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Liver Stiffness by Transient Elastography to Detect Porto-Sinusoidal Vascular Liver Disease With Portal Hypertension

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BACKGROUND AND AIMS: Porto-sinusoidal vascular liver disease (PSVD) is a rare cause of portal hypertension. PSVD is still often misdiagnosed as cirrhosis, emphasizing the need to improve PSVD diagnosis strategies. Data on liver stiffness measurement using transient elastography (TE-LSM) in PSVD are limited. The aim of this study was to evaluate the accuracy of TE-LSM to discriminate PSVD from cirrhosis in patients with signs of portal hypertension.

APPROACH AND RESULTS: Retrospective multicenter study comparing TE-LSM in patients with PSVD, according to Vascular Liver Disease Interest Group criteria, with patients with compensated biopsy-proven cirrhosis associated with alcohol (n = 117), HCV infection (n = 110), or NAFLD (n = 46). All patients had at least one sign of portal hypertension among gastroesophageal varices, splenomegaly, portosystemic collaterals, history of ascites, or platelet count < 150 × 10^9/L. The 77 patients with PSVD included in the test cohort had lower median TE-LSM (7.9 kPa) than the patients with alcohol-associated, HCV-related, and NAFLD-related cirrhosis (33.8, 18.2, and 33.6 kPa, respectively; P < 0.001). When compared with cirrhosis, a cutoff value of 10 kPa had a specificity of 97% for the diagnosis of PSVD with a 85% positive predictive value. A cutoff value of 20 kPa had a sensitivity of 94% for ruling out PSVD with a 97% negative predictive value. Of the patients, 94% were well-classified. Even better results were obtained in a validation cohort including 78 patients with PSVD.

CONCLUSIONS: This study including a total of 155 patients with PSVD and 273 patients with cirrhosis demonstrates that TE-LSM < 10 kPa strongly suggests PSVD in patients with signs of portal hypertension. Conversely, when TE-LSM is >20 kPa, PSVD is highly unlikely. (Hepatology 2021;74:364-378).

Porto-sinusoidal vascular disease (PSVD) has been recently proposed by Vascular Liver Disease Interest Group (VALDIG) as a term to describe a group of rare vascular liver entities causing portal hypertension. It has been traditionally known as idiopathic noncirrhotic portal hypertension. PSVD is characterized by the absence of cirrhotic modification of the liver parenchyma, the presence of microvascular histological lesions, and the absence of complete extrahepatic portal vein obstruction.[(1)] Thus, liver biopsy

Abbreviations: ANRS, Agence nationale de recherche sur le sida et les hépatites; AUROC, area under the receiver operating characteristic curve; IQR, interquartile range; PSVD, porto-sinusoidal vascular liver disease; TE-LSM, liver stiffness measurement using transient elastography; VALDIG, Vascular Liver Disease Interest Group.

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is necessary for the diagnosis of PSVD. PSVD is a much rarer cause of portal hypertension than cirrhosis, which explains, at least in part, why PSVD is still often overlooked and misdiagnosed as cirrhosis.[2-4] Moreover, liver biopsy, because of its limitations and risks, is less commonly performed as a first-line investigation in patients with chronic liver diseases and has been extensively replaced by noninvasive alternatives. Finally, histological diagnosis of PSVD is challenging, requiring an adequate liver biopsy, the latter being interpreted by an expert pathologist.[1,5,6] However, the management of patients with PSVD is different from those with cirrhosis. In particular, patients with cirrhosis should be screened for hepatocellular carcinoma, even when the causal factor is controlled.[7,8] This highlights the need to improve diagnostic strategies for PSVD and to better orientate patients to liver biopsy.

Liver stiffness measurement using transient elastography (TE-LSM; FibroScan) is routinely used for the diagnosis of advanced chronic liver disease (ACLD). In addition, it is routinely used for the assessment of portal hypertension. TE-LSM < 10 kPa is associated with a low risk of

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clinically significant portal hypertension[9-12] and, consequently, a low risk of developing clinical complications.[13] TE-LSM above 20-25 kPa suggests clinically significant portal hypertension with a specificity >90%.[9-12,14] Moreover, TE-LSM combined with platelet count allows for the identification of patients with compensated cirrhosis who can safely avoid endoscopic screening for gastroesophageal varices. Indeed, patients with TE-LSM < 20 kPa and platelet count > 150 × 10^9/L (the so-called "favorable Baveno VI criteria") have a <5% risk of having esophageal varices needing treatment and thus can safely avoid screening endoscopy.[15-17]

In contrast with ACLD, data on TE-LSM in patients with PSVD are limited to small and heterogeneous studies.[18-21] No cutoff value of TE-LSM has been established to raise a high suspicion of PSVD—and therefore to perform a diagnostic liver biopsy—or to confidently rule out PSVD in patients with portal hypertension. In addition, the relationship between TE-LSM values and the various histological lesions found in PSVD has never been assessed.[22]

The aims of the present retrospective multicenter study were thus (1) to assess the accuracy of TE-LSM, for discriminating PSVD from cirrhosis in patients with signs of portal hypertension, and (2) to evaluate the association between histological lesions and TE-LSM, in patients with PVSD.

Patients and Methods

STUDY POPULATION

Patients With PSVD

This retrospective study included all patients with PSVD, signs of portal hypertension, and available TE-LSM having had a liver biopsy in one of four centers. The test cohort included patients with PSVD who underwent a liver biopsy between 2011 and 2019 at Hôpital Beaujon (Clichy, France). The validation cohort included patients who underwent a liver biopsy between 2006 and 2019 at Hôpitaux Universitaires de Genève (Geneva, Switzerland), Hôpital Jean Verdier (Bondy, France), or Hospital Clinic (Barcelona, Spain) (Supporting Fig. S1). The study was approved by our institutional review board (N103006, CPP Ile de France IV, Paris; France) and conformed to the ethical guidelines of the 1975 Declaration of Helsinki. The requirement for informed consent was waived by the institutional review committee. This observational cohort study was designed, conducted, and written following the STROBE guidelines.[23]

Diagnosis of PSVD was based on the criteria proposed by VALDIG.[1] All liver biopsies from patients suspected of having PSVD were reviewed by pathologists and experts in vascular liver diseases (Valérie Paradis, Laura Rubbia-Brandt, and Alba Diaz). Liver biopsy was considered adequate when fulfilling certain criteria (≥20 mm long with ≥10 portal tracts and not too fragmented) or considered adequate for interpretation by an expert pathologist. Extrahepatic conditions associated with PSVD were classified into the following categories: immunological disorders (autoimmune conditions, common variable immune deficiency, history of solid organ transplantation, Crohn's disease), HIV infection, prothrombotic state (myeloproliferative syndrome, heterozygous factor II or V Leiden, or familial history of venous thromboembolism), medication or toxins, or genetic disorders.

