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Elastography, Spleen Size, and Platelet Count Identify Portal Hypertension in Patients With Compensated Cirrhosis

ANNALISA BERZIGOTTI,[1,2,3] SUSANA SEIJO,[1,3] UMBERTO ARENA,[4] JUAN G. ABRALDES,[1,3] FRANCESCO VIZZUTTI,[4] JUAN CARLOS GARCÍA-PAGÁN,[1,3] MASSIMO PINZANI,[4] and JAIME BOSCH[1,3]

[1]Hepatic Hemodynamic Laboratory, Liver Unit, Hospital Clinic, University of Barcelona, Spain; [2]Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (Ciberehd), Spain; [3]Centre de Diagnòstic per l'Imatge, Hospital Clínic, Barcelona, Spain; and [4]Dipartimento di Medicina Interna, University of Florence, Florence, Italy

BACKGROUND & AIMS: Noninvasive methods are needed to identify clinically significant portal hypertension (CSPH) and esophageal varices (EVs) in patients with compensated cirrhosis. We looked for markers of the presence of CSPH and EVs in patients with cirrhosis. **METHODS:** We performed a cross-sectional study that included a training set of 117 patients with compensated cirrhosis, confirmed by histology, from a tertiary referral center. Spleen diameter was measured by ultrasound and liver stiffness (LS) was measured by transient elastography; endoscopy was used as the standard for detection of EVs and measurements of hepatic venous pressure gradient were used as the standard for identifying CSPH. We assessed the ability of platelet count, spleen diameter, LS, and combinations of these factors (ie, ratio of platelet count to spleen size, and LS × spleen size/platelet count [LSPS]) to identify patients with CSPH and EV. The analysis included 2 new statistical models: the PH risk score and the varices risk score. Results were validated using an independent series of 56 patients with compensated patients from another center. **RESULTS:** LS was the best single noninvasive variable for identifying patients with CSPH (area under the receiver operating characteristic, 0.883; 95% confidence interval [CI], 0.824–0.943; $P < .0001$). The area under the receiver operating characteristic value increased when LS was combined with platelet count and spleen size, either as LSPS (0.918; 95% CI, 0.872−0.965; $P < .0001$) or PH risk score (0.935; 95% CI, 0.893–0.977; $P < .0001$). More than 80% of patients were accurately classified using LSPS and PH risk score. Analyses of the varices risk score and LSPS were superior to all other noninvasive tests for identifying patients with EVs (area under the receiver operating characteristic, 0.909; 95% CI, 0.841−0.954 and 0.882; 95% CI, 0.810–0.935, respectively); they correctly classified 85% of patients in the training set and 75% in the validation set. **CONCLUSIONS: Combined data on LS, spleen diameter, and platelet count can be used to identify patients with compensated cirrhosis most likely to have CSPH and EV.**

Keywords: HVPG; Predictive Models; Prognostic Factor; Liver Disease.

Portal hypertension constitutes the pathophysiological basis of most complications of cirrhosis. A portal pressure gradient ≥10 mm Hg, as estimated by hepatic venous pressure gradient (HVPG), is necessary for the development of esophageal varices (EVs),[1] ascites, and all other complications of this syndrome. The term *clinically significant portal hypertension* has been coined to name this condition, which is invariably found in patients with decompensated disease.

On the contrary, only about 50% to 70% of patients with compensated cirrhosis show clinically significant portal hypertension (CSPH)[1]; in this setting, CSPH is an independent predictor of clinical decompensation[2]; this holds true also for patients with potentially resectable hepatocellular carcinoma.[3] In turn, the presence of EVs is an independent predictor of mortality[4] and this has led to the recommendation that all patients with compensated cirrhosis be investigated for the presence of gastroesophageal varices[5] and CSPH should ideally be diagnosed or ruled out.

Because the diagnoses of EVs and CSPH require endoscopy and hepatic vein catheterization, which are invasive and need specific expertise, there is a need for noninvasive, simple, objective, reproducible, and accurate methods to predict the presence of CSPH and of EVs in patients with compensated cirrhosis.

The most commonly reported parameters associated with CSPH and EVs in compensated patients include signs of hypersplenism, such as low platelet count,[6–12] large spleen size,[7,10,13] or their combination (platelet to spleen ratio),[14] dilatation of the portal vein system or presence of collaterals on ultrasound[8,15,16] and increase in the Child-Pugh score.[6,8,9,17] However, none of these methods were accurate enough when tested in independent validation series,[5,13] and some of them, such as a complete assessment of the portal vein system by ultrasound, were

Abbreviations used in this paper: AUROC, area under the receiver operating characteristic curve; CI, confidence interval; CSPH, clinically significant portal hypertension; EV, esophageal varices; HVPG, hepatic venous pressure gradient; INR, International Normalized Ratio; LR, likelihood ratio; LS, liver stiffness; LSPS, liver stiffness × spleen diameter to platelet ratio.

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not easy to perform and required specific long-term training.[18]

More recently, transient elastography, which estimates liver stiffness (LS), has been proposed as a new method to noninvasively diagnose CSPH and EVs in patients with cirrhosis. While the accuracy of LS in predicting CSPH seems good, its discriminative ability in the prediction of EVs appears inadequate.[19]

The combination of different methods might ameliorate the accuracy of single tests by assessing different pathophysiological components of portal hypertension. Recently, the combination of 3 simple methods—LS, spleen size, and platelet count (LSPS)—in a single score showed high accuracy for diagnosing and ruling out EVs in patients with compensated hepatitis B virus−related chronic liver disease[20]; however, this score has not been tested for the prediction of CSPH and there are no data on its ability to identify varices in patients with different etiologies of liver disease.

We aimed at comparing the accuracy of simple routinely available noninvasive parameters and their combination for identifying CSPH and presence of EVs in patients with compensated cirrhosis. For this aim, the results of noninvasive tests were compared with those of the measurement of HVPG (ie, the gold standard for the diagnosis of CSPH) and upper gastrointestinal endoscopy (ie, the gold standard for diagnosing esophagogastric varices).

CLINICAL LIVER

Methods

This study was approved by the Ethics Committee of each participating center. The nature of the study was explained to the patients and a written informed consent was obtained in each case according to the principles of the Declaration of Helsinki (revision of Edinburgh 2000).

