

## Original Article

# Association between D-dimer level and portal venous system thrombosis in liver cirrhosis: a retrospective observational study

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**Abstract:** Objective: This study aimed to explore the association between D-dimer levels and presence of portal venous system thrombosis (PVST) in liver cirrhosis. Methods: All consecutive patients with a diagnosis of liver cirrhosis who underwent D-dimer test were retrospectively enrolled. Normal reference range of D-dimer level was 0-0.3 µg/mL. PVST was diagnosed on the basis of contrast-enhanced computed tomography and/or magnetic resonance imaging scans. Results: Of the 66 included patients, 24 were diagnosed with PVST. Mean D-dimer level was 0.51±0.72 µg/mL (range: 0.10-3.44). Mean D-dimer level was not significantly different between PVST and non-PVST groups (0.68±0.93 µg/mL versus 0.41±0.56 µg/mL, P=0.146). Area under the receiver operating curve for D-dimer level for predicting the presence of PVT was 0.606 (95% confidence interval: 0.478-0.724, P=0.1393). The optimal cut-off value for D-dimer was 0.22 with a sensitivity of 58.3% and a specificity of 69.0%. The subgroup analyses of patients without splenectomy or those with different Child-Pugh classes demonstrated no significant difference in the D-dimer level between PVST and non-PVST groups. Conclusion: D-dimer might not be useful to identify the presence of PVST in liver cirrhosis. However, given the retrospective nature of this study, further well-designed prospective study should be necessary to confirm this finding.

**Keywords:** Portal vein thrombosis, liver cirrhosis, D-dimer, fibrinolysis, pathogenesis

## Introduction

Liver cirrhosis is a worldwide public health problem with a high morbidity and mortality [1]. Portal vein thrombosis (PVT) is a life-threatening complication of liver cirrhosis, which may aggravate the severity of liver dysfunction and risk of portal hypertension [2-5]. Except for a decreased portal vein flow as the most important local risk factor for the occurrence of PVT in liver cirrhosis [6], coagulation disorders may be considered as systemic thrombotic risk factors. However, the levels of anticoagulant proteins (i.e., antithrombin, protein C, and protein S) might not be associated with the development of PVT in liver cirrhosis [7]. Recently, some studies have explored whether or not fibrinolytic abnormalities might increase the risk of PVT in liver cirrhosis. Zhang et al. found that D-dimer level was significantly higher in cirrhotic patients with PVT than in those without PVT, but tissue type plasminogen activator and

plasminogen activator inhibitor-1 levels were not significantly different between the two groups [8]. This finding suggested an increased risk of PVT in liver cirrhosis with hyperfibrinolysis. By comparison, Rossetto et al. showed that cirrhotic patients with PVT had higher levels of thrombin activatable fibrinolysis inhibitor and plasminogen activator inhibitor-1 than those without PVT [9]. This finding suggested a positive correlation between hypofibrinolytic condition and an increased risk of PVT in liver cirrhosis.

More recently, our published meta-analysis suggested that cirrhotic patients with PVT might have higher D-dimer concentrations than those without PVT (standardized mean difference: 1.249, 95% confidence interval: 0.740-1.758, P < 0.0001) [10]. However, it should be noted that the heterogeneity among these included studies was significant. To date, the role of fibrinolytic conditions in the occurrence of PVT in liver

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cirrhosis remains unclear. Herein, we conducted a retrospective observational study to further clarify whether or not D-dimer levels could predict the presence of portal venous system thrombosis (PVST) in cirrhotic patients.

### Patients and methods

#### Study population

This study was approved by the ethics committee of the General Hospital of Shenyang Military Region. The number was K (2014) 22. The informed consent for every patient was waived due to the retrospective observational nature of this study. All cirrhotic patients who were admitted to our hospital and underwent D-dimer tests between July 2011 and June 2014 were enrolled in this study. Eligibility criteria were as follows: 1) a diagnosis of liver cirrhosis based on the clinical presentations, laboratory tests, imaging tests, and liver biopsy if necessary; 2) no malignancy, especially hepatocellular carcinoma; 3) D-dimer tests; and 4) contrast-enhanced computed tomography (CT) and/or magnetic resonance imaging (MRI) to evaluate the vessel patency within the portal venous system, including intrahepatic portal vein branches, main portal vein, superior mesenteric vein, and splenic vein [11].

