Association of endoscopic variceal treatment with portal venous system thrombosis in liver cirrhosis: a case–control study

Le Wang*, Xiaozhong Guo*, Xiaodong Shao*, Xiangbo Xu, Kexin Zheng, Ran Wang, Saurabh Chawla, Metin Basaranoglu and Xingshun Qi

Abstract

Background: The association of endoscopic variceal treatment (EVT) with portal venous system thrombosis (PVST) in liver cirrhosis is still unclear.

Methods: PVST was assessed by contrast-enhanced CT or MRI in 406 cirrhotic patients from our prospective database. Case and control groups, which are defined as patients with and without PVST, respectively, were matched at a ratio of 1:1 according to age, gender, Child-Pugh class, and MELD score. History of EVT was reviewed. Logistic regression analysis was used to identify the risk factors for PVST. Odds ratios (ORs) were calculated. Subgroup analyses were further performed in terms of degree and location of PVST.

Results: Overall, 109 patients each were included in case and control groups. The case group had a significantly higher proportion of patients who had undergone EVT than the control group (53.2% versus 18.3%; p < 0.001). In detail, the case group had significantly higher proportions of patients who had undergone EVT for controlling bleeding (45.9% versus 14.7%; p < 0.001), endoscopic variceal ligation (EVL) alone (19.3% versus 9.2%; p = 0.033), and EVL combined with endoscopic cyanoacrylate glue injection (24.8% versus 5.5%; p < 0.001). EVT was independently associated with PVST (OR = 4.258; p < 0.001). In subgroup analyses, EVT remained independently associated with partial PVST (OR = 10.063; p < 0.001), complete PVST/fibrotic cord (OR = 4.889; p = 0.008), thrombosis within main portal vein (OR = 5.985; p < 0.001), and thrombosis within superior mesenteric and splenic veins (OR = 5.747; p < 0.001).

Conclusions: EVT may lead to a higher risk of PVST, especially more severe PVST, in liver cirrhosis. Screening for and prophylaxis of PVST after EVT should be further explored.

Keywords: cirrhosis, endoscopy, portal vein, risk factors, venous thrombosis

Introduction

Portal venous system thrombosis (PVST) is defined as blood clots in the main portal vein (MPV), which can extend downstream into intrahepatic portal vein branches and upstream into mesenteric and splenic veins.1 Nonneoplastic PVST more frequently develops in patients with liver cirrhosis.2 PVST can be asymptomatic, but may lead to liver dysfunction,3 gastroesophageal variceal bleeding (GEVB),4 variceal recurrence,5 and thrombotic ischemia in bowels6 and increase the technical complexity of liver transplantation.7 Except for sluggish portal vein blood flow8 and underlying hypercoagulability,9 splenectomy and devascularization have been recognized as major local risk factors for PVST in liver cirrhosis.10,11 Endoscopic variceal treatment (EVT) is the cornerstone choice for the management of gastroesophageal varices and variceal bleeding.12,13 However, it potentially affects portal vein blood flow and causes coagulation activation within the
portal venous system due to its injury to local varicose veins. Our previous meta-analysis has found that endoscopic injection sclerotherapy (EIS) can lead to a 2.25-fold increased risk of PVST in liver cirrhosis. Notably, EIS is rarely recommended for the management of gastroesophageal varices or variceal bleeding according to the current practice guideline. By comparison, endoscopic variceal ligation (EVL) and endoscopic cyanoacrylate glue injection (ECGI) have been widely recommended, but their associations with PVST have not been identified. More importantly, it remains unclear about the impact of EVT on the degree and location of PVST, which will influence the decision-making on screening for and prophylaxis of PVST after EVT.

Here, we conducted a case–control study to analyze the association of EVT with the development of PVST based on contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) in patients with liver cirrhosis.

**Methods**

The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.

**Study design**

This case–control study was conducted according to the World Medical Association Declaration of Helsinki and has been approved by the Medical Ethical Committee of the General Hospital of Northern Theater Command (Number Y2021-45). Patients’ written informed consents have been waived due to the retrospective nature of this study. All patient details have been de-identified. We reviewed the medical records of patients admitted between December 2014 and February 2021 from our prospective database, which have enrolled cirrhotic patients without malignancy who underwent contrast-enhanced CT or MRI scans and upper gastrointestinal endoscopy during their hospitalizations at the Department of Gastroenterology of the General Hospital of Northern Theater Command. Contrast-enhanced CT or MRI scans were performed to mainly evaluate the changes of portal hypertension-related complications, such as grade of ascites, portosystemic collaterals, splenomegaly, and PVST, and clarify the nature of hepatic nodules. Exclusion criteria were as follows: patients with repeated admissions; patients who underwent splenectomy or splenic arterial embolization and other abdominal surgeries; and patients with incalculable Child-Pugh or Model for End-stage Liver Disease (MELD) score. Patients with PVST were defined as the case group. Patients without PVST were selected as the control group by matching with the case group at a ratio of 1:1 according to four major variables: age (±5 years), gender, Child-Pugh class, and MELD score (±2 points).

