



Original article

Spontaneous portosystemic shunt embolization in liver transplant recipients with recurrent hepatic encephalopathy

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ABSTRACT

Introduction and objectives: Spontaneous portosystemic shunts (SPSS) are a common cause of recurrent hepatic encephalopathy (HE). Shunt occlusion is an effective and safe procedure when performed in patients with cirrhosis and preserved liver function. We aimed to describe our experience with SPSS embolization after liver transplantation (LT).

Patients: We identified five patients who underwent SPSS embolization after LT. Clinical, biochemical and technical procedure data were collected.

Results: At presentation, all patients had developed graft cirrhosis and HE after LT. Median Model for End-stage Liver Disease (MELD) at embolization was 9 (range 7–12), median Child-Pugh was 8 (range 7–9). Splenohepatic and mesocaval shunt were the most frequent types of SPSS found. Three patients have been completely free of HE. Of the two patients who had HE recurrence after embolization, one patient had two episodes of HE which was controlled well with medications. The other patient required three embolizations because of recurrent HE. Median follow-up was 4.4 years (range 1.0–5.0) and MELD score at last follow up was 13 (range 10–18) and median Child-Pugh score B, 7 points (range 5–12).

Conclusions: SPSS can be considered as a cause of HE after LT. SPSS embolization is feasible and safe in LT recipients.

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1. Introduction

Portal hypertension secondary to chronic liver disease leads to a compensatory response that forms collateral blood vessels known as portosystemic shunts. Spontaneous portosystemic shunts (SPSS) are present in approximately 45–70% of patients with cirrhosis and

recurrent or persistent hepatic encephalopathy (HE) [1–4]. HE can be a remarkable cause of morbidity due to impairment of patient's functionality and autonomy [4,5]. Percutaneous embolization of large SPSS is an option for those patients with preserved liver function. In well-selected patients, it is an effective and safe procedure to decrease recurrent HE and to improve the quality of life of patients with cirrhosis [6–9]. Also, liver function and survival might improve in those patients with modestly preserved liver function [8,10–13].

Liver transplantation (LT) is the definitive treatment for end-stage liver disease and its complications, but SPSS may persist after LT, causing HE even with normal liver function [9,14–17]. Moreover, LT recipients can develop graft cirrhosis and have portal hypertension manifestations, including HE, related to SPSS already present before LT or newly developed ones.

Abbreviations: CT, computed tomography; HCV, hepatitis C virus; HE, hepatic encephalopathy; LT, liver transplantation; MELD, Model for End-stage Liver Disease; PVT, portal vein thrombosis; SPSS, Spontaneous portosystemic shunts

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The impact of SPSS in the LT setting is broad, and may be related to the “portal flow steal phenomenon”. It can be associated with major postoperative morbidity [18], due to a diminished portal flow or peri-operative portal vein thrombosis (PVT), especially if SPSS are large [18–21]. For these reasons, some groups have advocated for intraoperative shunt ligation [18,22–24]. However, other groups have shown no differences on outcomes after LT, between patients with and without SPSS before LT [25].

The possibility of SPSS embolization after LT has hardly been explored, though the few reported cases have illustrated that SPSS embolization is an effective and safe option to treat HE after LT [7,14–16,26].

Therefore, we report here our experience with embolization of SPSS as a treatment of refractory HE in LT recipients with graft cirrhosis, and we describe the efficacy and safety of the procedure in this population. We also describe the characteristics of the SPSS in our series

2. Patients and methods

2.1. Study population and design

All LT recipients who underwent percutaneous embolization of SPSSs at the Hospital Universitari Vall d'Hebron were retrospectively identified. The Vall d'Hebron Institutional Review Board approved this study.

2.2. Definitions and outcomes

2.2.1. Hepatic encephalopathy and treatment

HE was characterized according to West Haven criteria and number of episodes. Recurrent HE was defined as bouts of HE in a time interval of 6 months or less, according to current guidelines [27].

Standard medical treatment consisted of lactulose with or without rifaximin. According to previous studies, the degree of disability was assessed by the Modified Rankin Scale [28].

