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Poor long-term outcome in patients with porto-sinusoidal vascular disease (PSVD): fact or disease misclassification?

Shiv K. Sarin[1], Ansgar W. Lohse[2,*], Patrick S. Kamath[3]

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Vascular disorders of the liver are separated out broadly into disorders of outflow, pre-hepatic or inflow, and hepatic parenchyma. Depending on the level of the obstruction, the outflow disorders are characterized as sinusoidal obstruction syndrome, and Budd-Chiari syndrome. Pre-hepatic vascular disorders include extrahepatic portal vein obstruction, usually diagnosed on radiological imaging. It is the parenchymal diseases with vascular involvement that pose particular challenges: does parenchymal injury lead to vascular anomalies, or do vascular disorders lead to parenchymal damage and hepatic dysfunction. The former group relates to cirrhosis, whereas the latter to non-cirrhotic portal fibrosis (NCPF) or idiopathic portal hypertension (IPH).[1,2] In IPH, liver function is largely maintained. Indeed, the entity "Idiopathic portal hypertension" (IPH) was described in 1967 by James Boyer working with Professor A.K. Basu in India. They described IPH as "a condition occurring throughout the world, and although different underlying disease processes may be involved, the portal hypertension in each patient is associated with good liver function and structure and patent portal and splenic veins".[2] IPH was subsequently named as NCPF and the terms are used interchangeably.[3] Hepatic venous pressure gradient (HVPG) and liver biopsy help distinguish between cirrhosis and IPH/NCPF.[3] Typical histology with or without elevated HVPG defines cirrhosis, whereas absence of cirrhosis with preserved hepatic parenchyma and a normal or mildly raised HVPG suggests a non-cirrhotic etiology. However, a proportion of patients fall between the two categories: a single liver biopsy sample may miss areas diagnostic of cirrhosis, and in some patients with IPH/NCPF, HVPG may be high depending on the location of fibrosis.

Very little progress has been made over the past 60 years in our understanding of IPH, and perhaps because of this, a variety of other terms have been used to describe what is essentially IPH. The concept of porto-sinusoidal vascular disorder probably rose from this void.[4] The VALDIG group in 2019 suggested the terminology "porto-sinusoidal vascular disease" (PSVD), the underlying concept being that the disease-causing mechanism rests in the hepatic vasculature, possibly triggered by systemic factors such as systemic inflammatory diseases and/or hypercoagulopathy.[5] It remains unclear what these factors might be, but there is general agreement that the condition may be associated with hematological diseases, coagulopathy, rheumatological and other immune-mediated diseases, HIV, drugs, common variable immunodeficiency, and more recently, telomere shortening disorders. In the current issue of the *Journal of Hepatology* the long-term follow-up of patients designated to have PSVD is presented. For the purposes of the study, PSVD was diagnosed on a good quality liver biopsy (>2 cm) by the absence of cirrhosis plus one specific sign of portal hypertension; or histological lesions specific for PSVD; or one sign not specific for portal hypertension plus one histological lesion not specific for PSVD, a significant overlap with existing terminology of IPH. Other similarities between IPH and PSVD include a liver biopsy documenting the presence of obliterative portal venopathy, incomplete septal cirrhosis or nodular regenerative hyperplasia, and a normal or mildly elevated HVPG.[1] Thus, the disease entity previously termed IPH is now termed PSVD. As Max Planck, the great German scientist stated in his autobiography: *A new scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die, and a new generation grows up that is familiar with it.* Once considered rare, the condition is being

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* Corresponding Author: Ansgar W. Lohse, I. Department of Medicine, University Medical Centre Hamburg-Eppendorf, Martinistr. 52, 20246 Hamburg, Germany, telephone +40 40 7410 53910, fax +40 40 7410 58531.
E-mail address: a.lohse@uke.de (A.W. Lohse).
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increasingly diagnosed, either due to better recognition of IPH/PSVD, or due to a true increase in prevalence.

