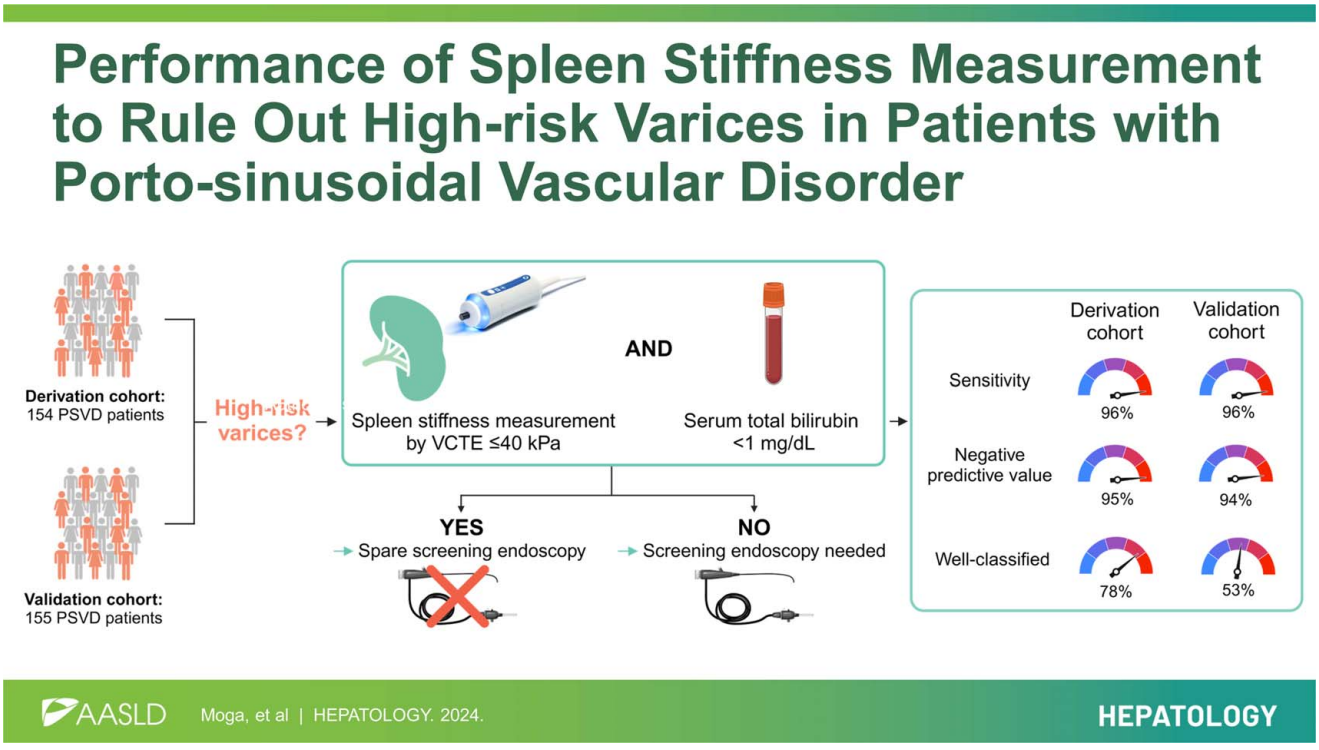
Performance of spleen stiffness measurement to rule out high-risk varices in patients with porto-sinusoidal vascular disorder

VISUAL ABSTRACT



Received: 7 March 2024 | Accepted: 26 May 2024

DOI: 10.1097/HEP.0000000000001004

ORIGINAL ARTICLE

Performance of spleen stiffness measurement to rule out high-risk varices in patients with porto-sinusoidal vascular disorder

Lucile Moga[1,2] | Valérie Paradis[2,3] | Joel Ferreira-Silva[4,5] | Koushik Gudavalli[6] | Federica Indulti[7] | Elton Dajti[8,9] | Oana Nicoara-Farcau[10,11] | Giulia Tosetti[12] | Antonina Antonenko[13] | Andreea Fodor[10] | Judit Vidal-González[14] | Laura Turco[15] | Francisco Capinha[16] | Laure Elkrief[17] | Teresa Monllor-Nunell[18] | Odile Goria[19] | Lorenz Balcar[20] | Adrien Lannes[21] | Vincent Mallet[22] | Armelle Poujol-Robert[23] | Dominique Thabut[24,25] | Pauline Houssel-Debry[26] | Yu Jun Wong[27,28] | Maxime Ronot[29] | Valérie Vilgrain[29] | Sai Prasanth Rampally[6] | Audrey Payancé[1,2] | Laurent Castera[2,30] | Thomas Reiberger[20] | José Ferrusquía-Acosta[18] | Carlos Noronha Ferreira[16] | Giovanni Vitale[15] | Macarena Simon-Talero[14] | Bogdan Procopet[10] | Annalisa Berzigotti[13] | Riccardo Caccia[12] | Fanny Turon[31] | Filippo Schepis[7] | Federico Ravaioli[8,9] | Antonio Colecchia[7] | Arun Valsan[6] | Guilherme Macedo[4,5] | Aurélie Plessier[1,2] | Pierre-Emmanuel Rautou[1,2] | on behalf of the ERN RARE-LIVER; a study of VALDIG, an EASL consortium

[1]Service d'Hépatologie, AP-HP, Hôpital Beaujon, DMU DIGEST, Centre de Référence des Maladies Vasculaires du Foie, FILFOIE, ERN RARE-LIVER, Clichy, France

[2]Centre de recherche sur l'inflammation,Université Paris-Cité, Inserm, Paris, France

[3]Département d'Anatomie Pathologique, Hôpital Beaujon, Clichy, France

[4]Gastroenterology Department, Centro Hospitalar e Universitário de São João, Porto, Portugal

[5]Faculdade de Medicina da Universidade do Porto, Porto, Portugal

[6]Hepatology and Transplantation Unit, Department of Gastroenterology, Amrita Institute of Medical Sciences, Kochi, Kerala, India

[7]Gastroenterology Unit, CHIMOMO Department, University Hospital of Modena, University of Modena & Reggio Emilia, Modena, Italy

[8]Division of Internal Medicine, Hepatobiliary and Immunoallergic Diseases, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy

[9]Department of Medical and Surgical Sciences (DIMEC), University of Bologna, Bologna, Italy

[10]Department of Hepatology, University of Medicine and Pharmacy "Iuliu Hatieganu", 3rd Medical Clinic and Regional Institute of Gastroenterology and Hepatology "Prof. Dr. Octavian Fodor", Cluj-Napoca, Romania

[11]Hepatic Hemodynamic Department, Liver Unit, Hospital Clinic, University of Barcelona, IDIBAPS, Barcelona, Spain

[12]Division of Gastroenterology and Hepatology, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy

[13]Department of Visceral Surgery and Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

[14]Liver Unit, Digestive Diseases Department, Vall d'Hebron University Hospital, Vall d'Hebron Institute of Research (VHIR), Vall d'Hebron Barcelona Hospital Campus, Universitat Autònoma de Barcelona, CIBERehd, Barcelona, Spain

[15]Internal Medicine Unit for the Treatment of Severe Organ Failure, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy

[16]Serviço de Gastrenterologia e Hepatologia, Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte, Lisboa, Portugal

[17]Service d'Hépato-Gastro-Entérologie, CHRU de Tours-Hôpital Trousseau, Faculté de Médecine de Tours, Tours, France

[18]Liver Unit, Hospital Universitari Parc Taulí, Institut d'Investigació i Innovació Parc Taulí (I3PT), Sabadell, Spain

[19]Service d'Hépatogastroentérologie et Oncologie digestive, Hôpital Charles Nicolle-CHU de Rouen, Rouen, France

[20]Department of Internal Medicine III, Division of Gastroenterology and Hepatology, Medical University of Vienna, Vienna, Austria

[21]Hépatogastro-entérologie et oncologie digestive, CHU Angers, Angers, France

[22]Service de Maladies du Foie, Groupe hospitalier Cochin-Port Royal, Assistance Publique-Hôpitaux de Paris, Université Paris Cité, Paris, France

[23]Department of Hépatologie, Hôpital Saint-Antoine-Assistance Publique-Hôpitaux de Paris, Paris, France

[24] Department of Hepatogastroenterology, Hôpital Pitié Salpêtrière-Assistance Publique-Hôpitaux de Paris, Liver Intensive Care Unit, Paris, France

[25]Centre de recherche Saint-Antoine, Inserm, Sorbonne Université, Paris, France

[26]Hôpital Pontchaillou-CHU de Rennes, Centre hépato-digestif-Maladies du foie, Rennes, France

[27]Department of Gastroenterology & Hepatology, Changi General Hospital, SingHealth, Singapore

[28]Duke-NUS Medical School, Singapore

[29]Department of Radiology, Beaujon Hospital, GHU AP-HP Nord-Université Paris Cité, Clichy, France

[30]Service d'Hépatologie, AP-HP, Hôpital Beaujon, Clichy, France

[31]Liver Unit, Hospital Clinic, IDIBAPS, CIBERehd, Barcelona, Spain

Correspondence
Pierre-Emmanuel Rautou, Service d'Hépatologie, Hôpital Beaujon, 100, Boulevard du Général Leclerc, Clichy 92110, France.
Email: pierre-emmanuel.rautou@inserm.fr

Abstract

Background and Aims: Baveno VII consensus suggests that screening endoscopy can be spared in patients with compensated cirrhosis when spleen stiffness measurement (SSM) by vibration-controlled transient elastography (VCTE) is $\leq$40 kPa as they have a low probability of high-risk varices (HRV). Conversely, screening endoscopy is required in all patients with porto-sinusoidal vascular disorder (PSVD). This study aimed to evaluate the performance of SSM-VCTE to rule out HRV in patients with PSVD and signs of portal hypertension.

