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ORIGINAL ARTICLE

Early, late, or no shunt embolization in patients with cirrhosis- and portosystemic shunt–related hepatic encephalopathy

Cyriac Abby Philips[1] · Sasidharan Rajesh[2] · Tom George[2] · Rizwan Ahamed[3] · Meera Mohanan[4] · Philip Augustine[4]

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Abstract

Background Portosystemic shunts (PSS) are associated with recurrent or persistent hepatic encephalopathy (HE), severe portal hypertensive (PHT) complications, and poor survival in cirrhosis patients. Shunt embolization improves HE in patients with recurrent or persistent HE. The role of early shunt embolization (ESE) in comparison with no and late SE (LSE) in cirrhosis patients with PSS and associated clinical outcomes are not studied.

Methods ESE was defined as occlusion of PSS in patients with the first episode of spontaneous HE, while LSE was that when performed in patients with recurrent/persistent PSS-related HE. We retrospectively analyzed (November 2016 to March 2019) clinical outcomes, liver disease severity, and survival between patients undergoing ESE ($n = 22$) vs. LSE ($n = 23$) and compared ESE with matched historical controls ($n = 22$) not undergoing shunt embolization, followed-up for 18 months.

Results Males predominated, and the lienorenal type of shunt was the most frequent. Significantly larger and multiple shunts were noted in the LSE group. Arterial ammonia, total bilirubin, and Child-Pugh scores were significantly higher at baseline in the LSE group. Post-procedure length of stay in the intensive unit (mean 0.6 vs. 2.1 days; $p = 0.04$), infections (31.8% vs. 66.7% beyond 100 days; $p = 0.02$), recurrence of HE in first 9 months (4.5% vs. 28.6%; $p = 0.03$), and liver- and PHT-related clinical events beyond 10 months were significantly higher in LSE compared with those in the ESE group respectively. HE beyond 10 months was comparable between both the groups. 18.2% died in ESE while 60.87% died in the LSE group ($p = 0.002$). Compared with patients on only standard medical care, the occurrence of ascites, variceal bleeding, recurrence of HE, and portal vein thrombosis were significantly lower in those undergoing ESE, even though differences in survival were not significant.

Conclusions Our study demonstrates the benefits of ESE of large PSS in patients with cirrhosis, probably by improving survival through a reduction in liver and PHT events that warrant validation through prospective randomized controlled multicenter trials.

Keywords Ascites · Cirrhosis · Encephalopathy · Portal hypertension · Shunt occlusion

Introduction

The development of portal hypertension (PHT) in cirrhosis leads to the portosystemic collaterals and splanchnic vasodilatation, which can worsen portal pressures. In some patients, PHT leads to the formation of portosystemic shunts (PSS) that impact the natural history of cirrhosis [1]. The development of PSS is not a compensatory mechanism for reducing portal pressures; instead, it is a direct marker of severity of PHT [1, 2]. The most common clinical manifestation related to PSS is hepatic encephalopathy (HE), which may recur in many patients without precipitating factors. This depends on the underlying severity of liver disease as well as the size of PSS (large PSS, diameter ≥ 8 mm) [2]. In a study by Simon-Talero et al., the prevalence of spontaneous PSS (SPSS) was 60% in a large cohort of cirrhosis patients, of whom 28% had large SPSS. The presence and size of SPSS linearly increase with the severity of liver disease and PHT. Cirrhosis patients with SPSS had higher PHT-related complications such as ascites

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✉ Cyriac Abby Philips
abbyphilips@gmail.com

Extended author information available on the last page of the article

Bullet points of the study highlights

What is already known?

- Portosystemic shunts (PSS) in cirrhosis lead to ascites, hepatic encephalopathy (HE), and poor transplant-free survival.
- The embolization of shunts leads to a reduction in HE and improves the quality of life.

What is new in this study?

- Early shunt embolization compared with no or late embolization leads to better reduction in portal hypertension events, lesser frequency of portal vein thrombosis, and improved disease status and survival.

What are the future clinical and research implications of the study findings?

- Management of PSS in cirrhosis early in the course of the disease may help change the natural course of the disease.
- Prospective trials on the timing of shunt occlusion are needed.

and acute variceal bleeding and a lower rate of transplant-free survival. In patients with HE, the occurrence of recurrent or persistent HE leads to poor quality of life. Even in those with preserved liver function (lower model for end-stage liver disease [MELD], 6–9 and Child-Pugh class A), PHT events and progressive liver failure were notable [3]. Portosystemic shunt embolization has been shown to improve PHT-related complications such as recurrent or refractory HE in patients with cirrhosis. Shunt embolization has also been utilized for improving short- and long-term control of variceal bleeding in cirrhosis patients with good survival outcomes in the intermediate-term [4, 5]. Even though multiple large single-center and multicenter series on outcomes associated with PSS embolization in patients with recurrent or refractory HE exist, no study evaluated the utility of early (after the first episode of spontaneous shunt–related overt HE) vs, late (in SPSS-related recurrent or refractory HE) shunt embolization of large PSS in patients with cirrhosis and HE. In this study, we retrospectively aimed to analyze patient outcomes after early (ESE) and late shunt embolization (LSE) of large symptomatic PSS at a single center with a dedicated liver disease treatment unit.

Study objectives

The primary objective was to study patient survival at 18 months between patient groups. The secondary objective was to compare portal hypertensive events such as recurrence of HE, new or worsening ascites, new or worsening variceal bleeding, and sepsis events after shunt embolization between groups.

