Research Article
Cirrhosis and Liver Failure

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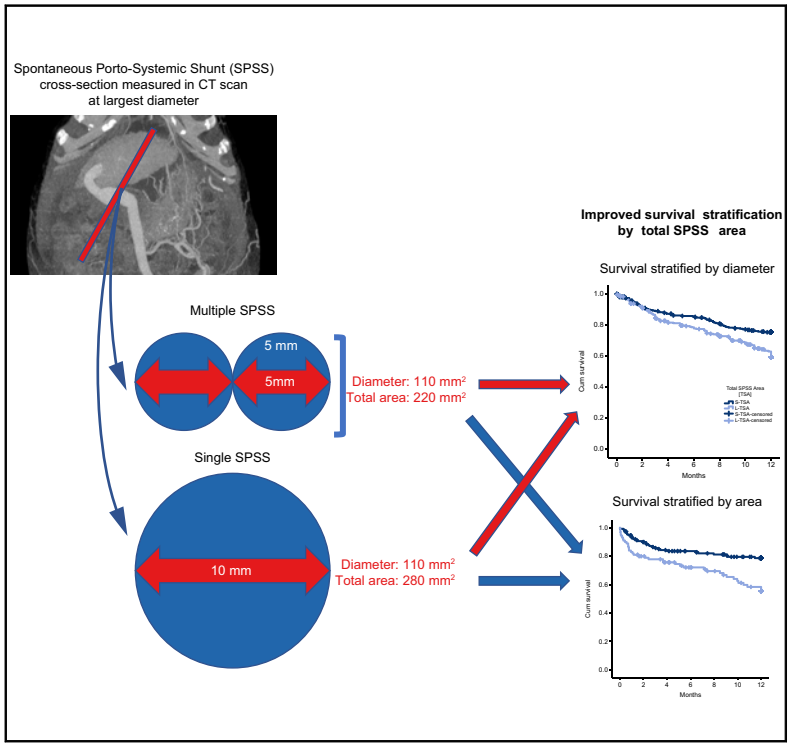
Total area of spontaneous portosystemic shunts independently predicts hepatic encephalopathy and mortality in liver cirrhosis☆

Graphical abstract



Highlights

- Total cross-sectional SPSS area (TSA) predicts survival in patients with advanced chronic liver disease.
- The cut-off for TSA that is associated with worse survival corresponds to a single shunt of >10 mm diameter.
- This study may impact on the clinical use of TSA/SPSS for risk stratification and decision-making in the management of patients with cirrhosis.

Authors

Michael Praktiknjo, Macarena Simón-Talero, Julia Römer, …, Aleksander Krag, Joan Genescà, Jonel Trebicka

Correspondence

jonel.trebicka@kgu.de (J. Trebicka), jgenesca@vhebron.net (J. Genescà).

Lay summary

The prevalence of spontaneous portosystemic shunts (SPSS) is higher in patients with more advanced chronic liver disease. The presence of more than 1 SPSS is common in advanced chronic liver disease and is associated with the development of hepatic encephalopathy. This study shows that total cross-sectional SPSS area (rather than diameter of the single largest SPSS) predicts survival in patients with advanced chronic liver disease. Our results support the clinical use of total cross-sectional SPSS area for risk stratification and decision-making in the management of SPSS.

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Total area of spontaneous portosystemic shunts independently predicts hepatic encephalopathy and mortality in liver cirrhosis ☆

Michael Praktiknjo[1,†], Macarena Simón-Talero[2,†], Julia Römer[1], Davide Roccarina[3], Javier Martínez[4], Katharina Lampichler[5], Anna Baiges[6], Gavin Low[7], Elba Llop[8], Martin H. Maurer[9], Alexander Zipprich[10], Michela Triolo[11], Geert Maleux[12], Annette Dam Fialla[13], Claus Dam[13], Judit Vidal-González[2], Avik Majumdar[3], Carmen Picón[14], Daniel Toth[5], Anna Darnell[15], Juan G. Abraldes[16], Marta López[8], Christian Jansen[1], Johannes Chang[1], Robert Schierwagen[23], Frank Uschner[23], Guido Kukuk[17], Carsten Meyer[17], Daniel Thomas[17], Karsten Wolter[17], Christian P. Strassburg[1], Wim Laleman[18], Vincenzo La Mura[19,20], Cristina Ripoll[10], Annalisa Berzigotti[21], José Luis Calleja[8], Puneeta Tandon[16], Virginia Hernandez-Gea[6], Thomas Reiberger[22], Agustín Albillos[4], Emmanuel A. Tsochatzis[3], Aleksander Krag[13], Joan Genescà[2,*], Jonel Trebicka[13,23,24,25,*], for the Baveno VI-SPSS group of the Baveno Cooperation

[1]Department of Internal Medicine I, University of Bonn, Bonn, Germany; [2]Liver Unit, Department of Internal Medicine, Hospital Universitari Vall d'Hebron, VHIR, Universitat Autònoma de Barcelona, CIBERehd, Barcelona, Spain; [3]Sheila Sherlock Liver Unit and UCL Institute for Liver and Digestive Health, Royal Free Hospital and UCL, London, United Kingdom; [4]Department of Gastroenterology and Hepatology, Hospital Universitario Ramón y Cajal, IRICYS, Universidad de Alcalá, CIBERehd, Spain; [5]Department of Biomedical Imaging and Image-guided Therapy, Medical University of Vienna, Austria; [6]Hepatic Hemodynamic Laboratory, Liver Unit, Hospital Clinic, IDIBAPS, Universitat de Barcelona, CIBERehd, Spain; [7]Department of Radiology, University of Alberta, Edmonton, Canada; [8]Liver Unit, Hospital U. Puerta de Hierro, Universidad Autónoma de Madrid, Madrid, Spain; [9]Department of Radiology, Inselspital, University of Berne, Berne, Switzerland; [10]First Department of Internal Medicine, Martin Luther University Halle-Wittenberg, Halle (Saale), Germany; [11]Medicina Interna, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) San Donato, Università Degli Studi di Milano, San Donato Milanese (MI), Italy; [12]Department of Interventional Radiology, University Hospitals Leuven, KU Leuven, Belgium; [13]Department of Gastroenterology and Hepatology, Odense University Hospital, Odense, Denmark; [14]Department of Radiology, Hospital Universitario Ramón y Cajal, IRICYS, Universidad de Alcalá, CIBERehd, Spain; [15]Department of Radiology, Hospital Clinic, IDIBAPS, Universitat de Barcelona, Barcelona, Spain; [16]Cirrhosis Care Clinic, University of Alberta, Edmonton, Canada; [17]Department of Radiology, University of Bonn, Bonn, Germany; [18]Department of Gastroenterology and Hepatology, University Hospitals Leuven, Leuven, Belgium; [19]Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, U.O.C. Medicina Generale-Emostasi e Trombosi, Milano, Italy; [20]Dipartimento di Scienze biomediche per la Salute and Centro di Ricerca Coordinata "A. M. e A. Migliavacca" per lo Studio e la Cura delle Malattie del Fegato, Università degli Studi di Milano, Milano, Italy; [21]Hepatology, Inselspital, University of Berne, Berne, Switzerland; [22]Vienna Hepatic Hemodynamic Lab, Division of Gastroenterology and Hepatology, Medical University of Vienna, Vienna, Austria; [23]Department of Internal Medicine I, University of Frankfurt, Frankfurt, Germany; [24]European Foundation for the Study of Chronic Liver Failure - EF CLIF, Barcelona, Spain; [25]Institute for Bioengineering of Catalonia, Barcelona, Spain

Background & Aims: Spontaneous portosystemic shunts (SPSS) frequently develop in liver cirrhosis. Recent data suggested that the presence of a single large SPSS is associated with complications, especially overt hepatic encephalopathy (oHE). However, the presence of >1 SPSS is common. This study evaluates the impact of total cross-sectional SPSS area (TSA) on outcomes in patients with liver cirrhosis.

