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Efficacy and safety of partial splenic embolization for hypersplenism in pre- and post-liver transplant patients: A 16-year comparative analysis☆,☆☆

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ABSTRACT

Purpose: To report the effect of partial splenic embolization (PSE) on hematological indices and the procedure's safety in pre- and post-liver transplant (LT) patients.

Materials and methods: A single-center retrospective study evaluating all patients who underwent PSE over a 16-year period was performed. Inclusion criteria were splenomegaly confirmed by imaging and at least one of the following cytopenias: hemoglobin ≤10 g/dL, WBC count ≤1500 μL^{-1}, or platelet count ≤100,000 μL^{-1}. 38 of 102 patients (37%) met criteria (24 pre- and 14 post-LT) for a total of 40 PSEs.

Results: No effect was seen on median hemoglobin beyond 2 weeks post-PSE. There was a significant and sustained increase in median WBC counts (from 3400 μL^{-1} to 5400 μL^{-1} at 2 years) and platelet count (from 65,000 μL^{-1} to 117,000 μL^{-1} at 3.5 years). In 6 out of 40 PSEs (15%) a major complication occurred which included pleural effusion, ascites, spontaneous bacterial peritonitis, pneumonia, and inferior vena cava thrombus. Similar efficacy was observed in pre- and post-LT cohorts, with a trend toward higher complication rate in pre-LT patients.

Conclusions: PSE is efficacious in increasing WBC count out to 2 years and platelet count out to 3.5 years in patients with hypersplenism. Efficacy and safety appeared independent of pre- or post-LT status. The intervention is associated with major complications and special care should be taken when selecting patients for PSE.

1. Introduction

Portal hypertension secondary to chronic liver disease is the most common cause of splenomegaly in the United States [1], with prevalence rates as high as 92% in patients with cirrhosis [2]. Hypersplenism, a reduction in one or more blood indices in association with splenomegaly [3], is a complication that affects between 15 and 70% of cirrhotics [2] and contributes to the 64–84% rate of cytopenias [4,5] in this patient population. Reductions in hematological indices may increase the risk of infection [6], restrict antiviral or antineoplastic therapies [7,8], and are correlated with reduced median survival [9].

The pathophysiology of hypersplenism in the setting of liver disease

Abbreviations: PSE, partial splenic embolization; ITP, idiopathic thrombocytopenia purport; EtOH, ethanol; SASS, splenic artery steal syndrome; SFSS, small-for-size syndrome; MELD, Model for End-Stage Liver Disease; MELD, Na-Model for End-Stage Liver Disease Sodium; CTP, Child-Turcotte-Pugh; LT, liver transplant; WBC, white blood cell; Hb, hemoglobin; LOS, length of stay; CF, cystic fibrosis; LVP, large volume paracentesis; PSC, primary sclerosing cholangitis; HCC, hepatocellular carcinoma; CRC, colorectal cancer; PVT, portal vein thrombosis; PT, prothrombin time; INR, international normalized ratio; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TPO, thrombopoietin; SBP, spontaneous bacterial peritonitis; ALD, alcoholic liver disease; NAFLD, non-alcoholic fatty liver disease; HBV, hepatitis B virus; HCV, hepatitis C virus; HTN, hypertension; BMI, body mass index; AlkPhos, alkaline phosphatase; Ct, count

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is multifactorial, involving declining thrombopoietin production [10], increased pooling [11] and immune-mediated destruction of platelets [12], as well as impaired bone marrow production [13,14]. Historically the treatment for symptomatic hypersplenism has been surgical splenectomy [15] though the procedure had a high risk of complications particularly in cirrhotics with portal hypertension [16]. Partial splenic embolization (PSE) was developed as an alternative that preserved splenic parenchyma to retain its immunological benefits [17]. The procedure was recently demonstrated to be nearly as efficacious and safer in both the short- and long-term compared to splenectomy for hypersplenism in cirrhotics [18,19].

Liver transplant (LT) recipients remain vulnerable to the clinical impact of hypersplenism due to viral hepatitis-associated bone marrow suppression [4]. Chronic hepatitis C infection (HCV) is the most common indication for LT with HCV recurrence as the norm post-transplant [20]. While liver transplantation may resolve pre-LT cytopenias [21], between 20 and 57% of post-LT patients will have persistent hypersplenism [22,23]. Hypersplenism in LT recipients may limit myelosuppressive [24,25] as well as maintenance immunosuppressive medications [26] for the transplanted organ.

