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CLINICAL—LIVER

Association Between Portosystemic Shunts and Increased Complications and Mortality in Patients With Cirrhosis

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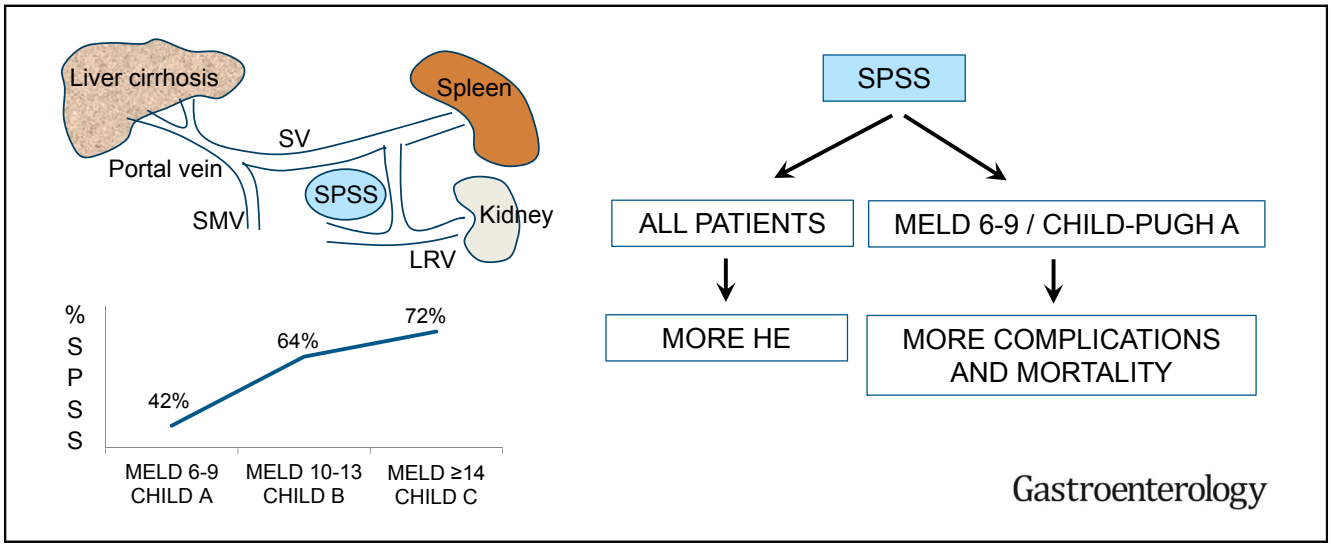

EDITOR'S NOTES

BACKGROUND AND CONTEXT

The presence of SPSS has been associated with recurrent or persistent hepatic encephalopathy (HE), but their prevalence in patients with cirrhosis remains unclear.

NEW FINDINGS

SPSS are very frequent in liver cirrhosis, and their presence increases considerably as liver function deteriorates. HE is more frequent in SPSS patients, independently of liver function. Patients with good liver function and SPSS develop more complications and have a lower transplant-free survival.

LIMITATIONS

The study was retrospective. Some data were not available in all patients. Imaging tests were only evaluated at one time point, with lack of information about radiological improvement or deterioration according to the disease course.

IMPACT

In patients with preserved liver function, SPSS identifies patients with a higher risk of worse outcomes and should be considered an important imaging biomarker in cirrhosis.

See editorial on page 1569.

BACKGROUND & AIMS: Spontaneous portosystemic shunts (SPSS) have been associated with hepatic encephalopathy (HE). Little is known about their prevalence among patients with cirrhosis or clinical effects. We investigated the prevalence and characteristics of SPSS in patients with cirrhosis and their outcomes. **METHODS:** We performed a retrospective study of 1729 patients with cirrhosis who underwent abdominal computed tomography or magnetic resonance imaging analysis from 2010 through 2015 at 14 centers in Canada and Europe. We collected data on demographic features, etiology of liver disease, comorbidities, complications, treatments, laboratory and clinical parameters, Model for End-Stage Liver Disease (MELD) score, and endoscopy findings. Abdominal images were reviewed by a radiologist (or a hepatologist trained by a radiologist) and searched for the presence of SPSS, defined as spontaneous communications between the portal venous system or splanchnic veins and the systemic venous system, excluding gastroesophageal varices. Patients were assigned to groups with large SPSS (L-SPSS, $\geq$8 mm), small SPSS (S-SPSS, $<$8 mm), or without SPSS (W-SPSS). The main outcomes were the incidence of complications of cirrhosis and mortality according to the presence of SPSS. Secondary measurements were the prevalence of SPSS in patients with cirrhosis and their radiologic features. **RESULTS:** L-SPSS were identified in 488 (28%) patients, S-SPSS in 548 (32%) patients, and no shunt (W-SPSS) in 693 (40%) patients. The most common L-SPSS was splenorenal (46% of L-SPSS). The presence and size of SPSS increased with liver dysfunction: among patients with MELD scores of 6–9, 14% had L-SPSS and 28% had S-SPSS; among patients with MELD scores of 10–13, 30% had L-SPSS and 34% had S-SPSS; among patients with MELD scores of 14 or higher, 40% had L-SPSS and 32% had S-SPSS ($P < .001$ for multiple comparison among MELD groups). HE was reported in 48% of patients with L-SPSS, 34% of patients with S-SPSS, and 20% of patients W-SPSS ($P < .001$ for multiple comparison among SPSS groups). Recurrent or persistent HE was reported in 52% of patients with L-SPSS, 44% of patients with S-SPSS, and 37% of patients W-SPSS ($P = .007$ for multiple comparison among SPSS groups). Patients with SPSS also had a larger number of portal hypertension-related complications (bleeding or ascites) than those W-SPSS. Quality of life and transplantation-free survival were lower in patients with SPSS vs without. SPSS were an independent factor associated with death or liver transplantation (hazard ratio, 1.26; 95% confidence interval, 1.06–1.49) ($P = .008$) in multivariate analysis. When patients were stratified by MELD score, SPSS were associated with HE independently of liver function: among patients with MELD scores of 6–9, HE was reported in 23% with L-SPSS, 12% with S-SPSS, and 5% with W-SPSS ($P < .001$ for multiple comparison among SPSS groups); among those with MELD scores of 10–13, HE was reported in 48% with L-SPSS, 33% with S-SPSS, and 23% with W-SPSS ($P < .001$ for multiple comparison among SPSS groups); among patients with MELD scores of 14 or more, HE was reported in 59% with L-SPSS, 57% with S-SPSS, and 48% with W-SPSS ($P = .043$ for multiple comparison among SPSS groups). Patients with SPSS and MELD scores of 6–9 were at higher risk for ascites (40.5% vs 23%; $P < .001$) and bleeding (15% vs 9%; $P = .038$) than patients W-SPSS and had lower odds of transplant-free survival (hazard ratio 1.71; 95% confidence interval, 1.16–2.51) ($P = .006$). **CONCLUSIONS:** In a retrospective analysis of almost 2000 patients, we found 60% to have SPSS; prevalence increases with deterioration of liver function. SPSS increase risk for HE and with a chronic course. In patients with preserved liver function, SPSS increase risk for complications and death. ClinicalTrials.gov ID NCT02692430.

Keywords: Collateral Vessels; Portal Hypertension; Advanced Chronic Liver Disease; Portal Pressure.

