

Journal Pre-proof



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

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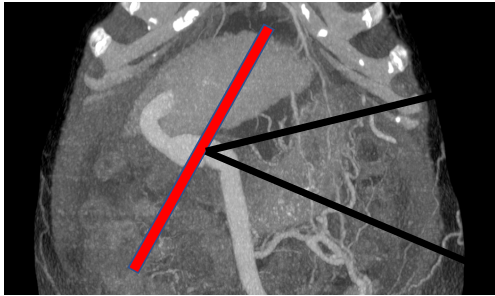
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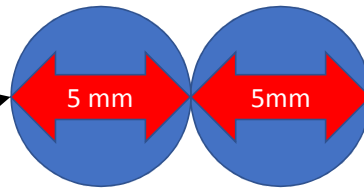
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Spontaneous Porto-Systemic Shunt (SPSS)
cross-section measured in CT scan
at largest diameter

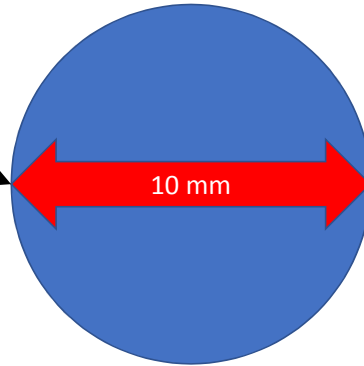


Multiple SPSS



Total Diameter: 10 mm
Total Area: 20 mm²

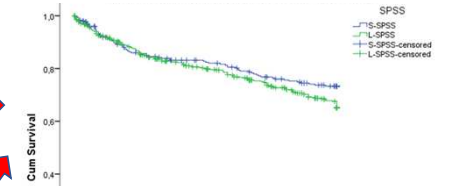
Single SPSS



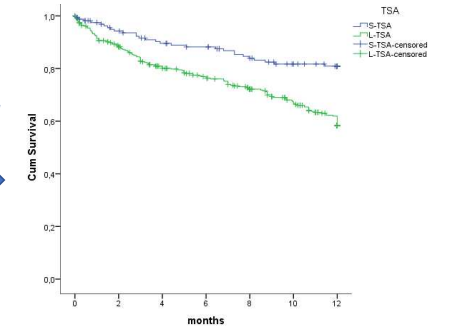
Total Diameter: 10 mm
Total Area: 80 mm²

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

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57 hepatic encephalopathy, acute-on-chronic liver failure, ACLF,

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66
67 **Abbreviations:** SPSS (spontaneous portosystemic shunt), HRS (hepatorenal
68 syndrome), ACLF (acute-on-chronic liver failure), CLIF-C (European Foundation for
69 the study of chronic liver failure consortium), AD (acute decompensation), CT
70 (computed tomography), ROC (receiver operating characteristics), AUC (area under
71 the curve), MELD (model of end-stage liver disease), INR (international normalized
72 ratio), WBC (white blood cell count), HR (hazard ratio), 95% CI (95 % confidence
73 interval), TSA (total SPSS area), TIPS (transjugular intrahepatic portosystemic shunt)

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103 **Author contributions:**

104 MP, MST: acquisition of data, analysis and interpretation of data, drafting of the
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108 VHG, TR, AA, EAT: acquisition of data, critical revision of the manuscript regarding
109 important intellectual content

110 JG, JT: study concept and design, acquisition of data, analysis and interpretation of
111 data, drafting of the manuscript, critical revision of the manuscript regarding important
112 intellectual content, funding recipient, administrative, technical and material support,
113 study supervision

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130 **ABSTRACT**

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

136 **METHODS:** In this retrospective international multicentric study, computed
137 tomography (CT) scans of 908 cirrhotic patients with SPSS were evaluated for TSA.
138 Clinical and laboratory data were recorded. Each detected SPSS radius was
139 measured and TSA calculated. 1-year survival was primary and acute
140 decompensation (oHE, variceal bleeding, ascites) secondary endpoint.

141 **RESULTS:** 301 patients (169 male) were included in the training cohort. 30% of all
142 patients presented >1 SPSS. TSA cut-off of 83 mm² was determined to classify
143 patients with small or large TSA (S-/L-TSA). L-TSA patients presented higher MELD
144 (11 vs. 14) and more commonly history of oHE (12% vs. 21%, p<0.05). During follow
145 up L-TSA patients developed more oHE episodes (33% vs. 47%, p<0.05) and
146 showed lower 1-year survival than S-TSA (84% vs. 69%, p<0.001). Multivariate
147 analysis identified L-TSA (HR 1.66, 1.02-2.70, p<0.05) as independent predictor of
148 mortality. An independent multicentric validation cohort of 607 patients confirmed L-
149 TSA patients with lower 1-year survival (77% vs. 64%, p<0.001) and more oHE
150 development (35% vs. 49%, p<0.001) than S-TSA.

151 **CONCLUSION:** This study suggests that TSA >83mm² increases the risk for oHE
152 and mortality in liver cirrhosis. Our results may have impact on clinical use of
153 TSA/SPSS for risk stratification and clinical decision-making considering
154 management of SPSS.