Methods

Group definitions for inclusion

From November 2016 to March 2019, a retrospective study on cirrhotic patients with PSS undergoing shunt embolization was performed. All patients with cirrhosis and overt HE associated with large (> 8 mm in diameter) PSS on contrast-enhanced computed tomography (CT) imaging undergoing shunt embolization were grouped into two arms. Patients with one episode of overt HE (West Haven grade ≥ 2) requiring in-hospital admission were considered for shunt embolization after informed consent, during the same admission, and grouped into ESE group. Patients with a history of at least two overt HE episodes within 6 months or earlier or those with medically refractory HE (patterns of behavioral alterations that are persistent, in the absence of primary central nervous system diseases, interspersed with relapses of overt HE) requiring intensive unit admission were included in the LSE group and considered for shunt embolization informed consent. Additionally, those patients who developed the first episode of PSS-related overt HE but did not undergo shunt embolization (controls) were also followed-up for clinical events and outcome and compared with the ESE group.

Exclusion criteria

Patients with diagnosed central nervous system diseases such as structural brain disease, vascular disease of the brain, and traumatic brain injury, severe sepsis requiring intensive care admission, hepatocellular carcinoma, refractory ascites, active

variceal bleeding, acute kidney injury, chronic kidney disease, active dyselectrolytemia, and portal vein thrombosis: those on mechanical ventilation; and patients with acute on chronic liver failure were excluded.

Patient selection

The hospital electronic record database was searched, using keywords "shunt" or "shunts," "portosystemic," "refractory," "HE," "recurrent," "encephalopathy," "embolization," "shunt syndrome," and "PSS"—terms to identify all patients with portosystemic shunts undergoing shunt embolization procedure. Patient electronic records and manual assessment of paper records of in-hospital stay were thoroughly reviewed for inclusion based on group definitions—either into early or late embolization groups. Shunt embolization was performed as previously described with modifications and a detailed description of the same is shown in Supplementary Document 1. All patients in the study groups were continued on standard medical management for secondary prophylaxis of HE. The study and retrospective collection of data were approved by the institutional ethics committee and have been performed following the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Statistical analysis

Statistical analysis was performed using MedCalc (Ostend, Belgium) and NCSS (Utah, Kaysville, USA) Statistical Software. Data are presented as mean and standard deviation or as median and range between brackets as applicable. The Shapiro-Wilk test, most frequently used to test normality, and Levene's test (for non-nominal) and Bartlett Homogeneity test (for nominal variables) were utilized to check for equality of variances. To decrease the variability of data and make data conform more closely to the normal distribution, logarithmic transformation was applied. Chi-square and Fisher's exact tests were used to compare nominal variables. The Mann-Whitney *U* test was used to evaluate continuous variables. One-way analysis of variance (ANOVA) was used to test for differences at baseline. Repeated measures ANOVA was used to assess significant differences by comparing means across one or more variables within subjects and between subjects in the two groups at different periods from baseline and post-treatment. The Greenhouse-Geisser method was utilized for adjusting for a lack of sphericity. Hotelling's T-squared test was utilized instead of repeated measures ANOVA, when the sphericity assumption did not hold. *P*-values < 0.05 were considered significant. The probability of patients surviving up to the study endpoint was calculated using the Kaplan-Meier method represented by the survival time curve. A comparison between the survival curves was made using the log-rank test, and *p*-values < 0.05 were considered significant.

Results

Patients and characteristics at baseline

From November 2016 to March 2019, a total of 188 patients were found to have overt HE and associated large PSS. Of them, 106 were excluded due to associated conditions precluding shunt embolization, identifiable causes for HE, and other central nervous system diseases. Furthermore, ten patients were found to have non-cirrhotic portal hypertension and three were lost to follow-up. Another 26 patients who had PSS-related HE did not undergo shunt embolization due to unwillingness and lack of informed consent. Of them, four patients who had a recurrence of HE provided informed consent and underwent shunt embolization. Hence, 22 patients with shunt-related HE did not undergo shunt embolization. Of the other 43 patients undergoing shunt embolization for HE, two were lost to follow-up after the procedure. Finally, 45 patients (22 with the first episode of HE, 23 with recurrent or refractory HE) undergoing shunt embolization and follow-up of 18 months were included in the study (Fig. 1). In both groups, males predominated ($n = 18/22$, 81.8% in ESE vs. 20/23, 87% in LSE). The most frequent etiology for cirrhosis was nonalcoholic steatohepatitis (NASH) in both groups ($n = 13/22$, 59.1% ESE vs. 15/23, 65.2% LSE) followed by alcoholic liver disease (31.8% vs. 30.4%). The mean age (in years) in the early embolization group was 56.5 ± 9.7, while in the late embolization group, it was 57.9 ± 8.5. The presence of metabolic diseases such as diabetes mellitus and systemic hypertension was comparable between patients in both groups. The presence of ascites and grade of ascites at baseline was comparable between groups. Even though statistically not significant, the esophageal varices grade 2 and above were notable in 31.8% and 21.7% in the early and late group of patients respectively. Among patients in the LSE group, 17 ($n = 23$, 73.9%) had recurrent and others had persistent HE. Higher grades of HE (≥ 3) as per West Haven criteria before the procedure were noted in patients undergoing LSE compared with those in the early procedure group (43.5% vs 22.7% respectively) that did not reach statistical significance. Significantly higher total bilirubin, lower serum sodium, hyperammonemia, and higher grades of Child-Pugh scores (but not MELD scores) were noted in patients undergoing LSE.

