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Hemorheological Alteration in Patients with Cirrhosis Clinically Diagnosed with Portal Vein System Thrombosis After Splenectomy

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Background: Portal vein system thrombosis (PVST) is a common and serious complication after splenectomy. Key factors, including wider diameters of the portal vein, decreased liver function, and high flow volume of portosystemic collateral vessel, are recognized PVST risks. Relationships between PVST and altered hemorheology, including increased plasma viscosity, remain unclear. We investigated hemorheological alterations and explored risk factors of PVST in patients with cirrhosis after splenectomy.





Material/Methods: Data on patients with cirrhosis who underwent splenectomy were collected retrospectively from January 2018 to June 2020. Color Doppler ultrasonography was performed after splenectomy. Hemorheological indexes were compared between groups. Receiver operating characteristic (ROC) analysis was conducted to analyze risk factor cutoff values. Univariate and multivariate analyses were conducted to explore risk factors of PVST.

Results: A total of 50 patients were divided into a PVST group (n=30) and control group (n=20). Hemorheological indexes of activated partial thromboplastin time, fibrinogen degradation products (FDP), D-dimer, middle shear rates 50 and 30, low shear rates 5 and 1, and hematocrit in the PVST group were significantly higher than those of the control group ($P<0.05$). FDP and low shear rate 1 were found to be risk factors of PVST after splenectomy by multivariate analysis. ROC analysis showed that the cutoff points for FDP and low shear rate 1 were ≥ 38.6 ug/mL and ≥ 16.855 mPa.s, respectively.

Conclusions: PVST after splenectomy is closely related to hemorheological alteration. FDP and low shear rate 1 may be valuable markers of PVST.

Keywords: Hemorheology • Liver Cirrhosis • Portal System

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Background

As an important organ in hemorheology, the liver synthesizes many crucial components of the body, including plasma proteins, lipids, and coagulation factors. The liver also controls the cell composition of the blood, having an important and decisive role in the changes of hemorheology. Liver function in patients with chronic liver disease is impaired to varying degrees, especially in cirrhosis, which leads to hemorheological alteration [1]. Portal vein system thrombosis (PVST) is a common and serious complication with different causes, including decreased antithrombin III activity, large splenic vein diameter, wider diameters of the portal vein, splenic sequela of babesiosis, and hemorheological abnormalities [2,3]. Although previous studies have comprehensively explored the risk factors of PVST [4-7], the effects of hemorheological alterations on thrombosis, including plasma viscosity, shear rate, erythrocyte deformation index, and erythrocyte rigidity index, have not been reported.

In liver cirrhosis, the chemical and physical properties of blood is changed, including changes in the deformation of erythrocytes and plasma protein abnormalities, which together lead to hemorheological abnormalities. With the progression of liver disease, the abnormality of blood composition becomes more serious.

Blood viscosity refers to the resistance formed by the friction between 2 adjacent parallel fluid layers when the blood flows. It is affected by hematocrit, deformation and aggregation of erythrocytes, plasma viscosity, and plasma proteins, including fibrinogen, globulins, and albumin. Furthermore, patients with cirrhosis have lower plasma viscosity owing to the lower concentration of fibrinogen, albumin, and other larger proteins in the body, which show less viscosity resistance [8]. In contrast, splenectomy can increase the viscosity of whole blood, increase platelets, and reduce the deformation of erythrocytes, thus affecting the changes in blood rheology [9,10].

PVST is a common and serious complication after splenectomy, which can aggravate portal hypertension, jaundice, hepatic encephalopathy, liver failure, and other serious complications. However, PVST forms easily in patients with cirrhosis and hypersplenism after splenectomy, which can be related to the increased plasma viscosity, recovery of coagulation function, and sharply elevated platelets [11]. Therefore, the prevention of PVST after splenectomy is important.

Currently, a few key factors, including wider diameters of the portal vein, worse liver function, and high flow volume of portosystemic collateral vessel, have been recognized as risk factors of PVST [12-15]. Although the risk factors of PVST have been studied, some novel factors regarding hemorheological

alterations have not. Hemorheological disorders are often secondary in patients who have concomitant cirrhosis and hypersplenism after splenectomy [16]. Furthermore, there are presently few studies on the relationship between hemorheology and PVST in patients with cirrhosis after splenectomy.

