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Porto-sinusoidal vascular liver disorder with portal hypertension: Natural History and Long-Term Outcome.

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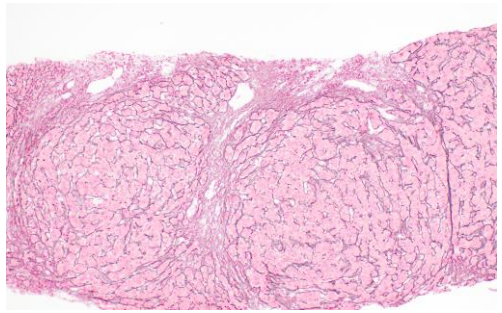
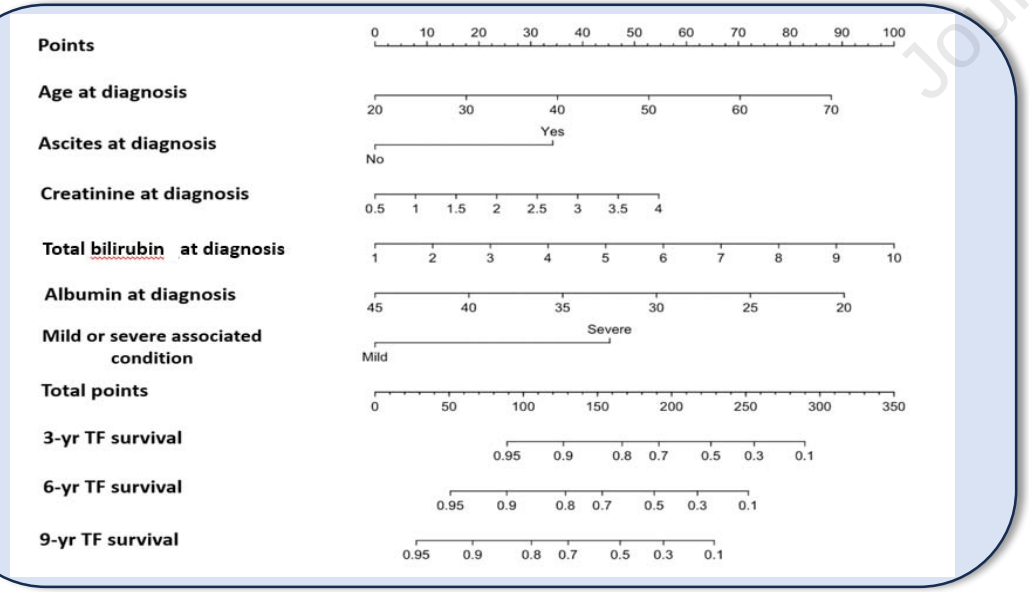


Prospective follow-up 68 [1-469] months

- **50 patients received a LT**
- **109 patients died.**

587 patients with PSVD and portal hypertension



LT-free survival	Independent risk factors	p
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**

Porto-sinusoidal vascular liver disorder with portal hypertension: Natural History and Long-Term Outcome.

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

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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

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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 however there is scarce information available regarding its clinical manifestations, natural history and prognostic factors.
- The present study, including the largest number of PSVD patients reported so far, shows that overall, when managed at centers of expertise, prognosis of PSVD patients is good with a LT-free survival 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 allows to develop a nomogram that predicts prognosis with good discrimination and calibration capacity and can be easily applied in the clinical practice.

ABSTRACT

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 natural history and prognostic factors using a large multicenter cohort of PSVD patients.

Methods: Retrospective multicentric study of PSVD patients and signs of portal hypertension (PH) prospectively registered in 27 centers.

Results: 587 patients were included, median age of 47 years and 38% were women. Four-hundred and one patient had an associated condition, that 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 of 15% at 5 years, with a 5-year rebleeding rate of 18%. Five-year cumulative incidence of new or worsening ascites was of 18% and of developing PVT of 16%. Fifty (8.5%) patients received a liver transplantation and 109 (19%) died, including 55 non-liver related death. Transplant-free survival was 97%, and 83% at 1 and 5 years. Variables independently associated with transplant-free survival were age, ascites, serum bilirubin, albumin and creatinine levels at diagnosis and severe associated conditions. This allowed the creation of a Nomogram that accurately predicted prognosis.

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

Abbreviations

PSVD, Porto-sinusoidal vascular liver disorder
IPH, Idiopathic portal hypertension
PH, Portal hypertension
HE, Hepatic encephalopathy
PVT, non-cirrhotic portal vein thrombosis
LT, Liver transplantation
REHEVASC, Spanish Hepatic Vascular Disease Registry
VALDIG, Vascular Liver Disease Group
DTAs, Data Transfer Agreements

LRE, Mortality attributed to liver-related events.

IQR, Interquartile range

ICI, Integrated calibration index

US, Abdominal ultrasonography

CT, Abdominal computed tomography

CRFs, Clinical record forms

HVPG, Hepatic venous pressure gradient

LSM, liver stiffness measurement

SD, Standard deviation

CI, Confidence interval

HR, Hazard ratio

VB, Variceal bleeding

HPS, Hepato-pulmonary syndrome

POPH, Porto-pulmonary hypertension

AST, Aspartate transaminase

ALT, Alanine transaminase

GGT, Gamma-glutamyl transferase

ALP, Alkaline phosphatase

ULN, Upper limit of normal

HIV, Human immunodeficiency virus

EV, Esophageal varices

MELD, Model for End-Stage Liver Disease

MPN, Myeloproliferative neoplasm

IBD, Inflammatory bowel disease

OPV, Obliterative portal venopathy

NRH, Nodular regenerative hyperplasia

ISF, Incomplete septal fibrosis

CO, Cardiac output

CI, Cardiac index

RAP, Right atrial pressure

PAP, Pulmonary arterial pressure

PCP, Pulmonary capillary pressure

SVR, Systemic vascular resistance

PVR, Pulmonary vascular resistance

LSM, Liver stiffness

CAP, Controlled attenuation parameter.

kPa, Kilopascals

EGD, Esophagogastroduodenoscopy

TIPS, Transjugular intrahepatic portosystemic shunt

SPSS, Surgical portosystemic shunt

BRTO, Balloon-occluded retrograde transvenous obliteration

SBP, Spontaneous bacterial peritonitis

HRS, Hepatorenal syndrome

NLH, Nodular-like hyperplasia

HCC, Hepatocellular carcinoma

TACE, Trans-arterial chemoembolization

INTRODUCTION

Porto-sinusoidal vascular liver disorder (PSVD), a term including the condition idiopathic intrahepatic portal hypertension (IPH), 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 a preserved liver function but can develop severe complications of portal hypertension (PH) (6–8), portal vein thrombosis (PVT), and some patients 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 single-centre 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 multicentre 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 centres 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 centres have active prospective PSVD registers.