Approach and Results: We retrospectively included patients with PSVD, $\geq$1 sign of portal hypertension, without a history of variceal bleeding, who underwent an SSM-VCTE within 2 years before or after an upper endoscopy in 21 VALDIG centers, divided into a derivation and a validation cohort. One hundred fifty-four patients were included in the derivation cohort; 43% had HRV. By multivariable logistic regression analysis, SSM-VCTE $>$40 kPa and serum bilirubin $\geq$1 mg/dL were associated with HRV. SSM-VCTE $\leq$40 kPa combined with bilirubin $<$1 mg/dL had a sensitivity of 96% to rule out HRV and could spare 38% of screening endoscopies, with 4% of HRV missed, and a 95% negative predictive value. In the validation cohort, including 155 patients, SSM combined with bilirubin could spare 21% of screening endoscopies, with 4% of HRV missed and a 94% negative predictive value.

Conclusions: This study gathering a total of 309 patients with PSVD showed that SSM-VCTE $\leq$40 kPa combined with bilirubin $<$1 mg/dL identifies patients with PSVD and portal hypertension with a probability of HRV $<$5%, in whom screening endoscopy can be spared.

Abbreviations: 2D-SWE, two-dimensional shear wave elastography; cACLD, compensated advanced chronic liver disease; HRV, high-risk varices; LPSP, liver stiffness – spleen diameter to platelet ratio score; LSM, liver stiffness measurement; NSBB, nonselective beta-blockers; PSVD, porto-sinusoidal vascular disorder; SSM, spleen stiffness measurement; VCTE, vibration-controlled transient elastography.

Preliminary data were presented at the International Liver Congress in Vienna in June 2023.

Supplemental Digital Content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's website, www.hepjournal.com.

INTRODUCTION

Porto-sinusoidal vascular disorder (PSVD) is a broad clinicopathological entity encompassing several overlapping histological patterns (nodular regenerative hyperplasia, obliterative portal venopathy, hepatoportal sclerosis, and incomplete septal cirrhosis) and clinical entities (noncirrhotic portal fibrosis, idiopathic portal hypertension, and noncirrhotic intrahepatic portal hypertension). All these entities are characterized by vascular alterations in the porto-sinusoidal region and potential development of portal hypertension in the absence of cirrhosis and of obstructive PVT.[1] PSVD is an underrecognized and often misdiagnosed entity. The diagnosis can only be made with a liver biopsy interpreted by an expert pathologist since analysis of histological lesions is challenging.[2] The main complications of PSVD include portal hypertensive bleeding and the development of PVT. There is currently no medical therapy specifically approved for PSVD that has shown beneficial effects on its natural history. Management is restricted to the treatment of portal hypertension and its complications. Importantly, the presence of clinical signs of portal hypertension critically determines the outcome of patients with PSVD.[3]

Noninvasive tests for liver fibrosis and portal hypertension have been widely studied in patients with cirrhosis. Liver stiffness measurement (LSM) by vibration-controlled transient elastography (VCTE) can be used to rule in clinically significant portal hypertension (ie, HVPG $\geq$10 mm Hg, risk of endoscopic signs of portal hypertension, and higher risk of decompensation) in patients with compensated advanced chronic liver disease (cACLD),[4] with a cutoff of 25 kPa, since LSM by VCTE correlates well with HVPG.[5] In patients with cACLD, spleen stiffness also seems an excellent surrogate of portal hypertension: spleen stiffness measurement (SSM) by VCTE accurately rules in and rules out an HVPG $\geq$10 mm Hg and estimates the size of esophageal varices.[6,7] SSM not only reflects increased hepatic resistance due to liver fibrosis but also portal blood inflow congestion and presinusoidal vasoconstriction, unlike LSM.[8] A recent individual patient data meta-analysis showed that combining LSM, SSM, and platelet count can substantially reduce the diagnostic gray zone for clinically significant portal hypertension in patients with cACLD.[9] SSM could even be superior to LSM in assessing portal hypertension, particularly in detecting dynamic changes.[10,11] Moreover, according to the Baveno VII consensus, SSM by VCTE $\leq$40 kPa can be used to identify patients with cACLD in whom screening endoscopy can be safely spared,[12] since they have a very low probability of having high-risk varices (HRV), defined as $<$5%.[13]

Patients with PSVD and portal hypertension usually have liver stiffness values much lower than those with cirrhosis; thus, cutoffs for clinically significant portal hypertension and HRV established in patients with cirrhosis cannot be used in this population.[14] Endoscopic screening for varices is consequently always required when diagnosing PSVD.[12] Data on SSM by VCTE in patients with PSVD are scarce,[15,16] and whether SSM could spare screening endoscopies in patients with PSVD is currently unknown. This study aimed to evaluate the performance of SSM by VCTE to rule out HRV in patients with PSVD.

METHODS

Derivation cohort

This retrospective study included all patients with PSVD with at least 1 sign of portal hypertension present at the time of diagnosis, who underwent a liver biopsy between 2012 and 2023 at Hôpital Beaujon (Clichy, France), and for whom SSM by VCTE using FibroScan (Echosens) was available during follow-up. Diagnosis of PSVD with signs of portal hypertension was based on the VALDIG criteria, as stated in the Baveno VII consensus: exclusion of cirrhosis and other causes of portal hypertension associated with (i) at least 1 feature specific for portal hypertension (varices, history of portal hypertensive bleeding, and/or portosystemic collaterals at imaging); or (ii) at least 1 feature not specific for portal hypertension (ascites, platelet count $<$150,000/mm^3, and/or spleen size $\geq$13 cm in the largest axis) together with 1 histologic lesion specific or suggestive although not specific for PSVD (Supplemental Table S1, http://links.lww.com/HEP/I542).[12] All liver biopsies were analyzed by a pathologist with expertise in vascular liver diseases (Valérie Paradis).

Noninclusion criteria were a history of variceal bleeding, other causes of portal hypertension (Budd-Chiari syndrome, cardiac insufficiency, Fontan surgery, hereditary hemorrhagic telangiectasia, congenital portosystemic shunts, history of bone marrow transplantation, chronic cholestatic disease, liver infiltration by tumor cells, and hepatic schistosomiasis diagnosed on liver biopsy), portal cavernoma or complete PVT at the time of liver biopsy, history of TIPS or surgical portosystemic shunt at the time of VCTE, history of splenectomy at the time of VCTE, and tense ascites at the time of VCTE.

Extrahepatic conditions associated with PSVD were extensively searched for and classified into 5 categories: immunological disorders (autoimmune conditions, common variable immune deficiency, Crohn disease, celiac disease, and history of solid organ transplantation), HIV infection, medication or toxins (azathioprine, platinum-based chemotherapy, and didanosine), hematological disorders or prothrombotic states (myeloproliferative neoplasm, lymphoma, myeloma, idiopathic thrombocytopenic purpura, antiphospholipid syndrome, paroxysmal nocturnal hemoglobinuria, protein C or protein S deficiency, antithrombin deficiency, and factor II or V Leiden mutation), and other conditions including genetic disorders.

TABLE 1 Characteristics of the patients in the derivation and validation cohorts at the time of spleen stiffness measurement by vibration-controlled transient elastography

