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Spontaneous portosystemic shunts in cirrhosis: Detection, implications, and clinical associations

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ABSTRACT

Background: Spontaneous portosystemic shunts (SPSS) are common in cirrhosis. Their characterization and clinical implications remain unclear.
Aims: To devise a system of assessment of these shunts, and assess their clinical implications
Methods: We retrospectively studied patients with cirrhosis who underwent imaging in a liver transplant program. A novel index was computed to assess total SPSS -the diameter of a circle having an area equivalent to the sum of the areas of all the existing shunts. This 'SPSS equivalent diameter' was compared with the clinical variables.
Results: Among 127 patients, 70% ($CI_{95\%}$ 62–77) had SPSS, and 57% ($CI_{95\%}$ 62–77) had multiple SPSS. The risk for SPSS was related to the severity of cirrhosis (Child-Pugh B/C vs. A: OR 2.4 $CI_{95\%}$ 1.1–5.4) and alcoholic aetiology (OR 2.9 $CI_{95\%}$ 1.2–7.1). The SPSS equivalent diameter was related to a history of HE, cognitive impairment (EEG/PHES) and ammonia($p<0.05$). The diameter of the inferior cava vein >19.5 mm was a predictor of large SPSS (AUC 0.77, $CI_{95\%}$:0.68–0.87, $p \leq 0.001$).
Conclusions: The SPSS equivalent diameter, a comprehensive assessment of portosystemic shunting, was associated with severity of liver disease, hyperammonemia, and cognitive dysfunction. The diameter of the inferior vena cava was a good predictor of SPSS.

1. Introduction

Spontaneous portosystemic shunts (SPSS) are common in patients with cirrhosis, being present in up to 60% of cases [1]. These veno-venous collaterals develop as a consequence of the effects of portal hypertension potentiated by the inflammatory and angiogenic milieu of cirrhosis [2,3]. Their presence is often linked with clinically significant portal hypertension. SPSS have been associated with more severe liver disease [4]. Large shunts may be a maladaptive phenomenon, often implicated in persistent, relapsing or refractory hepatic encephalopathy (HE) [5,6]. Closure of these shunts in selected patients may improve HE, liver fibrosis, hepatic function and survival, possibly through an improved hepatic perfusion [7–10]. SPSS have also been associated with portal vein thrombosis (PVT) in the post-transplant setting, [11–13].

The clinical implications of SPSS are inconsistent [1,14] and sometimes contradictory [15,16]. The likely reason is a combination of difference in diagnostic modalities (ultrasound vs cross-sectional imaging), and evaluation of only a specific shunt-type. More than a third of the patients may have multiple shunts [1], which are often not accounted for.

The aims of the present study were: *i)* to identify and characterize the frequency and extent of SPSS in patients with cirrhosis, and *ii)* to assess their clinical implications, with special focus on neurocognitive parameters.

2. Methods

This single centre, retrospective study was conducted at the University Hospital of Padova on patients assessed between 2009–2017.

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2.1. Study cohort

All adult patients with cirrhosis undergo evaluation for HE as a part of pre-transplant assessment, or when clinically indicated in our centre. These patients underwent a detailed clinical and neurocognitive evaluation. The diagnosis of cirrhosis was based on a combination of clinical, biochemical, imaging, elastography, and/or histological evidence. The radiological data was collected and analysed by observers who were not part of the clinical team to avoid bias.

Patients who had a cross-sectional imaging in the form of contrast enhanced computed tomography (CT) or magnetic resonance imaging (MRI) done within one year from clinical assessment were included in the study. We excluded patients under the following conditions: known neurological and psychiatric diseases, presence of transjugular intrahepatic portosystemic shunt (TIPS) or surgical portosystemic shunts, splenectomy, extrahepatic malignancy, non-cirrhotic forms of portal hypertension, Budd-Chiari syndrome, previous partial hepatectomy, prior liver transplant, prior left nephrectomy, or if imaging was unsuitable for analysis. In contrast, the existence of hepatoma nodules within the liver were not considered a cause of exclusion.

2.2. Assessment of liver disease and covert HE

The date of psychometric assessment was considered inclusion into the database. Demographic details, aetiology of cirrhosis, history of ascites, encephalopathy, oesophageal varices (assessed within one year), history of variceal bleeding, routine biochemical parameters were recorded. The Child-Pugh score (CPS), the Child-Pugh class (CPC), and the MELD were calculated.

The patients were assessed for minimal HE using the psychometric hepatic encephalopathy score (PEHS), using local values [17], critical flicker frequency (CFF), and electroencephalogram (EEG) quantified by spectral analysis [18]. A value of PHES ≤ -4 was taken as the cut-off for MHE based on previously validated data for Italian population [17]. A value of CFF ≤ 39 Hz was considered abnormal.