Patients

Training set. The training set was composed by 117 patients with compensated cirrhosis requiring measurement of HVPG with the aim of diagnosing or excluding CSPH, included in 3 prospective studies carried out at Hospital Clínic, Barcelona between May 2007 and September 2011 (Berzigotti et al,[21] Llop et al,[22] and CITRO study, ongoing) in which all noninvasive parameters under investigation were available. Valid LS measurements could not be obtained in 14 (10.7%) of the 131 patients initially evaluated due to obesity (n = 8, no valid shot) or unreliable results (n = 3, success rate <60%; n = 3, interquartile range/median <30%). This prevented the inclusion of these 14 patients in the study.

AQ: 6

AQ: 7

Sixty-three patients (53.8%) had a single nodule of hepatocellular carcinoma (diameter: 31 ± 19 mm), potentially susceptible of surgical resection. Multifocal hepatocellular carcinoma was ruled out in all 63 patients by hepatic magnetic resonance imaging according to international guidelines.[23]

Cirrhosis was biopsy-proven in all cases. Transjugular liver biopsy was performed during hepatic vein catheterization under x-ray videofluoroscopy through either aspiration technique (15G needle; Cook Europe, Bjaeverskov, Denmark) or, in the case of small or fragmented specimen, by a Tru-Cut needle (18G Tru-Cut needle; Cook Europe). Passes of the needle were repeated until a satisfactory sample (at least 15 mm of length in total) was obtained.[24] Specimens were processed and stained with H&E and Masson's trichromic, and fibrosis was scored according to Ishak score by an expert pathologist unaware of the condition of the patient and of the study protocol and skilled in the interpretation of transjugular liver samples.

According to the protocol of each study, patients were assessed on the same day by HVPG and transient elastography.

Exclusion criteria were previous or ongoing decompensation of liver disease (ie, ascites, bleeding, hepatic encephalopathy, or jaundice), portal vein thrombosis, multifocal hepatocellular carcinoma, and previous or ongoing treatment for portal hypertension.

Validation set. The validation set was composed of 56 patients with compensated advanced chronic liver disease (50 with biopsy-proven cirrhosis and 6 with F3 fibrosis but suspected of having cirrhosis on clinical grounds) requiring measurement of HVPG with the aim of diagnosing or excluding CSPH, consecutively observed in a referral University Hospital in a different European Country (Florence, Italy). Exclusion criteria were similar to those of the training set. None of the patients included in the validation set had hepatocellular carcinoma.

Laboratory Parameters

Laboratory parameters were obtained on the day of HVPG measurement and included albumin, bilirubin, International Normalized Ratio (INR), renal function, electrolytes, hemoglobin, hematocrit, leukocyte and platelet count, cholesterol, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and γ-glutamyltransferase. Child-Pugh score was calculated.[25]

Spleen Size

Spleen size is routinely measured and reported on ultrasound examinations at both our center and the validation set center.[18] For the current study, spleen size was recorded as it appeared in the last abdominal ultrasound, which, in 70%, was within 1 week of HVPG, and in all cases within 3 months of HVPG. Spleen size was assessed as spleen bipolar diameter (crossing the spleen hilium) using last-generation equipment (ACUSON Sequoia 512; Siemens Medical Solutions USA Inc., Malvern, PA or SONOLINE Antares; Toshiba Aplio SSA 270, Tokyo, Japan) with a 3.5-MHz multifrequency sector or convex probe, following published guidelines.[18] Operators were experienced in ultrasound and not aware of the hemodynamic data of the patients.

LS by Transient Elastography

LS was evaluated by transient elastography (Fibroscan; Echosens, Paris, France) in the morning in a fasted state.[26] Measurements of LS were performed on the right lobe of the liver through intercostal spaces on patients lying in the dorsal decubitus position with the right arm in maximal abduction. The tip of the probe transducer was placed on the skin between the ribs at the level of the right hepatic lobe. The operator, assisted by an ultrasonic time-motion image, located a liver portion of at least 6-cm−thick and free of large vascular structures. Ten successful measurements were performed on each patient. Success rate was calculated as the ratio of the number of successful measurements over the total number of acquisitions. Only LS measurements with a success rate of at least 60% and an interquartile range <30% were considered reliable. Results are expressed in kilopascals and median value was used as represen-

tative of LS. The whole examination duration was about 5 minutes.

Combination of Noninvasive Methods

Platelet to spleen ratio was calculated as described previously by Giannini and colleagues as the ratio between platelet number/mm^3 and bipolar diameter of the spleen in millimeters.[14] Similarly, spleen to platelet ratio was calculated as the ratio between bipolar diameter of the spleen in millimeters and platelet number/mm.[20]

LSPS was calculated as described previously by Kim and colleagues as: LS × spleen diameter/platelet ratio.[20]

Hepatic Hemodynamics and Endoscopy

In the morning, after fasting overnight and immediately after transient elastography examination, the patients were transferred to the hepatic hemodynamic laboratory. Under local anesthesia, an 8F venous catheter introducer was placed in the right internal jugular vein using the Seldinger technique. Under fluoroscopic control a 7F balloon-tipped catheter (Edwards Lifesciences, Irvine, CA) was advanced into the right hepatic vein to measure wedged and free hepatic venous pressures using precalibrated electromechanical transducer and polygraph (Mac-Lab; GE Healthcare, Freiburg, Germany). The wedged position was obtained by inflating the balloon and confirming the occlusion of the hepatic vein by injecting a small amount of contrast medium. HVPG was calculated as the difference between wedged and free hepatic venous pressures.[27] All measurements were performed in triplicate and permanent tracings were recorded.[27]

Endoscopy was performed within 6 months of the hemodynamic evaluation by a small number of endoscopy operators, experienced in the assessment of patients with cirrhosis. According to international expert recommendations,[5] varices were classified as absent, small (diameter <5 mm) and large (diameter >5 mm).

In patients with large varices, medical treatment with β-blockers was initiated after measuring the noninvasive parameters used for this study and after measuring HVPG.

Statistical Analysis

This study was designed as a phase III to IV study of diagnostic tests according to Lijmer et al,[28] aimed at investigating how well the test distinguishes between patients with or without the disease in patients suspected of having the disease (phase III), and how informative a test is considering additional information available at the moment of testing (phase IV).

