



Dual Effects of Large Spleen Volume After Splenectomy for the Patients With Chronic Liver Disease

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Background: After splenectomy in patients with chronic liver disease, a large spleen was reported to be not only a risk factor of portal/splenic vein thrombosis (PSVT), but also a prediction for favorable improvement of liver function. This study aimed to evaluate the risk of PSVT and the improvement of liver function after splenectomy, with special attention to spleen volume (SV).

Methods: This study included 50 patients who underwent splenectomy with diagnosed chronic liver disease between January 2005 and December 2017. After evaluation of risk factors for PSVT the cut-off value of SV for predicting PSVT was determined. According to the cut-off value of SV, 50 patients were divided into 2 groups: small-volume group (SVG) and large-volume group (LVG). Postoperative liver functions were compared between the 2 groups.

Results: Twenty-eight patients developed PSVT. Larger SV was the most significant independent risk factor for PSVT. The cut-off value of SV was 520 mL. Preoperatively, LVG had significantly higher total bilirubin, and MELD (model for end-stage liver disease) score, and had significantly higher rates of pancytopenia than SVG. Postoperatively, compared to SVG, platelet count, choline esterase, and total cholesterol in LVG were significantly increased.

Conclusion: After splenectomy in the patients with chronic liver disease, large SV is an independent risk factor for PSVT, with a clear benefit in improving liver function, if PSVT is properly diagnosed and managed.

Key words: Liver function – Portal vein thrombosis – Splenectomy – Hepatitis and portal hypertension

Splenectomy for the patients with chronic liver disease has been performed in an attempt to control portal pressure and to treat thrombocytopenia due to congestive splenomegaly from portal hypertension. After splenectomy in these patients, portal/splenic vein thrombosis (PSVT) has been known to develop more often compared with those without chronic liver disease. The significant factors for the development of PSVT in patients with liver cirrhosis is not only decreased portal venous flow,¹ but also coagulation disorder.^{2–4} Previously reported risk factors of PSVT after splenectomy included large spleen,⁵ large splenic vein diameter,⁶ high ratio of portal venous velocity before and after operation,⁷ and low antithrombin-III activity.⁸ Among them, splenomegaly is considered as risk factor, because a large stump of splenic vein causes blood turbulence, which in turn leads to hypercoagulable state and enhanced thrombus formation.^{9,10} Although PSVT after splenectomy used to be a critical complication, its outcomes have been improving in recent years with the introduction of early postoperative anticoagulant therapy. If the cut-off value of spleen volume (SV) for development of PSVT can be determined, we can introduce prophylactic anticoagulant therapy. However, the cut-off value of SV for the risk factor of PSVT after splenectomy has not yet been defined.

There have been several previous studies reporting that splenectomy improves the liver function in the patients with chronic liver disease.^{11,12} Because splenectomy reduces the portal blood flow, the liver function would be expected to worsen; however, the findings of previous experimental and clinical studies have reported conflicting results. Although the mechanism of the improvement of liver function has been uncertain, predictive factors for favorable improvement of liver function after splenectomy were found to be a large SV^{11,12} and an elevated liver volume after 6 months' splenectomy compared to preoperative liver volume.¹³

Therefore, it is considered that the large spleen is not only a risk factor for PSVT but also brings the merit of improving liver function for the patients with liver dysfunction who receive splenectomy. However, there have been no reports investigating the relation between the risk of PSVT and the improvement of liver function. This study aimed to first evaluate whether the large SV was a risk factor

of PSVT after splenectomy in patients with chronic liver diseases, and then to elucidate the effect of the large SV on the postoperative liver function.

Patients and Methods

Among the 113 splenectomies who did not have Hassab surgery performed at our department of Mie University Hospital between January 2005 and December 2017, 84 (74.3%) had chronic hepatitis or liver cirrhosis, whose surgical indication was an improvement of platelet counts for the treatment of interferon.¹⁴ Of these 84 patients, 12 underwent simultaneous hepatectomy, 5 could not take an abdominal computed tomography (CT) scan with intravenous contrast medium because of renal dysfunction and/or iodine hypersensitivity, 3 started interferon therapy for hepatitis C within 3 months after splenectomy, and 14 could not be followed regularly. By excluding these 34 patients, the subjects in the present study were 50 patients (33 males and 17 females) (Fig. 1). The mean age was 57.8 ± 8.2 years. The etiologies of liver disease were hepatitis C virus (HCV) in 41, hepatitis B virus (HBV) in 3, HCV and HBV in 1, alcoholic in 4, and primary biliary cirrhosis in 1. Preoperative Child-Pugh classification¹⁵ was A in 36 patients, B in 13, and C in 1. The procedure of splenectomy was totally laparoscopic surgery in 44 patients, laparoscopic conversion to open surgery in 5, and open surgery in 1. The other operations simultaneously performed were cholecystectomy for cholelithiasis in 7 and partial gastrectomy for gastrointestinal stromal tumors in 1. The mean operation time of splenectomy, which was based on operation record

