Portal vein thrombosis before and after transjugular intrahepatic portosystemic shunt placement

An observational study (STROBE compliant)

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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, with a reported prevalence ranging from 1% to 2.5%. Potential contributing factors of PVT include decreased velocity of portal vein flow, and concomitant thrombophilic disorders. Transjugular intrahepatic portosystemic shunt (TIPS) is an established therapeutic approach for controlling variceal bleeding or refractory ascites in patients with cirrhosis and portal hypertension.

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. 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. 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. Thus, it is of significant relevance for physicians to understand the risk for PVT development, the efficacies of different therapies to control...
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).

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 patent 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.

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. 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). χ² 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, Child-Pugh score (CPS), 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.

| Characteristics                  | 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%)       |
| **HCV-RNA, log10 copies/mL**     | 5.74 ± 1.33 (n = 22) |
| **HBeAg positivity, n (%)**      | 8 (12.5%)          |
| **HIV, n (%)**                   |                    |
| **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 bare stent, n (%) | 19 (15.1%) |
| **TIPS location**                |                    |
| Right hepatic vein to portal vein, n (%) | 59 (46.2%) |
| Middle hepatic vein to portal vein, n (%) | 47 (37.6%) |
| **Bleeding from the puncture site at the neck, n (%)** | 0 (0%) |
| **Portal vein thrombosis by univariate analysis.** |     |
| **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**                     |                    |
| **Alcohol, n (%)**               | 7 (13.5%)          | 3 (4.1%)        | .028     |
| **HBV, n (%)**                   | 30 (57.7%)         | 34 (45.9%)      | .725     |
| **HCV, n (%)**                   | 8 (15.4%)          | 14 (18.9%)      | .145     |
| **PBC, n (%)**                   | 0 (0.0%)           | 8 (10.8%)       | .006     |
| **Unknown, n (%)**               | 7 (13.5%)          | 15 (20.3%)      | .936     |
| **Concomitant diseases**         |                    |
| Primary hypertension             | 1 (1.9%)           | 2 (2.7%)        | .920     |
| Diabetes mellitus                | 5 (9.6%)           | 13 (17.6%)      | .094     |
| Hepatocellular carcinoma         | 7 (13.0%)          | 2 (2.7%)        | .896     |
| **Surgery history**              |                    |
| Splenectomy, n (%)               | 2 (3.8%)           | 1 (1.4%)        | .678     |
| PSE, n (%)                       | 9 (17.3%)          | 7 (9.5%)        | .140     |
| **TIPS site**                    |                    |
| Right hepatic vein               | 28 (53.8%)         | 30 (40.5%)      | .134     |
| Middle hepatic vein              | 24 (46.2%)         | 44 (59.5%)      | .436     |
| **Stent type and number**        |                    |
| One e-PTFE-covered stent, n (%)  | 44 (84.6%)         | 63 (85.1%)      | .936     |
| One e-PTFE-covered and one bare stent, n (%) | 8 (15.4%) |
| Baseline portal pressure, mm Hg  | 28.8 ± 5.8         | 27.7 ± 5.7      | .281     |
| Partial pressure gradient, mm Hg | 11.3 ± 4.7         | 10.2 ± 4.2      | .205     |
| Intrahepatic pressure, mm Hg     | 10.9 ± 3.7         | 11.5 ± 3.3      | .340     |
| **Antithrombotic agents (n = 64)** |                |
| Entecavir/lamivudine/tenofovir   | 22 (73.3%)         | 17 (50.0%)      | .004     |
| Lamivudine, n (%)                | 6 (20.0%)          | 13 (38.2%)      | .049     |
| Tenofovir, n (%)                 | 2 (6.7%)           | 4 (11.8%)       | .897     |
| HBeAg positivity, n (%)          | 2/30 (6.7%)        | 4/31 (12.9%)    | .139     |
| **HBV-DNA, log10 copies/mL**     | 5.96 ± 1.47 (n = 22) | 5.02 ± 1.47 (n = 52) | .376     |
| **HCV-RNA, log10 copies/mL**     | 5.06 ± 1.73 (n = 22) | 5.02 ± 1.47 (n = 52) | .897     |
| **Albumin (g/L)**                | 28.3 ± 4.5         | 30.2 ± 19.1     | .007     |
| **Total bilirubin (μmol/L)**     | 34.9 ± 24.1        | 34.2 ± 19.1     | .094     |
| **Prothrombin time (s)**        | 20.3 ± 3.5         | 19.8 ± 3.3      | .036     |
| **International normalized ratio** | 1.71 ± 0.31     | 1.75 ± 0.31     | .001     |
| **Creatinine (μmol/L)**          | 60.3 ± 18.1        | 67.3 ± 13.2     | .003     |
| **Child–Turcotte–Pugh (CTP) score** | 9.8 ± 1.7       | 11.2 ± 4.2      | .003     |
| **e-PTFE = expanded polytetrafluoroethylene, HVB = hepatitis B virus, HCV = hepatitis C virus, TIPS = transjugular intrahepatic portosystemic shunt.** | | | |

3.4. Adverse events during/after TIPS

Periprocedural complications were observed in 23 patients (19.3%), including inadvertent bile duct puncture (n = 8).

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%)            |
| HBV, n (%)        | 6 (24.0%)                | 7 (25.9%)            |
| MPV + SMV, n (%)  | 5 (20.0%)                | 0 (0.0%)             |
| MPV + SV, n (%)   | 4 (16.0%)                | 2 (7.4%)             |
| MPV + HBV, n (%)  | 5 (20.0%)                | 14 (51.9%)           |
| MPV + SMV + SV, n (%) | 5 (20.0%) | 0 (0.0%) |
| TIPS              | —                        | 1 (3.7%)             |

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.

intraportal 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 varical rebleeding was noted.

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
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 \( (0\% \text{ vs } 5.6\%, \ P = .211) \). 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.

Twenty-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

|                             | 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 (51.3%) |
| PR, n (%)                   | 3 (18.8%) | 2 (22.2%) | 3 (27.3%) | 0 (0.0%) |
| No improvement, n (%)       | 2 (12.5%) | 5 (56.6%) | 2 (18.2%) | 11 (68.7%) |
| \( P^2 \)                   | .044 | \( .013 \) | | |

CR = complete recanalization, PR = partial recanalization, PVT = portal vein thrombosis.

* = Fisher’s exact test.
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] In our study, the clinical outcomes of patients with preexisting or de novo PVT (Table 4). The underlying reason remains unknown. There may be 2 explanations for our results: First, the dosage of aspirin (100mg/day) or clopidogrel (75mg/day) used in our study does not achieve adequate platelet suppression, as shown to be more effective than aspirin or clopidogrel in achieving complete and partial recanalization of preexisting and de novo PVT (Table 4). The reason for this finding needs to be determined in future studies.

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.[13,16–20] 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. 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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