Noninvasive models to identify CSPH and EVs were built in a first set of patients from our center (training set), and subsequently validated in a separate, independent set of patients (validation set). To do so, those variables showing a $P < .10$ at univariate analysis (Student t test for parametric variables, and χ^2 or Fisher's exact test for frequencies) were included in a multivariable backward stepwise logistic regression. The interaction between these variables was also tested. Variables explaining a statistically significant proportion of the variance ($P < .1$) were maintained in the model using the likelihood ratio (LR) test. The discriminative ability of the different noninvasive methods for the identification of CSPH and of presence of EVs was assessed by means of receiver operating characteristic curve analysis and expressed as area under the receiver operating characteristic curve (AUROC). Comparison between AUROC was made using DeLong test. Sensitivity, specificity, positive, and negative likelihood ratio (+LR and −LR) and 95% confidence intervals (CIs) were calculated. McNemar test was used in the 2 × 2 contingency table for assessing differences in the proportion of misclassified patients with dichotomous cutoffs of different noninvasive tests. Similarly, McNemar-Bowker test was used for 3 × 3 contingency table for assessing differences in the proportion of misclassified patients with 2 cutoffs of different noninvasive tests. In addition, the performance of previously published cutoffs for the identification of CSPH and varices derived from prospective studies was tested; namely we tested 13.6 kPa[29] and 21.1 kPa[30,31] for the prediction of CSPH, and 17.6 kPa for the prediction of varices.[29]

Statistical analysis was performed with SPSS 16.0 package (SPSS, Chicago, IL), CIA software (v 2.2.0, University of Southampton, Southampton, UK) and MedCalc software (version 12.2.1.0, Belgium). The α value was set at 0.05. All P values are 2-sided.

Results

CSPH

Table 1 shows the main characteristics of the studied population. As shown, most patients both in the training set and in the validation set had viral liver disease. The prevalence of CSPH was 67% in the training set and 86% in the validation set.

On univariate analysis, in the training set, patients with CSPH had a higher prevalence of male sex, worse liver function (higher bilirubin and INR, lower albumin), higher LS, lower platelet count, and larger spleen as compared with patients without CSPH (Table 1). Because platelet count and spleen diameter are thought to reflect the same clinical consequence of portal hypertension (hypersplenism), we performed a first exploratory binary logistic regression analysis to evaluate which variable among platelet count, spleen size, and their combination (platelet count/spleen diameter ratio and spleen diameter/platelet count ratio) better explained the existence of CSPH. This analysis selected only spleen diameter/platelet count ratio, which was used in subsequent analysis.

Then, we performed a binary logistic regression including 6 variables (ratio events/variables entered: 13:1): bilirubin, INR, albumin, LS, spleen diameter/platelet count ratio, and sex. LS, spleen diameter/platelet count ratio, and sex were maintained in the final model; similar results were obtained when bilirubin, INR, and albumin were substituted by Child-Pugh score.

The equation of the model (PH risk score) is the following:

PH risk score = −5.953 + 0.188 × LS +1.583 × sex (1: male; 0: female) + 26.705 × spleen diameter/platelet count ratio

As for the performance of the different noninvasive variables tested and of the derived PH risk score in predicting CSPH, in the training set all of them were significantly associated with CSPH; AUROC were as follows: spleen diameter: 0.719 (95% CI, 0.618−0.819; $P < .0001$); AQ: 8
platelet count: 0.787 (95% CI, 0.705−0.869; $P < .0001$); AQ: 9
platelet count to spleen diameter ratio[14]: 0.811 (95% CI, 0.734−0.889; $P < .0001$); combination of laboratory vari- AQ: 10

Table 1. Main Characteristics of Patients Included in the Training Set and the Validation Set According to the Presence of CSPH

	Training set (N = 117)	Training set with CSPH (n = 78)	Training set without CSPH (n = 39)	*P* value[a]	Validation set (N = 56)[b]	VS vs TS, *P* value
Age, *y*	60 ± 11	60 ± 11	60 ± 10	.757	58 ± 11	.562
Sex, M/F, n	82/35	50/28	32/7	.035	36/20	.443
Body mass index[c]	26.8 ± 4.7	27.0 ± 4.3	26.1 ± 5.8	.600	24.7 ± 2.8	.160
Etiology, HCV/HBV/alcohol/other, n	78/11/16/12	51/4/13/10	27/7/3/2	.086	46/4/6/0	.142
Child–Pugh score	5.5 ± 0.8	5.7 ± 0.9	5.1 ± 0.4	.001	6.0 ± 1.3	.001
Child–Pugh class, A/B, n	103/14	64/13	39/1	.023	39/17	.003
Esophageal varices, no/small/large, n	80/23/14	42/22/14	38/1/0	<.0001	23/14/19	.001
Hepatic nodule, n (%)	63 (54)	29 (38)	34 (85)	<.0001	0	<.001
Bilirubin, *mg/dL*	1.2 ± 0.9	1.3 ± 1.0	0.8 ± 0.4	.003	1.3 ± 0.8	.267
INR	1.16 ± 0.016	1.20 ± 0.17	1.09 ± 0.09	<.0001	1.14 ± 0.18	.532
Albumin, *g/dL*	3.8 ± 0.6	3.7 ± 0.6	4.2 ± 0.5	<.0001	3.5 ± 0.6	.006
AST, *IU/mL*	81 ± 54	92 ± 59	75 ± 34	.224	87 ± 64	.530
ALT, *IU/mL*	78 ± 52	91 ± 52	68 ± 47	.198	80 ± 53	.838
HVPG, *mm Hg*	11.9 ± 5.5	14.9 ± 4.2	6.0 ± 2.2	<.0001	15.2 ± 5.7	<.0001
CSPH, n (%)	78 (67)	NA	NA	NA	48 (86)	.006
Platelets, $n \times 10^9/L$	137 ± 64	118 ± 56	175 ± 61	<.0001	116 ± 52	.027
Combination of laboratory variables[17]	3.77 ± 4.39	4.87 ± 4.80	1.87 ± 2.76	<.0001	4.88 ± 4.45	.155
Liver stiffness, *kPa*	25.2 ± 16.6	31.4 ± 16.9	13.2 ± 5.8	<.0001	27.4 ± 12.1	.377
Spleen diameter, *cm*	13.1 ± 3.0	13.9 ± 3.1	11.5 ± 2.1	<.0001	15.3 ± 2.9	<.0001
Platelet to spleen ratio[14]	1156 ± 704	922 ± 562	1606 ± 735	<.0001	817 ± 443	.001
Spleen to platelet ratio[20]	0.126 ± 0.096	0.153 ± 0.106	0.074 ± 0.031	<.0001	0.169 ± 0.114	.009
LSPS[20]	3.53 ± 3.94	4.83 ± 4.30	1.02 ± 0.62	<.0001	5.02 ± 4.62	.029

NOTE. Values are mean ± SD unless otherwise indicated.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; F, female; HBV, hepatitis B virus; HCV, hepatitis C virus; M, male; TS, training set; VS, validation set.

