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

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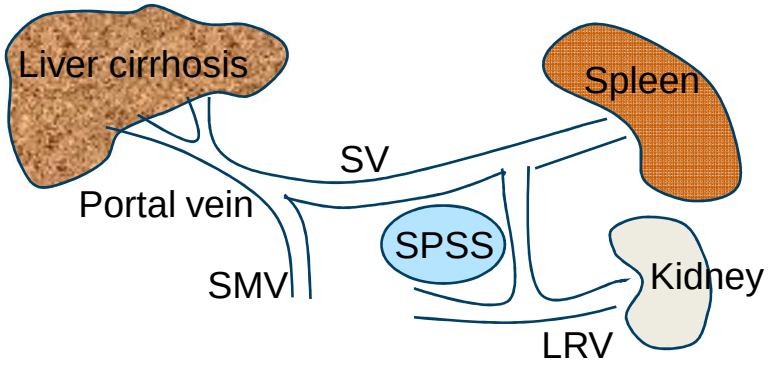

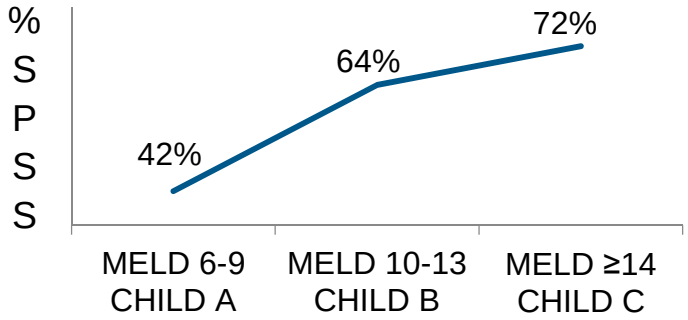

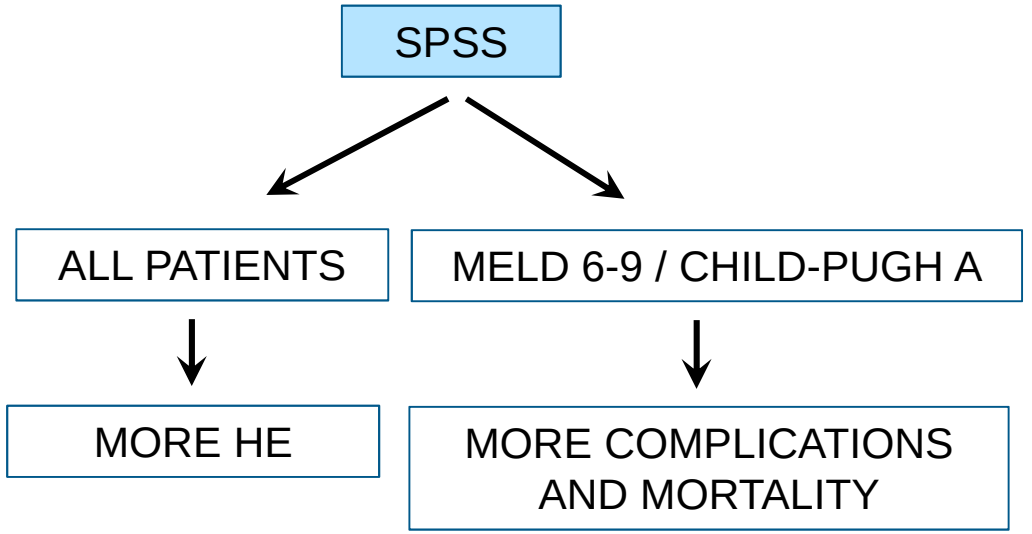

Gastroenterology

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Abbreviations: CI, confidence interval; CSPH, clinically significant portal hypertension; CT, computed tomography; EGD, esophagogastroduodenal; GI, gastrointestinal; HCV, hepatitis C virus; HR, hazard ratio; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; HRS, hepatorenal syndrome; HVPG, hepatic venous pressure gradient; IMV, inferior mesenteric vein; INR, International Normalized Ratio; IQR, median and interquartile range; LRV, left renal vein; L-SPSS, large spontaneous portosystemic shunts; MELD, model for end-stage liver disease; MRI, magnetic resonance imaging; SBP, spontaneous bacterial peritonitis; mRS, modified Rankin Scale; 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.

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- Analysis and interpretation of data: JG, MS, SA, ET, AA, TR, VH, PT, JA, JC, EL, JT, AB, CR, AZ, VL, WL, RB, RG, AK.
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- Critical revision of the manuscript for important intellectual content: TR, PT, AB, ET, AA, VH, JA, JC, EL, JT, CR, AZ, VL, WL, RB, RG, AK.