Methods: In this retrospective international multicentric study, CT scans of 908 cirrhotic patients with SPSS were evaluated for TSA. Clinical and laboratory data were recorded. Each detected SPSS radius was measured and TSA calculated. One-year survival was the primary endpoint and acute decompensation (oHE, variceal bleeding, ascites) was the secondary endpoint.

Results: A total of 301 patients (169 male) were included in the training cohort. Thirty percent of all patients presented with >1 SPSS. A TSA cut-off of 83 mm^2 was used to classify patients with small or large TSA (S-/L-TSA). Patients with L-TSA presented with higher model for end-stage liver disease score (11 *vs.* 14) and more commonly had a history of oHE (12% *vs.* 21%, p <0.05). During follow-up, patients with L-TSA experienced more oHE episodes (33% *vs.* 47%, p <0.05) and had lower 1-year survival than those with S-TSA (84% *vs.* 69%, p <0.001). Multivariate analysis identified L-TSA (hazard ratio 1.66; 95% CI 1.02–2.70, p <0.05) as an independent predictor of mortality. An independent multicentric validation cohort of 607 patients confirmed that patients with L-TSA had lower 1-year survival (77% *vs.* 64%,

Keywords: Spontaneous portosystemic shunt; Ascites; TIPS; SPSS; Computed tomography; Cirrhosis; Liver; Acute decompensation; Portal hypertension; Hepatic encephalopathy; Acute-on-chronic liver failure; ACLF.
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* Corresponding authors. Addresses: Department of Internal Medicine I, University of Frankfurt, Theodor-Stern-Kai 7, 60590 Frankfurt. Tel.: +49 69 6301 4256 (J. Trebicka), or Hospital Universitari Vall d'Hebron / Universitat Autònoma de Barcelona, Passeig de la Vall d'Hebron 119-129, 08035 Barcelona. Tel.: 93 489 30 00 (Centraleta) (J. Genescà).
E-mail addresses: jonel.trebicka@kgu.de (J. Trebicka), jgenesca@vhebron.net (J. Genescà).

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† Contributed equally as first author.

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p <0.001) and more oHE development (35% *vs.* 49%, p <0.001) than those with S-TSA.
Conclusion: This study suggests that TSA >83 mm^2 increases the risk for oHE and mortality in patients with cirrhosis. Our results support the clinical use of TSA/SPSS for risk stratification and decision-making in the management of patients with cirrhosis.
Lay summary: The prevalence of spontaneous portosystemic shunts (SPSS) is higher in patients with more advanced chronic liver disease. The presence of more than 1 SPSS is common in advanced chronic liver disease and is associated with the development of hepatic encephalopathy. This study shows that total cross-sectional SPSS area (rather than diameter of the single largest SPSS) predicts survival in patients with advanced chronic liver disease. Our results support the clinical use of total cross-sectional SPSS area for risk stratification and decision-making in the management of SPSS.

Introduction

In the course of liver cirrhosis, the development of portal hypertension is a major driver of complications and therefore a frequent cause of acute decompensation (AD).[1,2] AD may lead to a systemic inflammatory response and progress to acute-on-chronic liver failure (ACLF), a syndrome with high short-term mortality.[3–6] Portal hypertension also drives the development of spontaneous portosystemic shunts (SPSS) in patients with cirrhosis.

The association of SPSS or surgical/interventional shunting with hepatic encephalopathy is well-known and the first embolizations of SPSS, aimed at limiting the complications of portal hypertension, were reported more than 30 years ago.[7–9] However, since then, few reports on the role of SPSS in cirrhosis and their possible treatment have been published.[10–14] A large multicentric study confirmed the association of a single large (diameter >8 mm) SPSS with the occurrence of hepatic encephalopathy.[15] Other reports have also demonstrated that interventional embolization of SPSS can improve refractory hepatic encephalopathy and liver failure in selected patients.[16,17] Since the procedure of SPSS-embolization is invasive and in many cases requires direct portal venous access, there is an open discussion as to whether or when the procedure is indicated.[12,18–20] As a result, recommendations for the management of SPSS are still missing from current guidelines.[2,21–23]

The presence of SPSS and especially their cumulative size has not been associated with hard endpoints such as survival. From a pathophysiological point of view the total cross-sectional shunt area of an SPSS (or cumulative area of several SPSS) may reflect the portosystemically shunted blood volume[24] more accurately than SPSS diameter. With the improved quality of imaging, especially with CT, the detection of SPSS in clinical routine is feasible and reliable. This present study aimed to evaluate the role of the combined cross-sectional area of all SPSS, as a surrogate marker of portosystemically shunted blood volume, in the natural course of patients with liver cirrhosis.

Patients and methods

Study population

For this retrospective study, a total of 301 patients from the University Hospital of Bonn were identified for inclusion as a training cohort. Inclusion criteria were age 18 years or older, diagnosis of cirrhosis (clinical, radiologic or histologic) and SPSS of at least 5 mm of diameter in CT scans between October 2006 and April 2016. Since precision was needed to measure SPSS diameter, a minimum diameter of >5 mm was considered by our radiologist to provide accurate SPSS size. The date of CT scan was defined as baseline. Exclusion criteria were presence of hepatocellular carcinoma 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 neurologic, or psychiatric disorder preventing a proper hepatic encephalopathy evaluation and absence of critical information in the medical history.[15] The validation cohort was formed of 607 consecutive patients, identified between 2010 and 2015, with the same selection criteria as the training cohort from the rest of the participating centers in the previously published multicenter study.[15] Although excluding small SPSS of less than 5 mm was not an original criterion in the prior multicenter study, it was applied to the validation cohort for consistency. In all patients, cross-sectional area of all detectable SPSS was assessed and calculated in CT scans. Clinical and laboratory blood analysis data was followed up until end of follow-up, death or liver transplantation (LT).

The primary endpoint was 1-year survival and secondary endpoints were acute decompensations (hepatic encephalopathy, variceal bleeding and ascites) during follow-up.

The local ethics committee of the participating centers approved the study. The study was performed in accordance with the Helsinki Declaration.

Assessment of SPSS parameters

All CT scans were reviewed by radiologists with expertise in liver diseases. SPSS were defined as previously described.[15] The radiological study protocol is shown in the supplementary materials and methods. All CT scans were screened for any SPSS by scrolling through the abdominal CT scan in the axial plane. If available, portal venous phase was preferred. The radiologists looked for any additional veins leaving the inferior vena cava, portal vein, splenic vein, right/left renal vein and superior/inferior mesenteric vein. The presence of SPSS was verified in the coronal and sagittal plane.