2.3. Radiological assessment

CT or magnetic resonance cross-sectional imaging of abdomen was reviewed in the venous phase for presence of SPSS simultaneously by two observers (SR, SB). Presence of any dilated and/or tortuous collaterals ≥ 5 mm between the porto-mesenteric and systemic venous circulation were recorded. This value was chosen because a width of 5 mm could be reliably detected on CT scan.

In case of more than one SPSS, the total effective SPSS was calculated, based on the sum of cross-sectional area of the shunts. The SPSS effective shunt diameter was computed as the diameter of a circle with an area equivalent to the sum of all the areas of the SPSS detected in a single patient (Fig. 1A). As shunts are often tortuous and ectatic, the narrowest consistent segment was measured for dimensions. (Fig. 1B).

As portosystemic shunting would lead to a relative increase in flow into the systemic circulation, the dimensions of inferior vena cava (IVC) were measured in its intrahepatic course in the axial cuts. For consistency of assessment, the anteroposterior dimension of IVC was recorded at the level between bifurcation of portal vein and confluence of hepatic veins. (Fig. 1C) Similarly, presence of splenorenal shunt (SRS) would increase the flow into left renal vein (LRV), leading to its expansion. The left renal vein was measured at its widest segment. (Fig. 1D). Periesophageal collaterals were included in shunts only if there was a dominant collateral $>$ 6 mm in size. On the basis of total effective SPSS diameter, patients were finally divided into (a) presence or absence of shunts, or (b) extent of the shunt: SPSS$<$8 (small), SPSS 8–12 mm (large), or SPSS$>$12 mm (very large) for analysis. This subdivision was done so that about a same number of subjects were included into the three classes.

2.4. Statistical analysis

Quantitative variables were represented as median and interquartile range (IQR). Categorical variables were expressed as percentages and $CI_{95\%}$ calculated by the Wilson score interval. Comparison between variables was performed by Mann-Whitney-U test or Kruskall-Wallis test for quantitative variables. The Pearson's χ^2-test and the Fisher exact test were used to compare frequencies. Correlation between variables was tested by the Pearsons's r or the Spearman's R test. C-statistics was used to determine suitable cut-offs, area under ROC curve, sensitivity and specificity of continuous variables for binary predictors. P values ≤ 0.05 were considered statistically significant.

Mean substitution for missing data was applied. Statistical analysis was done using Statistica (StatSoft Italia srl (2005). STATISTICA version 7.1. www.statsoft.it) and by Sergeant, ESG, 2018. Epitools Epidemiological Calculators. Ausvet. Available at: http://epitools.ausvet.com.au.

3. Results

A total of 144 patients out of 614 patients who were evaluated for HE had imaging done within 1 year from psychometric assessment, and were thus considered in the study. Of those, 17 patients were excluded (11 TIPS, 1 splenectomy, 3 had prior liver transplant, 1 non-cirrhotic, 1 had prior shunt embolization). 127 patients were finally assessed. The final 127 patients had median age of 58 years, 74% were males, and nearly an equal number of patients had alcohol (37%) or viral (39%) as aetiology of cirrhosis. 120 underwent CT scan and 7 MRI. No association was found between the gender and the aetiology of cirrhosis. The main demographic and clinical findings are reported in Table 1. The severity of cirrhosis was marginally lower in the patients with alcoholic cirrhosis (MELD=11, IQR:8–13) than virus related cirrhosis (MELD=13, IQR:10–18) or other kinds of cirrhosis (MELD=14, IQR:10–18), $p = 0.02$.

3.1. Radiological findings

3.1.1. Distribution of SPSS

Out of the 127 patients with cirrhosis, 89 (70%, $CI_{95\%}$ 62–77) had at least one SPSS, and 38 (30% $CI_{95\%}$ 23–38) did not have SPSS, or they were negligible.

In the patients with SPSS, the splenorenal shunt was the most common (76% $CI_{95\%}$ 67–84), followed by a recanalized paraumbilical vein (44% $CI_{95\%}$ 34–54). Other SPSSs included short gastric/periesophageal (14, 16%), 2 mesorectal, 1 spleno-gonadal, 1 spleno-retroperitoneal, 1 meso–iliac, and 1 meso–caval shunt. Multiple SPSS (two or more) were found in 73 patients (i.e., 82% -$CI_{95\%}$ 73–89- of the patients with SPSS; 57% -$CI_{95\%}$ 62–77- of all the patients with cirrhosis).

Out of the 127 patients with cirrhosis, 24% ($CI_{95\%}$ 18–33) had small SPSS ($<$8 mm), 20% ($CI_{95\%}$ 14–28) patients had large SPSS (8–12 mm), 25% ($CI_{95\%}$ 18–33) patients had very large SPSS ($>$12 mm). The median SPSS equivalent diameter was 10 mm (IQR: 7–13).