Noninclusion criteria were as follows: clinical ascites at the time of liver biopsy because TE-LSM often fails in this context, other causes of portal hypertension (history of bone marrow transplantation, Budd-Chiari/hepatic venous outflow obstruction, portal cavernoma on the day on liver biopsy, hepatic schistosomiasis diagnosed on liver biopsy, cardiac failure, Fontan surgery, Abernethy syndrome, hereditary hemorrhagic telangiectasia, chronic cholestatic diseases, liver infiltration by tumor cells), a previous TIPS, and complete portal vein thrombosis at the time of liver biopsy to rule out prehepatic portal hypertension.

Patients With Cirrhosis

Patients with compensated alcohol-associated cirrhosis were included from the French multicentric CIRRAL cohort.[24] All had histologically proven cirrhosis with a history of excessive alcohol consumption without associated HBV or HCV infection. All had Child-Pugh class A cirrhosis at enrollment, but some

had a previous history of decompensated cirrhosis before enrollment.

Patients with compensated Agence nationale de recherche sur le sida et les hépatites (ANRS) HCV-related cirrhosis were selected from the French ANRS CO12 multicentric prospective CirVir cohort.[25] This study was sponsored and funded by the ANRS. The full CirVir protocol is available on the ANRS website (http://anrs.fr). All of the included patients had biopsy-proven compensated cirrhosis without any history of decompensation before inclusion. For the present analyses, we selected patients with positive HCV RNA at enrollment who did not subsequently achieve sustained virological response within 3 years after enrollment.

Patients with compensated NAFLD-related cirrhosis were included from two French tertiary centers (Hôpital Beaujon, Clichy, and Hôpital la Pitié-Salpêtrière, Paris, France). All had histologically proven cirrhosis with a history of metabolic syndrome or diabetes without associated excessive alcohol consumption, HBV infection, or HCV infection. All had Child-Pugh class A cirrhosis at enrollment, but some had a previous history of decompensated cirrhosis before enrollment.

In these three cohorts, we specifically selected patients with the following criteria: (1) at least one sign of portal hypertension, as proposed by VALDIG[1]; and (2) available TE-LSM using transient elastography performed within 3 years before or after the liver biopsy demonstrating cirrhosis (Supporting Fig. S2).

SIGNS OF PORTAL HYPERTENSION

Signs of portal hypertension were those proposed by VALDIG.[1] Specific signs of portal hypertension included varices (gastric, esophageal, or ectopic), portal hypertensive bleeding, and portosystemic collaterals at imaging. Nonspecific signs of portal hypertension included history of ascites, platelet count < 150×10^9/L, and splenomegaly.

Platelet count was collected within 1 year before or after liver biopsy in all groups of patients. Imaging data were obtained from liver ultrasonography, computed tomography scan, or magnetic resonance imaging performed within 1 year before or after the liver biopsy in all groups of patients. In patients with PSVD and patients with NAFLD-related cirrhosis, imaging data were systematically reviewed to assess portosystemic collaterals and spleen size. Splenomegaly was defined as spleen size ≥ 13 cm in the largest axis. In patients with alcohol-associated or HCV-related cirrhosis, presence of portosystemic collaterals was not available in the CIRRAL and CirVir databases. Splenomegaly was recorded in these databases, although precise spleen size was not available.

"History of ascites" was defined as either radiological ascites or ascites controlled with diuretic therapy.

ENDOSCOPIC DATA

Endoscopic data were recorded on an upper gastrointestinal endoscopy performed within 1 year before or after the liver biopsy and included presence and size of gastroesophageal varices, history of variceal band ligation, or glue. Varices needing treatment were defined as either medium or large esophageal or gastric varices, a history of portal hypertensive bleeding, or a history of variceal band ligation or glue.

LIVER STIFFNESS MEASUREMENT

TE-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 performed within 3 years before or after liver biopsy. TE-LSM was assessed in the right lobe of the liver through the intercostal spaces with the patient in the supine position and the right arm in maximal abduction, with or without requiring imaging guidance, in fasting condition. The median value of 10 successful measurements from the same location was considered to represent liver stiffness. TE-LSM was considered reliable when meeting the manufacturer's recommendations, i.e., interquartile range (IQR)/TE-LSM ≤ 0.30, and ≥10 valid measurements and a success rate ≥60%.[26] In patients with HCV-related cirrhosis, only failure and IQR were available.

DETAILED HISTOLOGICAL ANALYSIS

Hematoxylin and eosin, picrosirius, reticulin, and Perls stained liver biopsies of patients with PSVD from Beaujon Hospital were retrospectively reviewed

by an expert pathologist (Valérie Paradis) unaware of clinical data. The following features were analyzed using a semiquantitative scoring defined *a priori*: portal tract abnormalities according to a recent consensus by an international study group of liver pathologists[22]; liver architecture (nodular pattern); sinusoidal dilatation; perisinusoidal fibrosis; sinusoidal congestion; and centrolobular vein stenosis; lobular inflammation; fibrosis according to Metavir; steatosis; and bile and iron deposits.[1,27]

STATISTICAL ANALYSIS

Results are presented as median (IQR) or absolute number (percentage). Comparisons between quantitative variables were performed using the Mann-Whitney test. Comparisons between categorical variables were performed using the chi-square or Fisher's exact test, when appropriate. The discriminative value of TE-LSM for the identification of PSVD was assessed by measuring the area under the receiver operating characteristic curve (AUROC). AUROCs were provided with their 95% CI. Prespecified TE-LSM values, derived from Baveno VI consensus, were tested to have a high suspicion of PSVD and to rule out PSVD (10 and 20 kPa, respectively).[12] Sensitivity, specificity, and positive and negative predictive values as well as diagnostic accuracy (sum of true negative and positive) were computed for these cutoff values. All tests were two sided, and 0.05 was considered to be significant. Data handling and analysis were performed with SPSS 20.0 (SPSS Inc., Chicago, IL) and GraphPad Prism 5.2.

