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

Michael Praktiknjo, Macarena Simón-Talero, Julia Römer, Davide Roccarina, Javier Martínez, Katharina Lampichler, Anna Baiges, Gavin Low, Elba Llop, Martin H. Maurer, Alexander Zipprich, Michela Triolo, Geert Maleux, Annette Dam Fialla, Claus Dam, Judit Vidal-González, Avik Majumdar, Carmen Picón, Daniel Toth, Anna Darnell, Juan G. Abraldes, Marta López, Christian Jansen, Johannes Chang, Robert Schierwagen, Frank Uschner, Guido Kukuk, Carsten Meyer, Daniel Thomas, Karsten Wolter, Christian P. Strassburg, Wim Laleman, Vincenzo La Mura, Cristina Ripoll, Annalisa Berzigotti, José Luis Calleja, Puneeta Tandon, Virginia Hernandez-Gea, Thomas Reiberger, Agustín Albillos, Emmanuel A. Tsochatzis, Aleksander Krag, Joan Genescà, Jonel Trebicka for the Baveno VI-SPSS group of the Baveno Cooperation

Table of contents

Fig. S1. Schematic example of 2 SPSS with 5 mm diameter each (top) and one single SPSS with 10 mm diameter (bottom). Total SPSS diameter of both patients are equal, but total SPSS area (TSA) is vastly different.

Fig. S2. Kaplan-Meier curve showing 1-year survival of S-TSA (blue line) vs. L-TSA (green line) patient cohorts after exclusion of patients with platelet count >250 $x10^9$/L in the training cohort. Statistical analysis: log rank test.

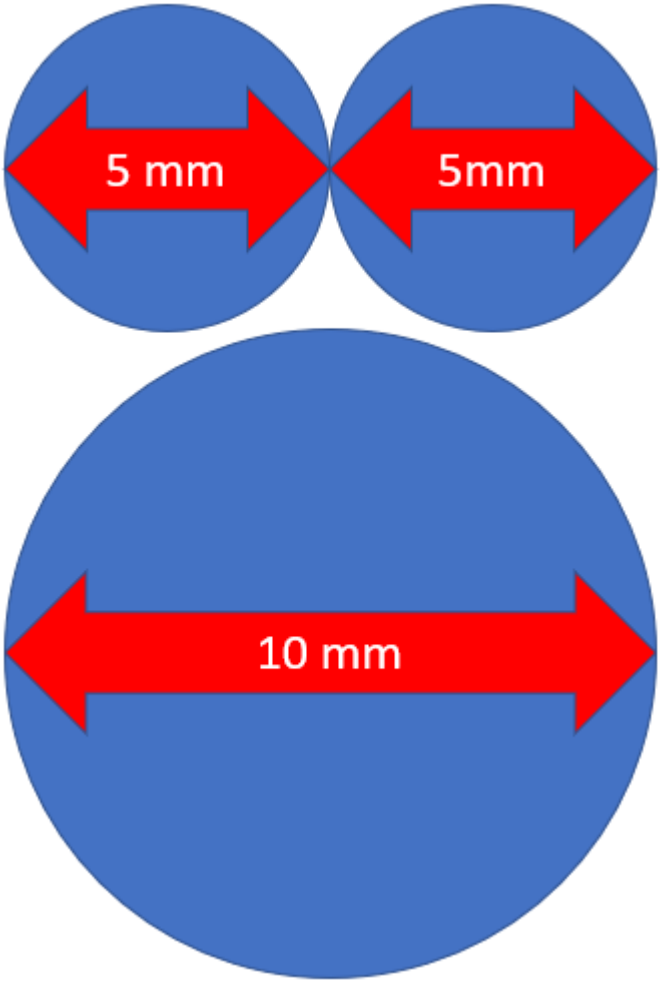
Fig. S3. Kaplan-Meier curve showing 1-year survival of S-TSA (blue line) vs. L-TSA (green line) patient cohorts after exclusion of patients with platelet count >250 $x10^9$/L in the validation cohort. Statistical analysis: log rank test.

Fig. S4. Venn diagram showing the distribution of patients in the whole cohort (training and validation cohort) according to classification to S-SPSS, L-SPSS, S-TSA and L-TSA. (S-/L-SPSS: small (<8mm) / large (≥8mm) spontaneous portosystemic shunt; S-/L-TSA: small (<83mm^2) / large (≥83mm^2) total SPSS area).

Fig. S5. Kaplan-Meier curve showing no significant difference in 1-year survival between S-SPSS (blue line) and L-SPSS (green line) patients in the whole (training and validation) cohort. Statistical analysis: log rank test.

Fig. S6. Kaplan-Meier curve of only L-SPSS patients showing impaired 1-year survival in L-TSA patients (green line) compared to S-TSA patients (blue line) in whole (training and validation) cohort. Statistical analysis: log rank test.

Fig. S1.



Total diameter: **10 mm**
Total Area: **20 mm²**

Total diameter: **10 mm**
Total Area: **79 mm²**

Fig. S2.