Abstract:

Background & Aims: Spontaneous portosystemic shunts (SPSSs) 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 SPSSs 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 SPSSs (L-SPSSs, ≥8 mm), small SPSSs (S-SPSSs, <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 SPSSs in patients with cirrhosis and their radiologic features.

Results: L-SPSS were identified in 488 patients (28%), S-SPSS in 548 patients (32%), and no shunt (W-SPSS) in 693 patients (40%). The most common L-SPSS was spleno–renal (46% of L-SPSSs). The presence and size of SPSS increased with liver dysfunction: among patients with MELD scores of 6–9, 14% had L-SPSSs and 28% had S-SPSSs; among patients with MELD scores of 10–13, 30% had L-SPSSs and 34% had S-SPSSs; among patients with MELD scores of 14 or more, 40% had L-SPSSs and 32% had S-SPSSs (P<.001 for multiple comparison among MELD groups). HE was reported in 48% of patients with L-SPSSs, 34% of patients with S-SPSSs, and 20% of patients W-SPSSs (P<.001 for multiple comparison among SPSS groups). Recurrent or persistent HE was reported in 52% of patients with L-SPSSs, 44% of patients with S-SPSSs, and 37% of patients W-SPSSs (P=.007 for multiple comparison among SPSS groups). Patients with SPSSs also had a larger number of portal hypertension-related complications (bleeding or ascites) than those W-SPSSs. Quality of life and transplant-free survival were lower in patients with SPSSs vs without. SPSSs were an independent factor associated with death or liver transplantation (hazard ratio, 1.26; 95% CI, 1.06–1.49) (P=.008) in multivariate analysis. When patients were stratified by MELD score, SPSSs were associated with HE independently of liver function: among patients with MELD scores of 6–9, HE was reported in 23% with L-SPSSs, 12% with S-SPSSs, and 5% with W-SPSSs (P<.001 for multiple comparison among SPSS groups); among those with MELD scores of 10–13, HE was reported in 48% with L-SPSSs, 33% with S-SPSSs, 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-SPSSs, 57% with S-SPSSs, 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=0.038) than patients W-SPSS and had lower odds of transplant-free survival (hazard ratio 1.71; 95% CI, 1.16-2.51) (P=.006).

Conclusions: In a retrospective analysis of almost 2000 patients, we found 60% to have SPSSs; prevalence increases with deterioration of liver function. SPSSs increase risk for HE and chronic course. In patients with preserved liver function, SPSSs increase risk for complications and death. ClincialTrials.gov no: NCT02692430.

KEY WORDS: collateral vessels, portal hypertension, advanced chronic liver disease, portal pressure

INTRODUCTION

Portal hypertension is the main consequence of cirrhosis and is responsible for the majority of severe complications, such as ascites, variceal haemorrhage and hepatic encephalopathy (HE) [1,2]. These events entail a detriment in quality of life and are associated with high mortality [3]. Furthermore, clinical decompensations often require hospital admissions 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 as the result of dilatation of preexisting 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 (i) to determine the prevalence and characteristics of SPSS in cirrhosis and (ii) 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 fourteen centers: five in Spain, two in Germany, one in United Kingdom, Austria, Canada, Switzerland, Italy, Belgium and Denmark. The protocol, conformed to the Declaration of Helsinki, 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 less than 6 months, presence of neurological 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 (EGD) endoscopy were analyzed, if available within a 12 month period before or after the CT/MRI. Also, liver stiffness by transient elastography (TE, FibroScan®, Echosens, Paris, France) and hepatic venous pressure gradient (HVPG), were 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 greater than 10 mmHg. 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 (HRS), spontaneous bacterial peritonitis (SBP), other infections and development of HCC from the time of inclusion (baseline) until liver transplant, death or last available during the study period (until one 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 one 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 since 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 three 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 larger than 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 radiological characteristics of SPSS.

Statistical analysis

The statistical software SPSS (version 22.0; SPSS Inc., Chicago, IL) was used for all analysis. Categorical variables were compared using the Pearson's X2 test, quantitative variables were compared among groups using the analysis of variance (ANOVA) and Student's t test was used for compare unpaired data between two groups. Results are presented in percentage, as mean and standard deviation (SD) or as median and interquartile range (IQR). All reported p values are two-tailed. P values ≤0.05 were considered as statistically significant. For statistical analysis of survival, transplant-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 ≤0.1 at univariate analysis. Well-known confounding factors (age, gender, 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 three 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 **Suppl. Table 1**. The median follow-up was 21 months (IQR 30-minimum 1 day, maximum 84 months): L-SPSS 16 months (IQR 27-1 day, 79 months), S-SPSS 18 months (IQR 25-1 day, 84 months); W-SPSS 28 months (IQR 34-1 day, 84 months) (p<0.001).