Features associated with portosystemic shunt syndrome between groups

The commonest portosystemic shunt in patients of both groups was of the lienorenal type (45.5% ESE vs. 62.5%

Fig. 1 Patient enrolment, inclusion, and exclusion and final study group flow diagram. *HE* hepatic encephalopathy

LSE) followed by large coronary vein (13.6%) and paraumbilical vein (13.6%) in the ESE group and multiple shunts (lienorenal + mesocaval, 13%) and mesocaval shunt (13%) in patients undergoing LSE. In patients with recurrent HE, undergoing late treatment for shunt syndrome, a trend towards significance was notable for the presence of multiple shunts in contrast to those undergoing ESE in whom singular shunts were more prevalent ($p = 0.059$). The size of the largest shunt was significantly larger in patients undergoing LSE compared with that in early shunt occlusion protocol (21.9 ± 7.2 mm vs. 14.8 ± 6.9 mm respectively, $p < 0.001$). The type of approach to shunt embolization did not differ between groups (transfemoral, transhepatic, or transjugular). The number of treatment sessions needed for shunt embolization did not significantly differ between groups. In analyzing the type of embolization method, the early embolization group of

patients underwent significantly more of a single type of procedure compared with patients undergoing late embolization in whom shunt occlusion involved a combination of procedures ($p = 0.014$).

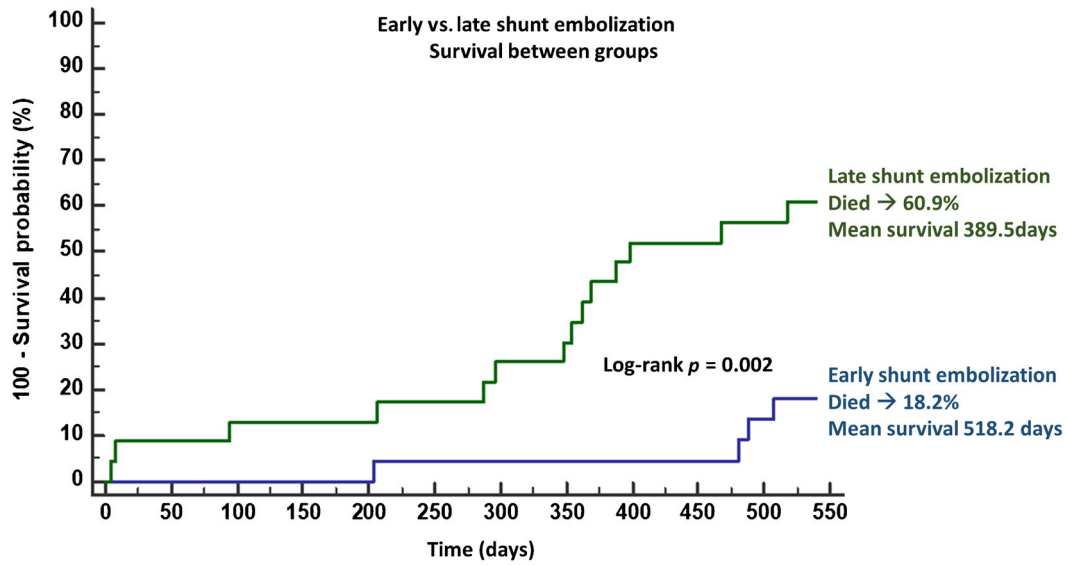
Clinical outcomes between groups after shunt embolization

Post-treatment, the number of days of stay in the intensive care unit was significantly higher among patients undergoing LSE (0.59 [mean] ± 0.38 [standard error of the mean] days vs. 2.09 ± 0.58 days; $p = 0.04$) while the total number of days in hospital was not. Trend towards the development of ascites and a significantly higher proportion of patients with ascites post shunt embolization was noted at 1 to 9 months (8/21, 38.1% vs. 3/22, 13.6%; $p = 0.07$) and 10 to 18 months (7/19, 36.8% vs. 2/21, 9.5%; $p = 0.04$) in the late compared with that in early treatment groups respectively. A trend towards the development of refractory ascites was notable in the late embolization group with three patients developing refractory ascites requiring large-volume paracentesis of whom one died at the end of follow-up. In the early embolization group, the occurrence of refractory ascites was not seen (0% [$n = 21$] vs. 15.8% [$n = 19$]; $p = 0.06$). A significantly higher proportion of patients developed overt HE in the first 9 months in the LSE group compared with those in the early group (6/21, 28.6% vs. 1/22, 4.5%; $p = 0.03$). However, the occurrence of HE beyond 9 months in both the groups was not significantly different. Adverse clinical events in the immediate post-procedure period, i.e. within 100 days, were comparable between both the groups.

Nevertheless, clinical adverse events occuring beyond 100 days after the procedure in patients undergoing LSE were higher (5/22, 22.7% ESE vs. 12/21, 57.1% LSE; $p = 0.02$). The first clinical event in the late embolization group after 100 days was liver failure and sepsis in 23.8% ($n = 5/21$) compared with 4.5% (1/22) in the early embolization group (Supplementary Fig. 1). Recurrence of shunt on follow-up was noted in one patient in the early embolization group compared with three patients (two of whom died at the end of follow-up) in the late embolization group ($p = $ ns).

