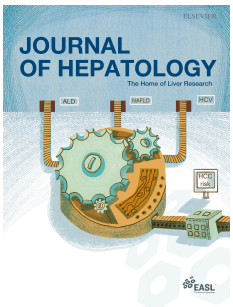

Total area of spontaneous portosystemic shunts independently predicts hepatic encephalopathy and mortality in liver cirrhosis

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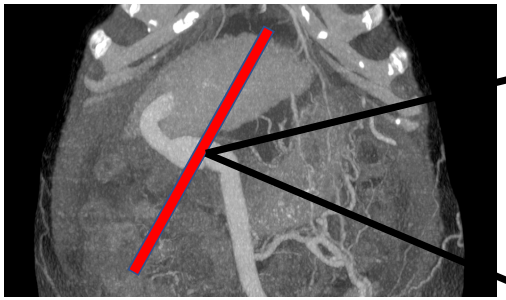
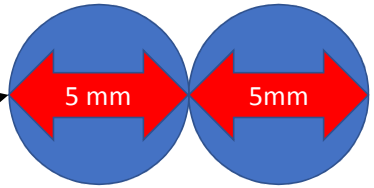
Spontaneous Porto-Systemic Shunt (SPSS) cross-section measured in CT scan at largest diameter

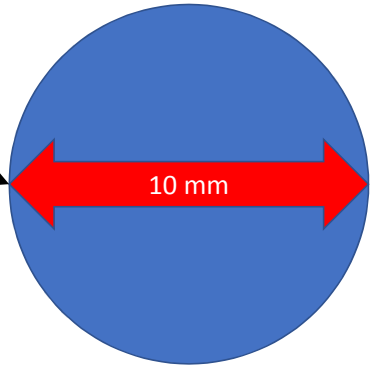


Multiple SPSS



Total Diameter: 10 mm
Total Area: 20 mm²

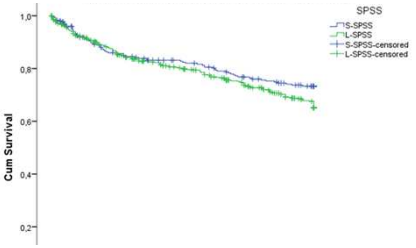
Single SPSS



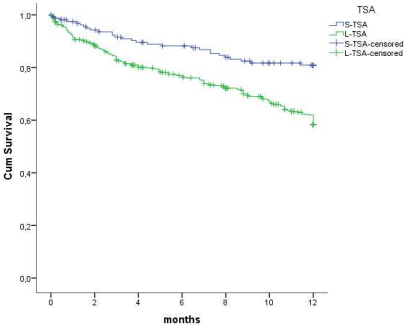
Total Diameter: 10 mm
Total Area: 80 mm²

Improved survival stratification by Total SPSS Area

Survival stratified by diameter



Survival stratified by area



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

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Short title: Large total SPSS area predicts mortality in liver cirrhosis

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Key words: spontaneous portosystemic shunt, portosystemic shunt, SPSS, computed tomography, cirrhosis, liver, acute decompensation, portal hypertension, hepatic encephalopathy, acute-on-chronic liver failure, ACLF,

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Abbreviations: SPSS (spontaneous portosystemic shunt), HRS (hepatorenal syndrome), ACLF (acute-on-chronic liver failure), CLIF-C (European Foundation for the study of chronic liver failure consortium), AD (acute decompensation), CT (computed tomography), ROC (receiver operating characteristics), AUC (area under the curve), MELD (model of end-stage liver disease), INR (international normalized ratio), WBC (white blood cell count), HR (hazard ratio), 95% CI (95 % confidence interval), TSA (total SPSS area), TIPS (transjugular intrahepatic portosystemic shunt)

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Author 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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ABSTRACT

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

METHODS: In this retrospective international multicentric study, computed tomography (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. 1-year survival was primary and acute decompensation (oHE, variceal bleeding, ascites) secondary endpoint.

RESULTS: 301 patients (169 male) were included in the training cohort. 30% of all patients presented >1 SPSS. TSA cut-off of 83 mm^2 was determined to classify patients with small or large TSA (S-/L-TSA). L-TSA patients presented higher MELD (11 vs. 14) and more commonly history of oHE (12% vs. 21%, $p<0.05$). During follow up L-TSA patients developed more oHE episodes (33% vs. 47%, $p<0.05$) and showed lower 1-year survival than S-TSA (84% vs. 69%, $p<0.001$). Multivariate analysis identified L-TSA (HR 1.66, 1.02-2.70, $p<0.05$) as independent predictor of mortality. An independent multicentric validation cohort of 607 patients confirmed L-TSA patients with lower 1-year survival (77% vs. 64%, $p<0.001$) and more oHE development (35% vs. 49%, $p<0.001$) than S-TSA.