The position of the SPSS with the largest diameter was then identified. At this position the short-axis diameter was reconstructed and measured between both walls of the vessel.

The 607 CT scans from the validation cohort were reviewed again to measure the total cross-sectional SPSS area (TSA) for the present study by the same radiologists who evaluated them in the prior study.[15] We have chosen to measure the cross-sectional area instead of the diameter because more than 1 SPSS can occur in patients with liver cirrhosis and portal hypertension.[15] Though the sum of diameters of all SPSS can be the same, the sum of cross-sectional areas can be vastly different as shown in Fig. S1. We hypothesized that TSA reflects the shunted blood volume better than diameters. For each SPSS we calculated the area by the formula πr^2. All SPSS areas were then summed up to calculate the TSA for each patient.

The diameters of the SPSS were measured twice (initial data were collected from the previous study by Simón-Talero *et al.*;[15] for the current work, all the CTs were reviewed again by the same expert radiologists). Therefore, the intra-rater variability of the measurement has been calculated, with an intraclass correlation coefficient of 0.95 (95% CI 0.94–0.96).

Esophageal and gastric varices were documented, but not measured. Rectal varices were neither measured nor

documented. This is because, in both cases, the shunts are more of a network than a single vessel that can be determined.

Statistical analysis

We performed descriptive statistics for all variables. Non-parametric testing was used to compare different groups when suitable. Paired non-parametric testing was used to compare data of baseline and follow-up of the same patients. Correlation of metric variables was performed using Spearman's correlation. For the selection of cut-off values of TSA, receiver-operating characteristics analysis with 1-year survival as the endpoint was calculated. To examine the impact of TSA on survival we used a Kaplan-Meier curve with log-rank test. Univariate and multivariate risk factor analyses were performed with Cox regression for 1-year mortality and episodes of hepatic encephalopathy as endpoints. Univariate analysis included general characteristics (age, sex) and clinical conditions (hepatic encephalopathy, hepatorenal syndrome, ascites, spontaneous bacterial peritonitis) as well as prognostic score (model for end-stage liver disease [MELD]) and laboratory parameters (Na, creatinine, bilirubin, international normalized ratio [INR]) at baseline. Multivariate analysis included all values with p <0.05 from univariate Cox regression. To avoid multicollinearity, calculated scores such as MELD were not entered simultaneously with their components, while scores with overlapping components (Child-Pugh) were not entered simultaneously either. Continuous variables are presented as median (range), unless otherwise specified. Categorical variables are presented as absolute cases and/or percentage. The intra-rater reliability was calculated using the interclass correlation coefficient. All data was analyzed using SPSS (version 24, IBM, Armonk, NY, USA) or R statistics (version 3.4.4, The R Foundation).

Results

General patient characteristics

Training cohort

Of all 908 patients, 301 patients from University of Bonn were included in the training cohort (Fig. 1), of whom 169 were male. Median age at baseline was 56 (28-85) years. Alcohol was the most common etiology of cirrhosis (57% of patients), while 20% of patients had chronic viral hepatitis B and/or C infection. Other etiologies were present in 23% of patients. Most of the patients were decompensated (Child-Pugh B or C in 59%) with 64% of the patients exhibiting ascites at time of CT scan; 16% had experienced at least 1 episode of hepatic encephalopathy and 26% had hepatic encephalopathy at baseline. A history of variceal bleeding was present in 28% of the patients. Median MELD score was 13 (6-40). Detailed general characteristics are displayed in Table 1. Of note, high platelet counts >250×10^9/L were found in 26 patients, of whom 9 had infection, 3 recent bleeding and 2 iron deficiency, as likely causes for high platelet counts. Median follow-up time was 15 (0–117) months. Median time from diagnosis of liver cirrhosis to CT scan was 17 months (0–1,322). Indications for CT scans are displayed in Table S1.

Follow-up data on survival status was available in 254 patients (Table 1). During follow-up MELD decreased slightly, while other prognostic scores (MELD-Na, Child-Pugh) did not change significantly. Compared to baseline, the rate of patients developing hepatorenal syndrome (23%) and episodes of hepatic encephalopathy (38%) increased significantly. The rate of patients with ascites and variceal bleeding did not change significantly (Table 1). In total, 23 patients were treated with TIPS (16 for refractory ascites, 7 for variceal hemorrhage) during follow-up. Detailed analysis of number of TIPS and LT in relation to MELD is shown in Table S2.

SPSS characteristics. In the training cohort of 301 patients, a total of 392 SPSS were identified. Most patients had a single SPSS (70%), while almost one-third (30%) were diagnosed with more than 1 SPSS (Table 1).

The most common SPSS types were para-umbilical shunts representing 57% of all shunts, followed by splenorenal shunts (32%), mesocaval shunts in the gastrorenal vein (5%) and in the adrenal vein (2%). Infero-mesenterico-caval, right renal vein and mesorenal shunts were each found in only 1% of SPSS.

Validation cohort

A total of 607 patients from 11 participating centers were included in the validation cohort (Table S3, Fig. 1). Median age

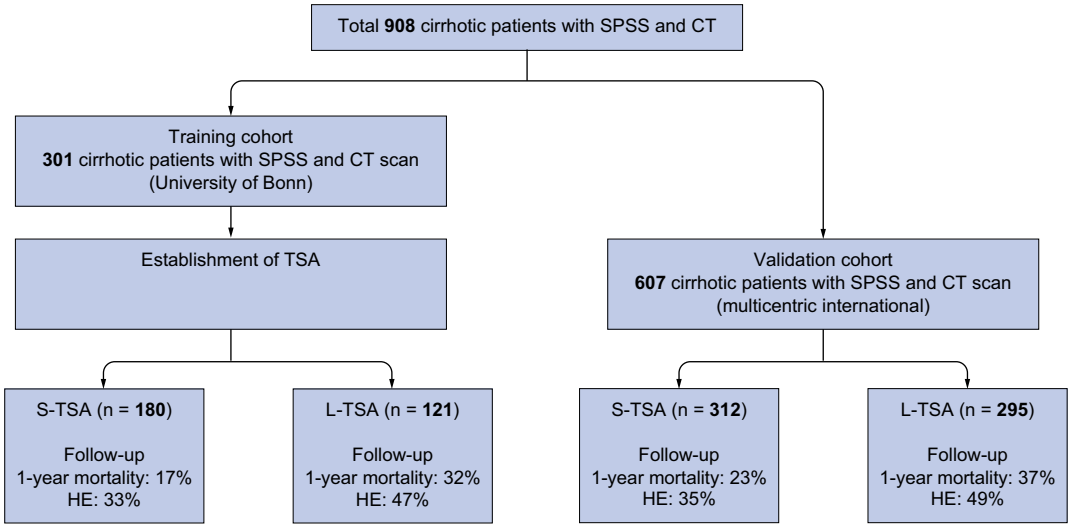

Fig. 1. Flowchart of patient selection.

Table 1. General characteristics of the training cohort (n = 301).

