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INTERVENTIONAL

Comparison of TIPS alone and combined with partial splenic embolization (PSE) for the management of variceal bleeding

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Abstract

Objectives Transjugular intrahepatic portosystemic shunt (TIPS) and partial splenic embolization (PSE) were two interventional radiological treatments for the complications of cirrhosis. This study aimed to investigate the effects of concomitant PSE on the long-term shunt patency and overall survival of TIPS-treated patients.

Methods Forty-eight patients with TIPS insertion were enrolled and studied retrospectively. They were divided into TIPS+PSE ($n = 16$) and TIPS groups ($n = 32$), undergoing combined therapy using TIPS and PSE, and monotherapy using TIPS alone, respectively.

Results The 5-year cumulative primary patency rate in the TIPS+PSE group was markedly higher than in the TIPS group (56.8% vs. 32.8%, $p = 0.028$), whereas the 5-year cumulative secondary patency rate (93.8% vs. 87.7%, $p = 0.749$) and overall survival rate (62.5% vs. 30.7%, $p = 0.414$) were not significantly different between the two groups. Cox-regression models revealed that group (hazard ratio [HR], 0.235; 95% CI, 0.084–0.665; $p = 0.006$), portal venous pressure decline (HR, 0.687; 95% CI, 0.563–0.838; $p = 0.000$), and baseline portal vein thrombosis (HR, 3.955; 95% CI, 1.634–9.573; $p = 0.002$) were significant predictors for shunt dysfunction, while only ascites (HR, 2.941; 95% CI, 1.250–6.920; $p = 0.013$) was a significant predictor for mortality. No severe adverse event was noted in the two groups except for the potential risk of splenic abscess development in the TIPS+PSE group.

Conclusions Concomitant PSE may help increase the long-term primary shunt patency rate, but not the overall survival of TIPS-treated patients. Further prospective studies are needed to validate these retrospective findings and to investigate the potential mechanisms.

Key Points

- *Combined therapy using TIPS and PSE is associated with higher primary patency rates than TIPS alone.*
- *Combined therapy using TIPS and PSE is associated with similar rates of secondary patency and overall survival of patients than TIPS alone.*
- *Group (TIPS alone or TIPS+PSE), PVD, and baseline PVT are three independent predictors for shunt dysfunction, while ascites is the only independent predictor for mortality.*

Keywords Portosystemic shunt, transjugular intrahepatic · Spleen · Embolization, therapeutic · Esophageal and gastric varices · Bleeding

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Abbreviations

B-RTO	Balloon-occluded retrograde transvenous obliteration
CI	Confidence interval
CT	Computed tomography
CTP	Child–Turcotte–Pugh
ePTFE	Expanded polytetrafluoroethylene
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HE	Hepatic encephalopathy

HR	Hazard ratio
MELD	Model for end-stage liver disease
PLT	Platelet
PSE	Partial splenic embolization
PTVE	Percutaneous transhepatic variceal embolization
PVD	Portal venous pressure decline
PVT	Portal vein thrombosis
TIPS	Transjugular intrahepatic portosystemic shunt
TJO	Transjugular retrograde obliteration
WBC	White blood cell counts

Introduction

Liver cirrhosis can lead to portal hypertension and subsequent development of many severe complications, such as gastroesophageal variceal bleeding, hepatic encephalopathy (HE), ascites, sepsis, and hypersplenism [1]. Transjugular intrahepatic portosystemic shunt (TIPS) and partial splenic embolization (PSE) were two interventional radiological methods that have been widely utilized for the management of some of these complications. For instance, previous studies have demonstrated that TIPS creation with or without concomitant variceal embolization is effective for secondary prevention of bleeding from gastroesophageal varices or cardiofundal varices and control of refractory ascites, because it can effectively reduce the intravascular pressure in the portal venous system [2–7]. And previous studies also showed that PSE was efficient in alleviating severe leucocytopenia and thrombocytopenia due to hypersplenism [8–10].

Intriguingly, several studies suggested that combined therapy using PSE and other radiological interventional procedures, including transjugular retrograde obliteration (TJO), percutaneous transhepatic variceal embolization (PTVE), and balloon-occluded retrograde transvenous obliteration (B-RTO), to obliterate portosystemic shunts, was more effective and beneficial than monotherapy with these procedures alone [11–14]. However, to our best knowledge, there is no study in the literature that reported the results of combined therapy using TIPS and PSE for the treatment of cirrhotic patients with recurrent variceal bleeding.

Therefore, we conducted the present study to investigate the safety, long-term shunt patency, and overall survival of patients receiving combined therapy using TIPS and PSE as compared with monotherapy with TIPS alone.

Materials and methods

The study was approved by our institutional ethics committee and conformed to the Helsinki Declaration of 1975, as revised in 2008. Individual written informed consent for the TIPS and PSE procedures and for participation in this study was obtained from all patients or their next-of-kins.

Patients

A total of 223 consecutive patients with cirrhosis who underwent TIPS placement in the Second Affiliated Hospital of Kunming Medical University were screened retrospectively. Indication for TIPS was recurrent gastroesophageal variceal bleeding confirmed by endoscopy. Exclusion criteria were aged > 75 years old [1]; with chronic kidney, lung, or heart disease [2]; active tuberculosis or human immunodeficiency virus infection [3]; with malignancy [4]; with a previous history of TIPS placement, portocaval surgery, or splenectomy [5]; and with alcohol dependence [6]. Overall, only 48 patients were included in the study. Among them, 16 patients underwent additional partial splenic embolization (PSE) indicated by severe hypersplenism with white blood cell counts (WBC) $< 2 \times 10^9$/L and/or platelet (PLT) counts $< 50 \times 10^9$/L (TIPS+PSE group). The other 32 patients were matched to the 16 patients in the TIPS+PSE group and serve as a control group (TIPS group) according to age, gender, laboratory parameters, and pre- and post-operative portal venous pressures (Fig. 1).