2.2.2. Spontaneous portosystemic shunts

Computed tomography (CT) images were reviewed for the purpose of this study by an expert radiologist with experience in SPSS evaluation. Splenomegaly was defined as a longitudinal diameter equal or larger than 13 cm.

The method of shunt occlusion, vascular access and complications related to the embolization were collected.

2.2.3. Statistical analysis

For this descriptive analysis, quantitative variables are presented as median and range, and categorical variables as frequency. STATA v13 (College Station, TX, USA) was used for all statistical analyses.

3. Results

Five LT recipients that underwent seven SPSS embolizations between June 2014 and December 2019 were identified. The demographic and baseline, clinical and biochemical characteristics are presented in Table 1. Three of the five patients were male, and median age at LT was 59 years (range 46–65). The indication for LT was hepatitis C virus (HCV) in four patients, and alcohol-related liver disease in one. Four of the five patients had presented with HE before LT. These four patients had SPSS identified in the pre-LT evaluation (pre-LT CT images from the remaining patient were impossible to obtain).

Table 1

Pre liver transplantation demographic and baseline clinical characteristics of embolized patients (n=5)

Age at LT, years, median (range)	59 (46–65)
Male, n	3
Comorbidities at LT, n*	
None	2
Hypertension	1
Diabetes Mellitus	2
Obesity	1
Indication for LT, n	
HCV	4
Alcohol-related liver disease	1
Hepatocellular carcinoma, n	3
MELD at LT	15 (11–28)

HCV, hepatitis C virus; LT, liver transplantation; MELD, Model for End-stage Liver Disease

*One patient with diabetes mellitus associated arterial hypertension.

3.1. Surgical management

None of the patients had PVT at LT. None of the SPSS were intraoperatively ligated. Intraoperative hepatic flow measurements, are shown in Table 2.

3.2. Patients' outcomes. Hepatic encephalopathy and portal hypertension

All five patients developed post-LT graft cirrhosis after a median time of 3.6 years (range 1.1–11.2), four HCV recurrence-related cirrhosis, and one de novo hepatitis B infection-related cirrhosis (Table 3). All five patients had a clinical diagnosis of cirrhosis. Besides, among the patients with HCV-related graft cirrhosis, two patients had a liver a biopsy, and in the other two a fibroscan was performed in all the cases confirming the clinical diagnosis.

All patients had presented with between two and four episodes of HE after LT and before first SPSS embolization. According to West Haven criteria all patients had recurrent grade 1 or 2 HE, except one who had experienced two episodes of grade 4 HE, and had needed admission to the intensive care unit and orotracheal intubation once. Medical treatment of recurrent HE consisted of lactulose and rifaximin in all patients (Table 3). One patient with large gastroesophageal varices underwent endoscopic band ligation before embolization. Only one patient had presented with ascites before shunt occlusion, and none had had variceal bleeding, spontaneous bacterial peritonitis or hepatorenal syndrome. One patient had partial PVT before SPSS embolization. In relation to patient's functionality and autonomy before embolization, only one patient was classified as “slight disability” according to the Modified Rankin Scale. None of the patients received treatment with drugs that could worsen the HE, such as opioids or benzodiazepines.

3.3. SPSS embolization

All patients were embolized once, except one patient who underwent three embolizations over two years due to clinical recurrence of HE and SPSS persistence after the first procedure. Main characteristics are detailed in Table 2.

Median age at first embolization was 69 years (range 58–73), with a median interval of time between LT and first procedure of 9.4 years (range 3.3–11.6) and a median interval of time between first episode of HE and embolization of 2 months (range 1–22).