[a]Comparison between patients with and without CSPH.

[b]Six patients had severe (F3) fibrosis and were included because cirrhosis was suspected on clinical ground.

[c]Calculated as kg/m^2.

CLINICAL LIVER

ables[17]: 0.691 (95% CI, 0.590−0.792; $P = .001$), LS: 0.883 (95% CI, 0.824−0.943; $P < .0001$); LSPS: 0.918 (95% CI, 0.872−0.965; $P < .0001$); PH risk score: 0.935 (95% CI, 0.893−0.977; $P < .0001$).

The parameters with better diagnostic performance for CSPH were LS, LSPS, and PH Risk score (Table 2). In particular, PH risk score and LSPS had the best discriminating capacity. LSPS was only marginally superior to LS alone for CSPH (DeLong test: $P = .087$; Figure 1), while PH Risk score was clearly superior to LS (DeLong test: $P = .021$), but not statistically different from LSPS (DeLong test: $P = .160$; Figure 1). Similar results were obtained when patients were analyzed according to the etiology of liver disease.

As expected, the proportion of patients with LS ≥ 13.6 (88 of 117) was significantly higher in patients with CSPH (91.0% vs 43.6%; $P < .0001$); the same happened in those with LS ≥ 21.1 kPa (54 of 117; 65.3% with CSPH vs 7.7% without CSPH; $P < .0001$). As previously observed by our group,[22] these values indicate that the 13.6 kPa cutoff had high sensitivity: 91.0% (95% CI, 82.6%−95.6%), but low specificity 56.4% (95% CI, 41.0%−70.7%), while the 21.1 kPa cutoff had a 92.3% specificity (95% CI, 79.7%−97.3%), but low sensitivity: 65.4% (95% CI, 54.3%−75.0%) for the prediction of CSPH. The 34 patients with values of LS between 13.6 and 21.1 kPa (29% of the included population) cannot be accurately classified, and should be considered indeterminate.

Table 2 shows the best cutoffs of the tested noninvasive parameters; as shown, only LSPS and PH risk score allowed identifying a single dichotomic cutoff combining both a sensitivity and a specificity >80% (respectively 1.72 for LSPS and 0.63 for PH risk score); LS, although close, did not fulfill this target.

The 1.72 LSPS cutoff classified correctly 98 of 117 (84%) (65 as having CSPH and 33 as not having CSPH), while 19 (16%) were misclassified (6 false-positive and 13 false-negative results). With the 0.63 PH risk score cutoff, 100 of 117 (85%) patients were well classified (66 as having CSPH and 34 as not having CSPH), while 17 (15%) were misclassified (5 false-positive and 12 false-negative results).

Results in the validation set confirmed the high discriminative power of LS, LSPS, and PH risk score for the prediction of CSPH (Table 2, Figure 2). In terms of well classified and misclassified patients, the PH risk score was significantly superior to the best cutoff (21.1 kPa) of transient elastography (McNemar test $P = .017$).

When, instead of using a dichotomic strategy, we applied a 90% sensitive cutoff to rule out CSPH, and a 90% specific cutoff to rule in CSPH (Figure 2), PH risk score showed again the best performance, with a low

Table 2. Performance of the Best Tested Noninvasive Methods for Identifying CSPH (HVPG ≥ 10 mm Hg) in the Training Set (n = 117) and in the Validation Set (n = 56)

	AUROC for predicting CSPH (95% CI)	Cutoff with ≥80% Sensitivity, % Specificity, % PPV, % NPV, % +LR −LR Well classified, %	Cutoff with ≥80% Specificity, % Sensitivity, % PPV, % NPV, % +LR −LR Well classified, %	Cutoff with ≥90% Sensitivity, % Specificity, % PPV, % NPV, % +LR −LR Well classified, %	Cutoff with ≥90% Specificity, % Sensitivity, % PPV, % NPV, % +LR −LR Well classified, %
LS, *kPa*					
Training set	0.883[a] (0.824−0.943)	17.4	17.8	13.0	20.6
	$P < .0001$	82.1 (72.1−89.0)	84.6 (70.3−92.8)	91.0 (82.6−95.6)	92.3 (79.7−97.3)
		76.9 (61.7−87.4)	78.2 (67.8−85.9)	56.4 (41.0−70.7)	66.7 (55.6−76.1)
		87.7 (78.2−93.4)	91.0 (81.8−95.8)	80.7 (71.2−87.6)	94.5 (79.7−97.3)
		68.2 (53.4−80.0)	66.0 (52.2−77.6)	75.9 (57.9−87.8)	58.1 (45.7−69.5)
		3.56 (1.99−6.37)	5.08 (2.41−10.71)	2.09 (1.45−3.00)	8.67 (2.89−26.00)
		0.23 (0.14−0.39)	0.26 (0.17−0.40)	0.16 (0.07−0.34)	0.36 (0.26−0.50)
		80.3	80.3	79.5	75.2
Validation set	0.901 (0.804−0.998)	Well classified, 80.4%	Well classified, 78.6%	Well classified, 89.2%	Well classified, 78.5%
LSPS[20]	$P < .0001$				
Training set	0.918[b] (0.872−0.965)	1.72	See previous column	1.08	2.06
	$P < .0001$	83.3 (73.5−90.0)		91.0 (82.6−95.6)	92.3 (79.7−97.3)
		84.6 (70.3−92.8)		64.1 (48.4−77.3)	75.6 (65.1−83.8)
		91.5 (82.8−96.1)		83.5 (74.2−89.9)	95.2 (86.7−98.3)
		71.7 (57.5−82.7)		78.1 (61.2−89.0)	65.5 (52.3−76.6)
		5.42 (2.58−11.38)		2.54(1.66−3.88)	9.83 (3.29−29.38)
		0.20 (0.12−0.33)		0.14 (0.07−0.30)	0.26 (0.18−0.39)
		83.7		82.1	81.2
Validation set	0.906 (0.818−0.995)	Well classified, 85.7%	See previous column	Well classified, 89.3%	Well classified, 78.6%
PH risk score	$P < .0001$				
Training set	0.935 (0.893−0.977)	0.63	See previous column	0.06	0.83
	$P < .0001$	84.6 (75.0−91.0)		91.0 (82.6−95.6)	92.3 (79.7−97.3)
	$P =$ vs LS	87.2 (73.3−94.4)		74.4 (58.9−85.4)	82.1 (72.1−89.0)
	$P =$ vs LSPS	93.0 (84.6−97.0)		87.7 (78.7−93.2)	95.5 (87.6−98.5)
		73.9 (59.7−84.4)		80.6 (65.0−90.2)	72.0 (58.3−82.5)
		6.60 (2.90−15.04)		3.55 (2.07−6.09)	10.67 (3.58−31.79)
		0.18 (0.10−0.30)		0.12 (0.06−0.25)	0.19 (0.12−0.32)
		85.5		85.5	85.5
Validation set	0.932 (0.853−1.000)	Well classified, 87.5%	See previous column	Well classified, 91.1%	Well classified, 85.7%
	$P < .0001$				
	$P =$ vs LSPS				