Results

STUDY POPULATION

Patients With PSVD

Seventy-eight patients with PSVD had available TE-LSM at Beaujon Hospital, including 77 patients with reliable TE-LSM (Supporting Fig. S1), forming the test cohort. Median (IQR) duration between liver biopsy and TE-LSM was 0 (0-3) months. TE-LSM was performed before liver biopsy in 16 (21%) patients, on the same day as liver biopsy in 40 (52%), and after liver biopsy in 21 (27%) (Supporting Fig. S3). Table 1 shows baseline characteristics of patients with PSVD who were included in the test cohort. Sixty-six (86%) patients with PSVD had at least one extrahepatic condition associated with PSVD. Sixty (78%) patients with PSVD had at least one specific sign of portal hypertension, including medium or large varices (35%), history of portal hypertensive bleeding (22%), and/or portosystemic collaterals at imaging (61%). In the other 17 (22%) patients, signs of portal hypertension included platelet count < 150 $\times 10^9$/L (n = 12) and/or splenomegaly (n = 11) and/or history of ascites (n = 2). At least one cause for cirrhosis was found in 13 (17%) patients with PSVD.

Patients With PSVD, Validation Cohort

Seventy-eight patients were included in the validation cohort, from Hôpitaux Universitaires de Genève (n = 10), Hôpital Jean Verdier (n = 18), and Hospital Clinic (n = 50) (Supporting Fig. S1). Characteristics of these patients are detailed in Table 1.

Patients With Cirrhosis

In the CIRRAL cohort, 147 patients with alcohol-associated cirrhosis had signs of portal hypertension and available TE-LSM, including 117 patients with reliable TE-LSM. In the CirVir cohort, 138 patients with HCV-related cirrhosis had signs of portal hypertension and available TE-LSM, including 110 patients with reliable TE-LSM. At Beaujon and Pitié-Salpêtrière Hospitals, 47 patients with histologically proven NAFLD-related cirrhosis had signs of portal hypertension and available TE-LSM, including 46 patients with reliable TE-LSM (Supporting Fig. S2). Although all patients had compensated cirrhosis at the time of enrollment, 58 (51%) patients with alcohol-associated cirrhosis and 7 (16%) of patients with NAFLD-related cirrhosis had a previous history of decompensation of cirrhosis, whereas none of the patients with HCV-related cirrhosis had such an event. Table 2 shows the main characteristics of these patients. Median (IQR) duration between liver biopsy and TE-LSM was 2.4 (0.09-11.4) months in the 273 patients with cirrhosis (Supporting Fig. S3).

TABLE 1. Characteristics of the Patients With PSVD at the Time of the Liver Biopsy Included in the Test Cohort and in the Validation Cohort

Characteristics	Test Cohort (n = 77)	Validation Cohort (n = 80)	*P* Value
Clinical features			
Male sex	40 (52)	51 (65)	0.09
Age (years)	56 (38-66)	49 (41-64)	0.52
Body mass index (kg/m^2)	23.0 (20.0-26.0)	23.9 (21.3-26.3)	0.37
At least one extrahepatic condition associated with PSVD	**66 (86)**	**54 (69)**	**0.014**
Immunological disorder	50 (65)	30 (39)	
HIV infection	3 (4)	14 (18)	
Medication or toxin	10 (13)	12 (15)	
Prothrombotic condition	13 (17)	1 (1)	
Genetic disorder	1 (1)	3 (4)	
At least one other cause of chronic liver disease	13 (17)	18 (23)	0.34
Excessive alcohol consumption*	8 (10)	6 (8)	
Metabolic syndrome and/or diabetes	10 (13)	13 (17)	
Positive anti-HCV antibodies†	3 (4)	4 (5)	
Positive HBs antigen†	0 (0)	3 (4)	
History of ascites‡	21 (27)	15 (19)	0.17
Hepatic encephalopathy	1 (1)	0 (0)	0.30
History of portal hypertensive bleeding	17 (22)	24 (31)	0.22
Medications			
Anticoagulation therapy	12 (16)	7 (9)	0.51
Diuretic therapy	17 (22)	7 (9)	0.02
Beta-blockers	35 (46)	34 (44)	0.22
Endoscopic data§			
Esophageal varices			**0.001**
Absent	**30 (46)**	**12 (23)**	
Small	**12 (19)**	**7 (13)**	
Medium or large or history of variceal band ligation	**23 (35)**	**34 (64)**	
Gastric varices	**12 (19)**	**1 (2)**	**0.007**
Varices needing treatment¶	**32 (49)**	**43 (71)**	**0.02**
Hemodynamic data			
HVPG (mm Hg)	**6 (3-9)**	**8 (5-10)**	**0.05**
Imaging data			
Portosystemic collaterals at imaging	47 (61)	38 (54)	0.12
Spleen size (cm‖)	17 (14-19)	15.4 (13.9-18.0)	0.60
Partial occlusion of the portal venous axis	7 (9)	16 (21)	0.05
Laboratory data			
Hemoglobin (g/dL)	12.5 (10.7-13.7)	12.8 (10.8-14.0)	0.76
White blood cell count (×10^9/L)	4.3 (2.9-6.2)	4.1 (3.2-5.2)	0.72
Platelet count (×10^9/L)	110 (69-169)	109 (69-145)	0.58
Prothrombin index (%)	**94 (71-104)**	**80 (67-95)**	**0.003**
Serum AST (IU/L)	36 (25-53)	34 (24-51)	0.89
Serum ALT (IU/L)	31 (20-48)	31 (19-51)	0.88
Serum ALK (IU/L)	100 (72-163)	106 (72-203)	0.68
Serum GGT (IU/L)	83 (29-139)	61 (36-213)	0.61
Serum bilirubin (μmol/L)	13 (8-22)	14 (9-22)	0.20