155 **Word count: 258**

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161 Lay Summary

162 Prevalence of spontaneous portosystemic shunt (SPSS) is higher in patients with
163 more advanced chronic liver disease. Presence of more than one SPSS is common
164 in advanced chronic liver disease and associated with development of hepatic
165 encephalopathy. This study shows that total cross-sectional SPSS area (rather than
166 diameter of the single largest SPSS) predicts survival in patients with advanced
167 chronic liver disease. The cut-off of the total cross-sectional SPSS area associated
168 with worse survival corresponds to a single shunt of more than 10mm diameter. This
169 study may have impact on clinical use of TSA/SPSS for risk stratification and clinical
170 decision-making considering management of SPSS.

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176 INTRODUCTION

177 In the course of liver cirrhosis the development of portal hypertension is a major
178 driver of complications and therefore a frequent cause of acute decompensations
179 (AD) (1,2). AD may lead to a systemic inflammatory response and progress to acute-
180 on-chronic liver failure (ACLF), a syndrome with high short-term mortality (3–6). Also
181 in cirrhotic patients, portal hypertension is the driver of spontaneous portosystemic
182 shunts (SPSS) development.

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

196 The presence of SPSS and especially their cumulative size has not been associated
197 with hard endpoints such as survival. From a pathophysiological point of view the
198 total cross-sectional shunt area of a SPSS (or cumulative area of several SPSS) may
199 reflect the portosystemically shunted blood volume (24) more accurate than SPSS
200 diameter. With the improved quality of imaging, especially in computed tomography

201 (CT), the detection of SPSS in clinical routine is feasible and reliable. This present
202 study aimed to evaluate the role of the combined cross-sectional area of all SPSS, as
203 a surrogate marker of portosystemically shunted blood volume, in the natural course
204 of patients with liver cirrhosis.

205

206 **METHODS**

207 **Study population**

208 For this retrospective study, a total of 301 patients from the University Hospital of
209 Bonn were identified for inclusion as training cohort. Inclusion criteria were age of 18
210 years or older, diagnosis of cirrhosis (clinical, radiologic or histologic) and SPSS of at
211 least 5 mm of diameter in CT scans between October 2006 and April 2016. Since
212 precision to measure SPSS diameter was needed, a minimum diameter of >5 mm
213 was considered by our radiologist to provide accurate SPSS size. Date of CT scan
214 was defined as baseline. Exclusion criteria were presence of hepatocellular
215 carcinoma (HCC) beyond Milan criteria, previous transjugular intrahepatic
216 portosystemic shunt (TIPS) or surgical shunt, any medical condition with expected
217 survival fewer than 6 months, presence of neurologic, or psychiatric disorder
218 preventing a proper hepatic encephalopathy evaluation and absence of critical
219 information in the medical history (15). The validation cohort was formed of a total of
220 607 consecutive patients, identified between 2010 and 2015 with the same selection
221 criteria as the training cohort from the rest of the participating centres in the
222 previously published multicenter study (15). Although excluding small SPSS of less of
223 5 mm was not an original criterion in this prior multicenter study, it was applied to the
224 validation cohort for consistency. In all patients, cross-sectional area of all detectable
225 SPSS was assessed and calculated in CT scans. Clinical and laboratory blood

226 analysis data was followed up until end of follow up, death or liver transplantation
227 (LT).

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

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

233 **Assessment of SPSS parameters**

234 All CT scans were reviewed by radiologists with expertise in liver diseases. SPSS
235 were defined as previously described (15). Radiological study protocol shown in
236 supplemental material 1. All CT scans were screened for any spontaneous
237 portosystemic shunt (SPSS) by scrolling through the abdominal CT scan in axial
238 plane. If available, portal venous phase was preferred. In particular, it was looked for
239 any additional veins leaving inferior vena cava, portal vein, splenic vein, right/left
240 renal vein and superior/inferior mesenteric vein. When detecting SPSS, it was
241 verified by coronal and sagittal plane.

242 Following, the position of the SPSS with the largest diameter was identified. At this
243 position the short-axis diameter was reconstructed and measured between both walls
244 of the vessel.

245 The 607 CT scans from the validation cohort were reviewed again to measure the
246 total shunt area (TSA) for the present study by the same radiologists who evaluate
247 them in the prior study (15). We have chosen to measure the cross-sectional area
248 instead of the diameter because more than one SPSS can occur in patients with liver
249 cirrhosis and portal hypertension (15). Though the sum of diameters of all SPSS can

250 be the same, the sum of cross-sectional areas can be vastly different as shown in
251 supplemental figure 1. We hypothesized, that cross-sectional area (TSA) reflects the
252 shunted blood volume better than diameters. For each SPSS we calculated the area
253 by the formula πr^2 . All SPSS areas were then summed up to calculate total SPSS
254 area (TSA) for each patient.

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

260 Esophageal and gastric varices were documented, but not measured. Rectal varices
261 were neither measured nor documented. We decided so, because in both cases
262 mostly the shunts are more of a network than a single vessel that can be determined.