#### Data collection

Clinical records from all patients with liver cirrhosis admitted during the period were retrospectively reviewed. The primary data collected were demographic data (age and sex), history of diagnosis of liver cirrhosis and prior splenectomy, clinical presentations, laboratory tests (regular blood test, liver function, and renal function), D-dimer levels, and Child-Pugh score and class. Two investigators were responsible for collecting the data (JD and YP), and one investigator was responsible for checking the data (XQ). PVST was diagnosed according to the findings from the contrast-enhanced CT and/or MRI scans. One investigator was also responsible for reading the CT and MRI scans for the presence of PVST (XQ). In the disagreement or uncertainty, these investigators would consult with two chief doctors (HL and XG).

#### D-dimer test

Fresh blood sample from peripheral veins 3 mL was collected in a sodium citrate anticoagulant

tube and was centrifuged with a speed of 3000 r/min. NycoCard D-dimer test kits were employed. Normal reference range of D-dimer level was 0-0.3  $\mu\text{g/mL}$ .

#### Statistical analysis

Continuous data were presented with mean  $\pm$  standard deviation (range) and were compared by using the independent sample t tests. Categorical data were expressed as frequency and were compared by using the Chi-square tests. Receiver operating curve (ROC) was employed to evaluate the specificity and sensitivity of D-dimer for predicting the presence of PVST. An optimal cut-off value was defined as the value of specificity plus sensitivity was maximal. Areas under ROC (AUROC) with 95% confidence interval (CI) were calculated. *P* value < 0.05 was of statistically significant. All statistical analyses were performed by using the MedCalc software.

### Results

During the enrollment period, a total of 66 cirrhotic patients without any malignancy underwent D-dimer tests and CT and/MRI scans at their admissions. Among them, 53 patients had contrast-enhanced CT scans alone, 11 patients had contrast-enhanced MRI scans alone, and 2 patients had both contrast-enhanced CT and MRI scans. Of them, 36% (24/66) were diagnosed with PVST. Location of PVST was the left portal vein branch (n=15), right portal vein branch (n=16), main portal vein (n=9), superior mesenteric vein (n=11), and splenic vein (n=6). Two patients had cavernous transformation of the portal vein.

Baseline characteristics of these included patients were shown in **Table 1**. Among them, 26, 28, and 12 patients had a Child-Pugh class A, B, and C, respectively. The etiology of liver cirrhosis was chronic hepatitis B virus (HBV) infection (n=24), hepatitis C virus (HCV) infection (n=5), HBV plus HCV (n=1), alcohol abuse (n=12), HBV infection plus alcohol abuse (n=3), 1 HCV plus alcohol abuse, autoimmune hepatitis (n=3), Wilson's disease (n=1), and unknown (n=16). Seven patients had a history of splenectomy.

#### Overall analysis

Mean D-dimer level was  $0.51 \pm 0.72$  (range: 0.10-3.44). Mean D-dimer level was not signifi-

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**Table 1.** Baseline characteristics in 66 patients