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 HCV infection was mostly found in W-SPSS group. Among the two 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 (**Suppl. Figure 1**) than patients with S-SPSS, and both had a worse liver function compared to the W-SPSS group. Biochemical parameters also showed higher serum levels of bilirubin and INR and lower levels of albumin, hemoglobin and platelet count in L-SPSS, followed 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 EGD 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 CT and 99 abdominal MRI were examined. The main reason for performing the imaging study was the assessment of a hepatic nodule found by ultrasound (29%), followed by the characterization of the underlying liver disease (28%). The two techniques allowed identifying L-SPSS in a similar proportion (28% with CT, 34% with MRI, p=0.16).

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 a third of patients (37%) with L-SPSS also had detectable small collaterals, with paraumbilical veins being the most common type described (48%). In the S-SPSS group, the type most frequently described was paraumbilical (54%), followed by splenorenal shunts (18%).

The mean portal diameter was 14.3 mm (14.5 mm (SD 3.8 mm) in L-SPSS, 15.0 mm (SD 2.8 mm) in S-SPSS and 13.6 mm (SD 2.7 mm) in W-SPSS, p<0.001), 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<0.001). Moreover, 6% of the total sample had a splanchnic thrombosis (L-SPSS 4%, S-SPSS 1% and W-SPSS 1%; p<0.001).

Splenomegaly was observed in 67% of the total sample (L-SPSS 81%, S-SPSS 71% and W-SPSS 54%, p<0.001). 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). 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<0.001). 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<0.001) (**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<0.001). 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 HRS more commonly during follow-up than patients of the W-SPSS group (**Table 3**). There was no difference in the frequency of these complications 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 (**Suppl. Table 2**). Gastric varices were more often found in patients with gastrorenal shunts, an association that has been previously reported [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 regards 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<0.001).

Transplant-free survival was significantly higher in the W-SPSS group, compared to S-SPSS and L-SPSS group (log-rank test p<0.001). 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 been transplanted (L-SPSS 36%, S-SPSS 34% and W-SPSS 30%). The Hazard Ratio (HR) for death/liver transplant 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/transplanted is shown in **Suppl. Table 3.** Variables significantly associated with the outcome and entered into the multivariate model were age, gender, diabetes mellitus, platelet count, MELD score, HCC and presence of SPSS. **Suppl. 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 transplant-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 three 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 onwards. Although MELD score seems more suitable to stratify patients according to liver function for outcome 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 two 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 (**Suppl. 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 ≥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 (**Supp. 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= 0.047, OR 2.66, CI 1.01-6.97).

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) (**Suppl. table 7**).

Transplant-free survival in the two subgroups of patients with MELD ≥10 was not significantly different between SPSS patients (L-SPSS+S-SPSS) and W-SPSS patients (**Figure 3B-C**). However, in the subgroup with the lowest MELD, differences were observed (log-rank test p=0.020): HR for death/liver transplant was 1.57 (95% CI, 1.08-2.30) in SPSS (L-SPSS+S-SPSS) with respect to W-SPSS group (**Figure 3A**). Individual HR for L-SPSS and S-SPSS are shown in **Suppl. Table 8**. The multivariate analysis including factors related to death/liver transplant (age, HCC and SPSS; **Suppl. Table 8**) in this subgroup showed that the presence of HCC (HR 4.34; 95% CI, 2.88-6.54; p<0.001) and SPSS (HR 1.71; 95% CI, 1.16-2.51; p=0.006) 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 **Suppl. Figure 2**, transplant-free survival was better in W-SPSS patients (HR for death/transplant 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 to mortality/transplant.

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 imaging, due to the improved sensitivity for visualising 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 HCV 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 mention report [29], alcoholic cirrhotic patients presented five 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 above 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 mmHg [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 regards 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, HRS 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 (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 with 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, TE, 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 analyse 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 transplant-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.

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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.