NPV, negative predictive value; PPV, positive predictive value.
De Long test:
[a] $P < .05$ vs spleen diameter and platelet count.
[b] $P < .05$ vs spleen diameter, platelet count, and platelet to spleen ratio; $P = .087$ vs LS.

proportion of misclassified patients and a lower proportion of indeterminate cases (McNemar−Bowker test: PH risk score vs LS: $P < .0001$ in TS and VS; PH risk score vs LSPS: $P = .025$ in the TS and $P = .016$ in VS).

CSPH in Patients With Hepatic Nodules

Given the importance of diagnosing CSPH in patients with hepatic nodules,[3,23] we performed a subanalysis in our 63 patients (29 with CSPH and 34 without) testing the performance of all noninvasive variables. AUROCs were as follows: spleen diameter: 0.627 (95% CI, 0.490−0.765; $P = .084$); platelet count: 0.675 (95% CI, 0.536−0.814; $P = .017$); platelet count to spleen diameter ratio[14]: 0.694 (95% CI, 0.558−0.830; $P = .008$); combination of laboratory variables[17]: 0.540 (95% CI, 0.384−0.696; $P = .592$), LS: 0.850 (95% CI, 0.751−0.949; $P < .0001$); LSPS: 0.852 (95% CI, 0.757−0.947; $P < .0001$); PH risk score: 0.884 (95% CI, 0.796−0.973; $P < .0001$). Again, the 3 best parameters were LS, LSPS, and PH risk score but no statistical difference was found comparing the 3 AUROCs. However, only PH risk score allowed identifying a cutoff with >80% sensitivity and specificity, namely 0.190: sensitivity 80.0% (95% CI, 62.7%−90.5%), specificity 84.8% (95% CI, 69.1%−93.3%), positive predictive value 82.8% (95% CI, 65.5%−92.4%), negative predictive value 82.4% (95% CI, 66.5%−91.7%), +LR 5.28 (95% CI, 2.31−12.07), and −LR 0.24 (95% CI, 0.11−0.49). By using this cutoff 82.5% of patients were correctly identified as having or not CSPH.

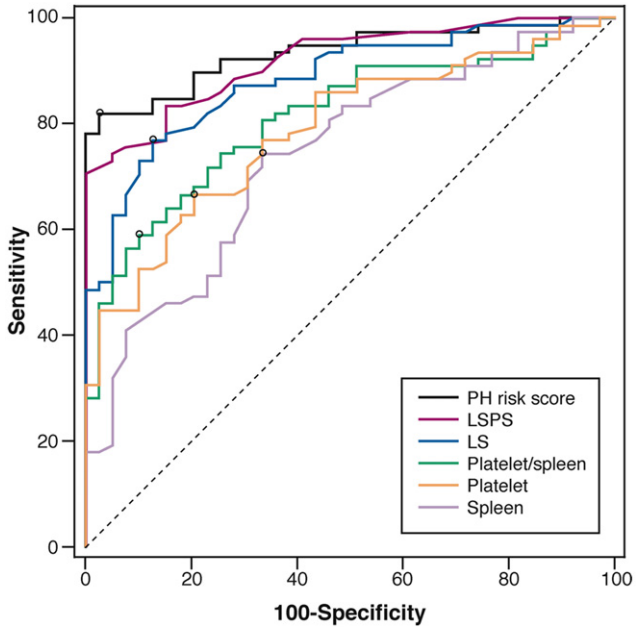

Figure 1. Prediction of CSPH in the training set. ROC curves of previously described noninvasive parameters and of the PH risk score for identifying CSPH. As shown, PH risk score, LSPS, and LS had the best diagnostic performance (De Long test: PH risk score vs LS $P = .021$; LSPS vs LS $P = .087$; PH risk score vs LSPS $P = .160$).

EVs

In the training set, 37 of 117 (32%) patients had EVs. In the validation set 33 of 56 (59%) patients had EVs. All patients with varices had CSPH.

In the training set (Supplementary Table 1) patients with and without varices differed in albumin, INR, Child-Pugh score, spleen diameter, platelet count, LS, platelet to spleen ratio, spleen to platelet ratio, and LSPS. Because LSPS includes spleen diameter, platelet count, and LS, we performed the multivariate analysis, including albumin, INR (and/or Child−Pugh score), spleen diameter, platelet count, and LS. In this step, spleen diameter, platelet count, and LS were maintained in the model. Then we added the first- and second-grade interaction terms of these 3 variables, that is, spleen diameter × platelet count; spleen diameter × LS; platelet count × LS and spleen diameter × platelet count × LS. By this method, a hierarchical model including spleen diameter, platelet count, LS, and platelet count × LS was calculated as follows:

varices risk score = −4.364 + 0.538 × spleen diameter − 0.049 × platelet count − 0.044 × LS +0.001 × (LS × platelet count).

The performance of the studied noninvasive parameters (Figure 3) and of the new model (the varices risk score) for identifying EVs expressed as AUROC was as follows: platelet count: 0.761 (95% CI, 0.674−0.935; $P < .0001$); spleen diameter: 0.785 (95% CI, 0.700−0.856; $P < .0001$); LS: 0.794 (95% CI, 0.709−0.863; $P < .0001$); platelet count to spleen ratio: 0.814 (95% CI, 0.732−0.880; $P < .0001$); LSPS 0.882 (95% CI, 0.810−0.935; $P < .0001$); varices risk score: 0.909 (95% CI, 0.841−0.954; $P < .0001$). Similar results were obtained when data were analyzed according to the etiology of liver disease.