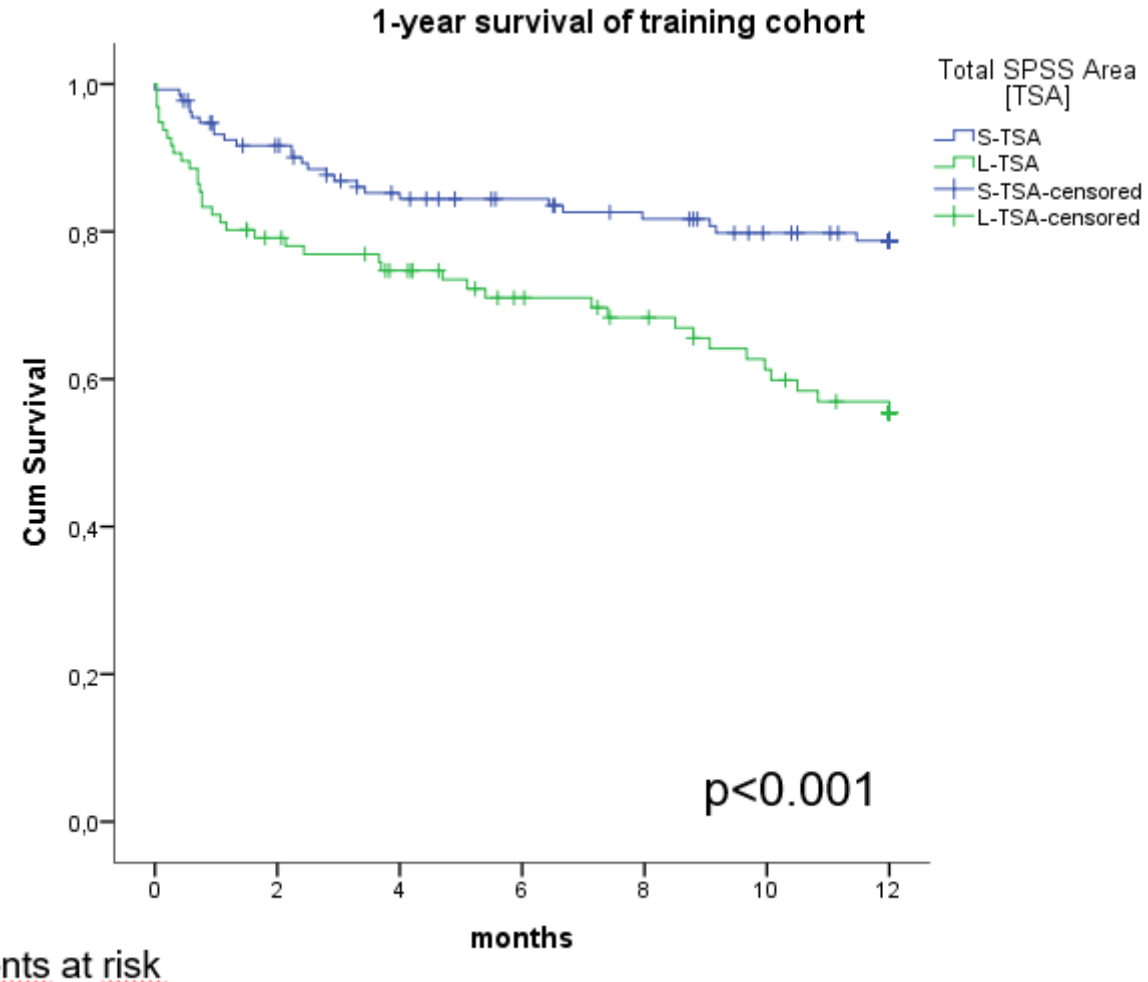
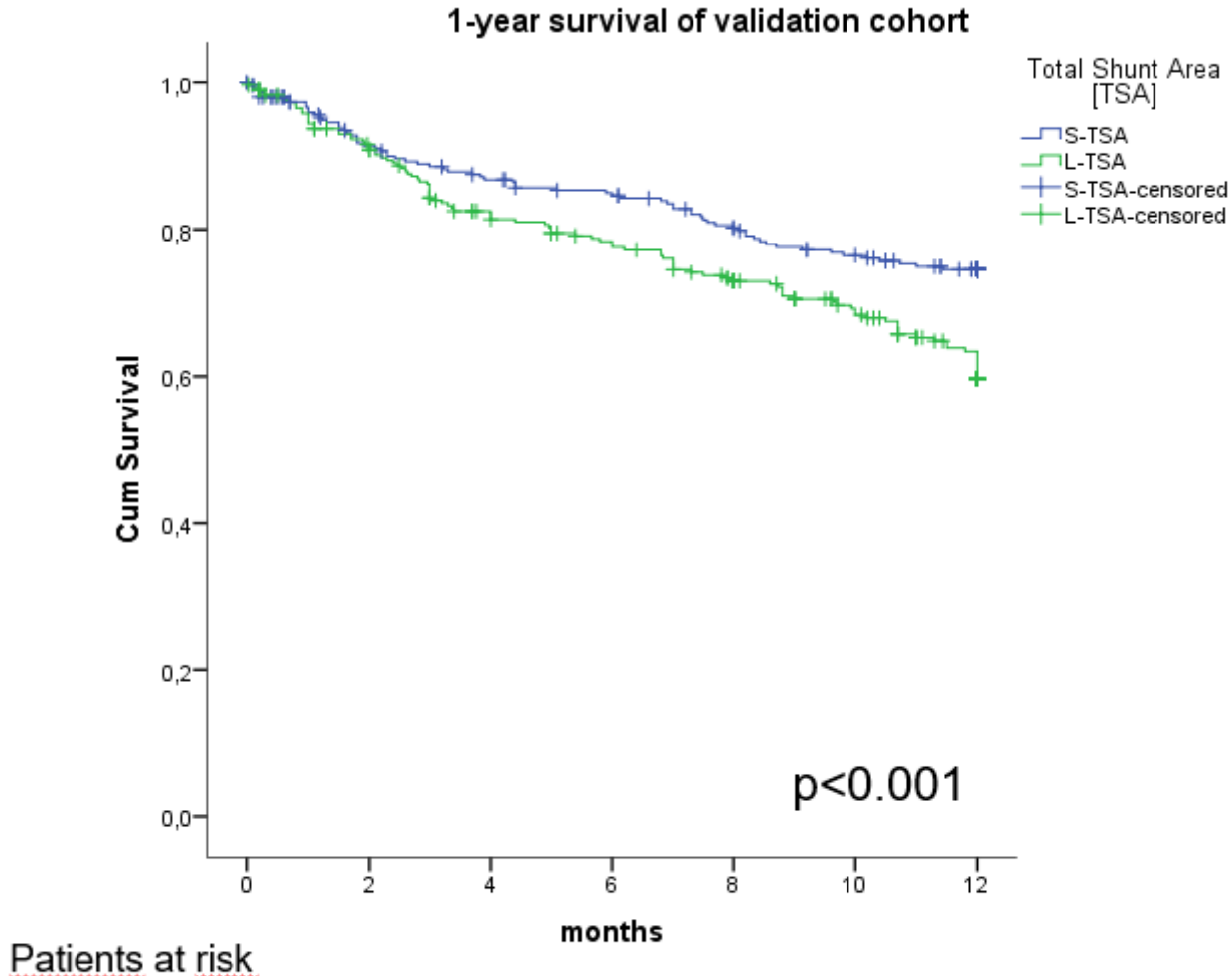