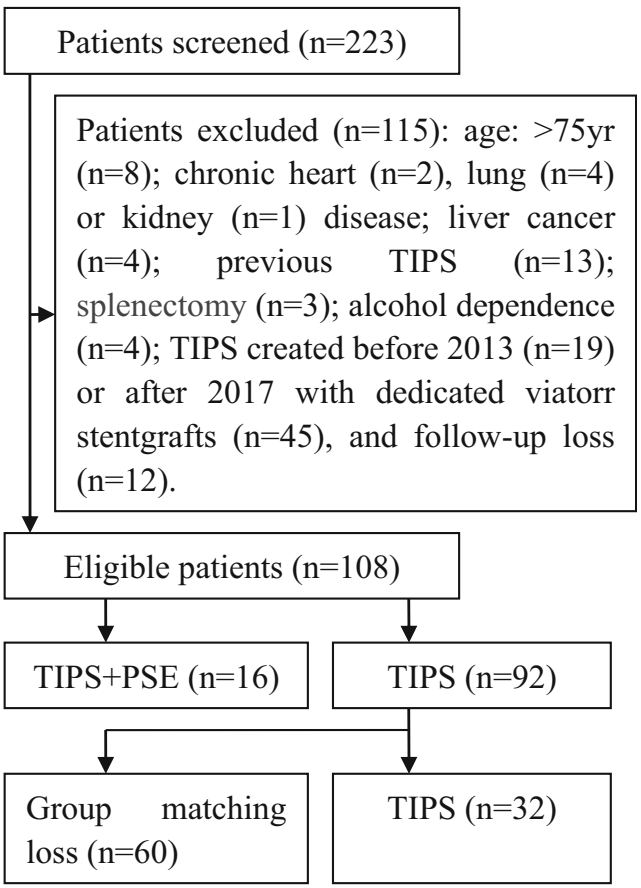

Fig. 1 Group allocation of the study population. TIPS, transjugular intrahepatic portosystemic shunt; PSE, partial splenic embolization

TIPS procedure

TIPS was performed by a group of experienced interventional radiologists as previously described [15–17]. Notably, during the procedure, RUPS 100 puncture kits (RUPS-100; Cook Medical), expanded polytetrafluoroethylene (ePTFE)–covered stents (8 mm × 40–60 mm, Fluency; C.R. Bard, Inc.; Fig. 2a) were used; dilated collaterals, i.e., short gastric vein and gastric coronary vein, were embolized with spring coils of different sizes (MReye; Cook Medical; Fig. 2a), and the portal venous pressures before and after TIPS placement, intra-TIPS pressure, and right atrial pressure were measured. The portal venous pressure decline (PVD) can then be derived from the difference between portal venous pressures before and after TIPS placement.

PSE procedure

Concomitant PSE was also conducted within 4 weeks following TIPS insertion by the same group of interventional radiologists according to the previously described procedure [18, 19]. Briefly, a 5-F catheter (Cobra; Terumo Medical Corporation) was introduced into the femoral artery by the Seldinger approach. Routine celiac angiography and selective splenic arterial angiography were performed to visualize the distribution of splenic arteries and collateral vessels. The catheter tip was subsequently advanced as distal as possible to the splenic hilus. Embolization was finally performed using spring coils of different sizes (MReye; Cook Medical) to embolize branches of the splenic arteries with a splenic infarction ratio set at ~ 50%, which could minimize the risk of severe complications while still attaining the potential benefit of improving leucocyte and platelet counts according to our experience and to a previous study [8] (Fig. 2b).

Follow-up study and data collection

After the procedures, routine follow-up visits were scheduled at the 1st, 3rd, 6th, and 12th month, and then annually thereafter or whenever symptoms recurred. Additional follow-up visits were arranged whenever a patient felt unwell. The follow-up visits included clinical assessment, biochemical tests, color Doppler ultrasonography, and portal venography via contrast-enhanced computed tomography (CT). When shunt dysfunction was suspected, direct portal vein angiography was performed via the transjugular route. All these data were prospectively collected and analyzed anonymously.

Outcomes

In this study, the primary outcome was the primary patency rate, while secondary outcomes were the secondary patency rate, patient overall survival, and adverse events.

Diagnosis, definitions, and TIPS revision

The diagnosis of cirrhosis was confirmed as previously described [20]. Portal vein thrombosis (PVT) was diagnosed as the intravenous solid material detected by ultrasound or contrast-enhanced CT scans [21]. Child–Turcotte–Pugh (CTP) and model for end-stage liver disease (MELD) scores were calculated as previously described [22]. Shunt dysfunction referred to a TIPS narrowing ≥ 50% or complete blockage [23]. Primary patency was defined as the period between TIPS placement and the onset of shunt dysfunction, while secondary patency referred to the duration between TIPS insertion and permanent shunt dysfunction [24]. Overall survival was defined as the interval between successful TIPS creation and death due to all causes. TIPS revision was performed as described previously [15–17].

Statistical analysis

All statistical analyses were performed using SPSS 17.0 software packages. Continuous data were presented as median (range) and compared by the Mann–Whitney *U* test. Categorical data were expressed as number and percentage, and analyzed by the chi-square test or Fisher's exact test.

