Research Article

Impact of Portal Vein Thrombosis on Endoscopic Variceal Band Ligation in Liver Cirrhosis

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Background. Portal vein (PV) thrombosis (PVT) is a common complication of liver cirrhosis and can refer to thrombosis within the PV that can extend to its left or right branches and in some cases to the superior mesenteric vein or the splenic vein (Chawla and Bodh, 2015). For severe PVT patients, there are possibilities of increasing PV resistance and reduction of the blood flow through PV towards liver, which exacerbate liver function damage meanwhile elevating the gastrointestinal variceal bleeding risk. Endoscopic Variceal band ligation (EVL) is often used to prevent esophageal variceal bleeding; postoperative complications such as severe gastrointestinal bleeding and bleeding-related death, fever, retrosternal pain, and esophageal stenosis may appear. There was absence of the research which evaluated the impact of PVT in liver cirrhosis on the complication of endoscopic Variceal band ligation for now. We herein aimed to compare cirrhosis patients with and without PVT of recent complications after EVL. **Method.** We established the retrospective investigation on 144 consecutive cirrhosis patients (excluding patients with hepatocellular carcinoma and who received portal vein-systemic circulation devascularization or shunt surgery, splenectomy, hepatectomy, liver transplantation, transjugular intrahepatic portal vein stent shunt (TIPS), endoscopic varices Variceal ligation, or sclerotherapy before) who have received first endoscopic esophageal varices band ligation in Gastrointestinal Endoscopy Center of the First Affiliated Hospital, College of Medicine, Zhejiang University, between January 2014 and December 2017. Portal vein Doppler ultrasonography, liver computerized tomography (CT), and angiography or liver-enhanced magnetic resonance imaging (MRI) were applied to evaluate the portal vein thrombosis of each patient before EVL. There were 18 patients confirmed with portal vein thrombosis while the other 126 patients without PVT. The primary end point for this research is the upper gastrointestinal hemorrhage and related death occurred from the date of ligation until leaving hospital, and the secondary end point is the appearance of postoperative fever and retrosternal pain. **Results.** There are no significant differences of gastrointestinal bleeding, bleeding-related death, fever, or retrosternal pain after EVL and the length of hospital stays between cirrhotic patients with or without PVT ($P = 0.34, 0.51, 0.58, 0.61, 0.88$). **Conclusion.** Liver cirrhosis with portal vein thrombosis did not increase incidence of recent complications of the endoscopic Variceal band ligation.

1. Introduction

The studies of the epidemiology of portal vein thrombosis (PVT) in cirrhosis are mainly established on liver transplant patients [1]. One study evaluated 41 indexes of the secondary PVT for liver transplant patients and finally reported that the prevalence of PVT is about 10% (2%–23%). A prospective cross section study established by 43 Italian research centers found that the prevalence of PVT for liver transplant patients is 7% [2]. According to the reports, PVT affects 0.6%–26% of

liver cirrhosis patients, while the prevalence of PVT in healthy people is ~0.7–1/100000 [3].

As we know, different factors can drive risk of thrombosis including endothelial injury, hypercoagulability, and static blood flow from the PH [4]. Routine ultrasound is the most common means of incidentally detecting PVT in cirrhosis. The majority of the thrombus of portal vein is asymptomatic and chronic, but patients with acute PVT and hepatic decompensation may suffer from pain in the abdomen and/or worsening ascites. Follow-up imaging is

generally necessary after ultrasound in order to confirm PVT diagnosis and exclude the possibility of tumor-related thrombosis, with MRI and CT being the primary imaging modalities used for this purpose.

The classification of PVT in early stage is mainly according to the anatomy position of thrombus. In 2002, a widespread application of classification standard raised by Yerdel and other scholars [5] has four different types and only defined by the anatomy position. The classification standard in the most recent guidance (from European Association for the Study of the Liver, EASL, and American Association for the Study of Liver Diseases, AASLD) has comprehensively gathered the past nomenclature (such as “acute” and “chronic”). At present, another “Anatomical-Functional Classification System” (Supplementary Table 1) has been indicated, which combined the anatomy position of thrombus, the duration of thrombosis formation, and the relationship with clinical outcomes [6]; this classification system is more capable to describe the disparity of different PVT types and provided a good standard for further clinical study.

