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Original Article

A comparison of the clinical characteristics and prognosis between cirrhotic and non-cirrhotic portal vein thrombosis

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Abstract: Background: Portal vein thrombosis (PVT) can develop in both cirrhosis and non-cirrhosis patients. However, little is known about how these two categories of patients are different or how they are connected. This study was designed to identify the different characteristics and prognoses between non-malignant cirrhotic PVT and non-cirrhotic PVT. Methods: The retrospective study recruited 142 non-malignant cirrhotic PVT and 43 non-cirrhotic PVT patients from May 2012 to December 2017. Their clinical characteristics, laboratory parameters, complications, and survival rates were compared. The subgroup analysis was stratified according to the degree of thrombus. Results: Coagulation, liver function, and the inflammatory parameters were significantly different between the cirrhotic and non-cirrhotic PVT groups. The degrees of ascites ($P < 0.001$) and varices ($P < 0.001$) in the cirrhotic patients were significantly more severe. The incidence of cavernoma was significantly higher (41.9 vs. 12.7, $P < 0.001$) in the non-cirrhotic group. Patients with cavernoma had higher splenectomy histories in both groups (cirrhotic: 50%, non-cirrhotic: 38.9%). Sixteen patients (13.3%) died in the cirrhotic group, but all the patients survived during the follow up period in the non-cirrhotic group. The difference in survival rates was statistically significant, with $P = 0.014$. Conclusions: The degrees of ascites, varices, and thrombus between PVT in non-malignant cirrhosis and non-cirrhosis were significantly different. Patients with PVT in the non-cirrhotic group showed a relatively optimistic prognosis. The patients with cavernoma had higher splenectomy history rates.

Keywords: Portal vein thrombosis, cirrhosis, non-cirrhosis, clinical characteristics, prognosis

Introduction

Portal vein thrombosis (PVT) is not a rare complication in cirrhosis patients, with a prevalence rate of about 10% to 23% [1]. The development of PVT is caused by multiple factors, yet the exact pathogenesis remains unclear. The most important risk factor for PVT formation in liver cirrhosis is considered to be the reduction of portal vein flow velocity [2]. Other risk factors include acquired coagulation dysfunctions and vascular endothelia damage [3]. With a deeper understanding of the poorer prognosis in cirrhotic patients with PVT, clinicians have begun to strengthen the screening procedures of portal vein thrombosis through contrast-enhanced computed tomography (CT) scanning or doppler ultrasonography.

In clinical practice, some patients suffer from persistent portal hypertension with the complication of portal vein thrombosis, but no evidence of cirrhosis is found. A hypercoagulable state and the inflammatory state have been considered as pivotal factors for the etiology of PVT [4, 5]. Attributed to persistent portal hypertension, non-cirrhosis patients with PVT may also have ascites or esophageal varices [4]. The

presence of PVT should be suspected in the presence of portal hypertension and a relatively normal liver function. The etiology of idiopathic thrombosis with portal hypertension remains a tough problem in the clinic. It is beneficial to systematically investigate the clinical characteristics of patients with non-cirrhotic PVT and how they differ from cirrhotic patients with PVT. Unfortunately, there currently is limited systematic research or summaries available on the characteristics [5] and prognoses of PVT in non-cirrhosis patients.

In this retrospective single center study, we examined the clinical and laboratory characteristics of 142 non-malignant cirrhosis patients with PVT and 43 non-cirrhosis patients with PVT. The study compared the two groups to elucidate the clinical characteristics and prognosis in these two categories and then revealed the differences and connections between them.

Patients and methods

Patients enrollment

From May 2012 to December 2017, a total of 261 consecutive patients with PVT at the Affiliated Drum Tower Hospital of Nanjing University Medical School participated in the study. Data were analyzed retrospectively from our prospectively collected database. Inclusion criteria: patients with portal vein thrombosis aged between 16 to 80 years old. Exclusion criteria: Patients with the complication of malignancies, patients who received a liver transplantation before, or patients lacking complete clinical data. The enrolled patients were divided into two groups: the PVT in non-malignant cirrhosis group and the PVT in non-cirrhosis group. According to existing guidelines and the Chinese experts' consensus [6, 7], the diagnosis of cirrhosis should meet at least one of the following criteria: the liver biopsy pathology shows diffuse hepatic fibrosis with false lobule formation; or there is standard evidence for cirrhosis and portal hypertension using the medical imaging method and the presence of liver dysfunction. The retrospective study was approved by the clinical research ethics committee of the Affiliated Drum Tower Hospital of Nanjing University Medical School. Informed consent was obtained from all enrolled patients.

Laboratory tests

Venous blood samples were drawn for laboratory tests on the first day of hospital admission. Routine blood tests were performed, including white blood cell count (WBC), neutrophil count, lymphocyte count, platelet count (PLT), and hemoglobin level. The NL ratio was defined as neutrophil count to lymphocyte count. Blood biochemistry tests were performed, including glutamic pyruvic transaminase (ALT), glutamic pyruvic aminotransferase (AST), total bilirubin (TBIL), direct bilirubin (DBIL), albumin, total bile acid, C-reactive protein (CRP), triglyceride, cholesterol, serum creatinine. Coagulation function tests were performed including prothrombin time (PT), activated partial thromboplastin time (APTT), and fibrinogen.

