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Effect of splenectomy on the outcomes in patients with cirrhosis receiving transjugular intrahepatic portosystemic shunt

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Key words

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Abstract

Background and Aim: Patients indicated to transjugular intrahepatic portosystemic shunt (TIPS) placement may have splenectomy history due to thrombocytopenia. This study aimed to evaluate the effect of prior splenectomy on TIPS procedure and post-TIPS outcomes.

Methods: We conducted a longitudinal analysis based on a cohort of 284 patients with cirrhosis submitted to TIPS; 74 patients had splenectomy history (splenectomy group) and 210 did not (non-splenectomy group). Cox proportional hazards models were used to evaluate the association between splenectomy and outcomes after TIPS. The primary outcome was shunt dysfunction. Secondary outcomes included all-cause mortality, clinical recurrence of bleeding or ascites, and overt hepatic encephalopathy (OHE).

Results: During a median follow-up of 16.2 months, the splenectomy group had significantly lower rates of postoperative shunt patency (85.5% vs 95.6% at 1 year and 75.2% vs 86.5% at 2 years; adjusted hazard ratio [HR] 2.53; 95% confidence interval [CI] 1.21–5.12; $P = 0.01$) and higher risk of OHE (adjusted HR 1.82; 95% CI 1.03–3.54; $P = 0.04$). But the risk of mortality (adjusted HR 0.87; 95% CI 0.41–1.87; $P = 0.73$) and recurrent bleeding or ascites (adjusted HR 1.17; 95% CI 0.53–2.35; $P = 0.77$) showed no statistical difference. Multivariate analysis confirmed splenectomy history and endoscopic therapy as independent predictors of shunt dysfunction. Besides, pre-TIPS splenectomy increased the difficulty of TIPS procedure by complicating portal vein puncture.

Conclusions: For patients with cirrhosis submitted to TIPS, prior splenectomy complicated TIPS procedure and increased the risk of shunt dysfunction and OHE after TIPS, but was not significantly associated with the occurrence of mortality and recurrent bleeding or ascites.

Introduction

Portal hypertension (PHT), defined as portal venous pressure gradient exceeding 5 mmHg, is a progressive complication of cirrhosis. PHT in cirrhosis is the consequence of increased intrahepatic vascular resistance and splanchnic blood flow.^{1,2} Currently, transjugular intrahepatic portosystemic shunt (TIPS) has emerged as an effective strategy for the treatment of PHT. By decreasing portal pressure of around 50% rapidly, TIPS is indicated to treat portal hypertensive complications such as gastroesophageal variceal bleeding and intractable ascites.^{3,4}

Splenectomy is another traditional approach in the management of PHT, especially in Asia.⁵ This surgery decompresses portal system by eliminating splenic blood flow on one side and alleviates thrombocytopenia caused by hypersplenism on the other.⁶ In addition, the combination therapy of splenectomy with pericardial devascularization or endoscopic band ligation has been reported effective in controlling variceal bleeding.^{7,8} But the

long-term effectiveness of this surgery remains elusive, and a portion of patients still experience recurrent bleeding or ascites, requiring further treatment including TIPS.

Splenectomy leads to a series of hemodynamic changes while relieving PHT, including decreased portal blood flow and subsequent portal vein shrinkage, which may complicate TIPS procedure and affect stent patency.^{9,10} Besides, elevated platelet count secondary to hypersplenism remission increases the risk of thrombosis.¹¹ These mechanisms may contribute to the recurrence of portal hypertensive complications and consequently affect patients' prognosis. Thus, this study aimed to evaluate the effect of pre-TIPS splenectomy on TIPS procedure and postoperative outcomes.

Methods

Study design. The present observational study was conducted at Wuhan Union Hospital. The study protocol conforms to the

ethical guidelines of the 1975 Declaration of Helsinki and was approved by the institutional ethics committee. Informed consent was waived because the data have been anonymized. The Strengthening the Reporting of Observational Studies in Epidemiology was applied for the study design.¹²

Study population and data collection. From January 2016 to November 2020, all consecutive patients with PHT admitted to our center to receive TIPS treatment were prospectively enrolled, and a database was built for several different researches on the prognosis of PHT, in which the data collection protocol was determined before patient recruitment. Baseline data incorporating clinical characteristics, laboratory results, and radiological findings were collected for each patient during hospitalization. Details on treatment were retrieved from electronic medical record. Follow-up was scheduled for all patients at 1, 3, 6, and 12 months after TIPS insertion and then annually. Laboratory tests, computed tomography scans, and an evaluation on clinical recurrence of bleeding and ascites, overt hepatic encephalopathy (OHE), and survival were performed at each outpatient visit, supplemented with telephone interviews every 3 months. Patients were followed until death, liver transplantation, or the end of this study (January 2021), and data were censored at the end of follow-up.

Patients with a confirmed diagnosis of cirrhosis whom successfully underwent TIPS were considered eligible for the study. The diagnosis of cirrhosis was established based on medical history, conclusive appearance in radiological imaging, and/or liver biopsy. Exclusion criteria included previous history of liver transplantation, previous history of TIPS, splenectomy performed after TIPS, hepatocellular carcinoma or other extrahepatic malignancy, hematologic disorder, and lost to follow-up within 6 weeks after TIPS. Patients without exclusion criteria were enrolled and divided into two groups based on whether they had splenectomy history (splenectomy group) or not (non-splenectomy group).

Transjugular intrahepatic portosystemic shunt procedure. Transjugular intrahepatic portosystemic shunt placement was implemented by experienced interventional radiologists. Briefly, catheterization of the hepatic vein was performed through the right internal jugular vein with a transjugular liver access set (RUPS-100; Cook Inc.). Then a TIPS needle was used to puncture the portal vein under fluoroscopic guidance. Afterwards, a 6- to 8-mm balloon was used to dilate the tract, and a bare metal stent (Bard E-LUMINEXX Vascular Stent, Karlsruhe, Germany) combined with an 8-mm expanded polytetrafluoroethylene-covered stent (Fluency; Bard Inc., USA) was deployed. Measurement of portal pressure gradient (PPG) was performed before and after shunt establishment.^{13,14} Balloon tamponade was used when massive bleeding occurred. TIPS revision with angioplasty or another stent placement was performed if shunt dysfunction was confirmed by angiography.