1-year survival of training cohort
Total SPSS Area [TSA]
S-TSA
L-TSA
S-TSA-censored
L-TSA-censored
Cum Survival
1,0
0,8
0,6
0,4
0,2
0,0
0
2
4
6
8
10
12
months
p<0.001
Patients at risk
S-TSA 134 108 95 86 76
L-TSA 96 70 55 46 38

Fig. S3.



Patients at risk					
S-TSA	303	252	235	208	185
L-TSA	290	238	205	173	135

Fig. S4.

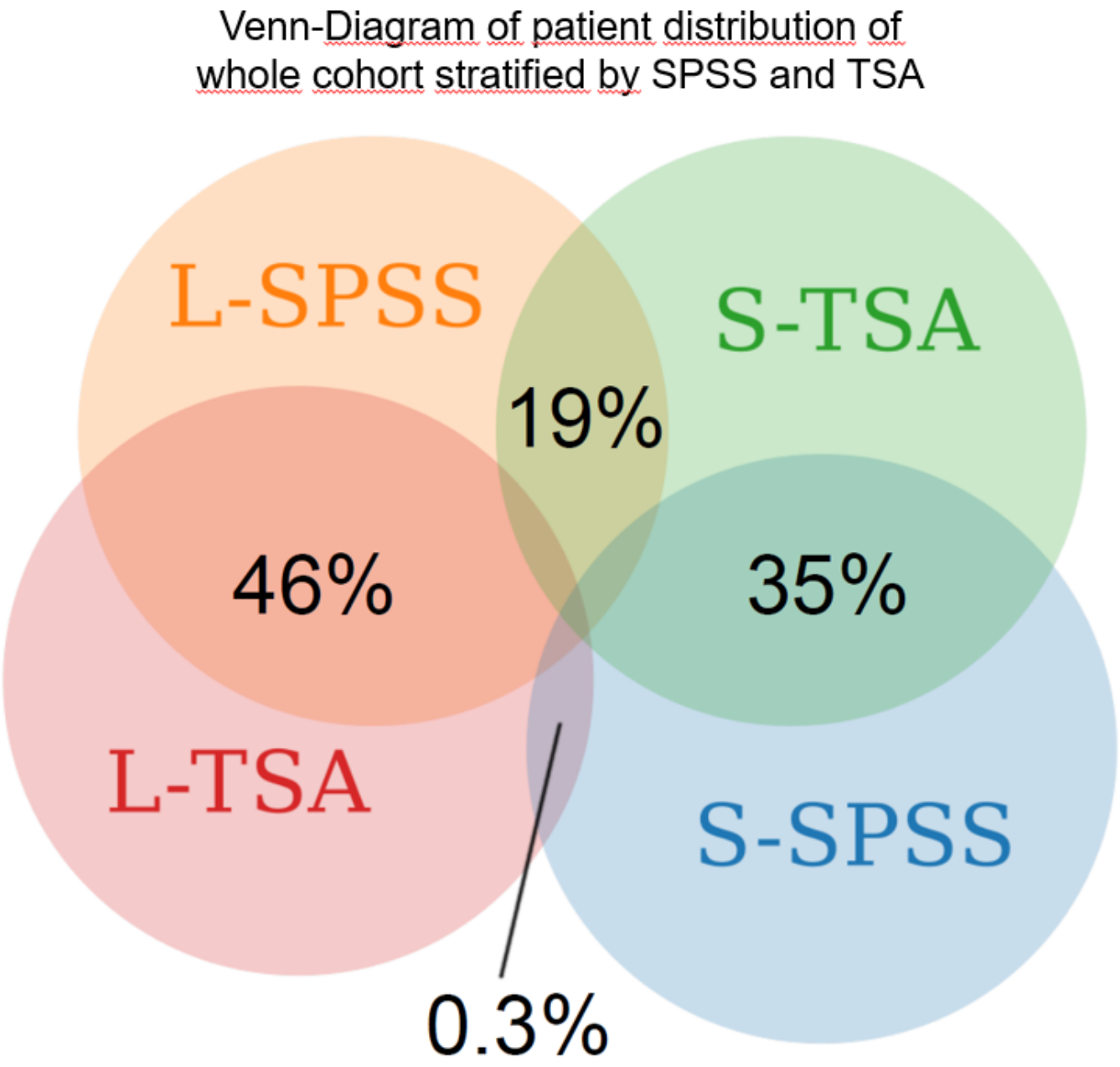
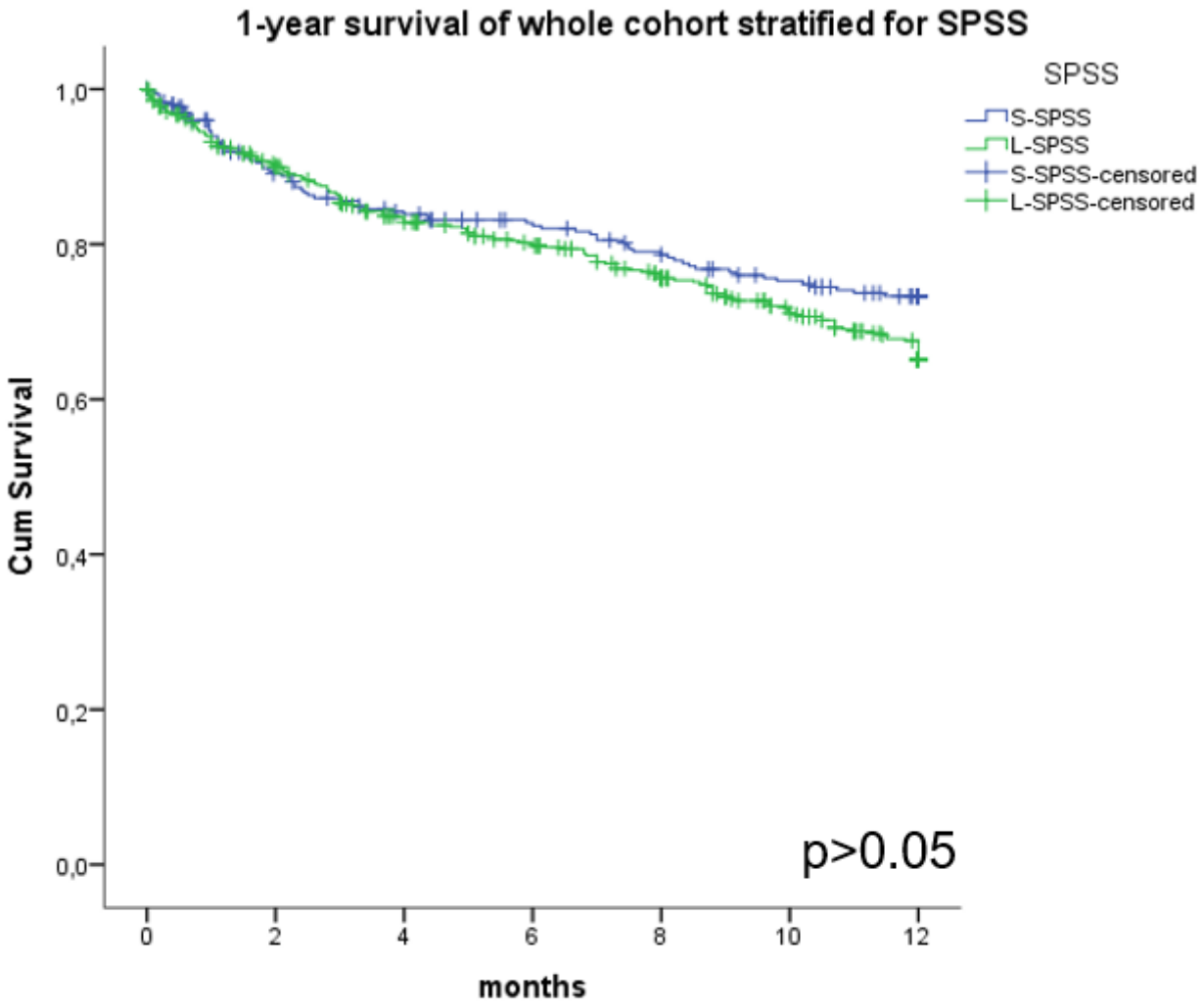
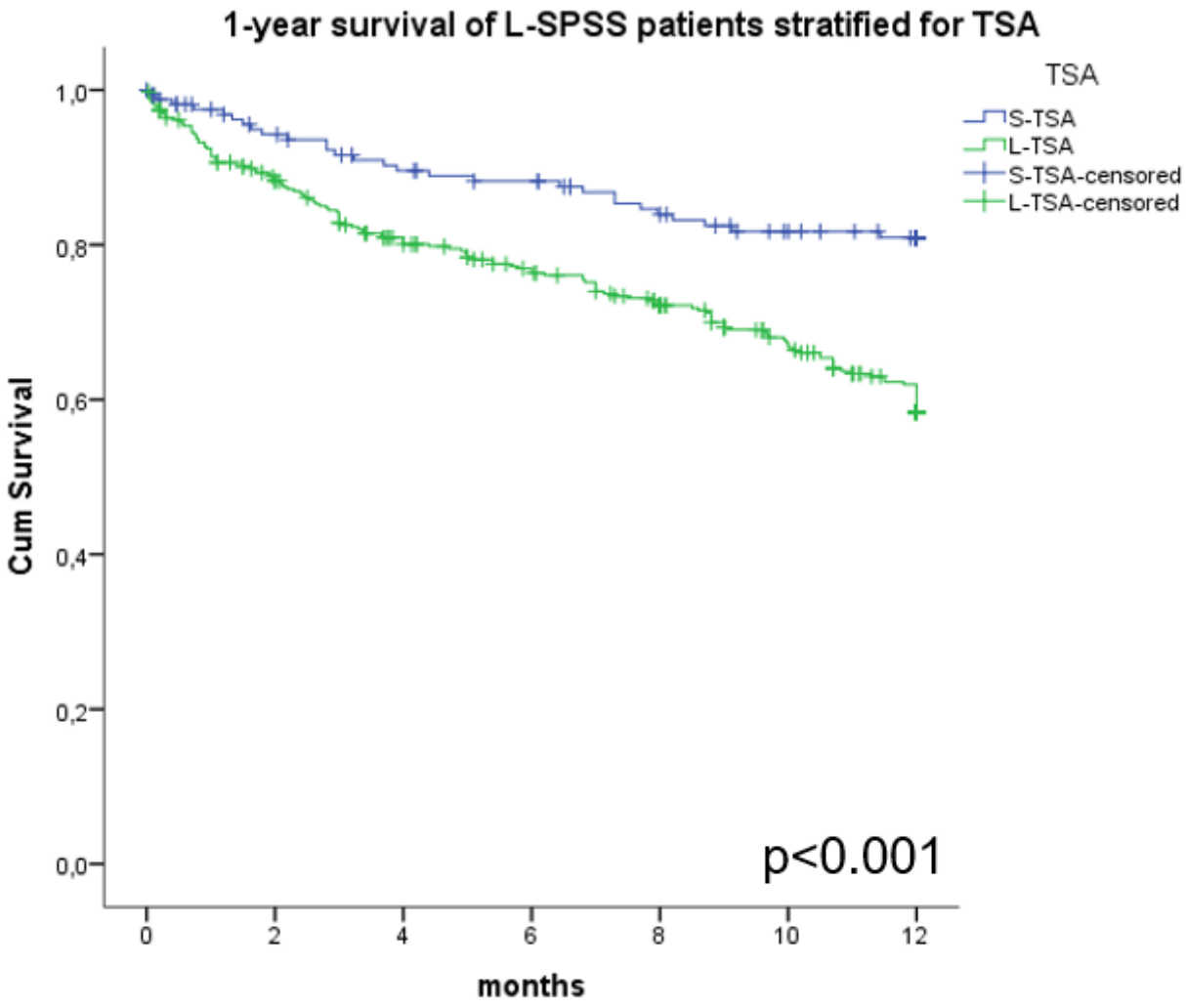