LT recipients have the same treatment modalities available for hypersplenism, but face unknown or greater associated risks. There is next to no clinical experience of using thrombopoietin in LT patients [25,27] and the therapy is associated with venous thrombotic events [28,29] that could be exacerbated by their typically hypercoagulable state [30]. Splenectomy in immunosuppressed patients correlates with a greater than three-fold rate of serious infection compared to immunocompetent counterparts [31] and a 40% mortality secondary to sepsis within one year [32].

In this context PSE offers an alternative, preserving baseline splenic function while possibly improving liver graft function in the setting of undiagnosed splenic artery steal syndrome (SASS) [33]. However PSE in cirrhotics has also been associated with morbidity ranging from 0 to 63% [25,34,35] meriting further investigation to determine its efficacy and safety.

The purpose of this study is to report the effect of PSE on key hematological indices and the procedure's safety in pre- and post-LT patients.

2. Materials and methods

2.1. Patient selection

This study was conducted with Institutional Review Board approval and complied with the Health Insurance Portability and Accountability Act. Informed consent was not required for this retrospective study. This was a single-center retrospective study evaluating all patients who underwent PSE at Columbia University Medical Center between January 2000 and August 2015.

2.2. Inclusion criteria

Inclusion criteria were: (1) splenomegaly (defined as maximal axial splenic width ≥ 11 cm on cross-sectional imaging) [36] secondary to portal hypertension; (2) associated cytopenia (defined as hemoglobin (Hb) ≤ 10 g/dL, WBC count $\leq 1500\,\mu L^{-1}$, or platelet count $\leq 100{,}000\,\mu L^{-1}$) [37].

2.3. Exclusion criteria

Exclusion criteria were: (1) cytopenia secondary to myelodysplasia, autoimmune, idiopathic thrombocytopenic purpura (ITP), or alcohol use; (2) PSE indicated for splenic trauma or SASS in the peri-LT period; (3) recurrent episodes of variceal hemorrhage in the past year.

Table 1
Liver pathology contributing to portal hypertension.[a]

	Pre-LT	Post-LT
HBV/HCV	4	5
ALD	1	1
NAFLD		1
Non-cirrhotic portal HTN	2	
Congestive hepatopathy	2	
Venous thrombosis	3	1
Cystic fibrosis	6	1
PSC		2
Hepatic sarcoidosis	1	
Cryptogenic cirrhosis		1
Progressive familial intrahepatic cholestasis		1
Noonan cirrhosis	1	
Fibrolamellar carcinoma		1
Cancer metastasis	3	

[a] Number of patients.

2.4. Patient demographics

One hundred and two patients underwent PSE between January 2000 and August 2015, 38 of which met the study criteria for a total of 40 PSEs (including two repeat PSEs). One patient developed an inferior vena cava thrombus and required emergent splenectomy prior to obtaining follow-up laboratory values so was excluded from baseline data, but was included in the complications analysis. Of the remaining 39 PSEs, 25 procedures were performed in 23 pre-LT patients and 14 in post-LT patients. Etiologies of the underlying portal hypertension by subgroup are listed in Table 1. Indications included refractory ascites (n = 12), cytopenia limiting therapy (n = 11), severe thrombocytopenia (n = 10), varices at risk of hemorrhage (n = 5), and enlarging splenic aneurysm (n = 1).

Repeat PSEs were performed in pre-LT patients at 1.5 months for modest platelet response and 2.5 years for recurrence of hypersplenism. Baseline patient characteristics are shown in Table 2. There were statistically significant differences between the pre-and post-LT subgroups that reflected their transplant status and primary indication for PSE, with over half of post-LT patients undergoing PSE for refractory ascites. The LT subgroup had lower baseline WBC and Hb levels, with all 14 post-LT patients on tacrolimus-based immunosuppression, and some taking additional anti-proliferative agents (including mycophenolate and azathioprine). Similarly, the LT subgroup had an elevated baseline creatinine level (likely attributable to a combination of chronic calcineurin inhibitor toxicity and diuretic use) with a corresponding difference in mean Model for End-Stage Liver Disease (MELD) score. There was no difference between subgroups by MELD-Na score. Low albumin levels in the presence of ascites (indicative of volume status rather than hepatic synthetic function) was responsible for an elevated baseline Child-Turcotte-Pugh (CTP) score in the LT subgroup, making up the majority of the CTP class B cirrhotics. No patients had CTP class C cirrhosis. Mean splenic size was the same in pre-LT and post-LT patients and there was no significant difference in mean platelet counts. However, nine pre-LT patients were profoundly thrombocytopenic (platelets $< 50 \times 10^3/\mu L$) compared to four in the post-LT group.

