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Portal vein thrombosis before and after transjugular intrahepatic portosystemic shunt placement

An observational study (STROBE compliant)

Yue-Meng Wan, MD, PhD[a,b], Yu-Hua Li, MD[a], Hua-Mei Wu, MD[a], Zhi-Yuan Xu, MD[a], Ying Xu, MD[a], Li-Hong Yang, MD[a], Xi-Nan Wu, MD, PhD[b], Jin-Hui Yang, MD[a,*]

Abstract

Portal vein thrombosis (PVT) is common in patients with cirrhosis undergoing transjugular intrahepatic portosystemic shunt (TIPS). This study had 3-fold aims: to assess risk factors for PVT; to determine the efficacy of anticoagulant therapy; to investigate the impact of PVT on clinical outcomes in TIPS-treated cirrhosis.

Between June 2012 and February 2016, 126 TIPS-treated patients with cirrhosis were enrolled and studied prospectively. Enrolled patients were screened for PVT before TIPS and at 3, 6, 12, and 24 months post-TIPS. All patients received warfarin (1.5–3.0 mg/day) or aspirin (100 mg/day) or clopidogrel (75 mg/day) post-TIPS. Results of patients with and without PVT (baseline and de novo) were compared.

White blood cell (WBC) counts (odds ratio (OR): 0.430, 95% confidence interval (CI): 0.251–0.739, $P = .002$) and Child–Turcotte–Pugh (CTP) score (OR: 2.377, 95% CI: 1.045–5.409, $P = .039$) were significant baseline predictors for PVT in TIPS-treated patients with cirrhosis. Warfarin resulted in markedly greater rates of complete recanalization than aspirin or clopidogrel ($P < .05$) in patients with PVT. Patients with PVT had markedly higher 2-year cumulative rates of variceal rebleeding, shunt dysfunction, hepatic encephalopathy, and hepatocellular carcinoma, and prominently lower overall survival than those without PVT ($P < .05$).

In TIPS-treated patients with cirrhosis, lower WBC count and higher CTP score were independent baseline predictors for PVT; patients with PVT had worse clinical outcomes than those without; warfarin may be more effective in recanalizing PVT than aspirin or clopidogrel.

Abbreviations: CT = computed tomography, CTP = Child–Turcotte–Pugh, e-PTFE = expanded polytetrafluoroethylene, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, HE = hepatic encephalopathy, INR = international normalized ratio, MELD = model for end-stage liver disease, PVT = portal vein thrombosis, TIPS = transjugular intrahepatic portosystemic shunt, WBC = white blood cell.

Keywords: cirrhosis, portal vein thrombosis, transjugular intrahepatic portosystemic shunt, variceal hemorrhage, warfarin

1. Introduction

Portal vein thrombosis (PVT) refers to thrombosis within the main portal vein, with or without thrombus extending to its tributaries,[1] with a reported prevalence ranging from 1% to 25%.[2,3] Potential contributing factors of PVT include decreased velocity of portal vein flow,[4,5] and concomitant thrombophilic disorders.[6,7] Transjugular intrahepatic portosystemic shunt (TIPS) is an established therapeutic approach for controlling variceal bleeding or refractory ascites in patients with cirrhosis and portal hypertension.[8]

After TIPS, there are concerns about thrombus development in patients without preexisting PVT and thrombus extension in patients with preexisting PVT, which may increase the risk of shunt dysfunction.[9,10] However, post-TIPS anticoagulation or antiplatelet therapy or neither has not been addressed in any consensus guideline to prevent TIPS dysfunction. Previous studies have linked PVT with worse clinical outcomes in patients with cirrhosis, as PVT may lead to increased hepatic decompensation, gastrointestinal hemorrhage, intestinal infarction, ascites, and posttransplant mortality.[2–4,11,12] To our best knowledge, there is no study that compared the post-TIPS clinical outcomes of patients with preexisting or de novo PVT with that of patients without any PVT in the literature. PVT was previously considered a contraindication of TIPS, but as the advancement of medical technology, an increasing number of cirrhotic patients with PVT had been reported to undergo TIPS.[13] Thus, it is of significant relevance for physicians to understand the risk for PVT development, the efficacies of different therapies to control

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[a] Gastroenterology Department II or Hepatology Center, The Second Affiliated Hospital of Kunming Medical University, [b] Public Health Institute of Kunming Medical University, Kunming City, Yunnan Province, China.