Diagnosis of PSVD was based on the following diagnostic criteria: 1) A good quality liver biopsy discarding cirrhosis plus one specific sign of portal hypertension (Gastric, esophageal, or ectopic varices; Portal hypertensive bleeding; Porto-systemic collaterals at imaging); 2) A good quality liver biopsy discarding cirrhosis plus one histological lesion specific for PSVD (Obliterative portal venopathy or nodular regenerative hyperplasia or Incomplete septal fibrosis or cirrhosis) and 3) A good quality liver biopsy discarding cirrhosis plus one sign not specific for portal hypertension (ascites, platelet count below 150.000 per uL 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 by transjugular or percutaneous route (17) and were evaluated by pathologists with an interest in liver disease. In addition to hematoxylin and eosin, in more than 90% of patients', liver biopsies were stained with reticulin. Liver histology data were captured from the pathological reports of each participating hospital. The liver biopsy specimen was considered of adequate size if it had $\geq$ 20 mm 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´s consensus (14).The presence of ascites (due to the high percentage of associated pathologies in this entity); was studied ruling out other causes 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) and after reapproved by each institution, and the corresponding Data Transfer Agreements (DTAs) were carried out and signed by the legal departments.

PSVD patients without an underlying associated condition or with an underlying condition that, according to its natural history, had a life expectancy similar to that of healthy individuals (*e.g.* autoimmune hypothyroidism or Grave´s disease) were classified as having no or a mild associated condition, as previously reported (18). The remaining PSVD 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) **(Supplementary Table 1)**. 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 haemoglobinuria, *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 (LRE) was recoded based on the International Statistical Classification of Diseases and Related Health Problems (ICD-10) causes (19). If PVT was detected by ultrasound (US), an abdominal computed tomography (CT) scan was performed to confirm and evaluate extension. High-risk varices were defined as large esophageal varices (EV), small EV 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 were available. LSM was performed by experienced hepatology nurses or hepatologists trained for transient elastography (more than 100 exams), using FibroScan™ (Echosens, Paris, France). TE-LSM was considered reliable when meeting the manufacturer's recommendations, i.e. interquartile range (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 US every 6-12 months during follow-up that, among other, evaluated the possible development of nodules or PVT. Clinical records of all patients were retrospectively reviewed, and the data were entered into a specifically designed clinical record forms (CRFs). One investigator per centre reviewed all CRFs before its inclusion in the database.

Statistical Analysis.

Continuous variables were reported as median, interquartile range [IQR], or mean ± standard deviation as required. Categorical variables were shown as numbers (n) and proportions (%) 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 portal hypertension.

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 9 parameters (8 variables, one of them with 2 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 6 variables (7 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 supplementary table 10). We applied uniform shrinking with bootstrapping. Performance was assessed with discrimination and calibration. Discrimination, which reflects how predictions separate high 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 the 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 (ICI) (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. In 445 (75.8%) patients the liver biopsy discarded cirrhosis together with the presence of at least one sign specific for portal hypertension, in 62 (10.5%) had no cirrhosis at liver biopsy plus at least one histological lesion specific for PSVD and finally 80 (13.7%) patients had no cirrhosis plus at least one sign not specific for portal hypertension 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 one year and in 171 of them (29% of the whole cohort) for more than 2 years. **Supplementary Figure 1** 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 diagnostic delay especially during the last 10 years.

Thirty-nine of the 587 patients (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 at the **Supplementary Table 2**, 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 familiars of index cases, the number of familiar cases that were asymptomatic at diagnosis were slightly higher.

Among the 13 patients with dyspnoea, 8 had hepato-pulmonary syndrome (HPS) and 3 patients had porto-pulmonary hypertension (PoPH); in the other two patients, the respiratory symptoms were due to the presence of severe ascites. Three additional patients had HPS diagnosed through dedicated screening, and 11 additional patients had POPH 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 transaminase (AST) and alanine transaminase (ALT) were altered in 86 (14.6%) of the patients, and only 62 patients (10.6%) had AST or ALT values above 2 upper limits of normal (ULN). Gamma-glutamyl transferase (GGT) and alkaline phosphatase (ALP) were mildly elevated. Forty-eight percent of patients had a GGT>1.5 ULN and 30% >3 ULN. ALP was>1.5 ULN in 17% of patients and >3 ULN in only 4%.

In 186 patients (31.7%), no associated condition was identified. By contrast, as shown in **Table 1 and supplementary Table 1,** 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 haematological 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 Human immunodeficiency virus (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 inosine analogue was

identified. Twenty patients had a history of previous solid organ transplantation (5 lung and 15 kidney) and 23 had familiar aggregation (**Table 1**).

Liver Histology

Supplementary Table 3 summarizes the histological findings of liver biopsy. The length of the liver biopsies was available in 439 (75%) patients and had a median of 20 mm (IQR:18-26), 151 (25.7%) had a liver biopsy > 20 mm. The median number of portal tracts, described in 262 (45%) patients, was 8 (IQR:5-20). Liver cirrhosis was excluded by the histopathology expert in liver. Three-hundred twenty-two patients (55%) had at least one specific histological lesion. Of those, 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). In only 9 of the 41 patients with ICS as a sole specific histological lesion, ISC was diagnosticated at liver explant. There is a debate whether ICS can only be assessed at liver explant and for that reason, we wanted to further analyze the subgroup pf PSVD patients with ICS. As shown in **supplementary table 4**, LSM and HVPG values as well as clinical characteristics of these patients were like that of the overall population of PSVD patients included in the study. Therefore, supporting the diagnosis of PSVD in those patients showing ISC at liver histology.

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

In addition, as a quality control of the study, we requested, to those centres including less than 15 patients (a total of 106 of the 567 (18%) of the included patients), scanned images of the liver biopsies for central reading by our experienced pathologist (AD). We received those from 67 of these patients (63%). In 59 of the 67 scanned biopsies (88%) cirrhosis was completely discarded after review. In the remaining 8 patients, review of the scanned images sent did not observed cirrhosis, but the number of portal tracts included were small. However, the clinical review of these 8 patients showed either a LSM below 10 Kpa and/or an HVPG below 10mmHg despite these 8 patients exhibited clear specific signs of portal hypertension supporting the diagnosis of PSVD. Altogether we think that the probability that there were false diagnosis of PSVD in the current cohort is, if any, 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 > 10mmHg, in whom it is especially relevant to discard cirrhosis, had LSM measurements. In 44 of them (59.5%) LSM vas < 10 kPa (a value rarely, if ever, found in patients with cirrhosis (5) and only in 3 patients (4%) LSM was > 20 Kpa (a value more frequently found in cirrhosis) (5). In addition, none of these 127 patients had positivity for HBsAg or for anti-HCV antibodies and only 3 of them had alcohol intake above levels that can potentially produce liver damage. Moreover, in 84/127 (66%) liver biopsy, in addition to exclude cirrhosis, identified at least one specific histological finding of PSVD. All these data reasonably allow us to rule out cirrhosis despite having an HVPG > 10 mmHg. In the 76 patients without adequate vein occlusion, the median HVPG was 5 (IQR:3-8.5) mmHg, only 8 patients (10.5%) had an HVPG $\geq$ 10, and only 1 had an HVPG $\geq$ 16 mmHg.