Portal hypertension is the main consequence of cirrhosis and is responsible for the majority of severe complications, such as ascites, variceal hemorrhage, and hepatic encephalopathy (HE).[1,2] These events entail a detriment to quality of life and are associated with high mortality.[3] Furthermore, clinical decompensations often require hospital admissions

Abbreviations used in this paper: **CI, confidence interval; CSPH, clinically significant portal hypertension; CT, computed tomography; EGD, esophagogastroduodenal; GI, gastrointestinal; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; HR, hazard ratio; HRS, hepatorenal syndrome; HVPG, hepatic venous pressure gradient; IQR, interquartile range; L-SPSS, large spontaneous portosystemic shunts; LRV, left renal vein; MELD, Model for End-Stage Liver Disease; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; SBP, spontaneous bacterial peritonitis; SD, standard deviation; SMV, superior mesenteric vein; SPSS, spontaneous portosystemic shunts; S-SPSS, small spontaneous portosystemic shunts; SV, splenic vein; TE, transient elastography; TIPS, transjugular intrahepatic portosystemic shunt; W-SPSS, without spontaneous portosystemic shunts.**

Most current article

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and close follow-up, implying substantial costs for the health care system.[4]

One of the consequences of portal hypertension is the formation of portosystemic collateral vessels, commonly defined as "spontaneous portosystemic shunts" (SPSS), as an attempt to decompress the portal venous system.[1] However, SPSS represent an insufficient compensatory mechanism, not allowing for an adequate reduction of portal pressure,[5] but decreasing hepatic portal–venous perfusion.[6] Although SPSS formation has been assumed to be the result of dilatation of pre-existing vascular channels, research studies have also implied an active process of neoangiogenesis.[7,8]

SPSS can be visualized and characterized on abdominal imaging.[9] Their presence has been associated with recurrent or persistent HE,[10–12] but very few small case–control and cohort studies describe the prevalence of SPSS, either using ultrasound or cross-sectional imaging methods.[13–16] Moreover, identification of SPSS has potential therapeutic implications; in the last years, large SPSS have been assessed as a therapeutic target by embolization, especially in patients with preserved liver function.[17–19] However, the true prevalence of SPSS in patients with cirrhosis remains unclear and whether the presence and size of SPSS are predictors of complications and mortality has not been systematically evaluated in large cohorts.

The aims of the present study were to determine the prevalence and characteristics of SPSS in cirrhosis and to assess the impact of SPSS on clinical outcomes and mortality.

Patients and Methods

In this multicenter international study, data from cirrhotic patients were retrospectively assessed. Patients were recruited from 14 centers: 5 in Spain, 2 in Germany, 1 in each the United Kingdom, Austria, Canada, Switzerland, Italy, Belgium, and Denmark. The protocol conformed to the Declaration of Helsinki and was approved by the ethical review boards of each participating center. All authors had access to the study data and reviewed and approved the final manuscript.

Study Cohort and Data Collection

All cirrhotic patients older than 18 years who underwent a contrast-enhanced abdominal computed tomography (CT) or an abdominal magnetic resonance imaging (MRI) for any reason between 2010 and 2015 were consecutively selected for the study. If available, CT was the imaging technique of choice. The diagnosis of cirrhosis was based on medical history, liver biopsy, or unequivocal clinical data with compatible findings on imaging techniques. Exclusion criteria were presence of hepatocellular carcinoma (HCC) beyond Milan criteria, previous transjugular intrahepatic portosystemic shunt (TIPS) or surgical shunt, any medical condition with expected survival of fewer than 6 months, presence of neurologic or psychiatric disorder preventing a proper HE evaluation, and absence of critical information in the medical history.

Patients were identified in each center through a search that combined reviewing the registry of imaging studies ordered by the Liver Unit, the registry of the Radiological Service and coded diagnoses that included general terms as cirrhosis or liver disease, restricted to years 2010–2015. All information was anonymized, coded, and gathered from medical records and clinical databases in every center. A coded database was used for data collection that was centrally processed.

Patients fulfilling inclusion and lacking exclusion criteria had their medical history reviewed. Date of inclusion was considered the date of CT/MRI and defined as baseline. Demographic characteristics, etiology of liver disease, comorbidities, previous complications of cirrhosis, and relevant treatment were recorded. Laboratory and clinical parameters were collected at baseline. Data from esophagogastroduodenal endoscopy were analyzed, if available, within a 12-month period before or after the CT/MRI. Also, liver stiffness by transient elastography (FibroScan; Echosens, Paris, France) and hepatic venous pressure gradient (HVPG) was also collected when available in the subgroup of patients with good liver function, if the tests had been performed within a 12-month period before or after the imaging. Clinically significant portal hypertension (CSPH) was defined as a HVPG >10 mm Hg. Liver function was evaluated at baseline with the Model for End-Stage Liver Disease (MELD) and Child-Pugh scores.[20,21] The degree of disability and dependence in daily activities was assessed through the modified Rankin Scale (mRS).[17,22] Follow-up was performed by recording all decompensating events and complications, including overt HE; ascites; gastrointestinal (GI) bleeding due to portal hypertension; hepatorenal syndrome; spontaneous bacterial peritonitis (SBP); other infections; and development of HCC from the time of inclusion (baseline) until liver transplantation, death, or last available during the study period (until 1 year after the inclusion period had finished). HE was characterized by the grade of its worst episode (according to the West-Haven scale[23]) and its clinical course, defined as episodic (isolated episodes), recurrent (in case of bouts that occur with a time interval of 6 months or less), or persistent (if the pattern of behavioral alterations was permanent).[10,11]

Radiological Data and Definitions

Abdominal CT and MRI were reviewed by a radiologist with expertise in hepatic disease at each center (in 13 of the 14 centers) or by an hepatologist trained by a radiologist (in 1 center) and instructed to search for the presence of SPSS. A predefined protocol for imaging analysis was not used. SPSS were considered as spontaneous communications between the portal venous system or splanchnic veins and the systemic venous system, excluding gastroesophageal varices. SPSS were classified in large or small size according to its maximum diameter, with a cut-off at 8 mm. This cut-off was chosen because it was the smallest size of a symptomatic shunt embolized reported in the literature.[24] According to the diameter and presence of SPSS, patients were classified into 3 groups: large SPSS (L-SPSS), small SPSS (S-SPSS), or without SPSS (W-SPSS). In addition to the SPSS details, other radiological information was collected (presence of portal or splanchnic vein thrombosis, spleen size, ascites). Splenomegaly was defined as a longitudinal diameter >13 cm. The result of a Doppler ultrasound that had been performed closest to the CT/MRI was also collected, recording venous portal flow direction and velocity, if available.

Outcomes

The main outcomes were the incidence of complications of cirrhosis and mortality according to the presence of SPSS.

Secondary measurements were the prevalence of SPSS in cirrhotic patients and the radiologic characteristics of SPSS.

Statistical Analysis

IBM SPSS Statistical Software (version 22.0, IBM Corp, Armonk, NY, 2013) was used for all analysis. Categorical variables were compared using the Pearson's χ^2 test, quantitative variables were compared among groups using the analysis of variance and Student t test was used for compare unpaired data between 2 groups. Results are presented in percentage, as mean and SD or as median and interquartile range (IQR). All reported P values are 2-tailed. P values $\leq$.05 were considered as statistically significant. For statistical analysis of survival, transplantation-free survival was considered. Survival curves were performed with the Kaplan–Meier method and the log-rank test was used to assess differences between groups. A multivariate analysis was performed to estimate the adjusted effect of SPSS using the forward selection method. Variables were included if P value was $\leq$.1 at univariate analysis. Well-known confounding factors (age, sex, and liver function) were also included in the models regardless of P value at univariate analysis. Liver function was assessed separately as MELD and Child-Pugh score in order to avoid collinearity. Disease duration was not included to avoid overfitting and collinearity with age. The selected potential confounders were assessed in a Cox proportional hazards model. After the global analysis, the different outcomes were stratified by MELD score to analyze the effect of liver function. Patients were divided and classified in 3 MELD subgroups (according to tertiles, using percentiles 33 and 66 as cut-offs). Child-Pugh stages A, B, and C were also used for the same purpose, but MELD was prioritized over Child-Pugh for being more objective and not including portal hypertensive parameters, such as ascites and HE (both outcome parameters).