CONCLUSION: This study suggests that TSA >83mm^2 increases the risk for oHE and mortality in liver cirrhosis. Our results may have impact on clinical use of TSA/SPSS for risk stratification and clinical decision-making considering management of SPSS.

Word count: 258

Lay Summary

Prevalence of spontaneous portosystemic shunt (SPSS) is higher in patients with more advanced chronic liver disease. Presence of more than one SPSS is common in advanced chronic liver disease and associated with 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. The cut-off of the total cross-sectional SPSS area associated with worse survival corresponds to a single shunt of more than 10mm diameter. This study may have impact on clinical use of TSA/SPSS for risk stratification and clinical decision-making considering 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 decompensations (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). Also in cirrhotic patients, portal hypertension is the driver of spontaneous portosystemic shunts (SPSS) development.

The association of SPSS or surgical/interventional shunting with hepatic encephalopathy (HE) is well-known and the first embolizations of SPSS as an option to limit complications of portal hypertension have been 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 to whether or when the procedure is indicated (12,18–20). As a result, in current guidelines recommendations for the management of SPSS are still missing (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 a SPSS (or cumulative area of several SPSS) may reflect the portosystemically shunted blood volume (24) more accurate than SPSS diameter. With the improved quality of imaging, especially in computed tomography

(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.

METHODS

Study population

For this retrospective study, a total of 301 patients from the University Hospital of Bonn were identified for inclusion as training cohort. Inclusion criteria were age of 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 to measure SPSS diameter was needed, a minimum diameter of >5 mm was considered by our radiologist to provide accurate SPSS size. Date of CT scan was defined as baseline. 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 fewer 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 a total of 607 consecutive patients, identified between 2010 and 2015 with the same selection criteria as the training cohort from the rest of the participating centres in the previously published multicenter study (15). Although excluding small SPSS of less of 5 mm was not an original criterion in this 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).

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

The local ethics committee of the of the participating centres 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). Radiological study protocol shown in supplemental material 1. All CT scans were screened for any spontaneous portosystemic shunt (SPSS) by scrolling through the abdominal CT scan in axial plane. If available, portal venous phase was preferred. In particular, it was looked for any additional veins leaving inferior vena cava, portal vein, splenic vein, right/left renal vein and superior/inferior mesenteric vein. When detecting SPSS, it was verified by coronal and sagittal plane.

Following, the position of the SPSS with the largest diameter was 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 shunt area (TSA) for the present study by the same radiologists who evaluate them in the prior study (15). We have chosen to measure the cross-sectional area instead of the diameter because more than one 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 supplemental figure 1. We hypothesized, that cross-sectional area (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 total SPSS area (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 (ICC) 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. We decided so, because in both cases mostly 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 (ROC) analysis with 1-year survival as end point was calculated. To examine the impact of TSA on survival we used 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 end points. Univariate analysis included general characteristics (age, sex) and clinical conditions (hepatic encephalopathy, hepatorenal syndrome, ascites, spontaneous bacterial peritonitis) as well as prognostic score (MELD) and

laboratory parameters (Na, creatinine, bilirubin, 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 and scores with overlapping components (Child-Pugh) were not entered simultaneously as well. 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 (figure 1). Of those 169 patients 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 one hepatic encephalopathy episode 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 $x10^9$/l were found in 26 patients. Of those 9 patients 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 (0-1322). Indications for CT scans are displayed in supplemental table 1.

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 (table1). 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 supplemental table 2.

SPSS characteristics

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

The most common SPSS types were para-umbilical shunts representing 57% of all shunts, followed by splenorenal shunts in 32%, mesocaval 5% and 2% each for gastrorenal and adrenal vein. 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 centres were included in the validation cohort (supplemental table 3, figure 1). Median age 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 exhibiting ascites at time of CT scan and 30% had experienced at least one hepatic encephalopathy episode 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, similar to 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 one single SPSS (79%), while 21% had multiple SPSS (table 2). Splenorenal shunt was the most common type with 41%, followed by para-umbilical shunt in 35%. Mesocaval shunt was present in 7%, gastrorenal in 6%, infero-mesenterico-caval in 3% and mesorenal in 1% of SPSS.

Patient stratification by total SPSS area (TSA)

A receiver operating characteristics analysis of TSA with 1-year survival as endpoint was performed and an AUC of 0.609 (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%; supplemental table 4). Patients with TSA above 83 mm^2 (corresponding to a single shunt of 10mm diameter) were classified as large TSA (L-TSA) and patients with TSA below 83 mm^2 were classified as 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 S-TSA and L-TSA patients. Time between diagnosis of cirrhosis and CT scan was not significantly different between S-TSA and L-TSA patients (15 (0-1322) vs. 24 (0-369) months, p=0.503).