263 **Statistical analysis**

264 We performed descriptive statistics for all variables. Non-parametric testing was used
265 to compare different groups when suitable. Paired non-parametric testing was used
266 to compare data of baseline and follow up of the same patients. Correlation of metric
267 variables was performed using Spearman's correlation. For the selection of cut off
268 values of TSA receiver-operating characteristics (ROC) analysis with 1-year survival
269 as end point was calculated. To examine the impact of TSA on survival we used
270 Kaplan-Meier curve with log-rank test. Univariate and multivariate risk factor analyses
271 were performed with Cox regression for 1-year mortality and episodes of hepatic
272 encephalopathy as end points. Univariate analysis included general characteristics
273 (age, sex) and clinical conditions (hepatic encephalopathy, hepatorenal syndrome,
274 ascites, spontaneous bacterial peritonitis) as well as prognostic score (MELD) and

275 laboratory parameters (Na, creatinine, bilirubin, INR) at baseline. Multivariate
276 analysis included all values with $p < 0.05$ from univariate Cox regression. To avoid
277 multicollinearity calculated scores, such as MELD, were not entered simultaneously
278 with their components and scores with overlapping components (Child-Pugh) were
279 not entered simultaneously as well. Continuous variables are presented as median
280 (range), unless otherwise specified. Categorical variables are presented as absolute
281 cases and/or percentage. The intra-rater reliability was calculated using the interclass
282 correlation coefficient. All data was analyzed using SPSS (version 24, IBM, Armonk,
283 NY, USA) or R statistics (version 3.4.4, The R Foundation).

284

285 **RESULTS**286 **General patient characteristics**287 ***Training cohort***

288 Of all 908 patients, 301 patients from University of Bonn were included in the training
289 cohort ([figure 1](#)). Of those 169 patients were male. Median age at baseline was 56
290 (28-85) years. Alcohol was the most common etiology of cirrhosis (57% of patients),
291 while 20% of patients had chronic viral hepatitis B and/or C infection. Other etiologies
292 were present in 23 % of patients. Most of the patients were decompensated (Child-
293 Pugh B or C in 59%) with 64% of the patients exhibiting ascites at time of CT scan;
294 16% had experienced at least one hepatic encephalopathy episode and 26% had
295 hepatic encephalopathy at baseline. A history of variceal bleeding was present in
296 28% of the patients. Median MELD score was 13 (6-40). Detailed general
297 characteristics are displayed in table 1. Of note, high platelet counts $>250 \times 10^9/l$ were
298 found in 26 patients. Of those 9 patients had infection, 3 recent bleeding and 2 iron
299 deficiency as likely causes for high platelet counts. Median follow up time was 15 (0-
300 117) months. Median time from diagnosis of liver cirrhosis to CT scan was 17 months
301 (0-1322). Indications for CT scans are displayed in supplemental table 1.

302 Follow up data on survival status was available in 254 patients (table 1). During
303 follow up MELD decreased slightly, while other prognostic scores (MELD-Na, Child-
304 Pugh) did not change significantly. Compared to baseline the rate of patients
305 developing hepatorenal syndrome (23%) and episodes of hepatic encephalopathy
306 (38%) increased significantly. The rate of patients with ascites and variceal bleeding
307 did not change significantly (table1). In total, 23 patients were treated with TIPS (16
308 for refractory ascites, 7 for variceal hemorrhage) during follow up. Detailed analysis
309 of number of TIPS and LT in relation to MELD is shown in supplemental table 2.

310 *SPSS characteristics*

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

314 The most common SPSS types were para-umbilical shunts representing 57% of all
315 shunts, followed by splenorenal shunts in 32%, mesocaval 5% and 2% each for
316 gastrosplenic and adrenal vein. Intrahepatic, right renal vein and
317 mesorenal shunts were each found in only 1% of SPSS.

318

319 ***Validation cohort***

320 A total of 607 patients from 11 participating centres were included in the validation
321 cohort (supplemental table 3, figure 1). Median age was 58 (18-87) years with 65%
322 male patients. Alcohol was the most common etiology of cirrhosis (43%), while 27%
323 had viral hepatitis. Most patients (66%) had decompensated cirrhosis (Child-Pugh B
324 or C); 53 % of the patients exhibiting ascites at time of CT scan and 30% had
325 experienced at least one hepatic encephalopathy episode and 25% had hepatic
326 encephalopathy at baseline. A history of variceal bleeding was present in 25% of the
327 patients. Median MELD score was 13 (6-37). Detailed general characteristics are
328 displayed in table 2.

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

333 *SPSS characteristics*

334 In the validation cohort of 607 patients, 754 SPSS were identified. The majority of
335 patients had one single SPSS (79%), while 21% had multiple SPSS (table 2).
336 Splenorenal shunt was the most common type with 41%, followed by para-umbilical
337 shunt in 35%. Mesocaval shunt was present in 7%, gastrosplenic in 6%, infero-
338 mesenterico-caval in 3% and mesorenal in 1% of SPSS.

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341 **Patient stratification by total SPSS area (TSA)**

342 A receiver operating characteristics analysis of TSA with 1-year survival as endpoint
343 was performed and an AUC of 0.609 (CI 0.531-0.687, p=0.007) was calculated. The
344 optimal cut-off value for the training cohort was found at 83 mm² (sensitivity 55.7%,
345 specificity 66.8%, positive predictive value 39.0%, negative predictive value 79.9%;
346 supplemental table 4). Patients with TSA above 83 mm² (corresponding to a single
347 shunt of 10mm diameter) were classified as large TSA (L-TSA) and patients with TSA
348 below 83 mm² were classified as small TSA (S-TSA). Median TSA was 59 mm² (6-
349 881). Patients with S-TSA had a median TSA of 35 mm² (6-82) and L-TSA of 141.46
350 mm² (83-881) (table 3). In total, 180 patients were classified as S-TSA (60%) and
351 121 as L-TSA (40%). There were no significant differences in type of SPSS between
352 S-TSA and L-TSA patients. Time between diagnosis of cirrhosis and CT scan was
353 not significantly different between S-TSA and L-TSA patients (15 (0-1322) vs. 24 (0-
354 369) months, p=0.503).

