ORIGINAL ARTICLE

Covered TIPS versus endoscopic band ligation plus propranolol for the prevention of variceal rebleeding in cirrhotic patients with portal vein thrombosis: a randomised controlled trial

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ABSTRACT

Objective Limited data are available on the prevention of variceal rebleeding in cirrhotic patients with portal vein thrombosis (PVT). This study aimed to compare transjugular intrahepatic portosystemic shunt (TIPS) with covered stents versus endoscopic band ligation (EBL) plus propranolol for the prevention of variceal rebleeding among patients with cirrhosis and PVT.

Design Consecutive cirrhotic patients (94% Child-Pugh class A or B) with PVT who had variceal bleeding in the past 6 weeks were randomly assigned to TIPS group (n=24) or EBL plus propranolol group (EBL+drug, n=25), respectively. Primary endpoint was variceal rebleeding. Secondary endpoints included survival, overt hepatic encephalopathy (OHE), portal vein recanalisation and rethrombosis, other complications of portal hypertension and adverse events.

Results During a median follow-up of 30 months in both groups, variceal rebleeding was significantly less frequent in the TIPS group (15% vs 45% at 1 year and 25% vs 50% at 2 years, respectively; HR=0.28, 95% CI 0.10 to 0.76, p=0.008), with a significantly higher portal vein recanalisation rate (95% vs 70%; p=0.03) and a relatively lower rethrombosis rate (5% vs 33%; p=0.06) compared with the EBL+drug group. There were no statistically significant differences in survival (67% vs 84%; p=0.152), OHE (25% vs 16%; p=0.440), other complications of portal hypertension and adverse events between groups.

Conclusion Covered TIPS placement in patients with PVT and moderately decompensated cirrhosis was more effective than EBL combined with propranolol for the prevention of rebleeding, with a higher probability of PVT resolution without increasing the risk of OHE and adverse effects, but this benefit did not translate into improved survival.

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INTRODUCTION

Portal vein thrombosis (PVT) is not uncommon in patients with cirrhosis, with a prevalence ranging from 10% to 23%.[1] It is generally regarded as a hallmark of poor outcomes.[2 3] Variceal bleeding (VB) is a life-threatening complication of cirrhosis with a 6-week mortality of approximately 15%–20%.[4 5] The 1-year rate of recurrent VB is approximately 60% in patients without prophylaxis treatment. Therefore, all patients who survive VB must receive active treatments to prevent rebleeding. In certain circumstances, acute VB occurs in cirrhotic patients with PVT. Due to the paucity of data, the optimal prophylaxis treatment for variceal rebleeding in this population has not been addressed in any consensus or guidelines.[2 3 5] Usually, these patients are submitted to rebleeding prophylaxis with endoscopic band ligation (EBL) combined with non-selective beta-blockers (NSBB) and, when necessary, anticoagulation is started after varices eradication.[6 7] Transjugular intrahepatic portosystemic shunts (TIPS) are reserved for those who failed endoscopic plus medical treatment or anticoagulation.[2 7]

However, PVT has been shown to be associated with a longer time to variceal eradication, a higher risk of variceal relapse and rebleeding in patients with cirrhosis who underwent EBL.[8–10] Additionally, NSBB treatment may induce thrombus formation by reducing splanchnic blood flow and causing further portal vein stasis.[11] Moreover, in a setting where anticoagulation is definitely indicated, clinicians often face the dilemma of either an increased risk of rebleeding with anticoagulation treatment, or potential PVT exacerbation if the patient is not anticoagulated or initiation of anticoagulation therapy was delayed after the variceal eradication.[7] Furthermore, later use of TIPS in cases of its urgent indication (such as uncontrollable VB), the procedure may have a higher risk of failure and inefficacy due to ageing of the thrombus or extension into intrahepatic branches.[12–15] In contrast, studies have shown that TIPS is effective in preventing variceal rebleeding similarly to patients without PVT, and is efficient in portal vein recanalisation and in the prevention of subsequent rethrombosis.[12–17] More importantly, the risk of hepatic encephalopathy

Significance of this study

What is already known on this subject?

- Portal vein thrombosis (PVT) is independently associated with an increased risk of variceal bleeding as well as failure of endoscopic control of bleeding and rebleeding, leading to a higher 6-week mortality compared with patients without PVT in cirrhosis.
- Observational studies have shown that the placement of transjugular intrahepatic portosystemic shunt (TIPS) is safe and effective for the prevention of variceal rebleeding and recanalisation of the portomesenteric system in cirrhotic patients with PVT.

What are the new findings?

- TIPS placement is feasible in the vast majority of patients and is more effective than endoscopic band ligation combined with propranolol in the prevention of variceal rebleeding, without increasing the risk of overt hepatic encephalopathy or other adverse events in patients with cirrhosis and PVT.
- TIPS, in patients with PVT and with Child-Pugh class A or B cirrhosis, did not improve survival, which mainly depended on the hepatitis B viral replication and the severity of the underlying cirrhosis rather than variceal rebleeding.
- TIPS creation was associated with a higher probability of portal vein recanalisation and a lower risk of subsequent rethrombosis, while superior mesenteric vein thrombosis is inversely associated with the portal vein recanalisation in cirrhotic patients with PVT.

How might it impact on clinical practice in the foreseeable future?

- In patients with cirrhosis and PVT, TIPS is a good alternative for preventing variceal rebleeding and improving PVT recanalisation and is especially valuable for liver transplantation candidates.
- Future studies addressing optimal selection criteria for TIPS in patients with cirrhosis presenting with variceal bleeding and PVT remain highly necessary.

(HE) may not increase after TIPS in patients with PVT[15] since studies have shown that the loss of portal perfusion prior to TIPS was associated with a decreased risk of overt hepatic encephalopathy (OHE) in patients with cirrhosis.[18 19] Therefore, TIPS implantation may be justified in patients without prior use of endoscopic/medical treatment or anticoagulants. Nevertheless, the available data are extremely scarce.

Therefore, the aim of this randomised controlled trial (RCT) was to assess the efficacy and safety of covered TIPS versus EBL combined with NSBB for rebleeding prophylaxis among cirrhotic patients with PVT.

METHODS

This was an open-label, randomised, single-centre trial comparing TIPS with EBL plus propranolol for the prevention of variceal rebleeding in cirrhotic patients with PVT who had bled from varices within the past 6 weeks. To achieve portal vein recanalisation or prevent further thrombus extension, anticoagulants were used in both groups. The study protocol and amendments were approved by our institute's ethics committee, and written informed consent was obtained for every procedure from all patients. The trial was registered with ClincalTrials.gov under NCT01326949.

Patient selection

Patients admitted at Xijing Hospital (a tertiary university hospital in China) were considered eligible for the study if they met the following criteria: liver cirrhosis (diagnosed by clinical presentations, laboratory tests, images or liver biopsies), age between 18 and 75 years, PVT >50% of the portal vein trunk (because we thought that PVT with less than half of the vessel lumen occluded may have little impact on portal flow), and a history of endoscopy-proven VB in the past 6 weeks. Exclusion criteria included uncontrolled active VB; technical impracticality of TIPS (eg, fibrotic cord of the portal vein); previous EBL+NSBB, TIPS placement or shunt surgery; concomitant renal insufficiency (serum creatine >170 μmol/L); severe cardiopulmonary diseases; uncontrolled systemic infection or sepsis; hepatocellular carcinoma or other extrahepatic malignancy; and contraindications for propranolol, anticoagulation or TIPS.

Patients presenting with acute bleeding were screened on day 6 after successful treatment of the index bleeding with vasoactive drugs (terlipressin or somatostatin), antibiotics and endoscopic treatment for 5 days. Those who failed to achieve primary haemostasis during acute bleeding were excluded. Patients with a history of recent VB were screened on day 1 after hospital admission and those who previously had received more than one session of ligation/sclerotherapy and NSBB were excluded.