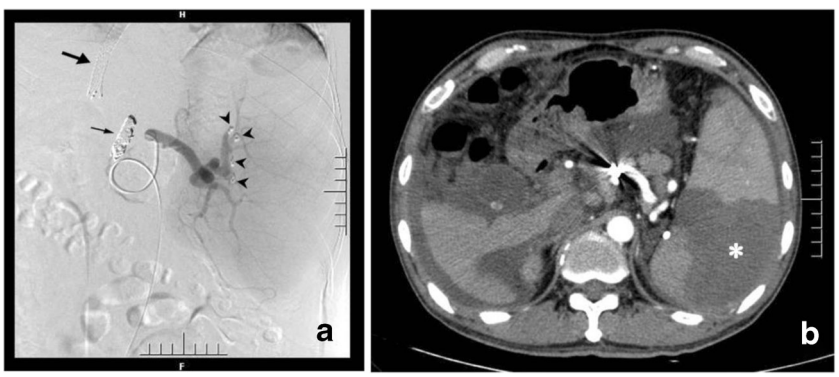

Fig. 2 **a** Venogram shows insertion of a 8 mm × 60-mm covered stent (wide arrow), embolization of portosystemic collaterals by a large spring coil (narrow arrow), and embolization of splenic artery by small spring coils (arrowhead). **b** CT scan reveals splenic infarction (asterisk) and spring coil used to embolization of portosystemic collaterals (arrow)

Survival curves were plotted by the Kaplan–Meier method and analyzed by the log-rant test. Univariate and multivariate analyses were performed to evaluate the predictors of shunt dysfunction and death using the Cox proportional hazards regression model. To overcome the issue of overfitting and collinearity, only predictors with $p < 0.05$ in the univariate analysis were evaluated in the multivariate model. Group was included in all multivariate models as it was the central factor to evaluate. Moreover, components of CTP score (albumin, PT, TBIL, and ascites) and model for end-stage liver disease MELD score (TBIL, INR, and creatinine) were not included in multivariate analysis along with the CTP and MELD scores regardless of their p values in the univariate analysis. A two-tailed p value < 0.05 were considered statistically significant.

Results

Patient characteristics

The patient characteristics, baseline laboratory, and radiological investigations at TIPS placement were summarized in Table 1. Patients in the two groups were well balanced in terms of age, sex, concurrent disease, etiology and severity of liver disease, hematological parameters, radiological indices at TIPS insertion, and follow-up period, except that patients in the TIPS+PSE group had significantly higher HCV-RNA values than those in the TIPS group ($p = 0.046$).

Shunt dysfunction, primary patency rate, and predictors

The shunt dysfunction rate was 47.9% (23 out of 48 patients) in all patients during the follow-up period, with no significant difference between the TIPS+PSE and TIPS groups (5/16 vs. 18/32, $p = 0.102$). Among the 23 patients with shunt dysfunction, 3 patients in the TIPS+PSE group and 12 in the TIPS group developed shunt narrowing, while 2 patients in the TIPS+PSE group and six in the TIPS group had shunt occlusion, respectively. The mean time to shunt dysfunction was markedly longer in the TIPS+PSE group than in the TIPS group (55.1 months; 95% confidence interval [CI], 45.1–65.0 vs. 35.6 months; 95% CI, 27.8–43.4; $p = 0.028$; Fig. 3a). The cumulative 1-, 2-, 3-, 4-, and 5-year primary patency rates in the TIPS+PSE group were significantly higher than in the TIPS group (TIPS+PSE group: 93.8%, 87.5%, 79.5%, 68.2%, and 56.8% vs. TIPS group: 84.4%, 61.7%, 39.3%, 32.8%, and 32.8%; $p = 0.028$; Fig. 3b). In the univariate analysis, significant predictors for the development of shunt dysfunction were group assignment, PVD, and baseline PVT. In the multivariate analysis, group assignment (hazard ratio [HR], 0.235; 95% CI, 0.084–0.665; $p = 0.006$), PVD (HR, 0.687; 95% CI, 0.563–0.838; $p = 0.000$), and baseline PVT (HR, 3.955; 95% CI, 1.634–9.573; $p = 0.002$) remained significant predictors for the development of shunt dysfunction (Table 2).

Shunt revision and secondary patency rate

All the 23 patients with shunt dysfunction underwent once or multiple TIPS revisions, including balloon angioplasty ($n = 15$), insertion of a new stent plus balloon angioplasty ($n = 10$), thrombectomy, thromboaspiration, and thrombolysis plus balloon angioplasty ($n = 4$) and parallel TIPS creation ($n = 2$). TIPS revisions failed in three patients (13.0%). Notably, one patient had hepatic parenchymal puncture by the stent at the hepatic end resulting a kink; two patients had a calcified thrombus within the portal trunk that subsequently led to cavernous transformation. The cumulative 1-, 2-, 3-, 4-, and 5-year secondary patency rates were not significantly different between the two groups (TIPS+PSE group: 93.8%, 93.8%, 93.8%, 93.8%, and 93.8% vs. TIPS group: 100%, 95.0%, 87.7%, 87.7%, and 87.7%; $p = 0.749$; Fig. 4a).