355 L-TSA patients had significantly higher rates of multiple SPSS, as well as higher
356 MELD scores (14 vs. 11). Moreover, L-TSA patients had higher rates hepatic
357 encephalopathy episodes in their medical history (table 3). In follow up MELD (12 vs.
358 15, p<0.01) and MELD-Na (13 vs. 16, p<0.05) score remained significantly higher in
359 L-TSA compared to S-TSA group. CLIF-C AD score was not significantly different.
360 Additionally, Child-Pugh score (6 vs 7, p<0.05) in follow up showed higher values for
361 L-TSA. This mainly derives from serum albumin levels being significantly lower in L-
362 TSA (35 vs 31 g/L, p<0.001) (table 3). There were no significant differences
363 detectable in term of hepatorenal syndrome, ascites and infections.

364

365

366 **L-TSA is associated with hepatic encephalopathy**

367 ***Training cohort***

368 L-TSA patients had significantly higher risk of developing hepatic encephalopathy as
369 shown in cumulative hazard function for hepatic encephalopathy in figure 2a. Blood
370 ammonia levels were available in 154 patients. Median blood ammonia level was 65
371 µmol/l (9-260). Patients were divided into high (>65 µmol/l) and low (≤65 µmol/l)
372 ammonia levels. L-TSA patients showed higher rates (57%) of high ammonia levels
373 than S-TSA patients (42%) (supplemental table 5).

374 ***Validation cohort***

375 In the validation cohort clinical but no blood parameters were available at follow up
376 (table 4). Importantly, the significantly higher rates of episodes of hepatic
377 encephalopathy were confirmed as shown in figure 2b.

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

379 ***Training cohort***

380 1-year survival data was available in 253 patients. Figure 3a shows Kaplan-Meier
381 curve for 1-year mortality. Kaplan-Meier curve for 1-year survival excluding patients
382 with high platelet counts showed similar results (supplemental figure 2). L-TSA
383 patients had a significantly higher mortality compared to S-TSA patients ($p < 0.001$).
384 Most deaths are attributed to infection (63%). Hepatocellular carcinoma and liver
385 failure attributed 10% and 13 % of deaths, respectively. 6% died of bleeding and
386 cardiovascular events (supplemental table 6).

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

390 peritonitis, ascites and L-TSA at baseline as dependent predictors of survival.
391 Multivariate Cox regression identified L-TSA alongside MELD, hepatic
392 encephalopathy, hepatorenal syndrome and ascites as independent risk factors for 1-
393 year survival (table 5).

394 A different model with TSA as continuous variable was calculated, which confirmed
395 TSA (as continuous variable) as an independent predictor of 1-year survival
396 (supplemental table 7).

397 ***Validation cohort***

398 In order to validate these results, the validation cohort was stratified for TSA. A total
399 of 312 patients were classified as S-TSA (51%) and 295 as L-TSA (49%). L-TSA
400 patients showed significantly higher MELD and Child-Pugh score. There were no
401 significant differences in type of SPSS between S-TSA and L-TSA patients.
402 Moreover, L-TSA had higher rates of hepatic encephalopathy episodes at baseline
403 and in their medical history (table 4). Survival data was available in 604 patients.
404 Figure 3b shows Kaplan-Meier curve for 1-year mortality. L-TSA patients had a
405 significantly higher mortality compared to S-TSA patients ($p < 0.001$). Kaplan-Meier
406 curve for 1-year survival excluding patients with high platelet counts showed similar
407 results (supplemental figure 3).

408 Most deaths in the validation cohort were attributed by liver failure (36%), infection
409 (19%) and HCC (12%). 6% died of bleeding. 27% died of other or unknown reasons
410 (supplemental table 8).

411 Univariate Cox regression to identify risk factors for 1-year mortality was performed.
412 In this validation cohort prognostic markers such as MELD, creatinine, bilirubin and
413 INR, also with hepatorenal syndrome, hepatic encephalopathy, spontaneous

414 bacterial peritonitis, ascites and TSA at baseline were dependent predictors of
415 survival. Multivariate Cox regression confirmed TSA and MELD as independent
416 predictors of 1-year mortality. Moreover, age, hepatorenal syndrome and ascites
417 were shown as independent risk factors for 1-year survival (table 6).

418 In an alternative model using TSA as a continuous variable, TSA was still an
419 independent predictor of 1-year mortality, suggesting a linear relationship
420 (supplemental table 9).

421 To further investigate the impact of TSA on survival in relation liver function, we
422 divided the whole cohort in tertials according to MELD (6-9, 10-13, 14-40) like in our
423 previous study (15). The rates of 1-year mortality were higher in the L-TSA group and
424 significant in MELD groups 6-9 and 14-40 (supplemental table 10).

425 **SPSS and TSA distribution**

426 In our recent multicenter study (15), a stratification of patients according to SPSS
427 diameter (8mm cut-off) did not show significant differences in survival between S-
428 SPSS (<8mm) and L-SPSS (≥ 8 mm). Therefore, we investigated the distribution of S-
429 /L-SPSS and S-/L-TSA of the whole cohort. The results are shown in supplemental
430 figure 4. In total, 35% of patients were classified S-SPSS and S-TSA, 0.3% S-SPSS
431 and L-TSA, 19% L-SPSS and S-TSA and 46% L-SPSS and L-TSA. This suggests
432 mostly concordant classification between S-SPSS and S-TSA. However, a
433 substantial fraction (19%) of patients with L-SPSS are classified as S-TSA as well.