Venn-Diagram of patient distribution of whole cohort stratified by SPSS and TSA
L-SPSS
S-TSA
19%
46%
35%
L-TSA
S-SPSS
0.3%

Fig. S5.



Patients at risk					
S-SPSS	303	244	223	201	179
L-SPSS	553	338	390	332	273

Fig. S6.



Patients at risk					
S-TSA	164	137	127	111	99
L-TSA	389	310	262	220	173

Table S1. Indications for CT scan in training cohort.

Indication for CT	n (%)
Suspected Shunt	9 (3%)
Focal Liver Lesion	68 (23%)
Decompensation	22 (7%)
LT evaluation	54 (18%)
TIPS evaluation	37 (12%)
other	111 (37%)

LT – liver transplantation, TIPS – transjugular intrahepatic portosystemic shunt, CT – computed tomography

Table S2. Patient distribution, number of TIPS and liver transplantations by MELD categories.

MELD	6-10	11-15	16-20	21-25	26-30	31-35	36-40
number of patients	100	105	64	15	4	8	5
number of TIPS	9 (9%)	12 (11%)	2 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
number of LT	0 (0%)	7 (7%)	4 (6%)	3 (20%)	3 (75%)	2 (25%)	0 (0%)

MELD – model of end-stage liver disease, LT – liver transplantation, TIPS – transjugular intrahepatic portosystemic shunt

Table S3. Patients included by centre.

Location (absolute)	Patients included
Bonn	301
Barcelona Vall d'Hebron	135
London Royal Free	88
Vienna	78
Madrid Ramón y Cajal	77
Barcelona H. Clínic	55
Edmonton	47
Leuven	32
Halle	26
Odense	25
Bern	22
Milan	22

Table S4. Diagnostic performance of TSA cut-off at 83 mm^2 for 1-year mortality and HE development [%].

1-year mortality	Sens	Spec	PPV	NPV
Training	55.7	66.8	39.0	79.9
Validation	59.9	56.6	36.3	76.6

HE	Sens	Spec	PPV	NPV
Training	45.2	68.1	46.9	66.7
Validation	56.7	57.9	49.3	64.9

HE – hepatic encephalopathy; Sens – sensitivity, Spec – specificity, PPV – positive redictive value, NPV – negative predictive value.

Table S5. Distribution of S-TSA and L-TSA patients stratified by blood ammonia levels (median)..

	S-TSA	L-TSA
low Ammonia	50 (58%)	29 (43%)
high Ammonia	37 (42%)	38 (57%)

High Ammonia (>65 µmol/l), Low Ammonia (≤65 µmol/l)

Table S6. Causes of death in the training cohort.

	absolute (percentage)	all (n=51)	S-TSA (n=22)	L-TSA (n=29)
cause of death	liver failure	7 (13%)	4 (18%)	3 (10%)
	bleeding	3 (6%)	2 (9%)	1 (3%)
	infection	32 (63%)	13 (59%)	19 (66%)
	HCC	5 (10%)	1 (4%)	4 (14%)
	cardiovascular	3 (6%)	1 (4%)	2 (7%)
	other malignoma	1 (2%)	1 (4%)	0 (0%)

HCC – hepatocellular carcinoma

Table S7. Univariate and multivariate Cox regression analysis of training cohort with 1-year mortality as endpoint (TSA as continuous variable).