3.1.2. Predictors of SPSS

When the relationship of the SPSS equivalent diameter was compared to the measures simply obtainable by a plain CT scan of the abdomen, the anteroposterior diameter of the IVC was found to be correlated to the SPSS equivalent diameter ($r = 0.36$, $P<0.001$,

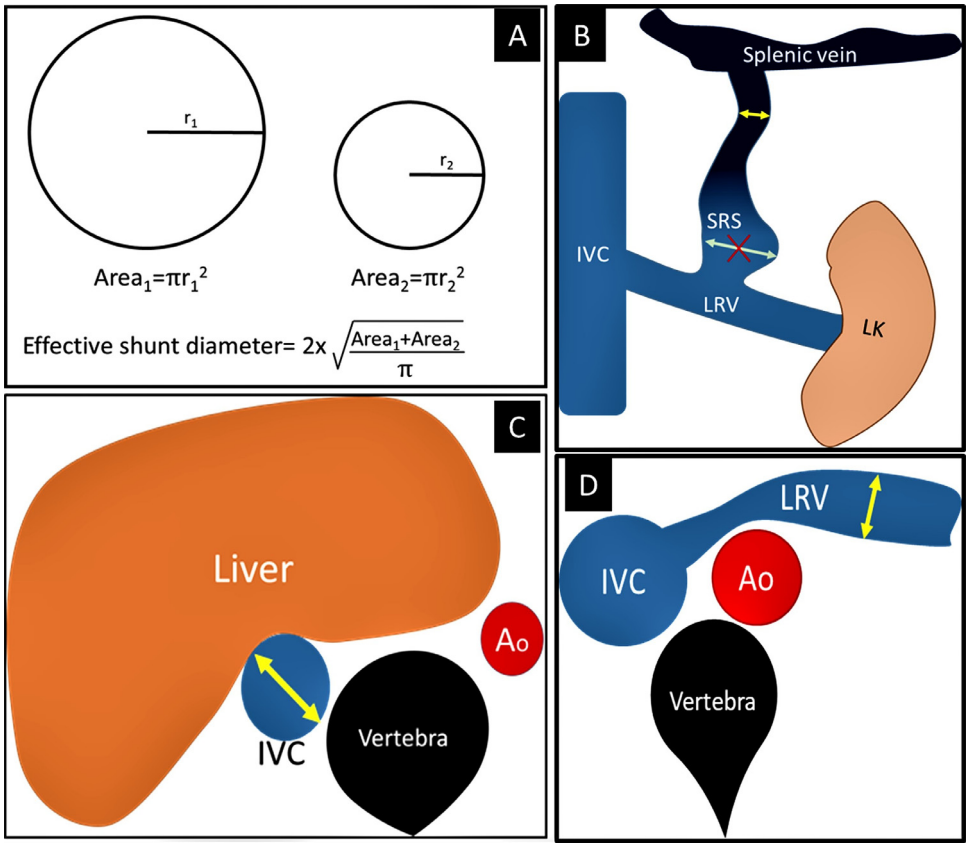

Fig. 1. Schema representing the calculation of the equivalent SPSS diameter: 1) the area of each shunt is calculated on the basis of its diameter, assuming that the shape is a circle 2) the sum of all areas is then calculated, 3) from this resulting area -assumed to be of a circle- the diameter is derived. This was called equivalent SPSS diameter, because is the diameter of a circle with an area equivalent to the sum of all the areas of the shunts that have been found.

Table 1
Demographic and clinical data of the study population compared with the patients who did not fulfil inclusion/exclusion criteria.

Parameter	Study population $N=127$	Excluded population $N=664$	P
Age (years) median and IQR	58 (52;64)	60 (51;68)	0.91
Gender (male,%)	74	73	0.58
Education(years)	8 (8;13)	8(6;13)	0.87
Aetiology (%)			
• Alcohol	37	25	
• Viral	39	32	
• Other	24	46	
Hepatocellular carcinoma (%)	41	12	≤0.001
MELD (median and IQR)	12 (9;16)	12(9;16)	0.20
Child class%			
• A	36	37	
• B	36	46	
• C	28	17	
Past overt HE (%)	57	65	0.10
No present signs of HE (even minimal) (%)	41	missing	
Minimal HE (EEG/PHES) (%)	22	34	0.53
HE grade ≥1 (%)	37		
PHES (median and IQR)	−1 (−4 to 1)	−1.5 (−5 to 0)	0.52
EEG- MDF(Hz)	10 (8–11)	10(8–11)	0.94
CFF (Hz)*	42 (39–44)	41(38–45)	0.77
Ammonia (mmol/L)	57 (31–68)	62(35–90)	0.05
Portal Vein Thrombosis (%)	24	19	
Previous variceal haemorrhage (%)	24	23	0.96
Refractory Ascites (%)	12	12	0.37
Ascites history (%)	60	54	0.25
Oesophageal varices (%)	63	68	0.88

Note: Data in median (IQR) or% Chi-Square test or Mann Whitney U Test.
* Performed in only 38% of the patients.