[*] Correspondence: Jin-Hui Yang, The Second Affiliated Hospital of Kunming Medical University, Kunming City, Yunnan Province, China (e-mail: 554007467@qq.com).

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PVT and the impact of PVT on clinical outcomes in patients undergoing TIPS.

Therefore, the aim of our study was to determine: the risk factors for PVT development; the efficacy of warfarin versus aspirin or clopidogrel in recanalizing PVT; the impact of PVT on the clinical outcomes in a cohort of patients with cirrhosis and TIPS insertion.

2. Patients and methods

2.1. Patients

Between June 2012 and February 2016, a total of 131 consecutive cirrhotic patients who underwent TIPS insertion in our institution were recruited and prospectively studied. The study protocol was permitted by the ethics committee of the Second Affiliated Hospital of Kunming Medical University. All patients provided written informed consent. TIPS was indicated in patients with cirrhosis for the treatment of recurrent variceal bleeding that occurred within 90 days despite repeated endoscopic band ligation/sclerotherapy/tissue adhesive injection. Cirrhosis was diagnosed by existing medical history of chronic liver disease, ultrasound findings, or computed tomography (CT) scans as coarse liver parenchyma with nodularity and small liver size and the presence of features of portal hypertension (e.g., thrombocytopenia, ascites, splenomegaly, and/or varices).[14] TIPS was contraindicated in the following cases: serum bilirubin above 100 μmol/L; an earlier history of hepatic encephalopathy (HE); tumor or other lesions on the puncture tract; PVT without potent main portal vein; liver malignancy and tumor invasion of the portal vein. Before TIPS, all patients were subjected to Doppler ultrasonography and CT. When PVT was detected, patency of the portal vein and its tributaries was evaluated. For patients with liver malignancy, tumor invasion of the portal vein was diagnosed if arterial-phase contrast enhancement of the thrombus on CT or arterial-like flow on Doppler ultrasound existed.[15,16]

2.2. TIPS procedure

TIPS was conducted by 2 experienced interventional radiologists in our institution. Briefly, RUPS 100 puncture kit (Cook, Inc., Bloomington, Indiana) and expanded polytetrafluoroethylene (e-PTFE)-covered and bare stents (fluency stent graft, 8 mm × 60 mm, Angiomed GmbH Co. subsidiary of C.R. Bard, Inc., New Jersey) were used in this study. Stents were inserted between the hepatic vein and portal vein. Dilated collaterals such as short gastric vein, gastric coronary vein were embolized with spring coils during the procedure.

2.3. Treatment and follow-up protocols

After TIPS, our treatment protocol was: patients were initially given low molecular weight Ca heparin (4100IU, Q12h subcutaneously) for 5 to 7 days; subsequently, patients without PVT were advised to take aspirin (100 mg/day) or clopidogrel (75 mg/day) if their platelets were above 50×10^9/L; patients with PVT were advised to take warfarin if their international normalized ratio (INR) was below 2.0 or antiplatelet with aspirin or clopidogrel if their platelets were above 50×10^9/L. Low molecular weight Ca heparin was stopped three days after oral warfarin was initiated (1.5 mg/day). INR was measured weekly for warfarin dosage adjustment to maintain INR value between 2.0 and 3.0. Patients were followed up in our hospital at 3, 6, 12, and 24 months. Then annual or additional visits were set up if they felt unwell. These follow-up visits consisted of clinical assessment, biochemical tests, Doppler-ultrasound, and CT imaging.

2.4. Imaging interpretation

PVT was defined as the presence of solid material in the vascular lumen.[9] It was defined as de novo if the thrombosis was not present at previous screenings with contrast enhanced CT. The recanalization after TIPS was considered complete if CT showed the complete absence of filling defects in the main portal vein and its tributaries. Recanalization was considered partial if it achieved a decrease in PVT severity in at least one vein. CT imaging interpretation was carried out by 2 specialized radiologists.

2.5. Endpoints

The primary endpoint was clinical outcomes, including variceal rebleeding, shunt dysfunction, HE, hepatocellular carcinoma (HCC), and overall survival. Secondary end points include risk factors for PVT, efficacy of warfarin versus aspirin/clopidogrel, and change in hepatic function and hematological parameters.