PVST is recognized as a serious and life-threatening complication after splenectomy [17,18]; however, the relationship between risk factors of PVST and hemorheology remains unclear [19,20]. Because of the severity of PVST and its associated risks, predicting the occurrence of PVST by monitoring the changes of hemorheology values is important [21]. Therefore, an optimal critical value of hemorheological changes that can be used as an important indicator of PVST should be determined. The present study aimed to explore the value of hemorheology in the portal vein thrombosis of patients with cirrhosis after splenectomy by comparing the hemorheological indexes between patients with PVST and patients without PVST. Further, we aimed to determine comprehensive hemorheological indicators to explore risk factors of PVST after splenectomy.

Material and Methods

At the Anhui Chinese Medical Research Institute of Surgery, the records of 63 consecutive patients with cirrhosis with hypersplenism who met the inclusion criteria from January 2018 to June 2020 were reviewed retrospectively (Figure 1).

The inclusion criteria were clinically diagnosed cirrhosis and portal hypertension with hypersplenism related to hepatitis B or hepatolenticular degeneration [22-24]. The exclusion criteria were (1) liver cirrhosis without severe hypersplenism; (2) previous partial splenic artery embolization or transjugular intrahepatic portosystemic stent shunting; (3) portal vein system or hepatic artery variation; (4) early postoperative transfer; and (5) no strict follow-up record. Hypersplenism was defined as a leukocyte count $<3500/\mu\text{L}$ and a platelet count $<7.5 \times 10^4/\mu\text{L}$ [25]. No surgical procedures were conducted as emergency operations. Of the 63 patients who met the inclusion criteria, 13 were excluded: 9 had previous partial splenic artery embolization, 3 had previous transjugular intrahepatic portosystemic stent shunting, and 1 had hepatic artery variations. Finally, 50 patients who meet the inclusion criteria were enrolled in the study.

Patients with PVST after splenectomy were divided into a PVST group and a control group. Records of all included patients who had cirrhosis with hypersplenism and splenomegaly were carefully analyzed. Collected data included age, sex, Child-Pugh grade of liver function, and surgical outcomes. Patients with Child-Pugh grade C received liver-protective treatment, regulation of blood coagulation, and nutrition until they were above

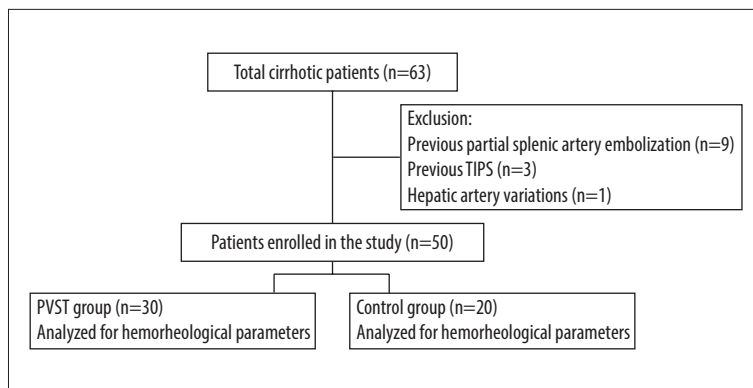


Figure 1. Classification and flow diagram of patients with cirrhosis. PVST – portal vein system thrombosis; TIPS – transjugular intrahepatic portosystemic stent shunting.

Child-Pugh grade B. Human albumin and vitamin K1 were usually used for improving the condition of patients. PVST referred to the thrombosis of the splenic vein, main portal vein, superior mesenteric vein, or portal vein branches in the liver [26]. The type of PVST could be divided by the location of the thrombosis. Postoperative monitoring by color Doppler ultrasound for PVST was performed routinely 7 days after surgery in all patients.

Before the surgical procedures, informed consent was provided by all patients or their relatives, and the investigation was conducted in accordance with the principles of the Declaration of Helsinki (as revised in Fortaleza, Brazil, October 2013). This study was approved by the Ethics Committee of the Anhui Provincial Traditional Chinese Hospital (approval no. 2019AH-32).