Liver Stiffness Measurement (LSM)

LSM was available in 393 (67%) patients, with a median value of 7.8 kPa (IQR:5.6-10.6). In 274 (70%) patients, LSM was <10 kPa, in 106 (27%) between 10 and 20 kPa, and only in 13 (3%) >20 kPa. Controlled attenuation parameter (CAP) was only available in 104 patients with a median value of 192 (IQR:148-232) dB/m. Only one patient had a CAP>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 (GEV: 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%) (**Supplementary Figure 2).**

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 (**Supplementary Figure 2).** 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 **(Supplementary Figure 2),** showing progression to HRV in 38 patients and stability in 22.

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

Two-hundred and eighty patients that had high-risk varices (230 Large EVs, 20 GOV1, 12 GOV2, 12 IGV1, 1 IGV2 and 5 ectopic varices; 205 (73.2%) received primary prophylaxis with nonselective 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, patients' 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 (**Figure 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 HE in 7). Patients with ascites at diagnosis were older, had more severe associated diseases, worse kidney function, and a higher HVPG and LSM (**Supplementary Table 6)** than those without. Ascites appeared during follow-up in 148 additional patients. In 143 of the 272 (52.6%) patients having ascites at some point, ascites was totally controlled after the resolution of a trigger event (bleeding), and in 50 patients' ascites was controlled with small doses of diuretics. However, in 30 patients, ascites persisted despite the use of diuretics, and in 49 became recurrent/refractory (23 received a TIPS, 14 a LT, and 12 had contraindications for LT and were managed with large volume paracentesis). The cumulative incidence 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 (**Supplementary figures 3A and 3B)**.

Hepatic encephalopathy (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). Hepatic encephalopathy was graded (per West Haven criteria (27)) 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 8 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 symptoms (15 ascites and 9 variceal bleeding). By contrast, when thrombosis was detected during follow-up, only 36/138 (26%) patients were symptomatic (VB 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. **Supplementary table 7** 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 (**Supplementary figure 4)**. As shown in **supplementary table 8a**, HIV associated condition, 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 priory selection of variables, these were additional individual regression analysis 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 (**Supplementary table 8b**). 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 **Supplementary Figure 5.** The recanalization rate was higher among anticoagulated 56/108 (51.9%) than non-anticoagulated patients 6/65 (9.2%). No other clinical or analytical characteristics predicted the probability of recanalization (28) (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. **Supplementary Table 9** 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 (**Figure 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 **Figure 3**. This model showed good discrimination and calibration **(Supplementary Table 10**). **Supplementary Table 10** also shows the formula to calculate the model. **Supplementary Figure 6** 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 in the follow-up (**supplementary Figure 7A**)**.** 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), **supplementary figure 7B.**

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%) (**Supplementary figure 8**). **Supplementary figures 9A and 9B** show cumulative LT-free survival in the most frequent PSVD-associated conditions. As shown, 10-year survival in PSVD-HIV patients was of 95.1% much better than the 53.2% 10-year survival observed in PSVD-associated oxaliplatin. In addition, 10-year survival of PSVD-HIV patients was better than that observed in other group of PSVD-patients (associated with common variable immunodeficiency or autoimmune associated-PSVD; Even when comparing survival of PSVD-HIV patients with that of PSVD patients in whom no associated condition was observed, 10-year survival was higher (95.1% vs 87.2%, although the difference did not reach statistical significance; log Rank P=0.078).

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 (**Figure 4**). The same composite endpoint but considering only liver-related death is shown in **Supplementary Figure 10.**

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 (**Supplementary figure 11**). The actuarial probability of remaining free of this composite endpoint, but only considering liver-related death and adding PVT, is depicted in **Supplementary Figure 12.**

Finally, the risk of being free of the first decompensation in patients asymptomatic at diagnosis is represented in **supplementary figure 13A** and the aactuarial probability of further decompensation-free survival in asymptomatic patients at diagnosis is represented in **supplementary figure 13B.**

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%) 2 nodules, 8 (11%) 3 nodules, and 14 (20%) patients 4 or more. 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.

In all 3 HCC cases, liver non-HCC tissue confirmed the diagnosis of PSVD (two with obliterative venopathy and one with nodular regenerative hyperplasia). Two of these patients had pure-idiopathic PSVD, and one was a didanosine-associated PSVD. The **supplementary table 11** 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 frequents), 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 (29,30) and, as a consequence, knowledge about its natural history, prognosis, and predictive factors is scarce. Indeed, to date, only small single-centre cohorts of patients with PSVD have been reported (6,31–33). The current international multicentre study is the largest and most detailed long-term follow-up study of well-characterized patients with PSVD and PH (34) 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 one year, and in 29%, more than two 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 of patients. 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, VB 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 as described in PSVD patients (in our study present in two-thirds of patients) would increase clinical suspicion of PSVD, corroborated by LSM and HVPG values lower than expected in patients with cirrhosis and similar signs of PH. PSVD patients 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 (35).

It has been previously suggested a strong association between PSVD and presence of inherited or acquired prothrombotic disorders. However, in the present cohort of PSVD patients, despite an extensive work-up for risk factors for thrombosis in more than 90% of the 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 (36–38). 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 (39). In addition, this data does not support to routinely perform a comprenhensive thrombophilic study in these patients.

NRH and obliterative OPV were the most frequent “specific” lesions, identified at liver biopsy in 33.4% and 22% of cases, respectively. These two histological lesions frequently co-existed. Thus, 25% of patients having NRH also had OPV and 38% of those with OPV also had NRH. The most common “non-specific” sign was sinusoidal dilatation, observed in almost half of the patients (48.4%). The combination of typical and atypical signs most frequently seen was nodular regenerative hyperplasia with sinusoidal dilatation (16.5%). Obliterative venopathy appeared to be more prevalent in patients with more advanced disease (those with ascites). However, without reaching statistical significance. It's important to note that our study merely identified the presence or absence of lesions in 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 portal hypertension. Future research could explore this intriguing avenue further, offering valuable insights into the mechanisms underlying portal hypertension.

It is important to remark that 45% of the PSVD patients in this cohort did not have any specific histological signs and almost 17% of the patients also do not have any unspecific histological sign of PSVD. These data, however, must be interpreted with caution because, although biopsies were performed and reviewed in referral centres, 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 PSVD patients is similar to that observed in patients with cirrhosis (40,41) and therefore supports following a similar screening. 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 risk predictors of it. Most patients with high-risk varices received treatment with NSBB, and only a few of them received EVL or no treatment for primary prophylaxis and therefore, it is not possible to establish the efficacy of these different strategies. However, the 19% 5-year probability of first PH-related bleeding is consistent with that previously reported and suggests that NSBB are a good treatment option for these patients (6).