2.6. Data collection and statistical analysis

Patients' demographic, laboratory, and imaging data were extracted from our electronic medical record system and analyzed anonymously. Data for continuous variables were presented as mean ± standard deviation (SD). χ^2 test, Student t test or Mann–Whitney test were executed when appropriate. Multivariate analysis for identifying risk factors of PVT was implemented by logistic regression analysis. Survival analysis was performed by the Kaplan–Meier method and compared by log rank test. All statistical tests were 2-sided, and a P-value $< .05$ was accepted as statistically significant. Statistical analysis was performed using SPSS 17.0 for windows.

3. Results

3.1. Patient characteristics

The baseline characteristics of the study population are shown in Table 1. Five patients were lost at follow-up after TIPS placement and were thus excluded from analysis. There were 84 males (66.7%) and 42 females (33.3%). Mean age was 52 (11.1) years (range 29–80). Mean CTP and model for end stage liver disease (MELD) scores were 9.8 and 11.2, respectively.

3.2. Preexisting and de novo PVT after TIPS

There were 25/126 (19.8%) patients with preexisting PVT. 27/126 (21.4%) patients developed de novo PVT after TIPS. The characteristics of all PVT are shown in Table 2. Overall, there were 52 patients with preexisting and de novo PVT and 74 patients without any PVT in this study.

3.3. Risk factors for PVT

As shown in Table 3, univariate analysis revealed that etiology, white blood cell (WBC), platelet, prothrombin time, and INR were significant predictors for PVT. However, Cox-multivariate analysis showed that only WBC (odds ratio (OR): 0.430, 95% confidence interval (CI): 0.251–0.739, $P = .002$) and CTP score

Table 1

Baseline characteristics of the study population.

	Patients (n = 126)
Age, y	52 ± 11.1
Sex (male), n (%)	84 (66.7%)
Etiology	
Hepatitis B virus, n (%)	64 (50.8%)
Hepatitis C virus, n (%)	22 (17.5%)
Alcoholic, n (%)	10 (7.9%)
Primary biliary cirrhosis, n (%)	8 (6.3%)
Unknown, n (%)	22 (17.5%)
HBV-DNA detectable rate, n (%)	31 (48.4%)
HBV-DNA, $\log_{10}$ copies/mL	4.95 ± 1.46 (n = 31)
HBeAg positivity, n (%)	8 (12.5%)
HCV-RNA, $\log_{10}$ copies/mL	5.74 ± 1.33 (n = 22)
Entecavir/lamivudine/telbivudine for HBV, n (%)	42 (65.6%)/18 (28.1%)/4 (6.3%)
Ascites	
No, n (%)	15 (11.9%)
Mild, n (%)	36 (28.6%)
Moderate to severe, n (%)	75 (59.5%)
Concomitant disease	
Diabetes mellitus, n (%)	3 (2.4%)
Primary hypertension, n (%)	18 (14.3%)
Hepatocellular carcinoma, n (%)	9 (7.1%)
Stent type	
One e-PTFE covered stent, n (%)	107 (84.9%)
One e-PTFE covered stent and one bared stent, n (%)	19 (15.1%)
TIPS location	
Right hepatic vein to portal vein, n (%)	59 (53.2%)
Middle hepatic vein to portal vein, n (%)	67 (46.8%)
Varices	
Esophageal/esophageal and gastric, n (%)	29 (23)/97 (77)
Endoscopic treatment	
Ligation and/or sclerosis/none, n (%)	70 (55.6%)/56 (44.4%)
Albumin (g/L)	28.3 ± 4.5
Total bilirubin (μmol/L)	34.9 ± 24.1
Prothrombin time (s)	20.5 ± 3.5
International normalized ratio	1.71 ± 0.31
Creatinine (μmol/L)	69.3 ± 18.1
Child–Turcotte–Pugh (CTP) score	9.8 ± 1.7
Model for end-stage liver disease (MELD) score	11.2 ± 4.2

e-PTFE = expanded polytetrafluoroethylene, HBV = hepatitis B virus, HCV = hepatitis C virus, TIPS = transjugular intrahepatic portosystemic shunt.