2.5. Defined variables and endpoints

Patients were followed until liver transplantation, subsequent splenic operation (including PSE, splenectomy, or splenic artery ligation), death, or when data were censored on August 31, 2016. Medical records were reviewed and relevant clinical, laboratory, and imaging data extracted. Values were binned by length of time relative to PSE date using intervals that increased from one week to a maximum of five months during biannual follow-up.

The primary end points were effect on hematological parameters,

Table 2
Baseline patient characteristics by subgroup.[a]

	All	Pre-LT	Post-LT	p
No. of patients	37	23	14	
No. of PSEs	39	25	14	
No. of men	16	9	7	0.52
No. of women	21	14	7	
Age (y)	45 ± 23	44 ± 24	48 ± 21	0.74
BMI	25 ± 5	26 ± 5	25 ± 5	0.54
WBC (10^3/μL)	3.8 ± 1.8	4.3 ± 1.8	3.0 ± 1.5	0.01*
Hb (g/dL)	11.4 ± 1.8	12 ± 1.7	10.2 ± 1.5	0.01*
Platelet Ct (10^3/μL)	72 ± 45	66 ± 37	82 ± 56	0.45
Albumin (g/dL)	3.7 ± 0.6	3.9 ± 0.5	3.5 ± 0.7	0.04*
PT (s)	15.4 ± 1.4	15.3 ± 1.2	15.5 ± 1.7	0.84
INR	1.2 ± 0.2	1.2 ± 0.1	1.2 ± 0.2	0.63
AST (U/L)	40 ± 28	42 ± 30	37 ± 24	0.7
ALT (U/L)	35 ± 40	31 ± 20	43 ± 59	0.73
AlkPhos (IU/L)	160 ± 170	174 ± 200	144 ± 94	0.75
Total bilirubin (mg/dL)	1 ± 0.8	1 ± 0.6	1.1 ± 0.9	0.66
Sodium (mEq/L)	138 ± 3	138 ± 3	138 ± 2	0.87
Creatinine (mg/dL)	1 ± 0.5	0.9 ± 0.4	1.3 ± 0.5	0.01*
MELD	11 ± 3	10 ± 3	12 ± 3	0.01*
MELD-Na	12 ± 3	11 ± 3	13 ± 3	0.09
CTP score	6 ± 1	6 ± 1	7 ± 1	0.01*
No. by CTP class				
A	23	18	5	0.01*
B	14	5	9	
Primary indication				
Cytopenia	23	17	6	0.005*
Refractory ascites	10	2	8	
Varices	5	5		
Splenic aneurysm	1	1		
Splenic width (cm)	16 ± 3	16 ± 3	15 ± 3	0.93
Splenic infarction volume (%)	64 ± 14	65 ± 15	64 ± 13	0.86
Infarction type				
Peripheral	28	19	9	0.44
Confluent	11	6	5	
F/u time (weeks)	116 ± 96	110 ± 106	127 ± 80	0.32

[a] Continuous variables reported as mean values ± one standard deviation.
* $P < 0.05$ considered statistically significant.

safety with regard to complications, and mortality. Secondary end points were safety with regard to MELD [38], MELD-Na [39], and CTP [40] score, length of hospital stay (LOS), and impact on liver function.

PSE-associated complications were classified using the clinical guidelines set forth by the Society of Interventional Radiology [41]. Major complication events included, but were not limited to, pleural effusion, ascites, spontaneous bacterial peritonitis, pneumonia, and inferior vena cava thrombus.

2.6. PSE protocol

Patients received pneumococcal polysaccharide vaccine (Pneumovax 23) within two weeks prior to the procedure and Cefazolin 1 g immediately prior to skin incision. Access was obtained through the femoral or radial artery (n = 1) and the splenic artery catheterized with a 5-French catheter. The catheter was advanced to the distal splenic artery or splenic hilum and diagnostic arteriography was performed. One of three general embolization techniques was employed according to operator preference: (1) non-selective delivery of embolic materials diffusely to the spleen (resulting in a peripheral infarct pattern); (2) deployment of a vascular plug in the mid-splenic artery (resulting in a peripheral infarct pattern secondary to collateral arterial flow); (3) selective delivery of embolic materials to the middle or lower splenic pole (resulting in a confluent infarct pattern) [35]. Representative examples of peripheral and confluent infarct patterns are shown in Fig. 1. Embolic materials included trisacryl gelatin microspheres (Embospheres; Merit Medical Systems; South Jordan, UT) ranging from 500 to 1200 um (n = 30), ethylene vinyl alcohol copolymer (Onyx; Medtronic; Minneapolis, MN) (n = 4), Amplatzer plugs (St. Jude Medical; St. Paul, MN) (n = 3), and Gelfoam slurry (Baxter Healthcare Corporation; Hayward, CA) (n = 2). Progressive embolization was performed by repeat injection until the therapeutic endpoint was achieved: approximately 60–70% reduction in splenic blush as visually estimated by the operator from digital subtraction arteriography.