Acute variceal bleeding was controlled in more than 80% of patients using a 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 PSVD patients maintain and comparable to that observed in Child A cirrhotic patients. Secondary prophylaxis, performed in most patients with NSBB 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 (42). These data suggest that the therapeutic strategies used in patients with cirrhosis may also be as effective in PSVD as in patients with cirrhosis and show a high efficacy like that observed in Child A cirrhotic patients.

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 main driver for PVT development. Interestingly, the recanalization rate obtained with anticoagulation (51.9%) was similar to that observed in patients with cirrhosis and PVT (43,44), and no factors predicted this possibility. This suggests that a pro-coagulant imbalance may represent a pathogenic mechanism ad target of therapy for the risk of PVT in PSVD.

The severity of the underlying associated condition and parameters evaluating liver and renal function (ascites as first manifestation, bilirubin, albumin, and creatinine levels) and age were all shown to be independent predictors of prognosis. Considering that 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 have a strong predictive value for survival, either because it can be directly the cause of a non-liver related death (more than 50% of patients who died, the cause of death was non-liver-related), but also because it may have precluded transplantation in the cases 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 had a 25% mortality rate and 90% of them liver-related. These patients probably have a different, more aggressive clinical course (45), and therefore, these patients are a specific group that should be differentially considered (46,47). On the contrary, survival of PSVD-HIV patients 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 pathophysiological involved in PSVD development in these patients, has a favourable impact on PSVD course. Unfortunately, despite being so far 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 in mortality.

Ascites at diagnosis, as previously described (32), 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 that 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 PSVD patients might reflect a more advanced disease involving the hepatic sinusoidal area and can lead to severe PH complications, liver deterioration, and death. Bilirubin, albumin, and creatinine parameters frequently found to have a prognostic value in patients with cirrhosis, although usually mildly altered, also have a prognostic value in PSVD patients. With all these parameters, independently associated with prognosis, we developed a nomogram that predicts LT-free survival, showing good discrimination and calibration and that it 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 (32) but similar to the 82% in a Spanish cohort of 69 patients (6). Notably, in the Dutch study (32), 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 3 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 can be because HVPG was only available in 60% of the patients and probably to the strong correlation 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 centres, 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 PSVD patients with PH because this was the selection criteria for inclusion.

In summary, a high proportion of PSVD patients 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.

REFERENCES

1. Hernández-Gea V, Baiges A, Turon F, et al. Idiopathic Portal Hypertension. Hepatology. 2018;68:2413–2423.

2. De Gottardi A, Sempoux C, Berzigotti A. Porto-sinusoidal vascular disorder. J. Hepatol. 2022;77:1124–1135.

3. **Cerda Reyes E, González-Navarro EA, Magaz M**, et al. Autoimmune biomarkers in porto-sinusoidal vascular disease: Potential role in its diagnosis and pathophysiology. Liver Int. 2021;41:2171–2178.

4. Lampichler K, Semmler G, Wöran K, et al. Imaging features facilitate diagnosis of porto-sinusoidal vascular disorder. Eur. Radiol. 2023;33:1422–1432.

5. **Elkrief L, Lazareth M**, Chevret S, et al. Liver Stiffness by Transient Elastography to Detect Porto-Sinusoidal Vascular Liver Disease With Portal Hypertension. Hepatology. 2021;74:364–378.

6. Siramolpiwat S, Seijo S, Miquel R, et al. Idiopathic portal hypertension: Natural history and long-term outcome. Hepatology. 2014;59:2276–2285.

7. Schouten JN, Garcia-Pagan JC, Valla DC, et al. Idiopathic noncirrhotic portal hypertension. Hepatology. 2011;54:1071–1081.

8. Wöran K, Semmler G, Jachs M, et al. Clinical Course of Porto-Sinusoidal Vascular Disease Is Distinct From Idiopathic Noncirrhotic Portal Hypertension. Clin. Gastroenterol. Hepatol. 2022;20:e251–e266.

9. Krasinskas AM, Eghtesad B, Kamath PS, et al S. Liver Transplantation for Severe Intrahepatic Noncirrhotic Portal Hypertension. 2005;11:627–634.

10. Dumortier J, Bizollon T, Scoazec JY, et al. Orthotopic liver transplantation for idiopathic portal hypertension: Indications and outcome. Scand. J. Gastroenterol. 2001;36:417–422.

11. Khanna R, Sarin SK. Non-cirrhotic portal hypertension - Diagnosis and management. J. Hepatol. 2014;60:421–441.

12. Siramolpiwat S, Seijo S, Miquel R, et al. Idiopathic Portal Hypertension: Natural History and Long-Term Outcome. 2013;2276–2285.

13. Penrice DD, Thakral N, Kezer CA, et al. Outcomes of idiopathic versus secondary nodular regenerative hyperplasia of the liver: A longitudinal study of 167 cases. Liver Int. 2022;42:1379–1385.

14. de Franchis R, Bosch J, Garcia-Tsao G, et al Baveno VII Faculty. Baveno VII - Renewing consensus in portal hypertension. J. Hepatol. 2022;76:959–974.

15. Wanless IR. micronodular transpormation (nodular regenerative hyperplasia) of the liver: A report of 64 cases among 2,500 autopsies and a new classification of benign hepatocellular nodules. Hepatology. 1990;11:787–797.

16. De Gottardi A, Rautou P, Schouten J, J, et al. Porto-sinusoidal vascular disease: proposal and description of a novel entity. Lancet Gastroenterol. Hepatol. 2019;4:399–411.

17. Neuberger J, Patel J, Caldwell H, , et al. Guidelines on the use of liver biopsy in clinical practice from the British Society of Gastroenterology , the Royal College of Radiologists and the Royal College of Pathology. 2020;1–22.

18. **Magaz M, Giudicelli-Lett H**, Nicoară-Farcău O, et al. Liver Transplantation for Porto-sinusoidal Vascular Liver Disorder: Long-term Outcome. Transplantation. 2023;107:1330–1340.

19. World Health Organization; WHO Collaborating Centres for Classification of Diseases. International statistical classification of diseases and related health problems. 10th revision ed. Geneva: World Health Organization; 1992.

20. Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. J. Am. Stat. Assoc. 1999;94:496–509.

21. Riley RD, Ensor J, Snell KIE, et al. Calculating the sample size required for developing a clinical prediction model. BMJ. 2020;m441.

22. McLernon DJ, Giardiello D, Van Calster B, et al. Assessing Performance and Clinical Usefulness in Prediction Models With Survival Outcomes: Practical Guidance for Cox Proportional Hazards Models. Ann. Intern. Med. 2023;176:105–114.