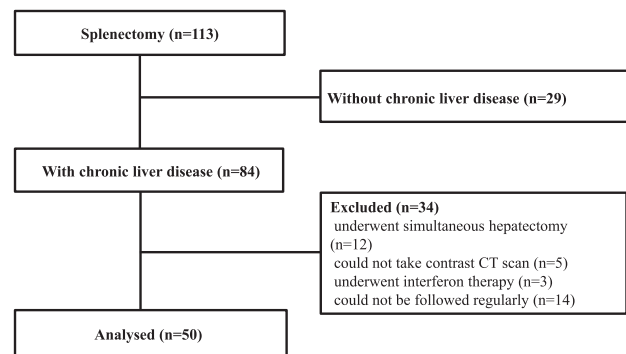


Fig. 1 Flow diagram of the study population.

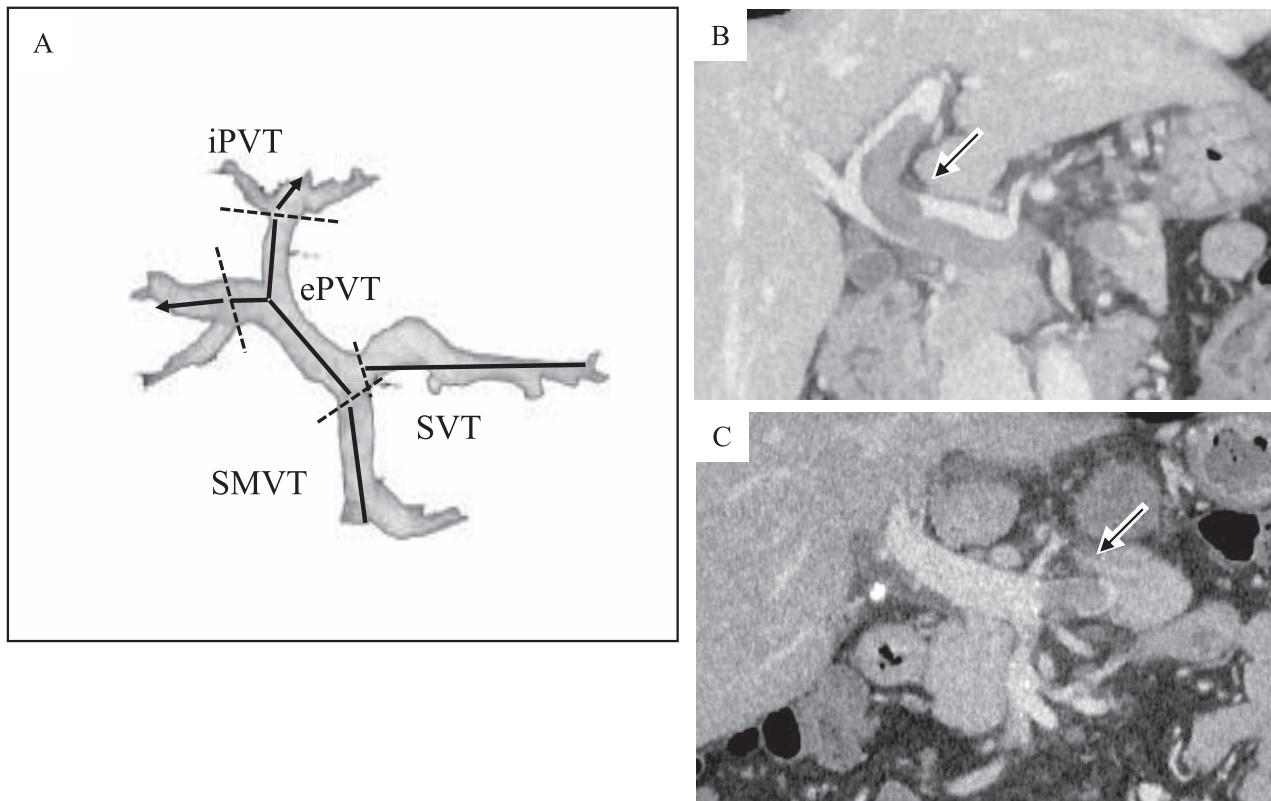


Fig. 2 Diagnosis of postoperative portal / splenic vein thrombosis (PSVT). (A) PSVT was divided according to the location of the thrombus: splenic vein thrombosis (SVT), superior mesenteric vein thrombosis (SMVT), extrahepatic portal thrombosis (ePVT) and intrahepatic portal thrombosis (iPVT). (B) Representative CT of portal vein thrombosis: iPVT+ePVT+SVT. (C) Representative CT of splenic vein thrombosis: SVT alone.