434 Kaplan-Meier survival curve shows no significant difference in survival between S-
435 SPSS and L-SPSS patients (supplemental figure 5), confirming our previous study
436 (15). Importantly, Kaplan-Meier survival analysis of only L-SPSS patients showed a
437 highly significant difference between patients classified as S-TSA and L-TSA,

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

440 We performed a Cox regression model for 1-year survival with L-SPSS instead of L-
441 TSA to evaluate the predictive value of presence of L-SPSS. In both the training and
442 validation cohort SPSS was not significant in multivariate analysis. In the validation
443 cohort, SPSS was not significant in the univariate analysis either (supplemental table
444 11 and 12).

445

446 **DISCUSSION**

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

451 These results build up on the previously reported data on the influence of the
452 diameter of largest SPSS, where a clear association with the risk of occurrence of
453 complications of liver cirrhosis was demonstrated (15). This study confirms those
454 results, which underlines the robustness of TSA. Another aspect to support the
455 plausibility of our data is the fact, that L-TSA was found in more advanced stages of
456 liver cirrhosis, reflected by higher MELD scores, which is in line with previous reports
457 (15,25). One might argue, that retrieving and calculating the cross-sectional area of
458 every SPSS is costly and more time consuming compared to just measuring the
459 diameter of the largest SPSS. However, having a single SPSS of 10 mm diameter or
460 more qualifies for L-TSA but not multiple SPSS with an added diameter of 10mm.
461 This situation of multiple SPSS is present in one third of the presented large cohort.
462 The present study demonstrates that the complete shunting volume, which might be
463 better reflected by TSA, gives independent insight in the progression of liver disease

464 and outcome of cirrhotic patients. This hypothesis is supported by this study because
465 the size of TSA has an independent impact on survival in cirrhotic patients, which
466 could not be demonstrated for diameter of the single largest SPSS (< 8 mm vs ≥ 8
467 mm) (15). This is especially impactful because, as shown in our and other cohorts,
468 about one third of the patients have more than one SPSS (15,26,27). Since this study
469 demonstrates TSA as a risk factor for survival independent of MELD, an
470 incorporation of TSA in MELD (TSA-MELD) could improve patient's risk stratification
471 and should be evaluated in future research.

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

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

489 Interestingly, the cut-off we found in our patients corresponds to a single shunt of
490 10mm diameter. In non-spontaneous SPSS, such as TIPS, it has been previously
491 shown also that small diameter shunts are associated with less hepatic
492 encephalopathy and survival compared to the usually used 10mm stents (37,38,40).
493 However, in case of TIPS the collaterals and the other SPSS have been rigorously
494 embolized in order to limit TSA to 10mm and other persisting collaterals (in many
495 patients present) may have contributed to non-significant results regarding survival.

496 This study presents a large, multicentric, international, well characterized cohort of
497 cirrhotic patients with SPSS. However, it has several limitations, which are mainly
498 based on the retrospective nature of the study. Some parameters such as endoscopy
499 and follow up blood work were not available in all patients. Patients were not
500 specifically screened for non-cirrhotic portal hypertension. Moreover, exploring a
501 pathophysiological mechanism is beyond the scope of this study. Longitudinal data of
502 the impact of SPSS on the natural history are needed. Especially, the development of
503 portal venous thrombosis and its relation to medical treatment, such as non-selective
504 betablockers and anticoagulants, should be addressed in future longitudinal studies
505 (41–45). In this study only cirrhotic patients who underwent CT scan were included.
506 This would lead to a selection bias towards patients without severe kidney
507 dysfunction because those patients would not receive CT scan due to contrast media
508 exposure. Moreover, no data on sarcopenia is available, which has recently been
509 recognized as a risk factor for the development of hepatic encephalopathy after TIPS
510 (46–50) and could be a competing factor to consider against TSA.

511 In conclusion, this study for the first time highlights the prognostic importance of TSA
512 (sum of all cross-sectional SPSS areas) in patients with mostly decompensated liver
513 cirrhosis. The prevalence of more than one SPSS among these patients is high and

514 increases with advancement of liver disease. L-TSA is an independent predictor of 1-
515 year mortality and is associated with higher rates of hepatic encephalopathy
516 compared to S-TSA. These data suggest that there is a cut-off for portosystemically
517 shunted blood volume where the beneficial effects get outweighed by the
518 deleterious ones. Our results may have impact on clinical use of TSA/SPSS for risk
519 stratification and clinical decision-making considering management of SPSS.

520 **Word count: 3729**

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Journal Pre-proof

522 **Literature**

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671

672

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 ($<83\text{mm}^2$) / large ($\geq 83\text{mm}^2$) 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 ($<83\text{mm}^2$) / large ($\geq 83\text{mm}^2$) 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 /μl]		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	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 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 median (range) or absolute (percentage)	S-TSA	L-TSA
		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 median (range) or absolute (percentage)	S-TSA	L-TSA
		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	L-TSA
		n= 312	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	L-TSA
		n= 312	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 Parameter	univariate Cox regression				multivariate Cox regression			
	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
<i>ascites at baseline</i>	0.002	2.566	1.427	4.615	0.507			
<i>SBP at baseline</i>	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 Parameter	univariate Cox regression			multivariate Cox regression				
	p	HR	CI	p	HR	CI	CI	
<i>age</i> 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
<i>hepatic encephalopathy at baseline</i>	<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
<i>SBP at baseline</i>	<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.