23. Karlas T, Petroff D, Sasso M, et al. Individual patient data meta-analysis of controlled attenuation parameter (CAP) technology for assessing steatosis. J. Hepatol. 2017;66:1022–1030.

24. Ferraioli G, Monteiro LBS. Ultrasound-based techniques for the diagnosis of liver steatosis. World J. Gastroenterol. 2019;25:6053–6062.

25. Sirli R, Sporea I. Controlled Attenuation Parameter for Quantification of Steatosis: Which Cut-Offs to Use? Can. J. Gastroenterol. Hepatol. 2021;2021:1–7.

26. Montagnese S, Romero Gómez M, Larsen FS, et al. EASL Clinical Practice Guidelines on the management of hepatic encephalopathy. J. Hepatol. 2022;77:807–824.

27. Elkrief L, Payancé A, Plessier A, et al. Management of splanchnic vein thrombosis. JHEP Reports. 2023;5:100667.

28. Schouten JN, Verheij J, Seijo S. Idiopathic non-cirrhotic portal hypertension: a review. Orphanet J. Rare Dis. 2015;10:67.

29. Valainathan SR, Sartoris R, Elkrief L, et al. Contrast-enhanced CT and liver surface nodularity for the diagnosis of porto-sinusoidal vascular disorder: A case-control study. Hepatology. 2022;76:418–428.

30. Hillaire S, Bonte E, Denninger M-H, et al. Idiopathic non-cirrhotic intrahepatic portal hypertension in the West: a re-evaluation in 28 patients. Gut. 2002;51:275–280.

31. Schouten JNL, Nevens F, Hansen B, et al. Idiopathic noncirrhotic portal hypertension is associated with poor survival: Results of a long-term cohort study. Aliment. Pharmacol. Ther. 2012;35:1424–1433.

32. Wöran K, Semmler G, Jachs M, et al. Clinical Course of Porto-Sinusoidal Vascular Disease Is Distinct From Idiopathic Noncirrhotic Portal Hypertension. Clin. Gastroenterol. Hepatol. 2022;20:e251–e266.

33. Sun Y, Lan X, Shao C, Wang T. Clinical features of idiopathic portal hypertension in China: A retrospective study of 338 patients and literature review. J. Gastroenterol. Hepatol. 2018;jgh.14552.

34. Ramsay M. Portopulmonary hypertension and right heart failure in patients with cirrhosis. Curr. Opin. Anaesthesiol. 2010;23:145–150.

35. M Patnaik SM. Inherited antithrombin deficiency: a review. Haemophilia. 2008;14:1229–1239.

36. **Dabit JY, Valenzuela-Almada MO**, Vallejo-Ramos S, et al. Epidemiology of

Antiphospholipid Syndrome in the General Population. Curr. Rheumatol. Rep. 2021;23:85.

37. Tait RC, Walker ID, Reitsma PH, Islam SI, McCall F, Poort SR, et al. Prevalence of protein C deficiency in the healthy population. Thromb. Haemost. 1995;73:87–93.

38. Nayak NC. Idiopathic portal hypertension (noncirrhotic portal fibrosis), thrombosis in portal venous system and protein C deficiency to the editor. Hepatology. 1989;10:902–902.

39. Bosch J, Berzigotti A, Garcia-Pagan JC, et al. The management of portal hypertension: Rational basis, available treatments and future options. J. Hepatol. 2008;48:S68–S92.

40. Garcia-Tsao G, Sanyal AJ, Grace ND, et al Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. Hepatology. 2007;46:922–938.

41. **Magaz M, Baiges A**, Hernández-Gea V. Precision medicine in variceal bleeding: Are we there yet? J. Hepatol. 2020;72:774–784.

42. Delgado MG, Seijo S, Yepes I, et al. Efficacy and Safety of Anticoagulation on Patients With Cirrhosis and Portal Vein Thrombosis. Clin. Gastroenterol. Hepatol. 2012;10:776–783.

43. Senzolo M, M. Sartori T, Rossetto V , et al. Prospective evaluation of anticoagulation and transjugular intrahepatic portosistemic shunt for the management of portal vein thrombosis in cirrhosis. Liver Int. 2012;32:919–927.

44. Szablewski V, René C, Costes V. Indolent cytotoxic T cell lymphoproliferation associated with nodular regenerative hyperplasia: a common liver lesion in the context of common variable immunodeficiency disorder. Virchows Arch. 2015;467:733–740.

45. Camões G, Fernandes DA, Ferreira DM, Severe Ascites in Common Variable Immunodeficiency. Cureus. 2022;14:e30274.

46. Pecoraro A, Crescenzi L, Varricchi G, et al. Heterogeneity of Liver Disease in Common Variable Immunodeficiency Disorders. Front. Immunol. 2020;11.

TABLES LEGEND

Table 1. Baseline charecteristics and associated disordes**.** AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase; INR, International normalized ratio; SD, standard deviation; POEMS, polyneuropathy, organomegaly, endocrinopathy, M protein,and skin changes; IBD, Inflammatory bowel disease; SLE, systemic lupus erythematosus; HIV, Human immunodeficiency virus; SD, standard deviation; PVT, Non-cirrhotic portal vein thrombosis.

Table 2. Univariate and multivariate analysis for trasplant-free survival. AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase; INR, International normalized ratio; HVPG, Hepatic venous pressure gradient.

FIGURES LEGEND

Figure 1A. Cumulative probability of having PH-related first bleeding considering LT and death as a competing event. PH, Portal hypertension; LT, liver transplant.

Figure 1B. Cumulative probability of having PH-related rebleeding considering LT and death as a competing event. PH, Portal hypertension; LT, liver transplant.

Figure 2. Actuarial probability of LT-free survival.

Figure 3: Nomogram predicting prognosis of PSVD patients.

Figure 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).

Table 1. Baseline characteristics and associated disorders**.**

	n (%) / median; IQR
Men	367 (62.5%)
Age at first manifestation	47 (33;59)
Asymptomatic at diagnosis **-Thrombocytopenia and splenomegaly** **-Abnormal imaging other than splenomegaly*/elevated liver enzymes**	377 (64.2%) 291 (77.2%) 86 (22.8%)
Symptomatic at diagnosis **-Only Variceal bleeding** **-Only Ascites** **-Variceal bleeding and ascites** **-Hepatic encephalopathy** **-Dyspnea**	210 (35.8%) 87 (41.4%) 92 (43.8%) 25 (12%) 11 (4.7%)(**) 13 (6.3%)(***)
Duration between first manifestation of portal hypertension and liver biopsy (months)	6 (0;34)
Splenomegaly **Spleen size in the largest axis (cm)**	478 (81.4%) 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: <40U/L/<116U/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 **-A/B/C/NA**	5 (5;6) 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%)
-Grave´s 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, Still´s 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%)

(*) 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.