TABLE 1. *Continued*

Characteristics	Test Cohort (n = 77)	Validation Cohort (n = 80)	*P* Value
Serum creatinine (μmol/L)	74 (61-87)	72 (60-88)	0.79
Serum albumin (g/L)	**37 (34-40)**	**40 (36-43)**	**0.003**

Data are presented as absolute numbers (%) or median (IQR). Bold indicates significant differences.
*Excessive alcohol consumption was defined according to the World Health Organization criteria (more than 14 glasses per week for women and more than 21 glasses per week for men). In the test cohort, 4 patients had active excessive alcohol consumption and 4 had a history of excessive alcohol consumption. In the validation cohort, 3 patients had active excessive alcohol consumption and 4 had a history of excessive alcohol consumption.
†In the test cohort, all 3 patients had undetectable HCV RNA. In the validation cohort, 1 patient had positive HCV RNA and 3 had negative HCV RNA. All 4 patients with positive HBs antigen had undetectable HBV DNA.
‡History of ascites was defined as either radiological ascites or ascites controlled with diuretics either before liver biopsy or at the time of liver biopsy.
§Upper gastrointestinal endoscopy was performed within 1 year before/after liver biopsy in 65/77 patients with PSVD in the test cohort and in 53/78 patients in the validation cohort.
¶Varices needing treatment were defined as either medium or large varices, and/or a history of variceal bleeding, and/or a history of variceal band ligation or glue. These data were available in 65/77 patients with PSVD in the test cohort and in 61/78 patients in the validation cohort
‖5/77 patients in the test cohort and 5/78 patients in the validation cohort had a history of splenectomy.
Abbreviations: ALK, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase.

DIAGNOSTIC ACCURACY OF LIVER STIFFNESS MEASUREMENT FOR DISCRIMINATING PSVD FROM CIRRHOSIS

Test Cohort

Patients with PSVD had lower TE-LSM (7.9 [6.2-11.6] kPa) than patients with alcohol-associated cirrhosis (33.8 [21.3-62.7] kPa), patients with HCV-related cirrhosis (18.2 [13.9-26.7] kPa), and patients with NAFLD-related cirrhosis (33.6 [19.1-48.9] kPa) ($P < 0.001$ for all three comparisons) (Fig. 1). AUROC (95% CI) of TE-LSM for the diagnosis of PSVD was 0.93 (0.90-0.97) when compared with patients with alcohol-associated cirrhosis, 0.88 (0.83-0.93) when compared with patients with HCV-related cirrhosis, and 0.95 (0.91-0.98) when compared with patients with NAFLD-related cirrhosis.

Fifty (65%) patients with PSVD had TE-LSM < 10 kPa. A cutoff value of 10 kPa had a specificity of 96%, 95%, and 100% for the diagnosis of PSVD as compared with patients with alcohol-associated, HCV-related, and NAFLD-related cirrhosis, respectively (Table 3; Fig. 2). Using this cutoff value, 4 (3%) patients with alcohol-associated cirrhosis, 5 (3%) patients with compensated HCV-related cirrhosis, and none of the patients with NAFLD-related cirrhosis would have been falsely diagnosed as PSVD. The main characteristics of these 9 patients are detailed in Supporting Table S1. The 5 patients with specific signs of portal hypertension only had small-size esophageal varices, without any history of portal hypertensive bleeding or band ligation. Liver biopsy was either fragmented and/or <10 mm length in 4 patients. All 4 patients with alcohol-associated cirrhosis stopped or strongly reduced alcohol consumption between liver biopsy and TE-LSM (2 to 28 month interval).

A cutoff value of 20 kPa had a sensitivity of 93%, 94%, and 94% for ruling out the diagnosis of PSVD in patients with signs of portal hypertension as compared with patients with alcohol-associated, HCV-related, and NAFLD-related cirrhosis, respectively (Table 3; Fig. 2). Using this cutoff value, 5 (6%) patients with PSVD would have been falsely diagnosed as having cirrhosis. The characteristics of these 5 patients are detailed in Table 4 and Supporting Fig. S4. At least one extrahepatic condition associated with PSVD and a cause for cirrhosis was present in 3 and 4 out of the 5 patients, respectively.

The discriminant capacity of TE-LSM was even clearer when restricting the analysis to patients in whom TE-LSM was performed within 1 year before or after liver biopsy (Table 5), patients with varices needing treatment (Supporting Table S2), and patients with PSVD without any cause for cirrhosis (Supporting Table S3). The discriminant capacity of TE-LSM remained excellent when restricting the analysis to patients in whom TE-LSM was

TABLE 2. Characteristics of the Patients With PSVD as Compared With Those of Patients With Cirrhosis

Variable	PSVD (n = 77)	Alcohol-Associated Cirrhosis (n = 117)	*P* Value Alcohol vs. PSVD	HCV-Related Cirrhosis (n = 110)	*P* Value HCV vs. PSVD	NAFLD-Related Cirrhosis (n = 46)	*P* Value NAFLD vs. PSVD
Age (years)	56 (38-66)	57 (50-63)	0.30	53 (46-62)	0.71	61 (51-66)	0.05
Male sex	40 (52)	83 (71)	0.007	67 (61)	0.22	27 (59)	0.47
Body mass index (kg/m^2)	23.0 (20.0-26.0)	26.3 (23.5-29.4)	<0.001	25.5 (22.7-28.6)	0.001	28.4 (25.7- 34.6)	<0.001
Medium or large esophageal varices or history of variceal band ligation*	29 (45)	28 (31)	0.07	22 (30)	0.07	8 (28)	0.34
Gastric varices	12 (19)	3 (3)	0.001	3 (4)	0.004	0 (0)	0.2
Varices needing treatment‡	32 (49)	28 (31)	0.02	22 (30)	0.02	8 (28)	0.05
History of ascites	21 (27)	41 (35)	0.24	0 (0)	<0.001	7 (16)	0.09
Splenomegaly†	58 (75)	47 (48)	<0.001	47 (48)	<0.001	38 (83)	0.61
Platelet count (×10^9/L)	110 (69-169)	129 (91-173)	0.04	110 (87-113)	0.97	141 (90-168)	0.01
Prothrombin index (%)	94 (71-104)	76 (67-90)	<0.001	87 (79-96)	0.24	85 (75-95)	0.17
Serum bilirubin (μmol/L)	13 (8-22)	14 (10-22)	0.39	13 (10-18)	0.85	12 (9-25)	0.56