(OR: 2.377, 95% CI: 1.045–5.409, $P = .039$) remained significant predictors for PVT.

3.4. Adverse events during/after TIPS

Periprocedural complications were observed in 23 patients (18.3%), including inadvertent bile duct puncture (n = 8), intraperitoneal hemorrhage (n = 7), acute shunt thrombosis (n = 6), transient respiratory distress and tachycardia (n = 5), which were successfully managed by conservative treatment. Early complications (≤2 weeks post-TIPS) included: nausea and vomiting (n = 25), short-lived and mild HE (grade I-II; n = 21), bleeding from the puncture site at the neck (n = 9), and moderate fever (≤39°C; n = 7). No early variceal rebleeding was noted.

Table 2

Characteristics of preexisting and de novo PVT after TIPS.

Thrombus extension	Preexisting PVT (n = 25)	De novo PVT (n = 27)
MPV, n (%)	0 (0%)	3 (11.1%)
IHB, n (%)	6 (24.0%)	7 (25.9%)
MPV + SMV, n (%)	5 (20.0%)	0 (7.4%)
MPV + SV, n (%)	4 (16.0%)	2 (7.4%)
MPV + IHB, n (%)	5 (20.0%)	14 (51.8%)
MPV + SMV + SV, n (%)	5 (20.0%)	0 (0%)
TIPS	—	1 (3.7%)

IHB = intrahepatic branches, MPV = main portal vein, PVT = portal vein thrombosis, SMV = superior mesenteric vein, SV = splenic vein, TIPS = transjugular intrahepatic portosystemic shunt.

Table 3

Risk factors for portal vein thrombosis by univariate analysis.

	Portal vein thrombosis		
Variables	Yes (n = 52)	No (n = 74)	*P*
Age, y	52.8 ± 11.2	52.2 ± 11.1	.765
Sex (male), n (%)	37 (71.2%)	47 (63.5%)	.370
Etiology			.028
Alcohol, n (%)	7 (13.5%)	3 (4.1%)	
HBV, n (%)	30 (57.7%)	34 (45.9%)	
HCV, n (%)	8 (15.4%)	14 (18.9%)	
PBC, n (%)	0 (0.0%)	8 (10.8%)	
Unknown, n (%)	7 (13.5%)	15 (20.3%)	
Concomitant diseases			.094
Primary hypertension	1 (1.9%)	2 (2.7%)	
Diabetes mellitus	5 (9.6%)	13 (17.6%)	
Hepatocellular carcinoma	7 (13.5%)	2 (2.7%)	
Surgery history			.264
Splenectomy, n (%)	2 (3.8%)	1 (1.4%)	
PSE, n (%)	9 (17.3%)	7 (9.5%)	
TIPSS site			.140
Right hepatic vein, n (%)	28 (53.8%)	30 (40.5%)	
Middle hepatic vein, n (%)	24 (46.2%)	44 (59.5%)	
Stent type and number			.936
One e-PTFE-covered stent, n (%)	44 (84.6%)	63 (85.1%)	
One e-PTFE-covered and one bare stent, n (%)	8 (15.4%)	11 (14.9%)	
Baseline portal pressure, mm Hg	28.8 ± 5.8	27.7 ± 5.7	.281
Portal pressure gradient, mm Hg	11.3 ± 4.7	10.2 ± 4.2	.205
Intrashunt pressure, mm Hg	10.9 ± 3.7	11.5 ± 3.3	.340
Antiviral agents (n = 64)			.161
Entecavir, n (%)	22 (73.3%)	17 (50%)	
Lamivudine, n (%)	6 (20.0%)	13 (38.2%)	
Telbivudine, n (%)	2 (6.7%)	4 (11.8%)	
HBeAg positivity, n (%)	2/34 (5.9%)	2/30 (6.7%)	.897
HBV-DNA, $\log_{10}$ copies/mL (n = 31)	5.02 ± 1.47 (n = 14)	4.88 ± 1.49 (n = 17)	.789
HCV-RNA, $\log_{10}$ copies/mL (n = 22)	5.96 ± 1.73 (n = 9)	5.60 ± 1.03 (n = 13)	.578
White blood cell count, $\times 10^9$/L	2.33 ± 0.79	3.62 ± 1.91	.000
Hemoglobulin, g/L	87.2 ± 19.3	86.2 ± 15.7	.758
Platelet, $\times 10^9$/L	55.5 ± 17.2	70.4 ± 36.0	.002
Prothrombin time, s	21.4 ± 2.7	19.9 ± 3.8	.010
International normalized ratio	1.79 ± 0.27	1.66 ± 0.33	.019
Albumin, g/L	27.8 ± 4.4	28.6 ± 4.5	.221
Alanine aminotransferase, U/L	33.5 ± 26.1	35.7 ± 31.3	.333
Aspartate aminotransferase, U/L	59.2 ± 63.9	52.3 ± 26.9	.466
Total bilirubin, μmol/L	34.2 ± 21.6	35.4 ± 25.9	.776
Direct bilirubin, μmol/L	16.1 ± 12.1	17.5 ± 17.6	.606
Creatinine, μmol/L	67.7 ± 19.3	70.5 ± 17.2	.399
Ascites			.947
No, n (%)	6 (11.5%)	10 (13.5%)	
Mild, n (%)	15 (28.8%)	21 (28.4%)	
Moderate to heavy, n (%)	31 (59.6%)	43 (58.1%)	
Endoscopic treatment			
None, n (%)	28 (53.8%)	28 (37.8%)	.075
Ligation and/or sclerosis, n (%)	24 (46.2%)	46 (62.2%)	
Child–Turcotte–Pugh score	10.1 ± 1.5	9.7 ± 1.9	.190
Model for end-stage liver disease score	11.2 ± 4.6	11.2 ± 4.0	.999