All patients (n=587)	Univariate		Multivariate	
	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 [1.30-2.06]	**<0.001**	1.36 [1.07-1.72]	**0.012**
Bilirubin (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)	0.90 [0.87-0.92]	**<0.001**	0.91 [0.89-0.94]	**<0.001**
Platelets ($\times 10^9$ /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		

Table 2.

(+) Only available in 352 patients. (++) Only available in 393 *patients.*

Table 2

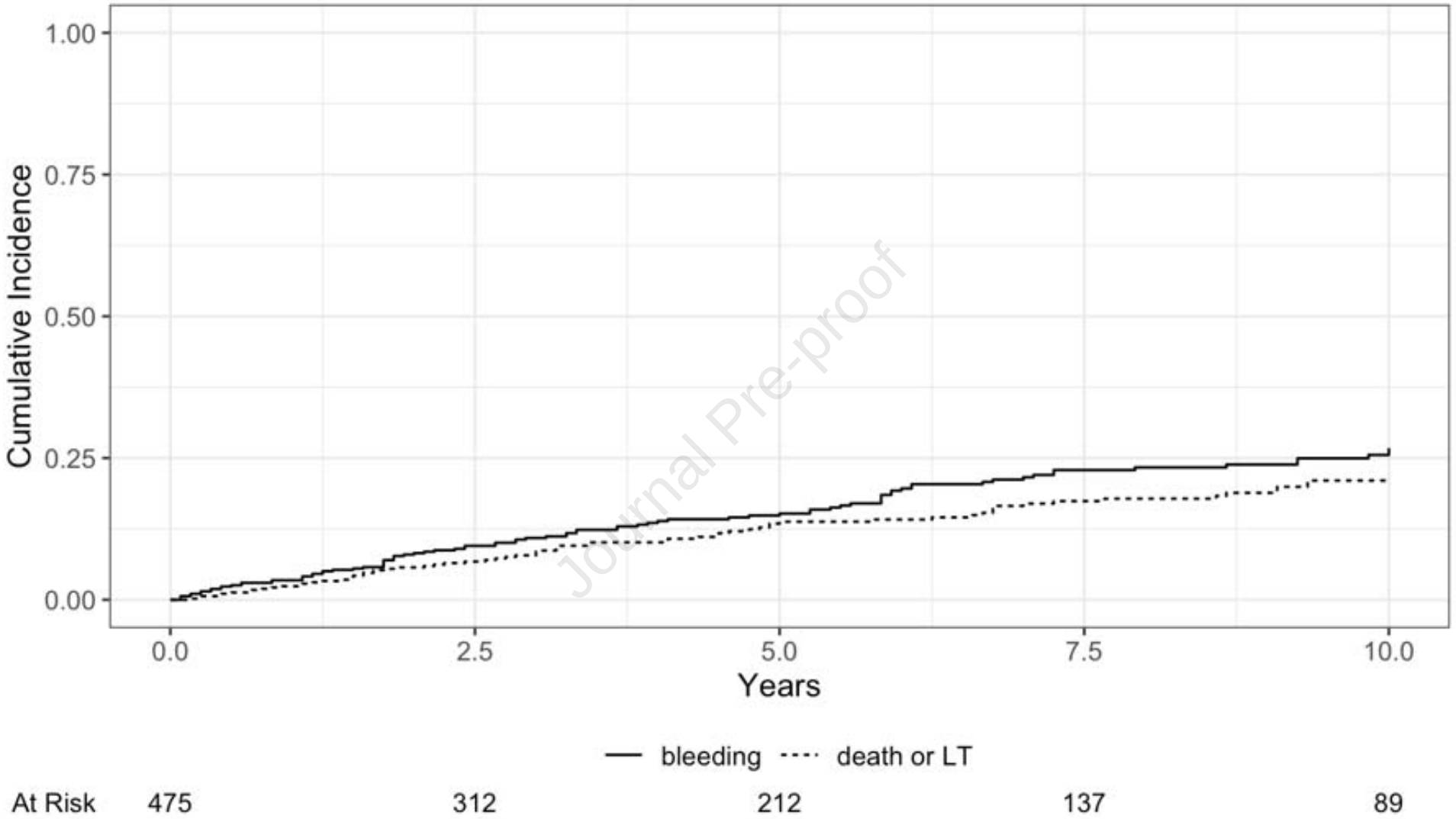

Figure 1A. Cumulative probability of having a first PH-related bleeding considering LT and death as a competing event. PH, Portal hypertension; LT, liver transplant.