Comparisons between quantitative variables were made using Mann-Whitney test. Comparisons between qualitative variables were made using chi-square test. Results are presented as median (IQR) or number (%).
*The presence of esophageal varices was available in 91/117 patients with alcohol-associated cirrhosis, 74/110 patients with HCV-related cirrhosis, and 29/46 patients with NAFLD-related cirrhosis.
†Data on splenomegaly were available in 72/77 patients with PSVD (because 5 patients with PSVD had a history of splenectomy), 98/117 patients with alcohol-related cirrhosis, 98/110 patients with HCV-related cirrhosis, and 44/46 patients with NAFLD-related cirrhosis.
‡Varices needing treatment were defined as either medium or large varices, and/or a history of variceal bleeding, and/or a history of variceal band ligation or glue.

performed on the day of diagnostic liver biopsy or after (Supporting Table S4).

In the test cohort, TE-LSM did not significantly differ between patients with PSVD with a cause of cirrhosis (n = 13) and those without (n = 64) (9.4 vs. 7.4 kPa, respectively; P = 0.9), nor between patients with PSVD with metabolic syndrome (n = 10) and those without (n = 67) (9.9 vs. 7.3 kPa, respectively; P = 0.3), nor between patients with PSVD with excessive alcohol consumption (n = 8) and those without (n = 69) (7.9 vs. 7.1 kPa, respectively; P = 0.3).

Validation Cohort

Patients with PSVD included in the validation cohort had lower TE-LSM (7.9 [5.6-10.5] kPa) than patients with alcohol-associated, HCV-related, and NAFLD-related cirrhosis (P < 0.001 for all three comparisons) (Fig. 1). AUROC of TE-LSM for the diagnosis of PSVD was 0.95 (0.92-0.98) when compared with patients with alcohol-associated cirrhosis, 0.91 (0.86-0.95) when compared with patients with HCV-related cirrhosis, and 0.97 (0.94-0.99) when compared with patients with NAFLD-related cirrhosis.

A cutoff value of 10 kPa had a specificity of 97%, 96%, and 100% for the diagnosis of PSVD as compared with patients with alcohol-associated, HCV-related, and NAFLD-related cirrhosis, respectively (Fig. 2; Supporting Table S5).

A cutoff value of 20 kPa had a sensitivity of 96% for PSVD in patients with signs of portal hypertension as compared with either patients with alcohol-associated, HCV-related, or NAFLD-related cirrhosis (Fig. 2; Supporting Table S5). Using this cutoff value, 3 (4%) patients with PSVD would have been falsely diagnosed as having cirrhosis. Among these 3 patients,

2 had a cause for cirrhosis, i.e., a past history of alcohol consumption in one and a metabolic syndrome in the other. The characteristics of these 3 patients are detailed in Supporting Table S6.

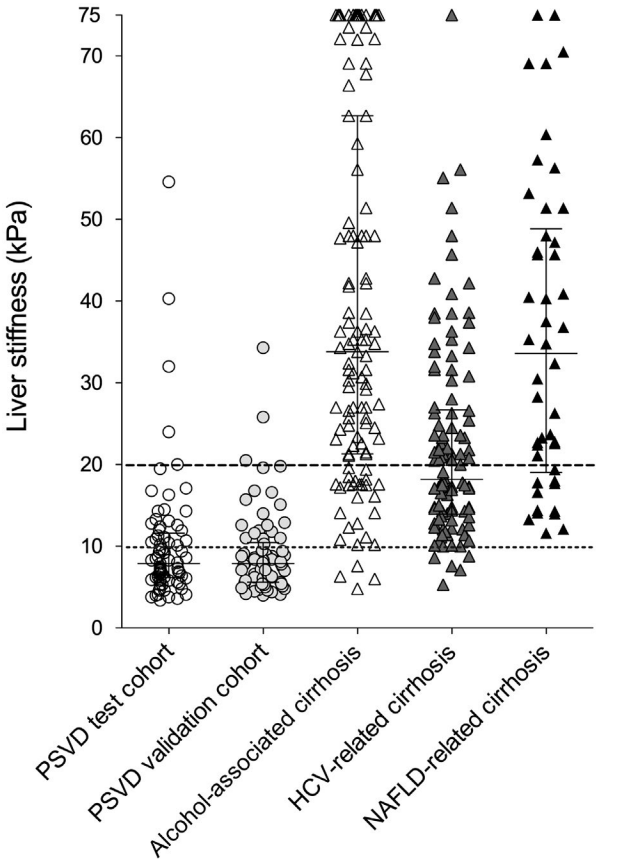

FIG. 1. Liver stiffness using transient elastography in patients with PSVD (test cohort, n = 77, white circle; validation cohort, n = 78, light gray circle), alcohol-associated cirrhosis (n = 117, white triangle), and HCV-related cirrhosis (n = 110, gray triangle), and NAFLD-related cirrhosis (n = 46, black triangle).

In the validation cohort, TE-LSM was significantly higher in patients with a cause for cirrhosis (n = 18) than in those without (n = 60) (8.9 vs. 7.6 kPa; P = 0.02) and in patients with excessive alcohol consumption (n = 9) than in those without (n = 69) (11.8 vs. 7.8 kPa; P = 0.03) but did not differ between patients with (n = 13) and without (n = 65) metabolic syndrome (8.9 vs. 7.8 kPa; P = 0.09).