Characteristics	Derivation cohort		Validation cohort		
	Available data (n)	Total (n = 154)	Available data (n)	Total (n = 155)	*p*
Gender (male, %)	154	83 (54)	155	86 (55)	0.779
Age (y)	154	55 (42–65)	155	51 (39–62)	0.238
Body mass index (kg/m^2)	152	24 (21–26)	151	25 (22–27)	**0.007**
At least 1 associated disorder (%)	154	120 (78)	155	99 (64)	**0.007**
Immunological disorder (%)	154	80 (52)	149	49 (33)	**0.001**
HIV infection (%)	154	11 (7)	154	4 (3)	0.109
Medication or toxin (%)	153	26 (17)	155	30 (19)	0.591
Hematological or prothrombotic condition (%)	153	38 (25)	150	39 (26)	0.816
Genetic disorder (%)	154	11 (7)	155	2 (1)	**0.011**
≥ 1 other cause of chronic liver disease (%)	154	29 (19)	154	22 (14)	0.272
Metabolic syndrome/diabetes (%)	154	14 (9)	155	18 (12)	0.467
History or active excessive alcohol consumption (%)	154	8 (5)	154	3 (2)	0.218
Positive HCV antibodies (%)	154	5 (3)	155	1 (< 1)	0.121
Positive HBs antigen (%)	154	3 (2)	155	1 (< 1)	0.371
Ascites moderate or controlled with diuretics (%)	154	13 (8)	155	23 (15)	0.080
Encephalopathy grade 1/2 of West-Haven (%)	153	1 (< 1)	155	1 (< 1)	1
Nonselective beta-blockers (%)	154	46 (30)	155	46 (30)	0.970
Anticoagulation therapy (%)	154	15 (10)	155	12 (8)	0.534
Diuretic therapy (%)	154	16 (10)	155	25 (16)	0.137
Platelet count (G/L)	154	113 (74–156)	155	117 (73–183)	0.485
Hemoglobin (g/dL)	148	13 (12–14)	0	NA	NA
International normalized ratio	149	1.07 (1.0–1.19)	146	1.1 (1.02–1.25)	**0.005**
Total serum bilirubin (mg/dL)	154	0.82 (0.53–1.12)	155	0.93 (0.60–1.34)	0.072
Serum conjugated bilirubin (mg/dL)	118	0.35 (0.24–0.47)	0	NA	NA
Serum AST (U/L)	152	39 (30–54)	154	33 (24–44)	**0.001**
Serum ALT (U/L)	153	32 (21–50)	155	32 (23–45)	0.998
Serum ALP (U/L)	151	112 (74–159)	148	107 (77–172)	0.916
Serum GGT (U/L)	152	85 (34–133)	137	56 (32–105)	0.144
Serum albumin (g/L)	152	38 (35–41)	149	41 (37–43)	**< 0.0001**
Serum creatinine (μmol/L)	152	70 (61–89)	154	71 (60–85)	0.702
No EV (%)	154	60 (39)	155	62 (40)	0.852
Small EV (%)	154	27 (18)	155	39 (25)	0.102
High-risk varices (%)[a]	154	67 (43)	155	54 (35)	0.119
Spleen size in the largest axis (cm)	154	15 (13–17)	152	16 (13–18)	**0.010**
Portosystemic collaterals (%)	153	101 (66)	153	88 (58)	0.126
Partial occlusion of the portal venous axis (%)	154	12 (8)	155	19 (12)	0.191
LSM by VCTE (kPa)	154	8.2 (5.9–11.3)	154	7.7 (6.2–9.6)	0.317
SSM by VCTE (kPa)	154	43.6 (30.2–67.2)	155	50 (36–70)	0.068
Use of 100 Hz probe for SSM by VCTE (%)	154	113 (73)	153	86 (56)	**0.002**

TABLE 1. (*continued*)

Characteristics	Derivation cohort: Available data (n)	Derivation cohort: Total (n = 154)	Validation cohort: Available data (n)	Validation cohort: Total (n = 155)	*p*
Controlled attenuation parameter of the liver (dB/m)	153	205 (183–242)	109	237 (196–269)	**< 0.001**
SSM by 2D-SWE (kPa)	84	37.1 (24.6–51.1)	48	29.8 (15.2–52.7)	0.108
LSPS	154	1.05 (0.61–2.32)	151	1.1 (0.52–2.25)	0.790

[a]Defined as either large varices, small varices with red spot signs, or a history of variceal band ligation or glue injection for primary prophylaxis.
Bold significant differences
Abbreviations: 2D-SWE, 2-dimensional shear wave elastography; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; EV, esophageal varices; GGT, gamma-glutamyl transferase; HB, hepatitis B surface; LSM, liver stiffness measurement; LSPS, liver stiffness – spleen diameter to platelet ratio score; NA, non-available; SSM, spleen stiffness measurement; VCTE, vibration-controlled transient elastography.

The study was performed in accordance with the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the institutional review board (CPP Sud Méditerranée V, Nice, France—Ethics approval number 2021-A02148-33). None of the patients refused permission to use their case records for medical research. This diagnostic accuracy study was designed, conducted, and written following the STARD guidelines.[17]

Validation cohort

The validation cohort included patients with PSVD from participating VALDIG centers, fulfilling the same inclusion and noninclusion criteria. Liver biopsies were analyzed by local pathologists specialized in liver diseases.

Clinical and laboratory data

Clinical and biological data were collected within 6 months before or after SSM by VCTE.

Imaging data

Imaging data were obtained from liver ultrasonography, CT, or MRI, performed within 6 months before or after SSM by VCTE.

Endoscopic data

Endoscopic data were recorded during an upper gastrointestinal endoscopy performed: (i) within 2 years before or after SSM by VCTE (with sensitivity analyses restricting this duration to 6 mo), or (ii) more than 2 years before SSM by VCTE in patients treated with nonselective beta-blockers (NSBB) for primary prophylaxis of variceal hemorrhage (with sensitivity analyses excluding patients receiving NSBB). HRV were defined as either large varices, small varices with red spot signs, or a history of variceal band ligation or glue injection for primary prophylaxis.

SSM and LSM

SSM by VCTE was performed with FibroScan 502 Touch or FibroScan 630 Expert (Echosens) by experienced clinical research technicians, nurses, or hepatologists trained for SSM by VCTE using FibroScan. SSM was considered reliable if performed in fasting condition ($\geq$2 h), with a 50 Hz probe (FibroScan 502 Touch) or the 100 Hz dedicated probe after ultrasound localization of the spleen (FibroScan 630 Expert), with at least 10 valid measurements, according to the manufacturer's recommendations, and a success rate (ratio of valid measurements to total number of measurements) $\geq$60%. SSM corresponds to the median value of all valid measurements. Since there is currently no recommendation about IQR reliability, we used the same as for LSM,[18] and considered an IQR/median SSM ratio $\leq$30% as reliable. In the derivation cohort, FibroScan 502 Touch was used until November 25, 2019, and FibroScan 630 Expert from November 26, 2019, to the end of the inclusion period (December 1, 2023). The impact of the type of FibroScan device was investigated.

LSM by VCTE was performed on the same day as SSM by VCTE, with the same reliability criteria, according to the 2015 EASL-ALEH guidelines.[18]

Liver stiffness – spleen diameter to platelet ratio score (LSPS) was calculated as described by Kim et al.[19]

Some patients also had SSM and LSM by 2-dimensional shear wave elastography (2D-SWE) using Aixplorer (SuperSonic Imagine). We considered an IQR/median SSM ratio $\leq$30% as reliable, as suggested by the Society of Radiologists in Ultrasound.[20]

Histological analysis

For the derivation cohort, all liver biopsies were reviewed by an expert pathologist (Valérie Paradis)—unaware of clinical, laboratory, imaging, and endoscopic data—according to predetermined criteria and classification.

Statistical analysis

Results are presented as absolute numbers (%) or median (IQR). Comparisons between categorical variables were performed using the chi-square or Fisher test when appropriate. Comparisons between quantitative variables were performed using the Student *t* test or Wilcoxon-Mann-Whitney test, when appropriate, according to the Shapiro-Wilk test. Correlations between quantitative variables were performed using the Spearman test. To identify variables associated with HRV, we fitted a multivariable binary logistic regression, including variables significantly associated with HRV at univariable logistic regression after Bonferroni correction. Sensitivity, specificity, and positive and negative predictive values were computed for the best cutoff value, defined with the Youden index. The missed HRV rate was defined as the number of patients with missed HRV divided by the number of patients with HRV.[21]

All tests were 2-sided and a p value ≤ 0.05 was considered significant. Statistical analyses were performed using R version 4.2.2 software. Figures were drawn using GraphPad Prism 10.0.1.

RESULTS

Study population

Derivation cohort

We screened 238 patients with PSVD and available SSM by VCTE performed at Beaujon Hospital. After the exclusion of patients without signs of portal hypertension (n = 33), patients with a history of variceal bleeding (n = 30), previous TIPS (n = 10) or splenectomy (n = 7), and patients with tense ascites (n = 4), we included 154 patients in the derivation cohort. Characteristics of patients at the time of SSM by VCTE are presented in Table 1 and Supplemental Table S2, http://links.lww.com/HEP/I542. At least 1 disorder associated with PSVD was present in 78% of the patients, mainly an immunological (52%) or hematological one (25%). Eight percent of the patients had ascites, and only 1 patient (< 1%) had HE at the time of SSM by VCTE. Sixty-seven (43%) patients had HRV, and 46 (30%) patients were receiving NSBB. The median time between VCTE and upper endoscopy was 85 days; 54% of the patients had VCTE within 6 months before or after endoscopy. Only 2 patients had HRV without other signs of portal hypertension.

Validation cohort

One hundred and fifty-five patients were included in the validation cohort from 20 VALDIG centers (Supplemental Table S3, http://links.lww.com/HEP/I542). Fifty-four patients (35%) had HRV. Characteristics of these patients are detailed in Table 1 and Supplemental Table S2, http://links.lww.com/HEP/I542. The median time between VCTE and upper endoscopy was 50 days; 55% of patients had VCTE within 6 months before or after endoscopy. Only 1 patient had HRV without other signs of portal hypertension.