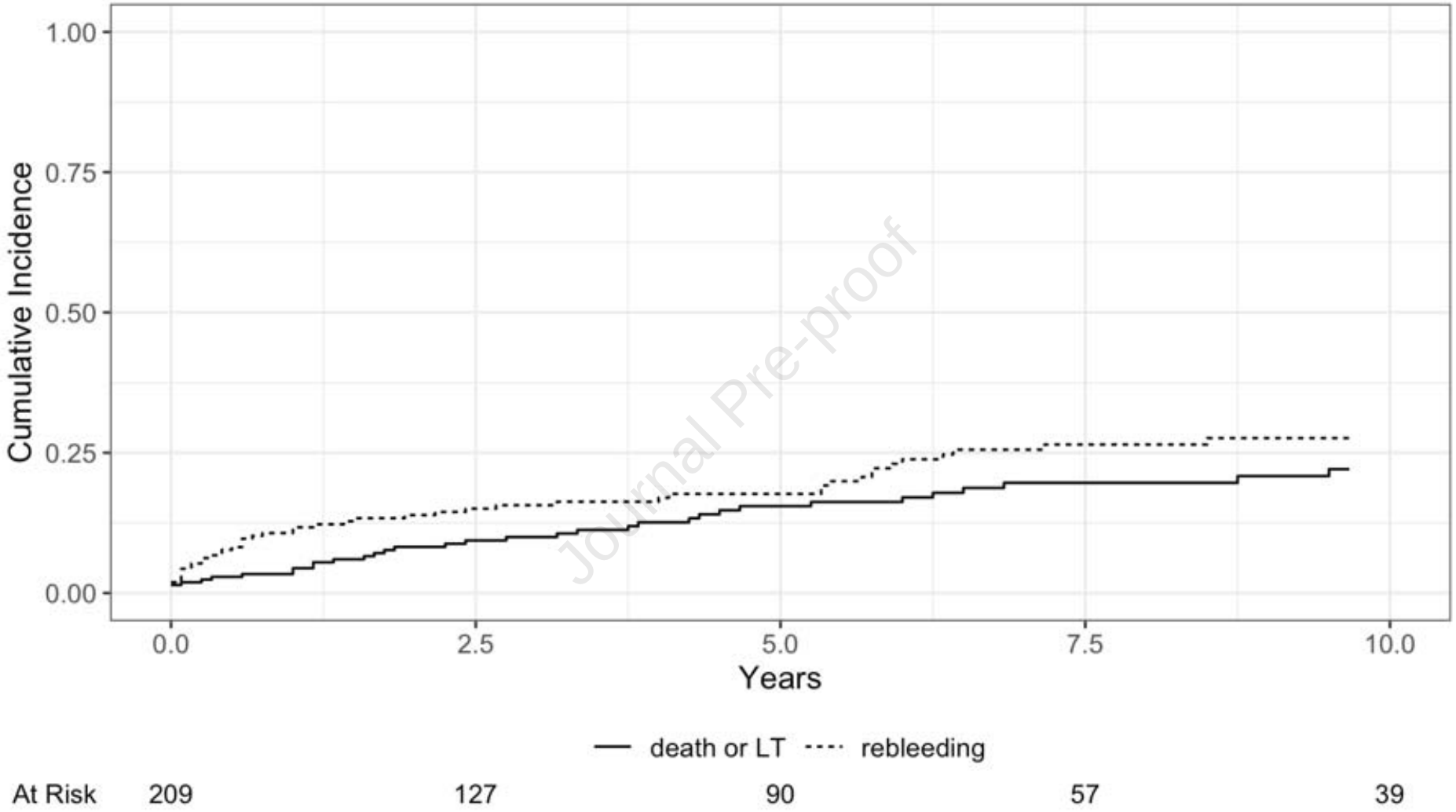

Figure 1B. Cumulative probability of having PH-related rebleeding considering LT and death as a competing event. PH, Portal hypertension; LT, liver transplant.

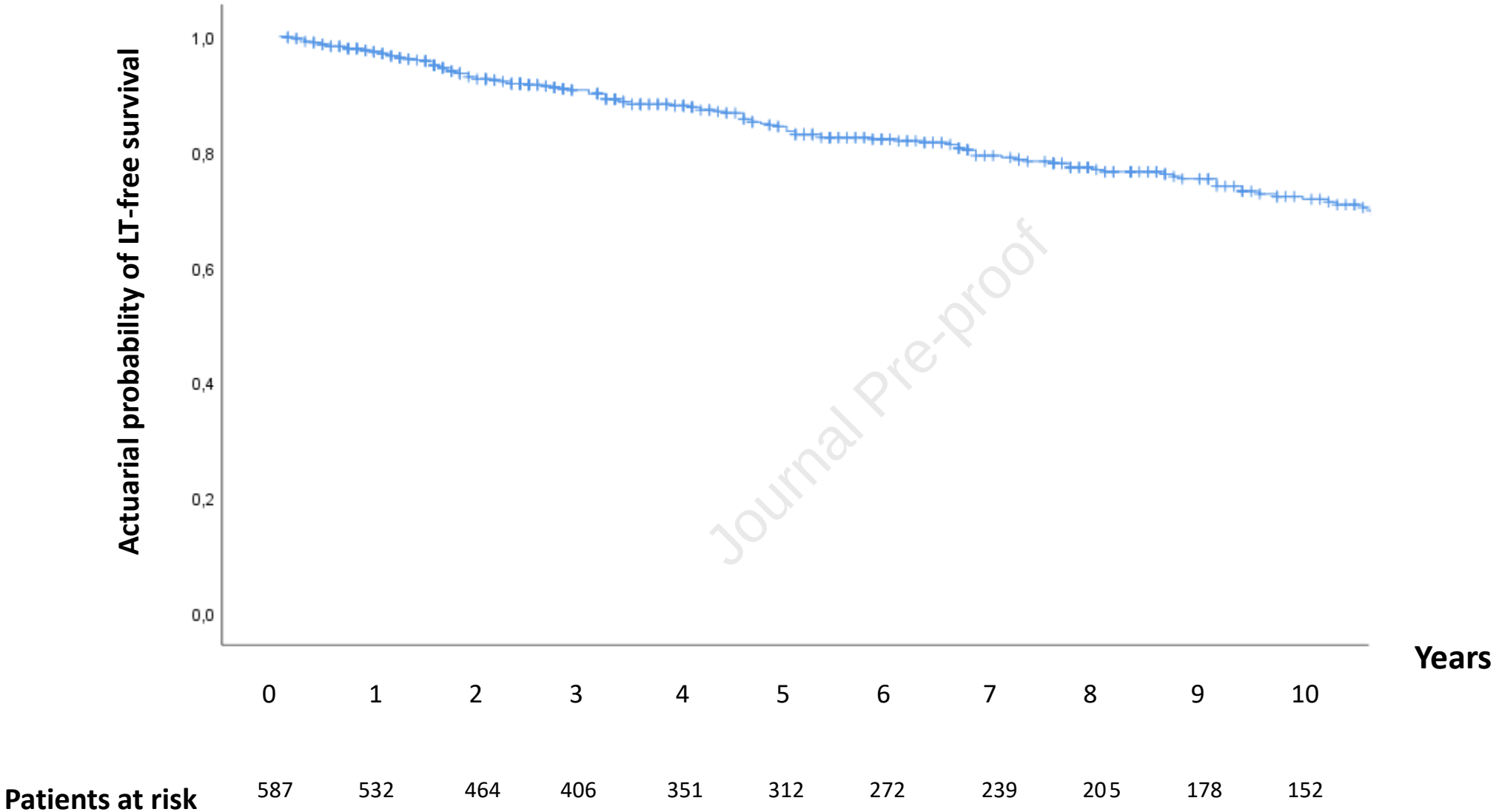

Figure 2. Actuarial probability of LT-free survival.