ASSOCIATION BETWEEN TE-LSM AND HISTOLOGICAL FEATURES OF PSVD

We then evaluated liver histological lesions associated with TE-LSM in patients with PSVD. We observed that portal venules stenosis, remnant portal tracts, hypervascularized portal tracts, perisinusoidal fibrosis, centrilobular vein stenosis, lobular inflammation and portal fibrosis were associated with higher TE-LSM. TE-LSM was slightly lower in patients with herniated portal vein (Fig. 3; Supporting Fig. S5). Portal venules stenosis, hypervascularized portal tracts, perisinusoidal fibrosis, lobular inflammation, and portal fibrosis were significantly associated with TE-LSM ≥ 10 kPa (Supporting Table S7). Other lesions were not associated with TE-LSM. None of the patient had iron or bile deposition.

Discussion

Despite the rarity of PSVD, the present study, joining the efforts of four reference centers for vascular liver disease, was able to include a large number of patients with PSVD with portal hypertension. This allowed for identifying thresholds of TE-LSM useful for routine

TABLE 3. Performance of TE-LSM for the Diagnosis of Patients With PSVD and Signs of Portal Hypertension

	Cutoff Value	Number of Patients With PSVD	Patients Without PSVD	Se (%)	Sp (%)	PPV (%)	NPV (%)	Well-Classified (n)	Diagnostic Accuracy (%)
PSVD (n = 77) vs. alcohol-associated cirrhosis (n = 117)	Rule-in <10 kPa	50	4	65	97	93	81	163	84
	Rule-out >20 kPa	5	90	94	77	73	95	162	84
PSVD (n = 77) vs. HCV-related cirrhosis (n = 110)	Rule-in <10 kPa	50	5	65	96	91	80	155	83
	Rule-out >20 kPa	5	53	94	48	56	91	125	67
PSVD (n = 77) vs. NAFLD-related cirrhosis (n = 46)	Rule-in <10 kPa	50	0	65	100	100	63	96	78
	Rule-out >20 kPa	5	34	94	74	86	88	106	86

Abbreviations: HCV, hepatitis C virus; NPV, negative predictive value; PPV, positive predictive value; Se, sensitivity; Sp, specificity.

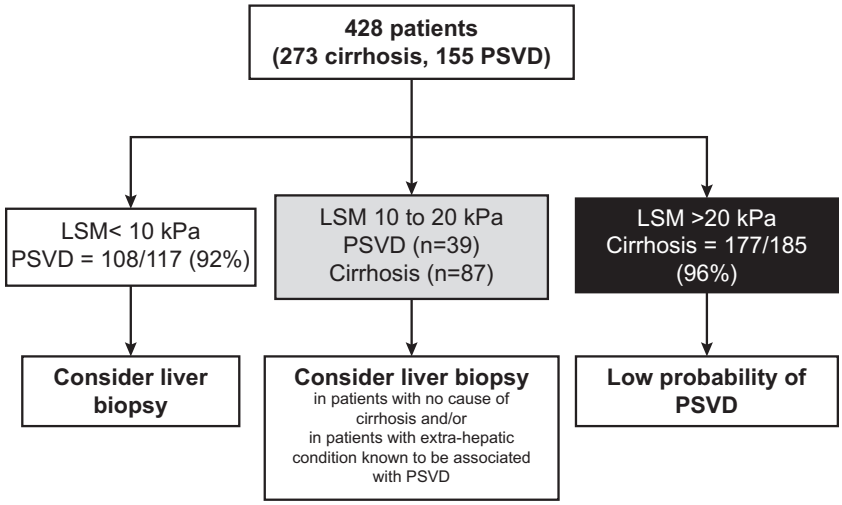

FIG. 2. Proposed algorithm to consider PSVD according to TE-LSM value. Abbreviation: LSM, liver stiffness measurement.

clinical practice. In patients with signs of portal hypertension, TE-LSM below 10 kPa strongly suggests PSVD; therefore, a biopsy should be performed to fully establish this diagnosis. Conversely, when TE-LSM is above 20 kPa, the probability of PSVD is very low.

The first major finding of the present study was that TE-LSM below 10 kPa, strongly suggests PSVD in patients with signs of portal hypertension and should prompt physicians to perform a liver biopsy. Small series reported low TE-LSM in patients with PSVD, but no threshold with a good sensitivity for the diagnosis of PSVD had been identified.[18-21,28,29] The present study was able to fill this gap in knowledge thanks to the inclusion of 3 large groups of patients with biopsy-proven compensated cirrhosis with signs of portal hypertension. Our results were confirmed in a validation cohort of 78 patients with PSVD. Although TE-LSM varies according to causal factors in patients with cirrhosis, the 10 kPa threshold was found to accurately discriminate PSVD from alcohol-associated, HCV-related, and NAFLD-related cirrhosis.[30-32] Although in this study all patients with PSVD and cirrhosis had signs of portal hypertension, patients with PSVD more commonly had medium or large varices. Because TE-LSM correlates with the severity of portal hypertension in patients with cirrhosis,[10,33] we can speculate that having matched patients with PSVD and cirrhosis on the severity of portal hypertension would have increased the differences in TE-LSM values between the two groups, thus reinforcing our conclusions. Because of its retrospective design, this study has potential selection bias, including the fact that some patients were referred to expert centers because of low TE-LSM contrasting with signs of portal hypertension. However, when restricting the analysis to patients in whom TE-LSM was performed on the same day or after liver biopsy did not change our results.

Despite the 93% to 96% specificity of TE-LSM < 10 kPa for the diagnosis of PSVD observed here, TE-LSM < 10 kPa should not deter from performing a liver biopsy to rule out cirrhosis. Indeed, the prevalence of cirrhosis is much higher than that of PSVD in the general population as well as among unselected patients with portal hypertension. Thus, we cannot exclude that a spectrum effect may negatively impact the performance of TE-LSM for discriminating PSVD from cirrhosis in a real-life setting.[34] Second, this threshold only applies to patients with clinical, laboratory, or radiological signs of portal hypertension and not to suspect PSVD without portal hypertension. Other noninvasive strategies, including TE-LSM together with other variables, like spleen size and platelet count, such as

TABLE 4. Characteristics of the 5 Patients With PSVD and Liver Stiffness Measurement Over 20 kPa Using Fibroscan