L-TSA patients had significantly higher rates of multiple SPSS, as well as higher MELD scores (14 vs. 11). Moreover, L-TSA patients had higher rates hepatic encephalopathy episodes in their medical history (table 3). In follow up MELD (12 vs. 15, p<0.01) and MELD-Na (13 vs. 16, p<0.05) score remained significantly higher in 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). There were no significant differences detectable in term of hepatorenal syndrome, ascites and infections.

L-TSA is associated with hepatic encephalopathy

Training cohort

L-TSA patients had significantly higher risk of developing hepatic encephalopathy as shown in cumulative hazard function for hepatic encephalopathy in figure 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. L-TSA patients showed higher rates (57%) of high ammonia levels than S-TSA patients (42%) (supplemental table 5).

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 figure 2b.

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

Training cohort

1-year survival data was available in 253 patients. Figure 3a shows Kaplan-Meier curve for 1-year mortality. Kaplan-Meier curve for 1-year survival excluding patients with high platelet counts showed similar results (supplemental figure 2). L-TSA patients had a significantly higher mortality compared to S-TSA patients ($p<0.001$). Most deaths are attributed to infection (63%%). Hepatocellular carcinoma and liver failure attributed 10% and 13 % of deaths, respectively. 6% died of bleeding and cardiovascular events (supplemental table 6).

Univariate Cox regression to identify risk factors for 1-year mortality was performed. This revealed besides the expected prognostic MELD score, creatinine, bilirubin and INR also hepatorenal syndrome, hepatic encephalopathy, spontaneous bacterial

peritonitis, ascites and L-TSA at baseline as 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 continuous variable was calculated, which confirmed TSA (as continuous variable) as an independent predictor of 1-year survival (supplemental table 7).

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%). L-TSA patients showed significantly higher MELD and Child-Pugh score. There were no significant differences in type of SPSS between S-TSA and L-TSA patients. Moreover, L-TSA had higher rates of hepatic encephalopathy episodes at baseline and in their medical history (table 4). Survival data was available in 604 patients. Figure 3b shows Kaplan-Meier curve for 1-year mortality. L-TSA patients had a significantly higher mortality compared to S-TSA patients ($p<0.001$). Kaplan-Meier curve for 1-year survival excluding patients with high platelet counts showed similar results (supplemental figure 3).

Most deaths in the validation cohort were attributed by liver failure (36%), infection (19%) and HCC (12%). 6% died of bleeding. 27% died of other or unknown reasons (supplemental table 8).

Univariate Cox regression to identify risk factors for 1-year mortality was performed. In this validation cohort prognostic markers such as MELD, creatinine, bilirubin and INR, also with 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 (supplemental table 9).

To further investigate the impact of TSA on survival in relation liver function, we divided the whole cohort in tertials according to MELD (6-9, 10-13, 14-40) like 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 (supplemental table 10).

SPSS and TSA distribution

In our recent multicenter study (15), a stratification of patients according to SPSS diameter (8mm cut-off) did not show significant differences in survival between S-SPSS (<8mm) and L-SPSS (≥8mm). Therefore, we investigated the distribution of S-/L-SPSS and S-/L-TSA of the whole cohort. The results are shown in supplemental figure 4. 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. Kaplan-Meier survival curve shows no significant difference in survival between S-SPSS and L-SPSS patients (supplemental figure 5), confirming our previous study (15). Importantly, Kaplan-Meier survival analysis of only L-SPSS patients showed a highly significant difference between patients classified as S-TSA and L-TSA,

demonstrating that TSA classification clearly outperforms classification by SPSS diameter (supplemental figure 6).

We performed a Cox regression model for 1-year survival with L-SPSS instead of L-TSA to evaluate the predictive value of 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 (supplemental table 11 and 12).

DISCUSSION

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

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 occurrence of complications of liver cirrhosis was demonstrated (15). This study confirms those results, which underlines the robustness of TSA. Another aspect to support 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 compared to 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 10mm. 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 in 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 one 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 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 L-TSA and S-TSA patients. Considering variceal bleedings, 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 10mm diameter. In non-spontaneous SPSS, such as TIPS, it has been previously shown also that small diameter shunts are associated with less hepatic encephalopathy and survival compared to the usually used 10mm stents (37,38,40). However, in case of TIPS the collaterals and the other SPSS have been rigorously embolized in order to limit TSA to 10mm 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. Especially, 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 for the first time highlights the prognostic importance of TSA (sum of all cross-sectional SPSS areas) in patients with mostly decompensated liver cirrhosis. The prevalence of more than one SPSS among these patients is high and

increases with advancement of 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 get overweighed by the deleterious ones. Our results may have impact on clinical use of TSA/SPSS for risk stratification and clinical decision-making considering management of SPSS.