Randomisation

Eligible patients were randomised in a 1:1 ratio to receive TIPS (TIPS group) or EBL plus drug treatment (EBL+drug group) stratified according to the Child-Pugh class (A or B/C) and degree of PVT (partial or complete obstruction) using a web-based allocation system (http://openrct.fmmu.edu.cn) with Pocock and Simon's minimisation method.[20] Randomisation was performed within 24 hours after enrolment by a clinical research coordinator who was not involved in the clinical setting or data analysis.

Interventions

The TIPS procedure was performed within 48 hours after randomisation with 8 mm polytetrafluoroethylene covered stents (Fluency, Bard Peripheral Vascular, Tempe, Arizona, USA) by the same team (GH, ZhanY, CH and WG with 17, 13, 11 and 11 years of experience with the TIPS procedure, respectively) as previously described (online supplementary figure 1 and online supplementary videos 1A–4C).[12 16] Local thrombolysis with bolus infusions of urokinase (500 000 units twice daily) was performed for 3 days in patients with occlusive thrombus remaining in the superior mesenteric vein (SMV) and/or the splenic vein (SV) after stent insertion to ensure adequate intrastent blood flow (online supplementary figure 2).

In the EBL+drug group, EBL was performed within 48 hours after randomisation and then scheduled every 1–2 weeks until variceal eradication was achieved. EBL was carried out with multiband devices (Wilson-Cook Medical, Winston-Salem, North Carolina, USA). After variceal eradication, endoscopic surveillance was performed at 1-month, 3-month and 6-month intervals and then every 6 months, with further treatment if new varices appeared. Propranolol was given continuously, with an initial dose of 20 mg twice daily and then with increasing doses until 55 beats per minute (bpm) or a 25% decrease in heart rate was achieved.

In both groups, anticoagulation was initiated based on a standardised protocol: intravenous heparin (8000–12 000 units daily) was first administered for 5 days, followed by warfarin for 6

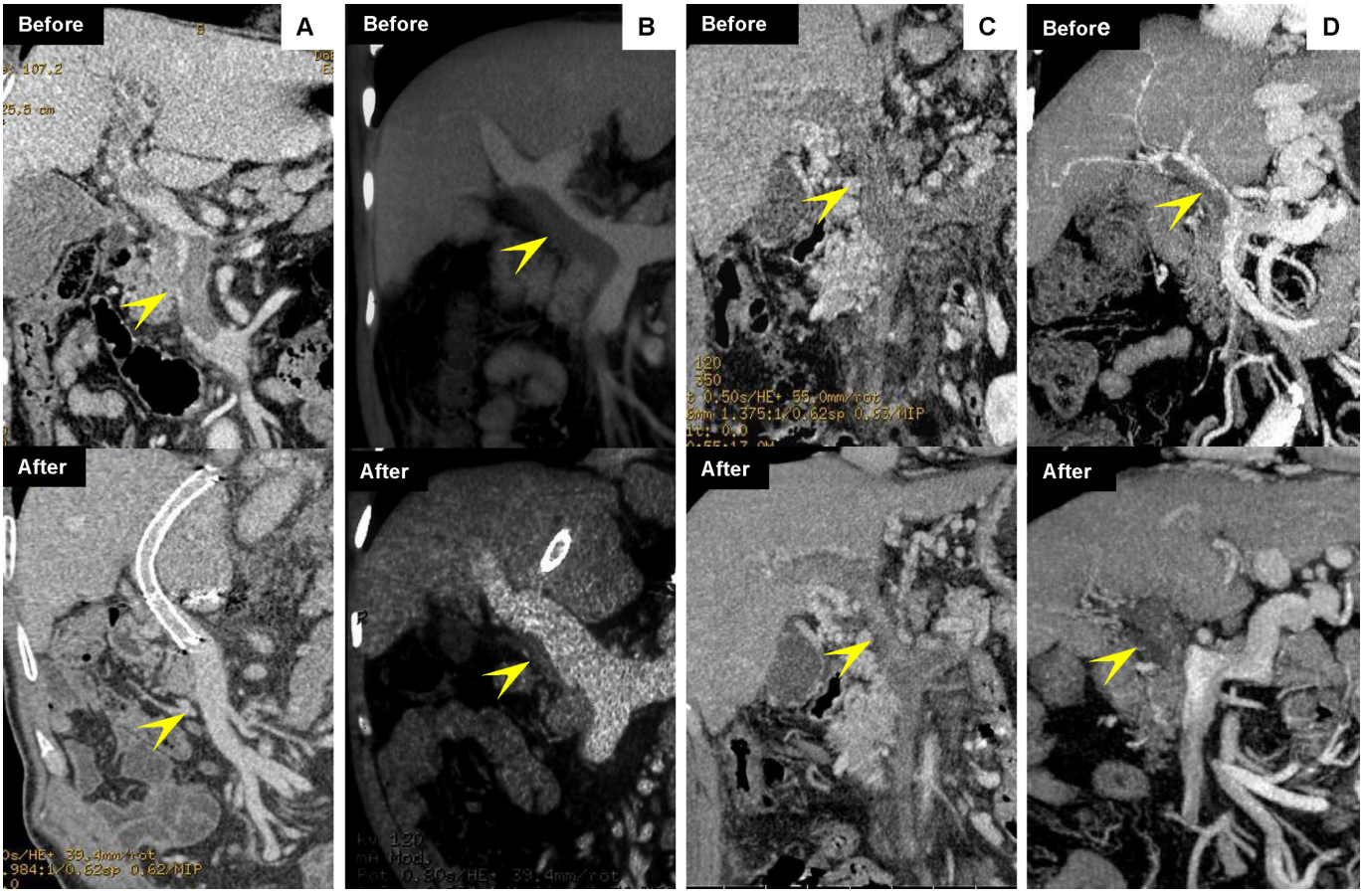

Figure 1 Pictorial depiction of portal vein thrombosis outcomes. Thromboses of portal vein with complete recanalisation (A), partial recanalisation (B), stability (C) or worsened (D) after treatment.

months or until PVT complete recanalisation had been achieved. Patients who achieved early recanalisation stopped treatment at 6 months, and patients were anticoagulated for longer than 6 months in the case of absent or partial recanalisation. Anticoagulation was started immediately after the TIPS procedure or after variceal eradication. Warfarin was started with an initial dosage of 2.5 mg daily and titrated carefully to achieve a target international normalised ratio (INR) of 2–3.

Follow-up

Follow-up visits were scheduled at 1, 3 and 6 months and then every 6 months thereafter or whenever there is clinical recurrence of portal hypertension, including clinical, biochemical, Doppler ultrasound and CT evaluations. The follow-up period was defined as the time interval from randomisation to either liver transplantation, death or the last randomised patient had been followed for 2 years.

Endpoints and definitions

The primary endpoint was variceal rebleeding, defined as recommended in the Baveno V consensus.[21] The secondary endpoints included survival, OHE, portal vein recanalisation and rethrombosis, other complications of portal hypertension and adverse effects.

OHE was diagnosed and graded according to current guidelines.[22] Portal vein recanalisation was evaluated on the basis of CT images. PVT was considered improved when portal vein complete or partial recanalisation was achieved (recanalisation was considered complete when the thrombus in the portal vein trunk, at least one of the two intrahepatic portal vein branches, SMV and SV all completely disappeared; partial when a reduction of more than 50% of the thrombus was achieved in the absence of extension), stable when the thrombus maintained the same dimensions or there was a reduction of less than 50%, and worsened when the thrombus was extended to unaffected segments of the splenoportomesenteric axis or to complete PVT[6] (figure 1).

Relevant amendments to the study protocol

After the onset of the trial, any drugs preplanned as encephalopathy prophylactics (arginine, branched-chain amino acids, L-ornithine-L-aspartate) and oral aspirin were not used in the TIPS group because their efficacy is not definite. In addition, NSSB was administered immediately after randomisation according to current guidelines[3 5] and the endoscopic sclerotherapy was not used in the EBL+drug group.