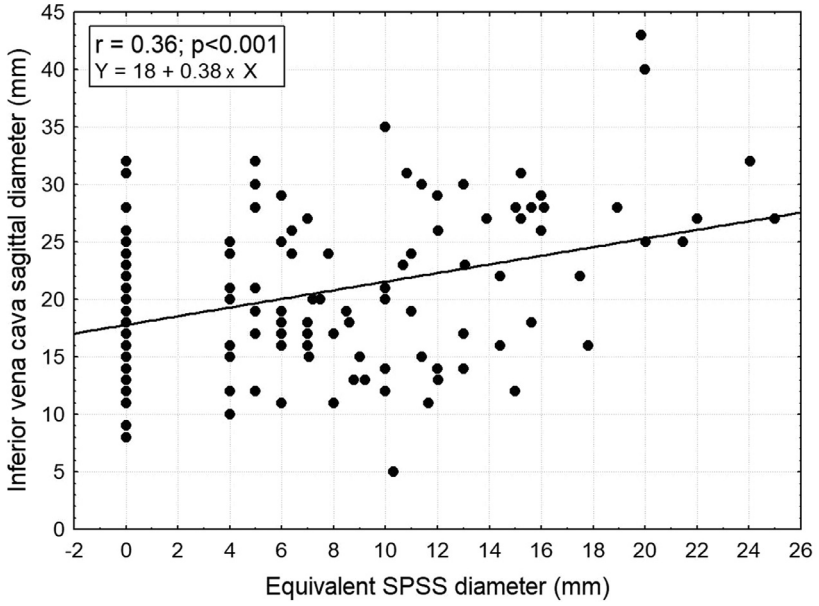

Fig. 2. Correlation between the SPSS size (equivalent SPSS diameter) and the sagittal (antero-posterior) diameter of the IVC. The plot shows that a wide IVC diameter tends to be a sensitive index of wide SPSS; however, it does nor result to be specific, since various factors influence IVC diameter.

Table 2
Relationship of the SPSS size (equivalent SPSS diameter) and the main demographic/clinical variables.

	No SPSS ($n=38$, 30%)	Small SPSS ($n=31$, 24%)	Large SPSS ($n=26$, 20%)	Very Large SPSS ($n=32$, 25%)
Age (years) (median and IQR)	61 (52;66)	56 (51;66)	58 (52;64)	57 (52;65)
Gender (male%)	68 $CI_{95\%}$: (53–81)	68 ($CI_{95\%}$:50–81)	81 ($CI_{95\%}$:62–91)	81 ($CI_{95\%}$:65–91)
Education(years)	8 ($CI_{95\%}$:7–13) *	8 ($CI_{95\%}$:5–13)	8 ($CI_{95\%}$:7–11)	9.5 ($CI_{95\%}$:8–13)
Aetiology (%)				
Alcohol (males 78%)	21 ($CI_{95\%}$:11–36)	45 ($CI_{95\%}$:29–62)	46 ($CI_{95\%}$:29–65)	41 ($CI_{95\%}$:26–58)
Viral (males 64%)	50 ($CI_{95\%}$:35–65)	29 ($CI_{95\%}$:16–47)	42 ($CI_{95\%}$:26–61)	34 ($CI_{95\%}$:20–52)
Other (males 83%)	29 ($CI_{95\%}$:17–45)	26 ($CI_{95\%}$:14–43)	38 ($CI_{95\%}$:22–57)	25 ($CI_{95\%}$:13–42)
HCC (%)	55 ($CI_{95\%}$:38–70)	35 ($CI_{95\%}$:19–54)	29 ($CI_{95\%}$:14–50)	40 ($CI_{95\%}$:23–59)
MELD (median and IQR)	11 (8;15)	12 (9;16)	13 (10;18)	12 (10;14)
Child-Pugh (%)				
Class A	50 ($CI_{95\%}$:34–66)	34 ($CI_{95\%}$:20–53)	39 ($CI_{95\%}$:22–59)	15 ($CI_{95\%}$:6–34) *
Class B	25 ($CI_{95\%}$:14–41)	34 ($CI_{95\%}$:20–53)	30 ($CI_{95\%}$:16–51)	58 ($CI_{95\%}$:39–74)
Class C	25 ($CI_{95\%}$: 14–41)	31 ($CI_{95\%}$:17–49)	30 ($CI_{95\%}$: 16–51)	27 ($CI_{95\%}$:14–46)
Portal Vein thrombosis§	8 ($CI_{95\%}$: 3–21)	26 ($CI_{95\%}$: 14–43)	15 ($CI_{95\%}$: 6–34)	47 ($CI_{95\%}$: 31–64) *
Refractory ascites	8 ($CI_{95\%}$: 2–24)	20 ($CI_{95\%}$: 8–42)	11 ($CI_{95\%}$: 3–31)	12 ($CI_{95\%}$: 4–31)
History of ascites	62 ($CI_{95\%}$:45–77)	71 ($CI_{95\%}$:51–85)	47 ($CI_{95\%}$:26–69)	52 ($CI_{95\%}$:32–72)
Ascites degree (median and IQR)	2 (1;2)	2 (1;2)	1 (1;1.5)	1 (1;2)
Mean grade (ascites + varices) (median and IQR) §	1.5 (0.5;2)	2.0 (1;2)	1.0 (1;1.5)	1.0 (1;1)

§ $p<0.05$ (Kruscal-Wallis ANOVA);.
* $p \leq 0.05$ Very large SPSS vs. No SPSS.