The common treatments of PVT are anticoagulation, intravenous thrombolysis, and TIPS. However, considering the risk of gastrointestinal bleeding, the anticoagulant using is still controversial.

Endoscopic Variceal band ligation (EVL) is a frequently used treatment for the esophageal variceal bleeding, which is recommended by the Chinese guidance of the prevention and treatment of gastroesophageal variceal bleeding [7] and also 2016 Practice Guidance by AASLD as primary prevention for moderate to severe esophageal varices and secondary prevention for all severity of esophageal varices [8]. Common postoperative complications include ulcer-related bleeding after the ligation (which can cause fatal haemorrhage), fever, and retrosternal pain.

There was absence of the research which evaluated the impact of PVT in liver cirrhosis on the complication of endoscopic Variceal band ligation for now. Alessandra et al. made a retrospective research to assess the impact of PVT in the eradication effect of endoscopic ligation for esophageal varices. The results showed that the portal vein thrombosis will not elevate the incidence of gastrointestinal bleeding events of the group of PVT patients who received EVL during follow-up [9]. However, they did not evaluate the other complications of EVL. Therefore, we designed a retrospective cohort study, with detailed instruction as follows.

2. Method

2.1. Patients. We established retrospective investigation on 144 consecutive cirrhotic patients receiving endoscopic Variceal band ligation (EVL) in first time in Gastrointestinal Endoscopy Center of the First Affiliated Hospital, College of Medicine, Zhejiang University, from January 2014 to December 2017. This study was approved by the First Affiliated Hospital Ethics Committee of Zhejiang University College of Medicine.

Inclusion Criteria. First, the diagnosis of liver cirrhosis is based on the clinical history, laboratory inspection, and

imageological examination. The etiology is separated into viral, alcoholic, and other reasons. Second, endoscopic esophageal varices were diagnosed by upper gastrointestinal endoscopy; meanwhile, the severity of esophageal varices was classified according to the endoscopic behaviors. Based on the form of the varices and whether had red signs with high risk of bleeding, the severity was separated into 3 types as follows: mild (G1): the appearance of endoscopic esophageal varices is linear or slightly tortuous and no red signs; moderate (G2): the appearance of endoscopic esophageal varices is linear or slightly tortuous and red sign appears or the appearance of endoscopic esophageal varices is serpentine, tortuously uplifted; severe (G3): the appearance of endoscopic esophageal varices is serpentine, tortuously uplifted along with red signs or the appearance of endoscopic esophageal varices is bead, nodular, or tuberculiform (no matter the red signs appeared or not).

Exclusion Criteria. First, patients who combined with hepatocellular carcinoma or once had hepatocellular carcinoma and treated by surgery are excluded. Second, patients who received endoscopic Variceal band ligation or sclerotherapy, TIPS, portal vein-systemic circulation devascularization or shunt surgery, splenectomy, and liver transplantation due to esophageal variceal bleeding are excluded. Patients selection is as shown in Figure 1.

2.2. Clinical Data Collection. Age, gender, etiology of liver cirrhosis, hemoglobin (HGB, g/dL), blood platelet count (PLT, 1000/mm³), serum total bilirubin (mg/dL), prothrombin time (PT, s), serum creatinine (mg/dL), international normalized ratio (INR), D-dimer (μ g/L), serum albumin (g/dL), severity of ascites, severity of hepatic encephalopathy, and status of portal thrombosis are collected retrospectively.

The Child-Pugh-Turcotte score (Table 1) and classification of patients and grade the model for end-stage liver disease (MELD) are calculated.

For primary biliary cirrhosis (PBC) or primary sclerosing cholangitis (PSC) patients, serum total bilirubin (μ mol/L) should be modified as follows: 17–68 as 1 point, 68–170 as 2 points, and > 170 as 3 points.