Regarding the type of shunt, splenorenal and mesocaval SPSS were found twice, and the preferred method for shunt occlusion was Onyx 34® (ethylene vinyl alcohol) combined with coils via right

Table 2
Characteristics of SPSS and embolizations

Patient	Type of SPSS before LT	Intraoperative Portocaval shunt flow (mL/min)	Age at first embolization (years)	Type of SPSS embolized after LT	Diameter of embolized shunt (mm)	Number of embolizations	Time from HE to CT (days)	Time from LT to first embolization (years)	Time from first episode of HE to first embolization (months)	Method of SPSS occlusion	Access to embolization
1	Mesocaval	1400	69	Mesocaval	8	2	150	3.3	22.0	Coils + Onyx 34®	Right IJV (2)
2	NA	1000	73	Splenorenal	NA	1	52	9.5	2.1	Glue + Amplatzer	Right IJV
3	Gastrorenal	NA	66	Gastroesophageal	NA	1	21	8.4	1.8	Coils + Onyx 34®	Transhepatic
	Coronary vein dilatation			Gastrorenal	18						Bilateral FV
4	Splenorenal	1400	71	Splenorenal	7	1	46	11.6	7.9	Coils	Right FV
5	Mesocaval	1000	58	Mesocaval	7	1	35	11.5	1.6	Coils + Onyx 34®	Right IJV
	Splenorenal										

CT, computed tomography; FV, femoral vein; HE, hepatic encephalopathy; IJV, Internal jugular vein; LT, liver transplantation; NA, not available; SPSS, spontaneous portosystemic shunt

3

Table 3
Patients outcomes, hepatic encephalopathy and portal hypertension complications after LT

Patient	Cause of graft cirrhosis	Time from LT to de novo cirrhosis (years)	Time from LT to first episode of HE (years)	Portal hypertension signs	Pre-embolization cirrhosis decompensation	Number of HE episodes (before first embolization)	Worst Grade of HE (West Haven)	Follow-up after embolization (years)	Survival
1	HCV recurrence	1.1	1.5	Splenomegaly Large	HE	4	Grade 2	4.4	No
2	HCV recurrence	3.6	9.3	GEV PHG	Ascites				
3	HCV recurrence	4.6	8.2	Small GEV GAVE	HE	2	Grade 1	4.9	Yes
				Splenomegaly Small	HE	2	Grade 2	5.0	Yes
				GEV PHG					
4	HCV recurrence	1.9	10.9	Splenomegaly Small	HE	3	Grade 1	1.2	Yes
				GEV PHG					
5	de novo HBV	11.4	11.3	Splenomegaly	HE	2	Grade 4	1.0	Yes

GAVE, Gastric antral vascular ectasia; GEV, gastroesophageal varices; HBV, hepatitis B virus; HCV, hepatitis C virus; HE, hepatic encephalopathy; LT, liver transplantation; PHG, Portal hypertensive gastropathy