e-PTFE = expanded polytetrafluoroethylene, HBV = hepatitis B virus, HCV = hepatitis C virus, PBC = primary biliary cirrhosis, PSE = partial splenic embolization, TIPSS = transjugular intrahepatic portosystemic shunt.

3.5. Efficacies and side effects of anticoagulant and antiplatelet therapy

The flow chart of this study is presented in Fig. 1. The efficacies of anticoagulation and antiplatelet therapy are summarized in Table 4. Overall, warfarin resulted in significantly higher rates of

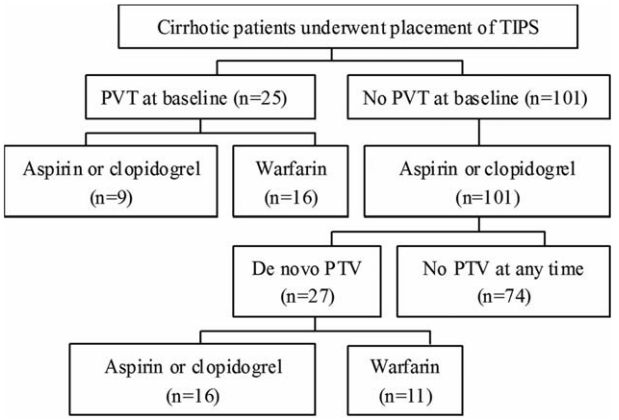

Figure 1. The study flow chart.

Figure 2. (A and B) CT scan illustrates an occlusive thrombus (white arrow) at the right posterior branch of portal vein (A), which showed complete recanalization (black arrow) 2 months after warfarin and TIPS (arrowhead) treatment (B) in a patient with cirrhosis. CT = computed tomography.

complete or partial recanalization but lower rates of no improvement of preexisting or de novo PVT during the study period ($P < .05$). Figure 2A and B CT scan illustrates an occlusive thrombus at the right posterior branch of portal vein (A), which showed complete recanalization 2 months after TIPS and warfarin therapy (B). Epigastric discomfort or heartburning was most reported in 11/27 (40.7%) patients treated by warfarin and in 42/90 (46.7%) patients treated by aspirin/clopidogrel ($P = .587$). Peptic ulcer disease occurred in 5 patients as proven by endoscopy, of whom none was treated by warfarin and 5 by aspirin/clopidogrel (0% vs 5.6%, $P = .211$). Nasal or gingival bleeding was observed in 5/27 (18.5%) patients receiving warfarin and 21/90 (23.3%) patients receiving aspirin/clopidogrel ($P = .598$). All these adverse events were successfully managed by conservative treatment. No severe adverse events were recorded.