Contrast-enhanced CT scan and doppler ultrasonography

A contrast-enhanced CT scan was used for confirming the existence and classification of portal venous thrombosis. Ultrasonography was used to record the diameter and velocity of the portal vein, as well as to evaluate the degree of ascites. We defined five types of PVT according to the size and the extension of the thrombus. Type I: partial PVT- the thrombus covers less than 50% of the PV lumen. Type II: PV obstruction greater than 50%, or complete occlusion with or without minimal extension into the superior mesenteric vein (SMV). Type III: complete thrombosis of both PVs, the thrombus extends to the proximal part of the SMV. Type IV: complete thrombosis- the PV thrombus affects both the proximal and distal SMV. Type V: cavernoma of the portal vein. With modification, this classification of PVT was derived from the method formulated by Yerdel's PVT classification [8]. The CT images and Doppler ultrasonography examinations were performed by senior radiologists in the hospital. Portal vein thrombosis in cirrhosis (A) and non-cirrhosis (B) measured by contrast-enhanced CT scan are shown in **Figure 2**.

Gastroscopy

Gastroscopies were performed by a team of senior experienced gastroenterologists. According to the consensus of Chinese medical experts [9], the esophageal varices were divided into three groups (mild, moderate, and

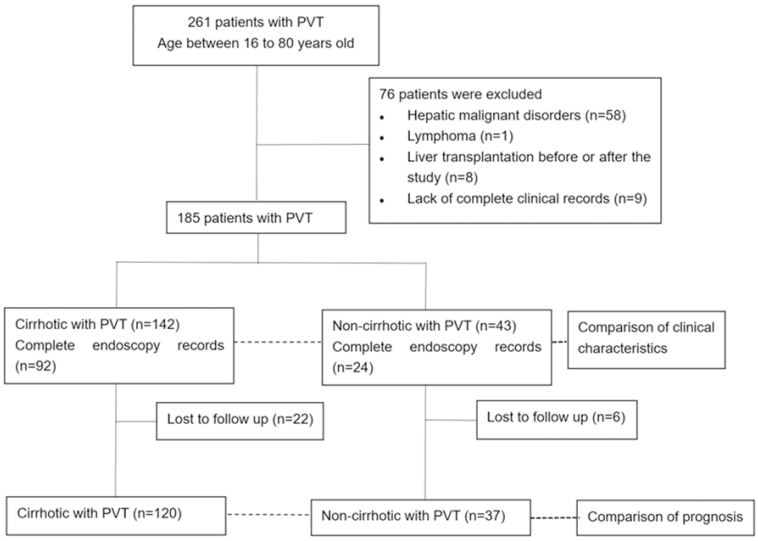

Figure 1. Flow diagram of the research design.

severe) according to the degree of esophageal varices and the risk of bleeding. Mild (EV1): esophageal varices are linear or slightly tortuous without any signs of redness. Moderate (EV2): esophageal varices are linear or slightly tortuous, with red signs or serpentine and tortuous esophageal varices but without any signs of redness. Severe (EV3): esophageal varices are serpentine and tortuous, with signs of redness or esophageal varices in the form of beads, nodules, or tumor-like (whether or not red). The gastric varices classification was based on their association with esophageal varices. The extension can be divided into three types as follows. GOV1: the varices extend continuously to the lesser curvature of the stomach to the gastroesophageal junction. GOV2: the varices extend along the greater curvature of the gastric fundus. GOV3: the varices extend to both the lesser curvature and the gastric fundus. Isolated gastric varices (IGV) without esophageal varices can be classified into two types. IGV1: varices are located in the fundus of the stomach, manifested as tortuous and interwoven, beaded, and nodular like. IGV2: varices are located in the body of the stomach, the antrum of the stomach or the pylorus [9].

Follow up

Patients were followed up by telephone at 1, 3, 6 months and then every 6 months after discharge from hospital. The primary endpoint of follow up was the date of death from all causes of illness related to liver dysfunction or the date of June 30, 2018. The secondary endpoint was main complications, including variceal bleeding, encephalopathy, refractory ascites, intestinal necrosis or obstruction and significant progression of thrombosis.

Data analysis

The Data was analyzed by IBM SPSS software for Windows (version 20, IBM, USA). A one-sample Kolmogorov-Smirnov test was applied to test the quantitative data for normality. The data were expressed as the mean ± standard deviation if the data was normally distributed and was compared by Student's *t*-test or a One-way ANOVA test, and the data was expressed as the median and range if it was skewed and was compared using a Mann-Whitney U test. The categorical data was expressed by frequencies and percentages and compared by a Chi-square test or Fisher's exact test. A survival curve was obtained through a Kaplan-Meier analysis and was compared using a log-rank test. A p-value < 0.05 was obtained, indicating a significant statistical difference.