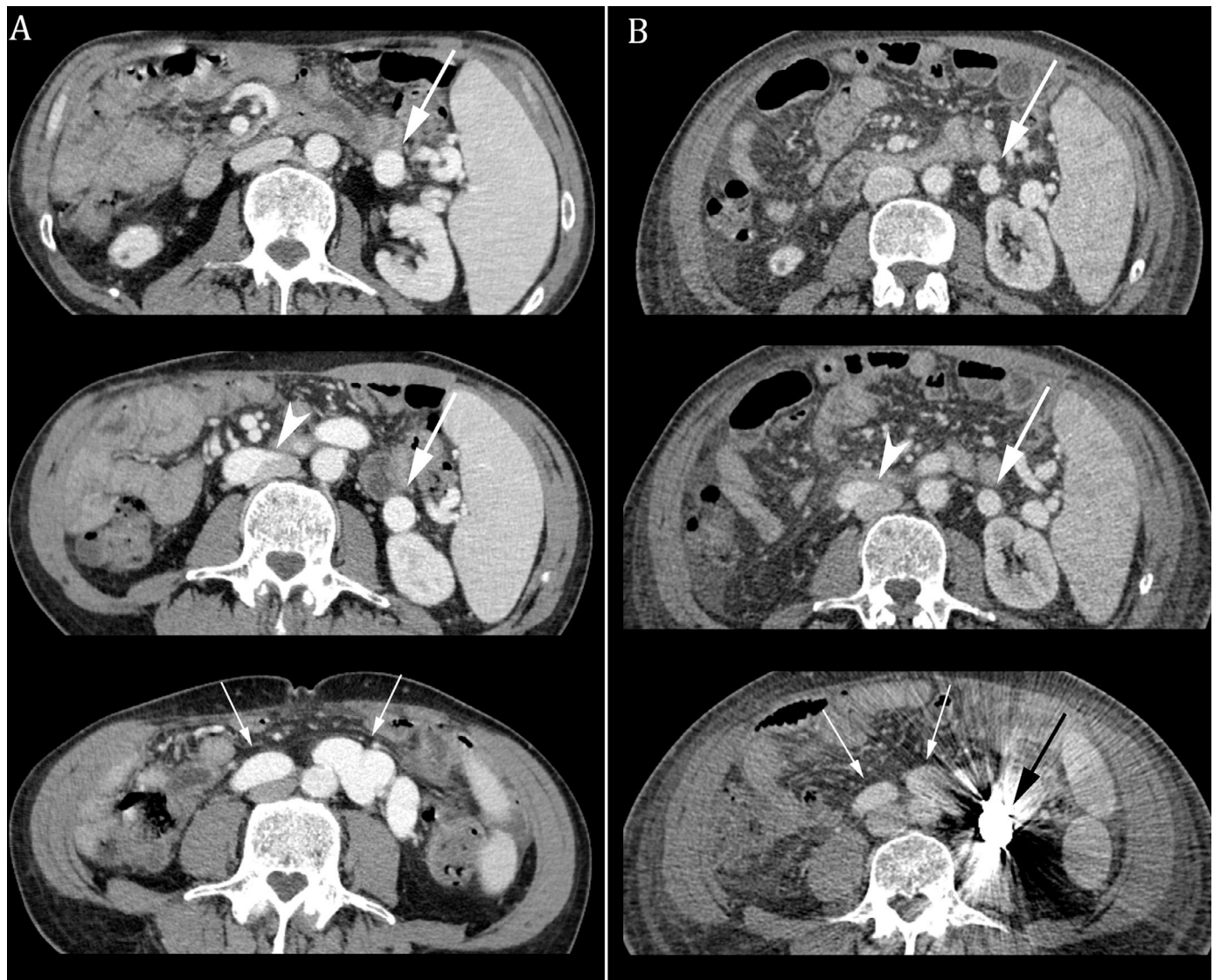


Fig 1. CT images before and after SPSS embolization

Axial contrast enhanced CT images before (A) and after SPSS embolization (B) show a dilated inferior mesenteric vein (arrows), retroperitoneal varices (thin arrows) and a systemic shunt to the inferior vena cava (arrowhead). Note the reduction in diameter (B) of the inferior mesenteric vein, the varicose veins and the shunt, as well as the presence of an artifact secondary to embolization material (black arrow).

CT, computed tomography; SPSS, spontaneous portosystemic shunt

internal jugular vein. The median diameter of the embolized SPSS was 7.5 mm (range 7–18).

One representative CT, and angiographic embolization images from one patient are shown in Fig 1, Fig 2 and Fig 3.

Embolization procedures were performed by the interventional radiology team.

3.4. Morbidity after SPSS embolization

Two patients suffered procedure-related complications. Patient 1 presented with fever as a minor complication after the procedure; blood cultures were negative and the patient was discharged 8 days later under antibiotic treatment.

Patient 3 had Onyx® migration to a small branch of the left pulmonary artery during the procedure, which was immediately and successfully removed.

Liver function parameters before, 30 and 90 days after SPSS embolization and at last follow-up are listed in Table 4. Median Model for End-stage Liver Disease (MELD) score before SPSS embolization, was 9 (range 7–12), and median Child-Pugh score was B, 7 points (range

7–9). Median MELD score 30 days after the procedure was 8 (range 7–11) and median Child-Pugh score A, 6 points (range 5–8).

3.5. Hepatic encephalopathy and portal hypertension after SPSS embolization

During a median follow-up of 4.4 years (range 1.0–5.0), two patients had new episodes of HE after embolization.