Endpoints and definitions. The primary endpoint of the study was shunt dysfunction. Secondary endpoints were (i) all-cause mortality; (ii) the composite endpoint of recurrent bleeding or ascites; and (iii) development of OHE. Enhanced computed tomography scans were performed to assess shunt patency at each

outpatient visit according to the protocol described earlier, or if patients had clinical symptoms related to shunt stenosis. Portography was performed to confirm the occurrence of shunt dysfunction, which was defined as the stent lumen stenosis $\geq 50\%$.¹⁵ Failure to control bleeding or rebleeding was defined on the basis of the Baveno V criteria.¹⁶ Refractory ascites was defined as sustained ascites requiring large-volume paracentesis beyond 1 month after procedure. The spectrum of HE occurred in a continuum and was subdivided into five grades based on the West Haven criteria,¹⁷ only grades II–IV (OHE) were considered for the study.

Statistical analysis. Quantitative variables were expressed as means and standard deviation or median and interquartile range (IQR) and compared with Student's *t*-test or Mann–Whitney test. Qualitative variables were presented as frequencies and percentages and compared by means of chi-squared test or two-tailed Fisher's exact test.

Time-to-event endpoints were evaluated by Kaplan–Meier curves and compared with log-rank tests. Hazard ratios (HRs) and 95% confidence intervals (95% CIs) for risk of the outcomes were estimated with Cox proportional hazards models, with adjustment for potential confounders according to different endpoints. Variables significantly associated with the endpoints ($P < 0.10$) in univariate analyses or causing at least 10% change in the HR for splenectomy in multivariable models were considered as potential confounders. Univariate and multivariate analyses with Cox regression model were used to explore risk factors for shunt dysfunction. Variables with a univariate P value < 0.1 were entered into a multivariable model. A backward stepwise elimination approach based on the Akaike information criterion was performed to avoid overfitting.

For covariates included in Cox regression analysis, the percentages of missing values were less than 5%; thus, a casewise deletion strategy was performed and a dataset of complete cases was analyzed. To verify the robustness of our results, additional analyses based on Fine and Gray competing risk model were implemented as sensitivity analysis, in which death and liver transplantation competed with shunt dysfunction, recurrence of bleeding or ascites, and OHE. A two-sided α of less than 0.05 was considered statistically significant. All analyses were performed using IBM SPSS (version 25.0) and R (version 4.0.3) with the add-on packages *rms*, *survival*, *survminer*, and *cmprsk*.

Results

Baseline characteristics. Three hundred eighty-three consecutive patients with cirrhosis and PHT who received TIPS placement at our center were retrospectively analyzed. After excluding 99 patients fulfilling one or more exclusion criteria, 284 patients were enrolled in the final cohort (Fig. 1), including 74 (26.0%) in the splenectomy group and 210 in non-splenectomy group. Baseline characteristics including age, sex, etiology of cirrhosis, and Child–Pugh score were comparable between two groups. Patients with splenectomy were all treated for variceal bleeding, while 18 (8.6%) patients in the non-splenectomy group were treated for intractable ascites. Compared with the non-splenectomy group, the splenectomy group had higher

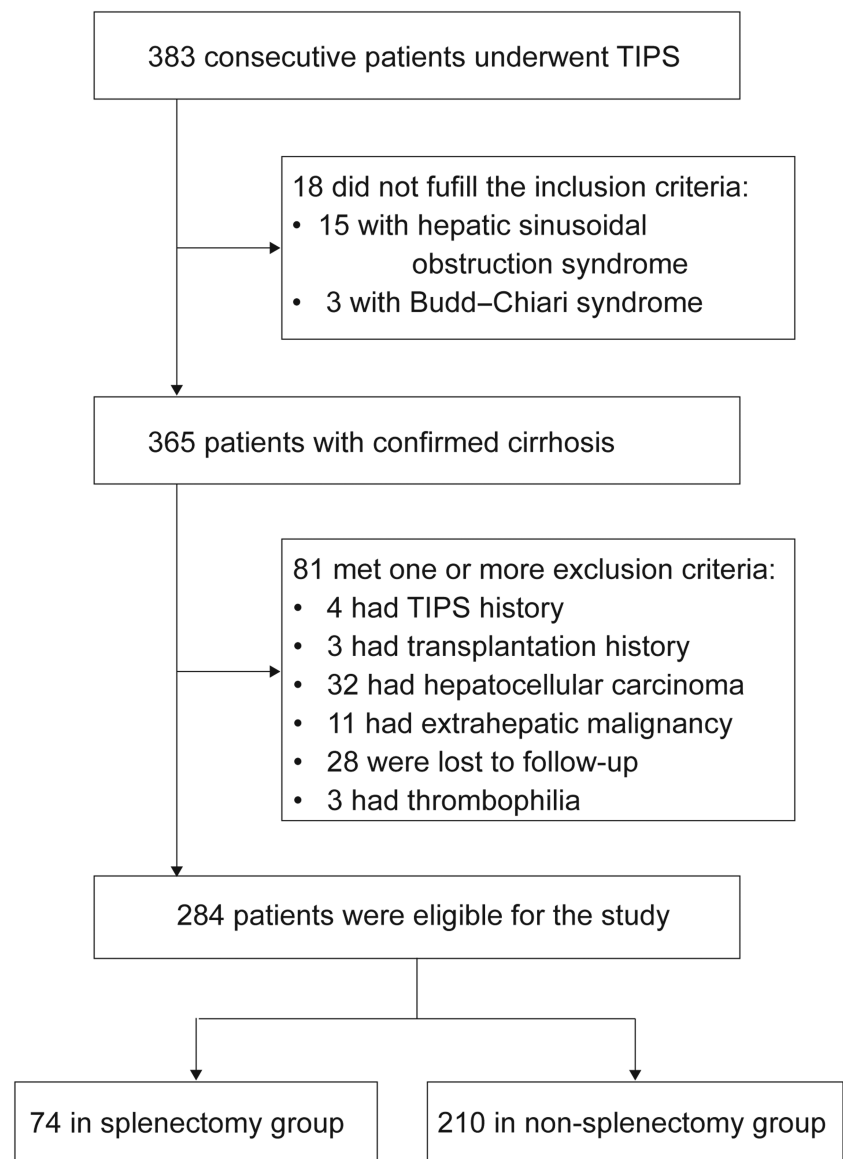


Figure 1 Flowchart of the patient selection protocol. TIPS, transjugular intrahepatic portosystemic shunt.

levels of platelet count, lower bilirubin, albumin, and MELD/MELD-Na score. Meanwhile, the splenectomy group had markedly smaller portal vein diameter and was prone to develop portal vein thrombosis (PVT) and cavernous transformation of portal vein (CTPV). Descriptive baseline characteristics are presented in Table 1.