Results

Demographic characteristics of patients enrolled in the study

185 patients were included in the final study and classified into two groups: the PVT in non-malignant cirrhosis group (n = 142) and the non-cirrhosis group (n = 43). In the cirrhosis group, there were 84 males (59.2%) and 58 females (40.8%). The average age was 56.08 ± 11.90 years old. In the non-cirrhosis group, there were 26 males (60.5%) and 17 females (39.5%). The average age was 50.09 ± 17.37 years old. The average CTP score in the cirrhosis group was 7.4 ± 1.5. The flow diagram of the research design is shown in **Figure 1**.

Patients in the non-cirrhosis group showed higher states of coagulation and inflammation

PT ($P < 0.001$), APTT ($P < 0.01$), platelet level ($P < 0.001$) between the two groups showed sig-

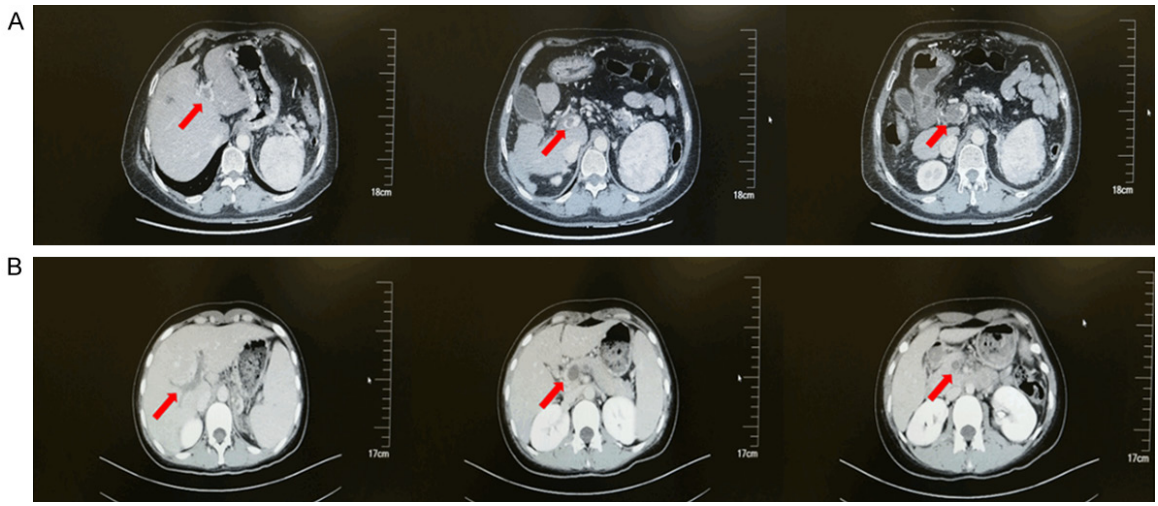

Figure 2. Portal vein thrombosis in cirrhosis (A) and non-cirrhosis patients (B). (A) was for portal vein thrombosis in cirrhosis patients and was classified as type II in the present study. (B) was for portal vein thrombosis in non-cirrhosis patients and was classified as type IV in the present study.

nificant statistical differences, indicating a relatively higher coagulation state in the non-cirrhosis group. The WBC level ($P < 0.001$), NL ratio ($P < 0.001$), and CRP level ($P < 0.001$) were significantly higher in non-cirrhosis group, indicating a relatively higher inflammatory state. The laboratory results are summarized in **Table 1**.

A comparison of the initial symptoms and etiology between the two groups

Hepatitis B was the leading cause in the cirrhotic group (52.1%), and umbilical cord infection was the leading cause in the non-cirrhotic group (20.9%). Patients in the cirrhotic PVT group tended to present variceal bleeding as an initial symptom, but in the non-cirrhotic PVT group, most of the patients manifested abdominal pain (51.2%). The results between groups were significantly different and are summarized in **Table 2**.

Comparison of PVT types and characteristics between the two groups

Type III and IV thrombus accounted for the majority of cirrhotic PVT. Cavernoma was the most common type of thrombus in non-cirrhotic PVT. There was a statistical difference between the groups in types of thrombus with $P < 0.001$ (**Table 2**). The portal vein diameters and velocities in both groups were beyond the normal range. In addition, the portal vein diameter in the cirrhotic group was larger than it was in the non-cirrhosis group ($P < 0.001$). Portal vein velocity in the cirrhosis group was faster than it was in the non-cirrhosis group ($P = 0.03$). The results are shown in **Table 2**.

Comparison of varices between two groups measured by gastroscopy

A total of 92 patients in the cirrhosis group and 24 patients in the non-cirrhosis groups underwent gastroscopy in this center. EV3 accounted for 33.7% of the population in the cirrhotic group, and GOV1 was 30.4%. However, 25% of the patients showed no varices in the non-cirrhotic group, and EV1 was 20.8% (**Table 2**). The degree of varices was significantly different between the cirrhosis and the non-cirrhosis groups ($P < 0.001$).

In the subgroup analysis, we combined types I, II, and III into one group (I-III), which might indicate a milder type of thrombus. We compared the main laboratory parameters between groups I-III, IV, and cavernoma. In the cirrhosis group, patients with cavernoma had a shorter PT ($P = 0.03$) and a higher platelet level ($P = 0.02$). In both the cirrhotic and non-cirrhotic groups, patients with cavernoma had higher rates of splenectomy histories (50% and 38.9%, respectively). The results are shown in **Tables 3**, **4**.

