

Study protocol

Title: The natural history of early porto-sinusoidal vascular disorder

Coordinators

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Background

Porto-sinusoidal vascular disorder (PSVD) is an entity that regroups several mild or moderate alterations of liver histology in the absence of cirrhosis. It may be associated with portal hypertension despite no portal vein obstruction is observed (1,2). According to a recent review article, PSVD is diagnosed when a liver biopsy >20 mm rules out cirrhosis and when there is one specific sign of portal hypertension (gastric, esophageal or ectopic varices, portal hypertensive bleeding, porto-systemic collaterals at imaging) or one specific histological lesion for PSVD (obliterative portal venopathy, nodular regenerative hyperplasia, incomplete septal fibrosis). In the absence of specific signs of portal hypertension and specific histological lesions, PSVD can be diagnosed when there is one non-specific sign of portal hypertension (ascites, platelet count < 150'000/mm³, spleen size ≥13 cm in the largest axis) and one non-specific histological lesion for PSVD (portal tract abnormalities, architectural disturbance: irregular distribution of the portal tracts and central veins, non-zonal sinusoidal dilatation, mild perisinusoidal fibrosis) (1).

While defining PSVD as a new entity has obvious advantages, little is known about the natural history of the disease. In 2011, Cazals-Hatem et al. reported 59 patients with obliterative portal venopathy of which 25% had no signs of portal hypertension at histological diagnosis. Among them 40% developed portal hypertension during a median 8.6-years follow-up (3). Later, Guido et al. studied the histological and clinical features in a cohort of 94 obliterative portal venopathy without portal hypertension. The authors suggested OPV without portal hypertension may be an early stage of what was previously called "idiopathic non-cirrhotic portal hypertension". They also suggested thrombotic and immunological disorders may be risk factors for the development of portal hypertension (4). More recently, Woran and colleagues discussed a population of 91 PSVD of which 8,8% had no signs of portal hypertension at histological diagnosis. These patients did not experience hepatic decompensation or liver-related mortality over a 3 -year follow-up (5). Currently, there is a gap in knowledge regarding the natural history of patients with histological lesions of PSVD and

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without signs of portal hypertension. In this study, we will aim to describe the natural history of these early stages of PSVD (without signs of portal hypertension) and to clarify risk factors for disease progression.

Study design

Health-related data of patients with PSVD seen in the participating hospital centers will be retrospectively collected. Participating centers will include Belgian centers recruited through a nation-wide study endorsed by the *Belgian Association for the Study of the Liver*, as well as centers belonging to VALDIG (Vascular Liver Disease Group). VALDIG is an independent network of researchers with a common interest in Vascular Liver Diseases. The aim of this network is to foster research in this field. All VALDIG centers are connected by one database, which allows for the coordination of joint research projects. VALDIG is conducting multicenter research projects. Those studies focus on the incidence, direct causes and consequences of vascular liver diseases. Vascular Liver Diseases are less common compared with other liver diseases. For this reason, a broad network of collaborating centers is necessary to obtain sufficient samples for data analysis. To date, 60 centers in 19 countries are affiliated to VALDIG network. The list of the members of VALDIG are available at <http://valdig.eu/whowe-are/>.

Patients with a histopathological diagnosis of obliterative portal venopathy, nodular regenerative hyperplasia and incomplete septal fibrosis that at diagnosis have not unequivocal signs of portal hypertension will be included. Participating centers will be asked to check pathology reports of liver biopsies to limit the risk of selection bias. Central review of histological slides by a pathologist expert in liver disease will be done. Follow-up will start at the time of histological diagnosis. Inclusion of cases will end on December 31, 2024.

Endpoints

Main endpoints are the development of biological or morphological signs of portal hypertension (esophageal or gastric varices, thrombopenia, splenomegaly), the development of clinical complications of portal hypertension (variceal hemorrhage due to portal hypertension, ascites, hepatic encephalopathy), and the development of portal vein thrombosis.

Secondary endpoints are liver and non-liver-related mortality.

Inclusion criteria

- Patients with at least one specific histological lesion for PSVD on a biopsy ≥ 20 mm long, without signs of portal hypertension.

Exclusion criteria

- Cirrhosis

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- Portal vein thrombosis
- Budd-Chiari syndrome / hepatic venous outflow obstruction
- Vascular invasion by a tumor
- Severe comorbidity with limited estimated life expectancy
- Presence of signs of PH, namely ascites or platelet count $< 150'000/\text{mm}^3$ or spleen size ≥ 13 cm in the largest axis or gastroesophageal varices or porto-systemic collaterals

Description of the health-related data

The following data will be retrospectively collected from the patient's medical files.