Patients were routinely monitored in the hospital overnight and discharged post-operative day one. Exceptions included patients already admitted for alternative diagnoses or those with postoperative complications. Patients were instructed to obtain follow-up laboratory tests including peripheral blood count and liver tests with their referring physician. Systematic follow-up imaging to evaluate extent of infarction was deemed unnecessary.

2.7. Statistical analysis

Data were analyzed using data analysis and statistical software package STATA for Macintosh, version 14.2 (STATA; College Station, TX). Baseline demographic and laboratory data are reported as means ± one standard deviation and follow-up laboratory data were reported as medians. The study followed a repeat-measures design in which multiple laboratory values were obtained for each patient at different time-points relative to PSE. After hematological parameters were deemed non-parametric by Shapiro-Wilk, a Skillings-Mack test [42] was employed to compare time point medians while accounting for the arbitrary missing-data structure (not all patients had data available for every time point). Wilcoxon signed-rank tests with Bonferroni corrections were used for post hoc analysis of relevant laboratory values. The independence of categorical and continuous variables between patient subgroups (pre-LT vs post-LT) was determined by Pearson's chi-squared test and Wilcoxon-Mann-Whitney test, respectively. Statistical significance was set at $p < 0.05$.

3. Results

3.1. Hemoglobin

Effects on hematologic indices are shown in Table 3. Among all patients there was a short-lived, significant one-unit drop in median hemoglobin at two weeks, with no significant difference from baseline thereafter. On subgroup analysis, this drop was only observed in pre-LT patients. Baseline differences in median hemoglobin levels between pre- and post-LT patients persisted in subsequent post-procedure time-points.

3.2. White blood cell count

For all patients the median WBC count was significantly elevated over baseline out to two years and remained above 4×10^3/μL out to three years post-PSE. Similar trends were observed in pre- and post-LT subgroups. WBC count peaked at two weeks (likely due to post-embolic inflammatory response) then declined, coming in-line with long-term trends at one month post-PSE. Of note, the significant difference in baseline WBC count between subgroups was also no longer observed.

3.3. Platelet count

In all patients there was a significant increase in median platelet count starting at two weeks post-PSE through 3.5 years. Median platelet count remained $> 100 \times 10^3$/μL out to five years, an approximate two-fold increase over baseline. Among pre- and post-LT subgroups median platelet count was significantly elevated out to 2.5 years and six months, respectively. Counts were most variable at two weeks post-PSE. By six months, median platelets in pre-LT patients were 2.1 times their baseline compared to 1.8 times in post-LT patients. There was no significant difference in median platelet counts between subgroups at

