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 ⓘD

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

Correspondence to:
Xingshun Qi
Liver Cirrhosis Study
Group, Department of
Gastroenterology, General
Hospital of Northern
Theater Command
(formerly called General
Hospital of Shenyang
Military Area), No. 83
Wenhua Road, Shenyang
110840, Liaoning Province,
China

China Medical University,
Shenyang, China
xingshunqi@126.com

Le Wang
Xiaozhong Guo
Liver Cirrhosis Study
Group, Department of
Gastroenterology, General
Hospital of Northern
Theater Command
(formerly called General
Hospital of Shenyang
Military Area), Shenyang,
China

China Medical University,
Shenyang, China

Xiaodong Shao
Xiangbo Xu
Kexin Zheng
Ran Wang
Liver Cirrhosis Study
Group, Department of
Gastroenterology, General
Hospital of Northern
Theater Command
(formerly called General
Hospital of Shenyang
Military Area), Shenyang,
China

Saurabh Chawla
Division of Digestive
Diseases, Department
of Internal Medicine,
School of Medicine, Emory
University, Atlanta, GA,
USA

Metin Basaranoglu
Division of
Gastroenterology,
Department of Internal
Medicine, Medical
School, Bezmialem Vakif
University, Istanbul,
Turkey

*These authors
contributed equally.

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 bowels[6] and increase

the technical complexity of liver transplantation.[7] Except for sluggish portal vein blood flow[8] 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.[14] 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.[15] Notably, EIS is rarely recommended for the management of gastroesophageal varices or variceal bleeding according to the current practice guideline.[12] 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.[16]

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 ($\geqslant 80\%$), and fibrotic cord (Figure 1).[17] 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.[18] 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
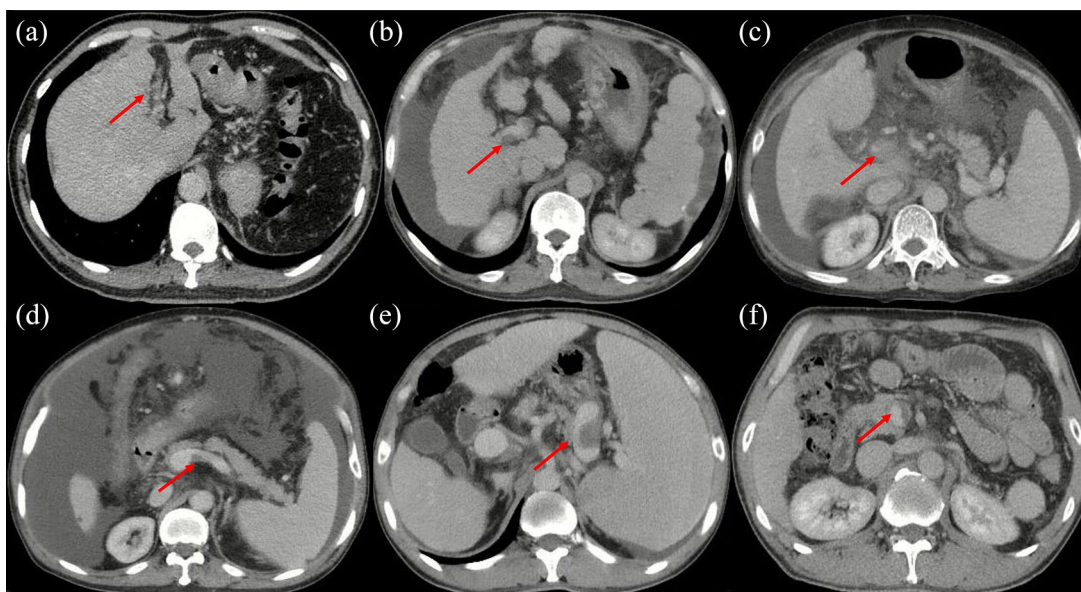
Figure 1. Contrast-enhanced CT images. (a) fibrotic cord within LPV (red arrow); (b) partial thrombosis within RPV (red arrow); (c) complete thrombosis within MPV (red arrow); (d) partial thrombosis within the confluence of SMV and SV (red arrow); (e) complete thrombosis within SV (red arrow); and (f) mural thrombosis within SMV (red arrow).