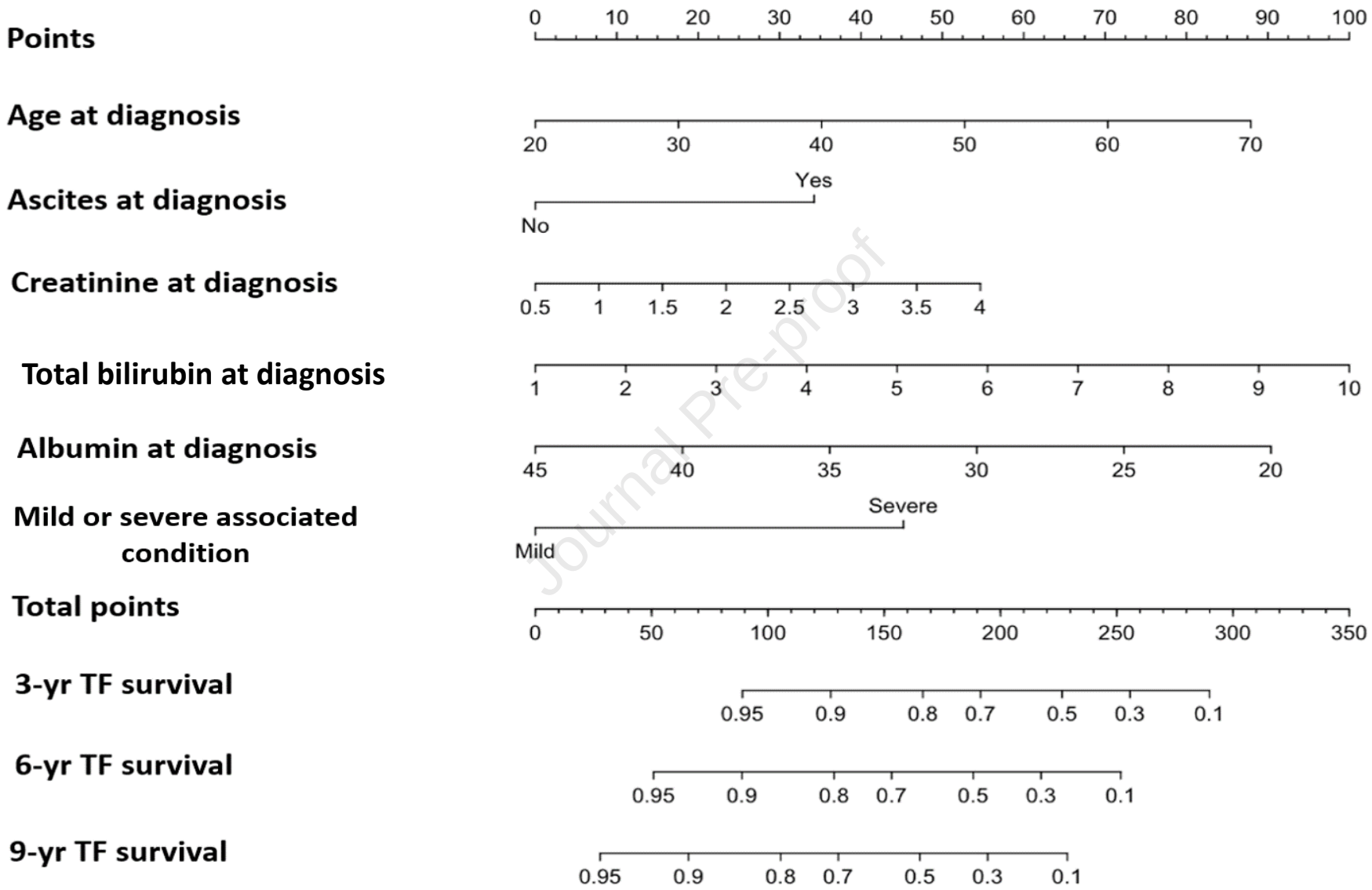

Figure 3. Nomogram predicting prognosis of PSVD patients.

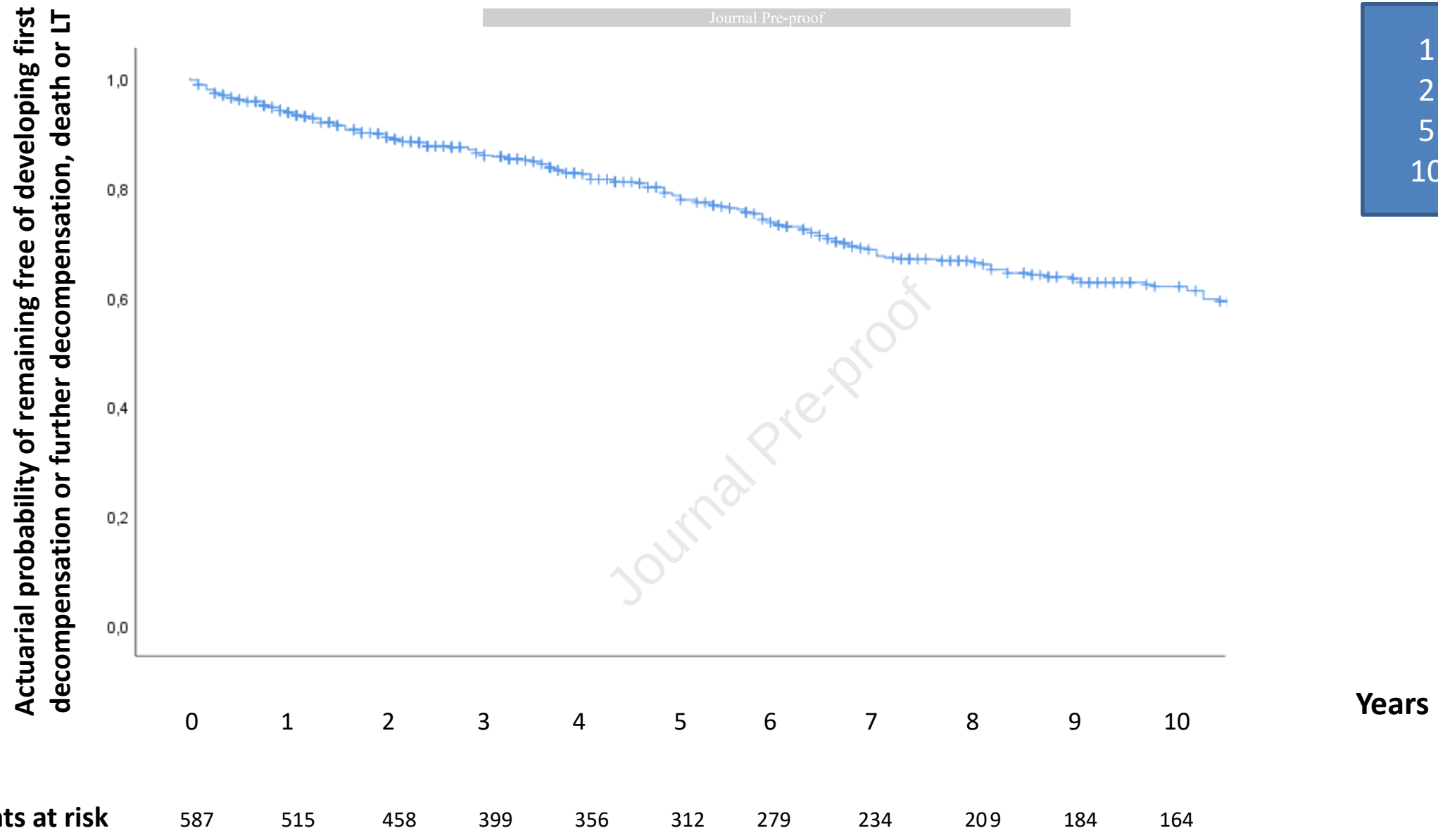

Figure 4. Composite endpoint (First bleeding or ascites or HE in asymptomatic patients at diagnosis or rebleeding or worsen ascites in those who had already presented it, further decompensation, death, or liver transplant).

HIGHLIGHTS

- Porto-sinusoidal vascular liver disorder (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 those expected in cirrhosis.
- Presence and severity of an associated condition, ascites, age, bilirubin, albumin and creatinine are associated with poor prognosis