Therapeutic strategy and follow up information of the study population

In the non-malignant PVT group, there were 37 patients who received EBL as secondary pro-

Table 1. Comparison of demographic characteristics and laboratory parameters between the cirrhosis group and the non-cirrhosis group

	Cirrhosis group n = 142	Non-cirrhosis group n = 43	*P* value	Normal range
Age (year)	56.08 ± 11.90	50.09 ± 17.37	0.04*	-
Gender (n, %)			0.88	-
Male	84 (59.2)	26 (60.5)		
Female	58 (40.8)	17 (39.5)		
CTP score	7.4 ± 1.5	-	-	-
CTP (n, %)				
A	43 (30.3%)	-	-	-
B	87 (61.2%)	-	-	-
C	12 (8.5%)	-	-	-
PT (s)	14.60 (11-22)	12.90 (11.3-18.3)	< 0.001*	10-15
APTT (s)	35.15 (24-100.5)	33.30 (22.7-76.6)	0.01*	25-31.3
Platelet (**10*^9)	118 (15-464)	170 (8-1078)	< 0.001*	125-350
WBC (**10*^9)	4.2 (0.7-32.4)	7.0 (2.6-22.6)	< 0.001*	3.5-9.5
NL ratio	2.33 (0.21-27.75)	3.64 (0.82-51.33)	< 0.001*	-
Hemoglobin (g/L)	79.0 (38-152)	108 (59-157)	< 0.001*	130-175
TBIL (umol/L)	18.25 (2.8-133.6)	15.4 (0.6-210.8)	0.31	5-20.5
DBIL (umol/L)	7.5 (1.7-130.6)	6.3 (1.7-164.2)	0.36	1.7-6.8
Albumin (g/L)	32.27 ± 4.36	35.98 ± 4.89	< 0.001*	40-55
ALT (U/L)	17.65 (4.6-120.3)	30.5 (9.6-538.1)	< 0.001*	5-40
AST (U/L)	29.2 (9.9-230.1)	28.1 (11.3-397)	0.75	8-40
CRP (mg/L)	5.15 (0.2-137.7)	14.1 (0.2-332.1)	< 0.001*	0-8
Total bile acid (umol/L)	17.5 (0.1-207)	12.8 (0.6-213.3)	0.19	0-15
Triglyceride mmol/L	0.68 (0.16-4.93)	1.02 (0.25-6.64)	< 0.001*	0.56-1.7
Cholesterol mmol/L	3.11 ± 0.93	3.91 ± 1.21	< 0.001*	2.9-5.72
Creatinine (umol/L)	60 (32-210)	57 (36-180)	0.99	44-106

Remarks: parameters having a statistical significance with P < 0.05 were expressed with *. WBC: white blood cells; PLT: platelet; NL ratio: neutrophil to lymphocyte ratio; PT: prothrombin time; APTT: activated partial thromboplastin time; ALT: glutamic pyruvic transaminase; AST: glutamic pyruvic aminotransferase; TBIL: total bilirubin; DBIL: direct bilirubin; TP: total protein; GGT: glutamyl transpeptidase; ALP: alkaline phosphatase; CRP: C-reactive protein.

Table 2. A comparison of the clinical characteristics of patients with PVT in the cirrhosis group and the non-cirrhosis group

	Cirrhosis group n = 142	Non-cirrhosis group n = 43	*P* value
Etiology (n, %)			< 0.001*
Hepatitis B	74 (52.1)	-	-
Hepatitis C	6 (4.2)	-	-
Alcoholic	9 (6.3)	-	-
Schistosome	13 (9.2)	-	-
Primary biliary	9 (6.3)	-	-
Autoimmune hepatitis	4 (2.8)	-	-
NAFLD	1 (0.7)	-	-
Budd-Chiari syndrome	2 (1.4)	-	-
Cryptogenic	24 (16.9)	-	-
JAK2V617F mutation	-	7 (16.3)	-
Thrombophilia	-	8 (18.6)	-