Shunt dysfunction. The median follow-up period was 15.9 (IQR 10.1–23.9) and 17.6 (IQR 7.5–28.5) months in the splenectomy group and non-splenectomy group, respectively. A primary endpoint event was adjudicated in 32 (11.2%) patients in the entire cohort. Among them, 15 patients received TIPS revision with angioplasty, and 13 patients underwent another stent placement. Details of the outcomes during follow-up are summarized in Table 2. Compared with the non-splenectomy group, the cumulative rates of shunt patency were significantly lower in the splenectomy group at 1 year (85.5% [95% CI 77.4–94.4] vs

95.6% [95% CI 92.7–98.7]; $P = 0.03$) and at 2 years (75.2% [95% CI 62.7–90.1] vs 86.5% [95% CI 80.0–93.5]; $P = 0.006$). The hazard ratio for shunt dysfunction was 2.78 (95% CI 1.39–5.59; $P = 0.004$) (Fig. 2). After adjusting for endoscopic therapy, the risk attenuated but remained high (adjusted HR 2.53; 95% CI 1.21–5.12; $P = 0.01$) (Table 3). When death was treated as a competing event in Fine–Gray model, the results remained similar (subdistribution HR [sHR] 2.81; 95% CI 1.42–5.53; Gray’s test $P = 0.003$) (Fig. 3).

Complete data from 276 participants were analyzed to explore risk factors for shunt dysfunction. In univariate Cox regression analysis, splenectomy history, sex, platelet count, portal vein diameter, and endoscopic therapy were significantly associated with the outcome. We excluded redundant variable (platelet count and portal vein diameter) and variables without clinical relevance according to previous studies (sex). We also included CTPV because it was suggested as a strong predictor of shunt dysfunction. Accordingly, splenectomy, endoscopic therapy, and

Table 1 Demographic, clinical, and biochemical characteristics between two groups

	Splenectomy group	Non-splenectomy group	P value
	n = 74	n = 210	
Demographics and clinical characteristics			
Age (years) [†]	54.3 ± 10.4	53.7 ± 11.6	0.69
Male (%)	46 (62.2)	136 (64.8)	0.69
Comorbidities (%) [†]	13 (17.6)	49 (23.3)	0.30
Etiology of cirrhosis			0.79
Chronic HBV infection	37 (50.0)	118 (56.2)	
Chronic HCV infection	10 (13.5)	25 (11.9)	
Alcohol	5 (6.8)	15 (7.1)	
Others	22 (29.7)	52 (24.8)	
TIPS indications			0.009
Variceal bleeding	74 (100)	192 (91.4)	
Refractory ascites	0 (0)	18 (8.6)	
Child–Pugh score [†]	7.4 ± 1.8	7.5 ± 1.6	0.92
Child–Pugh class (%)			0.47
A (5–6 points)	24 (32.4)	57 (27.1)	
B (7–9 points)	42 (56.8)	135 (64.3)	
C (10–13 points)	8 (10.8)	18 (8.6)	
MELD score [†]	10.6 ± 3.6	11.9 ± 3.4	0.006
MELD–Na score [†]	11.5 ± 4.6	12.6 ± 4.3	0.065
CLIF–C AD score [†]	45.7 ± 6.0	43.8 ± 5.6	0.24
Acute decompensation (%)	39 (52.7)	93 (44.3)	0.26
Laboratory parameters [†]			
Bilirubin (μmol/L)	21.9 ± 21.1	27.9 ± 24.4	0.10
Albumin (g/L)	29.5 ± 5.8	31.4 ± 5.5	0.05
ALT (U/L)	32.9 ± 31.0	38.2 ± 36.3	0.68
AST (U/L)	49.3 ± 44.4	44.5 ± 78.9	0.62
Creatinine (μmol/L)	76.2 ± 69.4	72.1 ± 33.4	0.08
Sodium (mmol/L)	138.3 ± 5.5	138.7 ± 4.2	0.56
Hemoglobin (g/L)	80.0 ± 16.6	79.1 ± 21.9	0.97
Platelet count (× 10 ⁹ /L)	191.9 ± 100.5	68.2 ± 38.1	< 0.001
Prothrombin time (s)	16.2 ± 2.6	16.8 ± 2.8	0.04
INR	1.3 ± 0.2	1.4 ± 0.2	0.08
Radiological and endoscopic findings			
Ascites (%)			0.39
No	17 (23.0)	40 (19.0)	
Mild	31 (41.9)	72 (34.3)	
Moderate	11 (14.9)	39 (18.6)	
Severe	15 (20.2)	59 (28.1)	
Portal vein diameter (mm) [†]	13.8 ± 3.1	15.6 ± 3.4	< 0.001
Portal vein thrombosis (%)			
Main portal vein	43 (58.1)	49 (23.3)	< 0.001
Right portal vein	32 (43.2)	29 (13.8)	< 0.001
Left portal vein	33 (44.6)	21 (10.0)	< 0.001
Superior mesenteric vein	27 (36.5)	44 (21.0)	0.008
CTPV (%)	17 (23.0)	7 (3.3)	< 0.001
Type of varices			< 0.001
EV	31 (41.9)	42 (20.0)	
GOV1	35 (47.3)	119 (56.7)	
GOV2	5 (6.7)	31 (14.7)	
IGV	3 (4.1)	18 (8.6)	
Treatments			
Splenectomy		—	
Laparoscopy (%)	33 (44.6)		
Interval between TIPS (m) [†]	60 (36–120)		
PSE (%)	—	49 (23.3)	

(Continues)

Table 1 (Continued)

	Splenectomy group		Non-splenectomy group	P value
	n = 74		n = 210	
Before TIPS			23 (10.9)	
After TIPS			26 (12.4)	
Endoscopic therapy (%)	22 (29.7)		35 (16.8)	0.02
Endoscopic band ligation	13 (17.6)		26 (12.5)	
Endoscopic sclerotherapy	9 (12.2)		9 (4.3)	
Post-TIPS lactulose (yes)	29 (39.2)		66 (31.4)	0.28
Post-TIPS diuretics (yes)	17 (23.0)		58 (27.6)	0.24

[†]Data were expressed as means and standard deviation. Other data were presented as frequencies and percentages.

[‡]Comorbidities include hypertension and diabetes.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CLIF-C AD, Chronic Liver Failure Consortium Acute Decompensation Score; CTPV, cavernous transformation of portal vein; EV, esophageal varices; GOV, gastroesophageal varices; HBV, hepatitis B virus; HCV, hepatitis C virus; IGV, isolated gastric varices; INR, international normalized ratio; MELD, model for end-stage liver disease; PSE, partial splenic embolization; TIPS, transjugular intrahepatic portosystemic shunt.