Parameter	History	Baseline	Follow-up
Median (range) or absolute (percentage)			
General			
Age [years]		58 (28-85)	
Gender [male/female]		169/132 (56/44%)	
Etiology of cirrhosis [alcohol, viral, other]		173/60/68 (57/20/23%)	
Number of shunts [1/2/3]		213/86/2 (71/29/1%)	
Total SPSS area [mm^2]		59 (6-881)	
Clinical events			
Ascites	143 (48%)	194 (64%)	116 (53%)
Variceal Bleeding	85 (28%)	48 (16%)	29 (13%)
Spontaneous Bacterial Peritonitis	20 (7%)	32 (11%)	20 (9%)
Hepatorenal Syndrome	30 (10%)	49 (16%)	50 (23%)***
Hepatic Encephalopathy	47 (16%)	78 (26%)	84 (38%)***
Scores			
MELD		13 (6-40)	12.5 (6-40)*
MELD-Na		15 (6-40)	14 (6-40)
Child-Pugh		7 (5-13)	7 (5-12)
Child-Pugh class A/B/C		103/143/34 (34/48/11%)	90/68/32 (41/31/15%)
CLIF-C AD		20.65 (10-29)	20.58 (9-32)
Laboratory			
Sodium [mmol/L]		138 (119-154)	140 (119-163)***
Creatinine [mg/dl]		0.97 (0.3-6.04)	1 (0.1-9.39)***
Bilirubin [mg/dl]		1.86 (0.21-48.44)	1.75 (0.19-42.49)
AST [U/L]		52 (12-653)	44.5 (9-5,644)
ALT [U/L]		31 (8-349)	33 (6-1,952)
Albumin [g/L]		29.2 (3.2-59.9)	32.8 (3.2-55)***
INR		1.2 (0.9-4.6)	1.2 (0.9-5.3)
WBC [10^3/μl]		5.86 (1.02-37.17)	5.795 (0.04-36.22)
Platelets [×10^9/L]		105.5 (11-653)	107.5 (14-479)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CLIF-C AD, Chronic Liver Failure Consortium acute decompensation; INR, international normalized ratio; MELD, model of end-stage liver disease; SPSS, spontaneous portosystemic shunts; WBC, white blood cell count.
*p <0.05; **p <0.01; ***p <0.001.

was 58 (18-87) years with 65% male patients. Alcohol was the most common etiology of cirrhosis (43%), while 27% had viral hepatitis. Most patients (66%) had decompensated cirrhosis (Child-Pugh B or C); 53% of the patients had ascites at the time of CT scan, 30% had experienced at least 1 episode of hepatic encephalopathy, and 25% had hepatic encephalopathy at baseline. A history of variceal bleeding was present in 25% of the patients. Median MELD score was 13 (6-37). Detailed general characteristics are displayed in Table 2.

Follow-up data is shown in Table 2. Briefly, like the training cohort, the rate of patients developing hepatorenal syndrome (11%), as well as episodes of hepatic encephalopathy (42%) increased significantly compared to baseline. The rate of ascites and variceal bleeding did not change significantly (Table 2).

SPSS characteristics

In the validation cohort of 607 patients, 754 SPSS were identified. The majority of patients had a single SPSS (79%), while 21% had multiple SPSS (Table 2). Splenorenal shunts were the most common, representing 41% of cases, followed by para-umbilical shunt (35%). Mesocaval shunt was present in 7% of cases, gastrorenal in 6%, infero-mesenterico-caval in 3% and mesorenal in 1% of SPSS.

Patient stratification by total SPSS area

A receiver-operating characteristics analysis of TSA with 1-year survival as an endpoint was performed and an area under the curve of 0.609 (95% CI 0.531–0.687, p = 0.007) was calculated. The optimal cut-off value for the training cohort was found at 83 mm^2 (sensitivity 55.7%, specificity 66.8%, positive predictive value 39.0%, negative predictive value 79.9%; Table S4). Patients with TSA above 83 mm^2 (corresponding to a single shunt of 10 mm diameter) were classified as having large TSA (L-TSA) and patients with TSA below 83 mm^2 were classified as having small TSA (S-TSA). Median TSA was 59 mm^2 (6–881). Patients with S-TSA had a median TSA of 35 mm^2 (6–82) and L-TSA of 141.46 mm^2 (83–881) (Table 3). In total, 180 patients were classified as S-TSA (60%) and 121 as L-TSA (40%). There were no significant differences in type of SPSS between patients with S-TSA and L-TSA. Time between diagnosis of cirrhosis and CT scan was not significantly different between patients with S-TSA and L-TSA (15 (0–1,322) *vs.* 24 (0–369) months, p = 0.503).

Patients with L-TSA had significantly higher rates of multiple SPSS, as well as higher MELD scores (14 *vs.* 11). Moreover, patients with L-TSA had higher rates of hepatic encephalopathy in their medical history (Table 3). During follow-up, MELD (12 *vs.* 15, p <0.01) and MELD-Na (13 *vs.* 16, p <0.05) score remained significantly higher in the L-TSA compared to S-TSA group. CLIF-C AD score was not significantly different. Additionally, Child-Pugh score (6 *vs.* 7, p <0.05) in follow-up showed higher values for L-TSA. This mainly derives from serum albumin levels being significantly lower in L-TSA (35 *vs.* 31 g/L, p <0.001) (Table 3). No significant differences were detectable in terms of hepatorenal syndrome, ascites and infections.

L-TSA is associated with hepatic encephalopathy

Training cohort

Patients with L-TSA had a significantly higher risk of developing hepatic encephalopathy, as shown by the cumulative hazard

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Table 2. General characteristics of external validation cohort (n = 607).

Parameter	History	Baseline	Follow-up
Median (range) or absolute (percentage)			
General			
Age [years]		58 (18-87)	
Sex male/female		397/210 (65/35%)	
Etiology of cirrhosis alcohol/viral/others		259/164/184 (43/27/30%)	
Number of shunts 1/2/3/4		480/110/14/3 (79/18/2/1%)	
Total SPSS area [mm^2]		79 (13-2205)	
Clinical events			
Ascites	345 (58%)	321 (53%)	341 (57%)
Variceal bleeding	151 (25%)	65 (11%)	96 (16%)
Spontaneous bacterial peritonitis	65 (11%)	39 (7%)	72 (12%)
Hepatorenal syndrome	18 (3%)	23 (4%)	63 (11%)***
Hepatic encephalopathy	183 (30%)	152 (25%)	247 (42%)***
Scores			
MELD		13 (6-37)	
MELD-Na		15 (6-40)	
Child-Pugh		8 (5-15)	
Child-Pugh class A/B/C		195/238/147 (34/41/25%)	
Laboratory			
Sodium [mmol/L]		138 (95-164)	
Creatinine [mg/dl]		0.8 (0.3-9.2)	
Bilirubin [mg/dl]		1.8 (0.1-45.2)	
Albumin [g/L]		32 (10-50)	
INR		1.4 (0.9-5.2)	
Platelets [×10^9/L]		87 (13-436)	

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CLIF-C AD, Chronic Liver Failure Consortium acute decompensation; INR, international normalized ratio; MELD, model of end-stage liver disease; SPSS, spontaneous portosystemic shunts; WBC, white blood cell count.
*p <0.05; **p <0.01; ***p <0.001.

function for hepatic encephalopathy in Fig. 2A. Blood ammonia levels were available in 154 patients. Median blood ammonia level was 65 μmol/L (9–260). Patients were divided into high (>65 μmol/L) and low (≤65 μmol/L) ammonia levels. Patients with L-TSA showed higher rates (57%) of high ammonia levels than patients with S-TSA (42%) (Table S5).