Sample size calculation

To achieve 80% power at a 5% significance level, 22 patients in each group were required to detect a difference of 0.35 assuming a rebleeding rate of 45% in the EBL+drug group and 10% in the TIPS group, which is based on previous studies (online supplementary table 1).[12 23] Considering a 10% patient dropout rate, 25 patients should be allocated to each group.

Statistical analysis

All analyses were conducted mainly by the intention-to-treat (ITT) principle and were supplemented by online supplementary perprotocol (PP) and 'as-treated' analyses. In the ITT analysis,

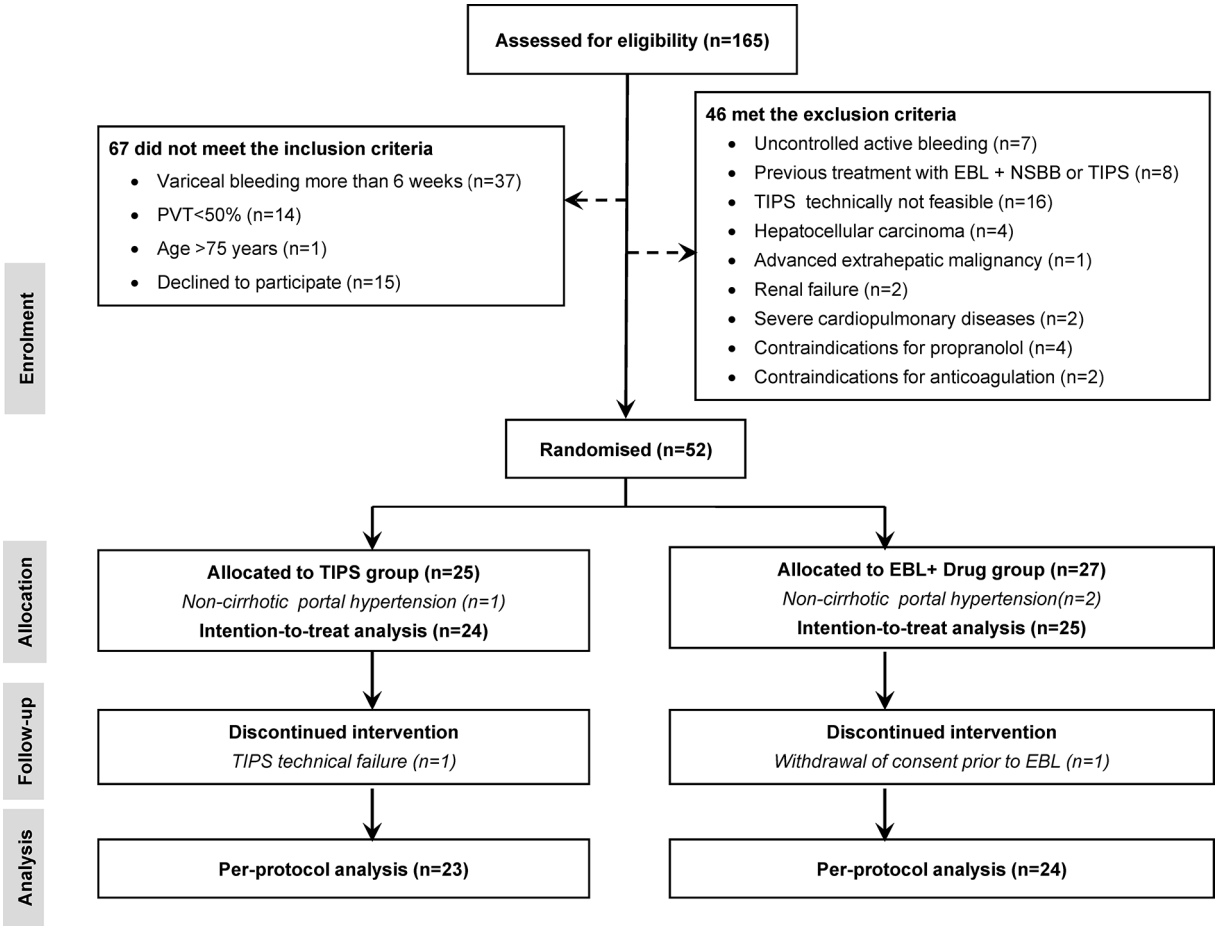

Figure 2 Flow chart showing the study design and patients' disposition. EBL, endoscopic band ligation; NSBB, non-selective beta-blockers; PVT, portal vein thrombosis; TIPS, transjugular intrahepatic portosystemic shunt.

all eligible patients were analysed according to the allocation, and censored at the time of death, liver transplantation, loss to follow-up or the last visit before study closure. In the 'as-treated' analysis, patients were analysed according to the treatment regimen that they received and censored at the moment they switched therapy, in addition to the censoring time points in the ITT analysis.

Quantitative variables were expressed as median (IQR) and compared using non-parametric Mann-Whitney U test. Qualitative variables were presented as numbers (percentages) and compared by means of the $\chi 2$ test or Fisher's exact test as appropriate. Cumulative risks were assessed with Kaplan-Meier curves and compared using the log-rank test. Stepwise Cox regression analysis was used to identify independent predictors for recurrent bleeding, survival, OHE and portal vein recanalisation. Variables with $p<0.10$ in univariate analyses were selected for the subsequent multivariate analysis. Redundant variables were not introduced in the final analysis to reduce possible colinearities. A post-hoc sensitivity analysis based on a competing risk approach (Fine and Gray method) was performed to assess the effects of overall death and liver transplantation as competing events on the occurrence of the outcome of interest. A two-tailed p value <0.05 was considered statistically significant in all analyses. All statistical calculations were performed using SPSS V.19.0 and R V.3.2.5 (http://www.R-project.org) software packages.

RESULTS

Study patients

Recruitment was performed from May 2011 to January 2014 and the final follow-up was completed in January 2016. During the study period, 156 patients were initially considered for the study. A total of 113 patients were excluded for the reasons shown in figure 2, and 52 patients were ultimately randomised. Three patients were excluded early after randomisation because of non-cirrhotic portal hypertension. Five (20%) of the 25 patients randomised to the EBL+drug group crossed over to TIPS, including one who withdrew consent before starting endoscopic therapy and four who switched to TIPS during the course of the study as a result of recurrent/uncontrollable variceal rebleeding (n=3) and refractory ascites (n=1). One (4%) of the 24 patients allocated to TIPS crossed over to the EBL+drug group. This patient was not treated with TIPS because of technical failure due to extensive thrombosis. Therefore, 49 patients were available for the ITT analysis or as-treated analysis, and 47 patients were available for the PP analysis (figure 2).

Baseline characteristics were comparable between the study groups either on an ITT or PP basis (table 1). One patient received liver transplantation in the EBL+drug group and none were lost to follow-up. The median follow-up was 30.4 months (IQR: 24.6–39.0) in the EBL+drug group and 30.9 months (IQR: 21.6–42.5) in the TIPS group (p=0.928).