Word count: 3729

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673 **Figure legends:**

674 **Figure 1.** Flowchart of patient selection.

675

676 **Figure 2.** a) Cumulative hazard function for the occurrence of overt hepatic
677 encephalopathy during 1-year follow up in L-TSA (green line) vs. S-TSA (blue line)
678 patients in training cohort. b) Cumulative hazard function for the occurrence of overt
679 hepatic encephalopathy during 1-year follow up in L-TSA (green line) vs. S-TSA (blue
680 line) patients in validation cohort. (S-/L-TSA: small (<83mm^2) / large (≥83mm^2) total
681 SPSS area). Statistical analysis: log rank test.

682

683 **Figure 3.** a) Kaplan-Meier curve showing impaired 1-year survival in L-TSA patients
684 (green line) compared to S-TSA patients (blue line) in training cohort. b) Kaplan-
685 Meier curve showing impaired 1-year survival in L-TSA patients (green line)
686 compared to S-TSA patients (blue line) in validation cohort. (S-/L-TSA: small
687 (<83mm^2) / large (≥83mm^2) total SPSS area). Statistical analysis: log rank test.

688

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

	Parameter median (range) or absolute (percentage)	History	Baseline	Follow Up
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 Shunt 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 (9-5644)
	ALT [U/l]		31 (8-349)	33 (6-1952)
	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 [$10^3/\mu l$]		5.86 (1.02-37.17)	5.795 (0.04-36.22)
	Platelets [$x10^9/L$]		105.5 (11-653)	107.5 (14-479)

MELD – model of end-stage liver disease, CLIF-C AD – Chronic Liver Failure Consortium Acute Decompensation, AST – Aspartate Aminotransferase, ALT – Alanine Aminotransferase, INR – international normalized ratio, WBC – White Blood Cell Count; *p<0.05; **p<0.01; ***p<0.001

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

	Parameter median (range) or absolute (percentage)	History	Baseline	Follow Up
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 Shunt 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 [$x10^9$/L]		87(13-436)	

MELD – model of end-stage liver disease, CLIF-C AD – Chronic Liver Failure Consortium Acute Decompensation, AST – Aspartate Aminotransferase, ALT – Alanine Aminotransferase, INR – international normalized ratio, WBC – White Blood Cell Count; *p<0.05; **p<0.01; ***p<0.001

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
Base 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 Shunt Area [mm^2]	34.72 (5.72-82.34)	141.46 (83.29-880.65)***
History 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%)*
Base 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%)
Base 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%)
Base 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
Follow Up	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 Follow Up	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%)*

MELD – model of end-stage liver disease, CLIF-C AD – Chronic Liver Failure Consortium Acute Decompensation, AST – Aspartate Aminotransferase, ALT – Alanine Aminotransferase, INR – international normalized ratio, WBC – White Blood Cell Count, FU – follow up, LT – liver transplantation; *p<0.05; **p<0.01; ***p<0.001

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

	Parameter median (range) or absolute (percentage)	S-TSA n= 312	L-TSA n= 295
Base 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 1/2/3/4	283/27/2/0(91/8/1/0%)	67/28/12/3(67/28/4/1%)***
	Total Shunt Area [mm^2]	38(13-79)	201(89-2205)***
History 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%)***
Base 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%)**
Base 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%)
Base 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[f]	1.4(0.9-5.2)	1.4(1.0-4.1)

	Parameter median (range) or absolute (percentage)	S-TSA n= 312	L-TSA n= 295
Follow Up	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 Follow Up	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%)***

MELD – model of end-stage liver disease, CLIF-C AD – Chronic Liver Failure Consortium Acute Decompensation, AST – Aspartate Aminotransferase, ALT – Alanine Aminotransferase, INR – international normalized ratio, WBC – White Blood Cell Count, FU – follow up, LT – liver transplantation; *p<0.05; **p<0.01; ***p<0.001