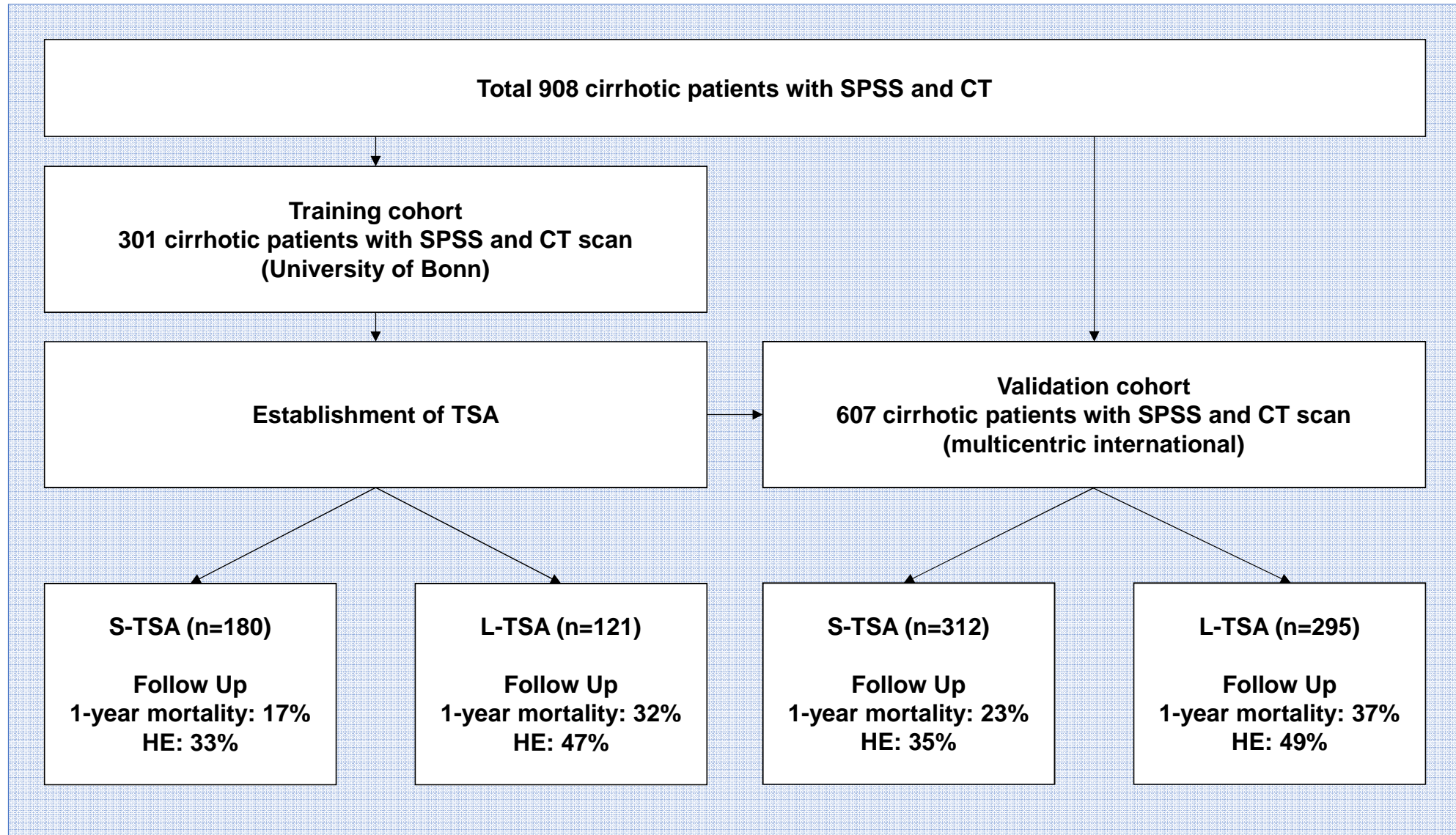
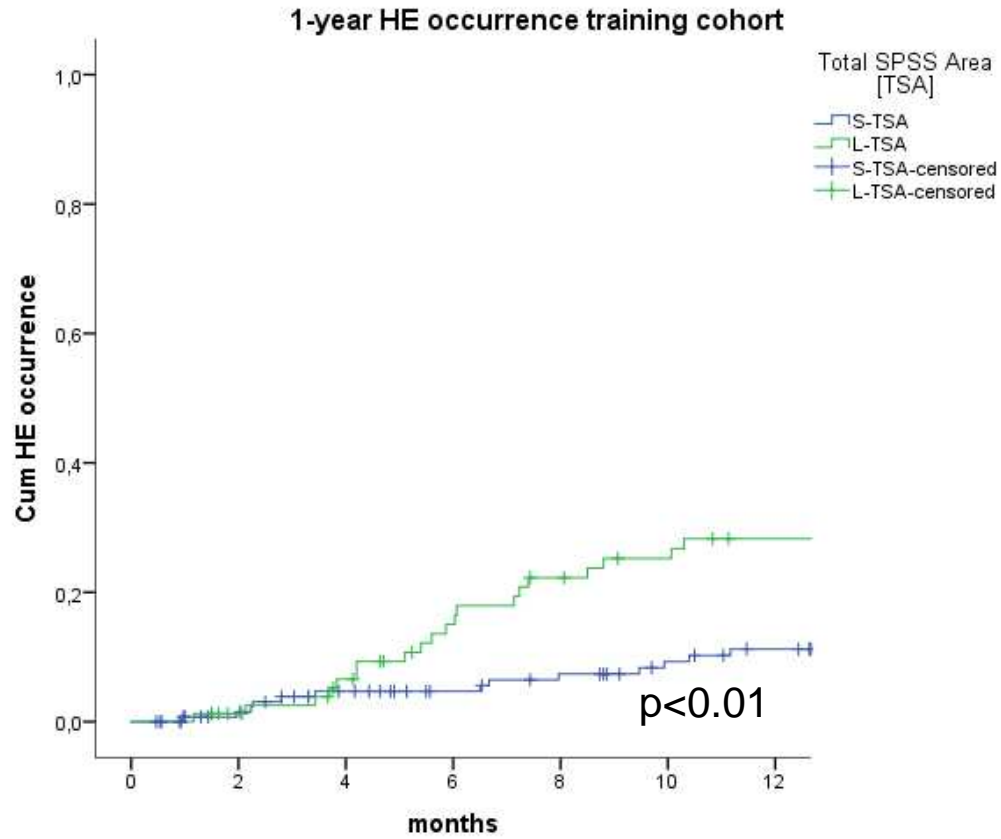