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							
TSA[2]	<0.001	1.315	1.115	1.551	0.028	1.210	1.021	1.435
hepatic encephalopathy at baseline	<0.001	3.519	2.190	5.657	0.003	2.118	1.285	3.491
hepatorenal syndrome at baseline	<0.001	5.781	3.561	9.386	0.015	2.009	1.145	3.526
ascites at baseline	0.002	2.566	1.427	4.615	0.655			
SBP at baseline	0.001	2.736	1.541	4.857	0.826			
MELD at baseline	<0.001	1.180	1.144	1.217	<0.001	1.176	1.130	1.223
sodium at baseline[3]	0.022	0.950	0.909	0.993				
creatinine at baseline[4]	<0.001	2.171	1.783	2.643				
bilirubin at baseline[4]	<0.001	1.122	1.092	1.153				
INR at baseline	<0.001	4.469	3.221	6.202				

1-[years], 2- [cm2], 3-[mmol/l], 4-[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 S8. Causes of death in the validation cohort

-	-	**all n=123**	**S-TSA n=45**	**L-TSA n=78**
cause of death	liver failure	44 (36%)	17 (38%)	27 (35%)
	bleeding	7 (6%)	2 (5%)	5 (6%)
	infection	23 (19%)	9 (20%)	14 (18%)
	HCC	15 (12%)	6 (13%)	9 (12%)
	unknown/other	34 (27%)	11 (24%)	23 (29%)

HCC – hepatocellular carcinoma

Table S9. Univariate and multivariate Cox regression analysis of validation cohort with 1-year mortality as endpoint (TSA as continuous variable).

1-year mortality	univariate Cox regression				multivariate Cox regression			
Parameter	**p**	**HR**	**CI**		**p**	**HR**	**CI**	
age[1]	0.148				0.006	1.020	1.006	1.034
sex	0.040	1.407	1.016	1.947				
TSA[2]	<0.001	1.107	1.043	1.175	<0.001	1.166	1.095	1.242
hepatic encephalopathy at baseline	<0.001	2.109	1.547	2.875	0.159			
hepatorenal syndrome at baseline	<0.001	4.998	2.885	8.658	0.037	1.964	1.040	3.709
ascites at baseline	<0.001	2.928	2.105	4.072	<0.001	2.183	1.513	3.149
SBP at baseline	<0.001	2.811	1.763	4.481	0.271			
MELD at baseline	<0.001	1.130	1.104	1.156	<0.001	1.109	1.080	1.139
sodium at baseline[3]	<0.001	0.943	0.924	0.961				
creatinine at baseline[4]	<0.001	1.870	1.560	2.242				
bilirubin at baseline[4]	<0.001	1.071	1.046	1.097				
INR at baseline	<0.001	2.047	1.693	2.475				

1-[years], 2- [cm2], 3-[mmol/l], 4-[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 S10. Mortality at 1 year stratified for large total shunt area (L-TSA) and MELD tertials in training and validation cohort combined.

MELD category absolute (percentage)	**S-TSA**	**L-TSA**
MELD 6-9	12(10%)	9(18%)*
MELD 10-13	30(18%)	29(24%)
MELD 14-40	57(31%)	106(50%)***

*p<0.05; ***p<0.001

Table S11. Univariate and multivariate Cox regression analysis of training cohort with L-SPSS (>8 mm diameter) 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	1.061	1.032	1.090
sex	0.332							
L-SPSS	0.035	1.687	1.036	2.746	0.305			
hepatic encephalopathy at baseline	<0.001	3.519	2.190	5.657	0.002	2.172	1.321	3.572
hepatorenal syndrome at baseline	<0.001	5.781	3.561	9.386	0.032	1.846	1.054	3.233
ascites at baseline	0.002	2.566	1.427	4.615	0.294			
SBP at baseline	0.001	2.736	1.541	4.857	0.965			
MELD at baseline	<0.001	1.180	1.144	1.217	<0.001	1.176	1.131	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- [cm2], 3-[mmol/l], 4-[mg/dl]
Italic – included in multivariate analysis, Bold – significant in multivariate analysis
MELD – model of end-stage liver disease, INR – international normalized ratio, L-SPSS – large spontaneous portosystemic shunt diameter >8mm, SBP – spontaneous bacterial peritonitis

Table S12. Univariate and multivariate Cox regression analysis of validation cohort with L-SPSS (>8 mm diameter) 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				0.014	1.017	1.003	1.031
sex	0.040	1.407	1.016	1.947				
L-SPSS	0.353							
hepatic encephalopathy at baseline	<0.001	2.109	1.547	2.875	0.098			
hepatorenal syndrome at baseline	<0.001	4.998	2.885	8.658	0.066			
ascites at baseline	<0.001	2.928	2.105	4.072	<0.001	1.953	1.371	2.782
SBP at baseline	<0.001	2.811	1.763	4.481	0.180			
MELD at baseline	<0.001	1.130	1.104	1.156	<0.001	1.115	1.087	1.144
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				