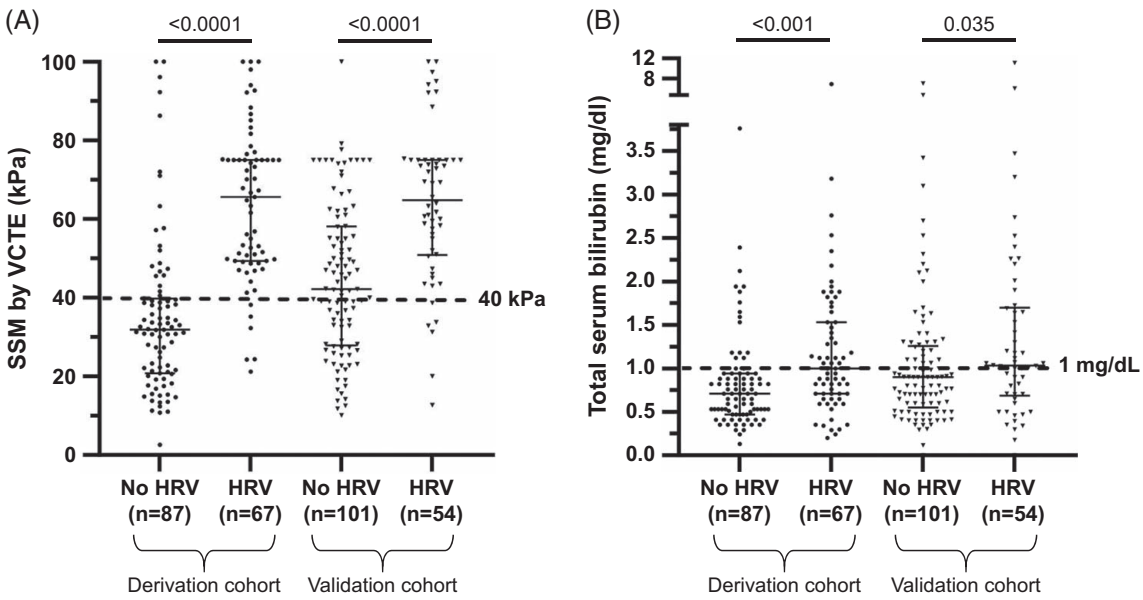


FIGURE 1 Spleen stiffness measurement by VCTE and total serum bilirubin according to HRV status. (A) Spleen stiffness measurement by VCTE according to HRV status. (B) Total serum bilirubin according to HRV status. Bars indicate the median and IQR. Statistical analysis: Comparisons were performed using the Student *t* test. Abbreviations: HRV, high-risk varices; SSM, spleen stiffness measurement; VCTE, vibration-controlled transient elastography.

TABLE 2 Features at the time of spleen stiffness measurement by vibration-controlled transient elastography associated with high-risk varices, defined as either large varices, small varices with red spot signs, or a history of variceal band ligation or glue injection for primary prophylaxis, by univariable analysis

	Derivation cohort (n = 154)			Validation cohort (n = 155)		
Characteristics	**No HRV (n = 87)**	**HRV (n = 67)**	***p***	**No HRV (n = 101)**	**HRV (n = 54)**	***p***
Gender (male, %)	50 (57)	33 (49)	0.311	54 (53)	32 (59)	0.489
Age (y)	55 (41–64)	57 (44–67)	0.531	48 (38–61)	56 (47–67)	**0.007**
Body mass index (kg/m^2)	24 (21–26)	24 (21–26)	0.779	25 (23–28)	24 (22–27)	0.225
≥1 associated disorder (%)	65 (75)	55 (82)	0.274	62 (61)	37 (69)	0.378
Immunological disorder (%)	43 (49)	37 (55)	0.475	32 (32)	17 (31)	0.842
HIV infection (%)	2 (2)	9 (13)	**0.011**	2 (2)	2 (4)	0.612
Medication or toxin (%)	11 (13)	15 (22)	0.117	16 (16)	14 (26)	0.155
Hematological or prothrombotic condition (%)	16 (18)	22 (33)	**0.043**	24 (24)	15 (28)	0.563
Genetic disorder (%)	5 (6)	6 (9)	0.443	1 (1)	1 (2)	1
≥1 other cause of chronic liver disease (%)	17 (20)	12 (18)	0.798	14 (14)	8 (15)	0.835
Metabolic syndrome/diabetes (%)	7 (8)	7 (10)	0.607	13 (13)	5 (9)	0.504
Excessive alcohol consumption (%)	5 (6)	3 (4)	1	2 (2)	1 (2)	1
Positive HCV antibodies (%)	2 (2)	3 (4)	0.653	0 (0)	1 (2)	0.348
Positive HBs antigen (%)	3 (3)	0 (0)	0.258	1 (1)	0 (0)	1
Ascites moderate or controlled with diuretics (%)	7 (8)	6 (9)	0.840	10 (10)	13 (24)	**0.018**
Encephalopathy grade 1/2 of West-Haven (%)	1 (1)	0 (0)	1	1 (1)	0 (0)	1
Nonselective beta-blockers (%)	6 (7)	40 (60)	< **0.001**	16 (16)	30 (56)	< **0.001**
Anticoagulation therapy (%)	8 (9)	7 (10)	0.795	5 (5)	7 (13)	0.075
Diuretic therapy (%)	8 (9)	8 (12)	0.580	13 (13)	12 (22)	0.131
Platelet count (G/L)	131 (99–172)	80 (68–125)	< **0.001**	132 (88–192)	82 (61–132)	< **0.001**
Hemoglobin	14 (12–15)	13 (12–14)	0.061	NA	NA	NA
INR	1.02 (0.96–1.12)	1.12 (1.03–1.26)	< **0.001**	1.09 (1.0–1.17)	1.18 (1.10–1.30)	< **0.001**
Total serum bilirubin (mg/dL)	0.71 (0.49–0.91)	1.0 (0.71–1.53)	< **0.001**	0.90 (0.59–1.25)	1.04 (0.67–1.68)	**0.035**
Serum conjugated bilirubin (mg/dL)	0.29 (0.18–0.35)	0.41 (0.29–0.53)	< **0.001**	NA	NA	NA
Serum AST (U/L)	36 (28–53)	40 (33–54)	0.461	33 (23–46)	32 (28–42)	0.660
Serum ALT (U/L)	35 (23–56)	31 (20–44)	0.118	32 (23–45)	32 (23–42)	0.979
Serum ALP (U/L)	114 (73–160)	107 (74–156)	0.579	102 (76–169)	113 (84–176)	0.568
Serum GGT (U/L)	86 (32–139)	74 (35–117)	0.632	61 (34–105)	50 (30–109)	0.629
Serum albumin (g/L)	39 (36–42)	36 (34–41)	**0.009**	41 (37–44)	40 (36–43)	0.321
Serum creatinine (μmol/L)	71 (60–86)	69 (63–91)	0.726	71 (61–85)	68 (57–86)	0.775
Spleen size in the largest axis (cm)	14 (12–16)	16 (13–17)	**0.002**	15 (13–17)	17 (15–20)	**0.002**
Portosystemic collaterals (%)	47 (55)	54 (85)	< **0.001**	49 (49)	39 (72)	**0.003**
Partial occlusion of the portal venous axis (%)	3 (3)	9 (13)	**0.032**	11 (11)	8 (15)	0.478
LSM by VCTE (kPa)	7.1 (5.8–10.2)	8.8 (6.8–12.5)	**0.027**	7.3 (5.7–9.3)	8.5 (7.1–10.3)	**0.032**
SSM by VCTE (kPa)	31.9 (21.0–39.7)	65.6 (49.4–75.0)	< **0.001**	42.3 (28.2–57.4)		< **0.001**

TABLE 2. (*continued*)

Characteristics	Derivation cohort (n = 154)			Validation cohort (n = 155)		
	No HRV (n = 87)	HRV (n = 67)	*p*	No HRV (n = 101)	HRV (n = 54)	*p*
					65.0 (51.3–75.0)	
Use of 100 Hz probe for SSM by VCTE (%)	63 (72)	50 (75)	0.758	53 (54)	33 (61)	0.367
Controlled attenuation parameter of the liver (dB/m)	199 (181–223)	218 (186–257)	**0.020**	244 (204–274)	223 (194–256)	0.220
SSM by 2D-SWE (kPa)	27.8 (21.2–44.2)[a]	45.0 (32.0–58.2)[b]	**0.001**	20.4 (15.0–38.2)[c]	45.8 (31.6–53.2)[d]	0.077
LSPS	0.72 (0.46–1.44)	1.64 (0.95–2.84)	**< 0.001**	0.88 (0.40–1.76)	1.68 (0.90–3.23)	**< 0.001**

[a]n = 43.
[b]n = 41.
[c]n = 31.
[d]n = 17.
Bold values indicates significant differences.
Abbreviations: 2D-SWE, 2-dimensional shear-wave elastography; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; HB, hepatitis B surface; HRV, high-risk varices; LSM, liver stiffness measurement; LSPS, liver stiffness – spleen diameter to platelet ratio score; NA, non-available; SSM, spleen stiffness measurement; VCTE, vibration-controlled transient elastography.