	Total (n =1729)	L-SPSS (n = 488)	S-SPSS (n =548)	W-SPSS (n = 693)	p
Age (yr; mean, SD):	59 (12)	58 (12)*	59 (12)	60 (12)§	0.001
Gender (male-%):	71	66	75	71	0.116
Hypertension (%):	33	31	35	34	0.472
Diabetes (%):	30	33	30	27§	0.050
Etiology:					
Alcohol (%)	36	43	40¥	29§	<0.001
HCV (%)	28	21	24¥	36§	<0.001
Cholestatic diseases (%)	9	11	9	8	0.046
Other (%)	27	25	27	27	0.141
MELD (median, IQR)	11 (7)	13 (7)*	11 (7)¥	9 (5)§	<0.001
Child-Pugh (%):					
A (n: 712)	45	32*	40¥	58§	
B (n: 575)	36	42	38¥	31§	<0.001
C (n: 299)	19	25	23¥	12§	
Previous decompensations (%):					
HE	18	32*	19¥	8§	<0.001
Ascites	46	57	55¥	32§	<0.001
GI hemorrhage	20	25	26¥	11§	<0.001
SBP	7	10	9¥	3§	<0.001
HRS	3	3	4¥	1	0.057
HCC	11	11	11	12	0.512
Endoscopy (n = 981)					
Esophageal varices (%)	67	71	71¥	59§	<0.001
Large size varices (%)	40	38	44	37	0.824
Gastric varices (%)	7	10	7	4§	0.046
Portal gastropathy (%)	56	59	62¥	48§	0.003
Analytical parameters (mean, SD):					
Bilirubin (mg/dL)	2.40 (3.52)	2.98 (4.17)*	2.37 (3.35)	2.02 (3.08)§	<0.001
Albumin (g/dL)	3.40 (0.72)	3.23 (0.68)*	3.34 (0.68)¥	3.56 (0.76)§	<0.001
INR	1.40 (0.44)	1.48 (0.43)*	1.41 (0.45)¥	1.33 (0.43)§	<0.001
Creatinine (mg/dL)	0.94 (0.58)	0.95 (0.70)	0.96(0.58)	0.92 (0.47)	0.451
Platelets ($x10^3/mm^3$)	116.5(67.8)	93.6 (52.3)*	115.9 (64.4)¥	133.2 (75.0)§	<0.001
Hemoglobin (g/dL)	12.1 (2.4)	11.7 (2.3)	11.8 (2.4)¥	12.6(2.3)§	<0.001
Treatment (%):					
Lactulose or Lactitol	24	35*	28¥	12§	<0.001
Rifaximin or Neomycin	9	17*	10¥	2§	<0.001
Diuretics	52	64	57¥	40§	<0.001
Beta-blockers	41	49	46¥	31§	<0.001

Continuous variables are presented as mean (SD) if normally distributed and median (IQR) if not. Significant differences among the three groups are reported as p value. Statistical differences ($p \leq 0.05$) between groups are indicated as * for comparison between L-SPSS versus S-SPSS, ¥ for S-SPSS versus W-SPSS and § for L-SPSS versus W-SPSS.

L-SPSS: Large spontaneous portosystemic shunt; S-SPSS: Small-SPSS; W-SPSS: Without-SPSS; IQR: Interquartile range; SD: Standard deviation; HCV: Hepatitis C virus; MELD: Model for End-stage Liver Disease; HE: Hepatic encephalopathy; GI: Gastrointestinal hemorrhage, SBP: Spontaneous bacterial peritonitis; HRS: Hepatorenal syndrome; HCC: Hepatocellular carcinoma; INR: International Normalized Ratio.

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

Results are shown as percentage.

SPSS: Spontaneous portosystemic shunt; L-SPSS: Large-SPSS; S-SPSS: Small SPSS. IMV: Inferior mesenteric vein.

Table 3. Decompensating events during follow-up distributed by SPSS group.

	Total (n=1729)	L-SPSS (n = 488)	S-SPSS (n =548)	W-SPSS (n = 693)	p
HE	33	48*	34¥	20§	<0.001
Recurrent or persistent HE#	45	52	44	37§	0.007
HE West-Haven grade III-IV#	45	45	44	47	0.658
GI bleeding	20	21	25¥	15§	0.004
Ascites	58	63	70¥	46§	<0.001
Refractory ascites&	30	30	33	27	0.397
Spontaneous bacterial peritonitis	13	16	17¥	9§	<0.001
Other infections:	30	31	28	30	0.730
- Spontaneous bacteremia	4	2	5	4	0.139
- Pneumonia	8	8	8	7	0.877
Hepatorenal syndrome	12	13	14¥	9	0.041
Hepatocellular carcinoma	20	18	22	19	0.552
TIPS	6	7	9¥	4§	0.011

Results are shown as percentages. # Percentages referred to the total number of patients with HE. & Percentages referred to the total number of patients with ascites. Significant differences among the three groups are reported as p value. Statistical differences ($p \leq 0.05$) between groups are indicated as * for comparison between L-SPSS versus S-SPSS, ¥ for S-SPSS versus W-SPSS and § for L-SPSS versus W-SPSS.

HE: Hepatic encephalopathy; GI: Gastrointestinal; SBP: Spontaneous bacterial peritonitis; HRS: Hepatorenal syndrome; HCC: hepatocellular carcinoma. L-SPSS: Large spontaneous portosystemic shunt; S-SPSS: Small-SPSS; W-SPSS: Without-SPSS; TIPS: Transjugular intrahepatic portosystemic shunt.