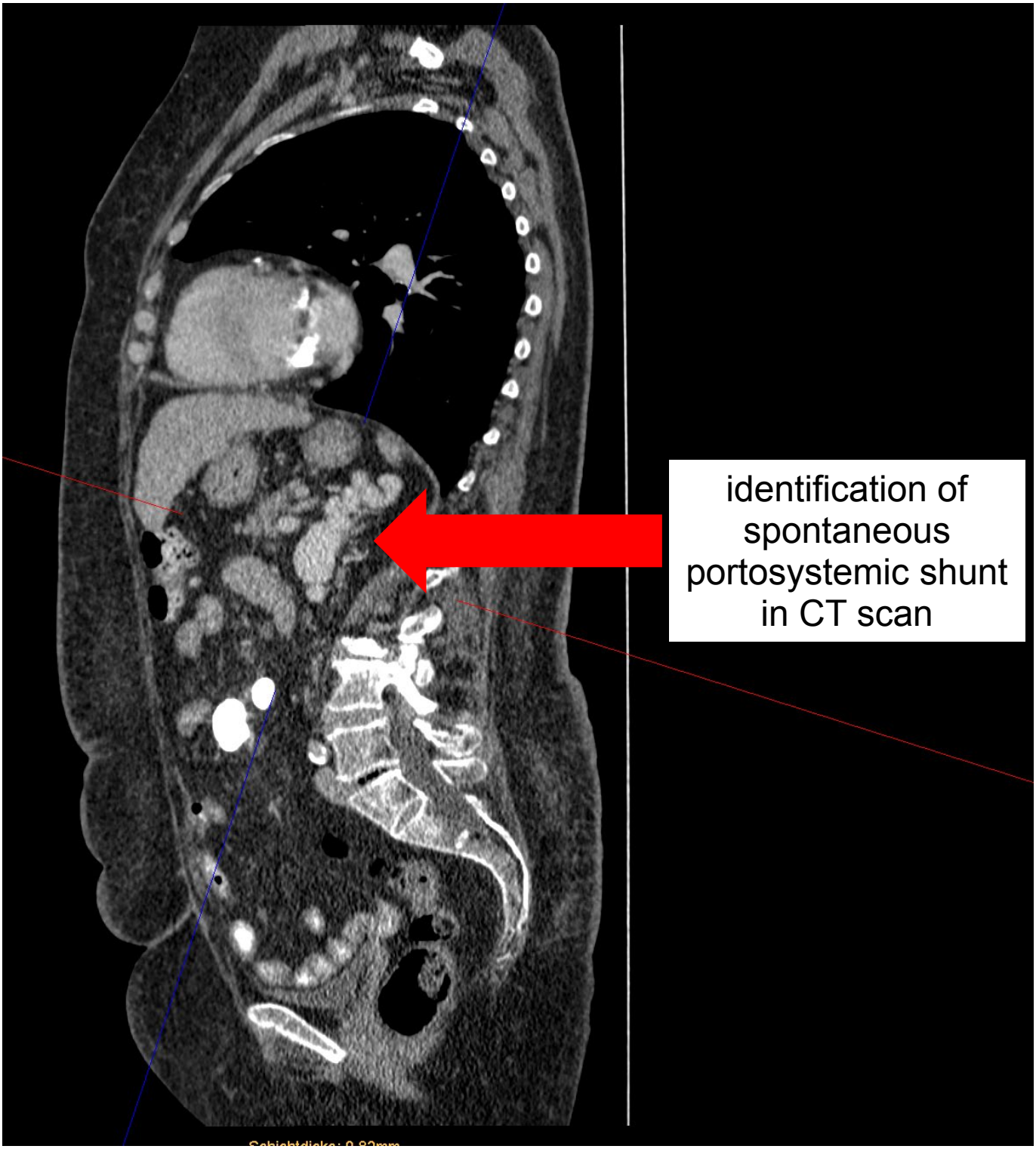
1-[years], 2- [cm2], 3-[mmol/l], 4-[mg/dl]
Italic – included in multivariate analysis, Bold – significant in multivariate analysis
MELD – model of end-stage liver disease, INR – international normalized ratio, L-SPSS – large spontaneous portosystemic shunt diameter >8mm, SBP – spontaneous bacterial peritonitis

Supplemental materials and methods

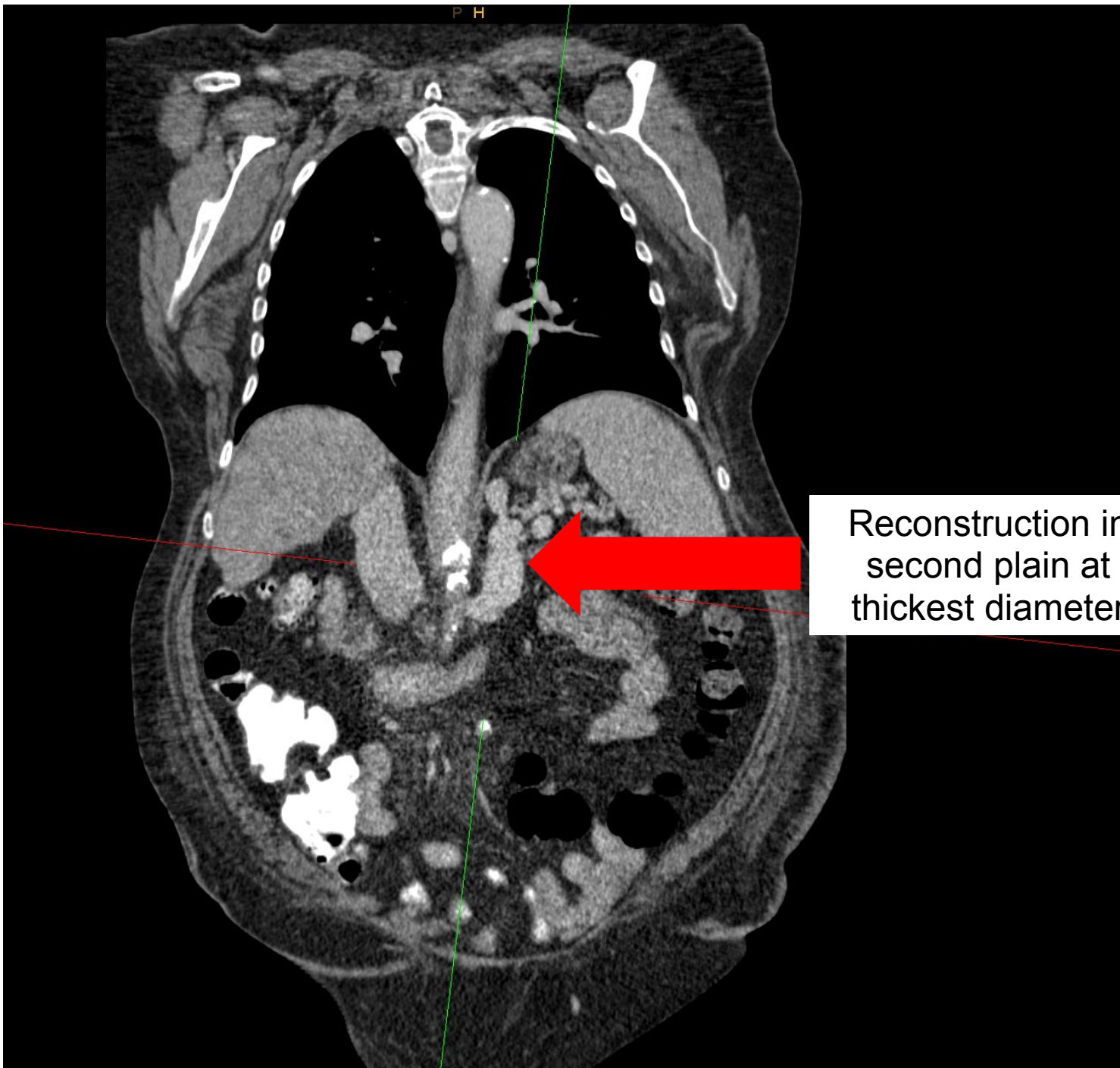
Radiologic protocol.