Variables	Values
Age (years)	53.88±12.91 (22-83)
Sex (Male/Female)-n	43/23
History of liver cirrhosis (years)	3.18±5.60 (0-30)
Prior splenectomy-n	7
Hepatic encephalopathy-n	2
Splenomegaly-n	55
Ascites-n	39
Upper gastrointestinal bleeding-n	29
Hemoglobin (g/L)	96.21±31.84 (1.6-164.0)
White blood cell (10 <sup>9</sup> /L)	5.16±4.34 (1.2-24.6)
Platelets count (10 <sup>9</sup> /L)	96.71±74.49 (12-341)
Total bilirubin (µmol/L)	35.61±54.30 (7.4-371.6)
Albumin (g/L)	33.42±6.90 (17.8-50.4)
Alanine aminotransferase (U/L)	46.88±54.66 (8-429)
Aspartate aminotransferase (U/L)	71.03±111.37 (14-889)
Alkaline phosphate (U/L)	114.22±85.56 (11-531)
Creatinine (µmol/L)	59.84±20.91 (28.6-164.0)
Prothrombin time (seconds)	17.02±6.73 (11.5-62.8)
International normalized ratio	1.43±0.91 (0.83-7.96)
D-dimer levels	0.51±0.72 (0.10-3.44)
Child-Pugh score	7.3±2.09 (5-15)

cantly different between PVST and non-PVST groups (0.68±0.93 versus 0.41±0.56,  $P=0.146$ ). In addition, 32% (21/66) of patients had an elevated D-dimer level. The prevalence of an elevated D-dimer level was not significantly different between PVST and non-PVST groups (37.5% [9/24] versus 28.6% [12/42],  $P=0.225$ ).

In the ROC analysis, AUROC for D-dimer level for predicting the presence of PVST was 0.606 (95% CI: 0.478-0.724,  $P=0.1393$ ). The optimal cut-off value for D-dimer was 0.22 with a sensitivity of 58.3% and a specificity of 69.0% (**Figure 1**).

### *Subgroup analysis in patients without splenectomy*

Mean D-dimer level was 0.4703±0.6815 (range: 0.10-3.44). In addition, 30.5% (18/59) of patients had an elevated D-dimer level.

In the ROC analysis, AUROC for D-dimer level for predicting the presence of PVST was 0.564 (95% CI: 0.429-0.693,  $P=0.4267$ ). The optimal cut-off value for D-dimer was 0.22 with a sensitivity of 55.6% and a specificity of 68.3% (**Figure 2**).

### *Subgroup analysis in patients with Child-Pugh class A*

Mean D-dimer level was 0.1865±0.1723 (range: 0.10-0.90). In addition, 7.7% (2/26) of patients had an elevated D-dimer level.

In the ROC analysis, AUROC for D-dimer level for predicting the presence of PVST was 0.61 (95% CI: 0.400-0.793,  $P=0.4483$ ). The optimal cut-off value for D-dimer was 0.1 with a sensitivity of 60.0% and a specificity of 61.9% (**Figure 3**).

### *Subgroup analysis in patients with Child-Pugh class B*

Mean D-dimer level was 0.7483±0.9370 (range: 0.10-3.44). In addition, 46.4% (13/28) of patients had an elevated D-dimer level.

In the ROC analysis, AUROC for D-dimer level for predicting the presence of PVST was 0.562 (95% CI: 0.367-0.745,  $P=0.5744$ ). The optimal cut-off value for D-dimer was 2.16 with a sensitivity of 23.1% and a specificity of 100% (**Figure 4**).

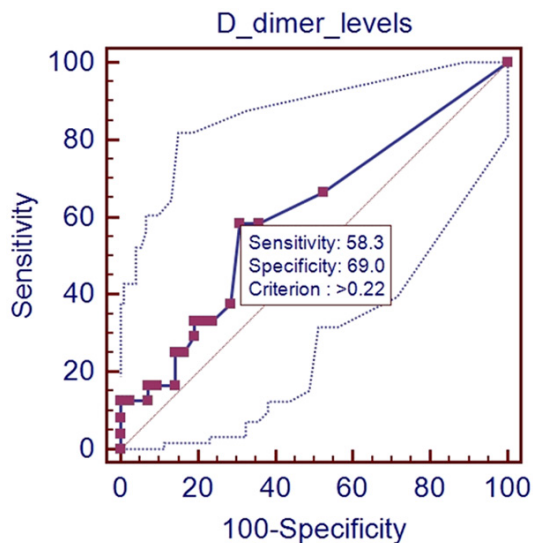
### *Subgroup analysis in patients with Child-Pugh class C*

Mean D-dimer level was 0.7583±0.6868 (range: 0.10-1.90). In addition, 58.3% (7/12) of patients had an elevated D-dimer level.