- Demographical data (age at diagnosis, gender, race),
- Indication for liver tissue sample,
- Conditions associated to PSVD at the time of diagnosis classified as drug/toxin exposure, immunological disorders, coagulation disorders, congenital and hereditary disorders (6),
- Laboratory data (aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, alkaline phosphatase, platelet count, INR, albumin, bilirubin) at diagnosis and during follow-up,
- Imaging data (ultrasonography, computed tomography scan, or magnetic resonance imaging) at diagnosis and during follow-up,
- Endoscopic data (if an upper gastro-intestinal endoscopy is available) at diagnosis and during follow-up,
- Liver stiffness and spleen stiffness (if transient elastography is available) at diagnosis and during follow-up,
- Specific and non-specific signs of portal hypertension at diagnosis and during follow-up,
- Liver-related events (portal vein thrombosis, ascites, hepatocellular carcinoma, hepatic encephalopathy),
- Medical interventions (transjugular intrahepatic portosystemic shunt, liver transplantation),
- Liver-mortality,
- Non-liver-mortality.

The following histological data will be recorded by the pathologist expert in liver disease.

- Specific histological lesion for PSVD: obliterative portal venopathy, nodular regenerative hyperplasia, incomplete septal fibrosis, as well as biopsy size, number of portal tracts, METAVIR score, lobular inflammation, portal inflammation.

Statistical analysis

Quantitative variables will be expressed as median and interquartile ranges (IQR) and categorical variables as absolute and relative frequencies. Quantitative variables will be compared using the Mann-Whiney test. Comparison of qualitative variables will be performed

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using the Chi-square or Fisher exact test as appropriate. Survival, as well as occurrence of complications will be assessed according to the Kaplan–Meier method and curves will be compared using the log-rank test. The risk of liver-related death could also be estimated with the cumulative incidence function taking into account death from non-liver-related causes as competing risk. To determine which factors are independently associated with survival, with the occurrence of another endpoint or the development of complications, we will perform univariate and multivariate Cox regression analyses. If competing risk analyses are performed, univariate and multivariate Fine and Gray proportional hazards model to identify factors associated with liver-related death will be used. All tests will be two-sided and $p \leq 0.05$ will be considered significant.

Non-coded data and coded data

Data will be collected by the local investigators and sent to the principal investigators of the study. Data collected will be anonymized. A number of inclusion (including the number assigned to the center, and the patient's number) will be assigned to patients included in the study, and patients will be identified using this number in the CRF. The inclusion number will not include information that could allow identification participants such as initials, year of birth, social security number... The correspondence between the patient and the inclusion number will be saved in a protected file in each center. Thus, data will be coded locally in each local center, before transmission to the principal investigator.

Data protection

Once completed, each patient data will be copied the principal investigators of the study in a dedicated file, and stored in CUB Hopital Erasme, Brussels, Belgium. This file will be protected with a password. All the changes will be saved by making copies of the file, identified with the date of savings. The correspondence between the patient and the inclusion number will be saved locally by each center.

How long will the data and/or samples be stored?

The copies of the data from the patient files will be destroyed after the publication of the article.

Ethics

This study will be carried out in compliance with the Declaration of Helsinki and Good Clinical Practice Guidelines. As a retrospective study, patients will not be subjected to any type of intervention that implies any risk due to their participation to this research project. The study protocol will be sent for approval to the Ethical committee of CUB Hopital Erasme, Brussels, Belgium. In Brussels, the principal investigator (Prof Pierre Deltenre) will ask the "Service de la Recherche Biomédicale" that each eligible patient did not decline the use of his data for

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research purposes. For the use of anonymous clinical routine data in the setting of a retrospective study, informed consent is waived. The present protocol (main document) will be sent to local centers. The respect of local ethics requirements, and the submission of this project to local Ethics committee is under the responsibility of each local investigator.

Publication policy and funding

This study has no financial support. Recruiting centers will not receive any financial compensation. The first and last author of the study will be the principal investigators. Senior experts from the VALDIG network will co-review the manuscript. Authors will include 1 to 3 Investigators per center (depending on the proportion of included patients, according to VALDIG publication rules).

References

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