**PVST**

We reviewed the contrast-enhanced CT or MRI images to evaluate the presence of PVST. The location of PVST was recorded, including left portal vein (LPV), right portal vein (RPV), MPV, confluence of superior mesenteric vein (SMV) and splenic vein (SV), SMV, and SV (Figure 1). The degree of occlusion at each vessel within the portal venous system was evaluated, including mural (<50%), partial (50–80%), complete (≥80%), and fibrotic cord (Figure 1). The degree of PVST was recorded according to the most severe one of all vessels within the portal venous system.

**EVT**

We reviewed the electronic medical records to identify the information regarding the history of EVT before contrast-enhanced CT or MRI scans. The goal of EVT was recorded, including treatment of bleeding and prevention from bleeding. The type of EVT was recorded, including EVL alone, ECGI alone, EIS alone, EVL combined with ECGI, and EIS combined with ECGI. At our center, two types of sandwich injection methods for ECGI procedures are mainly employed, as follows: lauromacrogol + tissue glue + lauromacrogol, and hypertonic glucose + tissue glue + hypertonic glucose. However, lipiodol + tissue glue + lipiodol was rarely used, because it might increase the risk of ectopic embolism. The selection of a specific method is not dependent on the type or severity of gastric varices.

**Data collection**

The following data were collected: demographic data, including age and gender, etiology of liver disease, and main laboratory data, including hemoglobin (Hb), white blood cell (WBC), platelet count, total bilirubin, albumin, alanine aminotransferase...
(ALT), alkaline phosphatase (AKP), serum creatinine, sodium, prothrombin time (PT), activated partial thromboplastin time, and international normalized ratio (INR). Child-Pugh score and class and MELD score were calculated.19

Statistical analyses
All statistical analyses were performed with IBM SPSS 22.0 (IBM Corp, Armonk, NY, USA). Continuous variables were expressed as median (range). Categorical variables were expressed as frequency (percentage). Non-parametric Mann–Whitney U test was used for continuous variables, and Chi-square test and Fisher’s exact test were used for categorical variables to compare the difference between case and control groups. A two-tailed \( p < 0.05 \) was considered statistically significant. Logistic regression analyses were performed to identify whether EVT was an independent risk factor for PVST. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. In subgroup analyses, the case group was classified according to the degree and location of PVST.

Results
Overall, 406 patients were eligible in this study, of whom 120 had PVST and 286 did not have PVST. Finally, 109 pairs of cases with PVST and controls without PVST were included (Figure 2).

Overall analyses
Compared with the control group, the case group had significantly lower levels of Hb, WBC, ALT, and AKP and higher level of INR at admission (Table 1). The case group had a significantly higher proportion of patients who had undergone EVT [53.2% (58/109) versus 18.3% (20/109), \( p < 0.001 \)]. According to the goal of EVT, the case group had a significantly higher proportion of patients who had undergone EVT for controlling bleeding [45.9% (50/109) versus 14.7% (16/109), \( p < 0.001 \)]. According to the type of EVT, the case group had significantly higher proportions of patients who had undergone EVL alone [19.3% (21/109) versus 9.2% (10/109), \( p = 0.033 \)] and EVL combined with ECGI [24.8% (27/109) versus 5.5% (6/109), \( p < 0.001 \)] (Figure 3(a)).

Multivariate logistic regression analysis demonstrated that Hb (OR = 0.988; 95% CI = 0.977–0.999; \( p = 0.026 \)) and EVT (OR = 4.258; 95% CI = 2.240–8.095; \( p < 0.001 \)) were independent risk factors for PVST (Table 2).
Subgroup analyses according to the degree of PVST

Mural PVST. In the subgroup analysis, we specifically selected patients with mural PVST as the case group. Finally, 25 patients with mural PVST and 25 patients without PVST were included as the case and control groups, respectively. Compared with the control group, the case group had significantly lower levels of Hb, ALT, and AKP at admission (Supplementary Table 1). The case group did not have a significantly higher proportion of patients who had undergone EVT [36.0% (9/25) versus 20.0% (5/25), \( p = 0.208 \)]. According to the goal of EVT, the case group did not have a significantly higher proportion of patients who had undergone EVT for controlling [36.0% (9/25) versus 16.0% (4/25), \( p = 0.107 \)] or preventing from bleeding [0% (0/25) versus 4.0% (1/25), \( p = 1.000 \)]. According to the type of EVT, the case group had a significantly higher proportion of patients who had undergone EVL combined with ECGI [24.0% (6/25) versus 4.0% (1/25), \( p = 0.042 \)] (Figure 3(b)).

Univariate logistic regression analysis demonstrated that EVT was not a risk factor for mural PVST (OR = 2.250; 95% CI = 0.628–8.057; \( p = 0.213 \)).

Partial PVST. In the subgroup analysis, we specifically selected patients with partial PVST as the case group. Finally, 56 patients with partial PVST and 56 patients without PVST were included as the case and control groups, respectively. Compared with the control group, the case group had significantly lower levels of Hb, ALT, and AKP at admission (Supplementary Table 2). The case group had a significantly higher proportion of patients who had undergone EVT [60.7% (34/56) versus 12.5% (7/56), \( p < 0.001 \)]. According to the goal of EVT, the case group had a significantly higher proportion of patients who had undergone EVT for controlling bleeding [53.6% (30/56) versus 12.5% (7/56), \( p < 0.001 \)]. According to the type of EVT, the case group had significantly higher proportions of patients who had undergone EVL alone [25.0% (14/56) versus 8.9% (5/56), \( p = 0.023 \)] and EVL combined with ECGI [25.0% (14/56) versus 3.6% (2/56), \( p = 0.001 \)] (Figure 3(c)).