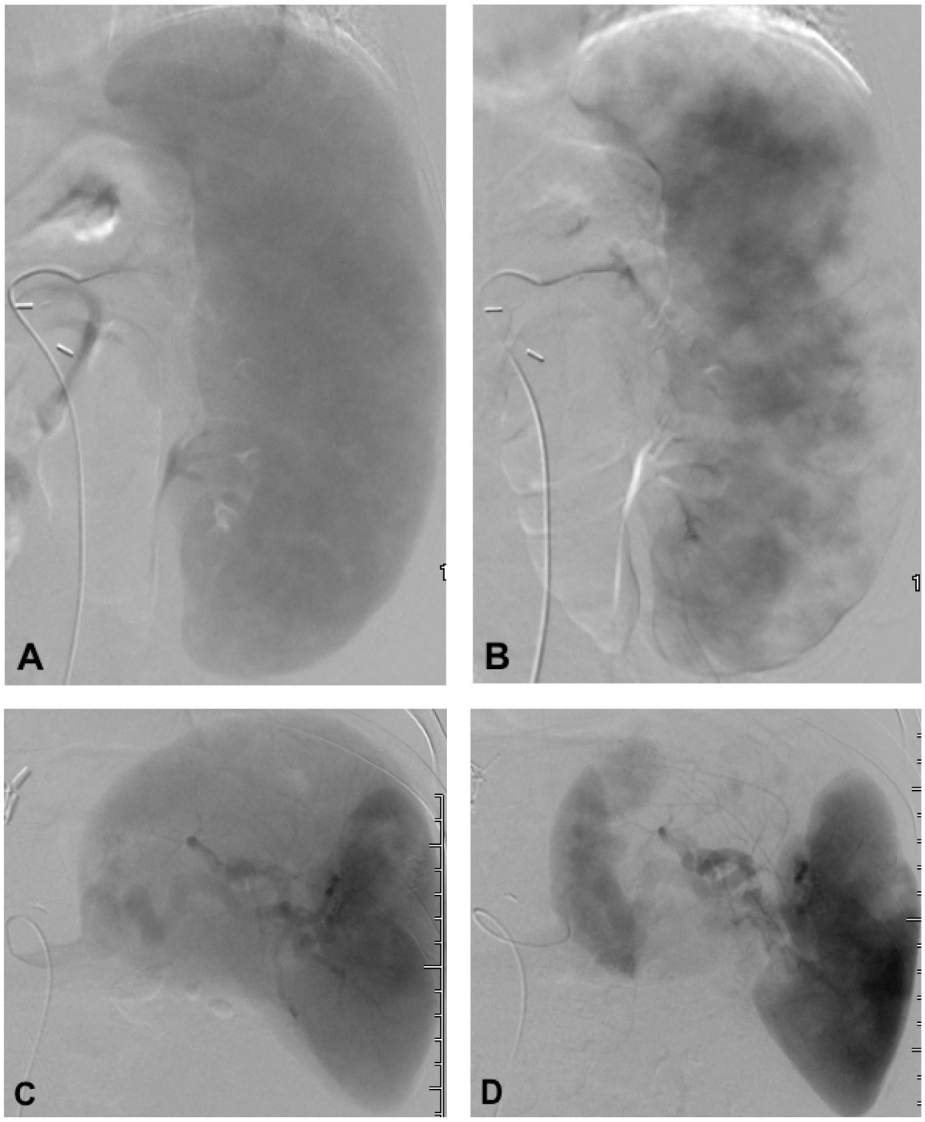

Fig. 1. Splenic arteriograms prior to (A) and following (B) non-selective PSE resulting in a peripheral infarct pattern. Selective embolization of the middle-pole arterial branch yielding a confluent infarct pattern in C and D. Infarction ratio was estimated at 60% in both cases.

baseline or any time point post-PSE.

3.4. MELD score

There was no significant difference from baseline in MELD score among all patients or by subgroup following PSE. Pre-LT patients had a wide range of MELD scores prior to PSE that continued out to one month.

3.5. Child-Turcotte-Pugh score

PSE did not result in a significant change in CTP score from baseline among the entire patient cohort, nor within subgroups. The baseline significant difference in CTP score between subgroups persisted from one month onward.

3.6. Other parameters

In all patients no sustained significant difference from baseline was observed in albumin, prothrombin time (PT), international normalized ratio (INR), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AlkPhos), total bilirubin, serum sodium, creatinine, or MELD-Na score out to one year post-PSE. There was a clinically significant drop in albumin at two weeks post-PSE in all patients and the pre-LT subgroup, however this resolved at one month and likely reflected common post-operative hypoalbuminemia [43]. There was a gradual trend toward improved PT in all and pre-LT patients. In post-LT patients there was a trend toward increased transaminases and decreased total bilirubin.

3.7. Length of hospital stay

Length of hospital stay (LOS) is shown in Table 4. Mean total LOS was five days for pre-LT versus ten days for post-LT patients, though this difference was not significant. The gap narrowed for post-PSE LOS, suggesting the difference in total LOS was due to prior diagnoses unrelated to embolization. The number of patients with prolonged stays (defined as greater than two days) was nearly proportional between subgroups. In the pre-LT subgroup, five of ten patients with prolonged total LOS were secondary to PSE, consisting of post-operative pain management, two patients receiving prophylactic intravenous antibiotics, monitoring of a high-risk cystic fibrosis patient, and weaning a patient to their home O_2 requirement. Two of six post-LT patients with prolonged stays were related to PSE, including large volume

Table 3
Effect on hematological indices by time point.[a]