Fig. 2). An anteroposterior IVC diameter >19.5 mm was found to have sensitivity 83% and specificity 50% for a SPSS equivalent diameter ≥12 mm (AUROC=0.77, $CI_{95\%}$:0.68–0.87, $p=<0.001$).

Similarly, the LRV diameter was found to be highly correlated with the size of spleno-renal SPSS ($R=0.70$ $p<0.001$). A diameter≥10.5 mm of the LRV was found to have sensitivity 0.77 and specificity of 0.68 for the existence of a spleno-renal shunt (AUROC=0.81, $CI_{95\%}$:0.75–0.89, $p<0.001$).

3.2. SPSS size and the clinical features of liver disease

The relationships between the width of the equivalent SPSS diameter and the main demographic/clinical variables are shown in Table 2.

3.2.1. Severity of liver disease

The prevalence of SPSS was 56% ($CI_{95\%}$ 41–70) in Child-Pugh class A, 78% ($CI_{95\%}$ 63–88) in class B and 72% ($CI_{95\%}$ 55–84) in class C; thus, the risk for the occurrence of SPSS was higher in class B-C patients (75% $CI_{95\%}$64–84) than in class A patients ($p<0.04$), odds-ratio 2.4 ($CI_{95\%}$ 1.1–5.4).

Of note, patients with very large shunts were not more class C than class B, actually a not-significant ($p=0.2$) trend in the opposite direction was found: class $C=30\%$ ($CI_{95\%}$ 16–51) vs. class $B=47$ $CI_{95\%}$ 31–64), odds-ratio 0.5 ($CI_{95\%}$ 0.2–1.5).The SPSS equivalent diameter did not correlate with the common indices of liver function: bilirubin, albumin, INR, sodium, MELD score. Upon dividing the population in 2 groups-with or without shunt, there was still no significant difference in any of these variables.

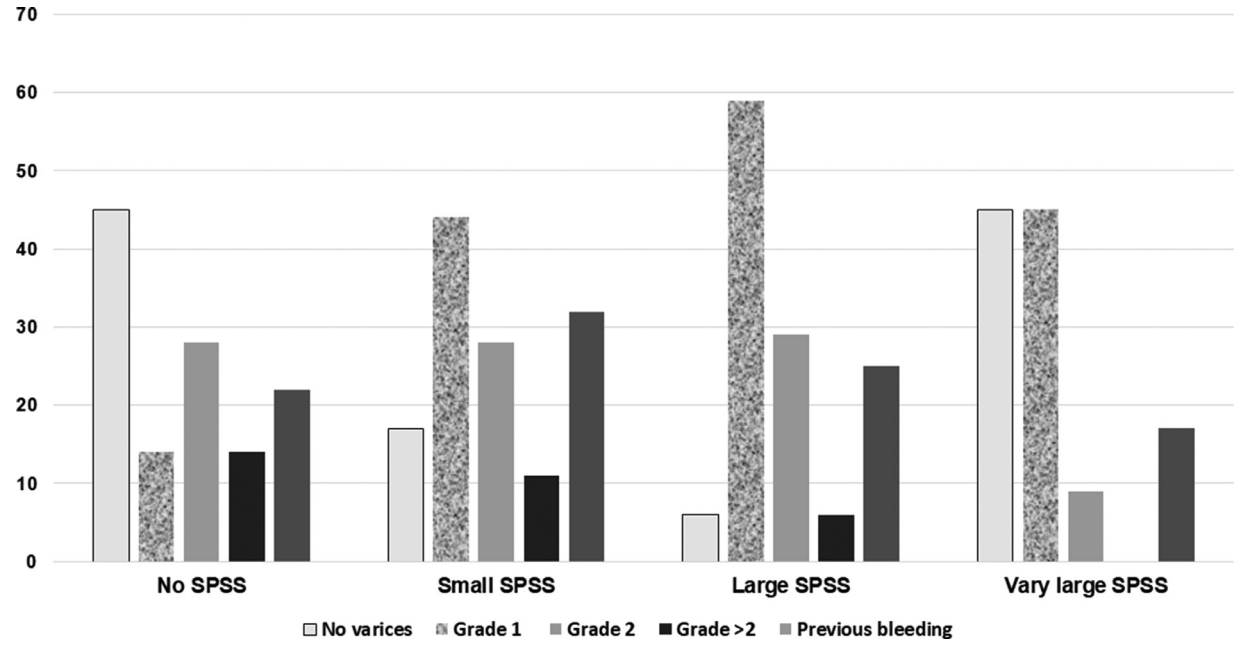

Fig. 3. Relationship between SPSS size (equivalent SPSS diameter) and the degree of oesophageal varices and bleeding. Of note, patients with very large shunts do not have large varices, as if very large shunts may represent an alternative route of outflow.