Patient Number	LSM (IQR) (kPa)	Age (Years)	Liver Histology	Presence of a Cause for Cirrhosis	Extrahepatic Condition Associated With PSVD	Specific Signs of Portal Hypertension	Nonspecific Signs of Portal Hypertension
3	32.0 (5.4)	51	Nodular regenerative hyperplasia Severe sinusoidal dilatation Mild perisinusoidal fibrosis Sinusoidal congestion Severe lobular inflammation Portal fibrosis with few septa	None	Common variable immunodeficiency	None	History of ascites
8	20.0 (0.8)	59	Incomplete portal venules stenosis Hypervascularized portal tracts Mild sinusoidal dilatation Portal fibrosis with few septa	Cured HCV infection	Myeloproliferative neoplasm	History of portal hypertensive bleeding	Thrombocytopenia (94×10^9/L) Splenomegaly
25	40.3 (8.1)	69	Complete portal venules stenosis Mild sinusoidal dilatation Mild perisinusoidal fibrosis Mild lobular inflammation Intrasinusoidal lymphocytes	Metabolic syndrome	History of kidney transplantation	Large esophageal varices	Thrombocytopenia (85×10^9/L) Splenomegaly Radiological ascites
63	54.6 (10.7)	63	Portal venules stenosis, portal spaces remnants, severe sinusoidal dilatation Mild perisinusoidal fibrosis Sinusoidal congestion Portal fibrosis with few septa	Excessive alcohol consumption (ongoing)	HIV infection	None	Thrombocytopenia (106×10^9/L) Radiological ascites
96	24.0 (2.1)	38	Portal spaces remnants Hypervascularized portal tracts Mild sinusoidal dilatation Portal fibrosis with few septa Mild sinusoidal dilatation	None	None	History of portal hypertensive bleeding	Thrombocytopenia (134×10^9/L) Splenomegaly Ascites controlled with diuretic

Abbreviation: LSM, liver stiffness measurement.

LSPS, may be even more accurate to discriminate PSVD from cirrhosis and will deserve future studies.

In the present study, 9 (4%) patients with cirrhosis had TE-LSM < 10 kPa despite the presence of signs of portal hypertension. However, individual analysis of the characteristics of these 9 patients showed that they had signs either nonspecific for portal hypertension (thrombocytopenia, splenomegaly) or only small-sized esophageal varices. Thrombocytopenia and splenomegaly are frequently found in patients with HCV-related cirrhosis, even in the absence of clinically significant portal hypertension.[35] Thrombocytopenia can be observed in patients with excessive alcohol consumption, even in the absence of cirrhosis.[36] Interobserver variability between an absence and a small size of esophageal varices is high.[37] Thus, we cannot exclude that these patients with cirrhosis and TE-LSM < 10 kPa in fact did not have portal hypertension. Although in 4 out of these 9 patients, liver biopsy was <10 mm long or fragmented, misdiagnosis of cirrhosis is unlikely because the positive predictive value of liver biopsy for the diagnosis of cirrhosis is excellent, even in small specimens.[38,39]

The second major finding of this study was that a cutoff value of 20 kPa was excellent to rule out PSVD. This result indicates that PSVD is very unlikely if TE-LSM is above 20 kPa, especially when a cause of cirrhosis is present. However, genuine PSVD was observed in 5 (6%) patients with TE-LSM > 20 kPa in the test cohort, including 4 with an extrahepatic condition known to be associated with PSVD and 3 with a possible cause for cirrhosis; similar results were observed in the validation cohort. Based on our systematic histological review, histological lesions that may account for a higher liver stiffness included portal venules stenosis in 3 patients and lobular inflammation in 2 patients. These cases indicate that TE-LSM above 20 kPa does not formally exclude PSVD, particularly in the context of an extrahepatic condition known to be associated with PSVD or in the absence of cause of cirrhosis.

Twenty-two (28%) patients with PSVD in the test cohort (17 [22%] in the validation cohort) had TE-LSM between 10 and 20 kPa, including 21 with an extrahepatic condition known to be associated with PSVD and 2 with a possible cause for cirrhosis. These results show that PSVD can be present in patients with signs of portal hypertension and a TE-LSM between 10 and 20 kPa, especially in the absence of any cause for cirrhosis and/or in the presence of an extrahepatic condition known to be associated with PSVD. A diagnostic liver biopsy should thus be considered in this setting.

Because 93% of the patients with PSVD and signs of portal hypertension had TE-LSM < 20 kPa, including a high proportion of patients with varices needing treatment, another consequence of the present study is that Baveno VI criteria[12,17] should not be used in patients with PSVD, and gastrointestinal endoscopy is needed in that population.

This study also allowed us to identify histological features influencing TE-LSM. Some features, including portal fibrosis, lobular inflammation, and perisinusoidal fibrosis were expected because they are well-known to increase TE-LSM in other liver

TABLE 5. Performance of TE-LSM for the Diagnosis of PSVD in Patients With Signs of Portal Hypertension and in Whom Liver Stiffness Measurement Was Performed Within 1 Year Before or After Liver Biopsy

	Cutoff Value	Number of Patients With PSVD	Patients Without PSVD	Se (%)	Sp (%)	PPV (%)	NPV (%)	Well-Classified (n)	Diagnostic Accuracy (%)
PSVD (n = 71) vs. alcohol-associated cirrhosis (n = 84)	Rule-in <10 kPa	46	2	65	98	96	77	128	83
	Rule-out >20 kPa	4	66	94	79	79	94	133	86
PSVD (n = 71) vs. HCV-related cirrhosis (n = 87)	Rule-in <10 kPa	46	3	65	97	94	77	130	82
	Rule-out >20 kPa	4	37	94	43	57	90	104	66
PSVD (n = 71) vs. NAFLD-related cirrhosis (n = 38)	Rule-in <10 kPa	46	0	65	100	100	60	84	77
	Rule-out >20 kPa	4	28	94	74	87	88	95	87

Abbreviations: HCV, hepatitis C virus; NPV, negative predictive value; PPV, positive predictive value; Se, sensitivity; Sp, specificity.