	LT status	Pre-PSE	Time post-PSE (months)			
			0.5	1	6	12
No. of patients	Pre	25	19	15	13	11
	Post	14	8	7	8	3
WBC (10^3/μL)	Pre	4	8.8*	6.3*	5*	4.7*
	Post	2.7	11*	4.6	4.4	5.8
Hb (g/dL)	Pre	10.7	11.8	11.8	12.4	13.5
	Post	10	9.6	9.6	10.2	10.8
Platelet Ct (10^3/μL)	Pre	61	267*	95*	131*	124*
	Post	74	190*	157*	145*	241
Albumin (g/dL)	Pre	4	3.4*	4	4.3	4.3
	Post	3.3	3	3.1	3.2	3
PT (s)	Pre	15	15.5	15	14.5	14.6
	Post	15	16.4	14.3	15.3*	13.6
INR	Pre	1.2	1.2	1.2	1.1	1.2
	Post	1.2	1.3	1.1	1.2	1
AST (U/L)	Pre	28	40	29	26	25
	Post	33	21	34	51	51
ALT (U/L)	Pre	24	25	24	28	23
	Post	22	17*	31	46	43
AlkPhos (IU/L)	Pre	128	191	125	124	143
	Post	127	139	142	194	169
Total bilirubin (mg/dL)	Pre	0.7	1.1	0.7	0.8	0.7
	Post	0.8	0.7	0.7	0.5	0.6
Sodium (mEq/L)	Pre	139	137	138	138	139
	Post	139	135	140	138	139
Creatinine (mg/dL)	Pre	0.8	0.7	0.9	0.7	0.9
	Post	1.3	1	0.9	1.1	1.7
MELD	Pre	9	10	9	8	9
	Post	12	11	9	11	12
MELD-Na	Pre	11	12	11	10	11
	Post	13	13	10	17	12
CTP score	Pre	5	6	5	5	5
	Post	8	8	8	8	6

[a] Median values.
* $P < 0.05$ considered statistically significant.

Table 4
Length of hospital stay, major complications, and readmissions associated with PSE by subgroup.

	Pre-LT	Post-LT	*p*
Total LOS (days)[a]	5 ± 6	10 ± 16	0.83
Post-PSE LOS (days)[a]	3 ± 4	5 ± 8	0.93
No. of LOS > 2 days	10	6	0.86
Major complications	5	1	0.26
Readmissions	7	1	0.11
Readmission POD (days)[a]	8 ± 4	8	0.12
Readmission LOS (days)[a]	8 ± 6	4	0.1

[a] Mean values ± one standard deviation.

paracentesis (LVP) of rapidly re-accumulating chronic ascites, and monitoring of high post-operative fever. In the seven patients with prolonged LOS secondary to PSE, mean post-PSE LOS was 6 and 3.5 days in the pre-LT and post-LT subgroups, respectively.

3.8. Complications

Complications are shown in Table 4. The majority of patients exhibited at least one symptom of post-embolic syndrome including abdominal pain, nausea, and low-grade fevers that were medically managed prior to discharge. Out of 40 PSEs, six (15%) resulted in major complication. There was a trend toward higher major complication rate in pre-LT patients, which included worsening of a chronic pleural effusion (successfully treated with chest tube and talc pleurodesis), high-grade fever concerning for occult infection (treated with intravenous antibiotics), spontaneous bacterial peritonitis (SBP), pneumonia resulting in hospitalization, and inferior vena cava thrombus requiring surgical declot and splenectomy. In the post-LT subgroup one patient developed rapid re-accumulation of their chronic ascites requiring early LVP. There were five deaths (three pre-LT, two post-LT) during follow-up, at two, three, six, 21, and 40 months post-PSE, none of which were related to the procedure (0% mortality rate).

Table 5
Baseline characteristics of patients who developed a major complication.[a]

	No complication	Major complication	*p*
No. of patients	32	6	
No. of PSEs	34	6	
No. of men	14	2	0.62
No. of women	18	4	
No. of post-LT patients	13	1	0.31
Age (years)	45 ± 23	42 ± 28	0.98
BMI	26 ± 5	23 ± 6	0.2
WBC (10^3/μL)	3.7 ± 1.8	4.2 ± 2.2	0.51
Hb (g/dL)	11.2 ± 1.8	12.3 ± 2.2	0.24
Platelet Ct (10^3/μL)	69 ± 40	99 ± 70	0.4
Albumin (g/dL)	4 ± 0.8	3.7 ± 0.6	0.54
PT (s)	15.3 ± 1.4	16.7 ± 1.5	0.07
INR	1.2 ± 0.2	1.3 ± 0.2	0.1
AST (U/L)	40 ± 25	41 ± 44	0.49
ALT (U/L)	36 ± 41	27 ± 19	0.76
AlkPhos (IU/L)	173 ± 172	82 ± 22	0.06
Total bilirubin (mg/dL)	1 ± 0.7	1 ± 1.1	0.45
Sodium (mEq/L)	138 ± 3	137 ± 3	0.61
Creatinine (mg/dL)	1.1 ± 0.5	0.7 ± 0.4	0.18
MELD	11 ± 3	11 ± 2	0.77
MELD-Na	12 ± 3	12 ± 3	0.6
CTP score	6 ± 1	7 ± 2	0.86
No. by CTP class			
A	20	4	0.89
B	12	2	
Primary indication			
Cytopenia	20	4	0.91
Refractory ascites	9	1	
Varices	4	1	
Splenic aneurysm	1		
Splenic width (cm)	16 ± 3	15 ± 3	0.47
Splenic infarction volume (%)	65 ± 14	65 ± 16	0.94
No. with infarct volume > 70%	2	2	0.04
Infarction type			
Peripheral	26	3	0.18
Confluent	8	3	
F/u time (weeks)	112 ± 93	133 ± 113	0.68

[a] Continuous variables reported as mean values ± one standard deviation.