Table 4. Presence of episodes of hepatic encephalopathy (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
MELD 6-9	23*	12¥	5§	<0.001
MELD 10-13	48*	33¥	23§	<0.001
MELD ≥14	59	57	48§	0.043
Recurrent or persistent HE	L-SPSS with HE (n = 234)	S-SPSS with HE (n = 186)	W-SPSS with HE (n = 139)	p
MELD 6-9	54	29	47	0.790
MELD 10-13	45	51	29	0.177
MELD ≥14	55	42	36§	0.013
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
MELD 6-9	35	29	47	0.482
MELD 10-13	45	40	43	0.753
MELD ≥14	46	51	51	0.438
GI bleeding	L-SPSS (n = 488)	S-SPSS (n =548)	W-SPSS (n = 693)	p
MELD 6-9	18	13	9§	0.038
MELD 10-13	22	30	20	0.444
MELD ≥14	21	30	21	0.847
Ascites	L-SPSS (n = 488)	S-SPSS (n =548)	W-SPSS (n = 693)	p
MELD 6-9	40	41¥	23§	<0.001
MELD 10-13	53	70	56	0.751
MELD ≥14	77	95	80	0.211

Results are shown as percentages. Significant differences among the three groups are reported as p value. Statistical differences ($p \leq 0.05$) between groups are indicated as * for comparison between L-SPSS versus S-SPSS, ¥ for S-SPSS versus W-SPSS and § for L-SPSS versus W-SPSS.

L-SPSS: Large spontaneous portosystemic shunt; S-SPSS: Small-SPSS; W-SPSS: Without-SPSS; HE: Hepatic encephalopathy; GI: Gastrointestinal.

Supplementary Table 1. Inclusion per center and SPSS proportion.

CENTER	TOTAL	L-SPSS	S-SPSS	W-SPSS
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%

Results are shown as total number and percentage.

L-SPSS: Large spontaneous portosystemic shunt; S-SPSS: Small-SPSS; W-SPSS: Without-SPSS.

Supplementary Table 2. Distribution of the different complications according to the type of L-SPSS.

	Splenorenal (n = 226)	Para-umbilical (n = 130)	Gastrorenal (n = 45)	Mesocaval (n = 24)	IMV-caval (n = 19)	Mesorenal (n = 16)	p
HE	50	52	40	63	44	30	0.226
GI bleeding	22	21	21	21	35	13	0.234
Ascites	61	71	53	71	63	56	0.134
SBP	16	18	12	21	12	20	0.234
HRS	17	11	9	8	12	7	0.286
Esophageal varices	71	75	68	79	61	57	0.072
Large varices	37	46	54	56	36	63	0.378
Gastric varices	13	2	28	10	9	0	0.020
Portal gastropathy	57	63	55	54	29	64	0.227

Results are shown as percentages.

L-SPSS: Large spontaneous portosystemic shunt; IMV: Inferior mesenteric vein. HE: Hepatic encephalopathy; GI: Gastrointestinal; SBP: Spontaneous bacterial peritonitis; HRS: Hepatorenal syndrome.

Supplementary Table 3. Univariate analysis for the identification of predictors at baseline (time 0) of mortality or liver transplant at the end of follow-up.

	Regression coefficient	p	HR (95% CI)
Age	0.006	0.069	1.01 (1.00-1.01)
Gender	0.177	0.045	1.19 (1.00-1.42)
Time of diagnosis of cirrhosis*	0.01	0.084	1.01 (0.99-1.02)
Etiology: HCV	-0.009	0.915	0.99 (0.84-1.17)
Etiology: Alcohol	0.077	0.349	1.08 (0.92-1.27)
Hypertension	-0.43	0.612	0.96 (0.81-1.13)
Diabetes mellitus	0.19	0.027	1.20 (1.02-1.42)
Platelets $<150x10^9/mm^3$	0.430	<0.001	1.54 (1.25-1.88)
MELD score	0.115	<0.001	1.12 (1.11-1.14)
Child-Pugh score	0.886	<0.001	1.36 (1.31-1.40)
HCC	0.649	<0.001	1.91 (1.55-2.36)
S-SPSS	0.307	0.001	1.36 (1.13-1.64)
L-SPSS	0.471	<0.001	1.60 (1.33-1.93)
SPSS (S + L)	0.387	<0.001	1.47 (1.26-1.73)

SD: Standard deviation; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; SPSS: Spontaneous portosystemic shunt; L-SPSS: Large-SPSS; S-SPSS: Small-SPSS. *Indicates duration of cirrhosis after initial diagnosis.

Supplementary Table 4. Multivariate (Cox) analysis of factors related to death/liver transplant.