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	**p**	**HR**	**CI**		**p**	**HR**	**CI**	
age[1]	0.025	1.027	1.003	1.051	<0.001	1.060	1.031	1.089
sex	0.332							
L-TSA	0.001	2.266	1.407	3.650	0.040	1.660	1.023	2.695
hepatic encephalopathy at baseline	<0.001	3.519	2.190	5.657	0.002	2.204	1.342	3.619
hepatorenal syndrome at baseline	<0.001	5.781	3.561	9.386	0.024	1.890	1.088	3.283
ascites at baseline	0.002	2.566	1.427	4.615	0.507			
SBP at baseline	0.001	2.736	1.541	4.857	0.693			
MELD at baseline	<0.001	1.180	1.144	1.217	<0.001	1.175	1.129	1.222
sodium at baseline[2]	0.022	0.950	0.909	0.993				
creatinine at baseline[3]	<0.001	2.171	1.783	2.643				
bilirubin at baseline[3]	<0.001	1.122	1.092	1.153				
INR at baseline	<0.001	4.469	3.221	6.202				

1-[years], 2- [mmol/l], 3-[mg/dl]
Italic – included in multivariate analysis, Bold – significant in multivariate analysis
MELD – model of end-stage liver disease, INR – international normalized ratio, L-TSA – large Total Shunt Area, SBP – spontaneous bacterial peritonitis,

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	**p**	**HR**	**CI**		**p**	**HR**	**CI**	
***age*[1]**	0.148				0.004	1.020	1.006	1.034
sex	0.040	1.407	1.016	1.947				
L-TSA	<0.001	1.724	1.276	2.330	<0.001	2.220	1.612	3.005
hepatic encephalopathy at baseline	<0.001	2.109	1.547	2.875	0.268			
hepatorenal syndrome at baseline	<0.001	4.998	2.885	8.658	0.014	2.222	1.172	4.214
ascites at baseline	<0.001	2.928	2.105	4.072	<0.001	2.054	1.434	2.941
SBP at baseline	<0.001	2.811	1.763	4.481	0.454			
MELD at baseline	<0.001	1.130	1.104	1.156	<0.001	1.112	1.081	1.143
sodium at baseline[2]	<0.001	0.943	0.924	0.961				
creatinine at baseline[3]	<0.001	1.870	1.560	2.242				
bilirubin at baseline[3]	<0.001	1.071	1.046	1.097				
INR at baseline	<0.001	2.047	1.693	2.475				

1-[years], 2- [mmol/l], 3-[mg/dl]
Italic – included in multivariate analysis, Bold – significant in multivariate analysis

MELD – model of end-stage liver disease, INR – international normalized ratio, L-TSA – large Total Shunt Area, SBP – spontaneous bacterial peritonitis

Figure 1.