Baseline and PSE characteristics of patients who experienced a major complication are shown in Table 5. The etiology of the underlying portal hypertension in the six patients with major complications included: primary sclerosing cholangitis (PSC), viral hepatocellular carcinoma (HCC), metastatic colorectal cancer (CRC), portal vein thrombus (PVT), and autoimmune hepatitis. There were no significant differences in baseline characteristics. There was no difference in the estimated splenic infarction ratio, although the complications subgroup trended toward a higher ratio of confluent infarctions and proportionally had more patients with > 70% infarction volume.

During follow-up one pre-LT patient with cystic fibrosis underwent LT eight months post-PSE, and one post-LT patient underwent a second transplant with splenectomy at nine months post-PSE. Two pre-LT patients underwent splenectomy post-PSE, one at two weeks secondary to PVT described previously and the other at nine months due to persistent portal hypertension and splenic aneurysms. Two post-LT patients underwent splenic artery ligation at 14 and 24 months post-PSE for persistent refractory ascites.

4. Discussion

The study demonstrates the efficacy of PSE in patients with portal hypertension from a broad range of etiologies leading to a significant

rise in WBC and platelet count out to two and 3.5 years, respectively. Subgroup analysis determined that PSE in post-LT patients with persistent hypersplenism is as efficacious as in pre-LT patients. Median WBC counts increased by 1–2 $\times 10^3$/μL above subgroup baselines, remaining $> 4 \times 10^3$/μL out to four years. The procedure resulted in a near doubling of median platelet counts at six months that remained $> 100 \times 10^3$/μL at all time-points in the subsequent five years. PSE appeared to have a longer lasting effect on WBC and platelet count in the current cohort when compared to the findings from the two largest studies on PSE [44,45]. This is likely related to differences in patient demographics and consistency in follow-up.

This study did not find that PSE significantly impacted hemoglobin levels beyond 2-weeks post-procedure. The negative finding is in agreement with other large PSE studies that determined no significant increase in Hb [46] or red blood cell (RBC) count [47]. Competing reports [18] exist that found a statistically significant 1.5–2 g/dL increase in average Hb levels at 6-months post-PSE, raising the concern that the myelotoxic immunosuppressive regimen in the current post-LT subgroup may have diluted the effect. However, this is unlikely because a significant increase in Hb has been demonstrated in a cohort of eight post-LT patients on similar regimens [25].

Hypersplenism in patients with liver disease results from a multitude of factors including those that originate in the liver and those in the spleen. In cirrhotics, the primary mechanisms by which PSE increases platelet count are by improving hepatic thrombopoietin (TPO) synthesis [46,48], lengthening platelet survival time through a reduction in platelet-associated immunoglobulins generated in the spleen [11,49], and decreasing splenic platelet sequestration [11,50]. This mixture of causes explains the resolution of hypersplenism in up to 80% of patients who undergo liver transplantation, which addresses TPO synthesis [22,23], and suggests that persistent hypersplenism after transplantation may be predominantly splenic in origin. In that scenario, splenic-directed therapy may be the ideal treatment in post-LT patients though has yet to be proven efficacious in the long-term. The current study demonstrates the utility of PSE in addressing this remaining splenic component in post-LT patients with persistent hypersplenism.

PSE does not affect the spleen in isolation though. The organ is linked to the liver by a shared celiac arterial supply (at least in classic anatomy) and its venous contribution to portal flow. Elusive post-transplant liver graft dysfunction has often been attributed to this intimate relationship. SASS describes a state of hepatic arterial hypoperfusion caused by the siphoning of blood by an enlarged spleen. Its corollary, small-for-size syndrome (SFSS), relates to a mismatch in size between liver graft vasculature and recipient portal veins engorged by chronic portal hypertension. There is controversy in the literature regarding the prevalence of these syndromes because they are diagnoses of exclusion with overlapping pathophysiology, connected by the proposed hepatic arterial buffer response [51]. Both may be treated by redirecting arterial flow with PSE [52,53] and were considered in this report. No patients in the post-LT subgroup had isolated graft dysfunction in the absence of perioperative/hospital course complication or frank rejection, central to the diagnosis of SASS or SFSS. Furthermore, there was no consistent improvement in liver function enzymes following PSE as would be expected. The results favor the conclusion that PSE improves post-LT hypersplenism primarily by its impact on the spleen rather than improved hemodynamic flow to the liver.