As shown in Table 3 and Figure 3, LSPS and varices risk score had very high discriminative ability in predicting varices. The analysis of the performance of previously published cutoffs of noninvasive variables disclosed that the 3.5 (sensitivity, 75.5%; 95% CI, 59.9−86.6; specificity, 88.8%; 95% CI, 80.5−93.8) and 5.5 (sensitivity, 43.2%; 95% CI, 28.7−59.1; Specificity 91.0%; 95% CI, 83.3−95.4) cutoffs of LSPS were not accurate enough for predicting or excluding the presence of varices (combined accuracy of 75.3%). Based on the analysis of the ROC curve, we here propose a new cutoff of LSPS, namely 3.21, with a good accuracy in both the training set (84.6%) and validation set (75%) (Figure 4).

Discussion

In recent years, the availability of noninvasive tools increased the proportion of patients with chronic liver disease diagnosed in the compensated stage of cirrhosis.[32,33] Because these patients, despite being completely asymptomatic, are those at risk of decompensation and require endoscopic screening for varices, objective and accurate noninvasive predictors of portal hypertension and EVs are especially needed.[5]

In this study, we confirm that, among the available and routinely used noninvasive methods, LS is the single better marker of CSPH, as assessed by the accepted gold standard, ie, HVPG measurement. We further demonstrate that its performance can be improved by combining it with platelet count and spleen size into a single parameter, the PH risk score, which had a very good diagnostic accuracy in both the training set and validation cohort from another European country. In this regard, it should be noted that PH risk score and LSPS (the first attempt at integrating empirically values of LS and spleen diameter to platelet count reported by Kim and colleagues to predict EVs in patients with hepatitis B virus−related chronic liver disease[20]) both show excellent AUROCs, which are similar from a statistical point of view. However, when applying the best cutoffs of the curves, PH risk score, calculated through a robust statistical analysis of the noninvasive parameters of our training set, further improved the performance as compared with LSPS by reducing the proportion of indeterminate findings (12% in the training set and 5% in the validation set). Certainly, such a predictive value, pointed out by an AUROC of 0.93 in the training and validation cohorts, is almost impossible to improve in clinical practice and allows substituting the measurement of HVPG in detecting CSPH. The relevance of this finding relates to the fact that patients with CSPH are at a much higher risk of developing varices, clinical decompensation, and hepatocellular carcinoma than compensated cirrhotic without CSPH. Therefore, being able to accurately predict if a patient belongs to such a higher-risk group has direct clinical implications.

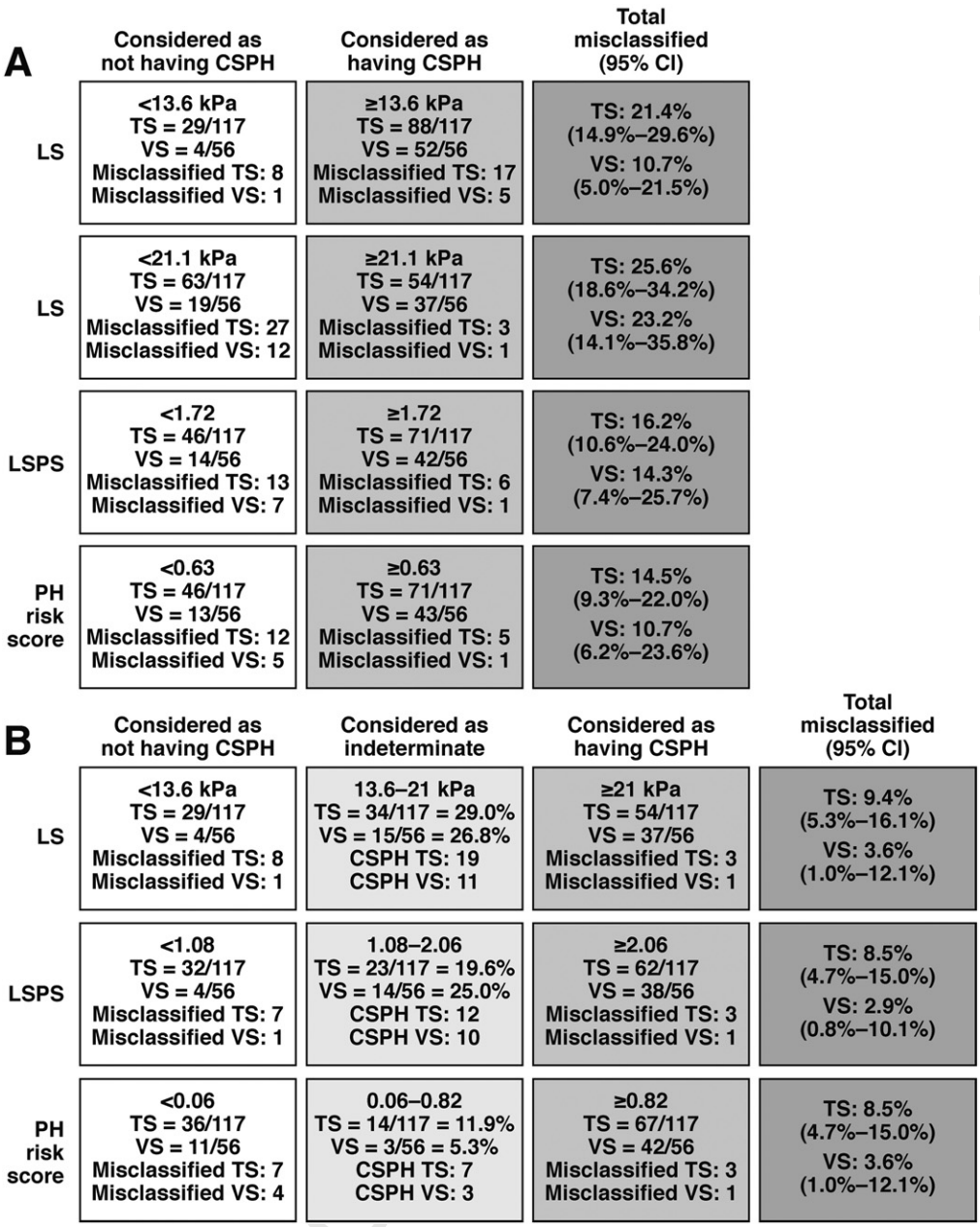

Figure 2. Performance of the chosen cutoffs of noninvasive variables for predicting CSPH. Performance of binary cutoffs (*A*) and of the use of 2 cutoffs (one to rule out CSPH, and one to rule in CSPH) (*B*) of LS, LSPS, and PH risk score for the identification of CSPH in the training set (TS) and in the validation set (VS). By using 2 cutoffs, PH risk score showed the best performance with low proportion of misclassified patients, and lower proportion of indeterminate cases (McNemar–Bowker test: PH risk score vs LS: $P < .0001$ in the TS and in the VS; PH risk score vs LSPS: $P = .025$ in the TS and $P = .016$ in the VS).