Results

From a total of 2978 patients who were assessed for eligibility (Figure 1), 1729 patients were included in the study and 1249 patients were excluded. L-SPSS were identified in 488 patients (28%), S-SPSS in 548 patients (32%), and no shunt was identified in 693 patients (W-SPSS: 40%). Distribution of SPSS across different centers is shown in Supplementary Table 1. The median follow-up was 21 months (IQR 30; minimum 1 day, maximum 84 months): L-SPSS, 16 months (IQR 27; minimum 1 day, maximum 79 months); S-SPSS, 18 months (IQR 25; minimum 1 day, maximum 84 months); and W-SPSS, 28 months (IQR 34; minimum 1 day, 84 months) ($P < .001$).

Baseline Characteristics and Previous Complications

Baseline characteristics and previous decompensating events of the study cohort are shown in Table 1. Alcohol was the main etiology in L-SPSS group, while hepatitis C virus infection was mostly found in W-SPSS group. Among the 2 most predominant types of L-SPSS (Table 2), alcoholic cirrhosis was mainly associated with paraumbilical shunts (53% of patients with paraumbilical shunts had alcoholic cirrhosis), and less with splenorenal shunts (37%). Patients had no differences in the distribution of comorbidities. Statistical differences in liver function were found: patients with L-SPSS had higher MELD scores and belonged more often to Child-Pugh B and C classes (Supplementary Figure 1) than patients with S-SPSS, and both had worse liver function compared to the W-SPSS group. Biochemical parameters also showed higher serum levels of bilirubin and international normalized ratio and lower levels of albumin, hemoglobin, and platelet count in L-SPSS, followed

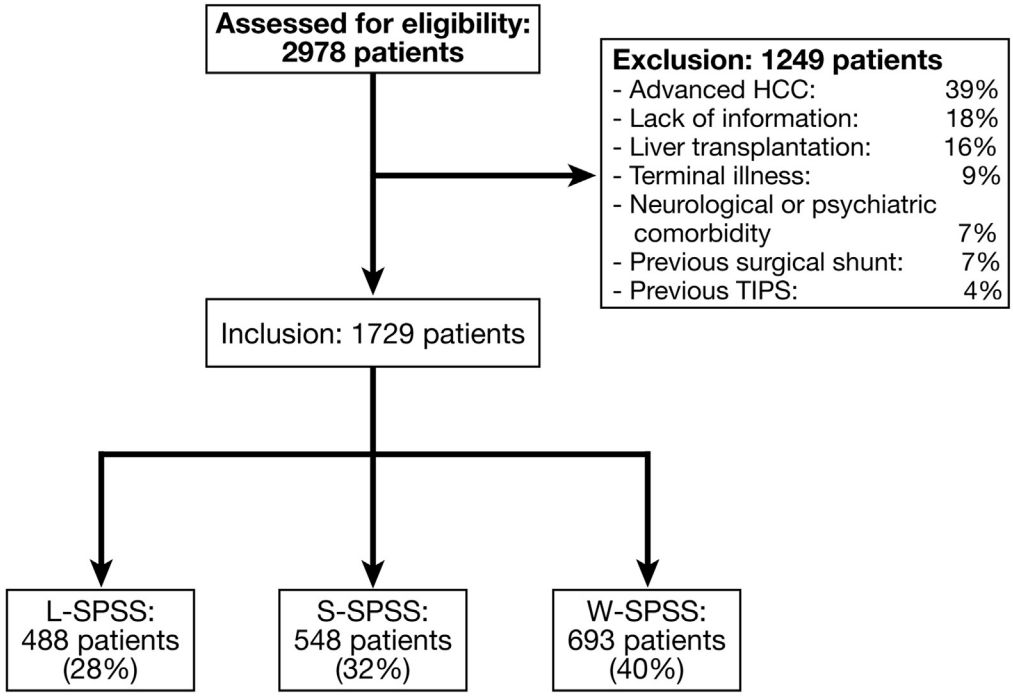


Figure 1. Flow diagram of participants in the study. HCC: Hepatocellular carcinoma; TIPS: Transjugular intrahepatic portosystemic shunt; L-SPSS: Large spontaneous portosystemic shunt; S-SPSS: Small SPSS; W-SPSS: Without SPSS.

Table 1. Demographic and Clinical Characteristics of the Patients Included in the Study Distributed According to the Presence of L-SPSS, S-SPSS, or W-SPSS

Characteristic	Total (n = 1729)	L-SPSS (n = 488)	S-SPSS (n = 548)	W-SPSS (n = 693)	*P* value
Age, *y*, mean (SD)	59 (12)	58 (12)[x]	59 (12)	60 (12)[z]	.001
Sex, *male*, %	71	66	75	71	.116
Hypertension, %	33	31	35	34	.472
Diabetes, %	30	33	30	27[z]	.050
Etiology, %					
Alcohol	36	43	40[y]	29[z]	<.001
Hepatitis C virus	28	21	24[y]	36[z]	<.001
Cholestatic diseases	9	11	9	8	.046
Other	27	25	27	27	.141
MELD (median, IQR)	11 (7)	13 (7)[x]	11 (7)[y]	9 (5)[z]	<.001
Child-Pugh, %					<.001
A (n = 712)	45	32[x]	40[y]	58[z]	
B (n = 575)	36	42	38[y]	31[z]	
C (n = 299)	19	25	23[y]	12[z]	
Previous decompensations, %					
HE	18	32[x]	19[y]	8[z]	<.001
Ascites	46	57	55[y]	32[z]	<.001
GI hemorrhage	20	25	26[y]	11[z]	<.001
SBP	7	10	9[y]	3[z]	<.001
HRS	3	3	4[y]	1	.057
HCC	11	11	11	12	.512
Endoscopy (n = 981), %					
Esophageal varices	67	71	71[y]	59[z]	<.001
Large size varices	40	38	44	37	.824
Gastric varices	7	10	7	4[z]	.046
Portal gastropathy	56	59	62[y]	48[z]	.003
Analytical parameters, mean (SD)					
Bilirubin, *mg/dL*	2.40 (3.52)	2.98 (4.17)[x]	2.37 (3.35)	2.02 (3.08)[z]	<.001
Albumin, *g/dL*	3.40 (0.72)	3.23 (0.68)[x]	3.34 (0.68)[y]	3.56 (0.76)[z]	<.001
INR	1.40 (0.44)	1.48 (0.43)[x]	1.41 (0.45)[y]	1.33 (0.43)[z]	<.001
Creatinine, *mg/dL*	0.94 (0.58)	0.95 (0.70)	0.96 (0.58)	0.92 (0.47)	.451
Platelets, $\times 10^3/mm^3$	116.5 (67.8)	93.6 (52.3)[x]	115.9 (64.4)[y]	133.2 (75.0)[z]	<.001
Hemoglobin, *g/dL*	12.1 (2.4)	11.7 (2.3)	11.8 (2.4)[y]	12.6 (2.3)[z]	<.001
Treatment, %					
Lactulose or lactitol	29	35[x]	28[y]	12[z]	<.001
Rifaximin or neomycin	9	17[x]	10[y]	2[z]	<.001
Diuretics	52	64	57[y]	40[z]	<.001
β-blockers	41	49	46[y]	31[z]	<.001

NOTE. Continuous variables are presented as mean (SD) if normally distributed and median (IQR) if not. Significant differences among the 3 groups are reported as *P* value.
[x,y,z]Statistical differences ($P \leq .05$) between groups are indicated as:
[x]For comparison between L-SPSS and S-SPSS.
[y]For comparison between S-SPSS and W-SPSS.
[z]For comparison between L-SPSS and W-SPSS.

by S-SPSS and W-SPSS. Patients from the L-SPSS group had experienced more complications of cirrhosis and were treated more frequently with liver-related drugs. Data from 1590 patients submitted to an esophagogastroduodenal endoscopy were available, but only those performed 12 months before or after the CT were analyzed (981 patients). Patients with SPSS had a higher prevalence of esophageal varices, gastric varices, and portal-hypertensive gastropathy, but without differences in terms of variceal size.