Table 1 Baseline characteristics

Variables	TIPS (n=24)	EBL+drug (n=25)	p Value
Age (years)	49 (46–62)	46 (38–56)	0.212
Male gender, n (%)	13 (54)	16 (64)	0.484
Aetiology of liver cirrhosis, n (%)			0.492
HBV	20 (83)	22 (88)	
HCV	1 (4)	0 (0)	
Alcoholic liver disease	1 (4)	0 (0)	
Autoimmune hepatitis	1 (4)	1 (4)	
HBV+autoimmune hepatitis	0 (0)	1 (4)	
Cryptogenic	1 (4)	1 (4)	
HBV-DNA positive, n (%)	7 (33)	8 (32)	0.921
Child-Pugh class, n (%)			0.815
A (5–6)	9 (38)	10 (40)	
B (7–9)	13 (54)	14 (56)	
C (10–13)	2 (8)	1 (4)	
Child-Pugh score, median (IQR)	7 (6–8)	7 (6–8)	0.477
MELD score, median (IQR)	12 (9–13)	10 (9–12)	0.669
MELD-Na score, median (IQR)	12 (9–14)	11 (9–15)	0.398
Interval from index bleeding to randomisation, n (%)			0.567
5–21 days	15 (63)	17 (68)	
>21 days	9 (37)	8 (32)	
Presentation as acute bleeding, n (%)	7 (29)	9 (36)	0.762
Location of varices at index gastroscopy, n (%)			0.619
Oesophageal varices only	15 (63)	14 (56)	
Oesophageal and gastric varices	9 (37)	11 (44)	
Oesophageal varices (medium or large), n (%)	22 (92)	21 (84)	0.667
Ascites, n (%)			0.784
Mild	13 (54)	13 (52)	
Moderate	3 (13)	2 (8)	
Severe	3 (13)	2 (8)	
Hydrothorax (moderate or severe), n (%)	1 (4)	1 (4)	0.976
Previous hepatic encephalopathy, n (%)	1 (4)	1 (4)	0.976
Previous bleeding, n (%)	8 (33)	12 (48)	0.387
Haemoglobin (g/L), median (IQR)	78.5 (65.2–86.7)	89.0 (77.0–98.5)	0.081
Albumin (g/L), median (IQR)	34.1 (30.4–36.5)	34.0 (30.2–37.4)	0.958
Total bilirubin (μmol/L), median (IQR)	20.6 (13.2–25.4)	17.0 (11.4–21.9)	0.333
INR, median (IQR)	1.40 (1.22–1.60)	1.33 (1.16–1.54)	0.441
Creatinine (μmol/L), median (IQR)	71.0 (60.5–76.8)	79.0 (66.0–95.5)	0.061
Sodium (mmol/L), median (IQR)	139.6 (136.4–142.1)	137.9 (135.2–141.9)	0.588
Heart rate (bpm), median (IQR)	76 (64–82)	74 (65–83)	0.826
Mean arterial pressure (mm Hg), median (IQR)	80 (72–84)	81 (72–87)	0.976
Acute PVT, n (%)*	2 (8)	3 (12)	0.189
Site of PVT, n (%)			0.667
Only trunk	2 (8)	4 (16)	
Trunk and branches	22 (92)	21 (84)	
Degree of PVT, n (%)†			0.762
Partial	16 (67)	18 (72)	
Complete	8 (33)	7 (28)	
Extent of PVT, n (%)			0. 017
MPV alone	2 (8)	12 (48)	
MPV+SMV	17 (71)	11 (44)	
MPV+SV	1 (4)	1 (4)	
MPV+SMV+SV	4 (17)	1 (4)	
Portal cavernoma, n (%)	11 (46)	11 (44)	0.897
Prothrombotic disorders, n (%)			
Protein S deficiency (<60%)	14 (58)	11 (44)	0.063
Protein C deficiency (<59%)	12 (50)	9 (36)	0.059

Continued

Table 1 Continued

Variables	TIPS (n=24)	EBL+drug (n=25)	p Value
Antithrombin III deficiency (<75%)	10 (43)	11 (48)	0.767
JAK2 V617F mutation	0 (0)	0 (0)	1.000
Factor II G20210A mutation	0 (0)	1 (4)	1.000
Factor V Leiden mutation	0 (0)	0 (0)	1.000
MTHFR C677T homozygous mutation	8 (33)	7 (28)	0.590
Hyperhomocysteinaemia (>15 µmol/L)	9 (38)	8 (33)	0.534

Intention-to-treat population. Values are expressed as median (IQR), other values are n (%).
*PVT was considered acute when patients presented with abdominal pain or intestinal ischaemia, or non-contrast-enhanced CT indicated a high intraluminal density within the portal vein. Such patients were considered to have developed chronic PVT if there was a definite finding of portal cavernoma at imaging investigations, or the original main portal vein was replaced with a fibrotic cord, or contrast-enhanced CT in the portal phase indicated a decreased intraluminal density.
†The degree and extent of PVT were evaluated based on axial and coronal images. The degree of PVT was classified as mural (cross-sectional occlusion <50% of vessel lumen), partial (cross-sectional occlusion ≥50% but <100%) and complete (occlusion occupying whole of the lumen or fibrotic cord replacing original main portal vein).
bpm, beats per minute; EBL, endoscopic band ligation; INR, international normalised ratio; JAK2, Janus kinase 2; MELD, Model for End-Stage Liver Disease; MPV, main portal vein; MTHFR, methylenetetrahydrofolate reductase; PVT, portal vein thrombosis; SMV, superior mesenteric vein; SV, splenic vein; TIPS, transjugular intrahepatic portosystemic shunt.

Treatment

In the TIPS group, TIPS was successfully performed in 23 (96%) of 24 patients: 18 patients received one stent and 5 patients required two stents. The mean portacaval pressure gradient (PPG) dropped from 27.7±4.4 to 8.7±4.4 mm Hg (p<0.001). After TIPS placement, four patients had a PPG greater than 12 mm Hg, but a PPG reduction >30% was achieved. Local thrombolysis and collateral embolisation were performed in five and seven patients, respectively. Twenty-two patients were on anticoagulation therapy for a median of 9.3 months (range: 0.5–18.6). Another two patients did not initiate anticoagulation because of early death (n=1) and prolonged bleeding time (n=1). The 1-year and 2-year primary shunt patency rates were 85% and 80%, respectively (online supplementary figure 3A).

In the EBL+drug group, all patients, except for one who withdrew consent, received propranolol (median dose 80 mg (range 20–170)). A 24% decrease was observed in the median heart rate after the maximum tolerated dose (from 74 to 56 bpm; online supplementary figure 3B). Variceal eradication was achieved in 17 patients after a median of 2 EBL sessions (range: 1–5) and a median of 21 days (range: 4–89). Among them, varices reappeared in four patients after a median of 123 days (range: 64–370) after eradication. In the remaining seven patients, eradication was not achieved because of death (n=3), transfer to rescue TIPS (n=3) and non-compliance (n=1). Twenty-two patients were on anticoagulation therapy with warfarin (median dose 2.5 mg (range: 1.25–3.75)) for a median of 17.8 months (range: 0.4–40.73), including five patients in whom eradication had not been achieved but the risk of VB was thought to be low after a careful evaluation by the investigators. The median delay from randomisation to the initiation of anticoagulation treatment was 32 days (IQR, 30–62).The remaining three patients did not initiate anticoagulation because of early death (n=2) and renal insufficiency (n=1).

All 15 HBV-DNA-positive patients were treated with entecavir, and a virological response (HBV-DNA could not be detected) was achieved in 13 patients on follow-up (seven in the EBL+drug group and six in the TIPS group).

Rebleeding

Five (21%) patients in the TIPS group and 15 (60%) patients in the EBL+drug group experienced rebleeding during follow-up (table 2). In 4 (17%) patients from the TIPS group and 13 (52%) patients from the EBL+drug group, recurrent bleeding was due to varices. In the TIPS group, two patients underwent TIPS revision and remained free from rebleeding thereafter, and three patients received medical or endoscopic treatment without an assessment of shunt patency as primary therapy for the management of rebleeding (two died of further bleeding and one required later shunt revision for stent stenosis associated with rebleeding). In the EBL+drug group, endoscopic haemostasis was achieved in nine patients, TIPS as a rescue therapy was required in three patients, and the remaining three patients died because of massive bleeding.