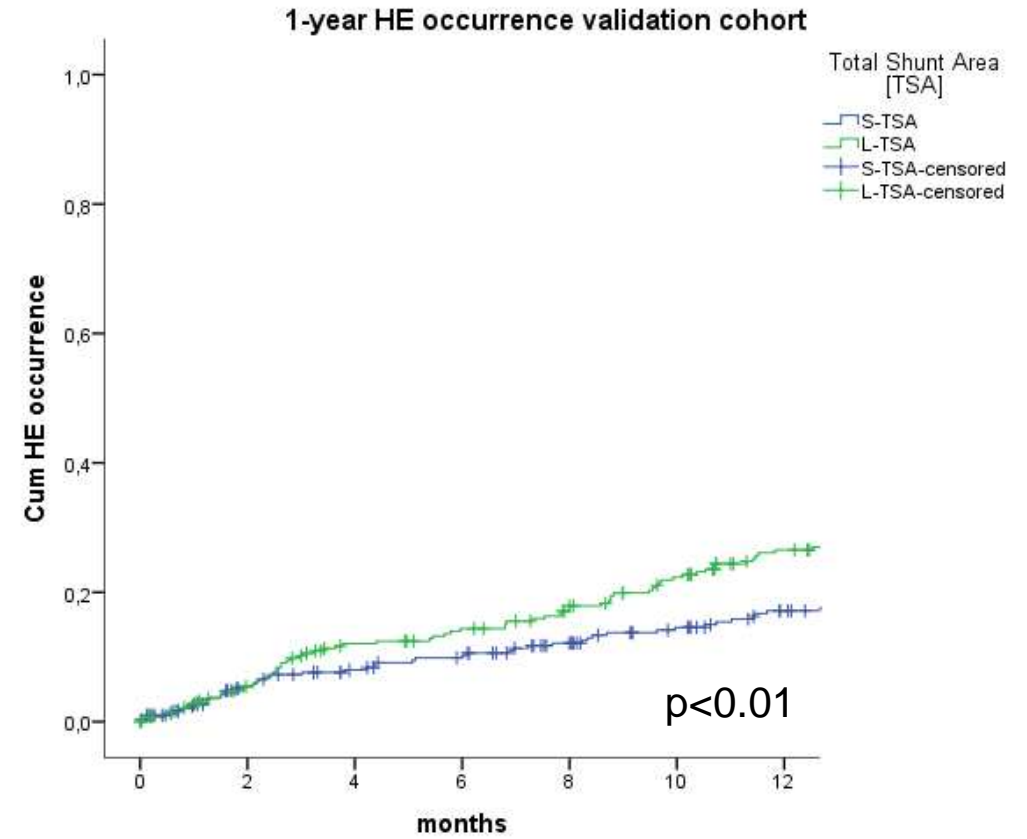
Figure 2

A



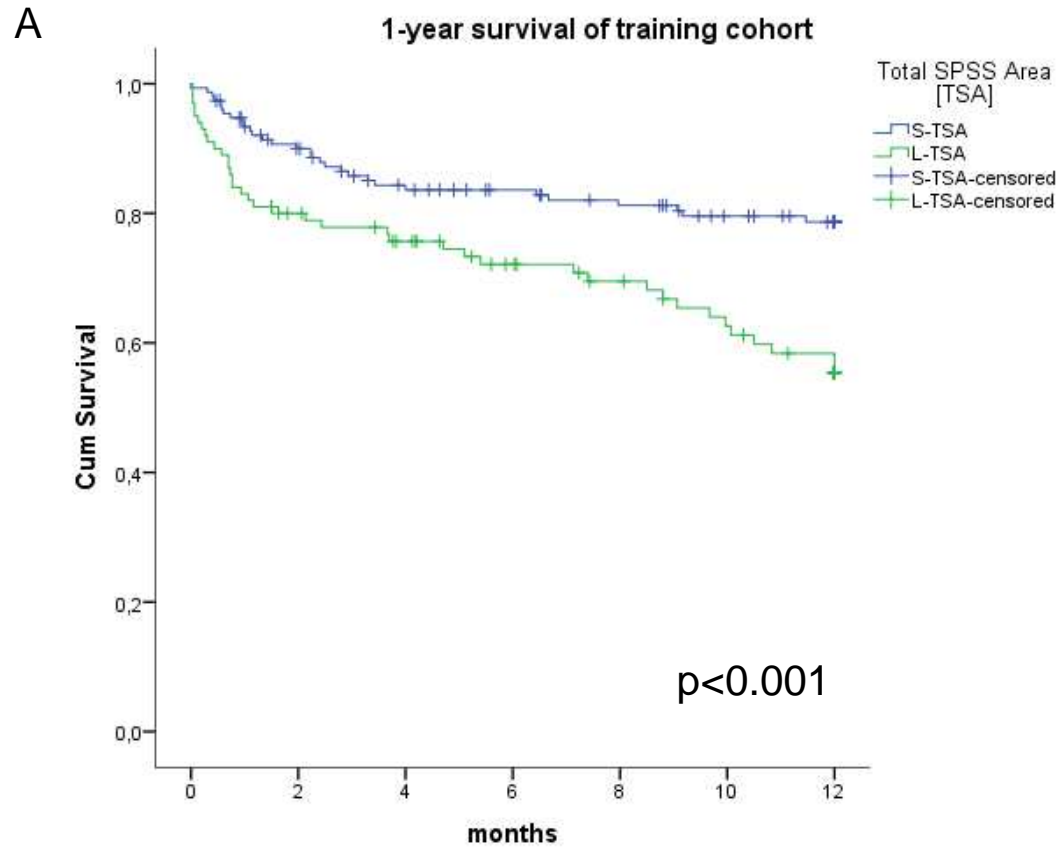
Patients at risk					
S-TSA	137	120	106	98	89
L-TSA	81	73	58	49	44

B

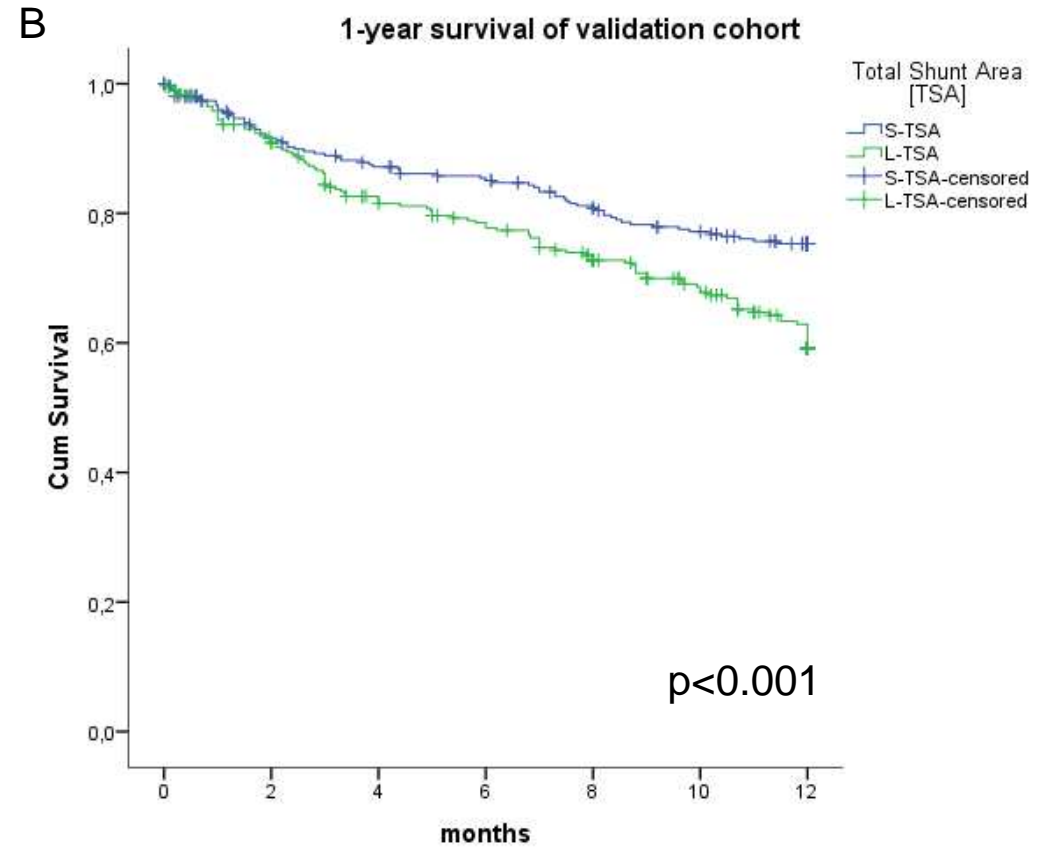


Patients at risk					
S-TSA	304	257	240	212	190
L-TSA	284	242	222	198	169

Figure 3



Patients at risk							
	0	2	4	6	8	10	12
S-TSA	153	120	106	97	85		
L-TSA	100	72	57	47	39		



Patients at risk							
	0	2	4	6	8	10	12
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.