Table 2 Summary of outcome measurements during follow-up

	Overall	Splenectomy group	Non-splenectomy group
	n = 284	n = 74	n = 210
Duration of follow-up (months) [†]	16.2 (9.0–28.1)	15.9 (10.1–23.9)	17.6 (7.5–28.5)
Shunt dysfunction	32 (11.2)	15 (20.3)	17 (8.1)
6 weeks	11 (3.9)	6 (8.1)	5 (2.4)
1 year	29 (10.2)	13 (17.6)	16 (7.6)
TIPS revision			
Angioplasty	15 (5.3)	8 (10.8)	7 (3.3)
Another stent	13 (4.6)	6 (8.1)	7 (3.3)
insertion			
Mortality	40 (14.1)	10 (13.5)	30 (14.3)
6 weeks	12 (4.2)	2 (2.7)	11 (5.2)
1 year	36 (12.7)	9 (12.2)	27 (12.8)
2 years	39 (13.7)	10 (13.5)	29 (13.8)
Liver transplantation	3 (1.1)	0 (0)	3 (1.4)
Failure to control bleeding or rebleeding	34 (12.0)	10 (13.5)	24 (11.4)
Failure to control bleeding (< 5 days)			
Early rebleeding (5 days to 6 weeks)	10 (3.5)	2 (2.7)	8 (3.8)
Late rebleeding (> 6 weeks)	23 (8.1)	8 (10.8)	15 (7.1)
Onset or worsening ascites	4 (1.4)	0 (0)	4 (1.9)
Overt hepatic encephalopathy	54 (19.0)	20 (27.0)	34 (16.2)
Grade III or higher	42 (14.8)	16 (21.6)	26 (12.4)
Recurrent	12 (4.2)	4 (5.4)	8 (3.8)
Within 1 year	52 (18.3)	20 (27.0)	32 (15.2)

[†]Data were expressed as median and interquartile range. Other data were presented as frequencies and percentages.

TIPS, transjugular intrahepatic portosystemic shunt.

pre-TIPS CTPV were entered into the multivariable model. Splenectomy (HR 2.31; 95% CI 1.13–4.97; $P = 0.02$) and endoscopic therapy (HR 1.96; 95% CI 1.02–4.07; $P = 0.04$) were

confirmed as independent predictor of the outcome in multivariate analysis. Details of univariate and multivariate analysis are demonstrated in Table 4.

Mortality, clinically recurrent bleeding or ascites, and overt hepatic encephalopathy. Forty (14.1%) patients died during follow-up, including 10 (13.5%) patients in the splenectomy group and 30 (14.3%) in non-splenectomy group. Causes of death mainly included liver failure (16 cases), multiorgan failure (7 cases), and severe rebleeding (4 cases). Three (1.4%) patients in the non-splenectomy group received liver transplantation 2, 6, and 12 months after TIPS treatment. Transplantation-free survival at 6 weeks, 1 year, and 2 years was 97.3%, 87.6%, and 85.2% in the splenectomy group, and 95.2%, 84.8%, and 82.9% in the non-splenectomy group, presenting no statistical difference between two groups (HR 0.91; 95% CI 0.44–1.86; $P = 0.79$) (Fig. 2). Similar results were obtained after adjusting for age, Child–Pugh score, and creatinine (adjusted HR 0.87; 95% CI 0.41–1.87; $P = 0.73$) (Table 3). In the sensitivity analysis, the association between splenectomy and mortality did not statistically differ when taking transplantation as a competing event (sHR 0.93; 95% CI 0.46–1.88; Gray's test $P = 0.84$) (Fig. 3).

During follow-up, 10 (13.5%) patients in the splenectomy group and 28 (13.3%) in non-splenectomy group experienced clinical recurrence of bleeding or ascites (Table 2). Three patients experienced refractory ascites 12, 21, and 32 months after procedure, and one patient treated for variceal bleeding developed refractory ascites 3 months after procedure. No marked difference in the cumulative rate of free of recurrent bleeding or ascites was shown between two groups (78.5% [95% CI 66.2–92.8] in splenectomy group vs 84.2% [95% CI 78.0–90.9] in non-splenectomy group; $P = 0.56$) (Fig. 2). The unadjusted and adjusted HRs for the outcome were 1.24 (95% CI 0.61–2.51; $P = 0.56$) and 1.17 (95% CI 0.53–2.35; $P = 0.77$), respectively. Furthermore, sensitivity analysis confirmed the lack of effect of splenectomy on the outcome (sHR 1.28; 95% CI 0.63–2.58; Gray's test $P = 0.51$) (Fig. 3).

Overt hepatic encephalopathy was observed in 54 (19.0%) patients in the entire cohort. Among them, 42 patients experienced