Radiological Characteristics

Among the 1729 patients studied, 1630 contrast-enhanced abdominal CTs and 99 abdominal MRIs were examined. The main reason for performing the imaging study was the assessment of a hepatic nodule found by ultrasound (29%), followed by characterization of the underlying liver disease (28%). The 2 techniques allowed identifying L-SPSS in a similar proportion (28% with CT, 34% with MRI; $P = .16$).

The most common type of L-SPSS identified was splenorenal (46%), followed by paraumbilical (27%) (Table 2). The mean diameter was 14 mm, with a minimum of 8 mm (according to the study definition) and a maximum of 50 mm. More than one L-SPSS was identified in 9% of the L-SPSS group. More than one-third of patients (37%) with L-SPSS also had detectable small collaterals, with paraumbilical veins being the most common type described

Table 2. Type of SPSS Identified in L-SPSS and S-SPSS Groups

Type of SPSS	Frequency of L-SPSS, % (n = 488)	Frequency of S-SPSS, % (n = 548)
Splenorenal	46	18
Paraumbilical	27	54
Gastrorenal	9	15
Mesocaval	5	8
IMV caval	4	0.5
Mesorenal	3	0.5
Others	4	3

IMV, inferior mesenteric vein.

(48%). In the S-SPSS group, the type most frequently described was paraumbilical (54%), followed by splenorenal shunts (18%).

The mean (SD) portal diameter was 14.3 (3.1) mm; 14.5 (3.8) mm in L-SPSS, 15.0 (2.8) mm in S-SPSS, and 13.6 (2.7) mm in W-SPSS ($P < .001$), suggesting a higher portal pressure in the SPSS groups. Portal vein thrombosis was found in 10% of the total sample (partial 5%, complete 2%, and cavernous transformation 3%). The distribution of portal vein thrombosis in relation with SPSS was 18% in L-SPSS (partial 7%, complete 4%, and cavernous transformation 7%), 10% in S-SPSS (partial 6%, complete 2%, and cavernous transformation 3%), and 5% in W-SPSS (partial 3%, complete 1%, and cavernous transformation 1%) ($P < .001$). In addition, 6% of the total sample had a splanchnic thrombosis (L-SPSS 4%, S-SPSS 1%, and W-SPSS 1%; $P < .001$).

Splenomegaly was observed in 67% of the total sample (L-SPSS 81%, S-SPSS 71%, and W-SPSS 54%; $P < .001$). HCC within Milan criteria was found on 16% of the imaging tests: the percentage did not differ significantly in the 3 groups, neither in the size of the larger nodule, nor in the number of nodules.

Data from the closest Doppler ultrasound were collected in 1082 patients. The median time between study inclusion and ultrasound imaging was 3.1 months (IQR 7.9 months). Hepatofugal flow was observed more frequently in patients with L-SPSS (5% of the total sample: 13% in L-SPSS group, 3% in S-SPSS group, and 2.5% in W-SPSS group; $P < .001$). In the group of patients with hepatopetal flow, mean velocity was slightly lower in the L-SPSS group (17.3 cm/s), compared with S-SPSS and W-SPSS (19.0 cm/s in both), but without statistical differences.

Follow-Up: Hepatic Encephalopathy

During follow-up, patients with L-SPSS developed episodes of HE more frequently than patients with S-SPSS and these than W-SPSS (48%, 34%, and 20% respectively; $P < .001$) (Table 3). A chronic course (both persistent and recurrent HE) was identified more often in the L-SPSS group, followed by S-SPSS and W-SPSS (25% for L-SPSS, 15% for S-SPSS, and 7% for W-SPSS; $P < .001$). However, differences in severity according to West-Haven criteria were not observed.

Follow-Up: Other Complications of Cirrhosis

Patients with shunts (L-SPSS and S-SPSS) experienced portal hypertension-related GI bleeding, ascites, SBP and hepatorenal syndrome more commonly during follow-up than patients of the W-SPSS group (Table 3). There was no difference in the frequency of these complications

Table 3. Decompensating Events During Follow-Up Distributed by SPSS Group

Event	Total, % (n = 1729)	L-SPSS, % (n = 488)	S-SPSS, % (n =548)	W-SPSS, % (n = 693)	*P* value
HE	33	48[x]	34[y]	20[z]	<.001
Recurrent or persistent HE[a]	45	52	44	37[z]	.007
HE West-Haven grade III–IV[a]	45	45	44	47	.658
GI bleeding	20	21	25[y]	15[z]	.004
Ascites	58	63	70[y]	46[z]	<.001
Refractory ascites[b]	30	30	33	27	.397
Spontaneous bacterial peritonitis	13	16	17[y]	9[z]	<.001
Other infections	30	31	28	30	.730
Spontaneous bacteremia	4	2	5	4	.139
Pneumonia	8	8	8	7	.877
Hepatorenal syndrome	12	13	14[y]	9	.041
Hepatocellular carcinoma	20	18	22	19	.552
TIPS	6	7	9[y]	4[z]	.011

NOTE. Significant differences among the 3 groups are reported as *P* value.
HRS, hepatorenal syndrome.
[x,y,z]Statistical differences ($P \leq .05$) between groups are indicated as:
[a]Percentages referred to the total number of patients with HE.
[b]Percentages referred to the total number of patients with ascites.
[x]For comparison between L-SPSS and S-SPSS.
[y]For comparison between S-SPSS and W-SPSS.
[z]For comparison between L-SPSS and W-SPSS.

between L-SPSS and S-SPSS groups. Overall, 6% of patients required a TIPS during follow-up; W-SPSS patients needed a TIPS in a significantly lower rate than both SPSS groups. The percentage of non-SBP infections and the development of HCC (relapse and new diagnosis) did not differ among groups.

Decompensating Events According to the Type of Collateral

According to the type of L-SPSS found, there were no differences in the kind of decompensating event that patients presented (Supplementary Table 2). Gastric varices were more often found in patients with gastrorenal shunts, an association that has been reported previously.[25] Nevertheless, no differences were observed in the prevalence and size of esophageal varices across the different types of SPSS.

Performance Status and Survival

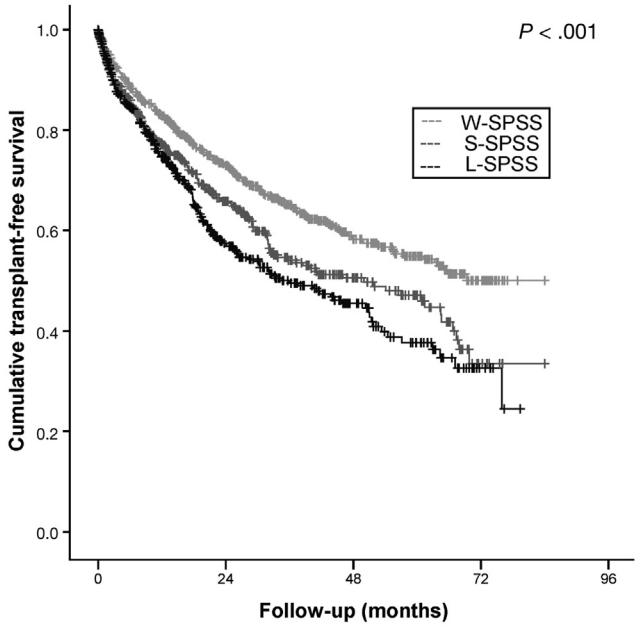
With regard to performance status, a higher proportion of patients from W-SPSS group were autonomous (mRS 0–1) compared to S-SPSS and L-SPSS (88%, 80%, and 75%, respectively), while the rate of patients with limited activities (mRS 2–3: 12%, 19%, and 23%) or disability (mRS 4–5: 0%, 1% and 2%) was larger in the L-SPSS group ($P < .001$).