3.6. Clinical outcomes

3.6.1. Variceal rebleeding. Twnty-five patients had gastrointestinal bleeding after TIPS. Endoscopy results included variceal rebleeding (n = 20), and peptic ulcer disease (n = 5). The 1- and 2-year cumulative rates of variceal rebleeding were significantly lower in patients without PVT than those with PVT (1-year: 3.4% vs 11.9%, 2-year: 17.0% vs 42.0%, $P = .035$) (Fig. 3A).

3.6.2. Shunt dysfunction and revision. Of the 20 patients with variceal rebleeding after TIPS, direct portal venography by digital subtraction angiography proved shunt stenosis (n = 14), and shunt occlusion (n = 6). Markedly slowed (n = 5) or absence of blood flow (n = 2) within the shunt were detected by Doppler ultrasonography in seven patients without rebleeding. Again direct portal venography showed shunt stenosis (n = 4) and shunt occlusion (n = 3). Thus, 27 patients had shunt dysfunction (stenosis or occlusion), which was revised by balloon dilation (n = 18) and stent placement (n = 8). Notably, 1 patient had occlusive thrombosis within the stent, which was not recanalized by guide wire puncture and subsequent injection of 100,000 unit of urokinase. The 1- and 2-year cumulative rates of shunt dysfunction were significantly lower in patients without PVT than those with PVT (1-year: 3.3% vs 20.2%, 2-year: 27.0% vs 53.1%, $P = .013$) (Fig. 3B).

3.6.3. HE. Forty-four patients had at least 1 episode of HE after TIPS, which was associated with 1 or more of the following factors: constipation (n = 15), hematemesis (n = 7), infection (n = 11), consumption of meat (n = 14), and unknown precipitators (n = 5). The cumulative 1- and 2-year rates of a first episode of HE

Table 4

Efficacy of anticoagulation and antiplatelet therapy.

	Preexisting PVT (n = 25)		De novo PVT (n = 27)	
	Warfarin (n = 16)	Clopidogrel/aspirin (n = 9)	Warfarin (n = 11)	Clopidogrel/aspirin (n = 16)
CR, n (%)	11 (68.8%)	2 (22.2%)	6 (54.5%)	5 (31.3%)
PR, n (%)	3 (18.8%)	2 (22.2%)	3 (27.3%)	0 (0.0%)
No improvement, n (%)	2 (12.5%)	5 (55.6%)	2 (18.2%)	11 (68.7%)
P^*	.044		.013	

CR = complete recanalization, PR = partial recanalization, PVT = portal vein thrombosis.
* Fisher's exact test.