Surgery

All included patients received endotracheal intubation and intravenous anesthesia for traditional splenectomy. Surgery was performed with patients in the supine position, and a paramedian incision was made on the left upper abdomen. The splenic artery was fully exposed for ligation and autologous splenic blood was transfused. With splenic vessels ligated by bundling, the spleen was removed and a latex drainage tube was placed in the splenic fossa for drainage effusion. The drainage tube was used to monitor postoperative bleeding and pancreatic leakage. The drainage tube was removed when there was only a small amount drainage fluid and the amylase level of the drainage fluid was normal. Five staff surgeons performed all of the operations. Postoperative complications, including bleeding, abdominal infection, abdominal collection, PVST, and hepatic failure, were routinely monitored for 2 weeks.

Color Doppler Ultrasound Detection

Color Doppler ultrasound detection was performed by a single experienced examiner with a color Doppler ultrasound system (ACUSON S2000, Siemens, USA) and a broadband convex

array probe (3-5 MHz). In general, all patients received routine ultrasound examination at admission and every 7 days after surgery to monitor for the occurrence of PVST.

Laboratory Tests

Preoperative laboratory examinations were done on admission. Coagulation and hemorheological parameters were collected on postoperative day 2. Coagulation function was detected by a hemagglutination analyzer, and the indexes of blood rheology were detected by an automatic hemorheology analyzer.

Statistical Analysis

A receiver operating characteristic (ROC) curve was analyzed to determine the optimal cutoff values of each hemorheological indicator. The association between the hemorheological indicators and influencing factors of PVST was assessed using univariate analyses, and those variables showing statistical significance ($P < 0.05$) were evaluated by multivariate logistic analyses to discover the main independent risk factors of PVST. Statistical analysis was done using the Statistical Package for the Social Sciences (SPSS, Version 13.0, Chicago, IL, USA). Continuous variables were reported as mean \pm standard deviation or ranges. Comparison between groups was carried out using the t test for measurement data and the χ^2 test with or without Fisher's exact test for categorical variables. Statistical significance was accepted at the 5% level by a 2-tailed test.

Results

A total of 50 patients with cirrhosis who underwent splenectomy, including 30 patients with PVST and 20 without PVST, were enrolled in this study (28 men, 22 women; mean age 31.7 ± 14.0 years). All postoperative pathology examinations showed chronic congestive splenomegaly. There was no significant difference in age or sex between the 2 groups. All clinical data is summarized in **Table 1**.

Table 1. Clinical characteristics of included patients, n (%).

Variable	PVST group (n=30)	Control group (n=20)
Sex		
Male	16 (53.3)	12 (60.0)
Female	14 (46.7)	8 (40.0)
Age (years, mean±SD)	30.5±13.5	32.9±14.8
Degree of splenomegaly		
Slight	12 (40.0)	9 (45.0)
Moderate	11 (36.7)	8 (40.0)
Severe	7 (23.3)	3 (15.0)
Child-Pugh grade		
Child A	15 (41.7)	10 (50.0)
Child B	13 (53.3)	9 (18.0)
Child C	2 (5.0)	1 (5.0)
Location of thrombus		
MPV/PB	13 (43.3)	NA
SV	4 (13.3)	NA
MPV/PB+SMV	2 (6.7)	NA
MPV/PB+SV	5 (16.7)	NA
MPV/PB+SMV+SV	6 (20.0)	NA
Operation time (min)	255.5±83.5	223.5±75.3
Blood loss (ml)	293.5±180.5	275.8±175.6
Complication		
Bleeding	1 (3.3)	1 (5.0)
Ascites	4 (13.3)	1 (5.0)
Encephalopathy	0	1 (5.0)
PVST	30 (100.0)	0
Incisional infection	1 (3.3)	1 (5.0)

PVST – portal vein system thrombosis; MPV/PB – main portal vein/portal branch; SMV – superior mesenteric vein; SV – splenic vein; NA – not applicable.

Outcomes and Complications

Splenectomy was performed successfully in all included patients. No patient died after surgery. Two patients had abdominal hemorrhage after surgery and received blood transfusions. Five patients who had ascites received diuretic therapy, and 2 patients developed incisional infections. A total of 30 patients had PVST 7 days after surgery and received heparin therapy. According to the location of the thrombus, the PVST group was divided into the following 5 subgroups: (1) main portal vein/portal vein branch (n=13); (2) splenic vein (n=4); (3) main portal vein/portal vein branch+superior mesenteric vein (n=2); (4) main portal vein/portal vein branch+splenic vein (n=5); and (5) main portal vein/portal vein branch+superior mesenteric vein+splenic vein (n=6). All patients fully recovered

after medical treatment. Patient outcomes and complications are listed in **Table 1**.