	Regression coefficient	p	HR (95% CI)
Age	0.02	<0.001	1.02 (1.01-1.02)
Gender	0.13	0.171	1.14 (0.95-1.36)
Diabetes mellitus	0.12	0.163	1.13 (0.95-1.34)
MELD score	0.13	<0.001	1.14 (1.12-1.15)
HCC	0.82	<0.001	2.25 (1.80-2.81)
Platelets $<150x10^9/mm^3$	0.23	0.036	1.26 (1.02-1.57)
SPSS (S + L)	0.23	0.008	1.26 (1.06-1.49)

L-SPSS was an independent factor related to death or liver transplant, with a HR 1.32 (1.08-1.61; p=0.006). The HR for S-SPSS was 1.20 (95% CI 0.98-1.46; p=0.071).

HR: Hazard ratio; CI: Confidence interval; MELD: Model for end-stage liver disease; HCC: Hepatocellular carcinoma; SPSS: Spontaneous portosystemic shunt; L-SPSS: Large-SPSS; S-SPSS: Small-SPSS.

Supplementary table 5. Presence of episodes of hepatic encephalopathy (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
Child A	28*	10	7§	<0.001
Child B	50	41¥	29§	<0.001
Child C	78	68	61§	0.010
Recurrent or persistent HE	L-SPSS with HE (n = 234)	S-SPSS with HE (n = 186)	W-SPSS with HE (n = 139)	P
Child A	51	40	52	0.984
Child B	50	47	33	0.074
Child C	57	44	37§	0.035
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
Child A	44	11	44	0.804
Child B	38	47	45	0.398
Child C	51	49	55	0.798

Results are shown as percentages. Statistical differences ($p \leq 0.05$) between groups are indicated as * for comparison between L-SPSS versus S-SPSS, ¥ for S-SPSS versus W-SPSS and § for L-SPSS versus W-SPSS.

HE: Hepatic encephalopathy; L-SPSS: Large spontaneous portosystemic shunt; S-SPSS: Small-SPSS; W-SPSS: Without-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
Platelets ($x10^9/mm^3$) mean (SD)	95.7 (49.8) *	114.9 (58.6) ¥	133.9 (65.7)§	<0.001
Spleen diameter (cm) mean (SD)	16*	14¥	13§	<0.001
EGD endoscopy (n = 371)	L-SPSS (n = 81)	S-SPSS (n = 108)	W-SPSS (n = 182)	
Esophageal varices (%)	74	68¥	47§	<0.001
Gastric varices (%)	7	7	3	0.068
Portal gastropathy (%)	46	58	41	0.180
TE (n = 150)	L-SPSS (n = 19)	S-SPSS (n = 40)	W-SPSS (n = 91)	
Liver stiffness (KPa) median (IQR)	19 (24)*	27 (27)¥	18 (17)	0.002
HVPG measurement (n = 106)	L-SPSS (n =23)	S-SPSS (n = 31)	W-SPSS (n = 52)	
HVPG (mmHg) mean (SD)	15 (5)*	19 (7)¥	11 (6)§	<0.001
CSPH n (%)	20 (87)	30 (97)¥	27 (52)§	<0.001

Results are shown as mean (SD), median (IQR) or percentages. Number of subjects available for every marker is indicated at the beginning of in every row. Statistical differences ($p \leq 0.05$) between groups are indicated as * for comparison between L-SPSS versus S-SPSS, ¥ for S-SPSS versus W-SPSS and § for L-SPSS versus W-SPSS.

Three patients with L-SPSS had no CSPH: one patient had primary biliary cholangitis, one patient with mixed alcohol and hepatitis C etiology was abstinent and on beta-blockers, and finally one patient with hepatitis C was also on beta-blockers. One patient with S-SPSS and no CSPH was an abstinent alcoholic patient on beta-blockers.

L-SPSS: Large-spontaneous portosystemic shunt; Small-SPSS: S-SPSS; W-SPSS: Without-SPSS; SD: Standard Deviation; EGD: Esophagogastroduodenal; TE: Transient elastography; IQR: Interquartile range; HVPG: Hepatic venous pressure gradient; CSPH: Clinically significant portal hypertension.

Supplementary table 7. Quality of life (modified Rankin Scale) according to presence of SPSS and MELD score subgroups.

	L-SPSS (n = 488)	S-SPSS (n =548)	W-SPSS (n = 693)	p
MELD 6-9				
Autonomous	84*	92	95§	0.001
Limitation	13	8	5	
Disability	3	0	0	
MELD 10-13				
Autonomous	82	82	88	0.071
Limitation	17	17	11	
Disability	1	1	1	
MELD ≥14				
Autonomous	69	71	75	0.188
Limitation	29	27	25	
Disability	2	2	0	