The 6-month, 12-month and 24-month actuarial probabilities of recurrent bleeding from any source were 5% (95% CI 0% to 24%), 15% (95% CI 0% to 29%) and 25% (95% CI 3% to 42%) in the TIPS group versus 37% (95% CI 14% to 55%), 45% (95% CI 21% to 62%) and 50% (95% CI 25% to 66%) in the EBL+drug group, respectively (HR=0.28, 95% CI 0.10 to 0.76, p=0.008; figure 3A). Likewise, variceal rebleeding was significantly lower in the TIPS group (5% vs 37% at 6 months, 15% vs 45% at 12 months and 20% vs 45% at 24 months, respectively; HR=0.27, 95% CI 0.09 to 0.83, p=0.014; figure 3B). Similar results were obtained using Gray's test and in the PP analysis population (online supplementary figures 4A,B and 5A,B). In the as-treated analysis, 4 (17%) patients treated with TIPS compared with 16 (64%) patients treated with EBL+drug experienced variceal rebleeding (p=0.001; online supplementary figure 6A,B). In the univariate Cox regression analysis, only allocation to the EBL+drug group was significantly associated with variceal rebleeding (table 3). The introduction of the extent of PVT in the final model did not alter its HR or CIs.

Survival

There were no significant differences in the 6-month, 12-month and 24-month actuarial probabilities of survival (TIPS: 84%, 83% and 73% vs EBL+drug: 88%, 88% and 84%, respectively; HR=2.10, 95 CI% 0.63 to 6.97, p=0.305; figure 3C). Similar results were obtained using competing risk, PP and as-treated analyses (online supplementary figures 4C, 5C and 6C). The proportion of patients who died due to non-liver-related disease in the TIPS group was slightly higher compared with the EBL+drug group (table 2). No significant difference in survival was observed among patients with or without ascites on propranolol in the EBL+drug group, although it was slightly higher in patients without ascites (online supplementary table 2).

In univariate analysis, HBV-DNA positivity at baseline, increased Child-Pugh score, Model for End-Stage Liver

Table 2 Summary of outcome measurements

Outcome	TIPS (n=24)	EBL+drug (n=25)	p Value
Duration of follow-up (months)*, median (IQR)	30.9 (21.6–42.5)	30.4 (24.6–39.0)	0.928
Rebleeding from any source, n (%)	5 (21)	15 (60)	0.032
Sources of bleeding, n (%)			
Variceal rebleeding	4 (17)	13 (52)	0.017
Portal hypertensive gastropathy	0 (0)	1 (4)	
Peptic ulcer bleeding	1 (4)	0 (0)	
Postendoscopic therapy	0 (0)	1 (4)	
Blood units transfused at rebleeding	2.4±3.2	4.1±4.0	0.025
Episodes per patient	0.29±0.62	1.04±1.27	0.013
Subgroup analysis, n (%)			
Baseline Child-Pugh class A	2 (22)	6 (60)	0.029
Baseline Child-Pugh class B/C	3 (20)	9 (60)	0.035
Interval from index bleeding to randomisation 6–21 days	3 (20)	10 (59)	0.036
Interval from index bleeding to randomisation >21 days	2 (22)	5 (63)	0.153
Orthotopic liver transplantation, n (%)	0 (0)	1 (1)	1.000
Mortality, n (%)	8 (33)	4 (16)	0.132
Cause of death, n (%)			0.152
Liver failure	3 (13)	1 (4)	
GI bleeding	2 (8)	3 (12)	
Lung cancer	1 (4)	0 (0)	
Cardiac infarction	1 (4)	0 (0)	
Pulmonary artery embolism	1 (4)	0 (0)	
Subgroup analysis, n (%)			
Baseline Child-Pugh class A	3 (33)	1 (10)	0.509
Baseline Child-Pugh class B/C	5 (38)	3 (21)	0.420
Interval from index bleeding to randomisation 6–21 days	4 (27)	4 (24)	0.631
Interval from index bleeding to randomisation >21 days	4 (44)	0 (0)	0.082
Overt hepatic encephalopathy, n (%)	6 (25)	4 (16)	0.440
Number of episode, n (%)			0.352
1	4 (17)	2 (8)	
2	1 (4)	0 (0)	
≥3	1 (4)	2 (8)	
Episodes per patient	0.4±1.2	0.4±0.9	0.942
Severe HE (grade III/IV), n (%)	2 (8)	2 (8)	0.662
Spontaneous OHE, n (%)	2 (8)	0 (0)	0.253
Precipitating OHE†, n (%)	4 (17)	4 (16)	0.950
Portal vein recanalisation‡, n (%)			0.030
Improved	21 (95)	16 (70)	
Complete recanalisation	19 (86)	12 (53)	
Partial recanalisation	2 (9)	4 (17)	
Stable	1 (5)	5 (22)	
Worsened	0 (0)	2 (8)	

Intention-to-treat population. ± Values are mean±SD, and other values are n (%).
*Outcomes were reported from trial inclusion to death, liver transplantation or the last randomised patient had been followed for 2 years.
†In the TIPS group, a possible precipitating event for OHE was identified in four patients: shunt revision in one, constipation in two and infection in one. In the EBL+drug group, four patients with OHE had a possible precipitating event: GI bleeding in one, use of diuretics in one, constipation in one and higher protein intake in one.
‡Follow-up images studies were available in 45 patients (22 in the TIPS group and 23 in the EBL+drug group).
EBL, endoscopic band ligation; HE, hepatic encephalopathy; OHE, overt hepatic encephalopathy; TIPS, transjugular intrahepatic portosystemic shunt.

Disease (MELD) score, INR and decreased albumin were significantly associated with increased mortality. When HBV-DNA positivity, INR and albumin were entered in the multivariate analysis, they remained the variables independently predicting mortality (table 3). The introduction of the extent of PVT in the final model did not alter the HRs or CIs of these variables or the allocation groups.

When a post-hoc composite endpoint of death and rebleeding was analysed, it did not differ between the groups (TIPS: 21%, 30% and 39% vs EBL+drug: 40%, 48% and 48%, respectively;