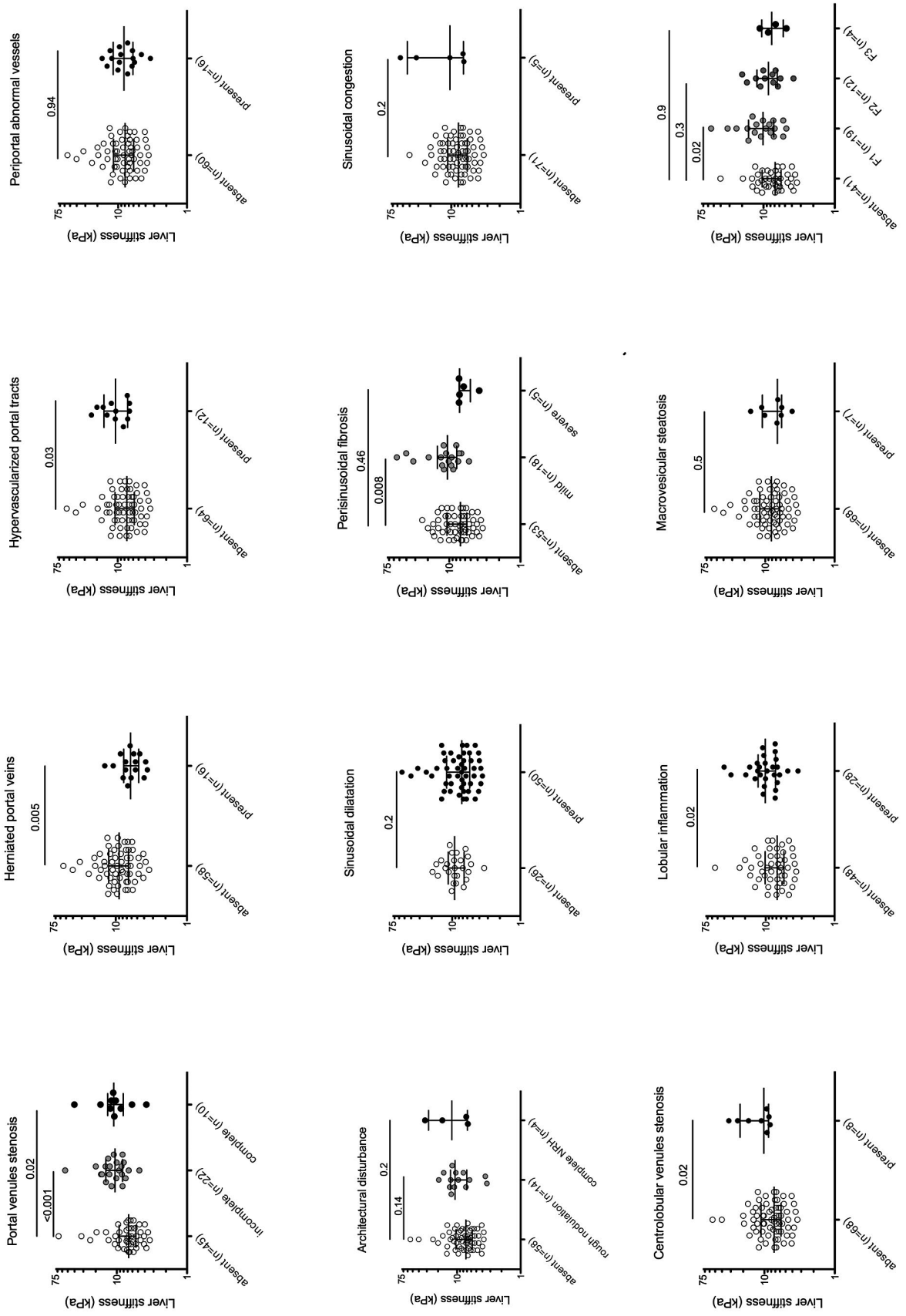

FIG. 3. Liver stiffness value according to histological lesions in 76 patients with PVSD. Portal fibrosis was graded according to Metavir: F0: no fibrosis (n = 41), F1: portal fibrosis (n = 19), F2: portal fibrosis with few septa (n = 12), and F3: bridging fibrosis (n = 4). Liver biopsy from 1 out of the 77 patients from Beaujon Hospital was available for ensuring adequacy for inclusion in the study but then could not be obtained when the detailed review of pathological features was carried out.

diseases.[30,40-42] However, liver vascular changes, including portal venule stenosis and centrilobular vein stenosis, also appeared as major histological determinants for TE-LSM. We can speculate that hyperarterialization, known to be associated with portal vein and hepatic vein obstruction, could account for this mild increase, as arterial hypertension seems to be.[43] In cirrhosis, the association between TE-LSM and the degree of portal hypertension as well as with patients' outcomes has been well-established.[13] The prognostic value of these histological lesions as well as TE-LSM in patients with PVSD need to be evaluated in further longitudinal studies. Importantly, in the present study, we could not evaluate whether TE-LSM can discriminate patients with PSVD from those with regression of cirrhosis following control of the cause for cirrhosis. Thanks to therapeutic advances, this situation is increasingly frequently observed. Discriminating PSVD from regressive cirrhosis can be challenging because histological features of PSVD include incomplete septal cirrhosis, an entity observed following regression of cirrhosis.[44] In addition, regression of cirrhosis is accompanied by a decrease in TE-LSM, frequently below 10 kPa.[45] Future studies will be needed to determine whether TE-LSM can help distinguish PSVD from regressive cirrhosis.

In conclusion, in patients with clinical, laboratory, endoscopic, or imaging signs of portal hypertension, TE-LSM has excellent performance to discriminate PSVD from cirrhosis. Patients with such signs of portal hypertension and TE-LSM below 10 kPa are likely to have PSVD, especially in the absence of cause for cirrhosis.

Author Contributions: Concept and design of the study: LE, PER Acquisition of the data : ML, LE, VP, LRB, AD, VR, LM; LB, JCN, M Magaz, M Malphettes Analysis and interpretation of the data: LE, ML, PER, CC, EA Writing the article, LE, ML, PER Critical revision of the article for important intellectual content and final approval: SC, VP, LRB, AP, LC, DV, PN, NG, JCGP, VR, FD.

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Supporting Information

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep.31688/suppinfo.