As for the remaining noninvasive variables, none of them allowed an accurate enough prediction of CSPH; interestingly, a model based on laboratory variables (albumin, INR, and alanine aminotransferase) published by our group[17] did not perform well in the present cohort composed of patients with chronic liver disease of different etiologies, although it confirmed a high discriminative power in the validation set, which was composed mainly of HCV patients as the population from which the model was derived.

Regarding the study population, we decided to include patients with a single hepatic nodule potentially susceptible to resection because in them the prediction of CSPH is central and changes the clinical management.[3,23] Although in this subpopulation, most noninvasive parameters have a reduced diagnostic accuracy, the PH risk score was still able to predict CSPH with an AUROC >0.85, even in this subgroup of "difficult" patients. The PH risk score has the advantage of not being significantly influenced by the etiology of cirrhosis or the presence of liver nodules.

As for the prediction of the presence of EVs, LSPS had a good diagnostic performance, with accuracy of 85% in the training set and 76% in the validation set, similar to that of our model-derived varices risk score. This combination of parameters was clearly superior to the performance of LS alone for predicting EV. Interestingly enough, while diagnostic accuracy of LSPS by AUROC was similar to that published by Kim et al,[20] the cutoffs of the original publication were not accurate in our population; we speculate that this might depend on the different etiologies of the included patients (hepatitis B virus in the original publication, various etiologies in the present). Of note also, all

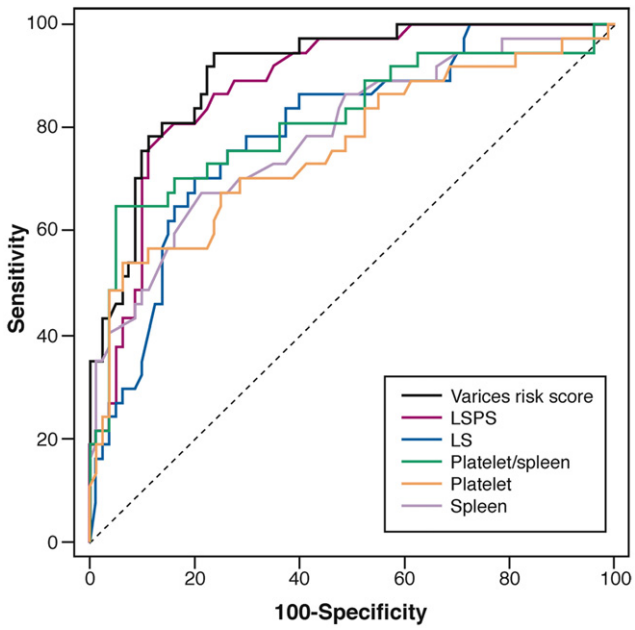

Figure 3. Prediction of varices in the training set. ROC curves of previously described noninvasive parameters for predicting varices. As shown, LSPS and varices risk score had the best diagnostic performance (by De Long test: LSPS vs LS $P = .010$; varices risk score vs LS $P = .002$; varices risk score vs LSPS $P = .181$).

remaining noninvasive variables, either used alone (spleen size, platelet count, LS) or in combination (platelet to spleen ratio), had an overall accuracy <80%, which is the minimum recommended for a diagnostic test. It is important to stress that being able to predict varices cannot be translated directly into number of endoscopies saved because the prediction does not extend to endoscopic signs of high-risk varices (big in size and/or with presence or red color signs over their wall). However, endoscopy can probably be obviated or delayed in patients with low predicted probability of varices.

This study suffers some potential limitations. First, we included in both the training set and the validation cohort only patients consecutively observed with valid measurements of LS, platelet count, and spleen size. Therefore, our results have been obtained according to a "per diagnostic protocol" analysis, and do not completely reflect the real-life situation in which technical failures of the tests might occur. Indeed, in the training set, 14 patients (10.6%) originally evaluated were excluded due to technical failure of transient elastography, confirming previous observations.[19] New transient elastography probes (XL probe), as well as new sonoelastography methods, might overcome this limitation of transient elastography,[34] with the added advantage of improving the applicability of measurement of spleen stiffness,

Table 3. Performance of the Best Combinations of Noninvasive Methods for Identifying Esophageal Varices in the Training Set (N = 117) and in the Validation Set (N = 56)