In regards to safety, post-LT status does not confer any additional risk, either in terms of predictive models based on laboratory values or post-operative complication rate. Following PSE there were no significant differences in median MELD, MELD-Na, nor CTP score out to one year in all patients or subgroups, suggesting a nominal impact on liver-based prognosis.

Post-PSE major complication rate among all patients was 15% with 0% mortality. These rates are in line with guidelines put forth by the *Society of Interventional Radiology* [41] and are on par with those reported by a larger study on PSEs in a patient cohort with a similar distribution of CTP scores [45]. Importantly, the concern that post-LT patients would be at an increased risk of complications due to their immunosuppressed status and thrombotic risk proved to be unfounded. In fact, there was a trend toward fewer complications in post-LT patients with only one (7%) event occurring in the LT subgroup. Although this lower complication rate did not translate into shorter total LOS given their medical complexity, it did result in a shorter post-operative LOS related to PSE.

The finding contrasts the 45% complication rate observed by Elfeki et al. [35] in 16 post-LT patients undergoing PSE primarily for severe thrombocytopenia or cytopenias interfering with antiviral therapy. Baseline patient characteristics (including MELD and CTP score) of this cohort were not described, however they had significantly larger splenic volumes with a mean of 1485 cm^3 compared to 805 cm^3 in the current study [36]. The degree of splenomegaly was reflected in the severity of hypersplenism, with average platelet count of 43×10^3/μL and WBC of 2.5×10^3/μL for 11 patients. As a consequence, despite their lower average splenic infarction rate at 54% (which should correlate with reduced complications), their patients had a higher absolute splenic infarction volume, which is associated with an increase in complications [46].

Similarly Barcena et al. reported a 63% complication rate in their cohort of eight post-LT patients with recurrent hepatitis C [25]. Baseline characteristics suggested their cohort had more advanced liver disease (average MELD score 14 compared to 12 in this report), significantly greater average splenic infarction ratio of 85% well into the range associated with increased complications [45], and active hepatitis C infection which has been associated with thrombotic risk factors [54].

There were next-to-no significant differences in the baseline characteristics between patients with and without PSE-associated complications. Notably the mean splenic infarction ratio between the two subgroups were virtually the same, however there was a statistically significant correlation between the patients with a > 70% infarction ratio and major complications. Zhu et al. found that a > 70% infarction rate resulted in a 60% complication rate in a prospective series of 60 patients, with only a 10% complication rate at < 70% infarction; results this study corroborates [45]. Additionally, there was a trend toward confluent splenic infarction pattern in the complications subgroup, supporting findings by Elfeki et al. associating increased complications with segmental approach to PSE [35]. Of course, in comparison to non-selective embolization, this segmental approach dramatically reduces the risk of over-infarcting the spleen so should not be entirely discounted. Of note, one patient treated with an Amplatzer plug in the mid-splenic artery for their PSE developed rapid worsening of their chronic right pleural effusion requiring a chest-tube. The patient is an outlier in regard to Gu et al. experience with distal splenic artery coiling resulting in a 0% complication rate, presumably due to the preservation of collaterals to the spleen [47]. The complications subgroup in the current study also trended toward a lower BMI (23 vs 26) and a higher prevalence of malignancy (50% vs 29%) implicating diminished reserve capacity as a possible contributing factor.

There are several limitations to this report. It is a retrospective study involving a small sample size in both the control pre- and post-LT population. The small sample size is of particular concern given the 16 years over which the patients underwent PSE: in that time there were nine different operators, evolution of medical management and procedural approach, as well variability in imaging technology. There was a significant difference in the indication for PSE between the control and post-LT population limiting comparison. Many patients were also receiving myelotoxic therapy which may have been tapered or changed during follow-up, impacting their hematological indices independent of PSE. Lastly, the results are restricted to patients with hypersplenism as the primary cause of their cytopenia(s) and PSEs performed in the non-emergent setting reflecting the strict exclusion

criteria.

5. Conclusion

This analysis shows that PSE is effective in increasing WBC and platelet count in both pre-LT and post-LT patients, with no statistically significant difference between subgroups. Moreover, the study demonstrates no significant difference in safety or complications associated with PSE in relation to transplant status.

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