Overall survival and predictors for mortality

Overall, death occurred in 15 patients due to the following causes: hepatocellular carcinoma ($n = 7$), liver failure ($n = 3$), sepsis ($n = 3$), and severe hepatic coma ($n = 2$). The cumulative rates of 1-, 2-, 3-, 4-, and 5-year overall survival rates were not significantly different between the two groups (TIPS+PSE group: 100%, 93.8%, 87.5%, 87.5%, and 62.5% vs. TIPS group: 96.9%, 93.8%, 90.3%, 79.3%, and 30.7%; $p = 0.414$; Fig. 4b). The mean survival periods were 54.2 months (95% confidence interval [CI], 47.9–60.4) in the TIPS+PSE group and 58.4 months (95% CI, 49.6–67.1) in the TIPS group, respectively ($p = 0.414$; Fig. 4b). In the univariate analysis, CTP score, ascites, and baseline PVT were found to be significantly associated with mortality. In the multivariate analysis, only ascites (hazard ratio [HR], 2.941; 95% CI, 1.250–6.920; $p = 0.013$) remained significantly associated with mortality (Table 3). Notably, group assignment was not associated with patients' mortality in both univariate (HR, 0.626; 95% CI, 0.199–1.970; $p = 0.423$) and multivariate analyses (HR, 0.455; 95% CI, 0.134–1.547; $p = 0.207$) (Table 3). Moreover, the CTP and MELD scores remained comparable between the two groups and within each group as compared with the baseline values at various time points except that the CTP score at the 4th and 5th year in the TIPS+PSE group was markedly lower than the baseline value (Fig. 5a, b).

Adverse events

After TIPS placement, early complications (≤ 14 days) were noted in 13 patients: nausea and vomiting ($n = 11$), puncture

Table 1 Baseline characteristics of the study population

Variables	TIPS+PSE ($n = 16$)	TIPS ($n = 32$)	p value*
Age (year)[a]	46.5 (29–59)	48 (35–59)	0.584
Sex: male, n (%)	12 (75.0%)	22 (68.8%)	0.653
Etiology, n (%)			
Hepatitis B virus	10 (62.5%)	21 (65.6%)	0.961
Hepatitis C virus	3 (18.8%)	6 (18.8%)	
Autoimmune liver disease	3 (18.8%)	5 (15.6%)	
HBV-DNA ($\log_{10}$ IU/mL)[a]	5.83 (4.76–6.09) ($n = 4$)	6.61 (3.14–6.69) ($n = 9$)	0.643
HCV-RNA ($\log_{10}$ IU/mL)[a]	7.68 (7.47–7.90) ($n = 2$)	6.30 (5.32–7.00) ($n = 6$)	0.046
Concurrent disease, n (%)			
Diabetes mellitus	4 (25.0%)	8 (25.0%)	1.000
Hypertension	2 (12.5%)	2 (6.3%)	0.460
Ascites, n (%)			
None	10 (62.5%)	21 (65.6%)	0.469
Mild	4 (25.0%)	4 (12.5%)	
Moderate to severe	2 (12.5%)	7 (21.9%)	
Child class, n (%)			
A	2 (12.5%)	7 (21.9%)	0.309
B	10 (62.5%)	22 (68.8%)	
C	4 (25.0%)	3 (9.4%)	
Endoscopic varices, n (%)			
Gastroesophageal varices	12 (75.0%)	23 (71.9%)	0.818
Esophageal varices	4 (25.0%)	9 (28.1%)	
Portal vein thrombosis, n (%)	7 (43.8%)	10 (31.3%)	0.393
Portosystemic collaterals, n (%)			
Short gastric vein	1 (6.3%)	5 (15.6%)	0.311
Coronary gastric vein	6 (37.5%)	16 (50.0%)	
Both short gastric and coronary veins	9 (56.3%)	11 (34.4%)	
Stent type and number, n (%)			
One covered stent	12 (75.0%)	22 (68.8%)	0.653
One covered stent along with one bare stent	4 (25.0%)	10 (31.3%)	
Stent location, n (%)			
From the middle hepatic vein to left portal branch	12 (75.0%)	14 (43.8%)	0.122
From the right hepatic vein to right portal branch	3 (18.8%)	13 (40.6%)	
From the inferior vena cava to the portal vein	1 (6.3%)	5 (15.6%)	
Pre-TIPS portal venous pressure (mmHg)[a]	29.5 (19–37)	27 (21–36)	0.653
Post-TIPS portal venous pressure (mmHg)[a]	21 (13–28)	19.5 (3–28)	0.660
Intra-shunt pressure (mmHg)[a]	11 (5–18)	11 (5–15)	0.676
Post-TIPS right atrial pressure (mmHg)[a]	7.5 (1–13)	7 (2–15)	0.982
Portal venous pressure decline (mmHg)[a]	7.5 (4–14)	8 (4–13)	0.741
Post-TIPS prophylaxis for thrombosis, n (%)			
Aspirin or clopidogrel	10 (62.5%)	21 (65.6%)	0.831
Warfarin	6 (37.5%)	11 (34.4%)	
White blood cell count ($3.5–9.5 \times 10^9$/L)[a]	4.1 (0.7–8.6)	2.7 (1.5–8.4)	0.289
Hemoglobin (female, 115–150 g/L; male, 130–175 g/L)[a]	81.5 (50–160)	83.5 (65–135)	0.592
Platelet count ($125–350 \times 10^9$/L)[a]	56 (33–278)	60 (39–144)	0.710
Prothrombin time (10.0–16.0 s)[a]	19.3 (12.8–24.6)	19.2 (13.2–24.0)	0.622
International normalized ratio[a]	1.63 (1.18–2.09)	1.59 (1.19–2.01)	0.577
Albumin (35–50 g/L)[a]	27.5 (20.8–41.3)	29.6 (22.1–36.1)	0.785
Alanine aminotransferase (5–40 U/L)[a]	28 (12–144)	32 (9–180)	0.512