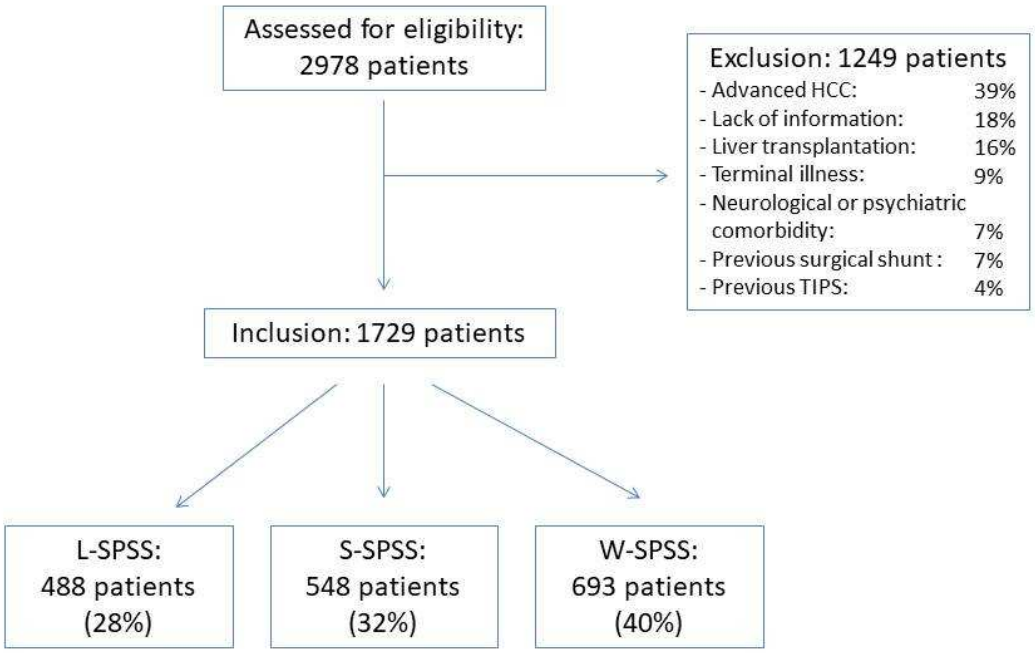
Results are shown as percentage. Statistical differences ($p \leq 0.05$) between pairs of value are indicated as * for comparison between L-SPSS and S-SPSS, ¥ for S-SPSS versus W-SPSS and § for L-SPSS versus W-SPSS.

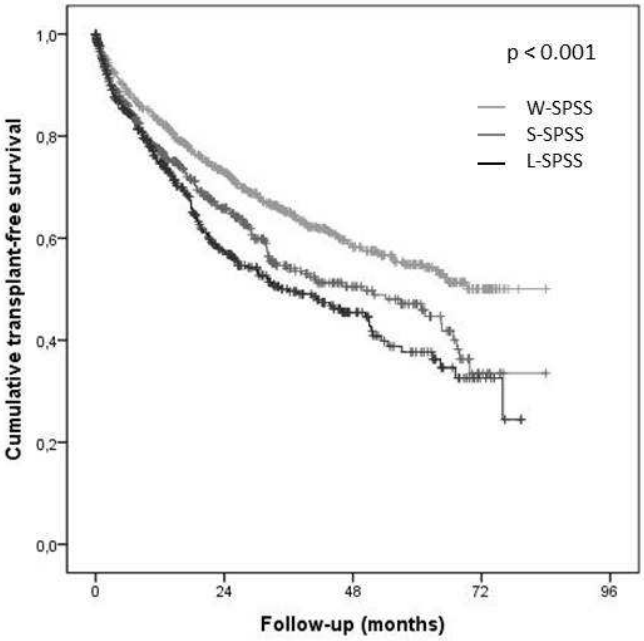
L-SPSS: Large spontaneous portosystemic shunt; S-SPSS: Small-SPSS; W-SPSS: Without-SPSS.

Supplementary table 8. Univariate (Cox) analysis of factors related to death or liver transplant in patients with preserved liver function (MELD score 6-9).

	Regression coefficient	p	HR (95% CI)
Age	0.02	0.050	1.02 (1.00-1.03)
Gender	-0.01	0.983	0.10 (0.67-1.48)
Time of diagnosis of cirrhosis*	0.21	0.208	1.02 (0.99-1.06)
Etiology: HCV	0.01	0.995	1.00 (0.68-1.47)
Etiology: Alcohol	0.34	0.105	1.41 (0.93-2.13)
Hypertension	0.21	0.283	1.23 (0.84-1.80)
Diabetes mellitus	0.29	0.147	1.33 (0.90-1.97)
Platelets $<150x10^9/mm^3$	0.10	0.619	1.12 (0.74-1.65)
HCC	1.46	<0.001	4.31 (2.89-6.43)
S-SPSS	0.49	0.024	1.64 (1.07-2.53)
L-SPSS	0.37	0.185	1.45 (0.84-2.52)
SPSS (S + L)	0.45	0.020	1.57 (1.08-2.30)