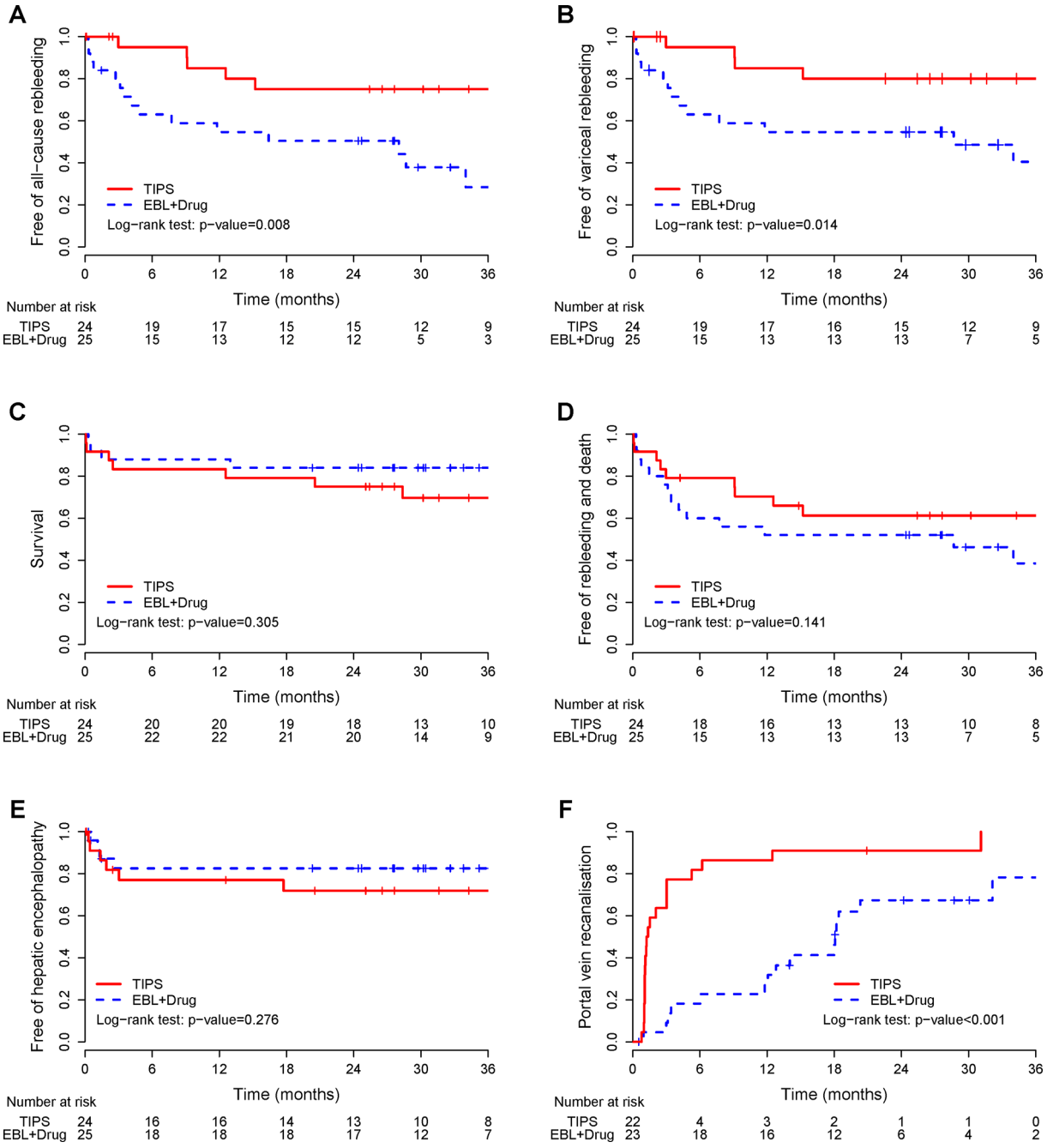

Figure 3 Kaplan-Meier curves according to treatment group in intention-to-treat population. Actuarial probability of remaining free of recurrent bleeding from any source (A), variceal rebleeding (B), survival (C), free of all-cause rebleeding or death (D), free of overt hepatic encephalopathy (E), and partial or complete recanalisation of portal vein system (F). EBL, endoscopic band ligation; TIPS, transjugular intrahepatic portosystemic shunt.

HR=0.54, 95 CI% 0.24 to 1.24, p=0.147; figure 3D). Similar results were observed in the PP analysis (online supplementary figure 5D). In the as-treated analysis, the results favoured TIPS treatment (online supplementary figure 6D).

Overt hepatic encephalopathy

Six (25%) patients in the TIPS group and four (16%) in the EBL+drug group developed at least one episode of OHE during follow-up (table 2). No significant differences in the 6–month, 12-month and 24-month actuarial probabilities of OHE were observed between the groups (TIPS: 23%, 23% and 28% vs EBL+drug: 17%, 17% and 17%, respectively; log-rank: HR=1.65, 95% CI 0.47 to 5.54, p=0.434; figure 3E, and Gray's test, p=0.460; online supplementary figure 4E). Among patients who experienced HE, the mean number of episodes was 2.2±1.3 in the TIPS group and 1.7±1.1 in the EBL+drug group, respectively (p=0.220). Two patients in the TIPS group and two in the EBL+drug group developed severe HE (grade III/IV). Encephalopathy was successfully controlled medically in all patients. OHE did not significantly differ in the PP and as-treated populations (online supplementary figures 5E and 6E).

In the univariate analysis, Child-Pugh score, MELD score, INR, ascites and serum creatinine were associated with increased OHE risk. When MELD score and ascites were included in a multivariate analysis, only MELD score was the independent predictor of OHE (table 3). The introduction of the extent of

Table 3 Univariate and multivariate analyses

	Univariate analysis*		Multivariate analysis	
Variable	**HR (95% CI)**	**p Value**	**HR (95% CI)**	**p Value**
Variceal rebleeding				
Allocation groups (EBL+drug vs TIPS)†	3.32 (1.19 to 9.27)	0.008		
Mortality				
HBV-DNA-positive (yes vs no)†	4.11 (1.20 to 14.07)	0.026	3.78 (1.07 to 13.37)	0.039
Child-Pugh score (per one point increase)	1.62 (1.05 to 2.48)	0.028		
MELD score (per one point increase)	1.16 (0.99 to 1.35)	0.060		
International normalised ratio†	4.85 (1.26 to 18.66)	0.022	6.39 (1.59 to 25.62)	0.009
Serum albumin (per one g/L decrease)†	1.12 (0.97 to 1.28)	0.056	1.17 (1.02 to 1.35)	0.021
Overt hepatic encephalopathy				
Child-Pugh score (per one point increase)	1.44 (0.95 to 2.19)	0.090		
MELD score (per one point increase)†	1.18 (1.01 to 1.37)	0.042	1.17 (1.01 to 1.37)	0.043
Ascites (yes vs no)†	3.44 (0.88 to 13.41)	0.076		
International normalised ratio	4.09 (1.04 to 16.12)	0.044		
Creatinine (per one µmol/L increased)	1.06 (1.03 to 1.16)	0.002		
Portal vein recanalisation				
MELD score (per one point increase)†	1.19 (1.03 to 1.37)	0.016		
International normalised ratio†	3.30 (0.95 to 11.44)	0.060		
SMV thrombosis (no vs yes)†	4.86 (2.12 to 10.99)	<0.001	3.32 (1.40 to 7.86)	0.006
Treatment (TIPS vs EBL+drug)†	3.92 (1.93 to 7.96)	<0.001	2.93 (1.37 to 6.28)	0.006

*Only variables with a p value <0.1 in the univariate analysis are shown. Variables selected into the univariate analysis were allocation groups, gender, age, aetiology of cirrhosis, HBV-DNA positive, Child-Pugh class, Child-Pugh score, MELD score, MELD-Na score, interval from index bleeding to randomisation, presentation as acute bleeding, location of varices at index gastroscopy, grade of oesophageal varices, ascites, hydrothorax, previous hepatic encephalopathy, previous bleeding, haemoglobin, serum albumin, serum total bilirubin, international normalised ratio, serum creatinine, stage of PVT (acute or chronic), degree of PVT, site of PVT, extent of PVT, portal cavernoma and prothrombotic disorders.
†Variables introduced in multivariable analysis.
EBL, endoscopic band ligation; MELD, Model for End-Stage Liver Disease; PVT, portal vein thrombosis; SMV, superior mesenteric vein; TIPS, transjugular intrahepatic portosystemic shunt.

PVT in the final model did not alter the HRs or CIs of MELD score or the allocation groups.

Portal vein recanalisation

Follow-up imaging studies were not available in four patients due to early death. In the remaining 45 patients, recanalisation (partial or complete) was observed in 21/22 (95%) patients in the TIPS group compared with 16/23 (70%) patients in the EBL+drug group (table 2). The 6-month, 12-month and 24-month actuarial probabilities of recanalisation were significantly higher in the TIPS group, regardless of analysis by ITT (TIPS: 82%, 86% and 91%; EBL+drug: 18%, 27% and 77%, respectively; HR=4.00, 95% CI 1.98 to 8.11, p<0.001; figure 3F), competing risk, PP or as-treated principles (online supplementary figures 4F, 5F and 6F). The dynamic changes of PVT in each individual are presented in figure 4. Among those who achieved complete recanalisation, 4/12 patients (33%) in the EBL+drug group had recurrent thrombosis after the cessation of anticoagulation therapy compared with 1/19 (5%) patients in the TIPS group (p=0.06).

In the univariate analysis, Child-Pugh score, MELD score, INR, the absence of SMV thrombosis and TIPS treatment were associated with portal vein recanalisation (partial or complete). When these variables were included in a multivariate analysis, only the absence of SMV thrombosis and allocation to the TIPS group independently predicted recanalisation (table 3).

Other complications of portal hypertension and adverse effects

There were no significant differences between the two groups in the incidence of new or worsening ascites (TIPS: 5% vs EBL+drug: 12%; p=0.17), hepatic hydrothorax (0% vs 4%; not significant [NS]), spontaneous bacterial peritonitis (0% vs 4%; NS) or hepatorenal syndrome (0% vs 4%; NS) (table 4). There were also no significant differences in the number of patients who experienced other serious or non-serious adverse events between both groups (table 4). A slight increase of bilirubin level was observed in the TIPS group. In contrast, creatinine values trended downwards (online supplementary figure 7).