Multivariate logistic regression analysis demonstrated that Hb (OR = 0.975; 95% CI = 0.957–0.994; \( p = 0.011 \)) and EVT (OR = 10.063; 95% CI = 3.538–28.620; \( p < 0.001 \)) were independent risk factors for partial PVST.

Complete PVST and fibrotic cord. In the subgroup analysis, we specifically selected patients with complete PVST and fibrotic cord as the case group. Finally, 28 patients with complete PVST and fibrotic cord and 28 patients without PVST were included as the case and control groups, respectively. Patients’ characteristics between the case and control groups were not significantly different at admission (Supplementary Table 3). The case group had a significantly higher proportion of patients who had undergone EVT [57.1% (16/28) versus 20.0% (5/25), \( p = 0.208 \)].
Table 1. Patients’ characteristics in case and control groups.

| Variables                          | Case group | Control group | p value |
|------------------------------------|------------|---------------|---------|
|                                    | No. of     | Median (range) or frequency (percentage) | No. of     | Median (range) or frequency (percentage) |
|                                    | patients   |               | patients |               |
| Age (years)                        | 109        | 56.4 (28.7–78.6) | 109       | 56.0 (30.4–78.1) | 0.817 |
| Sex (male)                         | 109        | 89 (81.7%)     | 109       | 89 (81.7%)     | 1.000 |
| Etiology of liver cirrhosis        |            |               |           |               |       |
| Hepatitis B virus infection        | 109        | 47 (43.1%)     | 109       | 40 (36.7%)     | 0.333 |
| Hepatitis C virus infection        | 109        | 7 (6.4%)       | 109       | 6 (5.5%)       | 0.775 |
| Alcohol abuse                      | 109        | 52 (47.7%)     | 109       | 65 (59.6%)     | 0.077 |
| Drug-related disease               | 109        | 10 (9.2%)      | 109       | 6 (5.5%)       | 0.299 |
| Laboratory tests                   |            |               |           |               |       |
| Hb (g/l)                           | 109        | 81 (43–157)    | 109       | 101 (33–174)   | <0.001 |
| WBC (10^9/l)                       | 109        | 2.9 (0.9–15.8) | 109       | 3.6 (1.3–20.8) | 0.019 |
| PLT (10^9/l)                       | 109        | 73 (26–285)    | 109       | 79 (29–423)    | 0.160 |
| TBIL (μmol/l)                      | 109        | 19.3 (6.4–177.9) | 109     | 23.6 (5.2–216.5) | 0.129 |
| ALB (g/l)                          | 109        | 32.9 (17.2–43.7) | 109   | 32.3 (18.7–50.6) | 0.794 |
| ALT (U/l)                          | 109        | 18.71 (6.78–115.40) | 109 | 30.00 (5.82–429.98) | <0.001 |
| AKP (U/l)                          | 109        | 78.99 (33.00–284.56) | 109 | 102.00 (34.54–337.00) | <0.001 |
| Scr (μmol/l)                       | 109        | 68.20 (16.50–141.50) | 109 | 65.61 (34.35–178.55) | 0.280 |
| Na (mmol/l)                        | 109        | 137.6 (130.9–145.7) | 109 | 137.0 (130.4–145.2) | 0.477 |
| PT (s)                             | 109        | 16.1 (10.4–27.1) | 109       | 15.4 (11.2–27.2) | 0.072 |
| APTT (s)                           | 109        | 39.7 (26.7–52.8) | 109       | 40.0 (19.8–60.5) | 0.646 |
| INR                                | 109        | 1.31 (1.00–2.43) | 109       | 1.23 (1.00–2.51) | 0.042 |
| Child-Pugh score                   | 109        | 7 (5–12)       | 109       | 7 (5–11)       | 0.945 |
| Child-Pugh class A/B/C             | 109        | 47 (43.1%)/54 (49.5%)/8 (7.3%) | 109 | 47 (43.1%)/54 (49.5%)/8 (7.3%) | 1.000 |
| MELD score                         | 109        | 10.54 (6.43–20.39) | 109 | 10.20 (6.65–20.00) | 0.590 |
| EVL                                | 109        | 58 (53.2%)     | 109       | 20 (18.3%)     | <0.001 |
| EVT for controlling bleeding       | 109        | 50 (45.9%)     | 109       | 16 (14.7%)     | <0.001 |
| EVT for preventing from bleeding   | 109        | 8 (7.3%)       | 109       | 4 (3.7%)       | 0.235 |
| EVL alone                          | 109        | 21 (19.3%)     | 109       | 10 (9.2%)      | 0.033 |
| EIS alone                          | 109        | 6 (5.5%)       | 109       | 2 (1.8%)       | 0.150 |
| EVL combined with ECGI             | 109        | 27 (24.8%)     | 109       | 6 (5.5%)       | <0.001 |
| EIS combined with ECGI             | 109        | 2 (1.8%)       | 109       | 0 (0%)         | 0.498 |

AKP, alkaline phosphatase; ALB, albumin; ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; ECGI, endoscopic cyanoacrylate glue injection; EIS, endoscopic injection sclerotherapy; EVL, endoscopic variceal ligation; EVT, endoscopic variceal treatment; Hb, hemoglobin; INR, international normalized ratio; MELD, Model for End-stage Liver Disease; Na, sodium; PLT, platelet count; PT, prothrombin time; PVST, portal venous system thrombosis; Scr, serum creatinine; TBIL, total bilirubin; WBC, white blood cell.