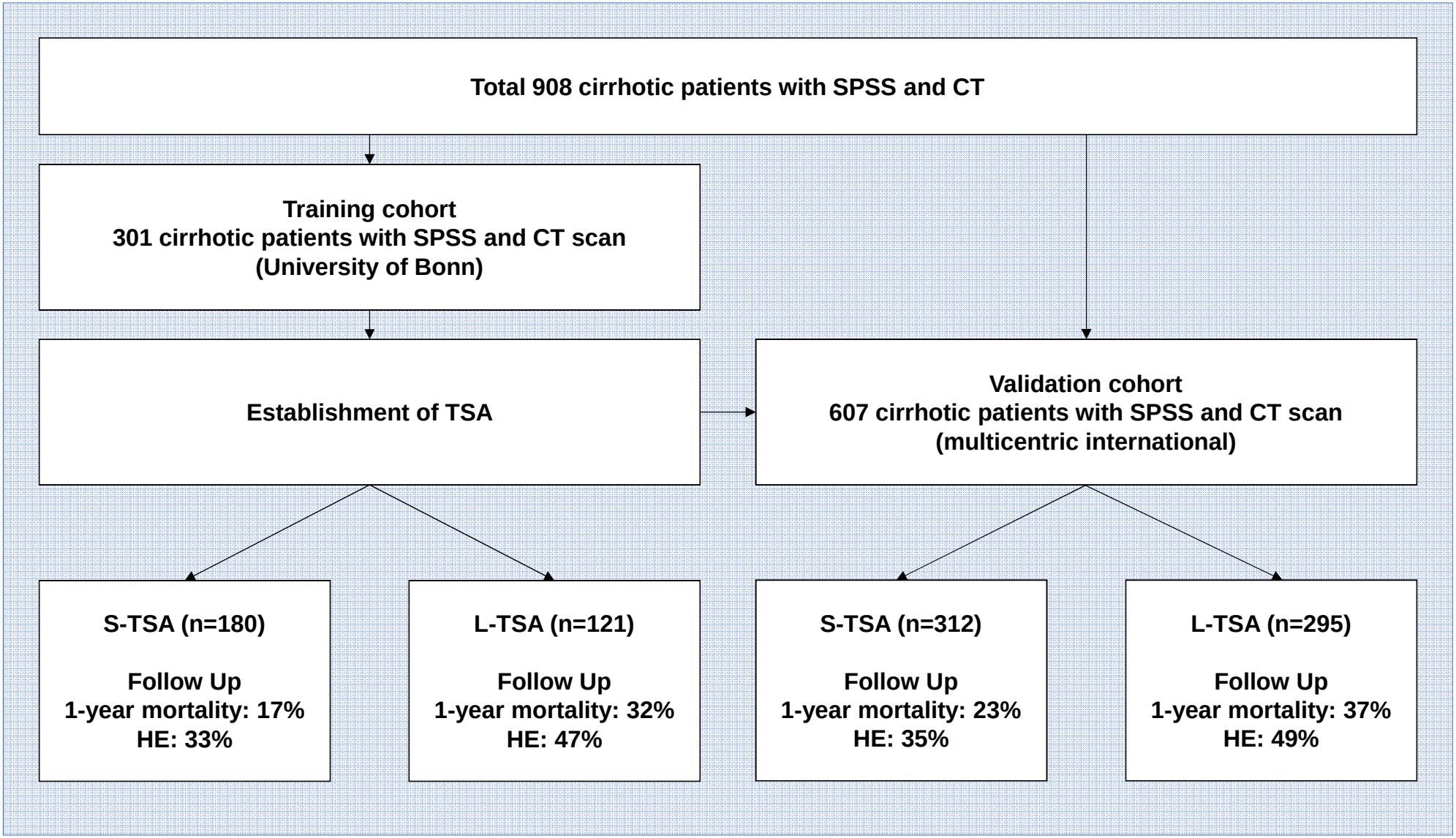
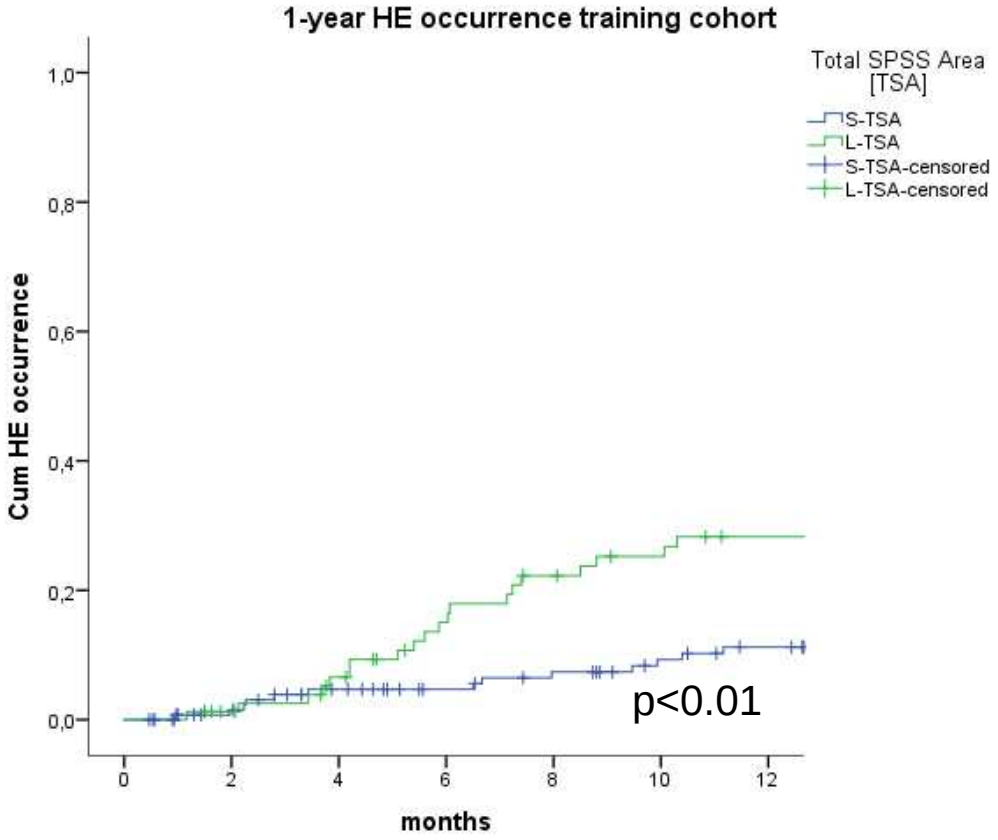