Umbilical cord infection	-	9 (20.9)	-
Pancreatitis	-	5 (11.6)	-
Diffuse peritonitis	-	2 (4.7)	-
PA-HVOD	-	2 (4.7)	-
Autoimmune diseases	-	3 (7.0)	-
Unclear	-	7 (16.3)	-
Initial symptoms (n, %)			< 0.001*
Variceal bleeding	92 (64.8)	10 (23.3)	< 0.001
Abdominal distention	20 (14.1)	6 (14.0)	0.98
Abdominal pain	13 (9.2)	22 (51.2)	< 0.001
Routine examination	8 (5.6)	3 (7.0)	0.75
Others	9 (6.3)	2 (4.6)	0.67
Ascites (n, %)			< 0.001*
None	30 (21.1)	21 (48.8)	< 0.001
Mild	36 (25.4)	9 (20.9)	0.55
Moderate to severe	76 (53.5)	13 (30.2)	0.01
PHB (n, %)	62 (43.7)	20 (46.5)	0.742
Thrombus (n, %)			< 0.001*
I	6 (4.2)	2 (4.7)	0.91
II	11 (7.7)	3 (7.0)	0.87
III	47 (33.1)	7 (16.3)	0.03
IV	60 (42.3)	13 (30.2)	0.16
Cavernoma	18 (12.7)	18 (41.9)	< 0.001*
Varices (n, %)			< 0.001*
EV1	6 (6.5)	5 (20.8)	0.09
EV2	5 (5.4)	2 (8.3)	0.74
EV3	31 (33.7)	3 (12.5)	0.02
GOV1	28 (30.4)	4 (16.7)	0.09
GOV2	7 (7.6)	0 (0.0)	0.05
GOV3	4 (4.3)	1 (4.2)	0.86
IGV1	3 (3.3)	1 (4.2)	0.93
IGV2	7 (7.6)	2 (8.3)	0.94
None varices	1 (1.1)	6 (25)	< 0.001
Ultrasound	n = 109	n = 22	
Portal vein diameter (cm)	1.42 (0.53-2.70)	1.20 (0.43-1.65)	< 0.001*
Portal vein velocity (cm/s)	23.90 (0-97.2)	16.70 (0-149)	0.03*

Remarks: parameters having a statistical signifcance with P < 0.05 were expressed with *. NAFLD: nonalcoholic fatty liver disease; PA-HVOD: Pyrrolizidine alkaloid-related hepatic vein occlusive disease; JAK2: Janus activating kinase 2.

phylaxis for variceal bleeding, 56 patients received TIPS as secondary prophylaxis, and 10 underwent TIPS for recanalization. Among the patients who underwent TIPS, 5 failed in the TIPS procedure and converted to anticoagulant treatment. Five patients underwent splenectomy with selective devascularization surgery. Thirty-four patients received anticoagulant treatment without any procedure. In the non-cirrhotic PVT group, 6 patients received EBL for bleeding, 2 patients received TIPS for bleeding, 4 patients underwent splenectomy, and the other 31 patients received conservative treatment mainly including anticoagulant or antiplatelet therapy. The procedures were performed by the same team in the hospital. Anticoagulant therapy was based on low molecular weight heparin as inpatient treatment and warfarin as outpatient treatment. The antiplatelet therapy was based on aspirin treatment.

The median follow-up time was 12 (1-66) months in the cirrhosis group, and 16 (1-64) months. Twenty-two patients in the cirrhosis

Table 3. Characteristics and laboratory parameter distribution of different types of PVT in cirrhosis patients

Cirrhosis group n = 142	I-III n = 65	IV n = 59	V n = 18	*P* value
Age (year)	57.92 ± 11.26	54.58 ± 12.13	54.33 ± 13.11	0.24
PT (s)	14.9 (11.5-21.1)	14.6 (11-22)	13.85 (11.3-16.4)	0.03*
APTT (s)	35.3 (25.7-72.4)	35.4 (24-100.5)	33.5 (27.3-45.7)	0.15
Platelet (**10*^9)	83 (27-464)	141 (15-420)	205.5 (31-416)	0.02*
WBC (**10*^9)	3.4 (0.7-28)	4.6 (1-32.4)	4.25 (1-26.1)	0.12
NL ratio	2.47 (0.27-18.79)	2.25 (0.21-27.75)	2.85 (0.57-16.67)	0.55
Hemoglobin (g/L)	80 (43-148)	77 (38-137)	89.5 (57-152)	0.20
TBIL (umol/L)	18.9 (3.9-133.6)	17.2 (5.5-64)	13.85 (2.8-31.2)	0.08
DBIL (umol/L)	8.1 (1.7-130.6)	7.4 (1.7-50.1)	5.15 (2.6-13.8)	0.02*
Albumin (g/L)	32.32 ± 4.61	32.07 ± 3.87	32.74 ± 5.12	0.85
ALT (U/L)	22.4 (7.6-99.9)	17.1 (4.6-120.3)	14.95 (9.8-41.6)	0.03*
AST (U/L)	33.7 (9.9-117)	27 (12.7-230.1)	24.9 (13.7-112.4)	0.02*
CRP (mg/L)	4.7 (0.2-98.5)	5.6 (0.2-137.7)	8.15 (0.2-70.5)	0.38
Triglyceride (mmol/L)	0.64 (0.16-1.87)	0.74 (0.24-4.93)	0.73 (0.43-1.38)	0.34
Cholesterol (mmol/L)	3.06 ± 0.90	3.16 ± 1.01	3.18 ± 0.77	0.79
Creatine (umol/L)	56 (32-210)	61 (35-117)	58 (39-89)	0.60
Splenectomy (n, %)	24 (36.9)	36 (61.0)	9 (50)	0.03*
Smoking history (n, %)	11 (16.9)	8 (13.6)	2 (11.1)	0.78
Drinking history (n, %)	10 (15.4)	7 (11.9)	1 (5.6)	0.53