Liver functions and disease severity between groups

At end of follow-up period of 9 months and 18 months, in the ESE group, a trend towards improvement in serum albumin ($p = 0.06$) and significantly lower arterial ammonia levels



Groups	Number at risk											
Early embolization	22	22	22	22	22	21	21	21	21	21	19	18
Late embolization	23	21	20	20	20	19	17	16	11	11	10	9

Hazard Ratios with 95% Confidence interval between groups		
Factor: Groups	Early embolization	Late embolization
Early embolization		0.21 0.08 to 0.53
Late embolization	4.85 1.9 to 12.4	

Fig. 2 Kaplan-Meier survival analysis between early and late shunt embolization groups

Table 1 Baseline and follow-up parameters between groups

Parameters	Early shunt embolization group ($n = 22$)		Late shunt embolization group ($n = 23$)		p-value[$]
Sex	Males, 81.8%		Males, 87%		0.64
Presence of diabetes mellitus	59.1%		60.9%		0.91
Presence of hypertension	18.2%		17.4%		0.94
Etiology of cirrhosis	ALD, 36.3% NASH, 59.2% HBV, 4.5%		ALD, 30.4% NASH, 65.3% HCV, 4.3%		0.53
Type of hepatic encephalopathy			Persistent, 26.1% Recurrent, 73.9%		–
Esophageal varices (and on maximal tolerable non-selective beta blockers)	86.4%		78.3%		0.65
Presence of ascites	22.7%		26.1%		0.79
Type of shunt on imaging	CV, 13.6% LGV + SGV, 4.5% LRS, 45.5% LRS + CV, 9.1% LRS + MCS, 4.5% LRS + PUV, 9.1% PUV, 13.6%		LGV + AZV, 4.3% LRS, 65.2% LRS + MCS, 13% MCS, 13% PUV, 4.3%		0.06
Approach for shunt occlusion	Transfemoral, 0% Transhepatic, 18.2% Transjugular, 81.8%		Transfemoral, 4.3% Transhepatic, 17.4% Transjugular, 78.3%		0.61
Number of sessions performed	One, 95.5% More than one, 4.5%		One, 95.7% More than one, 4.3%		0.97
Need for cyanoacrylate glue	9%		13%		0.68
Shunt embolization method	BRTO, 22.7% CAATO, 22.7% CARTO, 27.3% CARTO + Glue, 9% CARTO + PARTO, 4.5% PARTO, 13.8%		CAATO + Glue, 4.3% CARTO, 26.1% CARTO + BRTO, 4.3% CARTO + Glue, 8.7% CARTO + PARTO, 13% CARTO + PARTO + BRTO, 4.3% PARTO, 39.3%		0.01
	Mean	**SD**	**Mean**	**SD**	
Age (years)	56.5	9.7	57.9	8.5	0.61
Hemoglobin (g/L)	11.2	1.4	11.4	1.8	0.71
Total leukocyte count ($\times 10^9$/L)	5.5	1.64	5.8	2.4	0.58
Platelet count ($\times 10^9$/L)	95.7	31.7	87.6	31.2	0.39
Total bilirubin (mg/dl)	2.1	1.1	3.5	2.6	0.02
International normalized ratio	1.5	0.6	1.5	0.3	0.90
Albumin (g/dL)	3.1	0.67	2.8	0.5	0.09
Creatinine (mg/dL)	1	0.3	1.1	0.7	0.63
Sodium (mmol/L)	136.1	3.5	132.3	3.8	< 0.01
Ammonia (μmol/L)	127.1	65.2	217.2	93.9	< 0.01
Child-Pugh score	7.8	1.8	10	1.7	< 0.01
MELD score	12.5	3.5	14.8	4.5	0.1
Size of largest shunt (mm)	14.8	6.9	21.9	7.2	0.002

BRTO balloon-assisted retrograde transvenous occlusion, *CARTO* coil-assisted retrograde transvenous occlusion, *CAATO* coil-assisted antegrade transvenous occlusion, *PARTO* plug-assisted retrograde transvenous occlusion, *ALD* alcoholic liver disease, *NASH* nonalcoholic *steatohepatitis*, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *CV* coronary vein, *LGV* left gastric vein, *AZV* azygous vein, *SGV* short gastric vein, *LRS* lienorenal shunt, *MCS* mesocaval shunt, *PUV* paraumbilical vein

*Chi-square and Fisher's exact tests used to compare nominal variables; the Mann-Whitney *U* test for continuous variables; data shown in mean with standard deviation (SD) when normally distributed and median (interquartile range) in the absence of normal distribution

^ One-way analysis of variance (ANOVA) used to test for differences at baseline

Repeated measures ANOVA used to assess significant differences from baseline between subjects in study groups

$ p-values < 0.05 significant

($p < 0.001$) was noted compared with baseline values; in the ESE group, significant more reduction in platelet counts (p-0.02), increase in serum total bilirubin ($p = 0.002$) levels, and lower serum sodium ($p < 0.001$) levels were striking (Fig. 2).