One of the limitations of the current study is that cirrhosis was excluded only on the basis of a "good quality liver biopsy" not demonstrating cirrhosis. It is recognized from studies comparing macroscopic with microscopic assessment that, depending on the underlying liver disease, even a "good quality liver biopsy" may miss up to 30% of cases of cirrhosis. This is particularly true for primary sclerosing cholangitis and autoimmune hepatitis where fibrosis is patchy.[6–8] Similarly, fibrotic changes in sarcoidosis and schistosomiasis may be missed due to the considerable sampling error of percutaneous or, even more so, transjugular liver biopsy. In the current study, 17% of patients were reported to have incomplete septal fibrosis, suggesting that at least some of these patients may indeed have had cirrhosis. Furthermore, 40% of the patients had a liver stiffness measurement of >10 kPa, and in 8% the stiffness was >20 kPa – ranges that are more consistent with cirrhosis. In support of this, patients with metabolic dysfunction-, viral or alcohol-associated liver disease but with histological features of PSVD were included. This inclusiveness may be inappropriate as the liver biopsy sample may have missed cirrhosis in these patients. In support of possible misclassification is that the authors themselves suggest that PSVD must be suspected in patients with normal LSM and normal HVPG. The inclusion of patients with pre-existing portal vein thrombosis is also concerning as portal vein thrombosis may be secondary to PSVD, but is also a well-recognized disease entity in itself.

Long-term data on IPH/NCPF from Japanese nationwide surveys and other studies have shown good survival if variceal bleeding is well controlled with shunt surgery or endoscopic interventions.[9,10] A multicenter study from the Netherlands included only patients with Crohn's disease who were treated with thiopurines and noted improvement in liver biochemistry and portal hypertension complications with improvement of the underlying Crohn's disease.[11] The current study includes 587 patients seen at one of 27 European centers and followed up for a median of 68 months. This is an impressive effort for an uncommon disease, and thus presents data with much value despite its scientific shortcomings, mainly the retrospective nature of the study and the well-recognized difficulty in making a reliable histological diagnosis. The natural history of PSVD in the present study reported unfavorable outcomes, with 5- and 10-year survival rates of 83% and 72%. This is closer to the natural history of patients with Child-Pugh class B cirrhosis, and far worse than experienced in the real-world. Further, the outcome was reported to strongly correlate with HVPG (p = 0.0002), a feature typical of cirrhosis. The key limitation is that in the absence of a definite diagnostic hallmark of this disease, it is uncertain whether all patients had the same disease. Indeed, as the data are presented, PSVD in itself is a manifestation of a multitude of conditions that may lead to increased intrahepatic vascular resistance on one hand and merely histopathological features of PSVD with no portal hypertension on the other hand. This questions the accuracy of diagnosis and whether the clinical implications of this study remain valid for independent cohorts of patients diagnosed with PSVD.

Unfortunately, this study does not inform management protocols. Whereas the standard recommendation for managing portal hypertension in PSVD is analogous to cirrhotic portal hypertension, there are arguments to be made for a lower threshold for TIPS (transjugular intrahepatic portosystemic shunt) placement than in patients with cirrhosis, given the lower risk of hepatic encephalopathy and hepatic failure.[12] It is therefore unfortunate that the present study did not have sufficient data on the comparative efficacy of management approaches for portal hypertension. A randomized controlled trial may be difficult to perform given the relative rarity of the condition and the heterogenous nature of the patient populations. A follow-up of the present cohort assessing the efficacy and risks of TIPS placement would be extremely important. Future studies should also address specific biomarkers for diagnosis and attempt to unravel the pathogenesis of IPH/PSVD. Separating out disease etiologies of pure vascular nature from those associated with other diseases is also important. The outcomes are likely to be different in IPH/PSVD associated with telomere shortening disorders *vs.* common variable immunodeficiency *vs.* HIV *vs.* hematological diseases and infection, drugs or toxin-mediated disorders. We eagerly await studies that address these issues. Sound scientific outcomes will require global collaborative efforts. The present effort is a great step forward, but the road to better understanding and treatment of PSVD will be long.

Affiliations

[1]*Institute of Liver and Biliary Sciences, New Delhi, India;* [2]*I. Department of Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany;* [3]*Division of Gastroenterology and Hepatology Mayo Clinic College of Medicine and Science Rochester MN, USA*

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Conflict of interest

The authors of this study declare that they do not have any conflict of interest.

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Authors' contributions

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Supplementary data

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