Patient 1 underwent three SPSS occlusions. Before first embolization (mesocaval shunt) the patient had experienced four episodes of HE. The patient presented with another episode of HE 51 days after the embolization, so he underwent re-embolization of the same shunt that had been partially occluded. Nine days later, he presented with another episode of HE, well-managed with medical treatment, and another episode 7 months later, after which he underwent embolization of a splenorenal shunt (10 months after first embolization). The patient was free of HE for 10 months following the last embolization, but died 35 months after the first embolization due to complications related to end-stage liver disease, with anasarca,

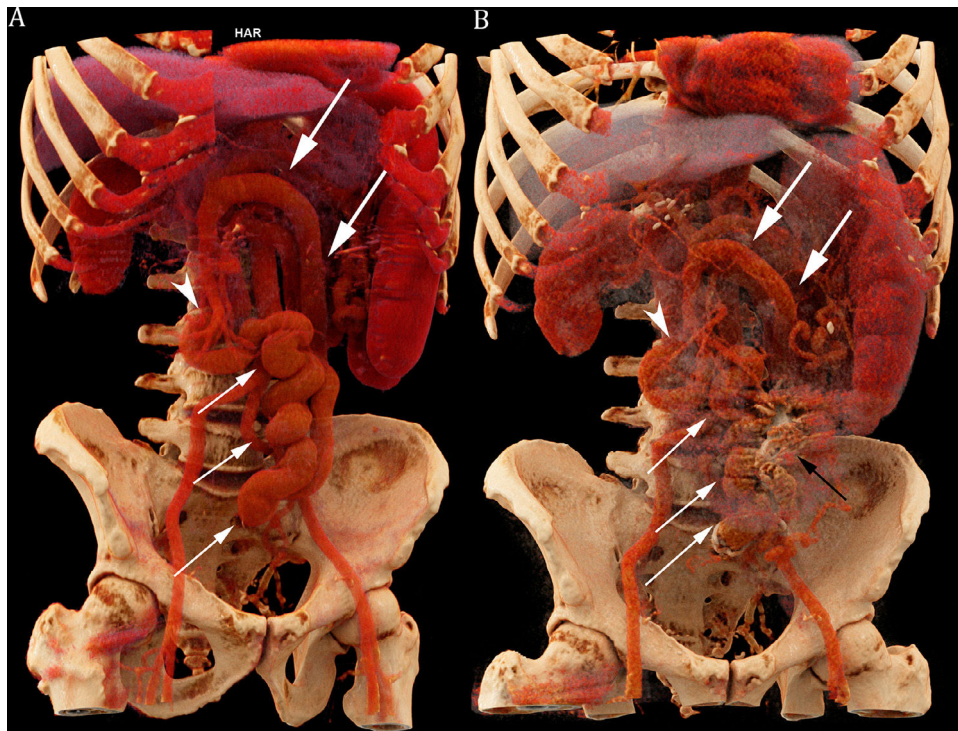


Fig 2. CT volume rendering reconstructions before and after SPSS embolization

CT volume rendering reconstructions before (A) and after SPSS embolization (B) show: inferior mesenteric vein (arrow), mesocaval shunt draining into the inferior vein cava (arrowhead), and retroperitoneal varices (thin arrows). Note the decrease in vessels involved in the mesocaval shunt and an artifact secondary to embolization material (black arrow). CT, computed tomography; SPSS, spontaneous portosystemic shunt