Transplant-free survival was significantly higher in the W-SPSS group, compared to S-SPSS and L-SPSS group (log-rank test, $P < .001$). At the end of the follow-up period, 416 patients of the 1729 included had died (L-SPSS 38%, S-SPSS 29%, and W-SPSS 32%) and 239 had received a liver transplant (L-SPSS 36%, S-SPSS 34%, and W-SPSS 30%). The hazard ratio (HR) for death/liver transplantation was 1.36 (95% confidence interval [CI], 1.13–1.64) for S-SPSS and 1.60 (95% CI, 1.33–1.93) for L-SPSS (Figure 2). The most common causes of death recorded were liver failure (33%), infections (22%), and HCC (14%), without statistical differences among groups.

The univariate analysis of baseline characteristics between patients alive at the end of follow-up and patients dead/received transplant is shown in Supplementary Table 3. Variables significantly associated with the outcome and entered into the multivariate model were age, sex, diabetes mellitus, platelet count, MELD score, HCC, and presence of SPSS. Supplementary Table 4 represents the results of the multivariate analysis for mortality/liver transplant: age, MELD score, a diagnosis of HCC and presence of SPSS were independent predictors of transplantation-free survival.

Analysis by Liver Function

Analysis of the data was performed stratifying patients by MELD strata (tertiles) in order to avoid the possible effect that the distribution of liver function could have had on the results. Patients were divided in 3 similar groups according to their MELD score, using percentiles 33 and 66 as the cut-off points: the first group included scores from 6 to 9; the second group, from 10 to 13 and the third group, from 14 onward. Although MELD score seems more suitable to stratify patients according to liver function for outcome



Patients at risk

Time	0	24	48	72
W-SPSS	693	392	162	28
S-SPSS	548	201	67	8
L-SPSS	488	170	56	7

Figure 2. Probability of transplant-free survival in all patients included in the study categorized according to the presence of spontaneous portosystemic shunts (SPSS) using Kaplan-Meier curves. Log-rank test: $P < .001$. L-SPSS: Large SPSS; S-SPSS: Small SPSS; W-SPSS: Without SPSS.

analyses including HE, we also performed the analysis stratifying by Child-Pugh stage.

The independent effect of etiology in the prevalence of SPSS (higher prevalence of alcoholic cirrhosis) was lost in the 2 higher MELD groups, however, it was maintained in the MELD 6–9 group. HE remained more frequent in patients with L-SPSS, independently on their liver function strata, as shown in Table 4. Similar results were obtained stratifying by Child-Pugh stage (Supplementary Table 5). Among patients with HE, a recurrent or persistent course was identified with more frequency in SPSS patients with worse liver function (MELD score $\geq$14).

Regarding other complications, the presence of SPSS was associated with a higher risk of portal hypertension-related GI bleeding and a high rate of ascites in patients with preserved liver function (MELD score 6–9) (Table 4) or Child-Pugh A patients (data not shown). Related to this, a more extensive analysis of markers of portal hypertension was performed with the available information in the group of patients with Child-Pugh A (Supplementary Table 6). As seen, SPSS patients presented more indicators of portal hypertension, including HVPG values and presence of CSPH, than W-SPSS patients. On the other hand, presence of SPSS had an effect on outcomes independent of presence of CSPH. Patients with SPSS and CSPH significantly developed more decompensating events (34 of 50 patients, 68%) than patients without SPSS and with CSPH (12 of 27 patients, 44%) ($P = .047$; odds ratio, 2.66; 95% CI, 1.01–6.97).

Table 4. Presence of Episodes of HE With a Recurrent or Persistent Course and Grade III–IV From West-Haven Criteria, and Other Decompensating Events During Follow-Up, According to Presence of SPSS and Liver Function Subgroups (MELD Score Tertiles)

Episodes of HE	L-SPSS (n = 488)	S-SPSS (n = 548)	W-SPSS (n = 693)	*P* value
MELD 6–9	23[x]	12[y]	5[z]	<.001
MELD 10–13	48[x]	33[y]	23[z]	<.001
MELD ≥14	59	57	48[z]	.043
Recurrent or persistent HE	**L-SPSS with HE (n = 234)**	**S-SPSS with HE (n = 186)**	**W-SPSS with HE (n = 139)**	***P* value**
MELD 6–9	54	29	47	.790
MELD 10–13	45	51	29	.177
MELD ≥14	55	42	36[z]	.013
West-Haven scale: Grade III-IV	**L-SPSS with HE (n = 234)**	**S-SPSS with HE (n = 186)**	**W-SPSS with HE (n = 139)**	***P* value**
MELD 6–9	35	29	47	.482
MELD 10–13	45	40	43	.753
MELD ≥14	46	51	51	.438
GI bleeding	**L-SPSS (n = 488)**	**S-SPSS (n = 548)**	**W-SPSS (n = 693)**	***P* value**
MELD 6–9	18	13	9[z]	.038
MELD 10–13	22	30	20	.444
MELD ≥14	21	30	21	.847
Ascites	**L-SPSS (n = 488)**	**S-SPSS (n = 548)**	**W-SPSS (n = 693)**	***P* value**
MELD 6–9	40	41[y]	23[z]	<.001
MELD 10–13	53	70	56	.751
MELD ≥14	77	95	80	.211

NOTE. Results are shown as percentages. Significant differences among the 3 groups are reported as *P* value.
[x,y,z]Statistical differences ($P \leq .05$) between groups are indicated as:
[x]For comparison between L-SPSS and S-SPSS.
[y]For comparison between S-SPSS and W-SPSS.
[z]For comparison between L-SPSS and W-SPSS.

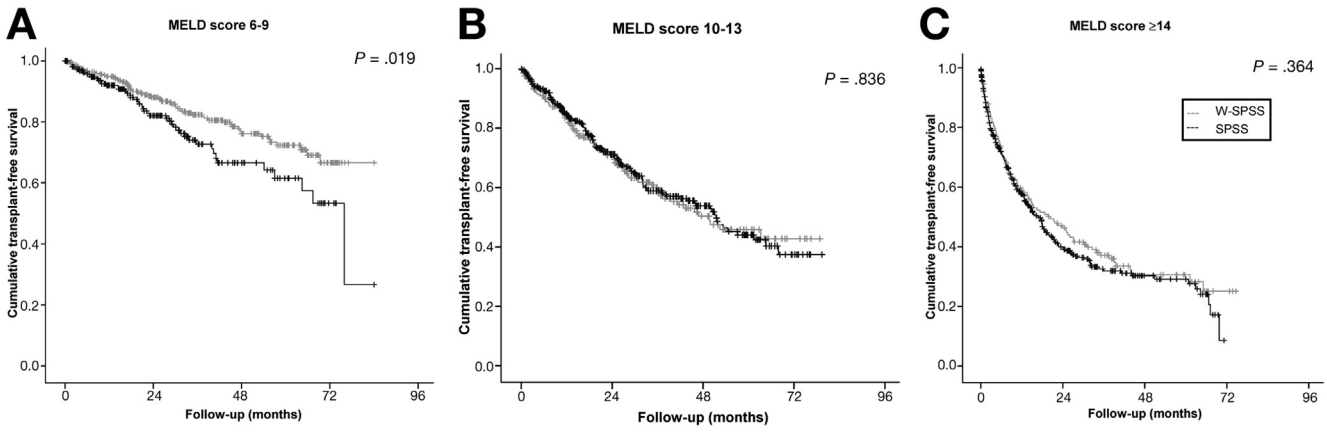
Performance status results showed a higher percentage of limitation or disability in L-SPSS patients compared to S-SPSS and W-SPSS, in the subgroup of patients with good liver function (MELD 6-9) (Supplementary Table 7).