DISCUSSION

The results from our prospective RCT suggest that TIPS is a good alternative to variceal rebleeding prophylaxis in cirrhotic patients with PVT based on the following findings: (1) the advantage of TIPS in the reduction of variceal rebleeding; (2) the superiority of TIPS in PVT resolution and the prevention of its recurrence; and (3) the non-increased risk of OHE, other

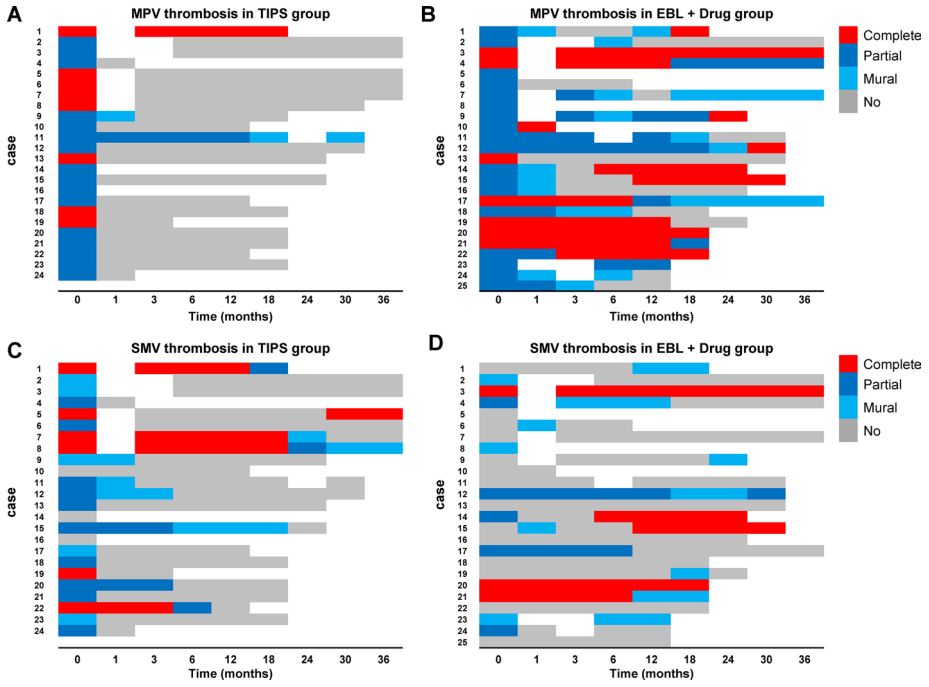

Figure 4 The variation of PVT throughout time according to treatment group in intention-to-treat population. Number in the ordinate axis indicates the number of each case and horizontal axis indicates time from inclusion. Each bar corresponds to the result of one examination. Red bars: complete PVT (occlusion occupying whole of the lumen); blue bars: partial PVT (cross-sectional occlusion ≥50% but <100%); light blue bars: mural PVT (cross-sectional occlusion <50% of vessel lumen); grey bars: no PVT. White intervals correspond to no images studies. EBL, endoscopic band ligation; MPV, main portal vein; PVT, portal vein thrombosis; SMV, superior mesenteric vein; TIPS, transjugular intrahepatic portosystemic shunt.

adverse events and mortality compared with EBL combined with drug therapy. Although recommendations for VB prophylaxis in patients without PVT are currently extended to those with PVT, this special population has not been sufficiently examined prospectively. To our knowledge, there has only been one randomised study in this field.[24] Compared with this RCT, the strengths of our study deserve from (1) greater homogeneity through the clear definition of the interval between index bleeding and randomisation; (2) patients with more severe PVT and unselected liver function; (3) prospective and individual descriptions of dynamic changes in PVT, for the first time; (4) consideration of the underlying prothrombotic state; and (5) more extended observation period, and more extensive and detailed evaluation of the outcomes.

The role of thrombophilic genetic defects in the development of PVT in cirrhosis remains controversial as the available studies report conflicting results. Our study demonstrated a very low prevalence of prothrombin G20210A and factor V Leiden gene mutations in Chinese patients with cirrhosis and PVT, which was significantly lower than that reported in some case series in which these two genotype mutations were seen in up to 50% of patients with PVT (online supplementary tables 3 and 4).[25–28] This variation in prevalence might be explained by ethnic differences. However, a recent large prospective study did not show any relationship between these two mutations and the development of PVT during follow-up.[29] The prevalence of methylenetetrahydrofolate reductase (MTHFR) C677T gene mutation was high in our patients. However, testing solely for MTHFR C677T gene mutation is unreliable since homozygosity for the MTHFR C677T variant could be observed in 10%–25% of the cirrhotic population without PVT (online supplementary table 5).[25 26 30] In contrast to the high prevalence in non-cirrhotic patients with PVT, the Janus kinase 2 V617F mutation may be uncommon in cirrhotic patients with PVT, with a reported prevalence ranging from 1.4% to 10% (online supplementary table 6).[31–34] This mutation was not observed in any of our patients, showing an extremely low prevalence. Consequently, our results suggest that thrombophilic genetic defects may be uncommon aetiological factors in the occurrence of PVT in Chinese patients with cirrhosis, which requires further confirmation in studies with larger sample sizes.

The rebleeding rate in our EBL+drug group is similar to that in previous RCT[24] and was within the reported range (29%–57%) of most studies on cirrhotic patients without PVT.[23 35–38] The 2-year survival rates of 75% (TIPS group) and 84% (EBL+drug group) in our study were also comparable to those reported in two recent RCTs with patients having similar liver function and the use of covered stents.[35 36] As expected, our results demonstrated a clear advantage of TIPS over EBL+drug with respect to the prevention of rebleeding. However, this advantage did not translate into improved survival. This may be explained by the characteristics of our patients. The multivariate analyses showed that INR and albumin rather than treatment modality were independent parameters associated with mortality, suggesting that the severity of liver function impairment instead of VB determines survival. Mortality was similar in both groups despite a much higher rebleeding rate in the EBL+drug group. This is consistent with previous findings showing that rebleeding is not associated with higher mortality in secondary prophylaxis,[35 36] which is in contrast to the findings in patients with acute bleeding.[39] As demonstrated recently by García-Pagán *et al*,[39] patients with an increased risk of early rebleeding had significantly improved survival when TIPS was performed early, demonstrating the importance of timing. Although early TIPS may improve survival in the acute bleeding phase, it may not have such effect in the prevention of rebleeding.[40] This is supported by our subgroup

Table 4 Adverse events

Adverse event	TIPS (n=24) <6 months	TIPS (n=24) >6 months until end follow-up	EBL+drug (n=25) <6 months	EBL+drug (n=25) >6 months until end follow-up	p Value*
Complications of portal hypertension, n (%)	5 (21)	2 (8)	5 (20)	5 (20)	0.426
Hepatic encephalopathy	5 (21)	1 (4)	4 (16)	0 (0)	
New or worsening ascites	0 (0)	1 (4)	1 (4)	2 (8)	
Hepatic hydrothorax	0 (0)	0 (0)	0 (0)	1 (4)	
Spontaneous bacterial peritonitis	0 (0)	0 (0)	0 (0)	1 (4)	
Hepatorenal syndrome	0 (0)	0 (0)	0 (0)	1 (4)	
Other serious adverse events, n (%)	4 (17)	2 (8)	4 (16)	4 (16)	0.588
Acute episode in chronic liver failure	1 (4)	0 (0)	0 (0)	0 (0)	
Hepatocellular carcinoma	0 (0)	2 (8)	0 (0)	1 (4)	
Pulmonary embolism	1 (4)	0 (0)	0 (0)	0 (0)	
Intraperitoneal bleeding	1 (4)	0 (0)	0 (0)	0 (0)	
Bleeding from banding ulcer	0 (0)	0 (0)	1 (4)	0 (0)	
Pneumonia	1 (4)	0 (0)	0 (0)	0 (0)	
Dysphagia	0 (0)	0 (0)	2 (8)	1 (4)	
Deep venous thrombosis	0 (0)	0 (0)	0 (0)	1 (4)	
Oesophageal stenosis	0 (0)	0 (0)	0 (0)	1 (4)	
Haematuria	0 (0)	0 (0)	1 (4)	0 (0)	
Non-serious adverse events, n (%)	5 (21)	4 (17)	7 (28)	3 (12)	0.610
Mispuncture of bile duct	1 (4)	0 (0)	0 (0)	0 (0)	
Chest pain (after EBL)	0 (0)	0 (0)	2 (8)	0 (0)	
Fever	2 (8)	0 (0)	1 (4)	0 (0)	
Fatigue	1 (4)	1 (4)	1 (4)	0 (0)	
Dizziness	0 (0)	1 (4)	1 (4)	1 (4)	
Diarrhoea	0 (0)	0 (0)	0 (0)	1 (4)	
Abdominal pain	0 (0)	0 (0)	1 (4)	0 (0)	
Vomiting	0 (0)	1 (4)	0 (0)	0 (0)	
Peripheral oedema	1 (4)	1 (4)	0 (0)	1 (4)	
Rash	0 (0)	0 (0)	1 (4)	0 (0)	