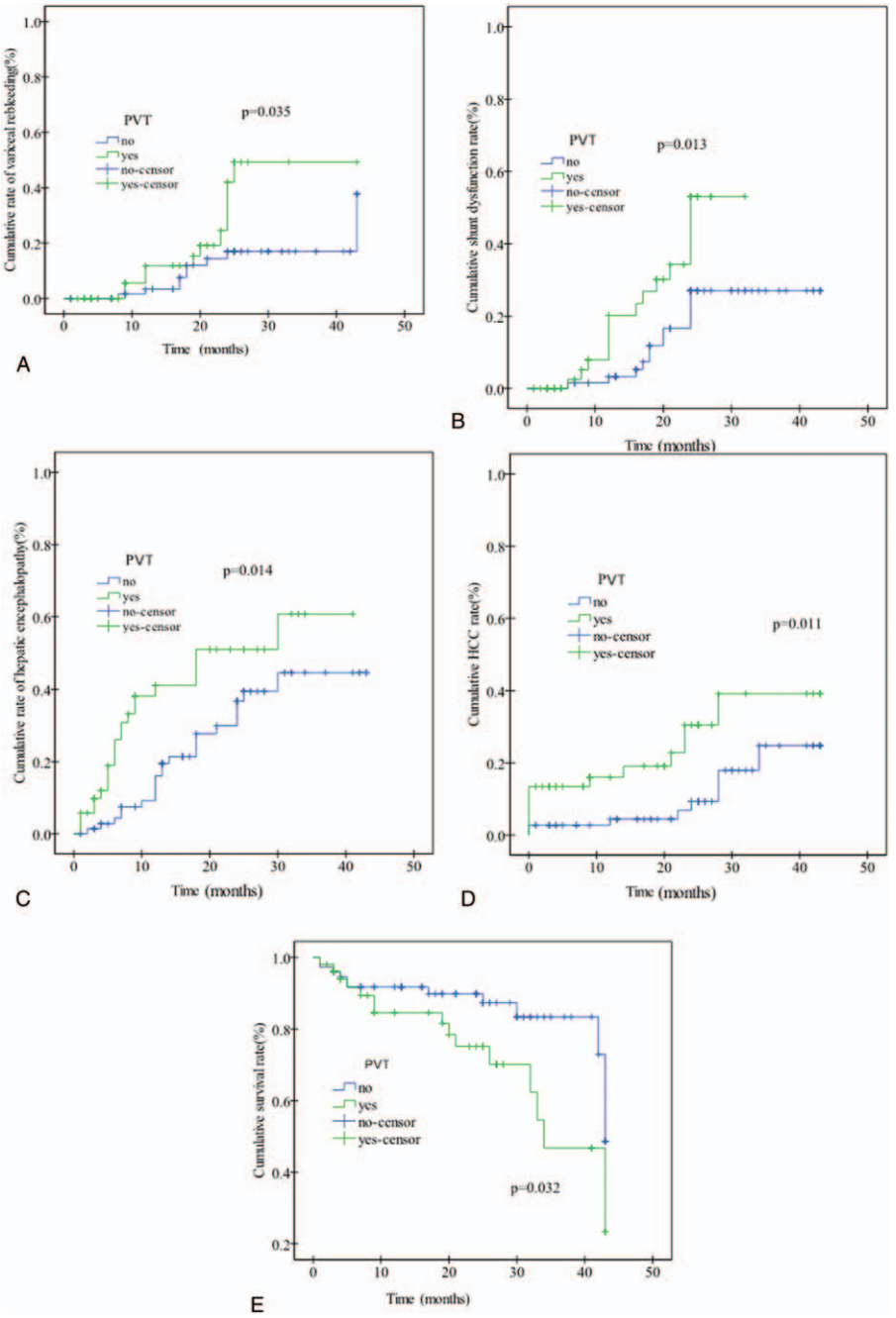

Figure 3. (A) Cumulative variceal rebleeding rates in patients with and without PVT ($P = .035$, by log-rank test). (B) Cumulative shunt dysfunction rates in patients with and without PVT ($P = .013$, by log-rank test). (C) Cumulative rates of a first episode of hepatic encephalopathy in patients with and without PVT ($P = .014$). (D) Cumulative HCC rates (including baseline and de novo HCC) in patients with and without PVT ($P = .011$). (E) Cumulative survival rates in patients with and without PVT ($P = .032$).

were prominently lower in patients without PVT than those with PVT (1-year: 16.0% vs 41.1%, 2-year: 36.7% vs 50.9%, $P = .014$) (Fig. 3C).

3.6.4. HCC. During the study, HCC was diagnosed in 6/52 (11.5%) patients with PVT, compared to that in 6/74 (8.1%) patients without PVT. The cumulative HCC rates were similar between these 2 groups ($P = .099$, by log-rank test). However, there were 7/52 (13.4%) patients with PVT and 2/74 (2.7%) patients without PVT who also had HCC before TIPS. If these 9 patients were included, the cumulative 1- and 2-year HCC rates were significantly lower in patients without PVT than those with PVT (1-year: 4.6% vs 16.0%, 2-year: 9.3% vs 31.5%, $P = .011$) (Fig. 3D).

3.7. Overall survival

In total, there were 28 death cases. Causes of death included: liver failure (n = 13), HCC (n = 8), variceal rebleeding (n = 4), and fatal sepsis (n = 3). The 1- and 2-year cumulative rates of overall survival were significantly higher in patients without PVT than those with PVT (1-year: 91.7% vs 84.6%, 2-year: 89.9% vs 75.1%, $P = .032$) (Fig. 3E).