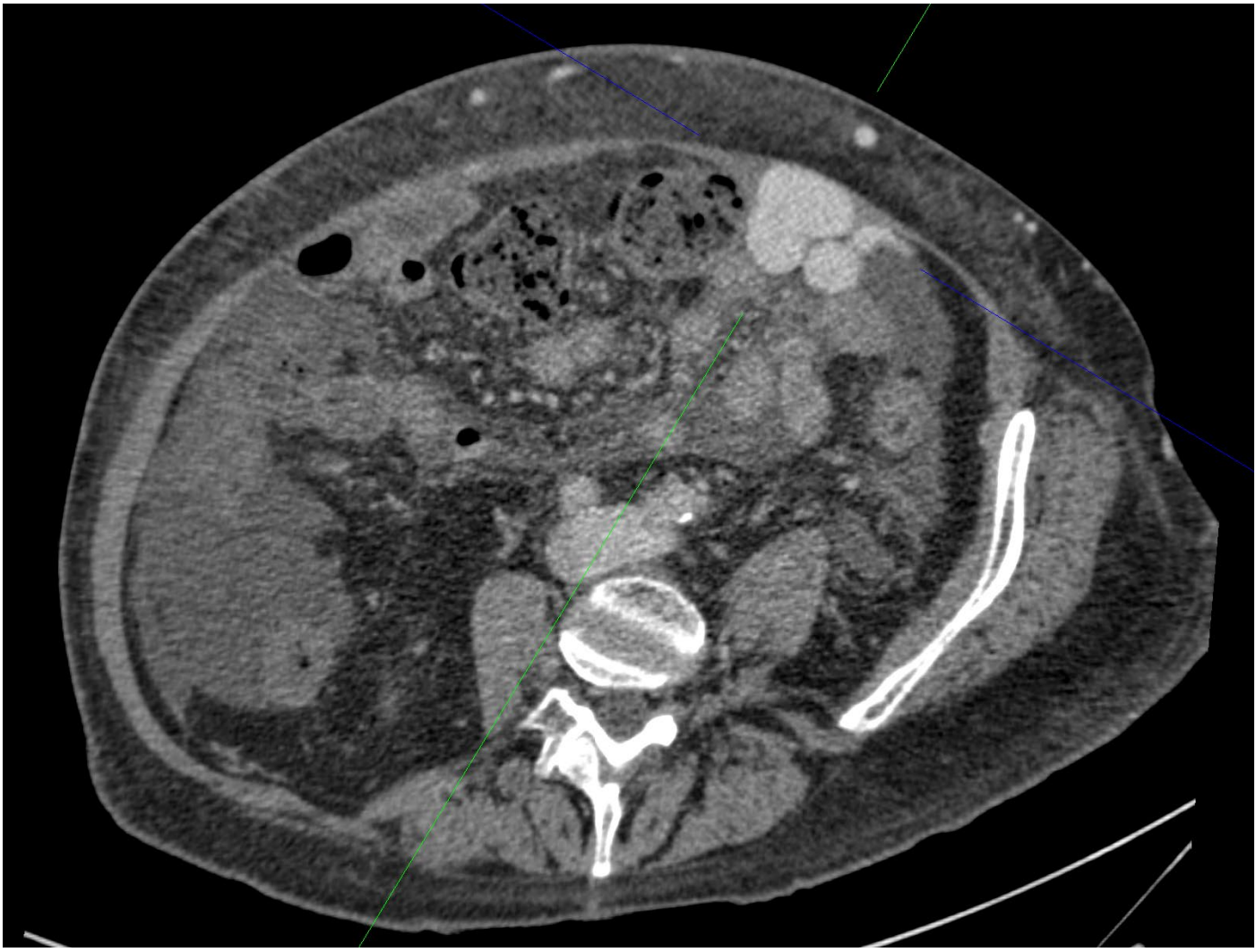
In all CTs we looked for any spontaneous portosystemic shunt (SPSS) by scrolling through the abdominal CT scan in axial plane. If available we preferred portal phase. In particular we looked for any additional veins leaving inferior vena cava, portal vein, splenic vein, right/left renal vein and superior/inferior mesenteric vein. When detecting SPSS we verified it by coronal and sagittal plane.
Following we looked for the position of the SPSS with the largest diameter in their complete length. At this point we measured the short-axis diameter between both walls of the vessel.
The minimum diameter of SPSS that was considered was 6 mm.
If there was any SPSS found we described them by the two veins that were connected e.g. infero-mesenterio-caval.
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.
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.

Sample 1a.


identification of spontaneous portosystemic shunt in CT scan

Sample 1b.





Sample 1c.