Performance of SSM by VCTE to rule out HRV

Derivation cohort

Median SSM by VCTE was twice higher in patients with HRV than in those without (Figure 1A). HRV were associated with HIV infection, hematological or prothrombotic disorder, signs of portal hypertension (portosystemic collaterals, treatment with NSBB, lower platelet count, larger spleen size, higher SSM by VCTE, and higher LSPS), signs of liver dysfunction (higher INR, lower serum albumin, and higher serum bilirubin), higher LSM by VCTE, higher controlled attenuation parameter, and partial occlusion of the portal venous axis (Table 2).

We entered into a multivariable binary logistic regression analysis features associated with HRV by univariable analysis after Bonferroni correction (ie $p < 0.001$)—namely platelet count, INR, total serum bilirubin, and SSM by VCTE. We chose to categorize these quantitative variables according to the following thresholds. Based on data available in patients with cirrhosis,[4] we applied 110 G/L as a threshold for platelet count; 66% of the patients with HRV had a platelet count <110 G/L, and 70% of the patients without HRV had a platelet count ≥ 110 G/L. We chose 1.05 as a threshold for INR according to the Youden index; 66% of the patients with HRV had INR ≥ 1.05, and 59% of the patients without HRV had INR <1.05. Based on data available in patients with cirrhosis,[22] we chose the threshold of 1 mg/dL (17 μmol/L) for total serum bilirubin. It happened that this value was also the one that maximized sensitivity and specificity according to the Youden index. Fifty-one percent of the patients with HRV had a total serum bilirubin ≥ 1 mg/dL, and 80% of the patients without HRV had a total serum bilirubin <1 mg/dL. Based on data available in patients with cirrhosis,[9,12]

TABLE 3 Features at the time of spleen stiffness measurement by vibration-controlled transient elastography associated with high-risk varices, defined as either large varices, small varices with red spot signs, or a history of variceal band ligation or glue injection for primary prophylaxis, by multivariable binary logistic regression analysis, in the derivation cohort

	Derivation cohort			
	Regression coefficient	Standard error	OR (95% CI)	*p*
Platelet count <110 G/L	0.272	0.500	1.312 (0.492–3.496)	0.587
INR ≥ 1.05	0.605	0.467	1.831 (0.733–4.573)	0.195
Total serum bilirubin ≥ 1 mg/dL	0.989	0.469	2.689 (1.073–6.740)	**0.035**
SSM by VCTE >40 kPa	3.312	0.502	27.444 (10.263–73.388)	**< 0.001**
Constant	−2.644	0.456	0.071 (—)	**< 0.001**

Bold values indicates significant differences.
Abbreviations: SSM, spleen stiffness measurement; VCTE, vibration-controlled transient elastography.

TABLE 4 Performance of spleen stiffness measurement by vibration-controlled transient elastography and serum bilirubin to rule out high-risk varices

SSM by VCTE ≤40 kPa and total serum bilirubin <1 mg/dL	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Well-classified (%)	AUROC[a]
Derivation cohort	96	64	67	95	78	0.843 (95% CI 0.781–0.906)
Validation cohort	96	30	42	94	53	0.714 (95% CI 0.632–0.796)

[a]AUROC of a score where 0 refers to "SSM-VCTE ≤40 kPa combined with bilirubin <1 mg/dL," 1 refers to "SSM-VCTE >40 kPa or bilirubin ≥1 mg/dL," and 2 refers to "SSM-VCTE >40 kPa and bilirubin ≥1 mg/dL."
Bold values indicates significant differences.
Abbreviations: SSM, spleen stiffness measurement; VCTE, vibration-controlled transient elastography.

we applied 40 kPa as a threshold for SSM; 91% of the patients with HRV had an SSM by VCTE >40 kPa, and 76% of the patients without HRV had an SSM by VCTE ≤40 kPa (Figure 1A). Treatment with NSBB was not included in this multivariable analysis because of collinearity with HRV; portosystemic collaterals were not included because the aim was to identify simple features that we could use in practice (ie, without performing CT scan every year), and LSPS was not included because of collinearity with platelet count.

At backward stepwise multivariable binary logistic regression, both SSM by VCTE >40 kPa and total serum bilirubin ≥1 mg/dL remained associated with HRV (Table 3).

A model combining a cutoff value of 40 kPa for SSM by VCTE and a cutoff value of 1 mg/dL for total serum bilirubin had a sensitivity of 96% and a negative predictive value of 95% for ruling out HRV and 78% of the patients were well classified (Table 4). This model would have spared 38% of screening endoscopies in the derivation cohort, with a rate of HRV missed of 4.5% (Figures 2 and 3). Characteristics of the 3 patients who would have been incorrectly classified as not having HRV with this model are presented in Supplemental Table S4, http://links.lww.com/HEP/I542.

Sensitivity analyses focusing on patients not treated with NSBB (n = 108), on patients strictly compensated—meaning with no ascites, and not receiving NSBB (n = 100)—on patients strictly compensated who underwent esophagogastroduodenoscopy and VCTE within 6 months (n = 64), or on patients with body mass index <30 kg/m^2 (n = 136), gave even better results, with 39%–53% of screening endoscopies spared, and a rate of HRV missed lower than 5% with the "SSM-bilirubin model" (Supplemental Table S5, http://links.lww.com/HEP/I542). Sensitivity analyses restricted to patients with myeloproliferative neoplasm (n = 8) showed no HRV missed, and 25% of screening endoscopies spared using the "SSM-bilirubin model" (Supplemental Table S5, http://links.lww.com/HEP/I542).

We also tested in our population other models proposed in patients with cirrhosis or with PSVD to rule out HRV (Supplemental Table S6, http://links.lww.com/HEP/I542): SSM by VCTE ≤40 kPa,[23] SSM by VCTE ≤60 kPa (Colecchia, personal communication, 2023), and the best SSM by VCTE cutoff value defined with the Youden index in the present derivation cohort (SSM ≤46 kPa). These models could spare between 47% and 71% of screening endoscopies, but the rate of HRV missed would have been ≥5%. Models combining SSM and platelet count proposed in patients with cirrhosis, namely SSM by VCTE ≤40 kPa and platelet count ≥150 G/L,[24] or SSM by VCTE ≤40 kPa and platelet count ≥110 G/L,[25] could spare 19% and 36% of screening endoscopies, respectively, and with a rate of HRV missed <5%.

Validation cohort

Patients with HRV had a higher value of SSM by VCTE than patients without HRV (Figure 1A). Similar to the derivation cohort, HRV were associated with signs of portal hypertension (ascites, portosystemic collaterals, treatment with NSBB, lower platelet count, larger spleen size, higher SSM by VCTE, and higher LSPS), signs of liver dysfunction (higher INR and higher serum bilirubin), and higher LSM by VCTE (Table 2). HRV were also associated with age. However, HRV were not associated with the presence of hematological or prothrombotic disorders nor partial occlusion of the portal venous axis.

The "SSM-bilirubin model," combining a cutoff value of 40 kPa for SSM by VCTE and a cutoff value of 1 mg/dL for total serum bilirubin, had a sensitivity of 96% and a negative predictive value of 94% for ruling out HRV, and 53% of patients were well classified regarding their HRV status (Table 4). This model would have spared 21% of screening endoscopies in the validation cohort, with a rate of HRV missed of 3.7% (Figures 2 and 3). Characteristics of the 2 patients who would have been incorrectly classified as not having HRV with this model are presented in Supplemental Table S4, http://links.lww.com/HEP/I542.

Sensitivity analyses restricted to patients not treated with NSBB (n = 109), to patients strictly compensated (n = 94), to patients strictly compensated who underwent esophagogastroduodenoscopy and VCTE within 6 months (n = 53), or to patients with body mass index <30 kg/m^2 (n = 131) gave similar results, namely 15%–

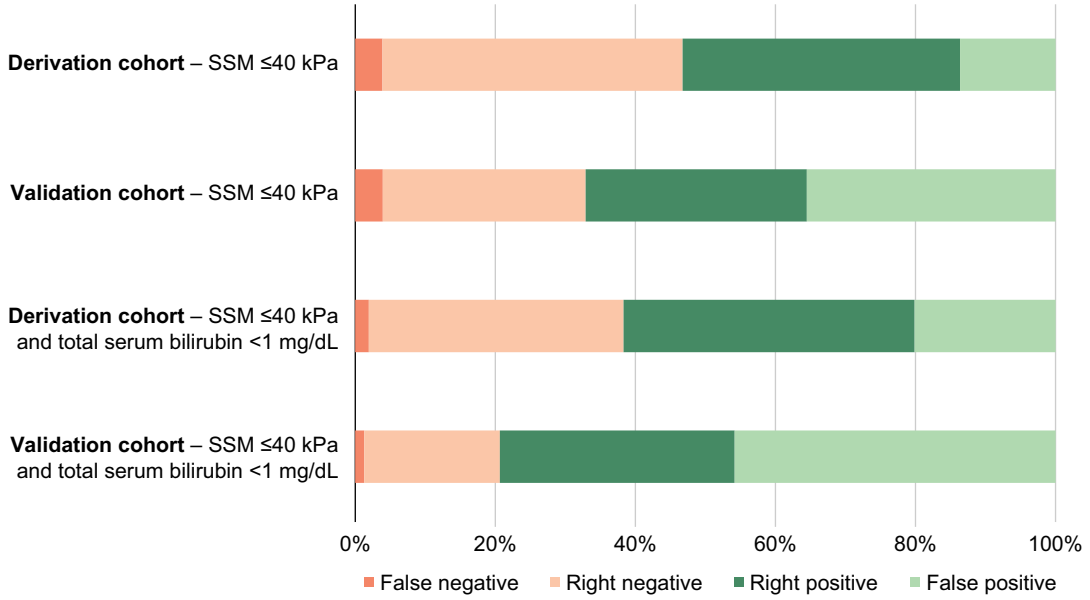


FIGURE 2 Performance of spleen stiffness measurement by VCTE to rule out high-risk varices in patients with porto-sinusoidal vascular disorder. False negative: patients with HRV, SSM ≤40 kPa and total serum bilirubin <1 mg/dL; true negative: patients without HRV, SSM ≤40 kPa and total serum bilirubin <1 mg/dL; true positive: patients with HRV, and SSM >40 kPa and/or total serum bilirubin ≥1 mg/dL; false positive: patients without HRV, and SSM >40 kPa and/or total serum bilirubin ≥1 mg/dL. Abbreviations: HRV, high-risk varices; SSM, spleen stiffness measurement; VCTE, vibration-controlled transient elastography.