Validation cohort

In the validation cohort clinical but no blood parameters were available at follow-up (Table 4). Importantly, the significantly higher rates of episodes of hepatic encephalopathy were confirmed as shown in Fig. 2B.

Large TSA is an independent risk factor for 1-year mortality

Training cohort

One-year survival data was available in 253 patients. Fig. 3A shows the Kaplan-Meier curve for 1-year mortality. The Kaplan-Meier curve for 1-year survival excluding patients with high platelet counts showed similar results (Fig. S2). Patients with L-TSA had a significantly higher mortality compared to patients with S-TSA (p <0.001). Most deaths are attributed to infection (63%). Hepatocellular carcinoma and liver failure caused 10% and 13% of deaths, respectively. Six percent died of bleeding and cardiovascular events (Table S6).

Univariate Cox regression was performed to identify risk factors for 1-year mortality. This revealed that besides the expected prognostic MELD score, creatinine, bilirubin and INR, as well as hepatorenal syndrome, hepatic encephalopathy, spontaneous bacterial peritonitis, ascites and L-TSA at baseline were dependent predictors of survival. Multivariate Cox regression identified L-TSA alongside MELD, hepatic encephalopathy, hepatorenal syndrome and ascites as independent risk factors for 1-year survival (Table 5).

A different model with TSA as a continuous variable was calculated, which confirmed TSA (as a continuous variable) as an independent predictor of 1-year survival (Table S7).

Validation cohort

In order to validate these results, the validation cohort was stratified for TSA. A total of 312 patients were classified as S-TSA (51%) and 295 as L-TSA (49%). Patients with L-TSA had significantly higher MELD and Child-Pugh score. There were no significant differences in type of SPSS between patients with S-TSA and L-TSA. Moreover, patients with L-TSA had higher rates of hepatic encephalopathy at baseline and in their medical history (Table 4). Survival data was available in 604 patients. Fig. 3B shows the Kaplan-Meier curve for 1-year mortality. Patients with L-TSA had a significantly higher mortality compared to those with S-TSA (p <0.001). Kaplan-Meier curve for 1-year survival excluding patients with high platelet counts showed similar results (Fig. S3).

Most deaths in the validation cohort were attributed to liver failure (36%), infection (19%) and hepatocellular carcinoma (12%). Six percent died of bleeding, 27% died of other or unknown causes (Table S8).

Univariate Cox regression was performed to identify risk factors for 1-year mortality. In this validation cohort prognostic markers such as MELD, creatinine, bilirubin and INR, as well as hepatorenal syndrome, hepatic encephalopathy, spontaneous bacterial peritonitis, ascites and TSA at baseline were dependent predictors of survival. Multivariate Cox regression confirmed TSA and MELD as independent predictors of 1-year mortality. Moreover, age, hepatorenal syndrome and ascites were shown as independent risk factors for 1-year survival (Table 6).

In an alternative model using TSA as a continuous variable, TSA was still an independent predictor of 1-year mortality, suggesting a linear relationship (Table S9).

Table 3. Clinical and laboratory characteristics of training cohort stratified for total shunt area.

Parameter	S-TSA	L-TSA
Median (range) or absolute (percentage)	n = 180	n = 121
Baseline general		
Age [years]	57 (28-85)	58 (31-78)
Sex male/female	99/81 (55/45%)	70/51 (58/42%)
Etiology of cirrhosis alcohol/viral/others	103/41/36 (57/23/20%)	70/19/32 (58/16/26%)
Number of shunts 1/2/3	162/18/0 (90/10/0%)	51/68/2 (42/56/2%)***
Total SPSS area [mm^2]	34.72 (5.72-82.34)	141.46 (83.29-880.65)***
History of clinical events		
Ascites	89 (49%)	54 (45%)
Variceal bleeding	48 (27%)	37 (31%)
Spontaneous bacterial peritonitis	12 (7%)	8 (7%)
Hepatorenal syndrome	19 (11%)	11 (9%)
Hepatic encephalopathy	22 (12%)	25 (21%)*
Baseline clinical events		
Ascites	126 (70%)	68 (56%)*
Variceal bleeding	34 (19%)	14 (12%)
Spontaneous bacterial peritonitis	18 (10%)	14 (12%)
Hepatorenal syndrome	26 (14%)	23 (19%)
Hepatic encephalopathy	42 (23%)	36 (30%)
Baseline scores		
MELD	11 (6-35)	14 (6-40)***
MELD-Na	14 (6-36)	16 (6-40)**
Child-Pugh	7 (5-11)	7 (5-13)
Child-Pugh class A/B/C	63/91/13 (35/51/7%)	40/52/21 (33/43/17%)
Baseline laboratory		
Sodium [mmol/L]	138 (119-148)	139 (122-154)
Creatinine [mg/dl]	0.96 (0.3-6.04)	0.99 (0.42-5.09)
Bilirubin [mg/dl]	1.56 (0.21-19.9)	2.45 (0.26-48.44)***
Albumin [g/L]	29.4 (3.2-51.6)	28.9 (4.8-59.9)
INR	1.2 (0.9-2.8)	1.3 (1-4.6)***

Parameter	S-TSA	L-TSA
Median (range) or absolute (percentage)	n = 180	n = 121
FU		
Survival FU 1 year [months]	12 (0-12)	8.5 (0-12)*
FU state 1-year dead/LT	22 / 9 (17%)	29 /10 (32%)**
Lost to FU	36 (20%)	23 (19%)
FU clinical events		
Ascites	76 (55%)	40 (49%)
Variceal bleeding	22 (16%)	7 (9%)
Spontaneous bacterial peritonitis	14 (10%)	6 (7%)
Hepatorenal syndrome	33 (24%)	17 (21%)
Hepatic encephalopathy	46 (33%)	38 (47%)*
FU scores		
MELD	12 (6-40)	15 (6-40) **
MELD-Na	13 (6-40)	16 (6-40)*
Child-Pugh	6 (5-12)	7 (5-12)*
Child-Pugh class A/B/C	63/41/14 (46/30/10%)	27/27/18 (33/33/22%)*

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CLIF-C AD, Chronic Liver Failure Consortium acute decompensation; FU, follow-up; INR, international normalized ratio; LT, liver transplantation; L-TSA, large total SPSS area; MELD, model of end-stage liver disease; SPSS, spontaneous portosystemic shunts; S-TSA, small total SPSS area; WBC, white blood cell count.
*p <0.05; **p <0.01; ***p <0.001.

To further investigate the impact of TSA on survival in relation to liver function, we divided the whole cohort into tertiles according to MELD (6–9, 10–13, 14–40), as in our previous study.[15] The rates of 1-year mortality were higher in the L-TSA group and significant in MELD groups 6–9 and 14–40 (Table S10).

SPSS and TSA distribution

In our recent multicenter study,[15] a stratification of patients according to SPSS diameter (8 mm cut-off) did not show significant differences in survival between S-SPSS (<8 mm) and L-SPSS (≥8 mm). Therefore, we investigated the distribution of S-/L-SPSS and S-/L-TSA of the whole cohort. The results are shown in Fig. S4. In total, 35% of patients were classified S-SPSS and S-TSA, 0.3% S-SPSS and L-TSA, 19% L-SPSS and S-TSA and 46% L-SPSS and L-TSA. This suggests mostly concordant classification between S-SPSS and S-TSA. However, a substantial fraction (19%) of patients with L-SPSS are classified as S-TSA as well.