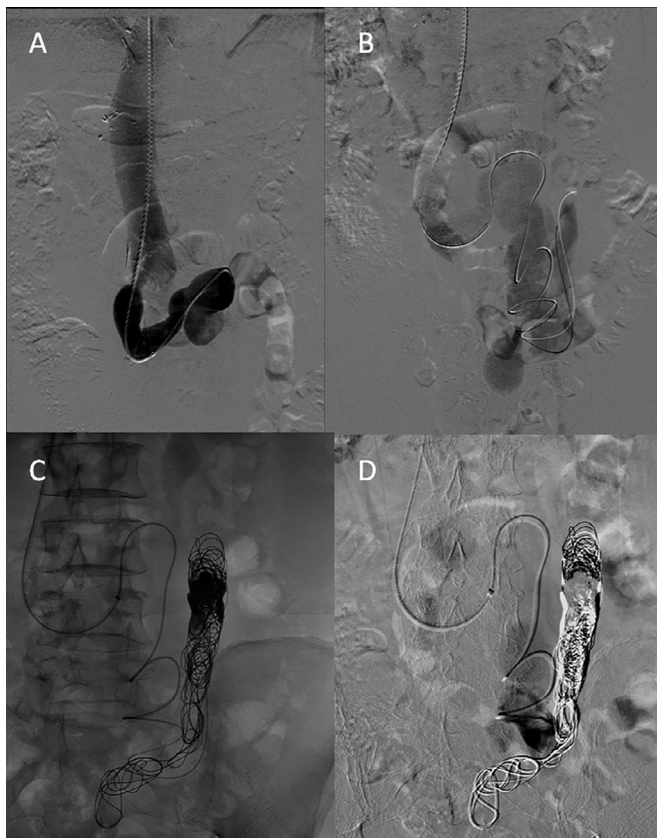


Fig 3. Embolization procedure

(A) Shunt catheterization via right internal jugular vein access. (B) Supraselective catheterization with a microcatheter (2.1Fr Progreat®, Terumo®). (C) Embolization with microcoils (Ruby coils®, Penumbra®) and Onyx 34®. (D) Post-embolization control.

refractory ascites and grade 4 HE. MELD score before each embolization was 8, 7, and 7.

Patient 5 had two episodes of grade 1 HE, well-managed with lactulose, one and nine months after embolization. He developed ascites 6 months after embolization, resolved with diuretic treatment. None of the remaining three patients have presented new episodes of HE or developed other complications of cirrhosis, and all of them maintain a Modified Rankin Scale score of 0 and good quality of life after SPSS embolization.

Regarding gastroesophageal varices, four of the patients had an upper endoscopy performed after embolization, one had no signs of portal hypertension, another had portal gastropathy, and two had small varices. The remaining patient, with known varices before the embolization, was under beta-blockers treatment and refused to have another upper endoscopy. No episodes of bleeding due to portal hypertension-related complications were observed. CTs after embolizations showed no signs of PVT or other vascular complications.

4. DISCUSSION

Positively, we show in this small series that SPSS embolization in LT recipients is feasible and safe. Results are comparable to those reported for non-transplant patients. Hence, we contribute to providing more evidence about the safety and efficacy of large SPSS embolization in cirrhotic patients with recurrent HE, especially in those with relatively preserved liver function [6–9,29]. Treatment options for HE include lactulose/rifaximin as medical treatment, SPSS embolization if these are present, and LT [29–31].

The selection of those non-transplanted patients with cirrhosis who might be candidates to SPSS embolization is not fully established. Different studies have identified patients who can benefit according to MELD score or liver stiffness. Based on these studies, SPSS embolization might be a good option for patients with a MELD

Table 4
Liver function parameters before and after SPSS embolization

	Before embolization	30 days after embolization	90 days after embolization	Last follow-up
Haemoglobin, g/dl, median (range)	10.6 (9.4–11.7)	11.1 (10.7–12.7)	13.1 (10.1–14.7)	10.5 (9.1–12.5)
Thrombocytes, 10 ³ /L, median (range)	67 (43–117)	114 (56–128)	97 (66–147)	87 (44–141)
INR, median (range)	1.2 (1.0–1.3)	1.1 (1.0–1.2)	1.2 (1.0–1.2)	1.2 (1.0–1.6)
Bilirubin, mg/dl, median (range)	1.1 (0.8–3.0)	1.1 (0.8–1.6)	1.2 (1.0–3.2)	1.4 (0.8–5.1)
Creatinine, mg/dl, median (range)	0.9 (0.7–1.3)	0.8 (0.7–1.5)	0.9 (0.6–1.4)	0.9 (0.7–1.6)
Albumin, mg/dl, median (range)	3 (2.2–3.4)	3.2 (2.9–3.7)	3.4 (3.0–4.1)	3.1 (1.7–3.9)
MELD score, median (range)	9 (7–12)	8 (7–11)	11 (8–13)	13 (10–18)
Child Pugh score, median (range)	7 (7–9)	6 (5–8)	6 (5–8)	7 (5–12)

INR, international normalized ratio; MELD, Model for End-stage Liver Disease; SPSS, spontaneous portosystemic shunt

score below 11 or even below 15 and for those patients who due to other reasons are not eligible for LT [6,8,12].