Bold and italics means that the value is <0.05.
According to the goal of EVT, the case group had a significantly higher proportion of patients who had undergone EVT for controlling bleeding (42.9% (12/28) versus 17.9% (5/28), \( p = 0.042 \)). According to the type of EVT, the case group had a significantly higher proportion of patients who had undergone EVL combined with ECGI (22.2% (6/27) versus 3.6% (1/28), \( p = 0.038 \)) (Figure 3(d)).

Multivariate logistic regression analysis demonstrated that EVT was the only independent risk factor for complete PVST and fibrotic cord (OR = 4.889; 95% CI = 1.513–15.793; \( p = 0.008 \)).

Subgroup analyses according to the location of PVST

MPV thrombosis. In the subgroup analysis, we specifically selected patients with MPV thrombosis as the case group. Finally, 63 patients with MPV thrombosis and 63 patients without PVST were included as the case and control groups, respectively. Compared with the control group, the case group had significantly lower levels of Hb and ALT at admission (Supplementary Table 4). The case group had a significantly higher proportion of patients who had undergone EVT [57.1% (36/63) versus 17.5% (11/63), \( p < 0.001 \)]. According to the goal of EVT, the case group had a significantly higher proportion of patients who had undergone EVT for controlling bleeding [46.0% (29/63) versus 12.7% (8/63), \( p < 0.001 \)]. According to the type of EVT, the case group had significantly higher proportions of patients who had undergone EVL alone [25.4% (16/63) versus 9.5% (6/63), \( p = 0.019 \)] and EVL combined with ECGI [25.4% (16/63) versus 3.2% (2/63), \( p < 0.001 \)] (Figure 4(a)).

Multivariate logistic regression analysis demonstrated that Hb (OR = 0.982; 95% CI = 0.967–0.998; \( p = 0.028 \)) and EVT (OR = 5.985; 95% CI = 2.468–14.511; \( p < 0.001 \)) were independent risk factors for MPV thrombosis.

LPV and/or RPV thrombosis. In the subgroup analysis, we specifically selected patients with LPV and/or RPV thrombosis as the case group. Finally, 51 patients with LPV and/or RPV...
thrombosis and 51 patients without PVST were included as the case and control groups, respectively. Compared with the control group, the case group had significantly lower levels of Hb, ALT, and AKP at admission (Supplementary Table 5). The case group did not have a significantly higher proportion of patients who had undergone EVT \[49.0\% (25/51) \text{ versus } 33.3\% (17/51), p=0.108\].

According to the goal of EVT, the case group did not have a significantly higher proportion of patients who had undergone EVT for controlling \[39.2\% (20/51) \text{ versus } 29.4\% (15/51), p=0.297\] or preventing from bleeding \[9.8\% (5/51) \text{ versus } 3.9\% (2/51), p=0.240\]. According to the type of EVT, the case group did not have a significantly higher proportion of patients who had undergone

### Table 2. Risk factors for PVST in liver cirrhosis: Results of logistic regression analyses.

| Factors                        | Univariate analyses | Multivariate analyses |
|--------------------------------|---------------------|----------------------|
|                                | OR (95% CI)         | p value              | OR (95% CI)         | p value              |
| Age (years)                    | 0.999 (0.971–1.028) | 0.945                | –                    | –                    |
| Sex (male/female)              | 1.000 (0.504–1.986) | 1.000                | –                    | –                    |
| Hepatitis B virus infection    | 1.308 (0.759–2.252) | 0.333                | –                    | –                    |
| Hepatitis C virus infection    | 1.178 (0.383–3.626) | 0.775                | –                    | –                    |
| Alcohol abuse                  | 0.618 (0.361–1.056) | 0.078                | –                    | –                    |
| Drug-related disease           | 1.734 (0.607–4.950) | 0.304                | –                    | –                    |
| Hb (g/l)                       | 0.982 (0.972–0.991) | \(<0.001\)           | 0.988 (0.977–0.999)  | \(0.026\)            |
| WBC (10^9/l)                   | 0.933 (0.843–1.033) | 0.180                | –                    | –                    |
| PLT (10^9/l)                   | 0.993 (0.987–1.000) | \(0.047\)           | 0.997 (0.989–1.005)  | \(0.428\)            |
| TBIL (μmol/l)                  | 0.993 (0.982–1.004) | 0.238                | –                    | –                    |
| ALB (g/l)                      | 0.994 (0.952–1.038) | 0.786                | –                    | –                    |
| ALT (U/l)                      | 0.977 (0.962–0.992) | \(0.003\)           | 0.989 (0.975–1.004)  | \(0.158\)            |
| AKP (U/l)                      | 0.989 (0.982–0.995) | \(<0.001\)           | 0.994 (0.987–1.000)  | \(0.059\)            |
| Scr (μmol/l)                   | 1.005 (0.990–1.020) | 0.507                | –                    | –                    |
| Na (mmol/l)                    | 1.035 (0.929–1.152) | 0.535                | –                    | –                    |
| PT (s)                         | 1.101 (0.978–1.238) | 0.110                | –                    | –                    |
| APTT (s)                       | 0.987 (0.939–1.037) | 0.608                | –                    | –                    |
| INR                            | 3.164 (0.965–10.379) | 0.057                | –                    | –                    |
| Child-Pugh score               | 0.997 (0.846–1.174) | 0.967                | –                    | –                    |
| Child-Pugh class (B + C/A)     | 1.000 (0.585–1.709) | 1.000                | –                    | –                    |
| MELD score                     | 1.018 [0.935–1.109] | 0.676                | –                    | –                    |
| EVT                            | 5.061 (2.739–9.350) | \(<0.001\)           | 4.258 (2.240–8.095)  | \(<0.001\)           |