The liver disease severity scores as measured by the Child-Pugh and MELD scores from baseline and at 9 and 18 months improved significantly in patients undergoing ESE compared with those in late shunt treatment. The complete baseline

Table 2 Baseline and follow-up parameters between early shunt embolization group of patients and patients on standard medical management*^

Parameter	Early shunt embolization ($n = 22$)			No shunt embolization ($n = 22$)			p-value#
	Baseline	1–9 months	10–18 months	Baseline	1–9 months	10–18 months	
Esophageal varices (and on maximal tolerable non-selective beta blockers)	86.4%	–	–	64.4%	–	–	0.09
Ammonia (micromol/L) **	117 (80)	43 (28)	42 (20)	99.5 (78)	84 (36)	84 (40)	0.001
Child-Pugh score***	7.8 ± 1.8	7.4 ± 1.8	7.5 ± 1.5	8.1 ± 1.2	9.5 ± 1.1	9.9 ± 1.5	< 0.001
MELD score***	12.5 ± 3.5	12 ± 7.1	15.1 ± 8.1	11.8 ± 2.4	14.1 ± 4.5	15.1 ± 7.2	0.54
Ascites	22.7%	13.6%	9.5%	27.3%	18.2%	57.1%	0.001
Hepatic encephalopathy	–	4.5%	9.5%	–	27.3%	38.8%	1–9 months, 0.04 10–18 months, 0.02
Acute variceal bleeding	4.5% ($n = 1$)			45.5% ($n = 10$)			0.002

*Chi-square and Fisher's exact tests used to compare nominal variables; the Mann-Whitney U test for continuous variables

**Data shown as median (interquartile range) when variables not normally distributed

***Data shown as mean (standard deviation) when variables normally distributed

^ One-way analysis of variance (ANOVA) used to test for differences at baseline

p-value < 0.05 considered significant

MELD model for end-stage liver disease

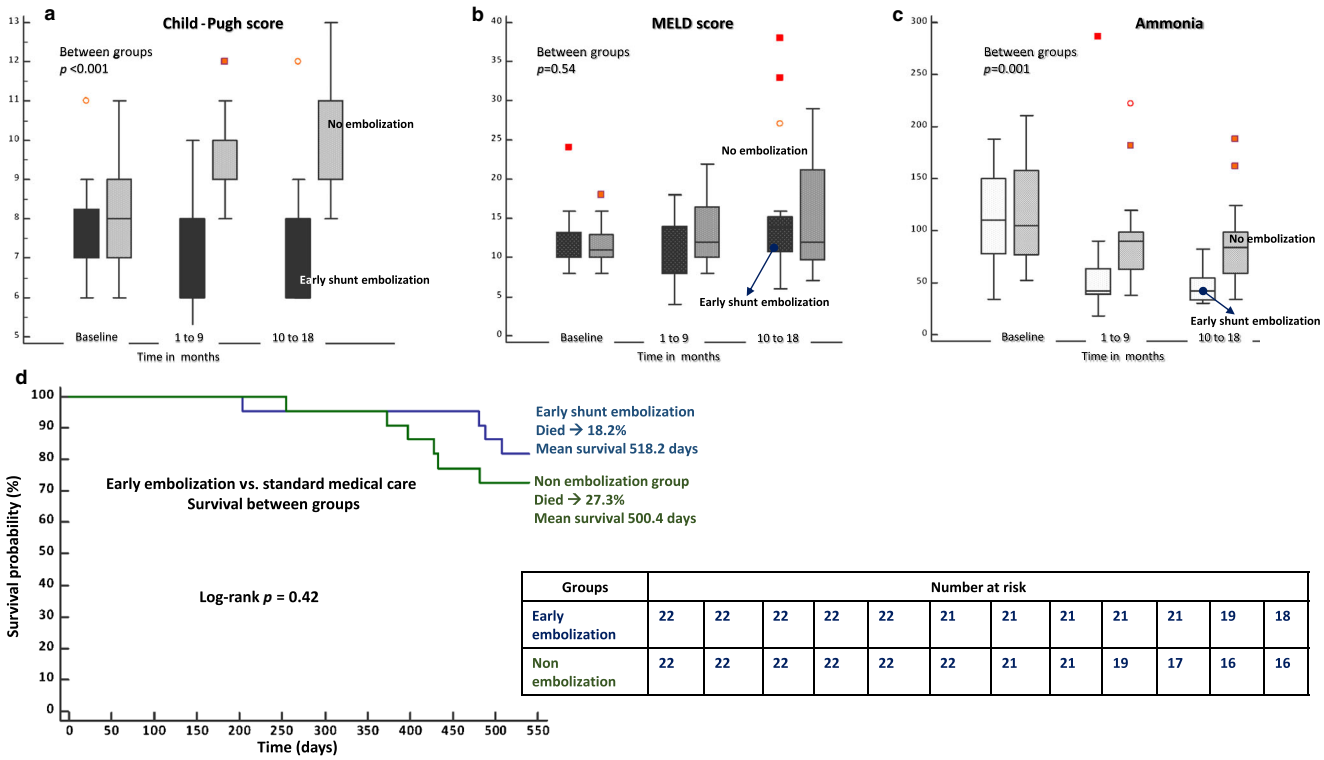
detail of patients in both the groups included in the study are shown in Table 1. Detailed post-procedure follow-up parameters between the groups are shown in Supplementary Table 1.