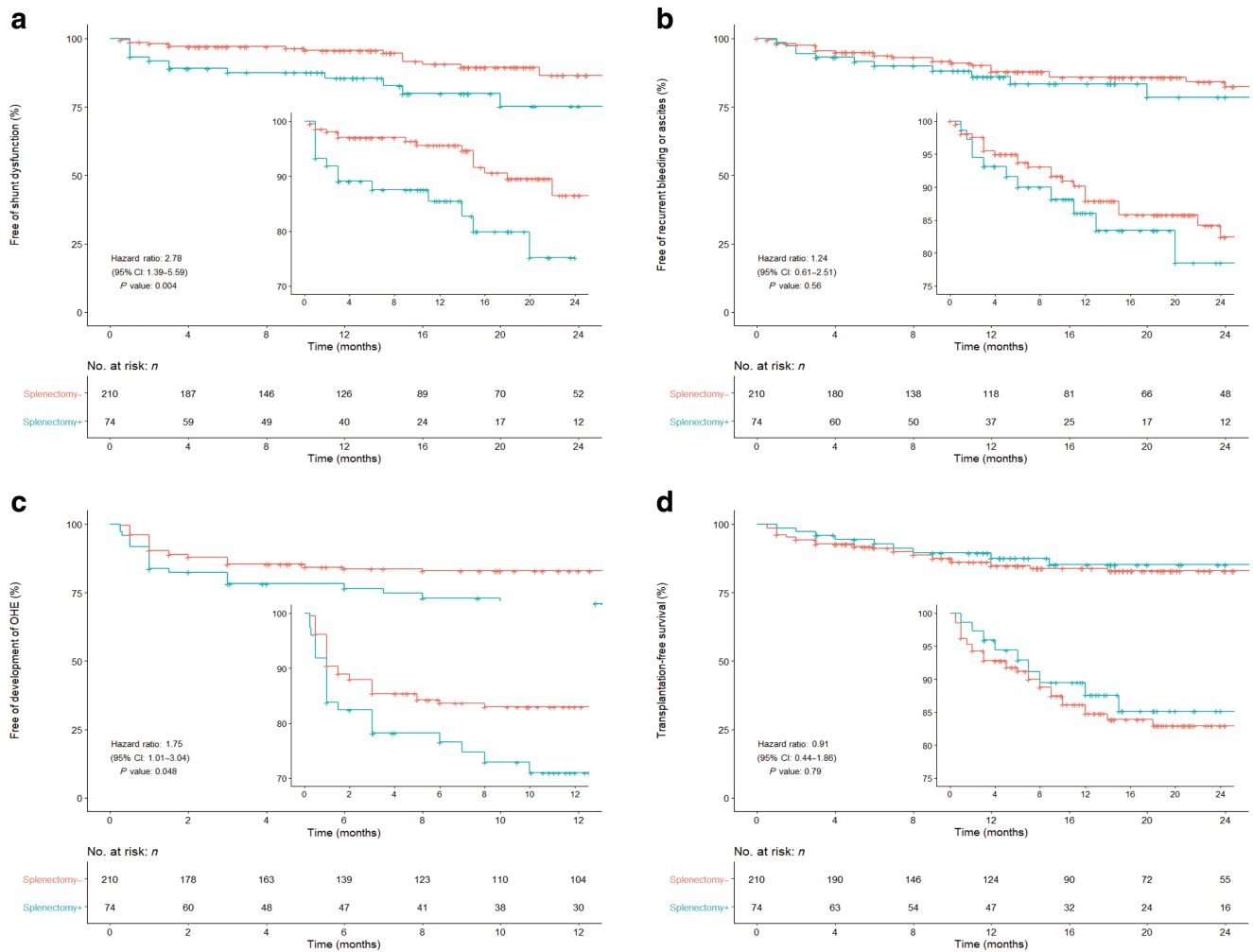


Figure 2 Kaplan–Meier survival curves of the splenectomy+ group and splenectomy– group. (a) Free of shunt dysfunction. (b) Free of recurrent bleeding or ascites. (c) Free of development of overt hepatic encephalopathy (OHE). (d) Transplantation-free survival. *P* values were calculated by log-rank tests. CI, confidence interval. +, splenectomy–; –, splenectomy+.

a grade III or higher HE, and 12 experienced more than one episode after TIPS insertion. No marked difference in terms of postoperative prevention of OHE were observed between two groups (Table 1). The cumulative rate of free of post-TIPS OHE was significantly lower in the splenectomy group (71.0% [95% CI 60.9–82.8] vs 83.0% [95% CI 77.9–88.4]; HR 1.75 [95% CI 1.01–3.04]; *P* = 0.048) (Fig. 2), and the risk increased in multivariable-adjusted model (adjusted HR 1.82; 95% CI 1.03–3.54; *P* = 0.04). Comparable results based on competing risk model were obtained (sHR 1.76; 95% CI 1.03–3.02; Gray's test *P* = 0.039) (Fig. 3).

Effect of splenectomy on transjugular intrahepatic portosystemic shunt procedure. Transjugular intrahepatic portosystemic shunt placement was successfully performed in all but two patients who had extensive CTPV and successfully performed at the second attempt. A post-TIPS PPG lower than 12 mmHg or a PPG reduction > 50% was achieved in 69 (93%) and 197 (94%) patients in the two groups,

respectively. TIPS effectiveness, reflected by PPG reduction, was similar between two groups (*P* = 0.62). The duration of TIPS procedure was substantially longer in the splenectomy group (*P* = 0.003). Similarly, patients requiring additional techniques to assist portal vein puncture were markedly higher in the splenectomy group (48.7% vs 21.4%; *P* < 0.001). Although patients with splenectomy had higher percentage of infection after TIPS, no statistical difference was observed (*P* = 0.33). Details of TIPS treatment are presented in Table S1.

Discussion

Although splenectomy is not routinely indicated in western countries, this surgery has been widely applied in Asia and a high proportion of patients submitted to TIPS have splenectomy history.^{18,19} Accordingly, knowledge of the impact of splenectomy on TIPS procedure and postoperative outcomes has clinical significance. In the present study, over a quarter of patients scheduled for TIPS treatment received splenectomy before, and splenectomy

Table 3 Impact of splenectomy on the outcomes after TIPS

Outcomes	Univariate analysis		Multivariate analysis		Variables adjusted [†]
	HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value	
Shunt dysfunction					
Splenectomy (+ vs –)	2.78 (1.39–5.59)	0.004	2.53 (1.21–5.12)	0.01	Endoscopy
Mortality					
Splenectomy (+ vs –)	0.91 (0.44–1.86)	0.79	0.87 (0.41–1.87)	0.73	Age (per year) Child–Pugh score Creatinine
Recurrent bleeding or ascites					
Splenectomy (+ vs –)	1.24 (0.61–2.51)	0.56	1.17 (0.53–2.35)	0.77	MELD–Na Prothrombin time Endoscopy [‡]
Development of OHE					
Splenectomy (+ vs –)	1.75 (1.01–3.04)	0.048	1.82 (1.03–3.54)	0.04	Child–Pugh score Post-TIPS PPG Creatinine [‡]

[†]Adjusted variables were selected based on their associations with different outcomes or significant impact on HR for splenectomy.

[‡]Variables not significantly associated with the outcomes but causing at least 10% change in the HR for splenectomy.

CI, confidence interval; HR, hazard ratio; MELD, model for end-stage liver disease; OHE, overt hepatic encephalopathy; PPG, portal pressure gradient; TIPS, transjugular intrahepatic portosystemic shunt.

complicated TIPS procedure and increased the risk of shunt dysfunction and OHE after TIPS, without affecting the incidence of mortality and recurrent bleeding or ascites. Additionally, splenectomy history and endoscopic therapy were confirmed as independent predictors of shunt dysfunction.

In the current study, patients with splenectomy had significantly higher rate of shunt dysfunction after TIPS, and splenectomy was confirmed as a risk factor for the outcome in both Cox regression model and competing risk model. The hemodynamic changes and hypercoagulable states may be the possible explanations. First, decreased portal blood flow and the subsequent reduction in portal vein diameter and blood velocity, as well as platelet elevation and activation, increased the risk of shunt thrombosis.^{20,21} Second, preexisting thrombus in the portal system affected portal hemodynamics and exacerbated stent stenosis. According to previous reports, the incidence of PVT ranges from 24% to 64% after splenectomy.^{22,23} In our study, patients with splenectomy had smaller portal vein diameter, higher platelet count, and higher proportion of PVT before TIPS, and both portal vein diameter and platelet count were associated with the outcome in univariate analysis. Moreover, prior endoscopic therapy was another independent predictor of shunt dysfunction in our analysis, which was in accordance with a recent study, and the potential mechanisms might also be related to the hemodynamic changes of portal system and PVT formation.²⁴ Thus, postoperative anticoagulation therapy may be an optimal choice and should be considered in patients with history of splenectomy and endoscopic therapy.