AKP, alkaline phosphatase; ALB, albumin; ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; CI, confidence interval; EVT, endoscopic variceal treatment; Hb, hemoglobin; INR, international normalized ratio; MELD, Model for End-stage Liver Disease; Na, sodium; OR, odds ratio; PLT, platelet count; PT, prothrombin time; PVST, portal venous system thrombosis; Scr, serum creatinine; TBIL, total bilirubin; WBC, white blood cell.
EVL alone, ECGI alone, EIS alone, EVL combined with ECGI, or EIS combined with ECGI (Figure 4(b)).

Univariate logistic regression analysis demonstrated that EVT was not a risk factor for LPV and/or RPV thrombosis (OR = 1.923; 95% CI = 0.864–4.281; p = 0.109).

Confluence of SMV and SV thrombosis. In the subgroup analysis, we specifically selected patients with thrombosis at the confluence of SMV and SV as the case group. Finally, 48 patients with thrombosis at the confluence of SMV and SV and 48 patients without PVST were included as the case and control groups, respectively. Compared with the control group, the case group had significantly lower levels of Hb, WBC, and ALT at admission (Supplementary Table 6). The case group had a significantly higher proportion of patients who had undergone EVT [52.1% (25/48) versus 20.8% (10/48), p = 0.001]. According to the goal of EVT, the case group had a significantly higher proportion of patients who had undergone EVT for controlling bleeding [41.7% (20/48) versus 18.8% (9/48), p = 0.014]. According to the type of EVT, the case group did not have a significantly higher proportion of patients who had undergone EVL alone, ECGI alone, EIS alone, EVL combined with ECGI, or EIS combined with ECGI (Figure 4(c)).

Multivariate logistic regression analysis demonstrated that Hb (OR = 0.984; 95% CI = 0.969–0.999; p = 0.043) and EVT (OR = 4.416; 95% CI = 1.669–11.684; p = 0.003) were independent risk factors for thrombosis at the confluence of SMV and SV.

SMV and/or SV thrombosis. In the subgroup analysis, we specifically selected patients with SMV and/or SV thrombosis as the case group. Finally, 66 patients with SMV and/or SV thrombosis and 66 patients without PVST were included as the case and control groups, respectively. Compared with the control group, the case group had significantly lower levels of Hb, WBC, ALT, and AKP at admission (Supplementary Table 7). The case group had a significantly higher proportion of patients who had undergone EVT [62.1% (41/66) versus 50% (33/66), p = 0.029]. According to the goal of EVT, the case group had a significantly higher proportion of patients who had undergone EVT for controlling bleeding [46.2% (31/66) versus 12.1% (8/66), p = 0.001]. According to the type of EVT, the case group had a significantly higher proportion of patients who had undergone EVL alone, ECGI alone, EIS alone, EVL combined with ECGI, or EIS combined with ECGI (Figure 4(d)).
versus 21.2% (14/66), \( p < 0.001 \). According to the goal of EVT, the case group had a significantly higher proportion of patients who had undergone EVT for controlling bleeding [54.5% (36/66) versus 16.7% (11/66), \( p < 0.001 \)]. According to the type of EVT, the case group had a significantly higher proportion of patients who had undergone EVL combined with ECGI [30.8% (20/65) versus 4.5% (3/66), \( p < 0.001 \)] (Figure 4(d)).

Multivariate logistic regression analysis demonstrated that Hb (OR = 0.977; 95% CI = 0.962–0.992; \( p = 0.003 \)) and EVT (OR = 5.747; 95% CI = 2.499–13.216; \( p < 0.001 \)) were independent risk factors for SMV and/or SV thrombosis.

Discussion

The main finding of this case–control study was that a history of EVT was an independent risk factor for PVST in liver cirrhosis. In addition, we have a major advantage in study design that we comprehensively identified the degree of PVST and observed all vessels within the portal venous system, including LPV, RPV, MPV, confluence of SMV and SV, SMV, and SV, by carefully reviewing all contrast-enhanced CT or MRI images. Thus, our study is able to clarify the relationship of EVT with the degree and location of PVST, which is of great importance for the decision-making on detection and prophylaxis of PVST after EVT. We found that a history of EVT significantly increased the risk of partial and complete PVST and that of thrombosis within MPV, SMV, and SV.