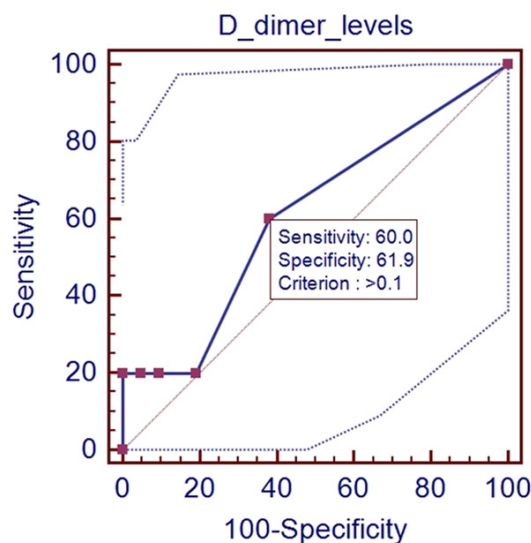
In the ROC analysis, AUROC for D-dimer level for predicting the presence of PVST was 0.750 (95% CI: 0.428-0.945,  $P=0.1368$ ). The optimal cut-off value for D-dimer was 0.9 with a sensitivity of 100% and a specificity of 66.7% (**Figure 5**).

## Discussion

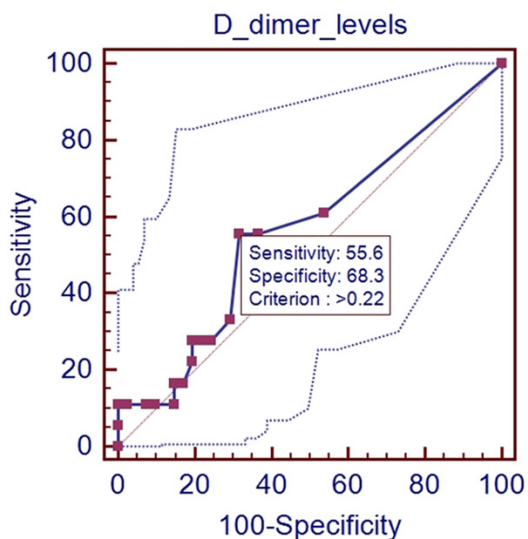
D-dimer test has been widely employed to establish a diagnosis of venous thromboembolism (i.e., deep vein thrombosis and pulmonary embolism), to predict the occurrence and recurrence of venous thromboembolism, and to guide the duration of anticoagulants in patients with venous thromboembolism [12-16]. It appears to be rational that D-dimer levels may be associated with the development of PVST in



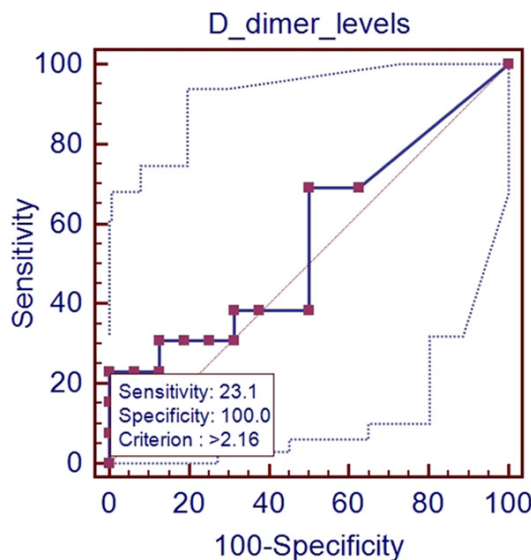
**Figure 1.** ROC analysis of D-dimer level for predicting the presence of PVST in all patients.