Splenectomy was suggested to prevent variceal bleeding and ascites with the potential mechanisms of decreasing portal pressure, raising platelet count and eliminating risky collaterals.^{5,19,25} However, the cumulative rate of recurrent bleeding or ascites did not significantly differ between two groups. This may be interpreted as compared with TIPS, the long-term effectiveness of splenectomy on controlling PHT remains unfavorable as this

approach is unable to ameliorate intrahepatic vascular resistance fundamentally.²⁶ Besides, variceal bleeding is predominantly caused by PHT instead of thrombocytopenia,²⁷ and varices and variceal bleeding may recur as a result of thrombus formation and shunt stenosis. In our cohort, 27% of recurrent bleeding or ascites were related to shunt dysfunction, indicating the risk of clinical relapse after TIPS may not mitigate in this subset of patients.

Although the incidence of OHE was in the reported ranges in both groups,^{17,28} the splenectomy group showed significantly higher risk of the outcome, which was in conflict with a recent study suggesting a decreased portal perfusion before TIPS placement could prevent post-TIPS HE because of the slight impact on hepatic hemodynamics.²⁹ This discrepancy may be attributed to the following reasons. First, blood containing ammonia and other gut-derived neurotoxins passing through TIPS shunt does not decline despite the elimination of splenic flow, and the concentration of these substances may even be higher when losing the buffer response provided by splenic blood. Second, spleen was revealed to act as a net ammonia-removing organ as it involves in the peripheral urea synthesis.³⁰ Additionally, PVT leads to a reduction in portal perfusion and a relative increment in shunt flow, further reducing hepatic clearance of neurotoxins. The earlier factors may abolish the protective effect of decreased portal perfusion and consequently increase the risk of post-TIPS OHE.

During follow-up, liver failure was the major cause of death in both groups. Several studies suggested that splenectomy may improve liver function and inhibit liver fibrosis because spleen secretes cytokines, which aggravate cirrhosis in the presence of hypersplenism.^{31,32} However, subsequent researches reported that spleen also releases cytokines, which could delay cirrhosis progression.³³ Furthermore, although patients with splenectomy had lower portal perfusion because of PVT, total liver perfusion might not or minimally be affected in the chronic setting as a result

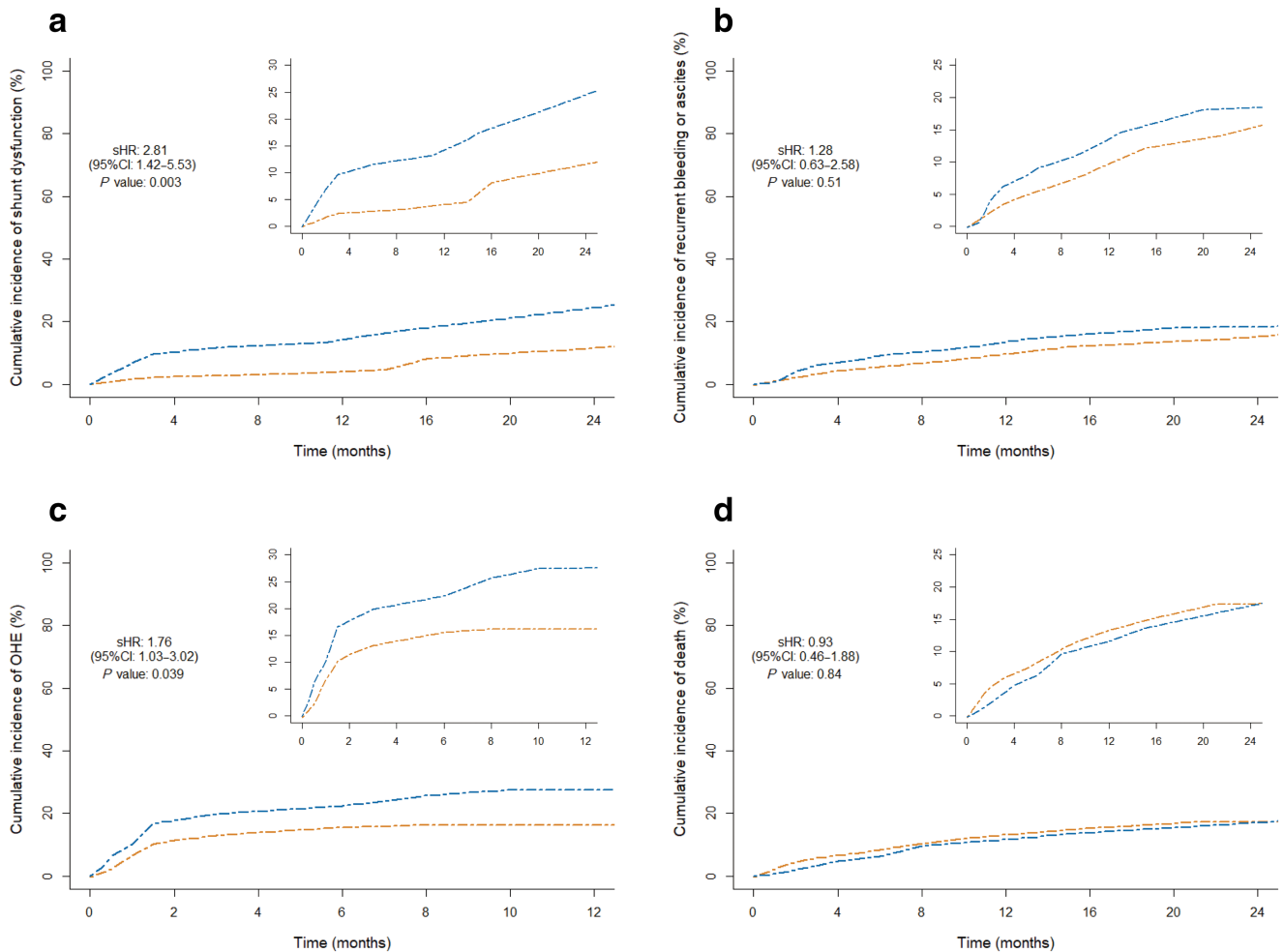


Figure 3 Cumulative incidence of different outcomes for patients with and without splenectomy based on competing risk models. (a) Shunt dysfunction. (b) Clinical recurrence of bleeding or ascites. (c) Overt hepatic encephalopathy (OHE). (d) Death. *P* values were calculated by Fine and Gray tests. CI, confidence interval; sHR, subdistribution. +, splenectomy+; -, splenectomy-.

of collateral formation.³⁴ In our study, the cumulative survival rate showed no significant difference between two groups, indicating splenectomy may have no apparent impact on post-TIPS mortality.