Patient outcomes

At the end of 18 months, overall, 4 patients ($n = 22$, 18.2%) died in the ESE group while 14 ($n = 23$, 60.87%) died in the LSE group (hazard ratio with 95% confidence intervals, 4.8 [1.9 to 12.3]; $p = 0.002$). The mean survival time for patients undergoing ESE was 518.2 days while those undergoing LSE was 389.5 days with overall survival of 452.4 days (Supplementary Fig. 2). Twenty-two patients during the same study period, with shunt-related HE, did not undergo shunt occlusion and were continued on standard medical care with oral disaccharides and non-absorbable antibiotics with zinc supplementation. Of these, two patients were lost to follow-up after 1 year and were considered to have died, while the rest were followed-up to 18 months. This group ($n = 22$; no shunt occlusion, NSE) had comparable baseline characteristics to the early shunt occlusion group, concerning age, gender, etiology of cirrhosis, presence of ascites, largest shunt size, ammonia levels, and liver disease severity scores (Child-Pugh and MELD). On follow-up, the occurrence of ascites ($p = 0.001$), acute variceal bleeding ($p = 0.002$), and recurrence of HE (1 to 9 months, $p = 0.04$; 10 to 18 months, $p = 0.02$) were significantly higher in patients on standard medical care compared with those in patients undergoing ESE. Among patients who developed ascites in the standard treatment group, a significantly higher proportion had refractory ascites requiring repeated paracentesis compared with those undergoing ESE (0% [$n = 21$] vs. 23.8% [$n = 21$]; $p = 0.02$). Patients who underwent ESE did not have portal vein thrombosis on follow-up compared with those on standard management of HE (0% vs. 22.7%; $p = 0.02$). Trend towards significance in a higher proportion of patients experiencing an adverse clinical event (other than ascites, HE, or variceal bleed) over 18-month follow-up was notable in those on standard of care compared with that in those undergoing ESE (50.8% vs. 22.7%, $p = 0.056$). Pertinent baseline and follow-up parameters between the early shunt embolization group of patients and patients on standard medical management are shown in Table 2. The Child-Pugh score (but not MELD) and mean ammonia levels were significantly better in patients undergoing ESE compared with those in patients on standard medical care even though the survival between both groups was not statistically different at the end of 18 months (Fig. 3). The post-procedure follow-up clinical events at 18 months between patients undergoing early shunt embolization compared with no shunt embolization are shown in Table 2.

Discussion

Our study compared clinical outcomes of shunt embolization at the first episode of spontaneous HE and late embolization in recurrent or persistent HE among patients with cirrhosis and



Groups	Number at risk											
Early embolization	22	22	22	22	22	21	21	21	21	21	19	18
Non embolization	22	22	22	22	22	22	21	21	19	17	16	16

Fig. 3 Liver disease severity (**a**, **b**) and ammonia levels (**c**) between patients undergoing early shunt embolization and those on standard medical care in the absence of shunt occlusion. Kaplan-Meier survival analysis (**d**) between patients with HE undergoing early and those in no shunt embolization. *MELD* model for end-stage liver disease, *HE* hepatic encephalopathy

portosystemic shunt syndrome. We also analyzed comparative outcomes between patients undergoing early embolization and those with shunt-related HE continued on standard medical care. Simón-Talero and colleagues demonstrated that the presence and size of PSS increased with liver disease severity. A significantly higher number of patients in their extensive retrospective analysis with lower MELD scores and large PSS developed portal hypertensive complications such as ascites and variceal bleeding than those without shunts [3]. In the current study, we report similar outcomes in patients with PSS and HE. We found that in patients with PSS, Child-Pugh scores (mostly because of HE), jaundice (a surrogate of worsening synthetic and excretory function), and hyponatremia (a surrogate of worsening portal hypertension) were higher among those with more frequent and severe HE. Ammonia levels were possibly higher in the LSE group due to more shunts and larger shunt size and associated with a higher frequency of HE, the latter playing an important role in increased Child-Pugh score. To the best of our knowledge, ammonia levels in shunt syndrome have not been demonstrated to predict clinical outcomes, and even though the bilirubin levels were higher at baseline in LSE patients, the better predictor of liver disease severity inclusive of bilirubin, the MELD score was comparable between both groups of patients. Hence, with respect to pertinent comparisons, both groups were well matched at baseline. The grade of HE and the number and size of shunts have not been demonstrated to predict or influence clinical outcomes, especially transplant-free survival in cirrhosis patients with portosystemic shunt syndrome in current literature. Embolizing the portosystemic shunt early on in the course of symptomatic presentation rather than late reduced portal hypertensive and related liver complications. This was also true in comparison with those patients in whom standard medical management was continued in the absence of shunt embolization. In a retrospective review of patients undergoing balloon-assisted retrograde transvenous occlusion (BRTO), Saad et al. found that hepatic synthetic functions improved (at the cost of an increase in ascites) significantly between 1.5 and 4 months post-procedure. This translated to significantly better MELD scores without a change in Child-Pugh scores [6].

In our study, we found that synthetic hepatic function improved, with amelioration in Child-Pugh and MELD scores, after ESE when compared with that of no/late embolization. In patients who underwent LSE, the functional liver reserve would have been more compromised leading to poor overall survival outcomes, but with significant control of HE beyond 9 months after the procedure. The incidence of ascites post-procedure was also significantly lower among patients undergoing ESE probably due to expeditious improvement in liver functions and better control of portal hypertension. The lower rates of ascites and better control of ascites as well as HE in the