Child-Pugh-Turcotte classification is as follows:

- (i) Class A : 5-6 points, low risk, the best prognosis
- (ii) Class B : 7-9 points, moderate risk
- (iii) Class C : ≥ 10 points, high risk, the worst prognosis

Computational formula of MELD score is as follows:

$R = 3.8 \ln [\text{bilirubin (mg/dl)}] + 11.2 \ln (\text{INR}) + 9.6 \ln [\text{creatinine (mg/dl)}] + 6.4$ (etiology: biliary or alcoholic = 0, others = 1). (Results in round numbers).

2.3. The Diagnosis and Evaluation Method for Portal Vein Thrombosis. Portal vein Doppler ultrasound is implemented for preliminary screening for all patients, the diagnosis is confirmed through liver-enhanced CT scan or liver CT angiography or liver-enhanced MRI, and the range of

FIGURE 1: Patients enrollment and screening.

TABLE 1: The standards of Child-Pugh-Turcotte score.

Clinical biochemical indicators	1 point	2 points	3 points
Hepatic encephalopathy (stage)	Non	1–2	3–4
Ascites	Non	Mild	Moderate or severe
Serum total bilirubin (umol/L)	< 34	34–51	> 51
Serum albumin (g/L)	> 35	28–35	< 28
Prolonged PT (s)	< 4	4–6	> 6

thrombus, portal vein occlusion degree, and whether portal vein cavernous transformation appeared are evaluated.

2.4. The Implementation and Used Equipment of Endoscopic Variceal Band Ligation (EVL). All the endoscopic esophageal varices ligation (EVL) was operated by senior gastroenterologist. Type of applied endoscopy is as follows: Gif-Q260 J, Olympus Corporation, Japan. Type of ligation device is as follows: MBL-6-F, Wilson Cook Medical, America (Six Shooter Saeed Multi-Band Ligator, Wilson Cook Medical Inc. Winston-Salem, NC).

2.5. Endpoints

- Post-EVL gastrointestinal bleeding: hematemesis, melena, or HGB reduction greater than 2 g/dL during the period after EVL until patient leaving hospital
- Bleeding-related death: death caused by massive gastrointestinal hemorrhage after the EVL, which are judged by the clinician
- Post-EVL fever: body temperature greater than 37.5°C after the EVL

- Post-EVL retrosternal pain: pain behind the sternum after the EVL

2.6. Data Collection and Analyze. Data are analyzed with SPSS 17.0 software; statistical methods such as chi-square test or one-way analysis of variance will be implemented for analyzing influence factor of interblock or intraclass. *P* value less than 0.05 will be admitted as statistical significance.

3. Results

3.1. Baseline Characteristics. 144 patients were enrolled in the study in total, 67.46% men with the mean age of 54.79 ± 11.15 years. Study population characteristics are counted statistically. There were no significant difference between cirrhotic patients with or without PVT of etiology, prophylaxis level, Child-Pugh class, Child-Pugh score, MELD score, severity of esophageal varices, hemoglobin, platelets count, creatinine, PT, INR, albumin, bilirubin, and NSBB use. The D-dimer level of the PVT group is significantly higher than that of non-PVT group ($P < 0.001$) (Table 2).

We made a further analysis of the 18 cirrhosis patients with PVT classified by the anatomical-functional classification of PVT (Table 3). All the patients' portal vein thrombus is asymptomatic chronic thrombus, including 8 (44.4%) cases of Type 1, 3 (16.7%) cases of Type 2, and 7 (38.9%) cases of Type 3. There are 5 (27.8%) cases with superior mesenteric vein thrombosis and 2 (11.1%) cases with splenic vein thrombosis. Only 1 (5.6%) case was occlusive with cavernous transformation of portal vein, while the other 17 (94.4%) cases were nonocclusive. The chi-square test shows that the site of portal vein thrombus is significantly correlated to the severity of esophageal varices ($P = 0.004$). It seems that the trunk of portal vein involved patients has more severe esophageal varices. Besides, there

TABLE 2: Patients baseline characteristics.