Remarks: parameters having a statistical signifcance with P < 0.05 were expressed with *. WBC: white blood cells; PLT: platelet; NL ratio: neutrophil to lymphocyte ratio; PT: prothrombin time; APTT: activated partial thromboplastin time. ALT: glutamic pyruvic transaminase; AST: glutamic pyruvic aminotransferase; TBIL: total bilirubin; DBIL: direct bilirubin; GGT: glutamyl transpeptidase; ALP: alkaline phosphatase; CRP: C-reactive protein.

group and 6 patients in the non-cirrhosis group were lost during the follow up period. 16 patients (13.3%) died from all causes of illness related to liver dysfunction in the cirrhosis group, but no one died in the non-cirrhosis group. The mortality rates of type I-III, IV and cavernoma PVT in the cirrhosis group were 12.3%, 14.0% and 15.4%, respectively. The uppermost complication was spontaneous hepatic encephalopathy (20.8%) in the cirrhosis group. In the non-cirrhosis group, the uppermost complication was variceal bleeding (18.9%), followed by intestinal necrosis or obstruction (10.8%). The results are summarized in **Table 5**. The survival curve of the mortalities of both groups is shown in **Figure 3**, with a statistical difference.

Discussion

The prevalence of PVT in cirrhosis ranges from 10% to 23%, and cirrhosis combined with hepato-carcinoma is considered the most frequent risk factor in forming portal vein thrombosis [2]. Tumors have an independent tendency to produce thrombus, and its characteristics are different from those with cirrhosis alone, so we excluded malignant patients from this study. During the same period, there were 946 non-malignant cirrhosis patients admitted to our hospital, and the morbidity of PVT in cirrhosis was calculated to be 16.8%. It was interesting to note that some patients manifested persistent portal hypertension without clear evidence of liver dysfunction. With the popularization and progress of medical imaging technology, some of them screened out of PVT. The clinical characteristics and prognoses of these patients were different from those with cirrhosis, so we designed this research accordingly.

In both the cirrhosis and non-cirrhosis groups with PVT, male participants accounted for more than half of the sample. The mean age of the patients in the non-cirrhosis group was younger. As to cirrhotic patients, there are studies demonstrating that the most common cause of developing PVT in cirrhosis patients was hepa-

Table 4. Characteristics and laboratory parameter distribution of different types of PVT in non-cirrhosis patients

Non-cirrhosis group n = 43	I-III n = 12	IV n = 13	V n = 18	*P* value
Age (year)	56.08 ± 19.47	55.46 ± 13.78	42.22 ± 15.92	0.04*
PT (s)	12.9 (12.4-18.3)	14 (11.8-15.6)	12.85 (11.3-16.1)	0.73
APTT (s)	32.3 (25.4-45.5)	31.2 (22.7-76.6)	35.8 (24-49.4)	0.73
Platelet (**10*^9)	129 (8-402)	170 (102-1078)	234 (54-910)	0.56
WBC (**10*^9)	8.75 (3.4-22.6)	12 (3.6-17.8)	5.65 (2.6-21.7)	0.07
NL ratio	7.91 (1.3-23.44)	5.36 (1.2-51.33)	2.43 (0.82-9.55)	0.02*
Hb (g/L)	116 (79-157)	122 (78-148)	104.5 (59-156)	0.46
TBIL (umol/L)	29.45 (4.5-210.8)	12.3 (0.6-130)	14.85 (4.4-29.9)	0.06
DBIL (umol/L)	15.65 (2.2-164.2)	5 (1.9-106.7)	5.65 (1.7-51.4)	0.03*
Albumin (g/L)	35.18 ± 3.93	34.99 ± 6.06	37.22 ± 4.50	0.38
ALT (U/L)	53.75 (10.5-538.1)	22.7 (10.8-152.5)	21.45 (9.6-97.1)	0.02*
AST (U/L)	37 (13-397)	32.6 (11.3-124.2)	25.2 (13.4-90.8)	0.30
CRP (mg/L)	53.75 (0.9-332.1)	52.2 (4.7-159)	4.45 (0.2-52.2)	< 0.001*
Triglyceride (mmol/L)	1.08 (0.39-6.64)	1.48 (0.5-4.04)	0.99 (0.25-1.66)	0.38
Cholesterol (mmol/L)	4.39 ± 1.68	3.73 ± 1.11	3.72 ± 0.82	0.28
Creatinine (umol/L)	68.5 (36-180)	61 (42-150)	56 (37-121)	0.14
Splenectomy (n, %)	0 (0)	0 (0)	7 (38.9)	< 0.001*
Smoking history (n, %)	4 (33.3)	1 (7.7)	6 (33.3)	0.21
Drinking history (n, %)	4 (33.3)	0 (0)	6 (33.3)	0.06

Remarks: parameters having a statistical significance with P < 0.05 were expressed with *. WBC: white blood cells; PLT: platelet; NL ratio: neutrophil to lymphocyte ratio; PT: prothrombin time; APTT: activated partial thromboplastin time; ALT: glutamic pyruvic transaminase; AST: glutamic pyruvic aminotransferase; TBIL: total bilirubin; DBIL: direct bilirubin; GGT: glutamyl transpeptidase; ALP: alkaline phosphatase; CRP: C-reactive protein.