The Kaplan-Meier survival curve shows no significant difference in survival between patients with S-SPSS and L-SPSS (Fig. S5), confirming our previous study.[15] Importantly, Kaplan-Meier survival analysis of only patients with L-SPSS showed a highly significant difference between patients classified as S-TSA and L-TSA, demonstrating that TSA classification clearly outperforms classification by SPSS diameter (Fig. S6).

We performed a Cox regression model for 1-year survival with L-SPSS instead of L-TSA to evaluate the predictive value of

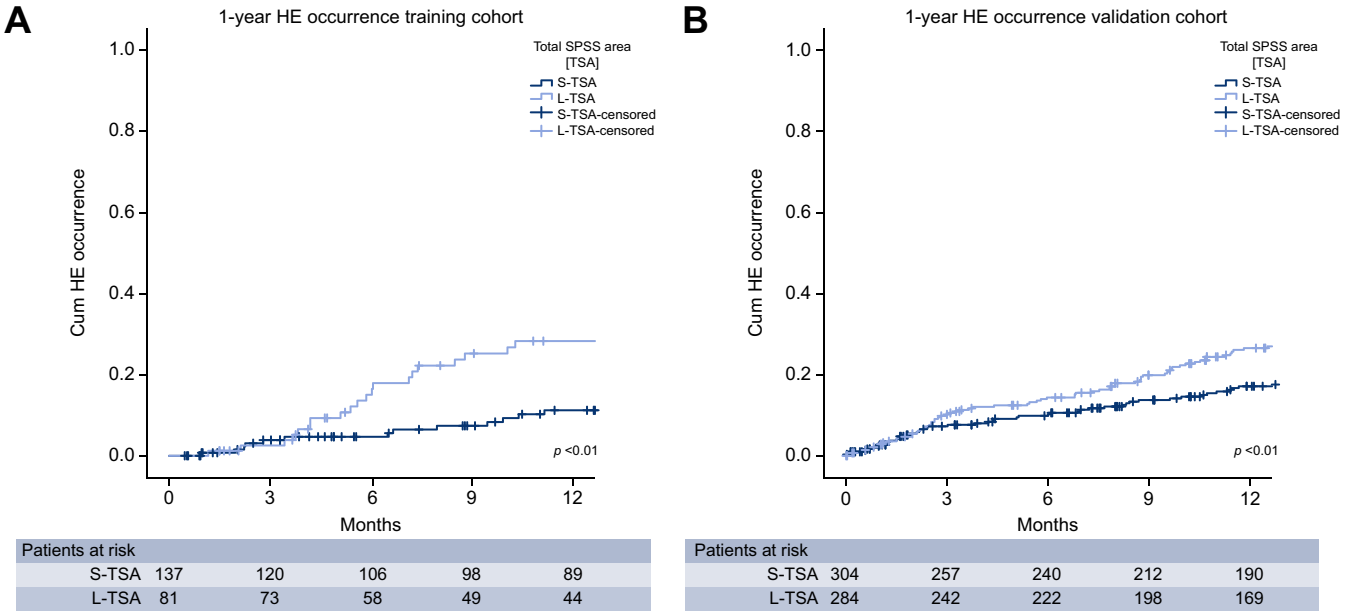

Fig. 2. Cumulative hazard function for the occurrence of overt hepatic encephalopathy in the training and validation cohorts. (A) Cumulative hazard function for the occurrence of overt hepatic encephalopathy during 1-year follow-up in L-TSA (green line) *vs.* S-TSA (blue line) patients in training cohort. (B) Cumulative hazard function for the occurrence of overt hepatic encephalopathy during 1-year follow-up in L-TSA (green line) *vs.* S-TSA (blue line) patients in validation cohort. (S-/L-TSA: small (<83 mm^2) / large (≥83 mm^2) total SPSS area). Statistical analysis: log-rank test. L-TSA, large total SPSS area; SPSS, spontaneous portosystemic shunts; S-TSA, small total SPSS area.

presence of L-SPSS. In both the training and validation cohort SPSS was not significant in multivariate analysis. In the validation cohort, SPSS was not significant in the univariate analysis either (Table S11 and S12).

Discussion

Using a large single center training and a large multicentric international validation cohort, this study demonstrates for the first time that portosystemic shunting is associated with increased mortality in cirrhotic patients independently of severity of liver disease.

These results build up on the previously reported data on the influence of the diameter of largest SPSS, where a clear association with the risk of complications of liver cirrhosis was demonstrated.[15] This study confirms those results, which underlines the robustness of TSA. Another factor supporting the plausibility of our data is the fact that L-TSA was found in more advanced stages of liver cirrhosis, reflected by higher MELD scores, which is in line with previous reports.[15,25] One might argue that retrieving and calculating the cross-sectional area of every SPSS is costly and more time consuming than just measuring the diameter of the largest SPSS. However, having a single SPSS of 10 mm diameter or more qualifies for L-TSA but not multiple SPSS with an added diameter of 10 mm. This situation of multiple SPSS is present in one-third of the presented large cohort. The present study demonstrates that the complete shunting volume, which might be better reflected by TSA, gives independent insight into the progression of liver disease and outcome of cirrhotic patients. This hypothesis is supported by this study because the size of TSA has an independent impact on survival in cirrhotic patients, which could not be demonstrated for diameter of the single largest SPSS (<8 mm *vs.* ≥8 mm).[15] This is especially impactful because, as shown in our and other cohorts, about one-third of the patients have more than 1 SPSS.[15,26,27] Since this study demonstrates TSA as a risk factor for survival independent of MELD, an incorporation of TSA in MELD (TSA-MELD) could improve patient's risk stratification and should be evaluated in future research.

The association of hepatic encephalopathy and SPSS is well established.[7,15,28–31] This association with hepatic encephalopathy is not only apparent for spontaneous shunts but also for therapeutically implanted shunts (*e.g.* TIPS and surgical shunts), where episodes of hepatic encephalopathy occur in up to 50% of patients.[31–33] Although only shown in a few cohorts, the deleterious effect of shunting seems to be additive by the number shunts (spontaneous and intentional) as the presence of SPSS and TIPS has been shown to be associated with more complications than TIPS alone.[34,35] Growing evidence has been published that suggests less complications after TIPS by using smaller diameter stents or dilatation of stents smaller than the nominal diameter, suggesting a beneficial effect of less shunt volume.[36–40]

Regarding other decompensating events, we were unable to find a significant difference in variceal bleeding, hepatorenal syndrome or spontaneous bacterial peritonitis between patients with L-TSA and S-TSA. Considering variceal bleeding, our data are supported by previous reports, in which only the presence of SPSS *vs.* no SPSS was shown to be associated with bleeding, but no differences between small and large SPSS were detected.[7,10,15,29]

Interestingly, the cut-off we found in our patients corresponds to a single shunt of 10 mm diameter. In non-spontaneous SPSS, such as TIPS, it has been previously shown that small diameter TIPS-shunts are associated with less hepatic encephalopathy and better survival than the commonly used 10 mm stents.[37,38,40] However, in case of TIPS, the collaterals and the

Table 4. Clinical and laboratory characteristics of validation cohort stratified for total shunt area.