Intention-to-treat population. EBL denotes endoscopic band ligation.
*p Values are a comparison between the TIPS and EBL+drug groups after entire follow-up.
EBL, endoscopic band ligation; TIPS, transjugular intrahepatic portosystemic shunt.

analysis (table 2) whereTIPS did not significantly reduce the risk of rebleeding in patients randomised more than 3 weeks after bleeding and likely only added adverse effects. Furthermore, anticoagulation has been shown to improve survival and decrease the rate of complications of cirrhosis.[41 42] Therefore, the relatively better survival and less deterioration of liver function in the EBL+drug group may be partially explained by the longer anticoagulation time due to less recanalisation compared with TIPS group.

The incidence of OHE was not significantly different between groups, which is consistent with that reported by Luo *et al*[24] but conflicts with studies on patients without PVT that show that TIPS resulted in an increased risk of HE.[23 35–38] This may be explained by the following facts. First, patients with diminished or abolished portal perfusion before TIPS procedure may tolerate the procedure better because the hepatic haemodynamics does not change after stent insertion. Studies have shown that a loss of portal perfusion before TIPS insertion protected against the risk of HE.[18 19] Second, we chose to place 8 mm stents in our patients, whereas 10 mm stents were usually used in previous studies. A recent study by Sauerbruch *et al*[36] showed that 8 mm stent is associated with a low overt encephalopathy rate with adequate bleeding prophylaxis, which was confirmed by our recent RCT.[43]

As expected, a higher portal vein recanalisation rate was observed in TIPS group compared with the EBL+drug group. More importantly, the time to the achievement of recanalisation was significantly shorter in the TIPS group. As shown in the Kaplan-Meier curves and the individual data of PVT variations (figure 4), more than half of PVT completely resolved at one month in the TIPS group. In contrast, in the EBL+drug group, recanalisation occurs over a period of time, ranging from a few months to more than 2 years. This might be largely ascribed to the increased velocity of blood flow established by the TIPS, which promotes the mechanical dissolution of a residual non-occlusive thrombus (so-called 'scouring effect').[13 44–46] Although local thrombolysis may also play a certain role, it was only indicated in selected patients to establish adequate portal vein and intrastent flow at the time of TIPS placement. Moreover, we found a higher recurrence rate of PVT with the discontinuation of anticoagulants after complete PVT recanalisation in the EBL+drug group, which is consistent with those suggested in previous observational studies.[6 13] This finding prospectively confirmed the view that portal flow stasis is the primary causal factor of PVT in cirrhosis[28] and further highlights the strong incentive to continue long-term anticoagulation even after complete recanalisation has been achieved.[2 6] In addition, it has been shown that the presence of PVT adversely

impacts the outcomes of liver transplantation by increasing surgical complexity and postoperative mortality.[47] Therefore, patients with PVT who are candidates for liver transplantation may particularly benefit from TIPS insertion due to the greater preserved portal venous patency.[45 46] In this setting, the shortest possible distance of the stent into the portal vein with no extension into the inferior vena cava should be implemented to avoid increasing the technical difficulty of liver transplantation.[45 46]

No difference regarding adverse effects was observed. However, these results, as all other prognostic parameters, must be interpreted with caution due to the small sample size and the absence of double-blind assessments. It should be noted that a fatal pulmonary embolism occurred in one patient in the TIPS group. Considering the long-term bedridden history of this patient, we speculate that this may have resulted from deep vein thrombosis migration as described in recent article,[48] although the possibility that the clot came from residual PVT after shunt creation could not be excluded entirely. However, clot migration resulting in significant lung embolisation was rare and was not seen in our recent large cohort of patients with PVT receiving TIPS treatment.[49]

There are several limitations that should be mentioned. First, our study was conducted at a single centre with a relatively small sample size. Future studies may be required to validate our results with a larger number of patients in multiple centres. Second, Fluency-covered rather than Viatorr-covered stents were used because only the former was available in China during the study period, which must be considered with caution when using a Viatorr stent. Third, the starting point of anticoagulation was not identical in both groups, which may influence outcomes such as PVT recanalisationdata and adverse events. However, our anticoagulation therapy strategy was consistent with the recommendations in the current practice guidelines that anticoagulation should be initiated after the implementation of an adequate prophylaxis for GI haemorrhage.[2 50] Fourth, since most patients had HBV-related liver cirrhosis, the results should be interpreted cautiously for patients with other chronic liver diseases. Fifth, the extent of PVT was not balanced at baseline between groups even though we applied randomisation stratified according to the degree of PVT. However, to determine whether this variable could confound the relationship between the therapeutic strategy and the risks of rebleeding, death and OHE, we forced it in the final multivariable models. No relevant changes were observed in the HRs (or the CIs) of the allocation groups, indicating that confusion was unlikely. Sixth, given the technical demands, TIPS creation in the setting of PVT is only feasible at experienced centres. The technical expertise should be further popularised.

In conclusion, the placement of covered TIPS is more effective than EBL plus propranolol for the prevention of rebleeding without increasing the risk of OHE in patients with PVT and moderately decompensated cirrhosis. Furthermore, TIPS placement is also associated with a higher rate of portal venous patency. Considering the similar survival between groups, treatment selection (drugs plus ligation or TIPS) can be based on individual preference, but TIPS may be especially valuable for liver transplantation candidates. Nevertheless, future studies addressing optimal selection criteria for TIPS to obtain a survival benefit in this population remain highly warranted.

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Contributors YL: study design, data collection, evaluation of clinical events, endpoint assessment, statistical analysis, and writing and revising the manuscript. XQ: study conception and design, as well as drafting of the study hypothesis and study protocol. CH: study design, patient recruitment, informed consent, patient administration, TIPS surgery, follow-up and critical revision of the manuscript. ZW: data collection, designed the follow-up, and performed telephone follow-up and endpoint assessment. ZhanY: study design, TIPS surgery, patient administration, follow-up and critical revision of the manuscript. JN: patient randomisation, data collection and regular follow-up. WG and WB: study design and TIPS surgery. HZ, HX and LY: study design and endoscopic therapy. JW and TL: study design, percutaneous puncture of the portal vein under ultrasound-guided transhepatic and trans-splenic approaches and ultrasound follow-up of the patients. HC, QW, HL, EW, DX and ZhiY: critical revision of the manuscript. BL, XL, JY, NH and YZ: data collection. JX and HC: study design as well as design of the computer randomisation system and statistical analysis plan. KW and DF: study supervision, study design, critical revision of the manuscript and funds collection. GH: study supervision, study conception and design, patient recruitment, patient administration, TIPS surgery, follow-up, critical revision of the manuscript and funds collection. All of the authors gave their final approval of the version to be published.

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