(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).
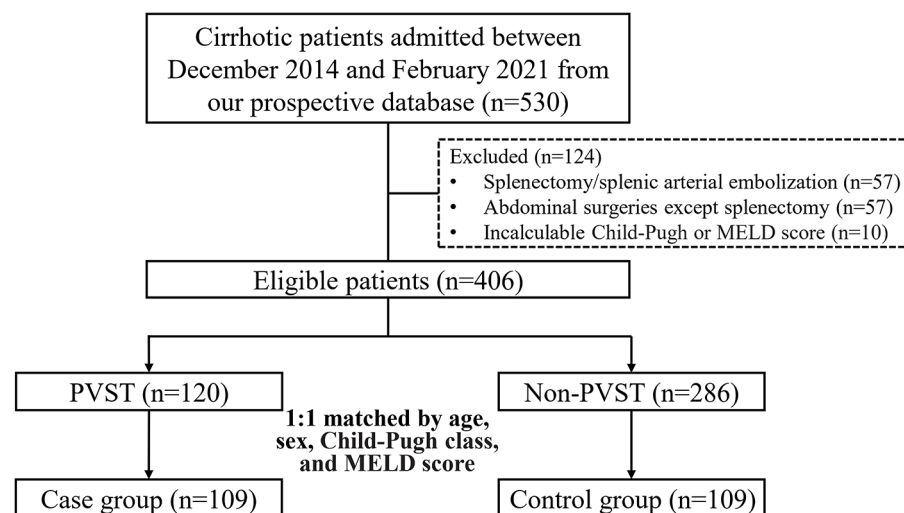
Figure 2. Flow chart of patient selection.

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)

Table 1. Patients' characteristics in case and control groups.

Variables	Case group		Control group		p value
	No. of patients	Median (range) or frequency (percentage)	No. of patients	Median (range) or frequency (percentage)	
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
EVT	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***
ECGI alone	109	6 (5.5%)	109	2 (1.8%)	0.150
EIS alone	109	2 (1.8%)	109	2 (1.8%)	1.000
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.
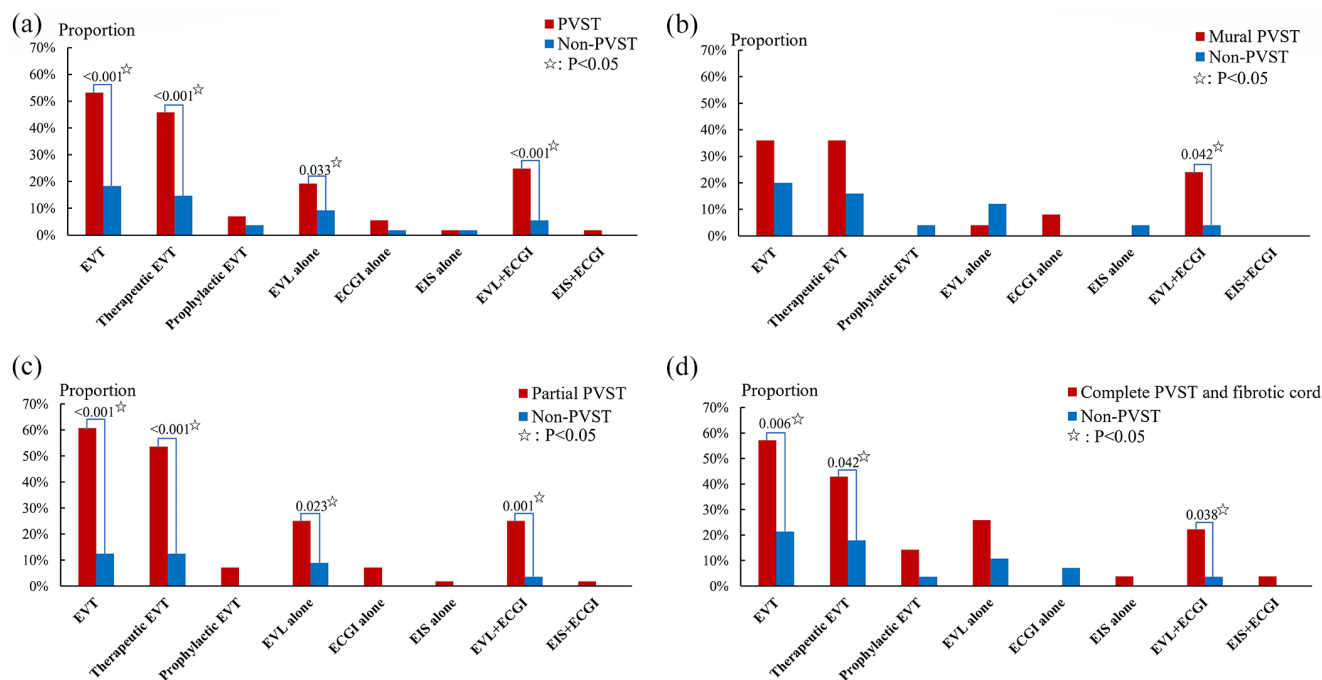Bold and italics means that the value is $<$0.05.

Figure 3. The difference in the proportion of patients who had undergone EVT between patients with and without PVST (a); between patients with mural PVST and without PVST (b); between patients with partial PVST and without PVST (c); and between patients with complete PVST and fibrotic cord and without PVST (d).
Therapeutic EVT refers to EVT for controlling bleeding; Prophylactic EVT refers to EVT for preventing from bleeding; EVL + ECGI refers to EVL combined with ECGI; EIS + ECGI refers to EIS combined with ECGI.

versus 21.4% (6/28), $p = 0.006$]. 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

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 (10⁹/l)	0.933 (0.843–1.033)	0.180	–	–
PLT (10⁹/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.