27% of screening endoscopies spared, with a rate of HRV lower than 5% (Supplemental Table S5, http://links.lww.com/HEP/I542). It should, however, be noted that only 16 patients of the validation cohort were strictly compensated and had HRV. Sensitivity analyses focusing on patients with myeloproliferative neoplasm (n = 17) showed no HRV missed, but only 6% of screening endoscopies were spared using the "SSM-bilirubin model" (Supplemental Table S5, http://links.lww.com/HEP/I542).

We also considered other models proposed in patients with cirrhosis to rule out HRV in the derivation cohort (Supplemental Table S6, http://links.lww.com/HEP/I542).

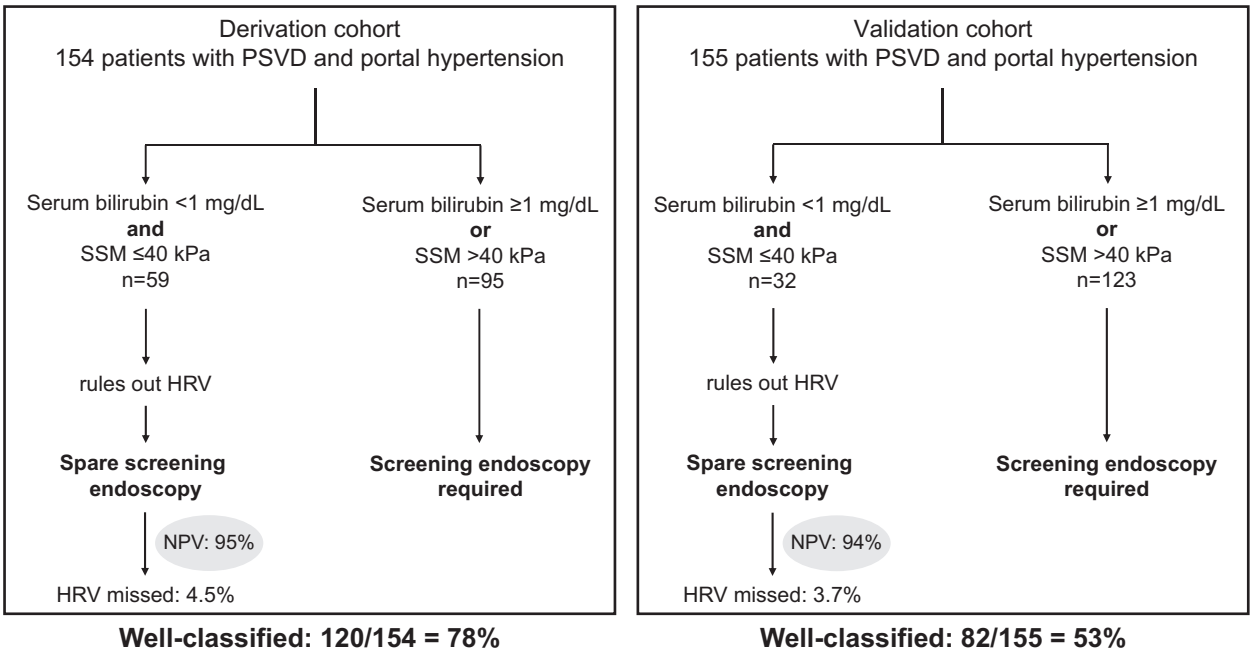


FIGURE 3 Proposed algorithm to consider screening endoscopy in patients with PSVD according to SSM-VCTE and total serum bilirubin. The rate of HRV missed was calculated as the number of patients with HRV with total serum bilirubin <1 mg/dL and SSM by VCTE ≤40 kPa divided by the total number of patients with HRV. Abbreviations: HRV, high-risk varices; NPV, negative predictive value; PSVD, porto-sinusoidal vascular disorder; SSM, spleen stiffness measurement; VCTE, vibration-controlled transient elastography.

SSM ≤40 kPa combined with platelet count ≥150 G/L had a rate of HRV missed <5% but spared only 15% of screening endoscopies. SSM ≤40 kPa combined with platelet count ≥110 G/L had a rate of HRV missed over 5%.

Features associated with SSM by VCTE

We then investigated features associated with SSM by VCTE in the derivation and validation cohorts. HRV were not taken into account in these analyses. At univariable analysis, in both cohorts, SSM by VCTE was significantly higher in patients receiving NSBB and in those with portosystemic collaterals. In both cohorts, SSM by VCTE was positively correlated with spleen size and LSPS and negatively correlated with platelet count (Supplemental Table S7, http://links.lww.com/HEP/I542). Multiple linear regression analysis, including features associated with SSM by VCTE at univariable analyses after Bonferroni correction (ie, $p < 0.002$), found 4 features independently associated with SSM in the derivation cohort, namely NSBB use, platelet count, portosystemic collaterals, and LSM; and 2 features independently associated with SSM in the validation cohort, namely platelet count and spleen size (Supplemental Table S8, http://links.lww.com/HEP/I542).

In the derivation cohort, 133 patients underwent SSM by VCTE within 3 years before or after liver biopsy, which was reviewed by an expert pathologist. None of the histological features analyzed was associated with SSM by VCTE (Supplemental Figure S1, http://links.lww.com/HEP/I542).

Two-dimensional shear wave elastography

In the derivation cohort, 84 patients underwent SSM by 2D-SWE within 2 years before or after screening endoscopy; 49% of them had HRV. Patients with HRV had higher values of SSM by 2D-SWE than patients without HRV (Supplemental Figure S2, http://links.lww.com/HEP/I542; Table 2). SSM by 2D-SWE correlated with SSM by VCTE ($r = 0.564$; $p < 0.0001$) (Supplemental Figure S3A, http://links.lww.com/HEP/I542). However, SSM by 2D-SWE did not remain associated with HRV by univariable analysis after Bonferroni correction (ie, $p < 0.001$). A model combining a cutoff value of 40 kPa for SSM by 2D-SWE and a cutoff value of 1 mg/dL for total serum bilirubin would have been able to spare 42% of screening endoscopies but with a rate of HRV missed of 24%. The 10 patients who would have been incorrectly classified as having no HRV with this model differed from the correctly classified patients in platelet count, INR, serum bilirubin, and SSM by 2D-SWE (Supplemental Table S9, http://links.lww.com/HEP/I542).

In the validation cohort, 48 patients had SSM by 2D-SWE; 35% of them had HRV. Patients with HRV had higher values of SSM by 2D-SWE than patients without HRV (Supplemental Figure S2, http://links.lww.com/HEP/I542), but this difference was not statistically significant. SSM by 2D-SWE was, however, correlated with SSM by VCTE ($r = 0.563$; $p < 0.0001$) (Supplemental Figure S3B, http://links.lww.com/HEP/I542). SSM by 2D-SWE ≤40 kPa, combined or not with total serum bilirubin <1 mg/dL, would have been able to spare 46% of screening endoscopies but led to a rate of HRV missed of 18% (data not shown). The 3 patients who would have been incorrectly classified as having no HRV with this model differed from the correctly classified 14 patients in body mass index, INR, and serum bilirubin (Supplemental Table S9, http://links.lww.com/HEP/I542).

DISCUSSION

Despite the rarity of PSVD, the present VALDIG study, joining the efforts of 21 European and Asian reference centers for vascular liver diseases, was able to include 309 patients with PSVD and signs of portal hypertension. This allowed for building and validating an "SSM-bilirubin model," based on VCTE that identifies patients with PSVD at a very low probability (<5%) of having HRV.