Table 5. Summary of prognoses in the cirrhosis group and the non-cirrhosis group

	Cirrhosis group n = 120	Non-cirrhosis group n = 37	*P* value
Major complications (n, %)			0.03*
Significant progression of thrombus	5 (4.2)	1 (2.7)	0.69
Refractory ascites	4 (3.3)	1 (2.7)	0.86
Spontaneous hepatic encephalopathy	25 (20.8)	1 (2.7)	0.01
Variceal bleeding	21 (17.5)	7 (18.9)	0.81
Intestinal necrosis or obstruction	3 (2.5)	4 (10.8)	0.05
Mortality (n, %)	16 (13.3)	0 (0)	0.02*
Subgroup mortality (n, %)			0.03*
I-III	7 (12.3)	0 (0))	0.05
IV	7 (14.0)	0 (0)	0.05
V	2 (15.4)	0 (0)	0.30

Remarks: parameters having a statistical signifcance with P < 0.05 were expressed with *. Loss of visit in the cirrhosis group: type I-III 7 patients withdrew, type IV 10 patients withdrew, type V 5 patients withdrew. Loss of visit in the non-cirrhosis group: type I-III 3 patients withdrew, type IV 1 patient withdrew, type V 2 patients withdrew.

titis B [10]. In our study, hepatitis B was observed in 52.1% of the cirrhosis sample. Schistosome ranked second of the leading etiological causes. The higher incidence rate of schistosome in China's population in the last few decades is due to the backwardness of economic development and poor health conditions. The leading etiologies summarized in this

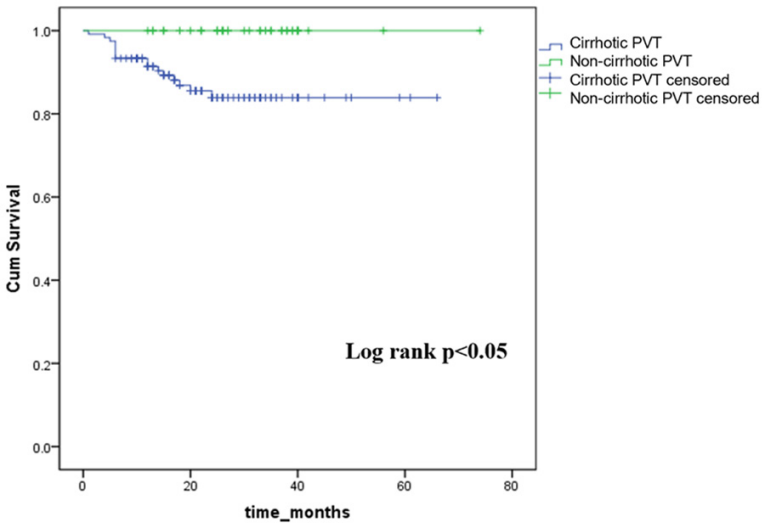

Figure 3. Comparison of the survival times in the cirrhosis and non-cirrhosis groups through a Kaplan-Meier curve.

study in the non-cirrhosis group were inflammatory state and hematological disorders. Patients with thrombophilia had a tendency for early onset of thrombosis [2, 11]. It is worth noting that Janus activating kinase 2 (JAK2) p. V617F mutation is an independent risk factor for thrombosis development in patients with myeloproliferative disorders [12]. A meta-analysis revealed that the calreticulin (CALR) mutation was not rare in splanchnic vein thrombosis (SVT), proposing that screening for CALR mutations might have a role in the management SVT patients. However, we did not find any CALR mutations in our study; instead, the JAK2V617F mutation is comparatively more common in the Chinese population. Given the fact that of the 7 patients with JAK2 mutations among the non-cirrhotic patients, 6 of them developed cavernoma, indicating the myeloproliferative disease had a severe impact on their portal vein systems. In the case of unexplained thrombosis in the portal venous system, clinicians should be highly vigilant for this disease. Thrombophilia is a condition that may increase the risk of developing thrombosis in the entire venous system. The most common form is deep venous thromboembolism [13]. In the Caucasian population, the most common thrombophilia mutations are the Factor V Leiden and the G20210 prothrombin mutations [13]; however, there has been limited related discoveries of such mutations in the Asian population. Congenital deficiencies of protein C, protein S and antithrombin constitute the major part of congenital thrombophilia in the Asian population [14]. Young patients with cryptogenic portal venous thrombosis, especially those combined with deep venous thrombosis, should be considered as a high-risk population for congenital thrombophilia. In our study, 64.8% in the cirrhosis group manifested variceal bleeding as the initial symptom when screening out for PVT. In the non-cirrhosis group, on the other hand, the most common initial symptom was abdominal pain, which may indicate a superior mesenteric vein narrow or obstruction. Some of the patients presented with obvious abdominal pain with the complication of black stools, strongly indicating a bowel infarction. The mortality remained high when diagnosis was delayed [15]. There are studies suggesting that superior mesenteric thrombosis are frequently associated with protein C and S deficiencies [2, 16]. In our study, most of the patients with thrombophilia suffered from abdominal pain as the initial symptom. Actually, among the eight thrombophilia patients, 3 developed into type IV thrombosis and 5 developed cavernoma, indicating that thrombophilia has a severe negative effect on the portal venous system. Another main etiology of PVT in the non-cirrhosis group in our study was the inflammatory state, including umbilical cord infection, pancreatitis, and peritonitis. There is a study confirming that the main risk for non-cirrhosis portal vein thrombosis is inflammatory conditions [17]. The inflammatory parameters crp and the NL ratio were significantly higher in the non-cirrhosis group. Inflammation factors trigger a coagulation cascade and are prone to develop thrombosis. Interestingly, umbilical cord infections ranked first on the etiology list in non-cirrhotic PVT, which might be a special phenomenon in China. A few decades ago in the remote rural areas of China, women gave birth at home instead of in hospitals, and umbilical cords were cut by unsterile scissors, so the umbilical cord was vulnerable to infection. On the anatomical level, the umbilical cord