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) *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) *versus* 29.4% (15/51), *p* = 0.297] or preventing from bleeding [9.8% (5/51) *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
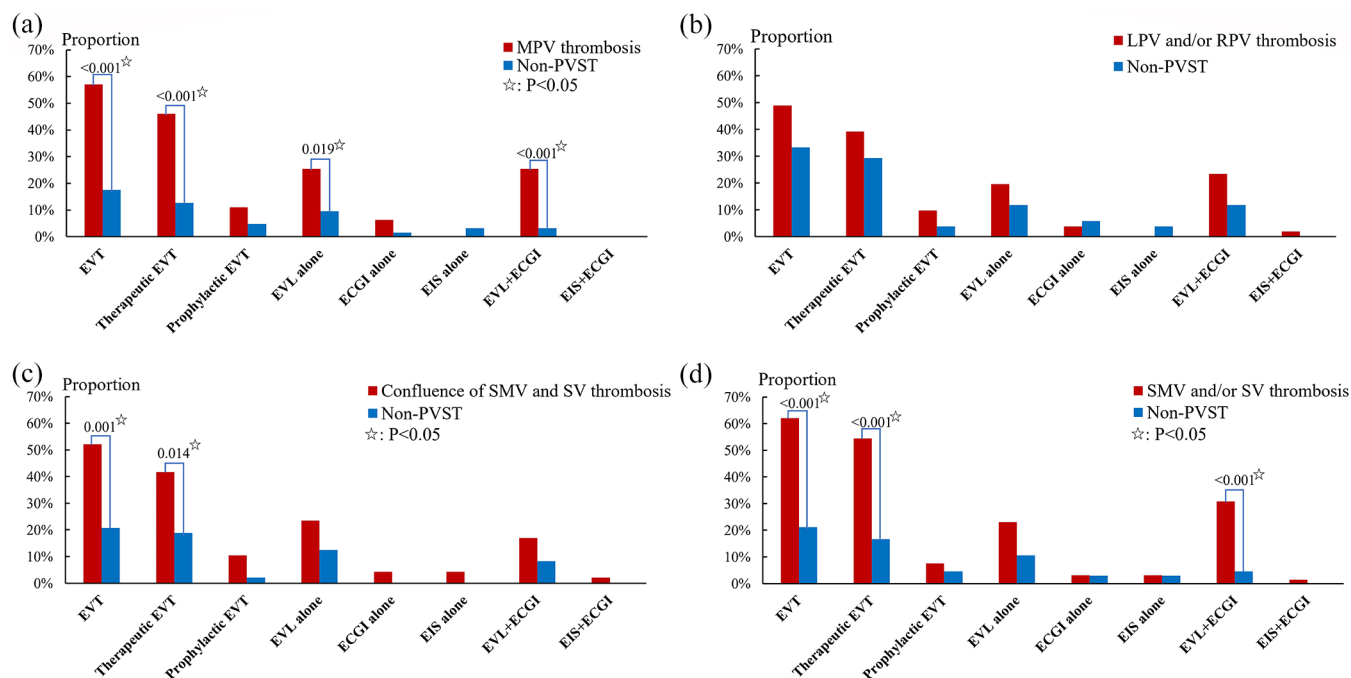
Figure 4. The difference in the proportion of patients who had undergone EVT between patients with MPV thrombosis and without PVST (a); between patients with LPV and/or RPV thrombosis and without PVST (b); between patients with confluence of SMV and SV thrombosis and without PVST (c); and between patients with SMV and/or SV thrombosis and without PVST (d).
Therapeutic EVT refers to EVT for controlling bleeding; Prophylactic EVT refers to EVT for preventing from bleeding; EVL + ECGI refers to EVL combined with ECGI; EIS + ECGI refers to EIS combined with ECGI.

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 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 ischemia.[11,13,32–33] Notably, anticoagulation may improve the survival of cirrhotic patients with

PVST.[34] In addition, prophylactic anticoagulation may protect against the development of PVST in patients with decompensated cirrhosis[3] and those undergoing splenectomy.[28,35] On the other hand, the assessment and monitoring of bleeding risk in cirrhotic patients receiving anticoagulation should not be ignored.[11] It seems that conventional coagulation tests, such as platelet count, bleeding time, and PT, are not effective to stratify bleeding risk in cirrhotic patients.[36–38] 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.[39]

Monitoring PVST after EVT seems to be necessary. Doppler ultrasound may be useful to initially diagnose clinically silent PVST and evaluate asymptomatic cases.[40] 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.[1,31] 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.[30,31] Our clinical practice also supported that anticoagulation should be safe and efficacious for acute occlusive PVST which developed after EVT.[6,41] 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 nonselective beta-blockers.[42] 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.

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

ORCID iD

Xingshun Qi ⓘD https://orcid.org/0000-0002-9448-6739

Supplemental material

Supplemental material for this article is available online.

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