Table 1 (continued)

Variables	TIPS+PSE ($n = 16$)	TIPS ($n = 32$)	p value*
Aspartate aminotransferase (8–40 U/L)[a]	44.5 (21–247)	44.5 (22–230)	0.870
Total bilirubin (3.4–20.5 μmol/L)[a]	29.4 (6.9–104.0)	27.7 (10.9–86.2)	0.341
Direct bilirubin (0.0–6.8 μmol/L)[a]	12.7 (2.8–54.6)	12.5 (4.6–57.8)	0.212
Creatinine (53–97 μmol/L)[a]	67 (31–115)	71 (35–100)	0.654
Child–Turcotte–Pugh score[a]	8 (5–12)	8 (6–10)	0.330
Model for end-stage liver disease score[a]	13.0 (1.7–14.7)	10.4 (5.2–14.2)	0.115
Follow-up duration (month)[a]	47 (17–69)	39.5 (10–69)	0.193

[a] Median (range). *By the Mann–Whitney *U* test or chi-square test. *HBV*, hepatitis B virus; *HCV*, hepatitis C virus; *TIPS*, transjugular intrahepatic portosystemic shunt

site bleeding from the neck ($n = 3$), temporary respiratory distress and cardiac arrhythmia ($n = 4$), and intra-abdominal bleeding due to hepatic capsular puncture ($n = 2$), which were successfully controlled conservatively. After the PSE procedure, nine patients (56.3%) had abdominal pain, vomiting, and moderate fever (below 39.0 °C). During the study, complete resolution of PVT occurred in all patients with baseline PVT, while new PVT was detected in four patients in the TIPS+PSE group and nine in the TIPS group. Neither the incidence (4/16 vs. 9/32, $p = 0.818$) nor the mean time remaining free of PVT (TIPS+PSE group: 57.8 months; 95% CI, 48.2–67.4 vs. TIPS group: 54.3 months; 95% CI, 46.5–62.0; $p = 0.574$, by log-rank test) was significantly different. Despite all patients with fever having treated with intravenous antibiotics, splenic abscess still occurred in two patients (12.5%), who were treated by ultrasound-guided percutaneous splenic puncture and abscess drainage with prolonged hospital stays of 28 days and 36 days, respectively. During follow-up, HE occurred in ten patients (four in the TIPS+PSE group and six in the TIPS group), which were not significantly different between the two groups in terms of incidence (4/16 vs. 6/32, $p = 0.615$) or mean time remaining free of first episode of HE (TIPS+PSE group: 54.4 months; 95% CI, 41.8–67.0 vs. TIPS group: 56.5 months; 95% CI, 47.5–65.5; $p = 0.704$, by log-rank test). Mortality related to the TIPS or PSE procedure was not recorded.

Discussion

In the present study, we demonstrated that combined therapy using TIPS and PSE was associated with markedly higher 1-, 2-, 3-, 4-, and 5-year cumulative rates of primary patency than monotherapy with TIPS alone, though the 1-, 2-, 3-, 4-, and 5-year cumulative rates of the secondary patency and overall survival of patients were not significantly different between the two groups. Notably, two patients (12.5%) in the TIPS+

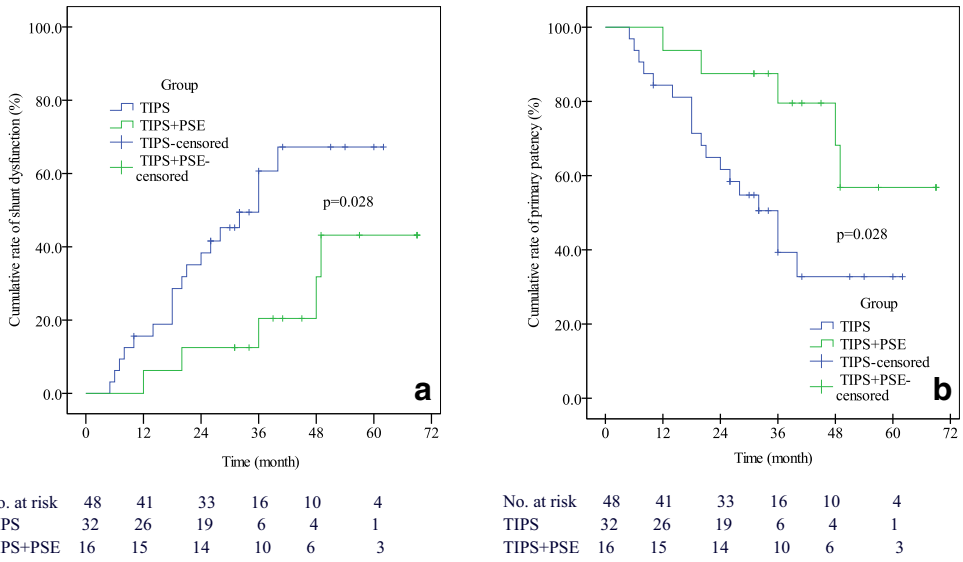

Fig. 3 Cumulative rates (%) of shunt dysfunction ($p = 0.028$, by log-rank test; **a**) and primary patency ($p = 0.028$, by log-rank test; **b**) in the two groups. TIPS, transjugular intrahepatic portosystemic shunt; PSE, partial splenic embolization

Table 2 Univariate and multivariate analyses for the predictors of shunt dysfunction

Baseline variables	Univariable analysis			Multivariable analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Group*	0.343	0.126–0.937	0.037	0.235	0.084–0.655	0.006
PVD (mmHg)	0.741	0.625–0.878	0.001	0.687	0.563–0.838	0.000
Baseline PVT#	2.415	1.040–5.608	0.040	3.955	1.634–9.573	0.002
Baseline HCV-RNA	0.501	0.149–1.686	0.264			

*Group: 0 = TIPS group, 1 = TIPS+PSE group; # Baseline PVT: 0 = absence, 1 = presence

HR, hazard ratio; *CI*, confidence interval; *PPD*, portal pressure decline pre- and post-TIPS insertion; *PVT*, portal vein thrombosis

PSE group developed splenic abscess, and the incidence of PVT was similar between the two groups.