Hemorheology Indexes

The coagulation and hemorheological indexes between the 2 groups on the second day after surgery are compared in **Table 2**. In comparison with the control group, the PVST group revealed significant differences in activated partial thromboplastin time, fibrinogen degradation products (FDP), D-dimer, middle shear rate 50, middle shear rate 30, low shear rate 5, low shear rate 1, and hematocrit level ($P<0.05$).

Table 2. Comparison of coagulation function and hemorheology between the portal vein system thrombosis (PVST) group and control group (n=50, mean±standard deviation).

Variable	PVST group (n=30)	Control group (n=20)	P value
PT (s)	15.83±4.21	14.67±3.04	0.29
APTT (s)	44.70±13.76	37.58±5.97	0.04
FBG (g/L)	2.61±1.18	2.61±0.95	0.98
FDP (ug/mL)	40.91±27.47	22.77±8.14	0.01
D-dimer (mg/L)	12.87±7.13	9.13±3.65	0.04
High shear rate 200 (mPa.s)	3.48±0.45	3.24±0.34	0.05
Middle shear rate 50 (mPa.s)	4.14±0.53	3.85±0.43	0.05
Middle shear rate 30 (mPa.s)	4.55±0.59	4.23±0.48	0.05
Low shear rate 5 (mPa.s)	7.66±1.04	7.07±0.94	0.05
Low shear rate 1 (mPa.s)	16.75±2.48	15.31±2.30	0.04
Plasma viscosity (mPa.s)	1.58±0.12	1.54±0.10	0.19
ESR (mm/L)	11.17±12.01	17.55±11.61	0.07
Hematocrit (L/L)	0.41±0.05	0.38±0.04	0.04
Erythrocyte deformation index	0.66±0.06	0.68±0.06	0.20
Erythrocyte rigidity index	2.94±0.42	2.98±0.46	0.75

PVST – portal vein system thrombosis; PT – prothrombin time; APTT – activated partial thromboplastin time; FBG – fibrinogen; FDP – fibrinogen degradation products; ESR – erythrocyte sedimentation rate.

Table 3. Receiver operating characteristic curve analysis for identifying the optimal cutoff values of influencing factors of portal vein system thrombosis after splenectomy.

Variable	AUROC	P value	95% CI	Cutoff value	Sensitivity	1-Specificity
PT (s)	0.553	0.53	0.390-0.715			
APTT (s)	0.648	0.08	0.495-0.800			
FBG (g/L)	0.493	0.93	0.331-0.654			
FDP (ug/mL)	0.695	0.02	0.546-0.844	38.6	0.5	0.05
D-dimer (mg/L)	0.659	0.06	0.510-0.809			
High shear rate 200 (mPa.s)	0.662	0.06	0.508-0.815			
Middle shear rate 50 (mPa.s)	0.667	0.05	0.513-0.822	3.75	0.8	0.5
Middle shear rate 30 (mPa.s)	0.67	0.04	0.516-0.824	4.165	0.767	0.4
Low shear rate 5 (mPa.s)	0.671	0.04	0.515-0.826	6.705	0.8	0.45
Low shear rate 1 (mPa.s)	0.677	0.04	0.522-0.833	16.855	0.567	0.2
Plasma viscosity (mPa.s)	0.601	0.23	0.439-0.763			
ESR (mm/L)	0.302	0.02	0.150-0.454	9	0.75	0.3
Hematocrit (L/L)	0.646	0.08	0.492-0.800			
Erythrocyte deformation index	0.428	0.39	0.262-0.593			
Erythrocyte rigidity index	0.469	0.71	0.303-0.636			

CI – confidence interval; PVST – portal vein system thrombosis; ROC – receiver operating characteristic; AUROC – area under the ROC curve; PT – prothrombin time; APTT – activated partial thromboplastin time; FBG – fibrinogen; FDP – fibrinogen degradation products; ESR – erythrocyte sedimentation rate

Table 4. Univariate and multivariate analysis of risk factors of portal vein system thrombosis observed by logistic regression.