early embolization group could have resulted in improved Child-Pugh as well as MELD scores noted in our study patients. It has been shown in multiple studies that the Child-Pugh scores improve initially in the first 9 months after BRTO, only to return to pre-BRTO levels after that. In patients with large PSS, the persistence of shunts was shown to be associated with worsening liver function and poor survival outcomes. Kumamoto and colleagues demonstrated long-term improvement in hepatic function and a protective role of shunt occlusion in their group of patients. Fukuda and colleagues demonstrated improvement in the Child-Pugh score in 50% of patients undergoing BRTO for gastric varices and recurrent HE 6 months after the procedure with notable improvement in serum albumin levels post-procedure. Improvement in liver disease severity persisted in only 26% of patients 1 year after BRTO. In our patients, the continued improvement in liver disease scores could have been due to the early timing of intervention and associated amelioration of portal hypertension with improvement in liver function [7, 8]. In patients who did not undergo shunt occlusion, we found that the incidence of ascites, variceal bleeding, and HE was significantly higher. Severe portal hypertension–related complications such as worsening liver function, sepsis events, and portal vein thrombosis were also higher in patients on standard medical care. Early embolization improved liver function and associated clinical events when compared with medical management alone. The MELD scores did not show significant changes from the baseline in patients on medical management when compared with those in patients undergoing early shunt occlusion. This could have been due to comparable liver synthetic functions at baseline in both the patient groups which also translated to insignificant survival outcomes at the end of follow-up, but improved portal hypertension outcomes as demonstrated by better Child-Pugh scores, and an only trend towards improvement in non-portal hypertensive events, in patients undergoing ESE. In line with current literature, reduction in ammonia levels was significant at all time points in patients undergoing shunt embolization (within and between subjects), more so among those undergoing early embolization when compared with that of late and no embolization.

Privitera et al. demonstrated that in patients with refractory HE undergoing shunt embolization, the neurological outcomes were significantly better and the presence of large PSS increased portal hypertensive complications especially bleeding varices. This has been shown by various groups world over. A substantial proportion of patients in the Privitera et al. study developed portal hypertensive complications after shunt embolization and they considered shunt embolization as a bridge to transplantation, for improving quality of life [9]. Laleman and colleagues reported on improved autonomy, decreased number of hospitalizations, and severity of the worst HE episode after embolization in three-quarters of their patients who underwent shunt embolization for recurrent/persistent HE. The authors concluded that there was a significant role for large PSS in chronic or recurrent HE and embolization of these shunts was safe and effective, in the presence of sufficient functional liver reserve [10]. Lynn and co-workers showed that shunt embolization was a viable therapeutic option to improve symptoms of HE, decrease hospitalizations, and potentially temporize the need for liver transplantation in those cirrhosis patients with chronic/recurrent HE [11]. Philips et al. demonstrated poor outcomes with shunt embolization in patients with Child-Pugh score > 11 [12]. An et al. also showed that cirrhotics with large PSS had more severe HE and embolization of large shunts was associated with improved survival and liver function and prevention of HE in the presence of modestly preserved liver function (defined as MELD score < 15). The authors also showed that in patients with higher MELD scores, even in the presence of shunt occlusion, the 2-year survival rates were poor and similar to those with similar disease severity not undergoing shunt embolization [13].

Similarly, in our study, we additionally show that in patients with recurrent or chronic HE and lower MELD scores, ESE was more beneficial than late intervention. The absence of intervention in a control group matched with the ESE group revealed worse portal hypertension–related events in the former, but comparable survival rates. In our patients, post-procedure bleeding from varices at 18-month follow-up was not significantly different between early and late embolization groups but was significantly more in patients on standard care compared with that in patients undergoing ESE. The occurrence of severe ascites even though higher in the late embolization group was not significant between the treatment groups but was significantly higher in patients on standard medical care, most probably due to significantly higher occurrence of portal vein thrombosis. Hence, the change in the course of portal hypertensive events and the neurological improvement which was significant in both treatment groups in the long-term and was in line with current published literature, better with early intervention. Transplant-free survival was evident in our patients who underwent ESE rather than conventional late embolization as described by Privitera et al. [9]. Survival outcomes were not significantly different between patients undergoing ESE and those on standard medical care probably due to good and comparable functional liver reserve in both, but worse in the LSE group (poor liver reserve) in whom intervention would only serve as a bridge to a liver transplant. Our study improves on the understanding that the presence of large PSS in patients with liver cirrhosis without liver failure is associated with the risk of developing HE and portal hypertensive complications and could benefit from early intervention. We also demonstrate the importance of Child-Pugh scores in assessing liver disease severity in patients with cirrhosis and PSS. Since MELD scores do not adequately reflect the severity of the liver disease, as they do not take into