A previous meta-analysis by our team found that EIS would increase the risk of PVST in cirrhotic patients.\(^{15}\) The potential mechanism of PVST after EIS is the escape of sclerosants into the portal vein tributaries with subsequent vascular endothelial damage.\(^{20–22}\) A recent observational study also confirmed that EIS was an independent risk factor for PVST in liver cirrhosis.\(^{4}\) However, the present study did not establish any significant association between EIS and PVST. This unexpected phenomenon might be attributed to a very low proportion of patients undergoing EIS alone in our study (1.8%).

Previous studies have not explored the association of EVL or ECGI with PVST yet. The present study found that patients with PVST had significantly higher proportions of EVL alone and EVL combined with ECGI. This may be because EVL and ECGI can cause a mechanical injury to local vascular endothelium while ligating varicose veins or injecting tissue glue into varicose veins.\(^{14}\) In addition, all EVT techniques may modulate portal venous hemodynamics while blocking varicose veins, manifesting as an increased portal vein blood flow\(^{23–25}\) and a turbulence to the blood flow within the portal venous system.\(^{26}\) Indeed, the present study also found that EVT mainly increased the risk of thrombosis within extrahepatic portal vein system vessels (i.e. MPV, SMV, and SV), but a mild impact on thrombosis within intrahepatic portal vein branches (i.e. LPV and RPV), suggesting that hemodynamic alterations after EVT mainly affect MPV and its upstream blood vessels, including the confluence of SMV and SV, SMV, and SV.

EVT for controlling bleeding, but not for preventing from bleeding, was significantly associated with PVST. Rupture of varicose veins itself can result in local vascular endothelial injury, hemodynamic perturbations, and coagulation activation, thereby further aggravating the risk of PVST. In addition, GEVB often indicates more severe portal hypertension and static portal vein blood flow, which also contribute to the development of PVST.\(^{27}\)

Splenectomy is a strong local risk factor for PVST in liver cirrhosis.\(^{11}\) Our previous observational study reported that splenectomy increased 10-fold the risk of PVST among cirrhotic patients.\(^{10}\) Theoretically, the mechanisms of PVST after EVT are a bit similar to those after splenectomy because both of them can cause mechanical injury to local vessel. But the impact of splenectomy on PVST seems to be stronger than that of EVT (OR = 11.494 in a previous study\(^{10}\) versus 5.061 in the current study), probably due to the fact that splenectomy can cause a more serious injury to local vessel when SV is dissected.\(^{28}\)

Meta-analyses have confirmed the efficacy and safety of anticoagulation for treating PVST in patients with liver cirrhosis.\(^{29–31}\) Current guidelines and consensuses also recommend anticoagulation as the first-line therapeutic option for PVST in liver cirrhosis, aiming to restore vascular flow, prevent thrombus progression and recurrence, and decrease the risk of mesenteric ische mia.\(^{11,13,32–33}\) Notably, anticoagulation may improve the survival of cirrhotic patients with
PVST. In addition, prophylactic anticoagulation may protect against the development of PVST in patients with decompensated cirrhosis and those undergoing splenectomy. On the other hand, the assessment and monitoring of bleeding risk in cirrhotic patients receiving anticoagulation should not be ignored. It seems that conventional coagulation tests, such as platelet count, bleeding time, and PT, are not effective to stratify bleeding risk in cirrhotic patients. Global hemostatic tests, such as thrombin generation and whole-blood viscoelastic tests, may better reflect general hemostatic status and predict bleeding risk in cirrhotic patients.

Monitoring PVST after EVT seems to be necessary. Doppler ultrasound may be useful to initially diagnose clinically silent PVST and evaluate asymptomatic cases. On the other hand, the implementation of prophylactic and therapeutic anticoagulation for PVST should be considered. Our present study found that EVT mainly correlated with partial and complete PVST and thrombosis within MPV and SMV/SV, in which anticoagulant therapy is more needed. However, the use of anticoagulation is greatly limited by a high risk of GEVB in patients undergoing EVT. Recent evidence suggests that anticoagulation may not increase the risk of GEVB and even protect against GEVB. Our clinical practice also supported that anticoagulation should be safe and efficacious for acute occlusive PVST which developed after EVT. A prospective study found that no patient experienced bleeding events among 16 cirrhotic patients who had esophageal varices and received anticoagulation after conducting prophylactic EVL or using non-selective beta-blockers. Certainly, the timing of anticoagulation should be explored in such patients.

The present study has several limitations. First, there was a potential selection bias because only patients who had contrast-enhanced CT or MRI images were included. Second, prothrombotic work-up, portosystemic shunts, and intrabdominal infections were not systematically evaluated, thereby restricting our conclusions. Third, the number of patients included in some subgroup analyses according to the degree and location of PVST was limited and underpowered.

In conclusion, a history of EVT might be a risk factor for PVST in liver cirrhosis. Patients who underwent therapeutic EVT, especially EVL alone and EVL combined with ECGI, should be cautious of developing PVST. Notably, EVT mainly increased the risk of partial and complete thrombosis and thrombosis within MPV, SMV, and SV. Well-designed prospective cohort studies are needed to further clarify the association of EVT with PVST in liver cirrhosis, in which all eligible patients should undergo contrast-enhanced CT or MRI scans before EVT to confirm the absence of prior PVST. In addition, the regimens of screening for and prophylaxis of PVST after EVT should be actively explored.