Furthermore, SPSS embolization could avert continuous episodes of HE in patients with good liver function and avoid lengthy waiting times in areas where HE is not considered for MELD exception points, as well as for those who are not candidates for LT or re-LT. Besides, LT could always be offered later if indicated.

The implications of SPSS in the LT setting are diverse. First, SPSS embolization itself may be associated with procedure-related thrombosis, which has been described in up to 10% of the procedures, but without clinical consequences [6]. Second, there is the option to ligate the SPSS while performing the LT. It has been previously shown that in some situations there is a need to intraoperatively occlude previous surgical shunts at the time of transplantation to avoid portal flow steal [32], however surgical approach to SPSS is controversial.

In a retrospective study, that included 66 patients with SPSS that underwent LT [18], SPSS were ligated intraoperatively in 54.4% of the patients. Complications were present in 44.4% and 73.3% of the patients of the ligated and non-ligated SPSS group, respectively, but only when evaluated as a composited endpoint (primary non-function, primary dysfunction, PVT and HE). Patient and graft survival rates were higher in the ligated SPSS group. In the light of these results, this strategy could be recommended to reduce the aforementioned complications.

Nevertheless, other studies have shown different results. Rodríguez et al. evaluated 326 patients with and without documented SPSS before the LT, to assess their impact on patient mortality and graft survival after LT [25]. After comparing patients without, and with small or large SPSS, they found no statistical differences in relation to patient survival and graft survival, suggesting that no steps to correct SPSS intraoperatively are necessary. Even a reduction in SPSS size after LT has been described in 48% of the patients [9].

Four of the five patients described in this report had SPSS and HE before LT. The other patient had not had HE before LT and we cannot confirm or rule out the presence of SPSS before LT. In four patients, portocaval shunt flow was measured and was greater than 1000 mL/min, so the probability of hemodynamic reperfusion of the SPSS was highly unlikely. Whether surgical ligation would have avoided the recurrence of HE will remain an unsolved question, as these patients could also have developed new SPSS despite ligation. We would only advocate for surgical ligation if there is any hemodynamic indication during the procedure, but not to prevent HE.

The persistence or development of new SPSS has to be suspected if HE is present after LT, in patients with normal graft function but especially in patients with graft cirrhosis. To the best of our knowledge, the scarce literature collects only seven LT recipients who underwent SPSS embolization because of HE after LT [7,14–17,26]. Six of them had good graft function and the presence of SPSS has to be interpreted as the persistence of large SPSS after LT. Only one patient had graft cirrhosis [7]. However, all five LT recipients from our series had graft cirrhosis when HE was reported again.

SPSS embolization is a safe and effective procedure when performed at a center with expertise in interventional radiology. In our

series, patients showed an initial improvement in their liver function, with de novo ascites only in one case that was well-managed with diuretic treatment. No other portal hypertension-related complications were present. We propose this approach as a safe and effective option that reduces hospital admissions and morbidity.

This analysis has several limitations. First, the number of patients was small, precluding us to evaluate the relation between SPSS size and severity of the HE.

Second, the prospective-retrospective data collection might have led to some missed data, also the nature of the study did not allow to evaluate the global frequency of HE or SPSS after LT. However, this series gathers information that can be useful for the management of HE in the uncommon scenario of the post-LT setting.

In conclusion, SPSS after LT should be suspected as a cause of HE. SPSS embolization is feasible and safe in LT recipients and can be considered as a final treatment or as a bridge to a second LT.

Conflicts of interest

The authors have no conflicts of interest to disclose

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