Total 908 cirrhotic patients with SPSS and CT
Training cohort
301 cirrhotic patients with SPSS and CT scan
(University of Bonn)
Establishment of TSA
Validation cohort
607 cirrhotic patients with SPSS and CT scan
(multicentric international)
S-TSA (n=180)
Follow Up
1-year mortality: 17%
HE: 33%
L-TSA (n=121)
Follow Up
1-year mortality: 32%
HE: 47%
S-TSA (n=312)
Follow Up
1-year mortality: 23%
HE: 35%
L-TSA (n=295)
Follow Up
1-year mortality: 37%
HE: 49%

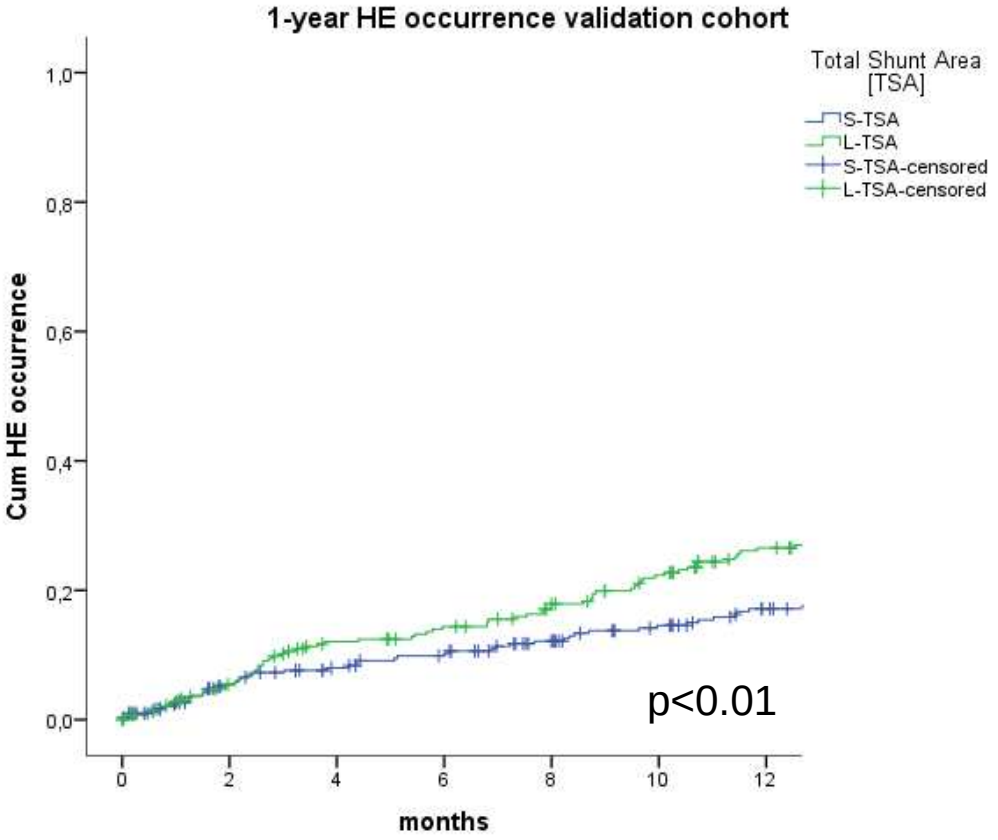
Figure 2

A



Patients at risk					
S-TSA	137	120	106	98	89
L-TSA	81	73	58	49	44

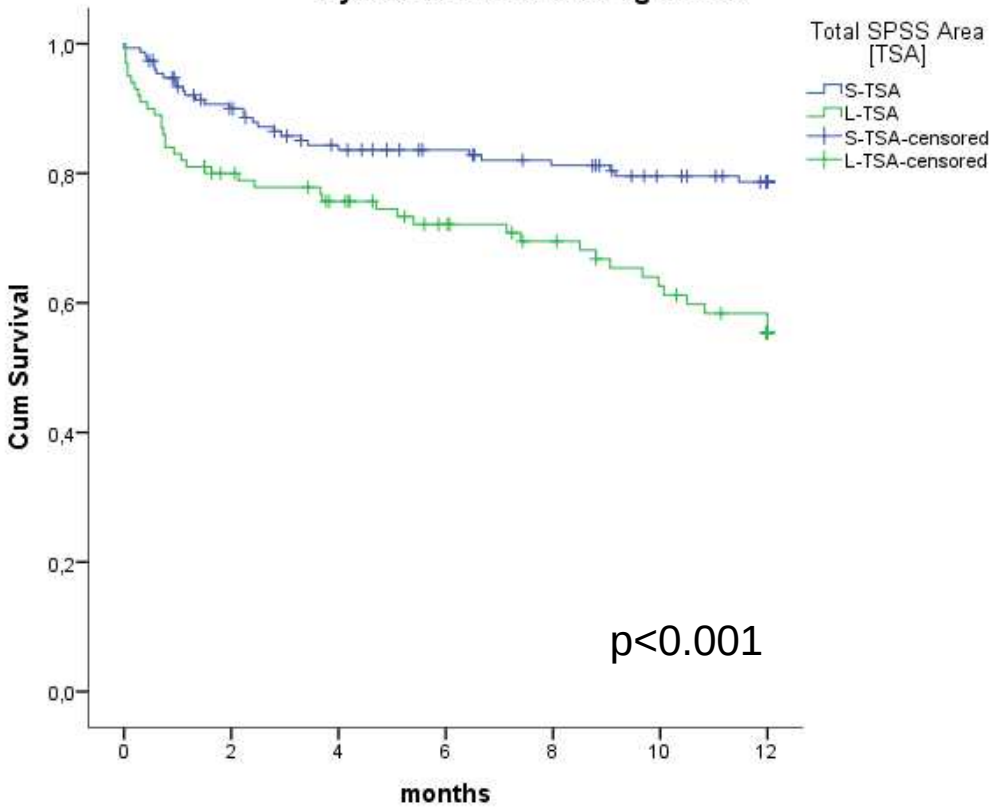
B



Patients at risk					
S-TSA	304	257	240	212	190
L-TSA	284	242	222	198	169