Acknowledgements
The authors would like to appreciate our study team for establishing and updating the prospective database, including Han Deng, Ran Wang, Jing Li, Yingying Li, Xiangbo Xu, Zhaohui Bai, Qianqian Li, Kexin Zheng, Fangfang Yi, Yanyan Wu, Li Luo, Shixue Xu, and Yue Yin.

Author contributions
Le Wang: Data curation; Formal analysis; Methodology; Software; Writing – original draft; Writing – review & editing.
Xiaozhong Guo: Methodology; Validation; Writing – original draft; Writing – review & editing.
Xiaodong Shao: Methodology; Writing – original draft; Writing – review & editing.
Xiangbo Xu: Data curation; Methodology; Writing – review & editing.
Kexin Zheng: Data curation; Methodology; Writing – review & editing.
Ran Wang: Data curation; Methodology; Writing – review & editing.
Saurabh Chawla: Methodology; Writing – review & editing.
Metin Basaranoglu: Methodology; Writing – review & editing.
Xingshun Qi: Conceptualization; Formal analysis; Investigation; Methodology; Project administration; Supervision; Validation; Writing – original draft; Writing – review & editing.

Conflict of interest statement
The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.
Funding
The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was partially supported by the Science and Technology Project Foundation of Shenyang (19-112-4-005) and Science and Technology Plan Project of Liaoning Province (2020JH2/10300163) for Dr Xingshun Qi.

All authors have made an intellectual contribution to the manuscript and approved the submission.

ORCID ID
Xingshun Qi  https://orcid.org/0000-0002-9448-6739

Supplemental material
Supplemental material for this article is available online.

References
1. Qi X, Li H, Liu X, et al. Novel insights into the development of portal vein thrombosis in cirrhosis patients. Expert Rev Gastroenterol Hepatol 2015; 9: 1421–1432.

2. Intagliata NM, Caldwell SH and Tripodi A. Diagnosis, development, and treatment of portal vein thrombosis in patients with and without cirrhosis. Gastroenterology 2019; 156: 1582–1599.

3. Villa E, Cammà C, Marietta M, et al. Enoxaparin prevents portal vein thrombosis and liver decompensation in patients with advanced cirrhosis. Gastroenterology 2012; 143: 1253–1260.

4. Zhang Y, Xu BY, Wang XB, et al. Prevalence and clinical significance of portal vein thrombosis in patients with cirrhosis and acute decompensation. Clin Gastroenterol Hepatol 2020; 18: 2564–2572.

5. Amitrano L, Guardascione MA, Scaglione M, et al. Splanchnic vein thrombosis and variceal rebleeding in patients with cirrhosis. Eur J Gastroenterol Hepatol 2012; 24: 1381–1385.

6. Wang L, Xu X, Hou Y, et al. Acute mesenteric vein thrombosis after endoscopic injection sclerotherapy for esophageal varices in a patient with liver cirrhosis. Drug Discov Ther 2019; 13: 118–121.

7. Lee JW, Kim TS, Ahn KS, et al. Liver transplant for patients with preexisting portal vein thrombosis: a single-center experience. Exp Clin Transplant 2019; 17: 753–758.

8. Stine JG, Wang J, Shah PM, et al. Decreased portal vein velocity is predictive of the development of portal vein thrombosis: a matched case-control study. Liver Int 2018; 38: 94–101.

9. Tripodi A, Primignani M, Chantarangkul V, et al. An imbalance of pro- vs anti-coagulation factors in plasma from patients with cirrhosis. Gastroenterology 2009; 137: 2105–2111.

10. Qi X, Han G, Ye C, et al. Splenectomy causes 10-fold increased risk of portal venous system thrombosis in liver cirrhosis patients. Med Sci Monit 2016; 22: 2528–2550.

11. Hepatobiliary Disease Study Group, Chinese Society of Gastroenterology, Chinese Medical Association. Consensus for management of portal vein thrombosis in liver cirrhosis (2020, Shanghai). J Dig Dis 2021; 22: 176–186.

12. Hwang JH, Shergill AK, Acosta RD, et al. The role of endoscopy in the management of variceal hemorrhage. Gastrointest Endosc 2014; 80: 221–227.

13. de Franchis R and Baveno VI Faculty. Expanding consensus in portal hypertension: report of the Baveno VI Consensus Workshop: stratifying risk and individualizing care for portal hypertension. J Hepatol 2015; 63: 743–752.

14. Bosch J and Berzigotti A. Letter: nonselective beta-blockers, endoscopic therapy and portal vein thrombosis in cirrhosis. Aliment Pharmacol Ther 2019; 49: 1370–1371.

15. Wang L, Guo X, Xu X, et al. Association of portal venous system thrombosis with endoscopic variceal treatment: a systematic review and meta-analysis. Eur J Gastroenterol Hepatol 2021; 32: 125–131.

16. von Elm E, Altman DG, Egger M, et al. The strengthening the reporting of observational studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. PLoS Med 2007; 4: e296.

17. Yi F, Guo X, Wang L, et al. Impact of spontaneous splenorenal shunt on liver volume and long-term survival of liver cirrhosis. J Gastroenterol Hepatol 2021; 36: 1694–1702.