According to our experience, splenectomy history would increase the complexity of TIPS procedure, manifested by prolonged procedure time and higher rates of assisted puncture techniques. This complexity is mainly attributed to the following reasons. First, reduced portal vein diameter increases the difficulty of portal vein puncture. Second, the portal system shrinks gradually and finally progresses to CTPV in the presence of chronic PVT, which makes access even harder.³⁵ Moreover, splenectomy makes the trans-splenic approach impossible, which is an important route to recanalize the occluded portal vein. Therefore, physicians should be aware of the complexity of TIPS procedure in this subgroup of patients and a rational procedural plan should be developed.

Our study has several limitations. First, a portion of patients with splenectomy history who had complete portal vein occlusion or extensive CTPV that could not undergo TIPS were excluded, which might lead to an underestimation of the current results.

Second, hemodynamic parameters were not available in the present study to support our results. Third, the duration between splenectomy and TIPS insertion varied in this study, and the effect on the correlation between splenectomy and post-TIPS outcomes needs further investigation. Fourth, a few baseline characteristics were not comparable between two groups. However, similar results obtained after adjusting for potential confounders and conducting sensitivity analysis confirmed the robustness of our results.

In conclusion, our results showed that splenectomy prior to TIPS complicated TIPS procedure and favored the development of postoperative shunt dysfunction and OHE. The mechanisms linking splenectomy history and shunt dysfunction may be related to the alternation in hemodynamic changes and hypercoagulable states caused by this surgery. Patients with splenectomy history should be carefully evaluated before TIPS treatment, and postoperative anticoagulation therapy and more intensive follow-up may help reduce the risk of shunt dysfunction and hepatic encephalopathy.

Table 4 Univariate and multivariate analysis of risk factors for shunt dysfunction

Variables	No. (%)	Univariate analysis		Multivariate analysis	
		HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value
Splenectomy			0.004		0.02
With (vs without)	74 (26.0)	2.78 (1.39–5.59)		2.31 (1.13–4.97)	
Age (per year)	—	0.99 (0.96–1.02)	0.403	—	—
Sex			0.085	—	—
Male (vs female)	182 (64.1)	1.95 (0.84–4.52)			
Etiology			0.536	—	—
Virus (vs non-virus)	190 (66.9)	1.30 (0.56–3.03)			
TIPS indication			0.775	—	—
Ascites (vs bleeding)	18 (6.3)	1.23 (0.29–5.19)			
Child–Pugh score	—	1.10 (0.88–1.36)	0.399	—	—
Child–Pugh class			0.750	—	—
B + C (vs A)	203 (71.5)	1.15 (0.49–2.71)			
MELD score	—	0.98 (0.88–1.09)	0.683	—	—
MELD–Na score	—	0.97 (0.89–1.06)	0.481	—	—
Total bilirubin	—	1.01 (0.99–1.02)	0.178	—	—
Albumin	—	0.96 (0.90–1.02)	0.225	—	—
Creatinine	—	0.99 (0.97–1.01)	0.244	—	—
Platelet count			0.009	—	—
> 100 × 10 ⁹ (vs ≤ 100 × 10 ⁹)	89 (31.3)	2.59 (1.26–5.31)			
Prothrombin time	—	1.01 (0.88–1.17)	0.836	—	—
INR	—	0.92 (0.45–1.89)	0.818	—	—
Ascites			0.785	—	—
With (vs without)	227 (79.9)	1.05 (0.75–1.46)			
Portal vein diameter	—	0.89 (0.79–1.00)	0.061	—	—
PVT [†]	132 (46.5)	1.51 (0.74–3.09)	0.256	—	—
CTPV	24 (8.4)	1.67 (0.68–3.93)	0.354	1.21 (0.47–2.59)	0.53
Endoscopic therapy			0.013		0.04
With (vs without)	57 (20.7)	2.51 (1.22–5.19)		1.95 (1.02–4.07)	
PPG (mmHg)	—			—	—
Pre-TIPS		1.01 (0.94–1.09)	0.773		
Post-TIPS		0.98 (0.90–1.08)	0.742		
PPG change		1.03 (0.94–1.13)	0.482		

[†]PVT indicates patients with at least one thrombosis in the portal system.

CI, confidence interval; CTPV, cavernous transformation of portal vein; HR, hazard ratio; INR, international normalized ratio; MELD, model for end-stage liver disease; No., number of events; PPG, portal pressure gradient; PVT, portal vein thrombosis; TIPS, transjugular intrahepatic portosystemic shunt.

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References

- Sanyal AJ, Bosch J, Blei A, Arroyo V. Portal hypertension and its complications. *Gastroenterology* 2008; **134**: 1715–28.
- Gracia-Sancho J, Marrone G, Fernández-Iglesias A. Hepatic microcirculation and mechanisms of portal hypertension. *Nat. Rev. Gastroenterol. Hepatol.* 2019; **16**: 221–34.
- Vilstrup H, Amodio P, Bajaj J *et al.* Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. *Hepatology* 2014; **60**: 715–35.
- European Association for the Study of the Liver. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. *J. Hepatol.* 2018; **69**: 406–60.
- Hassab MA. Gastroesophageal decongestion and splenectomy in the treatment of esophageal varices in bilharzial cirrhosis: further studies with a report on 355 operations. *Surgery* 1967; **61**: 169–76.
- Chen XP, Wu ZD, Huang ZY, Qiu FZ. Use of hepatectomy and splenectomy to treat hepatocellular carcinoma with cirrhotic hypersplenism. *Br. J. Surg.* 2005; **92**: 334–9.
- Hashizume M, Tanoue K, Morita M, Ohta M, Tomikawa M, Sugimachi K. Laparoscopic gastric devascularization and splenectomy for sclerotherapy-resistant esophagogastric varices with hypersplenism. *J. Am. Coll. Surg.* 1998; **187**: 263–70.
- Zhou J, Wu Z, Wu J *et al.* Transjugular intrahepatic portosystemic shunt (TIPS) versus laparoscopic splenectomy (LS) plus preoperative endoscopic varices ligation (EVL) in the treatment of recurrent variceal bleeding. *Surg. Endosc.* 2013; **27**: 2712–20.
- Kawanaka H, Akahoshi T, Kinjo N *et al.* Effect of laparoscopic splenectomy on portal haemodynamics in patients with liver cirrhosis and portal hypertension. *Br. J. Surg.* 2014; **101**: 1585–93.
- Dong F, Luo SH, Zheng LJ *et al.* Incidence of portal vein thrombosis after splenectomy and its influence on transjugular