	Cirrhosis without PVT (N%)	Cirrhosis with PVT (N%)	P value
N	126	18	
Age (year)	54.79 ± 11.15	53.39 ± 12.61	0.63
Male gender	85 (67.46)	12 (66.67)	0.95
<i>Etiology</i>			
Viral	76 (60.32)	7 (38.89)	0.05
Alcoholic	21 (16.67)	2 (11.11)	
Other	29 (23.02)	9 (50.00)	
<i>Prophylaxis</i>			
Primary	7 (5.47)	0	0.31
Secondary	119 (92.97)	18 (100)	
<i>Child-Pugh class</i>			
A	79 (62.70)	12 (66.67)	0.74
B	47 (37.30)	6 (33.33)	
C	0	0	
Child-Pugh score	6.20 ± 1.11	6.10 ± 1.02	0.75
MELD score	9.53 ± 2.11	9.67 ± 1.91	0.80
<i>Esophageal varices</i>			
G1	0	0	0.74
G2	11 (8.73)	2 (11.11)	
G3	115 (91.27)	16 (88.89)	
NSBB use	23 (18.25)	3 (16.67)	0.87
Hemoglobin (g/dl)	9.29 ± 2.40	8.48 ± 2.42	0.19
Platelets (×1000/mm ³)	68.14 ± 38.18	66.83 ± 33.85	0.89
Creatinine (mg/dl)	0.80 ± 0.21	0.85 ± 0.19	0.33
PT (s)	13.85 ± 1.59	13.91 ± 1.67	0.90
INR	1.21 ± 0.14	1.23 ± 0.16	0.72
Albumin (g/dl)	3.66 ± 0.54	3.78 ± 0.45	0.36
Bilirubin (mg/dl)	1.15 ± 0.76	1.10 ± 0.54	0.78
D-dimer (μg/L)	1539.72 ± 1659.62	3513.61 ± 4370.17	<0.001

None of the patients with PVT are given anticoagulant therapy. PVT: portal vein thrombosis; MELD: the model for end-stage liver disease; NSBB: nonselective beta blockers; PT: prothrombin time; INR: international normalized ratio.

TABLE 3: The classification of PVT.

Site + extent	Frequency (N)	Percentage (%)
Type 1	6	33.3
Type 1+M	1	5.6
Type 1+S	1	5.6
Type 2	3	16.7
Type 3	2	11.1
Type 3+M	4	22.2
Type 3+S	1	5.6
Total	18	100.0
<i>Degree</i>		
NO	17	94.4
O	1	5.6
Total	18	100.0

All cases accord with symptomatic chronic thrombus. O: occlusive; NO: nonocclusive; S: splenic vein; M: mesenteric vein.

are no significant correlation between extension or degree of PVT and the severity of esophageal varices ($P = 0.49, 0.72$) (Table 4).

3.2. Primary End Points: Gastrointestinal Bleeding after EVL and Bleeding-Related Death. The chi-square test shows that the prevalence of gastrointestinal bleeding and bleeding-related death of the cirrhosis patients with or without PVT

has no significant difference (0/18 versus 6/126, $P = 0.34$; 0/18 versus 3/126, $P = 0.51$) (Table 5).

3.3. Secondary End Points: Post-EVL Fever and Retrosternal Pain. The chi-square test shows that the prevalence of post-EVL fever and retrosternal pain of the cirrhosis patients with or without PVT has no significant difference (1/18 versus 12/126, $P = 0.58$; 1/18 versus 4/126, $P = 0.61$). One-way analysis of variance shows that the length of hospital stays of the two groups has no significant differences (20.61 ± 6.66 versus 20.87 ± 6.82 ; $P = 0.88$) (Table 5).

4. Discussion

Endoscopic ligation is often employed for treating patients with high risk of bleeding or rebleeding from esophageal varices, and its possible complications include gastrointestinal bleeding, fever, and retrosternal pain after ligation. PVT can worsen portal vein hypertension, can result in esophageal varices aggravated, and may finally raise the risk of gastrointestinal bleeding after ligation. Past studies have assessed the impact of PVT in the eradication effect of endoscopic ligation for esophageal varices. The results showed that the portal vein thrombosis will delay the time to eradicate esophageal varices but not increase the incidence

TABLE 4: The site\extension\degree of PVT with esophageal varices.