Variable	Total (n=50)	PVST (n=30)	χ^2	P	B	SE	Wals	P	Exp(B)	95% CI
FDP (ug/mL)										
≥38.6	16	15	11.17	P<0.01	0.084	0.03	6.31	0.01	1.088	1.019-1.162
<38.6	34	15								
Middle shear rate 50 (mPa.s)										
≥3.75	34	24	4.96	P<0.05	262.88	142	3.44	0.06	1.47E+114	0.000-6.782E234
<3.75	16	6								
Middle shear rate 30 (mPa.s)										
≥4.165	31	23	6.85	P<0.01	-258.16	142	3.32	0.07	0	0.000-2.897E8
<4.165	19	7								
Low shear rate 5 (mPa.s)										
≥6.705	33	24	6.55	P<0.05	-5.67	5.26	1.16	0.28	0.003	0.000-103.733
<6.705	17	6								
Low shear rate 1 (mPa.s)										
≥16.855	22	17	4.88	P<0.05	8.09	3.93	4.23	0.04	3252	1.461-7239699.185
<16.855	28	13								
ESR (mm/L)										
≥9	24	9	9.74	P<0.01	0.03	0.04	0.59	0.44	1.031	0.953-1.115
<9	26	21								

PVST – portal vein system thrombosis; FDP – fibrinogen degradation products; ESR – erythrocyte sedimentation rate.

Risk Factors of PVST

FDP >38.6 ug/mL, middle shear rate 50 >3.75 mPa.s, middle shear rate 30 >4.165 mPa.s, low shear rate 5 >6.705 mPa.s, low shear rate 1 >16.855 mPa.s, and erythrocyte sedimentation rate (ESR) >9.0 mm/L were determined as the optimal cut-off values by ROC curve analysis. The comparison of sensitivity and 1-specificity are shown in **Table 3**.

When the coagulation and hemorheological indexes were assessed by univariate analysis to determine their relationship to PVST, statistical significance was detected for FDP, middle shear rate 50, middle shear rate 30, low shear rate 5, low shear rate 1, and ESR (P<0.05). The FDP and low shear rate 1 were determined as independent risk factors of PVST by multivariate logistic analysis. The comparison of univariate and multivariate logistic analysis of risk factors of PVST in patients is shown in **Table 4**.

Discussion

In the continuous progression of cirrhosis, splenomegaly and hypersplenism can occur, which can cause hemorheological alterations. Splenectomy can effectively control the symptoms of hypersplenism; however, the blood rheology of patients after splenectomy is characterized by increased blood viscosity and a hypercoagulable state [27,28]. Furthermore, complications such as mesentery and portal vein thrombosis can easily occur with a rebounded platelet count, seriously affecting patient prognosis. Hemorheological alterations are mainly related to the changes of blood fluidity and blood viscosity. Splenomegaly can reduce the blood viscosity of patients and increase blood viscosity after splenectomy [29]. At the same time, the intima of blood vessels is damaged and platelet adhesion and aggregation occur, thereby allowing portal vein or mesentery thrombosis to easily form [30]. The process of thrombosis is closely related to changes in blood rheology; therefore, the relationship

between splenectomy and hemorheological alterations should be given increased attention. Although some risk factors of PVST, including a large main portal vein diameter, large splenic vein diameter, low white blood cell count, and decreased antithrombin III activity, have been reported in the literature, the hemorheological factors are rarely involved. The present study mainly focused on hemorheological alterations regarding PVST, including plasma viscosity, shear rate, FDP, erythrocyte deformation index, and erythrocyte rigidity index, which had not been reported before. At present, there is little research on the relationship between thrombosis and hemorheological alterations after splenectomy. Therefore, the study of changes of blood rheology in patients with cirrhosis and hypersplenism during the perioperative period of splenectomy can provide an important theoretical basis of the prevention of thrombosis in patients with liver cirrhosis. Therefore, we performed a comprehensive study of hemorheological alterations in patients with cirrhosis and investigated the associations between risk factors of PVST after splenectomy and hemorheological indicators to better prevent the occurrence of PVST.