3.2.2. Etiology of liver disease

The prevalence of SPSS was higher in the patients with alcoholic than in those without alcoholic aetiology 83% ($CI_{95\%}$ 70–91) vs. 63% ($CI_{95\%}$ 52–72) $\chi^2 = 5.0$ $p = 0.03$ (odds-ratio=2.9, $CI_{95\%}$ 1.2–7.1), notwithstanding the severity of liver disease was at least not higher in the patients with alcoholic than in those with non-alcoholic aetiology (alcoholic cirrhosis: class A = 37%, class B = 36%, class C = 27%, non-alcoholic cirrosis: class A = 35%. class B = 35%, class C=29%, $\chi^2 = 0.02$, $p = 0.98$).

3.2.3. Portal vein thrombosis

The prevalence of portal vein thrombosis was significantly higher in the subjects with SPSS (30%; $CI_{95\%}$ 22–41-) than in those without SPSS (8%; $CI_{95\%}$ 3–21), $\chi 2 = 7.4$ $p<0.01$, odds-ratio 5.1 ($CI_{95\%}$ 1.4–18.0). Further, the patients with very large equivalent SPSS diameter had higher prevalence of portal vein thrombosis (47%; $CI_{95\%}$ 31–63) than those with a smaller equivalent SPSS diameter (21%; $CI_{95\%}$ 12–33), $\chi 2 = 6.5$ $p<0.02$, odds-ratio 3.3 ($CI_{95\%}$ 1.3–8.5). The risk for portal-vein thrombosis was associated with the kind of SPSS ($\chi 2 = 18$, $p<0.001$): the subjects with paraumbilical shunt had lower risk for thrombosis than those with splenorenal shunt (odds-ratio 0.27 $CI_{95\%}$: 0.08–0.79) or other kind of shunts (odds-ratio 0.18 CI95%: 0.05–0.74), for all $p<0.02$.

3.2.4. Oesophageal varices

The relationship of the equivalent SPSS diameter and oesophageal varices degree [19] is shown in Fig. 3: it did not result to occur by chance ($\chi^2 = 20$, $p<0.02$). Indeed, the presence of very large oesophageal varices resulted inversely related to the size of the equivalent SPSS diameter ($p<0.05$), and the absence of varices had a clear reverse U relationship with the equivalent SPSS diameter: the patients without SPSS or with very large SPSS had less varices than those with SPSS of low or large equivalent diameter.

3.2.5. Ascites

The prevalence of refractory ascites tended to be lower in the patients without SPSS (8%, $CI_{95\%}$ 2–24) than in those with SPSS (14%; $CI_{95\%}$ 8–25), but the difference was not significant. The ascites degree, assessed as usual in the Child-Pugh classification [20], showed a non-significant trend to be lower in patients with large SPSS. Of note, considering that both oesophageal varices and ascites are related to portal hypertension, the information obtained by their severity was aggregated (both have a three-grade classification), computing the mean of the grade of ascites and oesophageal severity. The risk for severe ascites/severe varices in the patients with very large SPSS was lower than in the those without very large SPSS (odds-ratio 2.9 ($CI_{95\%}$ 1.2–6.2) $p = 0.02$) (Table 2).

3.2.6. Hepatic encephalopathy

The patients who had at least one previous episode of overt HE had a significantly larger SPSS equivalent diameter than the patients who did not have previous episodes of overt HE: 9.2 mm (IQR 0–12) vs. 4 mm (IQR 0–8.5), $p = 0.03$ (Table 3). Further, the patients with a very large equivalent SPSS diameter had a higher risk to have present minimal or overt HE (odds-ratio =2.37; $CI_{95\%}$:1.47–6.19) than the other patients; further, the patients with at least a large equivalent SPSS diameter had a higher risk for having had previous bouts of overt HE (odds-ratio=3.63; $CI_{95\%}$: 1.56–8.41).

The SPSS equivalent diameter correlated significantly with the PHES (Spearman R −0.27, $P = 0.046$) and mean dominant frequency on EEG ($r = 0.27$, $P = 0.004$), but not with critical clicker frequency. At any rate, when the presence vs, the absence of SPSS was considered, CFF was found to be lower in the patients with SPSS than in those without SPSS (39.6 Hz, IQR 37.0–42.6 vs. 42.4 Hz, IQR 40.0–46.2 Hz), similarly the PHES (−2, IQR −7–0 vs. 0, IQR −2.5 to 2.0) and the MDF of the EEG (9.9 Hz, IQR 8.0–10.9 vs 10.4, IQR 9.1–12.2) were lower in the subjects with SPSS then in those without shunt (for all $p<0.05$).

