis, we developed a nomogram that predicts LT-free survival, showing good discrimination and calibration, and that is easy to apply in routine clinical practice.

Differences in these clinical characteristics may explain the different LT-free survival reported in other PSVD cohorts. Indeed, in the current multinational cohort, the actuarial probability of LT-free survival at 10 years was 72%, much higher than the 40% reported in a Dutch cohort of 63 patients[30] but similar to the 82% in a Spanish cohort of 69 patients.[6] Notably, in the Dutch study,[30] a high number of patients with severe associated conditions were included, and most patients died from non-liver-related causes.

The fact that the prognosis of patients with PSVD, especially in those without a severe associated disorder, is much better than that of patients with cirrhosis and similar manifestations of PH at presentation, reinforces the importance of an accurate and timely diagnosis. In addition, whilst HCC is a frequent complication in patients with cirrhosis and one of the main reasons for LT in these patients, in the current cohort, only three patients developed HCC after a median follow-up of 52 months, clearly showing that this is very uncommon. Although cholangiocarcinoma has been described in patients with PSVD (48), it was not described in the current cohort. However, it important to mention that 12% of patients had one or more benign “nodular hyperplasia-like regenerative nodules” at imaging studies that can be misdiagnosed as HCC. This is especially relevant because, due to the high-risk of PVT development, these patients are recommended to be submitted to imaging surveillance.[14]

Our study also shows that despite HVPG underestimating true portal pressure, HVPG was associated with prognosis. However, HVPG does not add predictive capacity to the clinical-biochemical prognostic model. This could be because HVPG was only available in 60% of patients and is probably strongly correlated with albumin and creatinine parameters that were present in the model.

The retrospective nature of our study is its main limitation. However, the large size of the cohort and the fact that data were extracted from a prospective registry from international reference centers allows us to draw robust conclusions in patients with PSVD. It must be considered that the data of the current study can be extrapolated only to the adult population, since patients aged under 14 years were excluded, and to patients with PH because this was the selection criteria for inclusion.

In summary, a high proportion of patients with PSVD have associated conditions. Clinicians should be aware of this association, as it should raise suspicion of PSVD. The current study shows that prognosis of PSVD is strongly determined by the age, severity of associated underlying conditions, ascites, age, bilirubin and creatinine levels, and albumin levels. These parameters should be closely monitored to determine the prognosis of these patients.

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Abbreviations

EGD, esophagogastroduodenoscopy; EVs, esophageal varices; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; HR, hazard ratio; HVPG, hepatic venous pressure gradient; ISC, incomplete septal cirrhosis; LREs, liver-related events; LSM, liver stiffness measurement; LT, liver transplantation; NRH, nodular regenerative hyperplasia; OPV, obliterative portal venopathy; PH, portal hypertension; PSVD, porto-sinusoidal vascular disease; PVT, non-cirrhotic portal vein thrombosis; TIPS, transjugular intrahepatic portosystemic shunt; ULN, upper limit of normal.

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Conflict of interest

JCGP advisory for GORE, Cook and grant from Mallinckrodt and AstraZeneca. The remaining authors declare no conflicts of interest that pertain to this work.

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

Authors' contributions

Marta Magaz, Heloïse Giudicelli-Lett, Juan Abraldes, Oana Nicoară-Farcău, Pierre-Emmanuel Rautou and Juan Carlos García-Pagán designed the research, analyzed data and wrote the paper. Marta Magaz, Heloïse Giudicelli-Lett, Oana Nicoară-Farcău, Lara Orts, Ashish Goel, Nicolas Drilhon, Sophie Hillaire, Laura Turco, Luis Téllez, Stefania Gioia, Hélène Larrue, Lena Smets, Karlien Raymenants, Giulia Tosetti, Niccolò Bitto, Chiara Becchetti, Edilmar Alvarado, Cristina Roig, Raquel Diaz, Michael Praktiknjo, Anna-Lena Konicek; Xavier Verhelst, Helena Degroote, Pol Olivas, Elba LLop, Filipe Nery, Anna Baiges, José Ignacio Fortea, Helena Masnou, Alba Ardèvol, Ángela Puente, Virginia Hernández-Gea, Fanny Turon, Victoria Aguilera, Carmen A Navascués, Marta Romero-Gutiérrez, Laure Elkrief, Bernhard Scheiner, Georg Semmler, Mattias Mandorfer, Akash Shukla, Filipe Damião, Macarena Simón-Talero, Carlos González-Alayón, Ángeles García-Criado, Andrea de Gottardi, Alba Díaz, Asuncion Ojeda, Joan Genescà, Carlos Noronha Ferreira, Thomas Reiberger, Manuel Rodríguez, Rosa María Morillas, José Luis Calleja, Javier Crespo, Jonel Trebicka, Rafael Bañares, Xavier Verhelst, Bogdan Procopet, Càndid Villanueva, Annalisa Berzigotti, Massimo Primignani, Vincenzo La Mura, Frederik Nevens, Agustín Albillos, Filipe Schepis and Dhiraj Tripathi collected, reviewed the data and the manuscript.

Data availability statement

Data supporting this study will be available at Barcelonaś University deposit and the Access to the data is subject to reasonable request.

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Supplementary data

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Author names in bold designate shared co-first authorship

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