The first major finding of the present study was that SSM by VCTE ≤40 kPa, combined with total serum bilirubin <1 mg/dL (17 μmol/L), identifies patients with PSVD and signs of portal hypertension with a probability of HRV <5%, a usual threshold.[4,13,26] Even if PSVD is a rare disease, it affects predominantly young adults, in whom sparing a screening endoscopy every 2 years would have an individual benefit. Two previous studies suggested the potential interest of SSM in estimating HRV in patients with PSVD. Ferreira-Silva et al[15] reported SSM by VCTE in 42 patients with noncirrhotic portal hypertension and proposed the threshold of 35.4 kPa to affirm HRV but with a negative predictive value of 90.9%, lower than our model. The authors found that serum bilirubin was not different between patients with HRV and patients without HRV. However, the population of this study was different from ours: 48% of the patients had extrahepatic portal vein obstruction. Zhou et al[27] performed 2D-SWE in 86 patients with idiopathic portal hypertension and observed good performance of SSM for estimating HRV, with a threshold of 44 kPa. These 2 studies lacked a validation cohort, a standardized definition of idiopathic portal hypertension/PSVD, and did not assess the interest of SSM to rule out HRV. Despite its retrospective nature, the present study could overcome these limitations since (i) our results were obtained in a monocentric cohort of 154 patients and were thereafter validated in an independent multicenter cohort of 155 patients with PSVD from both European and Asian countries; (ii) all patients included had PSVD according to the VALDIG

and Baveno definitions,[1,12] ensuring the reproducibility of our findings; (iii) the "SSM-bilirubin model" we developed identifies patients with a very low probability of having HRV, in whom endoscopy can be spared.[13] The thresholds we chose for the "SSM-bilirubin model" are similar to those proposed in cirrhosis,[23,28] facilitating the clinical applicability of our findings. Indeed, Baveno VII guidelines stated that SSM by VCTE $\leq$40 kPa is associated with a very low probability of HRV in patients with cirrhosis.[12] A threshold of 1 mg/dL (17 μmol/L) for total serum bilirubin has been proposed to predict, together with the HVPG, the outcome of patients with cirrhosis undergoing surgical resection of HCC, justifying our choice.[22] It happened that this value was also the one that maximized sensitivity and specificity according to the Youden index. Of note, the strong association between HRV and total serum bilirubin we observed here was due to unconjugated serum bilirubin. This might reflect chronic hemolysis associated with portal hypertension related to hypersplenism[29] and hematological diseases. Contrary to the cirrhosis setting where platelet count is helpful to rule out HRV, we observed that platelet count was associated with HRV at univariable logistic regression but not at multivariable binary logistic regression analysis. Moreover, even if the models combining SSM by VCTE and platelet count had good performances in the derivation cohort, in the validation cohort, the model combining SSM by VCTE $\leq$40 kPa and platelet count $\geq$110 G/L led to a rate of HRV missed >5%, and the model combining SSM by VCTE $\leq$40 kPa and platelet count $\geq$150 G/L could spare only 15% of screening endoscopies. This difference might be explained by the prevalence of hematological conditions associated with PSVD (25% here in both cohorts) that could affect platelet count.

In the present study, 5 patients were "false negative," meaning they had HRV but SSM by VCTE $\leq$40 kPa and total serum bilirubin <1 mg/dL. One of them had no other sign of portal hypertension than HRV, so one may hypothesize that the diagnosis of HRV by endoscopy was made by mistake. Three other patients had an SSM $\leq$40 kPa but >35 kPa. Four of these 5 patients were treated with NSBBs, which may have reduced SSM.[10] Indeed, SSM is a dynamic surrogate of portal hypertension since it decreases following beta-blocker instauration in patients with cirrhosis who are responders[10]; we can expect similar changes in patients with PSVD.

A limitation of our study was that we included some patients with obesity, some patients with a history of ascites, and patients using NSBB. However, sensitivity analyses excluding those patients yielded even better results. Another limitation is that we included patients with myeloproliferative neoplasm, that is associated per se with elevated spleen stiffness values.[30] However, in this subgroup of patients, no HRV were missed with the "SSM-bilirubin model", but the rate of spared endoscopies was low. Finally, longitudinal validation of the model would be useful given the relatively small number of patients with SSM by VCTE $\leq$40 kPa and total serum bilirubin <1 mg/dL in the validation cohort (n = 32).

It should be noted that the "SSM-bilirubin model" was established in patients with at least 1 sign of portal hypertension and is therefore not applicable to patients without signs of portal hypertension. In our total population of 301 patients, 3 patients (<1%) had HRV without other signs of portal hypertension. In these patients, the use of the "SSM-bilirubin model" would have been impossible since upper endoscopy was necessary for the diagnosis of PSVD. However, this limitation only affects an insignificant fraction of patients with PSVD.

The second major finding of this study was that values of SSM by VCTE were strongly associated with signs of portal hypertension but not with intrahepatic lesions in patients with PSVD. Indeed, SSM by VCTE was independently associated with platelet count in both cohorts and with treatment with NSBB, spleen size, and portosystemic collaterals in 1 of the 2 cohorts. Conversely, despite the reanalysis of all the liver biopsies from the derivation cohort by an expert pathologist, we could not identify any histological feature associated with SSM by VCTE, contrarily to LSM by VCTE that is associated with several lesions in patients with PSVD.[14] This suggests that SSM reflects the dynamic components of portal hypertension rather than the intrahepatic structural changes. Besides, it should be noted that SSM by VCTE was not associated with gender, age, body mass index, ascites, associated disorders, nor other causes of chronic liver disease, which makes SSM by VCTE a robust tool in all patients with PSVD and portal hypertension. Moreover, in the present study, we used the 50 Hz as well as the 100 Hz probe in both cohorts, suggesting that the type of probe does not influence our results. This, together with the expected future wider availability of SSM in clinical centers, will facilitate the translation of our results into routine practice. In addition, as the knowledge and recognition of PSVD increases among physicians, we can expect that the diagnosis of PSVD will be less often triggered by the discovery of esophageal varices so that the place of the "SSM-bilirubin model" will possibly grow.

The third major finding of this study was that, in patients with PSVD, SSM by 2D-SWE could not rule out HRV with an acceptable rate of missed varices, alone or combined with serum bilirubin. The results we obtained with SSM by VCTE can thus not be extrapolated to other techniques of SSM.

In conclusion, in patients with PSVD and portal hypertension, a noninvasive algorithm based on SSM by VCTE $\leq$40 kPa combined with total serum bilirubin <1 mg/dL allows to identify patients with a very low probability of HRV (<5%), in whom screening endoscopy can be safely spared.

AUTHOR CONTRIBUTIONS

Study concept and design: Lucile Moga, Pierre-Emmanuel Rautou. Acquisition of data: Lucile Moga, Valérie Paradis, Koushik Gudavalli, Sai Prasanth Rampally, Arun Valsan, Joel Ferreira-Silva, Filippo Schepis, Federica Indulti, Elton Dajti, Federico Ravaioli, Oana Nicoara-Farcau, Giulia Tosetti, Antonina Antonenko, Andreea Fodor, Judit Vidal-González, Laura Turco, Francisco Capinha, Laure Elkrief, Teresa Monllor-Nunell, Odile Goria, Lorenz Balcar, Adrien Lannes, Vincent Mallet, Armelle Poujol-Robert, Dominique Thabut, Pauline Houssel-Debry, Yu Jun Wong, Maxime Ronot, Thomas Reiberger, and Bogdan Procopet. Statistical analysis: Lucile Moga, Pierre-Emmanuel Rautou. Drafting the manuscript: Lucile Moga and Pierre-Emmanuel Rautou. Critical revision of the manuscript: all the authors.

ACKNOWLEDGMENTS

The authors thank Djalila Rezigue for her help in collecting the data and performing spleen stiffness measurements. They also thank Anissa Attout, Cathia Beuve, Cécilia de Freitas, Ibtissem Grami, Hanane Mir, Maryse Moinat, and Christiane Stern for having performed spleen stiffness measurements.

FUNDING INFORMATION

Judit Vidal-González is a recipient of the PFIS grant FI19/00330 from Instituto de Salud Carlos III, Spain. Macarena Simon-Talero is a recipient of the grant PI21/00312 from Instituto de Salud Carlos III, Spain, co-funded by the European Union (ERDF/ESF, "A way to make Europe"/"Investing in your future"). CIBERehd is supported by Instituto de Salud Carlos III. Pierre-Emmanuel Rautou's laboratory is supported by the Fondation pour la Recherche Médicale (FRM EQU202303016287), "Institut National de la Santé et de la Recherche Médicale" (ATIP AVENIR), the "Agence Nationale pour la Recherche" (ANR-18-CE14-0006-01, RHU QUID-NASH, ANR-18-IDEX-0001, ANR-22-CE14-0002) by "Émergence, Ville de Paris," by Fondation ARC and by the European Union's Horizon 2020 research and innovation program under grant agreement no. 847949.