Transplant-free survival in the 2 subgroups of patients with MELD ≥10 was not significantly different between SPSS patients (L-SPSS+S-SPSS) and W-SPSS patients (Figure 3*B* and 3*C*). However, in the subgroup with the lowest MELD, differences were observed (log-rank test $P = .019$): HR for death/liver transplantation was 1.57 (95% CI, 1.08–2.30) in SPSS (L-SPSS+S-SPSS) with respect to W-SPSS group (Figure 3*A*). Individual HR for L-SPSS and S-SPSS are shown in Supplementary Table 8. The multivariate analysis including factors related to death/liver transplantation (age, HCC, and SPSS; Supplementary Table 8) in this subgroup showed that the presence of HCC (HR, 4.34; 95% CI, 2.88–6.54; $P < .001$) and SPSS (HR, 1.71; 95% CI, 1.16–2.51; $P = .006$) were independently associated with mortality and liver transplantation. Similar results were obtained by analyzing the subgroup of patients with Child-Pugh A; as seen in Supplementary Figure 2, transplantation-free survival was better in W-SPSS patients (HR for death/transplantation of 1.41 [95% CI, 1.04–1.91] in SPSS patients) and the multivariate analysis also showed that HCC (HR 4.06; 95% CI, 2.91–5.67), diabetes mellitus (HR 1.38; 95% CI, 1.01–1.88) and SPSS (HR 1.49; 95% CI, 1.09–2.02) were independently associated with death/transplantation.

Discussion

This is the first study that evaluates a large cohort of patients with cirrhosis to determine whether the presence of SPSS correlates with clinical events during the course of the disease. Our results suggest that SPSS might develop as a consequence of a progressive increase in portal pressure and their presence identifies cirrhotic patients at higher risk for more complications and worse outcomes.

The current study shows, first of all, that SPSS are very frequent in liver cirrhosis. In the present series, 60% of cirrhotic patients had some type of SPSS detected by imaging. Among L-SPSS, the type most often identified was splenorenal, followed by paraumbilical. This is in line with the results of previous small studies performed using ultrasound.[26–28] Our study allows diagnosing other SPSS that can be identified more easily using cross-sectional



Patients at risk

	A. (n = 544)				B. (n = 560)				C. (n = 544)			
Time	0	24	48	72	0	24	48	72	0	24	48	72
W-SPSS	317	209	98	19	201	111	36	5	155	60	21	3
SPSS	227	102	32	5	359	159	59	9	399	98	27	0

Figure 3. Probability of survival in patients with SPSS compared to patients without SPSS categorized according to MELD score subgroups (tertiles). SPSS: Spontaneous portosystemic shunts. W-SPSS: Without-SPSS.

imaging, due to the improved sensitivity for visualizing deep vessels in comparison to ultrasound. Another interesting finding is that alcoholic cirrhosis is more frequently associated to SPSS than other etiologies, specifically in patients with preserved liver function. This is an unexplained association that was already reported in a study from Taiwan.[29] In our patients, cirrhosis was diagnosed before in hepatitis C virus patients than in alcoholic patients with respect to time of inclusion in the study. It might be plausible that cirrhosis secondary to chronic viral hepatitis are diagnosed earlier in the course of the disease that cirrhosis secondary to alcoholic liver disease. In the report mentioned,[29] alcoholic cirrhotic patients presented 5 times more paraumbilical collaterals detected by ultrasound than patients with viral cirrhosis. In accordance with that, alcoholic cirrhosis was the predominant etiology (53%) in patients with paraumbilical L-SPSS.

Another aspect to highlight is that the presence of SPSS increases considerably as liver function deteriorates; the finding of SPSS was more probable if MELD score was >10 than with MELD 6–9. Similar data were obtained with Child-Pugh staging. Our interpretation of these results is that increasing portal pressure is the main driving force in SPSS development. These results are in line with a previous small study that involved HVPG measurement and evaluation of collaterals on ultrasound, showing that SPSS were more often observed in patients with HVPG ≥16 mm Hg.[30] Regarding HE, the experience with TIPS and surgical shunts has clearly shown that portosystemic shunting plays a key role in HE development. After TIPS placement, the incidence of overt HE increases to 10%–50% during the first year,[31] with similar data obtained with surgical shunts.[32] The association of HE and the presence of L-SPSS has been reported in case reports, limited clinical series, and few small-sized case-control studies.[13–15,24,33] Riggio, et al[13] showed that the percentage of L-SPSS was higher among patients with recurrent or persistent HE (71%) with respect to the control group with no HE (14%), but in a limited sample (14 patients per group). The present study clearly confirms the association between HE and SPSS, especially L-SPSS, across all different liver function subgroups. In addition HE shows a more chronic and recurrent course in these patients, affecting quality of life. However, we were unable to demonstrate an association between SPSS and the severity of HE measure by the West-Haven scale. The reason for this is probably explained by the study protocol design, in which only the worst episode of HE was recorded, without considering the total number of grade III/IV per patient.

With regard to the relation between SPSS and other complications of cirrhosis, the available information up to date was scarce and contradictory; the finding of SPSS has been related to portal hypertension, but with different conclusions. The case–control study performed by Riggio et al[13] found that patients with chronic HE and L-SPSS had less ascites, esophageal varices and portal-hypertensive gastropathy than patients without SPSS, suggesting than L-SPSS could have a protective role. Nevertheless, in former studies,[14–16] presence of SPSS was not associated with lower risk of bleeding or ascites as compared to controls. Berzigotti et al[27] evaluated the relationship between SPSS detected by ultrasound and the presence of esophageal varices, concluding that the development of new SPSS was associated with a higher rate of varices formation and growth. In the present study, SPSS were associated with more portal hypertension-related signs and complications, such as splenomegaly, gastroesophageal varices, GI bleeding, ascites, hepatorenal syndrome and SBP. This association was especially relevant in cirrhotic patients with preserved liver function (MELD 6–9 or Child-Pugh A), who showed higher HVPG values and more CSPH, and exhibited significantly more portal hypertension related complications (bleeding and ascites) during follow-up than patients without SPSS. In addition, the presence of SPSS in

patients with CSPH was associated to higher rate of complications compared to W-SPSS patients with CSPH. Thus, the finding of SPSS in patients with good liver function probably identifies a subgroup of patients with more advanced portal hypertension, who are more likely to develop complications and might have a worse prognosis. It is worth to mention that regarding the risk of complications related to portal hypertension, patients with L-SPSS and S-SPSS seem to behave similarly, with a similar incidence of complications during follow-up.

Even more important, however, is the association between SPSS and decreased transplant-free survival. Although there is a clear relationship between the presence of SPSS and liver function, SPSS were independently associated to mortality/transplant on multivariate analysis. Moreover, it is precisely in the subset of patients with low MELD (score 6–9) or Child-Pugh A, in which this association with lower survival was more remarkable. Therefore, in the subgroup of cirrhotic patients with preserved liver function, the presence of SPSS is a prognostic marker for a higher risk of complications and lower survival. These patients would probably benefit from a closer surveillance and more intensive therapy.

Few reports have been published about the characteristics of collaterals in cirrhosis. Some of them have suggested an association among the type of SPSS and the predominant kind of complication.[25] Anatomically, splenorenal and gastrorenal shunts have been linked more frequently with gastro-esophageal varices, and an increased risk of bleeding.[28] Paraumbilical shunts, that drain into the external iliac vein, without feeding the esophageal venous area, have been associated with less variceal bleeding and more ascites,[34,35] while their relation with HE remained questionable.[36] These results were not confirmed in other series.[37] In this large cohort, an association between the type of complication and SPSS was not observed, except for a higher percentage of gastric varices in gastrorenal shunts, an association already reported.[25,27] As explained, HE was more frequent in L-SPSS, indicating that the diameter of the shunt plays a role in this complication, but portal-hypertensive complications results were similar in patients with L-SPSS and S-SPSS, suggesting that both are indicators of severe portal hypertension.

Our results have the limitations of a retrospective study, mainly originated from data retrieval by reviewing medical charts. Some data, such as HVPG, transient elastography, ultrasound, or endoscopy results, were not available in all patients. In addition, the lack of a predefined systematic protocol for imaging analysis might explain differences of SPSS prevalence among centers. Finally, imaging tests were only evaluated at one time point and a prospective longitudinal study should be performed to analyze data about radiological improvement or deterioration according to the disease course.