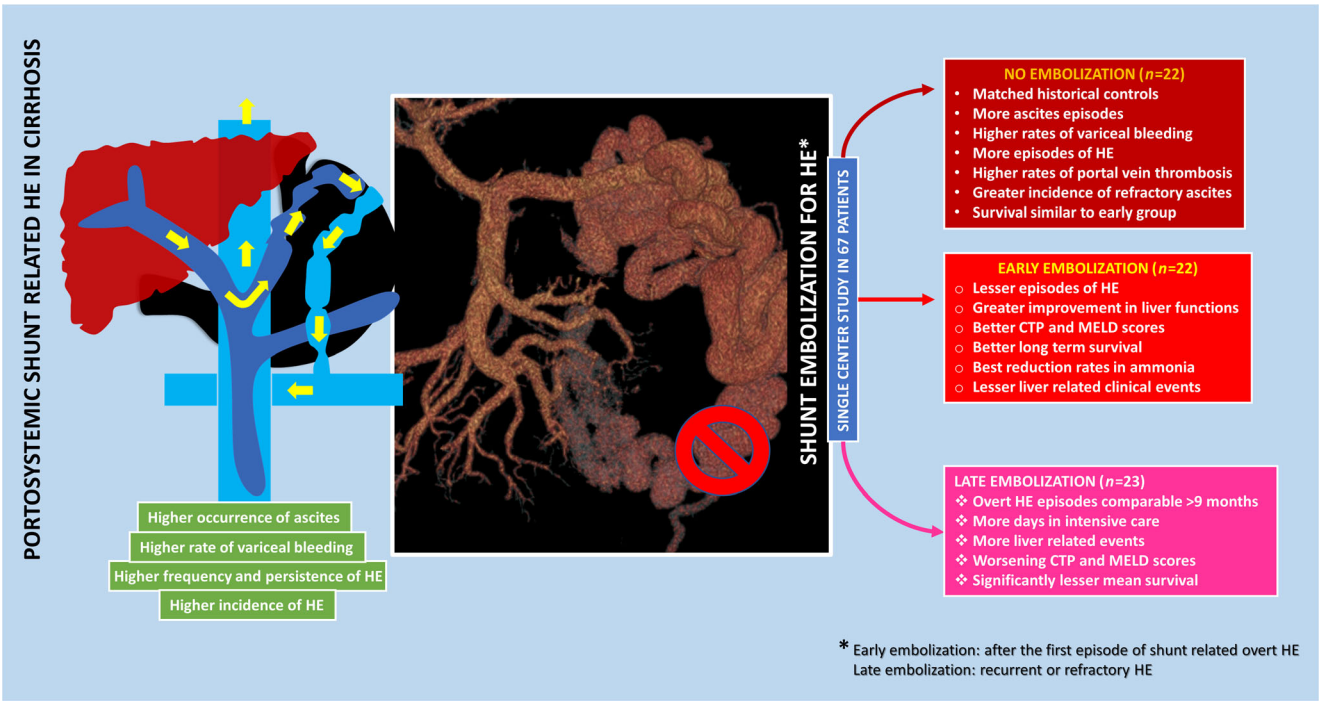


Fig. 4 Summary of visual abstract of the study. *HE* hepatic encephalopathy, *CTP* Child-Turcotte-Pugh, *MELD* model for end-stage liver disease

account HE or ascites, the Child-Pugh score could be a better surrogate for disease severity associated with shunt complications. This is also evident in our patient groups in whom Child-Pugh scores (but not MELD) were found to improve on long-term follow-up, with early compared with no intervention [2, 11] (Summary, Fig. 4).

Our study has strengths as well as limitations. Ours is the first study to compare early, late, or no intervention in cirrhosis patients with shunt-related encephalopathy that provide some clarity in improving clinical outcomes in this special subset of patients. We also provide long-term follow-up outcomes of study patients to improve on the understanding that a portosystemic shunt syndrome is a significant event in the natural history of cirrhosis and portal hypertension that probably needs a different approach rather than the conventional treatment decisions. Our study was retrospective and from a single center and needed to be validated from other centers and in prospective trials. We did not assess the role of beta blocker therapy among our study patients or the response to beta blockers, and higher dosing of beta blockers could have impacted portal hypertension events in our patients. This aspect would require long-term longitudinal studies for a comprehensive understanding of clinical events. Even though our patients were matched for cirrhosis etiology at the baseline, the impact of etiology such as continued alcohol use, weight gain, and poor control of metabolic syndrome could have affected outcomes. Such data was lacking/incomplete in our study cohort due to the retrospective nature of the protocol.

To conclude, our study, the first to compare early vs. late embolization of large PSS in patients with cirrhosis, sheds new light on the beneficial role of ESE in the amelioration of portal hypertension–related complications such as HE, variceal bleeding, ascites, sepsis, renal dysfunction, and transplant-free survival. Early intervention also reduced liver and portal hypertension–related events, but not survival, in patients with stable liver disease compared with those continued on standard medical care. Extensive multicenter-based prospectively performed studies are an unmet need to confirm our findings as early interventional management of portosystemic shunt syndrome could become an essential step in modifying a downhill course associated with symptomatic portal hypertension in patients with cirrhosis.

Author roles CAP and SR designed the study and wrote the manuscript; CAP and RA collated data and performed the analysis; SR, TG, MM, and PA made critical revisions to the manuscript; all authors agreed to the final version of the manuscript for submission.

Compliance with ethical standards

Conflict of interest CAP receives consulting and advisory fees from Cipla®, Waterley®, Mylan®, and Samarth Life Sciences™; SR, TG, RA, MM, and PA declare that they have no conflict of interest.

Ethics statement The study and retrospective collection of data were approved by the institutional ethics committee and have been performed following the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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Affiliations

Cyriac Abby Philips[1] · Sasidharan Rajesh[2] · Tom George[2] · Rizwan Ahamed[3] · Meera Mohanan[4] · Philip Augustine[4]

[1] The Liver Unit and Monarch Liver Lab, Cochin Gastroenterology Group, Ernakulam Medical Center, Kochi 682 028, India

[2] Interventional Radiology, Department of Gastroenterology and Hepatology, Cochin Gastroenterology Group, Ernakulam Medical Center, Kochi 682 028, India

[3] Gastroenterology and Advanced Gastrointestinal Endoscopy, Cochin Gastroenterology Group, Ernakulam Medical Center, Kochi 682 028, India

[4] Department of Anaesthesia and Critical Care, Cochin Gastroenterology Group, Ernakulam Medical Center|, Kochi 682 028, India