Shunt dysfunction is a major problem after TIPS placement despite using the ePTFE-covered stent grafts. Post-TIPS reduction of the intravascular pressure in the portal venous system may affect the long-term shunt patency, as evidenced by our recent study which showed that patients with PVDs > 9 mmHg were associated with higher shunt patency compared with those with PVDs ≤ 9 mmHg after TIPS insertion [17]. From the portal hemodynamic point of view, previous studies had reported that PSE was associated with the reduction of the splenic blood flow, the decrement of the portal venous pressure and the wedged hepatic venous pressure, and improvement of the arterio-venous oxygen content difference; thus, combined therapy using PSE and other transvenous retrograde obliteration techniques, including TJO, B-RTO, and PTVE, was associated with better control of recurrent variceal bleeding and/or refractory HE due to the presence of portosystemic shunts [11–14]. In line with these studies [11–14], our study showed that combined therapy using TIPS and PSE resulted in markedly lower shunt dysfunction rates and significantly higher primary shunt patency rates than monotherapy using TIPS alone in the long term, which may be due to the further reduction in portal venous pressure and PVD by PSE. Moreover, the potentially increased flow via the superior mesenteric vein with less blood going to the spleen and then back via the splenic vein and/or the improvement in hematological parameters after PSE may also play a role in improving the shunt patency. However, all these possibilities are only speculative at this stage.

PVD and baseline PVT were previously shown to be significant predictors of shunt dysfunction [15–17]. In agreement with these studies, the present study also showed that PVD and baseline PVT were significantly associated with the incidence of shunt dysfunction. Moreover, in the present study, group assignment was another significant predicator for shunt dysfunction, and the TIPS+PSE group (HR, 0.235; 95% CI, 0.084–0.655; p = 0.006) was associated with 76.5% reduction in risk of developing shunt dysfunction compared with the TIPS group (Table 2), which further support our conclusion that concomitant PSE

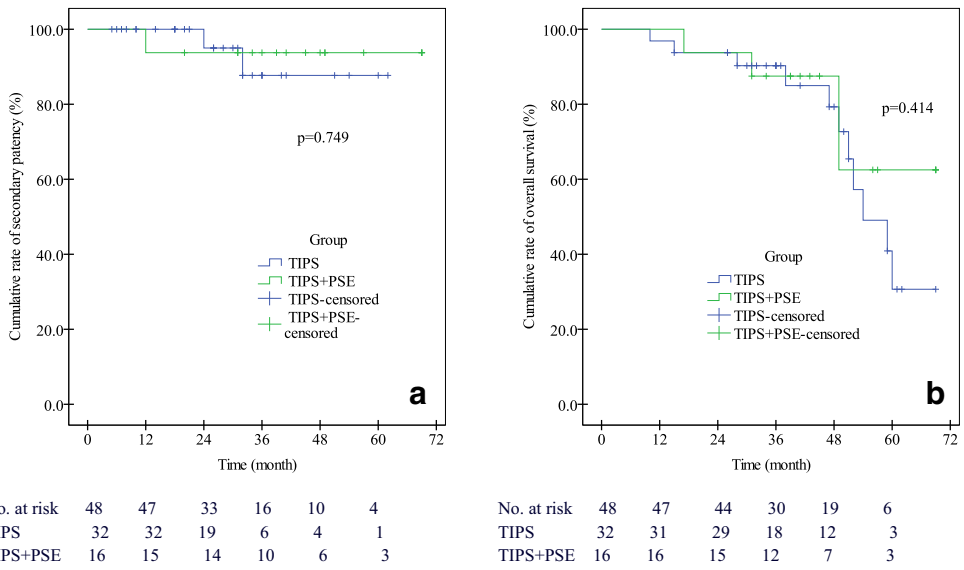

Fig. 4 Cumulative rates (%) of secondary patency (p = 0.749, log-rank test; **a**) and overall survival (p = 0.414, by log-rank test; **b**) in the two groups. TIPS, transjugular intrahepatic portosystemic shunt; PSE, partial splenic embolization

Table 3 Univariate and multivariate analyses for the predictors of mortality

Baseline variables	Univariable analysis			Multivariable analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Group*	0.626	0.199–1.970	0.423	0.455	0.134–1.547	0.207
CTP score	1.449	1.014–2.069	0.041			
Ascites&	3.177	1.683–6.164	0.001	2.941	1.250–6.920	0.013
Baseline PVT#	3.783	1.271–11.257	0.017			

*Group: 0 = TIPS group, 1 = TIPS+PSE group; & Ascites: 0 = no ascites, 1 = mild ascites, 2 = moderate to severe ascites; # Baseline PVT: 0 = absence, 1 = presence

HR, hazard ratio; *CI*, confidence interval; *CTP*, Child–Turcotte–Pugh; *PVT*, portal vein thrombosis

may help decrease the shunt dysfunction and increase the primary shunt patency rate in the long run.