**Figure 3.** ROC analysis of D-dimer level for predicting the presence of PVST in patients with Child-Pugh class A.



**Figure 2.** ROC analysis of D-dimer level for predicting the presence of PVST in patients without splenectomy.



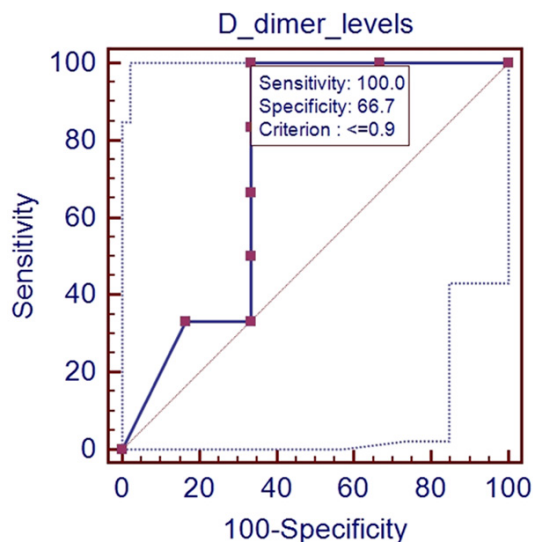
**Figure 4.** ROC analysis of D-dimer level for predicting the presence of PVST in patients with Child-Pugh class B.

liver cirrhosis. Our study did not find any significant difference in the D-dimer levels between cirrhotic patients with and without PVST. Considering that splenectomy might increase the risk of PVST [17], a subgroup analysis was performed in patients without splenectomy. In addition, three subgroup analyses were performed in patients with Child-Pugh class A, B, and C, because the degree of liver dysfunction influences the development of PVST in liver cirrhosis. However, these subgroup results were

the same to the overall result. These findings suggested that abnormal D-dimer levels might not be associated with the presence of PVST in liver cirrhosis.

A similar study by Zhang et al. also explored the association between D-dimer level and PVT in liver cirrhosis [8]. In contrast to our study, they found that D-dimer was significantly higher in PVT group than in non-PVT group, and that the





**Figure 5.** ROC analysis of D-dimer level for predicting the presence of PVST in patients with Child-Pugh class C.

significant difference remained regardless of Child-Pugh classes. Notably, compared with our study, the patients included in their studies had worse liver function (Child-Pugh class A, n=21; class B, n=49; class C, n=46) and higher D-dimer levels. But the information might not be adequate to explain the reasons why the conclusions were different between the two studies. Repeated studies were needed to further confirm their relationship in a larger number of patients.

About one third of our patients had a D-dimer level of beyond the upper limit of normal reference range. In agreement with previous studies, D-dimer levels might reflect the severity of liver cirrhosis. Compared with healthy individuals, the patients with liver diseases had significantly elevated D-dimer levels [18]. An increased degree of D-dimer level was influenced by the progression of liver disease and status of cirrhosis (cirrhosis or not, compensated or decompensated cirrhosis, Child-Pugh class, and liver failure or not) [18]. Studies also suggest that D-dimer levels at baseline should be associated with the presence of ascites, esophageal variceal bleeding, and hepatocellular carcinoma in cirrhotic patients [19, 20]. Additionally, an elevated D-dimer plasma level can predict an increased risk of gastrointestinal hemorrhage and a worse outcome of esophageal variceal bleeding during follow-up in cirrhotic patients [21, 22].

The major strength of our study should be the strict eligibility criteria. All included patients had contrast-enhanced CT and/or MRI scans. The imaging data were re-checked to identify the presence of PVST. However, a major limitation should be emphasized that all patients were retrospectively enrolled in this study. Thus, the potential bias of patient selection should be acknowledged. Although our study had a large number of patients who underwent D-dimer tests, only a small proportion of them (12%, 66/554) had adequate imaging data for evaluating the portal vein patency or occlusion.

In conclusion, our study demonstrated that D-dimer levels might not predict the presence of PVST in liver cirrhosis. The contribution of fibrinolytic conditions to the development of PVST in liver cirrhosis should be further analyzed.

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#### Disclosure of conflict of interest

None.

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