	Esophageal varices		P value
	G2	G3	
N	2	16	0.004
<i>Site of PVT</i>			
Type 1	0	8	
Type 2	2	1	
Type 3	0	7	0.49
<i>Extension of PV system</i>			
PV alone	2	9	
M	0	5	
S	0	2	0.72
<i>Degree of PVT</i>			
NO	2	15	
O	0	1	

PV: portal vein; PVT: portal vein thrombosis; O: occlusive; NO: nonocclusive; S: splenic vein; M: mesenteric vein.

TABLE 5: Complications of EVL and the length of hospital stay.

	Cirrhosis without PVT (N%)	Cirrhosis with PVT (N%)	P value
N	126	18	0.34
Post-EVL gastrointestinal bleeding	6 (4.76)	0	
Bleeding-related death	3 (2.38)	0	0.51
Post-EVL fever	12 (9.52)	1 (5.56)	0.58
Post-EVL retrosternal pain	4 (3.17)	1 (5.56)	0.61
The length of hospital stays	20.87 ± 6.82	20.61 ± 6.66	0.88

PVT: portal vein thrombosis; EVL: endoscopic Variceal band ligation.

of recurrence of esophageal varices. The gastrointestinal bleeding events of the group of PVT patients during follow-up had not significantly increased [9]. This study aimed to evaluate the impact of cirrhosis with PVT on postoperative complications of endoscopic Variceal band ligation.

Despite the past study suggested the anticoagulant therapy in cirrhotic patients with PVT is safe [10], as all the PVT cases were clinically asymptomatic chronic thrombosis, according to the American association of liver disease recommendations [11], meanwhile, considering the risk of GI bleeding after EVL, none of the patients with PVT were given anticoagulant therapy.

The results of our study revealed no significant differences in postoperative gastrointestinal bleeding events, bleeding-related death events, fever, and retrosternal pain in cirrhotic patients with PVT compared with those without PVT. It suggests that endoscopic band ligation is still a safe treatment option for cirrhotic patients with PVT. Further analysis of the patients in the PVT group showed that the site of PVT was significantly associated with the severity of esophageal varices ($P = 0.004$), among which the degree of esophageal varices in the patients with the trunk of portal vein involvement was more serious, while the extension site and the degree of obstruction were not significantly correlated with the severity of esophageal varices. This result reveals the importance of classification of PVT, and further attention should be paid to the effect of different types of PVT on patient prognosis and endoscopic treatment in clinical practice and future studies. Considering this is a retrospective study, it has certain limitations. For one,

inclusion bias cannot be ruled out since people experienced death threatening gastrointestinal bleeding may choose TIPS or surgery as the first treatment option rather than EVL, leaving only low-risk patients in the study cohort, such as Child-Pugh class A or class B patients. Second, this study included a limited number of cirrhotic patients with PVT, which might not be enough for statistical purposes. Hence, caution is required to interpret these conclusions, and we are looking forward a further scale up prospective research which could confirm the impact of PVT on EVL. Third, considering the risk of gastrointestinal hemorrhage, none of the patients with PVT were treated with anticoagulants; thus, we could not evaluate the impact of anticoagulants on PVT and EVL. Fourth, there was absence of the data of follow-up because of the poor treatment compliance of the patients. We are forward to promote prospective cohort study and find out a best strategy for the prevention of esophageal variceal bleeding of the cirrhotic patients with PVT.

In summary, endoscopic band ligation is an effective and safe treatment for cirrhotic patients without or with PVT. The incidence of GI bleeding and bleeding-related death after EVL is relatively low and does not get impacted by the presence of PVT and so does the incidence of fever and retrosternal pain after EVL.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The author declares that there are no conflicts of interest.

Supplementary Materials

Supplementary Table 1: anatomical-functional classification of portal vein thrombosis in cirrhosis. (*Supplementary Materials*)

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