In recent years, the technical failure of TIPS revision was relatively uncommon [15, 16, 24]. In the present study, TIPS revision only failed in two patients in the TIPS group and one in the TIPS +PSE group, leading to high and comparable secondary patency rates between the two groups ($p = 0.749$; Fig. 4a), which is consistent with previous studies [15, 16, 24]. In the present study, the overall survival rates were comparable between the two groups, although the TIPS+PSE group had markedly lower shunt dysfunction rate and higher primary patency rate than the TIPS group, which is in agreement with previous studies [7, 15–17, 23, 25]. This may be explained by that overall survival is not determined by the shunt patency, but by the severity of liver disease, because most patients in the present study died from liver-related causes, including hepatocellular carcinoma, liver failure, and severe coma. Moreover, in the present study, ascites was shown to be associated with elevated risk of mortality (Table 3), which further supports our explanation since ascites is an indicator of more severe liver disease.

PVT was a severe and potentially fatal complication of PSE, and chronic PVT occluding the portal trunk may worsen portal hypertension and complicate the TIPS procedure, requiring a modified TIPS combined with transhepatic or transsplenic approaches; thus, early detection of PVT and prompt anticoagulation were recommended to avoid serious consequences of PVT [19, 26]. In the present study, the incidence of PVT and mean time remaining free of PVT were comparable between the two groups, which may be related to the routine, long-term prophylactic use of antiplatelet or anticoagulant therapy against PVT formation after TIPS placement in our institution. Notably, two patients in the TIPS+PSE group developed splenic abscess at 7 days and 10 days following the PSE procedure despite routine perioperative use of antibiotics, which prolonged the patients' hospital stays and increased the medical costs.

Our study has several shortcomings. First, it is a retrospective study and group assignment is not randomized, but at the discretion of patients' physicians. Second, the sample size, particularly for the TIPS+PSE group, is small, and we did not measure the portal venous pressure and hemodynamic parameters after the PSE procedure, which may render our study inadequate to

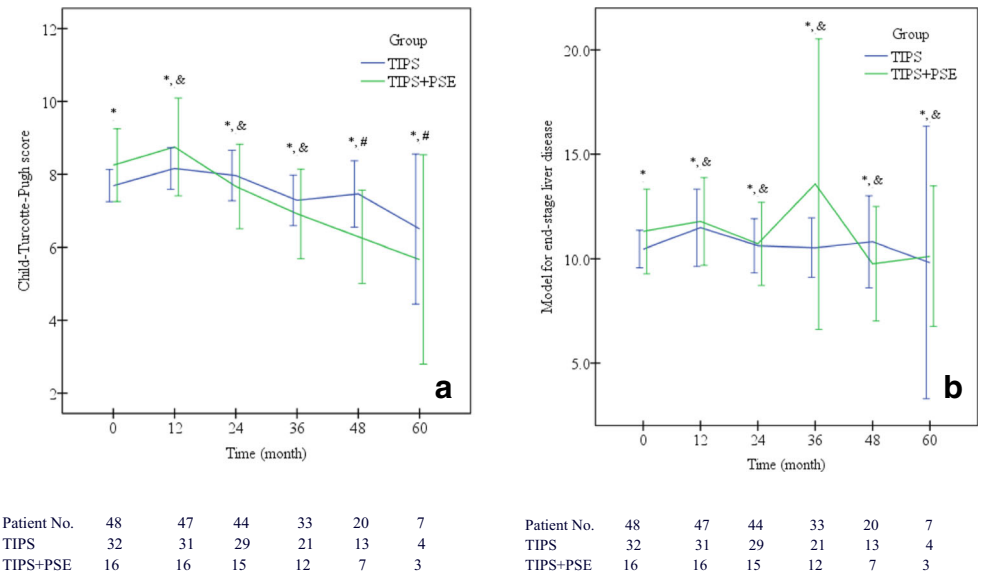

Fig. 5 Change of Child–Turcotte–Pugh (**a**) and model for end-stage liver disease scores (**b**) in the two study groups. *$p > 0.05$, compared between the two groups; &$p > 0.05$, compared with the baseline value within each group; #$p < 0.05$, compared with the baseline value within the TIPS+PSE group

achieve definitive conclusions. However, measuring the portal venous pressure is an invasive procedure that bears the risk of bleeding and medical cost, which is thus not routinely performed. Moreover, our study compared the combined therapy using TIPS and PSE with the monotherapy using TIPS alone, and the results of our study may impact the decision-making for the management of cirrhostic patients with variceal bleeding in the clinical practice.

In conclusion, our study illustrated that combined therapy using TIPS and PSE was superior to monotherapy using TIPS alone in terms of shunt dysfunction and primary patency rates, though the secondary patency and overall survival rates were not different between the two therapeutic modalities. More prospective randomized studies are warranted to validate our findings and to further investigate the potential mechanisms.

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Compliance with ethical standards

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Informed consent Written informed consent was obtained from all subjects (patients) in this study.

Ethical approval Institutional Review Board approval was obtained.

Study subjects or cohorts overlap Some study subjects or cohorts have been previously reported in "Predictors of Shunt Dysfunction and Overall Survival in Patients with Variceal Bleeding Treated with Transjugular Portosystemic Shunt Creation Using the Fluency Stent Graft."