There are several strengths of the study. Participants involved were all from tertiary-care university hospitals, with a protocolized management of cirrhotic patients. This is the largest cohort ever reported about SPSS with data provided from 14 hospitals, from 9 different countries, allowing the generalization of the results. The review of the imaging tests by expert radiologists is also an added value. Finally, the stratified analysis by MELD score and Child-Pugh class is an important element of the study eliminating the confounding factor of liver function in the relationship between SPSS and clinical outcomes.

In conclusion, SPSS are frequent in patients with cirrhosis, with splenorenal collaterals found to be the most common type of L-SPSS. The prevalence of SPSS increases as liver function deteriorates, probably as a consequence of worsening portal hypertension, but without achieving an effective protection against its complications. Recurrent or persistent HE is more frequent in patients with SPSS, independently of liver function. Patients with good liver function and SPSS develop more portal hypertension-related complications (GI bleeding and ascites) and have a lower transplantation-free survival. In patients with preserved liver function, SPSS therefore identifies patients with a higher risk of worse outcomes, and should be considered an important imaging biomarker in cirrhosis.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://doi.org/10.1053/j.gastro.2018.01.028.

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Author contributions: Study concept and design: JG, MS-T, SA, EAT, AA, TR, VH-G, PT, JGA, JLC, JT, AB, CR, AZ, VLM, WL, RB, AK. Acquisition of data: MS-T, DR, JM, KL, GL, EL, MP, MHM, MT, GV, RG-M, AD, AM, CP, DT, AD, ML, GK. Analysis and interpretation of data: JGA, MS-T, SA, EAT, AA, TR, VH-G, PT, JGA, JEC, EL, JT, AB, CR, AZ, VL, WL, RB, RG-M, AK. Drafting of the manuscript: MS-T, SA, JG. Critical revision of the manuscript for important intellectual content: TR, PT, AB, EAT, AA, VH-G, JGA, JC, EL, JT, CR, AZ, VLM, WL, RB, RG-M, AK.

Conflicts of interest
The authors disclose no conflicts.

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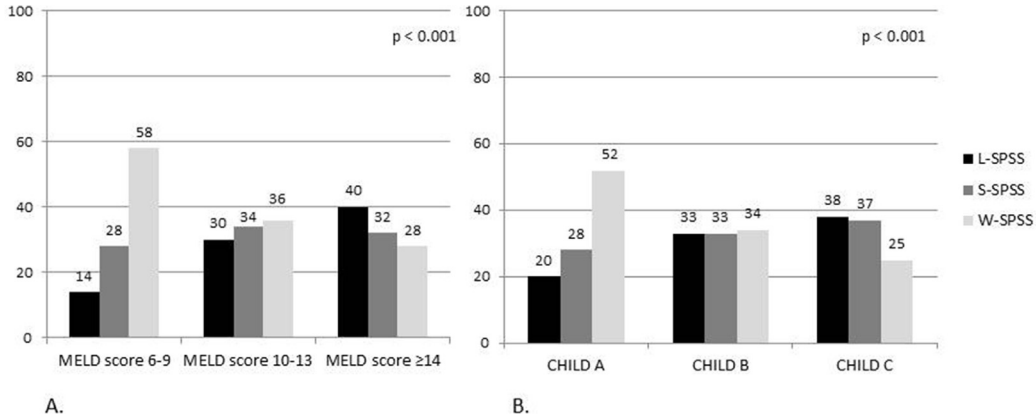
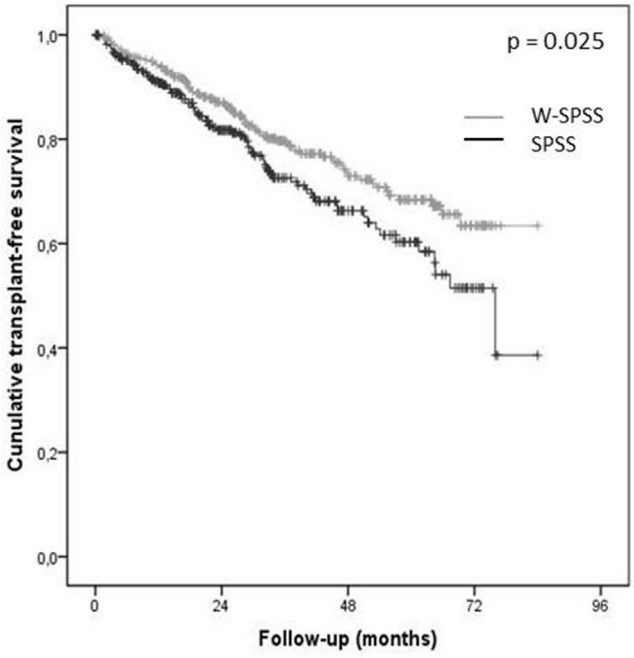


Supplementary Figure 1. Presence and size of SPSS according to MELD score subgroups (*A*) and Child-Pugh classes (*B*). Data are shown as percentages. L-SPSS: Large-Spontaneous portosystemic shunt; S-SPSS: Small-SPSS; W-SPSS: Without-SPSS.



Patients at risk

Time	0	24	48	72
W-SPSS	372	248	114	20
SPSS	340	174	65	10

Supplementary Figure 2. Probability of transplant-free survival for W-SPSS and SPSS (L-SPSS and S-SPSS) in Child-Pugh A patients. SPSS: Spontaneous portosystemic shunt; W-SPSS: Without-SPSS.

Supplementary Table 1. Inclusion per Center and SPSS Proportion

Center	Total, n	L-SPSS, n (%)	S-SPSS, n (%)	W-SPSS, n (%)
Hospital Universitari Vall d'Hebron (Barcelona, Spain)	299	74 (25)	103 (34)	122 (41)
Royal Free Hospital and UCL (London, United Kingdom)	288	65 (23)	58 (20)	165 (57)
Hospital Universitario Ramón y Cajal (Madrid, Spain)	185	48 (26)	29 (16)	108 (58)
Medical University of Vienna (Vienna, Austria)	149	57 (38)	87 (58)	5 (3)
Hospital Clinic (Barcelona, Spain)	141	48 (34)	30 (21)	63 (45)
University of Alberta (Edmonton, Canada)	116	41 (35)	57 (49)	18 (16)
Hospital Universitario Puerta de Hierro (Madrid, Spain)	95	9 (9)	8 (8)	78 (82)
University of Bonn (Bonn, Germany)	94	47 (50)	46 (49)	1 (1)
Inselspital (Berne, Switzerland)	79	14 (18)	47 (59)	18 (23)
Martin Luther University Halle-Wittenberg, Halle (Halle, Germany)	63	13 (21)	17 (27)	33 (52)
IRCCS San Donato (Milan, Italy)	62	18 (29)	15 (24)	29 (47)
University Hospitals Leuven (Leuven, Belgium)	61	22 (36)	27 (44)	12 (20)
Hospital General Universitario Gregorio Marañón (Madrid, Spain)	49	17 (34)	16 (33)	16 (33)
Odense University Hospital, (Odense, Denmark)	48	15 (31)	8 (17)	25 (52)
Total	1729	488 (28)	548 (32)	693 (40)

Supplementary Table 2. Distribution of the Different Complications According to the Type of L-SPSS

	Splenorenal (n = 226)	Paraumbilical (n = 130)	Gastrorenal (n = 45)	Mesocaval (n = 24)	IMV-caval (n = 19)	Mesorenal (n = 16)	*P* value
HE	50	52	40	63	44	30	.226
GI bleeding	22	21	21	21	35	13	.234
Ascites	61	71	53	71	63	56	.134
SBP	16	18	12	21	12	20	.234
HRS	17	11	9	8	12	7	.286
Esophageal varices	71	75	68	79	61	57	.072
Large varices	37	46	54	56	36	63	.378
Gastric varices	13	2	28	10	9	0	.020
Portal gastropathy	57	63	55	54	29	64	.227

NOTE. Results are shown as percentages.
HRS, hepatorenal syndrome; IMV, inferior mesenteric vein.