	AUROC for predicting EV (95% CI)	Cutoff with ≥80% Sensitivity, % Specificity, % PPV, % NPV, % +LR −LR Well classified, %	Cutoff with ≥80% Specificity, % Sensitivity, % PPV, % NPV, % +LR −LR Well classified, %	Cutoff with ≥90% Sensitivity, % Specificity, % PPV, % NPV, % +LR −LR Well classified, %	Cutoff with ≥90% Specificity, % Sensitivity, % PPV, % NPV, % +LR −LR Well classified, %
LSPS[20]					
Training set	0.882[a] (0.810−0.935)	3.21	2.94	2.06	3.85
	$P < .0001$	81.1 (65.8−90.5)	80.0 (70.0−87.3)	91.9 (78.7−97.2%)	90.0 (81.5−94.8)
		86.3 (77.0−92.1)	83.8 (68.9−92.3)	65.0 (54.1−74.5)	70.3 (54.2−82.5)
		73.2 (58.1−84.3)	66.0 (51.7−77.8)	54.8 (42.5−66.6)	76.5 (60.0−87.6)
		90.8 (82.2−95.5)	91.4 (82.5−96.0)	94.5 (85.1−98.1)	86.(77.8−92.4)
		5.90 (3.33−10.43)	4.19 (2.64−6.64)	2.63 (1.92−3.59)	7.03 (3.53−14.01)
		0.22 (0.11−0.43)	0.20 (0.10−0.43)	0.13 (0.04−0.37)	0.33 (0.20−0.55)
		84.6	81.2	73.5	83.8
Validation set	0.808 (0.693−0.923)	Well classified, 75.0%	Well classified, 75.0%	Well classified, 76.8%	Well classified, 69.6%
Varices risk score	$P < .0001$				
Training set	0.909[b] (0.841−0.954)	−0.16	−0.40	−0.71	0.20
	$P < .0001$	81.1 (65.8−90.5)	80.0 (70.0−87.3)	91.9 (78.7−97.2)	90.0 (81.5−94.8)
		86.3 (77.0−92.1)	83.8 (68.9−92.3)	77.5 (67.2−85.3)	70.3 (54.2−94.8)
		73.2 (58.1−84.3)	66.0 (51.7−77.8)	65.4 (51.8−76.8)	76.5 (60.0−87.6)
		90.8 (82.2−95.5)	91.4 (82.5−96.0)	95.4 (87.3−98.4)	86.7 (77.8−92.4)
		5.90 (3.33−10.43)	4.19 (2.64−6.64)	4.08 (2.69−6.20)	7.03 (3.53−14.01)
		0.22 (0.11−0.43)	0.20 (0.10−0.43)	0.10 (0.03−0.31)	0.33 (0.20−0.54)
		84.6	81.2	82.1	83.8
Validation set	0.759 (0.627−0.891)	Well classified, 75.0%	Well classified, 76.8%	Well classified, 75.0%	Well classified, 72.6%
	$P < .0001$				

NPV, negative predictive value; PPV, positive predictive value.
De Long test:
[a]$P < .05$ vs spleen diameter, platelet count, and liver stiffness.
[b]$P < .05$ vs spleen diameter, platelet count, and platelet to spleen ratio and LS.

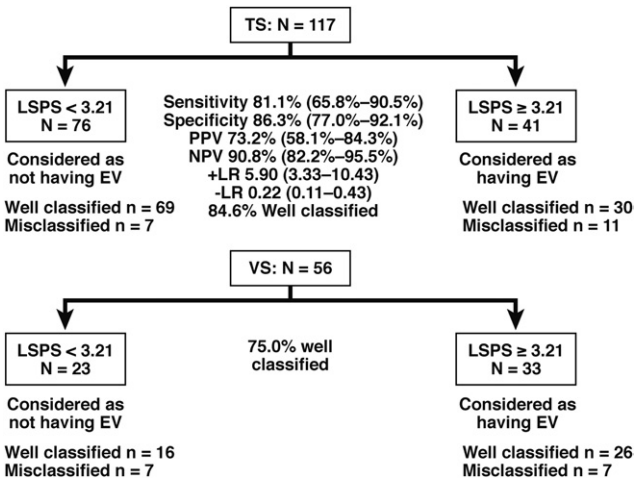

Figure 4. Performance of the LSPS cutoff 3.21 for the prediction of EVs in the training set and in the validation set.

which is emerging as a novel noninvasive parameter closely correlating with HVPG and presence of EVs.[35,36] Second, the prevalence of EVs in our population of compensated patients was relatively low, which might represent a bias for the generalizability of our results[37]; however, the prevalence of varices in the validation cohort was exactly as anticipated. It should also be noted that patients included in the training set and in the validation set differed in a number of characteristics; however, the similar results obtained by applying our models in the validation set further confirms the robustness of our findings. Finally, we acknowledge that PH risk score and varices risk score are more difficult to calculate than LSPS at the bedside. In order to reduce the impact of this limitation, we have made a calculator available online (www.ciberehd.org/platforms-and-services/calculator?set_language=en) in which data can be easily introduced and the individual probability of CSPH and of EV can be instantaneously visualized.

In conclusion, LS combined with spleen diameter and platelet count (either as LSPS or our new model-derived PH risk score) allows a highly accurate noninvasive identification of CSPH in patients with compensated cirrhosis. Presence of EVs in patients with compensated cirrhosis of different etiologies can also be determined accurately enough by a varices risk score and LSPS, but cutoffs of the latter in our population are different than those previously published.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2012.10.001.

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Address requests for reprints to: Jaime Bosch, MD, Hepatic Hemodynamic Laboratory, Liver Unit, Hospital Clínic, Villarroel 170, 08036 Barcelona, Spain. e-mail: jbosch@clinic.ub.es; fax: +34 93 227 93 48. AQ: 2

Acknowledgments AQ: 3
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Supplementary Table 1. Main Characteristics of Patients Included in the Training Set According to the Presence of Esophageal Varices

	Patients with varices (n = 37)	Patients without varices (n = 80)	*P* value
Age, *y*	59 ± 12	60 ± 9	.435
Body mass index[a]	27.7 ± 4.2	26.2 ± 4.9	.340
Sex, M/F, n	24/13	58/22	.209
Etiology, HCV/HBV/alcohol/other	24/1/6/6	54/10/10/6	.137
Child–Pugh score	5.9 ± 1.0	5.3 ± 0.6	.001
AST, *U/L*	89 ± 48	79 ± 56	.405
ALT, *U/L*	75 ± 38	81 ± 57	.663
Bilirubin, *mg/dL*	1.4 ± 0.8	1.0 ± 0.9	.033
INR	1.25 ± 0.18	1.12 ± 0.12	<.0001
Albumin, *g/dL*	3.5 ± 0.4	4.0 ± 0.6	<.0001
HVPG, *mm Hg*	16.8 ± 4.4	9.61 ± 4.3	<.0001
Platelets, n^3/mmc	104 ± 61	152 ± 59	<.0001
Liver stiffness, *kPa*	36.3 ± 18.2	20.1 ± 13.0	<.0001
Spleen diameter, *cm*	15.2 ± 3.6	12.1 ± 2.1	<.0001
Platelet to spleen ratio	749 ± 587	1336 ± 680	<.0001
Spleen to platelet ratio	0.198 ± 0.130	0.094 ± 0.046	<.0001
LSPS	6.67 ± 5.07	2.09 ± 2.09	<.0001
Varices risk score	0.96 ± 2.16	−4.00 ± 3.39	<.0001

NOTE. Values are mean ± standard deviation unless otherwise indicated.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; F, female; HBV, hepatitis B virus; HCV, hepatitis C virus; M, male.

[a]Calculated as kg/m^2.