- intrahepatic portosystemic shunt stent patency. *World J. Clin. Cases* 2019; **7**: 2450–62.
- 11 Intagliata NM, Caldwell SH, Tripodi A. Diagnosis, development, and treatment of portal vein thrombosis in patients with and without cirrhosis. *Gastroenterology* 2019; **156**: 1582–99.
 - 12 von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening of Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007; **370**: 1453–7.
 - 13 Liu J, Shi Q, Xiao S *et al.* Using transjugular intrahepatic portosystemic shunt as the first-line therapy in secondary prophylaxis of variceal hemorrhage. *J. Gastroenterol. Hepatol.* 2020; **35**: 278–83.
 - 14 Rössle M, Haag K, Ochs A *et al.* The transjugular intrahepatic portosystemic stent-shunt procedure for variceal bleeding. *N. Engl. J. Med.* 1994; **330**: 165–71.
 - 15 Perarnau JM, Le Gouge A, Nicolas C *et al.* Covered vs. uncovered stents for transjugular intrahepatic portosystemic shunt: a randomized controlled trial. *J. Hepatol.* 2014; **60**: 962–8.
 - 16 de Franchis R. Revising consensus in portal hypertension: report of the Baveno V consensus workshop on methodology of diagnosis and therapy in portal hypertension. *J. Hepatol.* 2010; **53**: 762–8.
 - 17 American Association for the Study of Liver Diseases, European Association for the Study of the Liver. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases. *J. Hepatol.* 2014; **61**: 642–59.
 - 18 Cheng LF, Jia JD, Xu XY *et al.* Esophagogastric variceal bleeding in cirrhotic portal hypertension: consensus on prevention and management (2008). *Chin. Med. J. (Engl)* 2009; **122**: 766–75.
 - 19 Ikegami T, Shimada M, Imura S. Recent role of splenectomy in chronic hepatic disorders. *Hepatol. Res.* 2008; **38**: 1159–71.
 - 20 Matsui T, Usui M, Wada H *et al.* Platelet activation assessed by glycoprotein VI/platelet ratio is associated with portal vein thrombosis after hepatectomy and splenectomy in patients with liver cirrhosis. *Clin. Appl. Thromb. Hemost.* 2018; **24**: 254–62.
 - 21 Pietrabissa A, Moretto C, Antonelli G, Morelli L, Marciano E, Mosca F. Thrombosis in the portal venous system after elective laparoscopic splenectomy. *Surg. Endosc.* 2004; **18**: 1140–3.
 - 22 Kinjo N, Kawanaka H, Akahoshi T *et al.* Risk factors for portal vein thrombosis after splenectomy in patients with cirrhosis and portal hypertension. *Br. J. Surg.* 2010; **97**: 910–6.
 - 23 de'Angelis N, Abdalla S, Lizzi V *et al.* Incidence and predictors of portal and splenic vein thrombosis after pure laparoscopic splenectomy. *Surgery* 2017; **162**: 1219–30.
 - 24 Zhang Y, Xu B-Y, Wang X-B *et al.* Prevalence and clinical significance of portal vein thrombosis in patients with cirrhosis and acute decompensation. *Clin. Gastroenterol. Hepatol.: Off. Clin. Pract. J. Am. Gastroenterol. Assoc.* 2020; **18**.
 - 25 Sugawara Y, Yamamoto J, Shimada K *et al.* Splenectomy in patients with hepatocellular carcinoma and hypersplenism. *J. Am. Coll. Surg.* 2000; **190**: 446–50.
 - 26 Bolognesi M, Merkel C, Sacerdoti D, Nava V, Gatta A. Role of spleen enlargement in cirrhosis with portal hypertension. *Dig. Liver Dis.* 2002; **34**: 144–50.
 - 27 Basili S, Raparelli V, Napoleone L *et al.* Platelet count does not predict bleeding in cirrhotic patients: results from the PRO-LIVER study. *Am. J. Gastroenterol.* 2018; **113**: 368–75.
 - 28 Nolte W, Wiltfang J, Schindler C *et al.* Portosystemic hepatic encephalopathy after transjugular intrahepatic portosystemic shunt in patients with cirrhosis: clinical, laboratory, psychometric, and electroencephalographic investigations. *Hepatology* 1998; **28**: 1215–25.
 - 29 Hassoun Z, Deschênes M, Lafortune M *et al.* Relationship between pre-TIPS liver perfusion by the portal vein and the incidence of post-TIPS chronic hepatic encephalopathy. *Am. J. Gastroenterol.* 2001; **96**: 1205–9.
 - 30 Olde Damink SW, Jalan R, Redhead DN, Hayes PC, Deutz NE, Soeters PB. Interorgan ammonia and amino acid metabolism in metabolically stable patients with cirrhosis and a TIPSS. *Hepatology* 2002; **36**: 1163–71.
 - 31 Asanoma M, Ikemoto T, Mori H *et al.* Cytokine expression in spleen affects progression of liver cirrhosis through liver–spleen cross-talk. *Hepatol. Res.* 2014; **44**: 1217–23.
 - 32 Bai DS, Zhou BH, Qian JJ, Zhang C, Jin SJ, Jiang GQ. Effects of laparoscopic splenectomy and azygoportal disconnection on liver synthesis function and cirrhosis: a 2-year prospective study. *Surg. Endosc.* 2020; **34**: 5074–82.
 - 33 Aoyama T, Kuwahara-Arai K, Uchiyama A *et al.* Spleen-derived lipocalin-2 in the portal vein regulates Kupffer cells activation and attenuates the development of liver fibrosis in mice. *Lab. Invest.* 2017; **97**: 890–902.
 - 34 Lv Y, He C, Wang Z *et al.* Association of nonmalignant portal vein thrombosis and outcomes after transjugular intrahepatic portosystemic shunt in patients with cirrhosis. *Radiology* 2017; **285**: 999–1010.
 - 35 Luo J, Li M, Zhang Y *et al.* Percutaneous transhepatic intrahepatic portosystemic shunt for variceal bleeding with chronic portal vein occlusion after splenectomy. *Eur. Radiol.* 2018; **28**: 3661–8.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Details of TIPS procedure and TIPS-related complications.