Parameter	S-TSA	L-TSA
Median (range) or absolute (percentage)	n = 312	n = 295
Baseline general		
Age [years]	59 (18-87)	57 (20-84)
Sex male/female	209/103 (67/33%)	188/107 (64/36%)
Etiology of cirrhosis alcohol/viral/others	129/86/97 (41/28/31%)	130/78/87 (44/26/30%)
Number of shunts 1/2/3	283/27/2/0 (91/8/1/0%)	67/28/12/3 (67/28/4/1%)***
Total SPSS area [mm^2]	38 (13-79)	201 (89-2205)***
History of clinical events		
Ascites	180 (58%)	165 (57%)
Variceal bleeding	75 (25%)	76 (26%)
Spontaneous bacterial peritonitis	37 (12%)	28 (10%)
Hepatorenal syndrome	9 (3%)	9 (3%)
Hepatic encephalopathy	71 (23%)	112 (38%)***
Baseline clinical events		
Ascites	176 (56%)	145 (49%)
Variceal bleeding	42 (14%)	23 (8%)*
Spontaneous bacterial peritonitis	22 (7%)	17 (6%)
Hepatorenal syndrome	15 (5%)	8 (3%)
Hepatic encephalopathy	64 (21%)	88 (30%)**
Baseline scores		
MELD	12 (6-37)	14 (6-33)**
MELD-Na	15 (6-37)	15 (6-40)
Child-Pugh	8 (5-15)	8 (5-15)*
Child-Pugh class A / B / C	109/120/73 (36/40/24%)	86/118/74 (31/42/27%)
Baseline laboratory		
Sodium [mmol/L]	137 (117-164)	138 (95-148)
Creatinine [mg/dl]	0.8 (0.3-3.8)	0.8 (0.4-9.2)
Bilirubin [mg/dl]	1.5 (0.1-42.9)	2.1 (0.3-45.2)*
Albumin [g/L]	32 (10-50)	32 (15-50)
INR	1.4 (0.9-5.2)	1.4 (1.0-4.1)
Parameter	**S-TSA**	**L-TSA**
Median (range) or absolute (percentage)	n = 312	n = 295
FU		
Survival FU 1 year [months]	12 (0-12)	11 (0-12)*
FU state 1-year dead/LT	45/28 (23%)	78/31 (37%)***
Lost to FU	42 (13%)	56 (19%)
FU clinical events		
Ascites	182 (59%)	159 (56%)
Variceal bleeding	55 (18%)	41 (14%)
Spontaneous bacterial peritonitis	37 (12%)	35 (12%)
Hepatorenal syndrome	34 (11%)	29 (10%)
Hepatic encephalopathy	107 (35%)	140 (49%)***

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CLIF-C AD, Chronic Liver Failure Consortium acute decompensation; FU, follow-up; INR, international normalized ratio; LT, liver transplantation; L-TSA, large total SPSS area; MELD, model of end-stage liver disease; SPSS, spontaneous portosystemic shunts; S-TSA, small total SPSS area; WBC, white blood cell count.
*p <0.05; **p <0.01; ***p <0.001.

other SPSS have been rigorously embolized in order to limit TSA to 10 mm and other persisting collaterals (in many patients present) may have contributed to non-significant results regarding survival.

This study presents a large, multicentric, international, well characterized cohort of cirrhotic patients with SPSS. However, it has several limitations, which are mainly based on the retrospective nature of the study. Some parameters such as endoscopy and follow-up blood work were not available in all patients. Patients were not specifically screened for non-cirrhotic portal hypertension. Moreover, exploring a pathophysiological mechanism is beyond the scope of this study. Longitudinal data of the impact of SPSS on the natural history are needed. The development of portal venous thrombosis and its relation to medical treatment, such as non-selective betablockers and anticoagulants, should be addressed in future longitudinal studies.[41–45] In this study only cirrhotic patients who underwent CT scan were included. This would lead to a selection bias towards patients without severe kidney dysfunction because those patients would not receive CT scan due to contrast media exposure. Moreover, no data on sarcopenia is available, which has recently been recognized as a risk factor for the development of hepatic encephalopathy after TIPS[46–50] and could be a competing factor to consider against TSA.

In conclusion, this study highlights, for the first time, the prognostic importance of TSA (sum of all cross-sectional SPSS areas) in patients with mostly decompensated liver cirrhosis. The prevalence of more than 1 SPSS among these patients is high and increases with advancing liver disease. L-TSA is an independent predictor of 1-year mortality and is associated with higher rates of hepatic encephalopathy compared to S-TSA. These data suggest that there is a cut-off for portosystemically shunted blood volume where the beneficial effects are outweighed by the deleterious ones. Our results support the clinical use of TSA/SPSS for risk