Methodology
- Retrospective
- Observational
- Performed at one institution

References

1. Berzigotti A, Seijo S, Reverter E, Bosch J (2013) Assessing portal hypertension in liver diseases. Expert Rev Gastroenterol Hepatol 7: 141–155
2. Garcia-Tsao G, Bosch J (2010) Management of varices and variceal hemorrhage in cirrhosis. N Engl J Med 362:823–832
3. García-Pagán JC, Caca K, Bureau C et al (2010) Early use of TIPS in patients with cirrhosis and variceal bleeding. N Engl J Med 362: 2370–2379
4. European Association for the Study of the Liver (2010) EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. J Hepatol 53:397–417
5. Grunwald D, Tapper EB, Jiang ZG, Ahmed M, Malik R (2016) A standardized assessment of functional disability predicts 1-year mortality in patients undergoing transjugular intrahepatic portosystemic shunt for refractory ascites. J Clin Gastroenterol 50: 75–79
6. Adebayo D, Neong SF, Wong F (2018) Refractory ascites in liver cirrhosis. Am J Gastroenterol. https://doi.org/10.1038/s41395-018-0185-6
7. Yu J, Wang X, Jiang M et al (2018) Comparison of transjugular intrahepatic portosystemic shunt (TIPS) alone and combined with embolisation for the management of cardiofundal varices: a retrospective study. Eur Radiol. https://doi.org/10.1007/s00330-018-5645-2
8. Zhu K, Meng X, Qian J et al (2009) Partial splenic embolization for hypersplenism in cirrhosis: a long-term outcome in 62 patients. Dig Liver Dis 41:411–416
9. Gu JJ, He XH, Li WT et al (2012) Safety and efficacy of splenic artery coil embolization for hypersplenism in liver cirrhosis. Acta Radiol 53:862–867
10. Ozturk O, Eldem G, Peynircioglu B et al (2016) Outcomes of partial splenic embolization in patients with massive splenomegaly due to idiopathic portal hypertension. World J Gastroenterol 22:9623–9630
11. Chikamori F, Inoue A, Okamoto H, Kuniyoshi N, Kawashima T, Takase Y (2010) Hemodynamic effects of combined therapy using partial splenic embolization and transjugular retrograde obliteration for gastric varices with gastrorenal shunt. World J Surg 34:1046–1051
12. Waguri N, Hayashi M, Yokoo T et al (2012) Simultaneous combined balloon-occluded retrograde transvenous obliteration and partial splenic embolization for portosystemic shunts. J Vasc Interv Radiol 23:650–657
13. Chikamori F, Okamoto H, Kuniyoshi N, Takase Y (2013) Effects of combined therapy using partial splenic embolization and transjugular retrograde obliteration on systemic hemodynamics in patients with gastric varices and a splenorenal shunt. Surg Laparosc Endosc Percutan Tech 23:149–153
14. Duan X, Zhang K, Han X et al (2014) Comparison of percutaneous transhepatic variceal embolization (PTVE) followed by partial splenic embolization versus PTVE alone for the treatment of acute esophagogastric variceal massive hemorrhage. J Vasc Interv Radiol 25:1858–1865
15. Wan YM, Li YH, Xu Y et al (2018) Predictors of shunt dysfunction and overall survival in patients with variceal bleeding treated with transjugular portosystemic shunt creation using the fluency stent graft. Acad Radiol 25:925–934
16. Li YH, Xu ZY, Wu HM et al (2018) Long-term shunt patency and overall survival of transjugular intrahepatic portosystemic shunt placement using covered stents with bare stents versus covered stents alone. Clin Radiol 73:580–587
17. Wan YM, Li YH, Xu ZY et al (2018) Transjugular intrahepatic portosystemic shunt: the impact of portal venous pressure declines on shunt patency and clinical efficacy. Acad Radiol. https://doi.org/10.1016/j.acra.2018.05.015
18. Buechter M, Kahraman A, Manka P et al (2017) Partial spleen embolization reduces the risk of portal hypertension-induced upper

gastrointestinal bleeding in patients not eligible for TIPS implantation. PLoS One 12:e0177401
19. Cai M, Zhu K, Huang W et al (2013) Portal vein thrombosis after partial splenic embolization in liver cirrhosis: efficacy of anticoagulation and long-term follow-up. J Vasc Interv Radiol 24: 1808–1816
20. Schuppan D, Afdhal NH (2008) Liver cirrhosis. Lancet 371:838–851
21. Luca A, Miraglia R, Caruso S et al (2011) Short- and long-term effects of the transjugular intrahepatic portosystemic shunt on portal vein thrombosis in patients with cirrhosis. Gut 60:846–853
22. Zhou C, Hou C, Cheng D, Tang W, Lv W (2015) Predictive accuracy comparison of MELD and Childe Turcotte Pugh scores for survival in patients underwent TIPS placement: a systematic meta-analytic review. Int J Clin Exp Med 8:13464–13472
23. Perarnau JM, Le Gouge A, Nicolas C et al (2014) Covered vs. uncovered stents for transjugular intrahepatic portosystemic shunt: a randomized controlled trial. J Hepatol 60:962–968
24. Weber CN, Nadolski GJ, White SB et al (2015) Long-term patency and clinical analysis of expanded polytetrafluoroethylene-covered transjugular intrahepatic portosystemic shunt stent grafts. J Vasc Interv Radiol 26:1257–1265
25. Qi X, Guo X, Fan D (2015) A trend toward the improvement of survival after TIPS by the use of covered stents: a meta-analysis of two randomized controlled trials. Cardiovasc Intervent Radiol 38: 1363–1364
26. Luo J, Li M, Zhang Y et al (2018) Percutaneous transhepatic intrahepatic portosystemic shunt for variceal bleeding with chronic portal vein occlusion after splenectomy. Eur Radiol 28:3661–3668