The SPSS equivalent diameter was correlated with plasma ammonia levels ($r = 0.43$, $P<0.001$) and the patients who had SPSS had higher ammonia than those without SPSS (51 μmol/L, IQR 43–80 vs. 35, IQR 23–5, $p<0.001$).

Of note, the IVC diameter was found to be directly correlated with plasma ammonia ($r = 0.28$, $p<0.01$) and inversely with the PHES ($r=-0.46$ $p<0.01$). An IVC diameter ≥19.5 cm showed a trend for an association with previous episodes of overt HE (63% vs. 48% $p = 0.08$).

Table 3
Relationship of the SPSS size (equivalent SPSS diameter) and HE/ammonia.

	No SPSS ($n=38$, 30%)	Small SPSS ($n=31$, 24%)	Large SPSS ($n=26$, 20%)	Very Large SPSS ($n=32$, 25%)
Asterixis (%)	21 ($CI_{95\%}$: 9–40)	19 ($CI_{95\%}$: 7–43)	12 ($CI_{95\%}$: 3–34)	35 ($CI_{95\%}$: 18–57)
Previous overt HE (%)	47 ($CI_{95\%}$: 31–64)	40 ($CI_{95\%}$: 23–59)	85 ($CI_{95\%}$: 64–95)[§]	65 ($CI_{95\%}$: 46–81)
Overt HE (%)	37 ($CI_{95\%}$:23–54)	32 ($CI_{95\%}$:18–51)	30 ($CI_{95\%}$:16–51)	48 ($CI_{95\%}$:31–66)
Minimal HE (%)	17 ($CI_{95\%}$:8–33)	21 ($CI_{95\%}$:10–40)	26 ($CI_{95\%}$:13–36)	26 ($CI_{95\%}$:13–45)
Ammonia (μmol/L)[§] (median and IQR)	35 ($CI_{95\%}$:23–53)	48 ($CI_{95\%}$:30–67)	52 ($CI_{95\%}$:43–73)[*]	61 ($CI_{95\%}$:43–120)[*]
PHES (median and IQR)	0 (−2.5; 2)	−3.5 (−4; −1)	−1 (−2; 0)	−1 (−7; 1)
CFF(Hz) (median and IQR)	40 (37; 43)	42 (40–47)	41 (40; 46)	42 (39; 46)
EEG MDF(Hz) (median and IQR)	10.4 (9.1; 12.2)	10.3 (9.4; 11.5)	10.1 (8.0; 10.8)	(7.8;10.5)[*]

[§] $p<0.05$ (Kruscal-Wallis ANOVA).
[*] $p<0.05$ vs. No SPSS.

4. Discussion

This study confirmed that SPSS are common in cirrhosis, and among them, SRS and paraumbilical vein patency are the most common. Since multiple SPSS in the same patient occur frequently (in our series in about 70% of patients) a novel index to comprehensively estimate the extent of SPSS was calculated; i.e., the SPSS equivalent diameter. This index correlated with measures of overt and minimal HE (previous bouts of HE and present psychometrical and neurophysiological measures) and plasma ammonia level. In addition, it provided insight into the relationship with oesophageal varices. Of note, a dilated IVC was found a simple marker of the presence of huge SPSS, which presumably leads to additional flow into the systemic circulation. Similarly, a dilated LRV predicted the presence of SRS. These simple measures on contrast enhanced CT or MRI may be quick detection tools for some features of cirrhosis which often go unreported in routine scans.

The frequent presence of multiple SPSS warrants inclusion of all shunts when assessing the implications on liver disease. Therefore we accounted for total burden of shunting with a comprehensive index- SPSS equivalent diameter [21]. A similar approach was used by a recent paper [22], which considered total shunt area. However, the use of the equivalent shunt diameter is more intuitive than total area (even if it is the same measure divided by a fix parameter), as it is easier to comprehend linear rather than area dimensions [23,24] . In fact, TIPS and vessel size are referred by diameter and not by their area.

The prevalence of SPSS in our series of patients with cirrhosis was higher than some previous studies. Zardi et al. [25] in Italy found about 40% prevalence of SPSS on an US. However, US may under-estimate the occurrence of SPSS. Saks et al. [26] showed a prevalence of 23% based on CT scan for liver transplantation, but accounted only for splenorenal shunts. In contrast, the prevalence that we found is in line with the wide study by Simón-Talero et al. [1] who found 60% prevalence of SPSS using abdominal CT. Our series had marginally higher prevalence of SPSS, possibly due to a higher proportion of Child class C in our study (28%) compared to Simon-Talero et al. (19%). Moreover, as our unit is oriented to HE care, there may have been a referral bias towards more patients with history of HE, which might explain a higher prevalence of SPSS.