is located between the umbilical branch and the left branch of the hepatic portal vein and directly communicates with the left branch of the portal vein [18]. Therefore, umbilical cord infection at birth is likely to develop into PVT in later age. Despite the umbilical cord infection, there were usually no other risk factors for the formation of PVT in these patients. Clinicians asking about the birth situations of the patients could help increase diagnostic efficacy.

Since variceal bleeding was a common and severe complication in patients with portal hypertension [19], all PVT patients should undergo a gastroscopy exam. Due to retrospective limitations, some of the information on patients' gastroscopy results were incomplete. Most of the cirrhosis patients with cirrhotic PVT were characterized with severe esophageal varices. In the non-cirrhosis patients, only 12.5% of patients had complications involving severe esophageal varices, but most of them only had the mild types. This coincided with a higher incidence of variceal bleeding in the cirrhosis group discussed above. In the cirrhosis group, cavernoma only accounted for 12.7% of the patients. Cavernoma is more common in non-cirrhosis patients. It is worth noting that we counted the number of patients with portal hypertensive biliopathy (PHB), discovering that the incidences of PHB in both groups were nearly a half percent of the enrolled population. The formation of PHB was highly correlated to extrahepatic portal vein obstruction in cirrhosis and leads to anatomic changes of the biliary tract, which can develop into symptomatic portal biliary tract disorders in the later stage with cholestasis, jaundice, biliary sludge, gallstones, cholangitis, and biliary cirrhosis [20]. The prevalence of PHB was not statistically significant between the groups, indicating that the impact of hypertension on the biliary tract between cirrhotic and non-cirrhotic patients was similar. In both groups, patients with cavernoma had higher rates of splenectomy. We hypothesize that splenectomy may accelerate the progress of developing cavernoma, providing a new perspective in therapeutic strategy. PVT is a common complication of splenectomy [21]. Previous studies showed that portal vein thrombosis development after splenectomy is correlated with reflexively high levels of platelets as pro coagulant factors and the presence of abnormal blood flow [21]. Ahmed discovered that lower levels of hemoglobin and increased portal vein diameter are associated with PVT formation, which is consistent with our results [22].

Cirrhosis patients complicated with PVT were considered a hallmark for negative prognoses. There was no recognized therapy to improve survival. The mortality rate was 13.3% in the cirrhosis group during the follow up period in our research. With the more severe PVT type, the mortality rate increased slightly. Most of the patients in the non-cirrhosis group in our study received anticoagulant therapy, and they showed a better prognosis with no deaths, which may indicate that anticoagulant therapy may have a positive effect on survival in non-cirrhotic PVT. The most common complications in cirrhotic PVT were encephalopathy and variceal bleeding, but in the non-cirrhotic group, the most common complications were variceal bleeding and intestinal necrosis or obstruction.

There are several limitations to this study. It used a retrospective design and lacked some important clinical parameters. The enrolled sample was small and data collected from a single center are not universally applicable. The subgroup analysis showed a distribution difference between the groups, but a causal relationship was not revealed. Further research based on a prospective randomized controlled trial design will be pivotal in confirming the conclusions drawn here.

This research revealed that the clinical characteristics of PVT between cirrhosis and non-cirrhosis patients were different, and the patients in the non-cirrhosis group had an optimistic prognosis. In both groups, the patients with cavernoma had higher splenectomy rates. A comprehensive understanding of the disease in both groups is necessary for improving patients' care in the clinical setting, improving diagnostic and therapeutic efficacy, as well as reducing the mortality rate. Future research can be conducted to investigate the exact mechanisms related to the discoveries above.

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Disclosure of conflict of interest

None.

Abbreviations

PVT, portal vein thrombosis; CT, computed tomography; TIPS, transjugular intrahepatic portosystemic shunts; EBL, endoscopic band ligation; WBC, white blood cells; NL ratio, neutrophil to lymphocyte ratio; ALT, glutamic pyruvic transaminase; AST, glutamic pyruvic aminotransferase; TBIL, total bilirubin; DBIL, direct bilirubin; CRP, C-reactive protein; PT, prothrombin time; APTT, activated partial thromboplastin time; JAK2, Janus activating kinase 2; CALR, calreticulin; SVT, splanchnic vein thrombosis; PHB, portal hypertensive biliopathy.

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