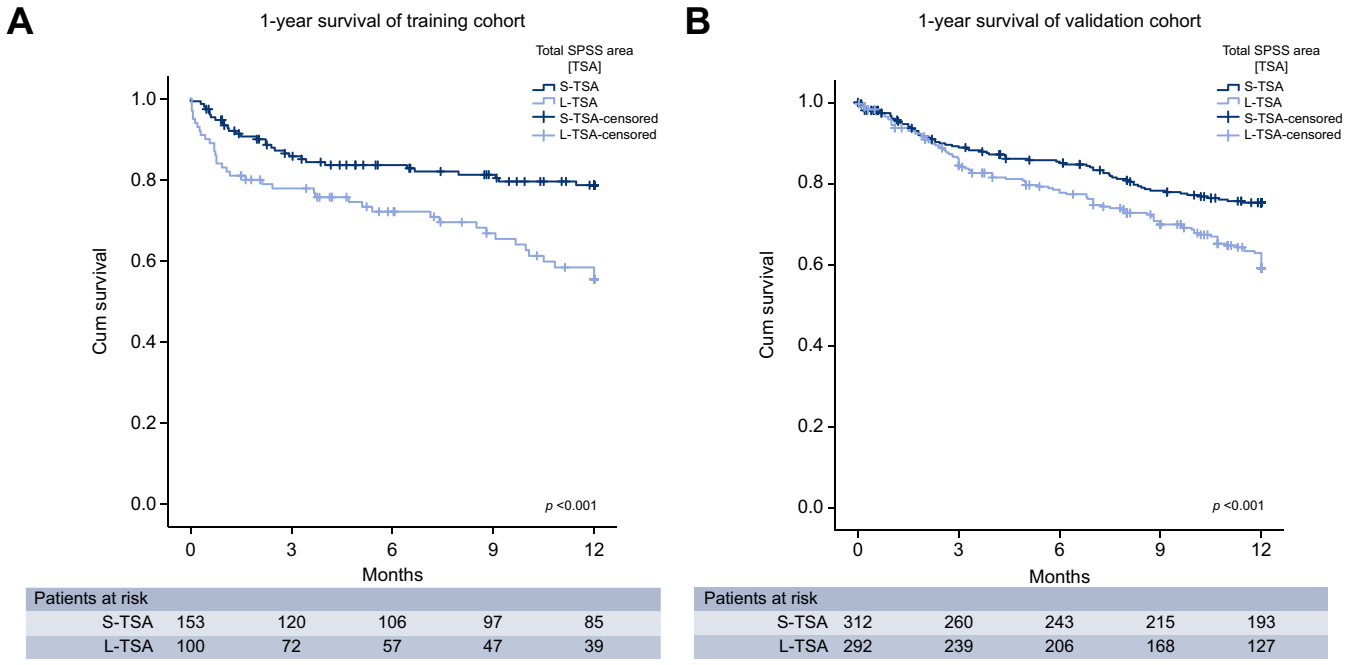

Fig. 3. Kaplan-Meier curve of 1-year survival in training and validation cohorts. (A) Kaplan-Meier curve showing impaired 1-year survival in L-TSA patients (green line) compared to S-TSA patients (blue line) in training cohort. (B) Kaplan-Meier curve showing impaired 1-year survival in L-TSA patients (green line) compared to S-TSA patients (blue line) in validation cohort. (S-/L-TSA: small (<83 mm^2) / large (≥83 mm^2) total SPSS area). Statistical analysis: log-rank test. L-TSA, large total SPSS area; SPSS, spontaneous portosystemic shunts; S-TSA, small total SPSS area.

Table 5. Univariate and multivariate Cox regression analysis of training cohort with 1-year mortality as endpoint.

1-year mortality	Univariate Cox regression				Multivariate Cox regression			
Parameter	**HR**		**95% CI**	***p* value**	**HR**		**95% CI**	***p* value**
***Age*[1]**	1.027	1.003	1.051	0.025	1.060	<0.001	1.089	<0.001
Sex				0.332				
L-TSA	2.266	1.407	3.650	0.001	1.660	0.040	2.695	0.040
Hepatic encephalopathy at baseline	3.519	2.190	5.657	<0.001	2.204	0.002	3.619	0.002
Hepatorenal syndrome at baseline	5.781	3.561	9.386	<0.001	1.890	0.024	3.283	0.024
Ascites at baseline	2.566	1.427	4.615	0.002		0.507		0.507
SBP at baseline	2.736	1.541	4.857	0.001		0.693		0.693
MELD at baseline	1.180	1.144	1.217	<0.001	1.175	<0.001	1.222	<0.001
Sodium at baseline[2]	0.950	0.909	0.993	0.022				
Creatinine at baseline[3]	2.171	1.783	2.643	<0.001				
Bilirubin at baseline[3]	1.122	1.092	1.153	<0.001				
INR at baseline	4.469	3.221	6.202	<0.001				

[1]years; [2]mmol/L; [3]mg/dl
Italic, included in multivariate analysis; Bold, significant in multivariate analysis.
INR, international normalized ratio; L-TSA, large total SPSS area; MELD, model of end-stage liver disease; SBP, spontaneous bacterial peritonitis; SPSS, spontaneous portosystemic shunts.

stratification and decision-making in the management of patients with cirrhosis.

Abbreviations

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CLIF-C AD, Chronic Liver Failure Consortium acute decompensation; FU, follow-up; HR, hazard ratio; HRS, hepatorenal syndrome; INR, international normalized ratio; LT, liver transplantation; L-TSA, large total SPSS area; MELD, model of end-stage liver disease; SBP, spontaneous bacterial peritonitis; SPSS, spontaneous portosystemic shunts; S-TSA, small total SPSS area; TIPS, transjugular intrahepatic portosystemic shunt; WBC, white blood cell count.

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Table 6. Univariate and multivariate Cox regression analysis of validation cohort with 1-year mortality as endpoint.

1-year mortality	Univariate Cox regression				Multivariate Cox regression			
Parameter	**HR**		**95% CI**	***p* value**	**HR**		**95% CI**	***p* value**
***Age*[1]**			0.148	0.148	1.020	1.006	1.034	0.004
Sex	1.407	1.016	0.040	0.040				
L-TSA	1.724	1.276	<0.001	<0.001	2.220	1.612	3.005	<0.001
Hepatic encephalopathy at baseline	2.109	1.547	<0.001	<0.001				0.268
Hepatorenal syndrome at baseline	4.998	2.885	<0.001	<0.001	2.222	1.172	4.214	0.014
Ascites at baseline	2.928	2.105	<0.001	<0.001	2.054	1.434	2.941	<0.001
SBP at baseline	2.811	1.763	<0.001	<0.001				0.454
MELD at baseline	1.130	1.104	<0.001	<0.001	1.112	1.081	1.143	<0.001
Sodium at baseline[2]	0.943	0.924	<0.001	<0.001				
Creatinine at baseline[3]	1.870	1.560	<0.001	<0.001				
Bilirubin at baseline[3]	1.071	1.046	<0.001	<0.001				
INR at baseline	2.047	1.693	<0.001	<0.001				

[1]years; [2]mmol/L; [3]mg/dl
Italic, included in multivariate analysis; Bold, significant in multivariate analysis.
INR, international normalized ratio; L-TSA, large total SPSS area; MELD, model of end-stage liver disease; SBP, spontaneous bacterial peritonitis; SPSS, spontaneous portosystemic shunts.

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Conflict of Interest

MP Sponsored lectures: Gore; AZ Sponsored lectures: Gilead, Abbvie, Norgine, Grifols, Bayer, Gore, BMS; AD Sponsored lectures: Bayer; WL Grants: Boston Scientific, Consultant: Boston Scientific, Abbvie, Gilead, Norgine, Gore; VLM Grants: Gilead Sciences research Scholar Program, Consultant: Gore, Sponsored lectures (National or International): Gore, Abbvie, Alfa-sigma; CR Grant: Schweine Stiftung; VHG Sponsored lectures (National or International): GORE; TR Grants: Abbvie, Boehringer Ingelheim, Gilead, MSD, Philips Healthcare, Gore; Consultant: Abbvie, Bayer, Boehringer-Ingelheim, Gilead, Intercept, MSD, Siemens; Sponsored lectures (National or International): Abbvie, Gilead, Gore, Intercept, Roche, MSD; AA Grants: Gilead Sciences, Consultant: AbbVie, Gilead Sciences, Gore, Griffols, Intercept Pharmaceuticals, Pfizer and Merck & Co., Sponsored lectures (National or International): AbbVie, Gilead Sciences, Gore, Griffols, Intercept Pharmaceuticals, Pfizer and Merck & Co.; EAT Consultant: Pfizer, Intercept, Gilead, Promethera, Astra Zeneca; JT Grants: Gore, Consultant: Martins Pharma, Ironwood, Gore, Alexion, BMS, Grifols, Sequana Medicals, Versantis, Sponsored lectures (National or International): Gilead, Gore, Alexion, BMS, Grifols, Sequana Medicals, Norgine, Intercept.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

MP, MST: acquisition of data, analysis and interpretation of data, drafting of the manuscript, statistical analysis. JR, DR, JM, KL, AB, GL, EL, MHM, AZ, MT, GM, AD, CD, JVG, AM, CP, DT, AD, JGA, ML, JC, CJ, RS, FU, GK, CM, DT, KW, AK, CS, WL, VLM, CR, AB, JLC, PT, VHG, TR, AA, EAT: acquisition of data, critical revision of the manuscript regarding important intellectual content. JG, JT: study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript regarding important intellectual content, funding recipient, administrative, technical and material support, study supervision.

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Supplementary data

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Author names in bold designate shared co-first authorship

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