18. Seewald S, Sriram PV, Naga M, et al. Cyanoacrylate glue in gastric variceal bleeding. Endoscopy 2002; 34: 926–932.

19. Peng Y, Qi X and Guo X. Child-Pugh versus MELD score for the assessment of prognosis in liver cirrhosis: a systematic review and meta-analysis of observational studies. Medicine (Baltimore) 2016; 95: e2877.
20. Leach SD, Meier GH and Gusberg RJ. Endoscopic sclerotherapy: a risk factor for splanchnic venous thrombosis. J Vasc Surg 1989; 10: 9–12; discussion 12–13.

21. Hunter GC, Steinkirchner T, Burbige EJ, et al. Venous complications of sclerotherapy for esophageal varices. Am J Surg 1988; 156: 497–501.

22. de Franchis R, Cipolla M, Primignani M, et al. Activation of coagulation in cirrhotics after endoscopic variceal sclerotherapy. Am J Gastroenterol 1987; 82: 1287–1291.

23. Chaudhary A, Tatke M and Aranya RC. Endoscopic sclerotherapy: the far and near effects. Br J Surg 1990; 77: 963.

24. Ohnishi K, Nakata H, Terabayashi H, et al. The effects of endoscopic sclerotherapy combined with transhepatic variceal obliteration on portal hemodynamics. Am J Gastroenterol 1987; 82: 1138–1142.

25. Sugimoto K, Shiraki K, Murata K, et al. The effect of endoscopic injection sclerotherapy on portal blood flow and liver function. Hepatogastroenterology 2002; 49: 1587–1590.

26. Rice S, Lee KP, Johnson MB, et al. Portal venous system after portosystemic shunts or endoscopic sclerotherapy: evaluation with Doppler sonography. AJR Am J Roentgenol 1991; 156: 85–89.

27. Zocco MA, Di Stasio E, De Cristofaro R, et al. Thrombotic risk factors in patients with liver cirrhosis: correlation with MELD scoring system and portal vein thrombosis development. J Hepatol 2009; 51: 682–689.

28. Wu Y, Li H, Zhang T, et al. Splanchnic vein thrombosis in liver cirrhosis after splenectomy or splenic artery embolization: a systematic review and meta-analysis. Adv Ther 2021; 38: 1904–1930.

29. Qi X, De Stefano V, Li H, et al. Anticoagulation for the treatment of portal vein thrombosis in liver cirrhosis: a systematic review and meta-analysis of observational studies. Eur J Intern Med 2015; 26: 23–29.

30. Loffredo L, Pastori D, Farcomeni A, et al. Effects of anticoagulants in patients with cirrhosis and portal vein thrombosis: a systematic review and meta-analysis. Gastroenterology 2017; 153: 480–487.

31. Wang L, Guo X, Xu X, et al. Anticoagulation favors thrombus recanalization and survival in patients with liver cirrhosis and portal vein thrombosis: results of a meta-analysis. Adv Ther 2021; 38: 495–520.

32. Simonetto DA, Singal AK, Garcia-Tsao G, et al. ACG clinical guideline: disorders of the hepatic and mesenteric circulation. Am J Gastroenterol 2020; 115: 18–40.

33. EASL Clinical Practice Guidelines: vascular diseases of the liver. J Hepatol 2016; 64: 179–202.

34. Pettinari I, Vukotic R, Stefanescu H, et al. Clinical impact and safety of anticoagulants for portal vein thrombosis in cirrhosis. Am J Gastroenterol 2019; 114: 258–266.

35. Qi X, Bai M, Guo X, et al. Pharmacologic prophylaxis of portal venous system thrombosis after splenectomy: a meta-analysis. Gastroenterol Res Pract 2014; 2014: 292689.

36. Violi F, Basili S, Raparelli V, et al. Patients with liver cirrhosis suffer from primary haemostatic defects? Fact or fiction? J Hepatol 2011; 55: 1415–1427.

37. Tripodi A, Caldwell SH, Hoffman M, et al. Review article: the prothrombin time test as a measure of bleeding risk and prognosis in liver disease. Aliment Pharmacol Ther 2007; 26: 141–148.

38. Basili S, Raparelli V, Napoleone L, et al. Platelet count does not predict bleeding in cirrhotic patients: results from the PRO-LIVER study. Am J Gastroenterol 2018; 113: 368–375.

39. Northup PG, Garcia-Pagan JC, Garcia-Tsao G, et al. Vascular liver disorders, portal vein thrombosis, and procedural bleeding in patients with liver disease: 2020 practice guidance by the American Association for the Study of Liver Diseases. Hepatology 2021; 73: 366–413.

40. Margini C and Berzizgiti A. Portal vein thrombosis: the role of imaging in the clinical setting. Dig Liver Dis 2017; 49: 113–120.

41. Xu X, Guo X, Wang R, et al. Low-molecular-weight heparin followed by rivaroxaban for acute occlusive portomesenteric vein thrombosis in a cirrhotic patient treated with multiple endoscopic variceal procedures. Ann Hepatol 2020; 19: 573–577.

42. Butera G, Simone F, Iacò A, et al. Anticoagulant treatment for not neoplastic portal vein thrombosis in patients with liver cirrhosis and esophageal varices. Dig Liver Dis 2010; 42: S37.