Supplementary Table 3. Univariate Analysis for the Identification of Predictors at Baseline (Time 0) of Mortality or Liver Transplantation at the End of Follow-Up

Variable	Regression coefficient	*P* value	HR (95% CI)
Age	0.006	.069	1.01 (1.00–1.01)
Sex	0.177	.045	1.19 (1.00–1.42)
Time of diagnosis of cirrhosis[a]	0.01	.084	1.01 (0.99–1.02)
Etiology: HCV	–0.009	.915	0.99 (0.84–1.17)
Etiology: Alcohol	0.077	.349	1.08 (0.92–1.27)
Hypertension	–0.43	.612	0.96 (0.81–1.13)
Diabetes mellitus	0.19	.027	1.20 (1.02–1.42)
Platelets $<150 \times 10^9/mm^3$	0.430	<.001	1.54 (1.25–1.88)
MELD score	0.115	<.001	1.12 (1.11–1.14)
Child-Pugh score	0.886	<.001	1.36 (1.31–1.40)
HCC	0.649	<.001	1.91 (1.55–2.36)
S-SPSS	0.307	.001	1.36 (1.13–1.64)
L-SPSS	0.471	<.001	1.60 (1.33–1.93)
SPSS (S + L)	0.387	<.001	1.47 (1.26–1.73)

[a]Duration of cirrhosis after initial diagnosis.

Supplementary Table 4. Multivariate (Cox) Analysis of Factors Related to Death/Liver Transplantation

Variable	Regression coefficient	*P* value	HR (95% CI)
Age	0.02	<.001	1.02 (1.01–1.02)
Sex	0.13	.171	1.14 (0.95–1.36)
Diabetes mellitus	0.12	.163	1.13 (0.95–1.34)
MELD score	0.13	<.001	1.14 (1.12–1.15)
HCC	0.82	<.001	2.25 (1.80–2.81)
Platelets $<150 \times 10^9/mm^3$	0.23	.036	1.26 (1.02–1.57)
SPSS (S + L)	0.23	.008	1.26 (1.06–1.49)

NOTE. L-SPSS was an independent factor related to death or liver transplantation, with a HR 1.32 (95% CI, 1.08–1.61; $P = .006$). The HR for S-SPSS was 1.20 (95% CI, 0.98–1.46; $P = .071$).

Supplementary Table 5. Presence of Episodes of HE, With a Recurrent or Persistent Course and Grade III–IV From West-Haven Criteria During Follow-Up, According to Presence of SPSS and Liver Function Subgroups (Child-Pugh Class)

Episodes of HE	L-SPSS (n = 488)	S-SPSS (n = 548)	W-SPSS (n = 693)	*P* value
Child A	28[x]	10	7[z]	<.001
Child B	50	41[y]	29[z]	<.001
Child C	78	68	61[z]	.010
Recurrent or persistent HE	**L-SPSS with HE (n = 234)**	**S-SPSS with HE (n = 186)**	**W-SPSS with HE (n = 139)**	***P* value**
Child A	51	40	52	.984
Child B	50	47	33	.074
Child C	57	44	37[z]	.035
West-Haven scale Grade III-IV	**L-SPSS with HE (n = 234)**	**S-SPSS with HE (n = 186)**	**W-SPSS with HE (n = 139)**	***P* value**
Child A	44	11	44	.804
Child B	38	47	45	.398
Child C	51	49	55	.798

NOTE. Results are shown as percentages.
[x,y,z]Statistical differences ($P \leq .05$) between groups are indicated as:
[x]For comparison between L-SPSS and S-SPSS.
[y]For comparison between S-SPSS and W-SPSS.
[z]For comparison between L-SPSS and W-SPSS.

Supplementary Table 6. Markers of Portal Hypertension (Platelet Count, Spleen Size, Rate of Varices and Portal Gastropathy on EGD Endoscopy, TE, HVPG, and Percentage of CSPH) According to Presence of SPSS in Child-Pugh A Patients

Child-Pugh A (n = 712)	L-SPSS (n = 144)	S-SPSS (n = 196)	W-SPSS (n = 372)	*P* value
Platelets, $\times 10^9/mm^3$, mean (SD)	95.7 (49.8)[x]	114.9 (58.6)[y]	133.9 (65.7)[z]	<.001
Spleen diameter, *cm*, mean (SD)	16 (3)[x]	14 (3)[y]	13 (3)[z]	<.001
EGD endoscopy (n = 371)	L-SPSS (n = 81)	S-SPSS (n = 108)	W-SPSS (n = 182)	*P* value
Esophageal varices, %	74	68[y]	47[z]	<.001
Gastric varices, %	7	7	3	.068
Portal gastropathy, %	46	58	41	.180
TE (n = 150)	L-SPSS (n = 19)	S-SPSS (n = 40)	W-SPSS (n = 91)	*P* value
Liver stiffness, *KPa*, median (IQR)	19 (24)[x]	27 (27)[y]	18 (17)	.002
HVPG measurement (n = 106)	L-SPSS (n = 23)	S-SPSS (n = 31)	W-SPSS (n = 52)	*P* value
HVPG (mmHg), mean (SD)	15 (5)[x]	19 (7)[y]	11 (6)[z]	<.001
CSPH, n (%)	20 (87)	30 (97)[y]	27 (52)[z]	<.001

NOTE. Number of subjects available for every marker is indicated at the beginning of in every row. Three patients with L-SPSS had no CSPH: 1 patient had primary biliary cholangitis, 1 patient with mixed alcohol and hepatitis C etiology was abstinent and on β-blockers, and finally 1 patient with hepatitis C was also on β-blockers. One patient with S-SPSS and no CSPH was an abstinent alcoholic patient on β-blockers.
EGD, esophagogastroduodenal; TE, transient elastography.
[x,y,z]Statistical differences ($P \leq .05$) between groups are indicated as:
[x]For comparison between L-SPSS and S-SPSS.
[y]For comparison between S-SPSS and W-SPSS.
[z]For comparison between L-SPSS and W-SPSS.

Supplementary Table 7. Quality of Life (Modified Rankin Scale) According to Presence of SPSS and MELD Score Subgroups

Variable	L-SPSS (n = 488)	S-SPSS (n = 548)	W-SPSS (n = 693)	*P* value
MELD 6–9				
Autonomous	84[x]	92	95[z]	
Limitation	13	8	5	.001
Disability	3	0	0	
MELD 10–13				
Autonomous	82	82	88	
Limitation	17	17	11	.071
Disability	1	1	1	
MELD ≥14				
Autonomous	69	71	75	
Limitation	29	27	25	.188
Disability	2	2	0	

NOTE. Results are shown as percentages.
[x,z]Statistical differences ($P \leq .05$) between pairs of value are indicated as:
[x]For comparison between L-SPSS and S-SPSS.
[z]For comparison between L-SPSS and W-SPSS.

Supplementary Table 8. Univariate (Cox) Analysis of Factors Related to Death or Liver Transplantation in Patients With Preserved Liver Function (MELD Score 6–9)

	Regression coefficient	*P* value	HR (95% CI)
Age	0.02	.050	1.02 (1.00–1.03)
Sex	–0.01	.983	0.10 (0.67–1.48)
Time of diagnosis of cirrhosis[a]	0.21	.208	1.02 (0.99–1.06)
Etiology: HCV	0.01	.995	1.00 (0.68–1.47)
Etiology: alcohol	0.34	.105	1.41 (0.93–2.13)
Hypertension	0.21	.283	1.23 (0.84–1.80)
Diabetes mellitus	0.29	.147	1.33 (0.90–1.97)
Platelets $<150 \times 10^9/mm^3$	0.10	.619	1.12 (0.74–1.65)
HCC	1.46	<.001	4.31 (2.89–6.43)
S-SPSS	0.49	.024	1.64 (1.07–2.53)
L-SPSS	0.37	.185	1.45 (0.84–2.52)
SPSS (S + L)	0.45	.019	1.57 (1.08–2.30)

HCV, hepatitis C virus.
[a]Duration of cirrhosis after initial diagnosis.