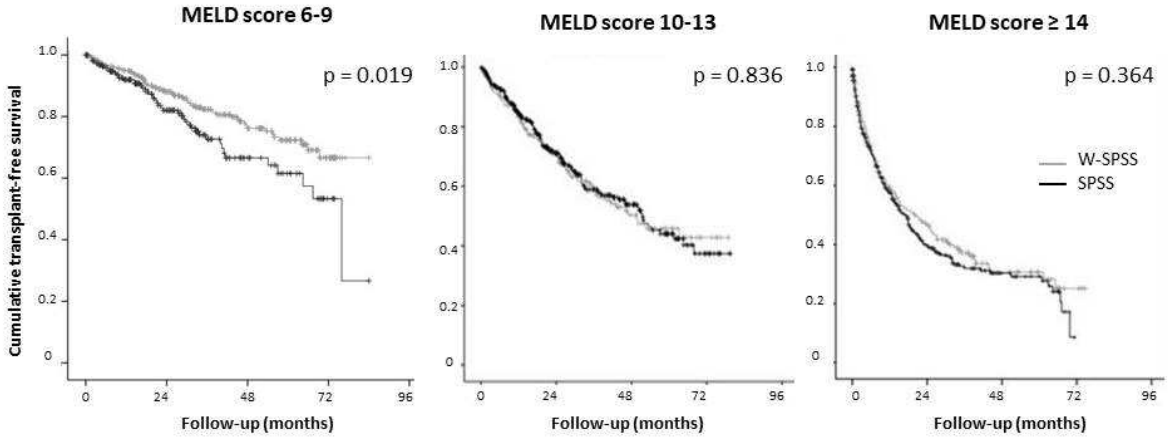
CI: confidence interval; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; HR: Hazard ratio; SPSS: Spontaneous portosystemic shunt; L-SPSS: Large-SPSS; S-SPSS: Small-SPSS. *Indicates duration of cirrhosis after initial diagnosis.





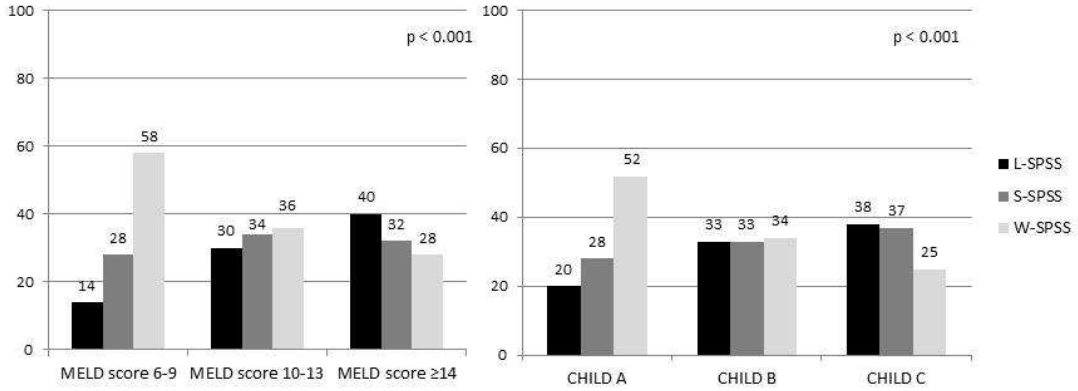
Patients at risk

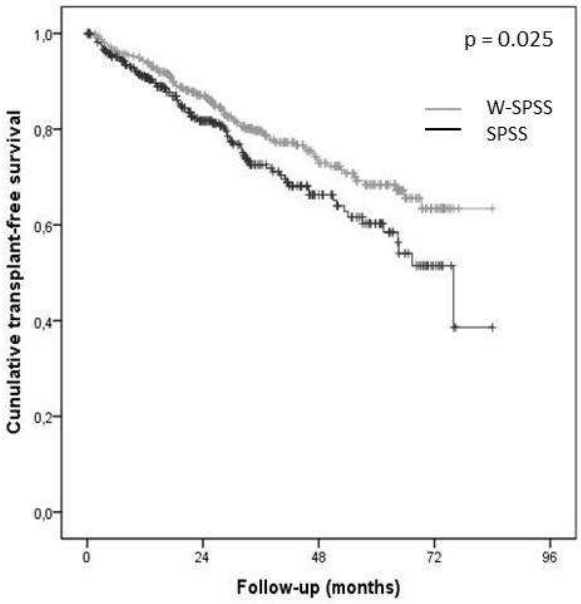
Time	0	24	48	72
W-SPSS	693	392	162	28
S-SPSS	548	201	67	8
L-SPSS	488	170	56	7



Patients at risk

	A. (n= 544)				B. (n= 560)				C. (n= 554)			
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





Patients at risk

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