Our study corroborated a rough relationship between SPSS and the severity of cirrhosis already proved by Simón-Talero et al. [1] The higher risk for SPSS in subjects with alcoholic aetiology too is in agreement with previous observations. Possibly alcohol has some angiogenetic action. Also, periods of higher portal pressure caused by enlarged, steatotic hepatocytes may force collateral opening.

The equivalent SPSS diameter was useful to investigate what Kumamoto et al. [27] called the *portosystemic shunt syndrome*. This syndrome was described by Saad et al. [28] who suggested the existence of three stages: the first characterized by large SPSS with good liver function, the second with good liver function but with HE, the third with shunt and liver failure characterized by the occurrence of ascites and jaundice, frequently with portal vein thrombosis. Our data emphasized the association between large SPSS and portal thrombosis. This is likely consequent to sluggish portal venous flow due to its diversion into shunt. This has previously been described in post-transplant settings [26]. In addition, liver insufficiency alters blood coagulability and increases the risk for thrombosis [29]. However, from our cross-sectional study it is also possible to argue that thrombosis came first and predisposed to the development of shunts. This is a limit of the study that lacks prospective observations.

Intriguing and novel observations were obtained about the link oesophageal varices and SPSS, probably facilitated by the use of the equivalent SPSS diameter. We observed a reverse U-shaped relationship between oesophageal varices and SPSS equivalent diameter; i.e. the patients without SPSS or with very large SPSS had lower prevalence of oesophageal varices than those with small or large SPSS. A similar pattern was seen with refractory ascites, which was less common in patients with very large SPSS. This is explainable by the fact that the absence of SPSS indicates low portal pressure, while on the other hand, a very large SPSS may act as an auto-TIPS reducing portal pressure and decompressing the varices.

Why some patients developed larger shunts leading to better control of portal hypertension is curious. Different levels of individual predisposition to high vein/shunt compliance in splanchnic district, and possibly different levels of pro-angiogenic milieu may be responsible for differences in type of SPSS. Further, the distension of vein will increase wall tension (which is proportional to vessel radius x pressure) leading to further distension, as occurs for arterial aneurisms. In addition, it should be admitted that once dilated, the shunt wall does not reduce with the decrease of portal pressure. This reflects the hysteresis properties of vein wall that does not retour at its previous length after strain. This is proved by the observation that SPSS persist after liver transplantation [30], although they may reduce in size [31].

It is also possible that only those who could tolerate the high degree of shunting without decompensations survived, creating a survivorship bias. Interestingly, we noted that many of these large

shunts actually persisted for years in well compensated patients (data not shown), further bolstering the adaptive nature of this phenomenon in some patients.

At any rate the extent of SPSS was confirmed to be clearly related to the occurrence of overt HE, in line with previous observations [2,4,15,19] and with the prospective Praktinjo et al's multicentre study that used total shunt area [22]. Our study emphasized that SPSS is related to brain dysfunction, assessed by psychometry and brain electrogenesis(EEG). Fasting ammonia level too appeared a rough, but simple biochemical marker of the existence and extent of SPSS, in agreement with Tarantino et al. [32] Thus, the clinical impact of *portal-systemic shunt syndrome* [33], together with the simplicity to suspect its existence by properly done fasting ammonia measuring, suggest that its routine introduction in clinical hepatology is reasonable.

Increased flow bypassing from portal into systemic circulation could led to dilation of systemic vessels. The anteroposterior diameter of IVC >19.5 mm (measured at the level between the bifurcation of portal vein and the confluence of hepatic veins) predicted the presence of substantial degree of portosystemic shunting (SPSS equivalent diameter ≥ 12 mm) and can serve as a simple and quick observation to suspect their presence. Similarly, dilated left renal vein predicted SRS, an observation that lead some authors to emphasize the use of the splenic-portal vein ratio as an index of SRS [34]. It should be noted that the diameter of IVC may be affected by various other parameters like compression by caudate lobe, volume status, diastolic function of the heart. Therefore, this criterion is not specific, and only may serve only as an indicator to actively look for a SPSS.

Our study has limits: it is a retrospective and monocentric study and, thus, selection bias cannot be excluded; in addition, radiological evaluation was performed together by two of the authors (SR and SB), thus the limit of the repeatability across various assessor was not considered. In addition, no measure of flow direction and its extent was obtained and the effects of beta-blockers and other drugs was not taken into account. Only a prospective and multicentre study can provide conclusive data about the many issues involved in SPSS.

In conclusion, our study provided: *i)* additional information about the prevalence and implication of SPSS in cirrhosis, in particular about minimal and overt HE, *ii)* a novel way to manage the information coming by multiple SPSS, by the use of the equivalent SPSS diameter *iii)* cues for simple signs of SPSS both on routine cross-sectional imaging (IVC and renal vein dimensions) and on biochemical screening, supporting the use of routine measuring of fasting ammonia in cirrhosis assessment.

Declaration of Competing Interest

In the name of all the authors, I undersigned Piero Amodio, declares that no Author has any conflict of interest with the paper.

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