Patients with cirrhosis have lower plasma viscosity than do people without cirrhosis due to the lower concentration of fibrinogen, albumin, and other larger proteins in the body, which show less viscosity resistance [31]. However, the elevated plasma viscosity in patients with cirrhosis after splenectomy can be related to the increase in fibrinogen, which is increased from the inflammatory reaction and other elevated macromolecular proteins. Splenectomy alone will lead to an obvious inflammatory reaction in the body, thereby increasing the fibrinogen and the plasma viscosity of the body after splenectomy [32]. Blood viscosity refers to the resistance formed by the friction between 2 adjacent parallel fluid layers when the blood flows. It is a physical property of blood and represents the inherent resistance of blood against the flow within blood vessels [31]. Blood viscosity is influenced by factors such as hematocrit, fibrinogen, albumin, deformation and aggregation of erythrocytes, and plasma viscosity. Patients with cirrhosis have adapted to the low plasma viscosity over an extended time; therefore, the sudden increase in plasma viscosity after splenectomy, together with elevated platelets, can easily lead to a coagulation function disorder and PVST.

It is well known that the liver synthesizes many crucial components of the body, including plasma proteins, lipids, and coagulation factors, and meanwhile controls the cell composition of the blood. All of these processes are crucial influencing factors of hemorheology; therefore, the liver has a critical role in hemorheology [33-35]. Studies on hemorheology mainly involve the changes of blood fluidity, coagulation, and viscosity [36,37]. In the present study, we found that elevated blood viscosity easily formed PVST after splenectomy and affected the prognosis of patients at the same time. Therefore, the process

of PVST is closely related to hemorheological alteration. After splenectomy, PVST is prone to occur in patients with cirrhosis with splenomegaly, which may be related to the increase in blood viscosity and changes of erythrocyte membrane structure. At present, there are few clinical studies focused on the relationship between PVST and hemorheological alteration after splenectomy in patients with cirrhosis.

FDP and low shear rate 1 were recognized as independent risk factors for PVST after splenectomy in our study ($P<0.05$). The independent risk factors of PVST can be illustrated by the Virchow theory for hypercoagulability after splenectomy [38]. In our study, FDP >38.6 $\mu\text{g/mL}$, middle shear rate 50 >3.75 $\text{mPa}\cdot\text{s}$, middle shear rate 30 >4.165 $\text{mPa}\cdot\text{s}$, low shear rate 5 >6.705 $\text{mPa}\cdot\text{s}$, low shear rate 1 >16.855 $\text{mPa}\cdot\text{s}$, and ESR <9.0 mm/L were determined to be the optimal cutoff values by ROC curve analysis. The incidence of PVST, which was measured in patients with high FDP, elevated shear rate, and low ESR, indicated that these indicators could be used as markers of PVST prediction in patients with cirrhosis after splenectomy. Early heparin therapy should be recommended in patients who have these factors after surgery [39,40].

Ordinarily, the blood viscosity of patients with cirrhosis increases after splenectomy and the platelet count temporarily increases, which leads to the formation of PVST [41,42]. The present study can aid future studies on the mechanism of PVST by comparing changes in blood rheology and D-dimer between the PVST group and control group. We discovered that middle shear rate 50, middle shear rate 30, low shear rate 5, low shear rate 1, and hematocrit were higher in the PVST group. At the same time, activated partial thromboplastin time, FDP, and D-dimer were also higher in the PVST group, and the differences were statistically significant ($P<0.05$). This suggests that the changes in coagulation function and blood viscosity are the main factors in the formation of PVST. Overall, the formation of PVST is related to the increase of platelet count, blood rheology, hypercoagulability, and intimal lesion after splenectomy. Therefore, regular observation of platelet count and hemorheological indexes, color ultrasound examination, and early application of heparin anticoagulation can effectively prevent PVST after splenectomy [43,44].

Spleen autotransplantation has been recognized as a simple and effective method to compensate for splenic function after total splenectomy. A recent study showed that spleen autotransplantation could be useful to preserve the filtration function and alter red blood cell aggregation [45]. Because the influence of spleen resection on erythrocyte aggregation parameters in animal models is controversial, our hemorheological changes after splenectomy may help to improve the hemodynamic effects of spleen autotransplantation.

There are several limitations in the present study. First, this study was a retrospective and single-center investigation, which means it had a limited number of patients and contained accidental errors and biases. Second, the number of patients with cirrhosis was limited; therefore, data bias will appear in the results. These limitations will be considered in our future prospective studies, which will be improved over the present study if we conduct a randomized controlled trial with additional centers, thereby providing more data for further research.

Conclusions

In conclusion, hypersplenism after splenectomy in patients with cirrhosis can lead to hemorheological alterations and the easy formation of PVST. FDP and low shear rate 1 were independent risk factors for PVST after splenectomy in our study.

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Conflicts of Interest

None.

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