4. Discussion

The results from our study showed that lower WBC count and higher CTP score were independent baseline predictors for PVT; warfarin may be more effective in recanalizing PVT than aspirin or clopidogrel; PVT was associated with worse clinical outcomes in patients with cirrhosis undergoing TIPS for recurrent variceal hemorrhage. Our study is clinically relevant because an increasing number of patients with cirrhosis and portal hypertension have undergone TIPS placement. Therefore, understanding of risk factors for PVT development, the efficacies of anticoagulation or antiplatelet therapy for recanalizing PVT, and the impact of PVT on clinical outcomes in patients undergoing TIPS may aide physicians in better managing this cohort of patients.

Previous studies showed that patients with more severe or advanced cirrhosis had higher risk of PVT.[2,3,17] In our study, WBC count and CTP score were 2 independent risk factors for PVT in cirrhotic patients undergoing TIPS insertion. Interestingly, odds ratios of CTP score and WBC count were 2.377 and 0.430, respectively, suggesting that higher CTP score and lower WBC count were associated with higher PVT risk, which was in line with previous studies,[2,3,17] as higher CTP score and lower WBC count reflected more severe liver disease.

There is no established management algorithm for nontumor PVT in cirrhotic patients.[18] Previous studies showed that TIPS insertion or anticoagulant therapy could be used to treat PVT, and allow for complete recanalization in some cases.[3,9,18–20] To our best knowledge, there is no study that evaluated the efficacy of combining TIPS with anticoagulation therapy or antiplatelet therapy in recanalizing PVT after TIPS. In our study, warfarin was shown to be more effective than aspirin or clopidogrel in achieving complete and partial recanalization of preexisting and de novo PVT (Table 4). The underlying reason remains unknown. There may be 2 explanations for our results: First, the dosage of aspirin (100 mg/day) or clopidogrel (75 mg/day) used in our study does not achieve adequate platelet suppression, similar to the case reported by James et al.[21] Second, the contribution of platelets to PVT development in our study is minimal due to low platelet counts, which is supported by the facts that lower platelet count is a risk factor for PVT,[3,17] and splenectomy is commonly complicated by PVT in patients with cirrhosis.[22] On the contrary, warfarin is a well-know effective drug for recanalizing PVT.[20] However, these 2 explanations can only be judged by a formal evaluation of platelet function in future studies.

Numerous studies showed that PVT was associated with poorer clinical outcomes.[11,12,20,23,24] In our study, the clinical outcomes of patients with preexisting or de novo PVT were worse than those without any PVT, which was in agreement with these studies.[11,12,20,23,24] The reasons for this finding include: First, as discussed previously, slowed velocity of portal vein flow[5] and concomitant thrombophilic disorders[6,7] contributed to the hypercoagulable state and PVT formation in cirrhosis. By reconstructing the portal venous system, TIPS can increase portal vein flow velocity and reduce portal hypertension.[25] However, after TIPS, the hypercoagulable state persists, which may cause extension of the residual PVT or rethrombosis,[9] which has the potential effect to offset the increasing of portal velocity, leading to increased rates of shunt dysfunction and portal hypertension-related bleeding, ascites, or HE.[26] Second, PVT may interrupt the hepatic perfusion, causing hepatocyte ischemia and hormonal deprivation,[27–30] which could result into hepatocyte death, parenchymal extinction and ultimately deterioration of liver fibrosis and liver function, leading to increased rates of HE and mortality.[26,27,29,30]

HCC is commonly associated with PVT, and advanced stage, higher Child class, major vessel involvement, low serum albumin, and high serum alpha-fetoprotein are significant predictors for PVT in patients with HCC.[31] However, the exact association between PVT and HCC development remains elusive. In our study, we found that patients with preexisting or de novo PVT had significantly higher rates of HCC than patients without any PVT. The reason for this finding needs to be determined in future studies.

The limitations of our study include the absence of randomization to the therapy algorithm and the lack of a control group. However, our study represented a relatively large series of cirrhosis patients undergoing TIPS placement. Moreover, we prospectively investigated several poorly defined topics including the baseline predictors for PVT, the anticoagulation or antiplatelet therapy for PVT and the impact of PVT on the prognosis of TIPS-treated patients, which may be helpful in clinical setting.

In summary, for TIPS-treated patients with cirrhosis, lower WBC count, and higher CTP score were independent predictors for PVT; warfarin may be more effective in recanalizing PVT than aspirin or clopidogrel with similar safety profile; patients with PVT had poorer clinical outcomes than those without.

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