CONFLICTS OF INTEREST

Antonina Antonenko received grants from the Swiss National Science Foundation. Dominique Thabut consults, is on the speakers' bureau, and received grants from AbbVie and Gilead. She consults and is on the speakers' bureau for W.L. Gore. She consults for Alfasigma. She is on the speakers' bureau for Cellaïon. Yu Jun Wong is on the speakers' bureau for AbbVie and Gilead. Maxime Ronot consults for Quantum Surgical. She is on the speakers' bureau and has other interests with Angiodynamics, AstraZeneca, General Electrics, and Guerbet. She is on the speakers' bureau for Ipsen and Terumo. Laurent Castera consults and is on the speakers' bureau for Echosens and Novo Nordisk. She consults for Madrigal, MSD, Pfizer, Sagimet, and Siemens. She is on the speakers' bureau for Gilead and Inventiva. Thomas Reiberger consults, advises, is on the speakers' bureau, and received grants from AbbVie, Gilead, Intercept/Advanz, and MSD. He consults, advises, and received grants from Boehringer Ingelheim and Siemens. He is on the speakers' bureau and received grants from Roche and W.L. Gore. He consults and advises AstraZeneca, Bayer, and Resolution Therapeutics. He received grants from Dr. Falk, Myr, Philips Healthcare, and Pliant. José Ferrusquía-Acosta consults for AstraZeneca. Macarena Simon-Talero consults for Grifols. Bogdan Procopet is on the speakers' bureau and received grants from AbbVie. He is on the speakers' bureau for Echosens. He received grants from Alfasigma. Annalisa Berzigotti consults and advises Boehringer Ingelheim. She is on the speakers' bureau for General Electric Healthcare and Hologic. Fanny Turon is on the speakers' bureau for W.L. Gore. Filippo Schepis consults and is on the speakers' bureau for Echosens. He is on the speakers' bureau and received grants from COOK Medical and W.L. Gore. Pierre-Emmanuel Rautou consults for Abbelight, Boehringer Ingelheim, GENFIT, HemostOD, and Mursla. He is on the speakers' bureau for AbbVie and Tillots. He received grants from Terrafirma. The remaining authors have no conflicts to report.

REFERENCES

1. De Gottardi A, Rautou PE, Schouten J, Rubbia-Brandt L, Leebeek F, Trebicka J, et al. Porto-sinusoidal vascular disease: Proposal and description of a novel entity. Lancet Gastroenterol Hepatol. 2019;4:399–411.
2. De Gottardi A, Sempoux C, Berzigotti A. Porto-sinusoidal vascular disorder. J Hepatol. 2022;77:1124–35.
3. Wöran K, Semmler G, Jachs M, Simbrunner B, Bauer DJM, Binter T, et al. Clinical course of porto-sinusoidal vascular disease is distinct from idiopathic noncirrhotic portal hypertension. Clin Gastroenterol Hepatol. 2022;20:e251–66.
4. Abraldes JG, Bureau C, Stefanescu H, Augustin S, Ney M, Blasco H, et al. Noninvasive tools and risk of clinically significant portal hypertension and varices in compensated cirrhosis: The "Anticipate" study. Hepatol Baltim Md. 2016;64:2173–84.
5. Kumar A, Maruyama H, Arora A, Sharma P, Anikhindi SA, Bansal N, et al. Diagnostic accuracy of transient elastography in diagnosing clinically significant portal hypertension in patients with chronic liver disease: A systematic review and meta-analysis. J Med Ultrason 2001. 2022;49:333–46.
6. Stefanescu H, Grigorescu M, Lupsor M, Procopet B, Maniu A, Badea R. Spleen stiffness measurement using Fibroscan for the noninvasive assessment of esophageal varices in liver cirrhosis patients. J Gastroenterol Hepatol. 2011;26:164–70.
7. Colecchia A, Ravaioli F, Marasco G, Colli A, Dajti E, Di Biase AR, et al. A combined model based on spleen stiffness measurement and Baveno VI criteria to rule out high-risk varices in advanced chronic liver disease. J Hepatol. 2018;69:308–17.
8. Reiberger T. The value of liver and spleen stiffness for evaluation of portal hypertension in compensated cirrhosis. Hepatol Commun. 2022;6:950–64.
9. Dajti E, Ravaioli F, Zykus R, Rautou PE, Elkrief L, Grgurevic I, et al. Accuracy of spleen stiffness measurement for the diagnosis of clinically significant portal hypertension in patients with

compensated advanced chronic liver disease: A systematic review and individual patient data meta-analysis. Lancet Gastroenterol Hepatol. 2023;8:816–28.
10. Marasco G, Dajti E, Ravaioli F, Alemanni LV, Capuano F, Gjini K, et al. Spleen stiffness measurement for assessing the response to β-blockers therapy for high-risk esophageal varices patients. Hepatol Int. 2020;14:850–7.
11. Buechter M, Manka P, Theysohn JM, Reinboldt M, Canbay A, Kahraman A. Spleen stiffness is positively correlated with HVPG and decreases significantly after TIPS implantation. Dig Liver Dis. 2018;50:54–60.
12. de Franchis R, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll C, Baveno VII. Faculty. Baveno VII—Renewing consensus in portal hypertension. J Hepatol. 2022;76:959–74.
13. de Franchis R, Baveno VI Faculty. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. J Hepatol. 2015;63:743–52.
14. Elkrief L, Lazareth M, Chevret S, Paradis V, Magaz M, Blaise L, et al. Liver stiffness by transient elastography to detect porto-sinusoidal vascular liver disease with portal hypertension. Hepatol Baltim Md. 2021;74:364–78.
15. Ferreira-Silva J, Gaspar R, Liberal R, Cardoso H, Macedo G. Transient splenic elastography predicts high-risk esophageal varices in patients with non-cirrhotic portal hypertension. Scand J Gastroenterol. 2021;56:1462–6.
16. Ferreira-Silva J, Gaspar R, Liberal R, Cardoso H, Macedo G. Splenic-hepatic elastography index is useful in differentiating between porto-sinusoidal vascular disease and cirrhosis in patients with portal hypertension. Dig Liver Dis. 2023;55:75–80.
17. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig L, et al. STARD 2015: An updated list of essential items for reporting diagnostic accuracy studies. BMJ. 2015;351:h5527.
18. European Association for Study of Liver, Asociacion Latinoamericana para el Estudio del Higado. EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis. J Hepatol. 2015;63:237–64.
19. Kim BK, Han KH, Park JY, Ahn SH, Kim JK, Paik YH, et al. A liver stiffness measurement-based, noninvasive prediction model for high-risk esophageal varices in B-viral liver cirrhosis. Am J Gastroenterol. 2010;105:1382–90.
20. Barr RG, Wilson SR, Rubens D, Garcia-Tsao G, Ferraioli G. Update to the Society of Radiologists in Ultrasound Liver Elastography Consensus Statement. Radiology. 2020;296:263–74.
21. Calès P, Buisson F, Ravaioli F, Berger A, Carboni C, Marasco G, et al. How to clarify the Baveno VI criteria for ruling out varices needing treatment by noninvasive tests. Liver Int. 2019;39:49–53.
22. Llovet JM, Fuster J, Bruix J. Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: Resection versus transplantation. Hepatol Baltim Md. 1999;30:1434–40.
23. Stefanescu H, Marasco G, Calès P, Fraquelli M, Rosselli M, Ganne-Carrié N, et al. A novel spleen-dedicated stiffness measurement by FibroScan® improves the screening of high-risk oesophageal varices. Liver Int. 2020;40:175–85.
24. Dajti E, Ravaioli F, Marasco G, Alemanni LV, Colecchia L, Ferrarese A, et al. A combined Baveno VII and spleen stiffness algorithm to improve the noninvasive diagnosis of clinically significant portal hypertension in patients with compensated advanced chronic liver disease. Am J Gastroenterol. 2022;117:1825–33.
25. Augustin S, Pons M, Maurice JB, Bureau C, Stefanescu H, Ney M, et al. Expanding the Baveno VI criteria for the screening of varices in patients with compensated advanced chronic liver disease. Hepatol Baltim Md. 2017;66:1980–8.
26. Zhang X, Song J, Zhang Y, Wen B, Dai L, Xi R, et al. Baveno VII algorithm outperformed other models in ruling out high-risk varices in individuals with HBV-related cirrhosis. J Hepatol. 2023;78:574–83.
27. Zhou H, Zhang Z, Zhang J, Sang L, Liu L, Gong X, et al. Performance of spleen stiffness measurement by 2D-shear wave elastography in evaluating the presence of high-risk varices: Comparative analysis of idiopathic portal hypertension versus hepatitis B virus. BMC Med Imaging. 2023;23:30.
28. Wong GLH, Kwok R, Hui AJ, Tse YK, Ho KT, Lo AOS, et al. A new screening strategy for varices by liver and spleen stiffness measurement (LSSM) in cirrhotic patients: A randomized trial. Liver Int. 2018;38:636–44.
29. Gonzalez-Casas R, Jones EA, Moreno-Otero R. Spectrum of anemia associated with chronic liver disease. World J Gastroenterol. 2009;15:4653–8.
30. Benedetti E, Tavarozzi R, Morganti R, Bruno B, Bramanti E, Baratè C, et al. Organ stiffness in the work-up of myelofibrosis and Philadelphia-negative chronic myeloproliferative neoplasms. J Clin Med. 2020;9:2149.

How to cite this article: Moga L, Paradis V, Ferreira-Silva J, Gudavalli K, Indulti F, Dajti E, et al. Performance of spleen stiffness measurement to rule out high-risk varices in patients with porto-sinusoidal vascular disorder. Hepatology. 2024;■■:■■–■■. https://doi.org/10.1097/HEP.0000000000001004