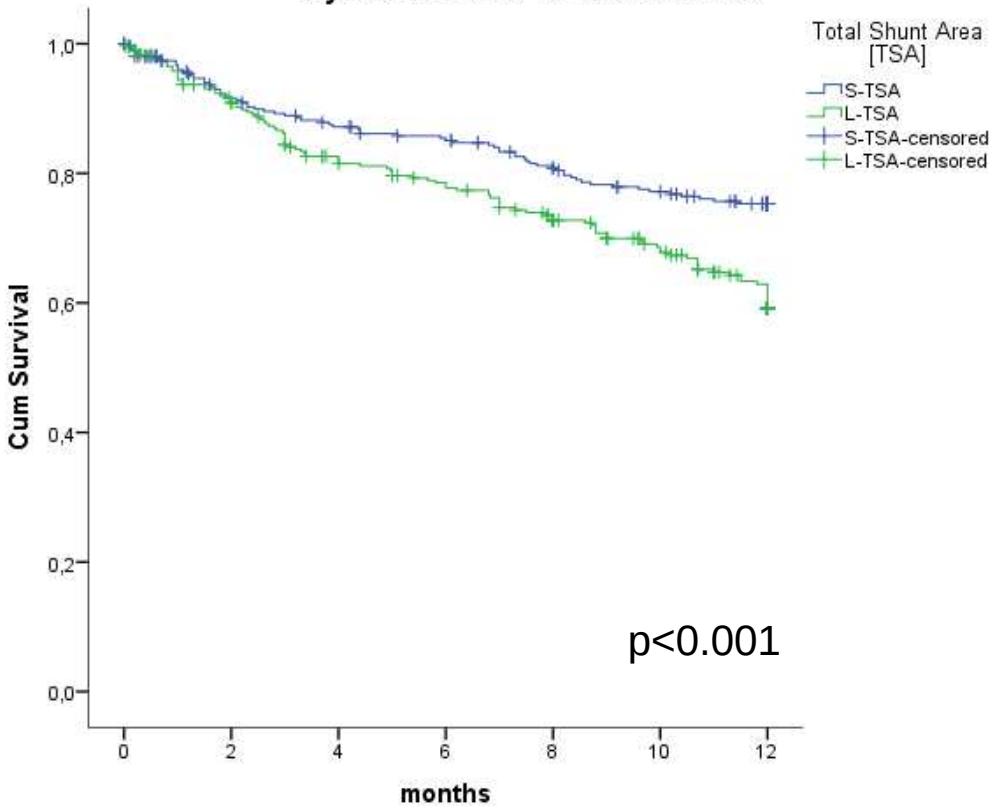
Figure 3

A



Patients at risk					
S-TSA	153	120	106	97	85
L-TSA	100	72	57	47	39

B



Patients at risk					
S-TSA	312	260	243	215	193
L-TSA	292	239	206	168	127

HIGHLIGHTS:

- Total cross-sectional area of spontaneous portosystemic shunt (SPSS), rather than diameter of the single largest SPSS, predicts survival in patients with advanced chronic liver disease.
- The cut-off of the total cross-sectional SPSS area associated with worse survival corresponds to a single shunt of more than 10mm diameter.
- This study may have impact on clinical use of TSA/SPSS for risk stratification and clinical decision-making considering management of SPSS.