and excluded the time of the other simultaneous operation, was 161.1 ± 45.1 minutes. The mean blood loss was 645.0 ± 907.9 mL. Postoperative thromboprophylaxis was administered according to the attending surgeon's preference as follows: anticoagulant therapy such as intravenous heparin followed by oral warfarin administration in 23, antiplatelet therapy such as aspirin or ticlopidine in 12, anticoagulant and antiplatelet therapy in 5, and no treatment in 10, respectively. The mean length of hospital stay was 13.4 ± 5.8 days. Seventeen (34%) of 50 patients developed postoperative complications with Clavien-Dindo grade 2 or more (postoperative bleeding in 8, surgical site infection in 1, portal vein thrombosis in 9, number overlapped); however, there was no hospital mortality. The study protocol was approved by the Medical Ethics Committee of Mie University (authorization number: 2866), informed consent was obtained from each subject, and the study was performed in accordance with the ethical standards established in the 2013 Declaration of Helsinki.

Diagnosis of PSVT and measurement of spleen size

All 50 patients underwent pre- and post-operative multidetector CT with intravenous contrast media. The spleen and liver volume was measured by CT volumetry with contrast enhancement. All volumetric measurements were performed by a single doctor to eliminate interobserver variability. Postoperative CT was performed after splenectomy between postoperative day (POD) 3 and 24 (median POD7) to diagnose PSVT, and 3 months after splenectomy to measure liver volume. PSVT was divided according to the location of the thrombus: splenic vein thrombosis (SVT), superior mesenteric vein thrombosis (SMVT), extrahepatic portal thrombosis (ePVT), and intrahepatic portal thrombosis (iPVT) (Fig. 2a).¹⁶

Measurement of liver function

Blood samples were taken before splenectomy and 1 and 3 months after splenectomy for measurements

Table 1 Number of cases with postoperative PSVT and its location in the 50 patients with splenectomy

Location of thrombosis	Number of case (%)	Disappearance rate of PVT (%)	Disappearance rate of SVT (%)
PVT	9 (18.0)	8/8 (100)^a	7/8 (87.5)^a
iPVT	2	2/2 (100)	2/2 (100)
iPVT+ePVT	2	2/2 (100)	2/2 (100)
iPVT+ePVT+SVT	1	— ^a	— ^a
ePVT+SMVT+SVT	1	1/1 (100)	1/1 (100)
ePVT+SVT	1	1/1 (100)	1/1 (100)
SMVT+SVT	2	2/2 (100)	1/2 (50.0)
SVT alone	19 (38.0)	—	15/17 (88.2)^b
Total	28 (56.0)		

ePVT, extrahepatic portal vein thrombosis; iPVT, intrahepatic portal vein thrombosis; SMVT, superior mesenteric vein thrombosis; SVT, splenic vein thrombosis.

^aLost to long-term follow-up in 1 case.

^bLost to follow-up in 2 cases.

of complete blood cell counts and blood chemistry such as liver functional tests: aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), albumin (Alb), total bilirubin (TB), cholinesterase (Ch-E), total cholesterol (T-Cho), and prothrombin time international ratio (PT-INR). The severity of hepatic cirrhosis was graded according to Child-Pugh score and model for end-stage liver disease (MELD) score.¹⁷ The absolute change values in platelet count (Δ Plt), AST (Δ AST), ALT (Δ ALT), ALP (Δ ALP), T-Bil (Δ TB), Alb (Δ Alb), Ch-E (Δ Ch-E), T-Cho (Δ T-Cho), and liver volume (Δ liver volume) were calculated as follows: the value at 3 months after splenectomy —preoperative value.

Statistical analysis

Continuous data were expressed as mean \pm SD, unless otherwise specified. Statistical analysis was performed using the chi-square test or the Fisher's exact test for categorical data and the student's *t*-test for continuous data. The Wilcoxon signed-rank test was used to compare preoperative and postoperative data. To demonstrate the risk factors for PSVT, the pre- and intra operative factors that had *p* value less than 0.1 in the univariate analysis were selected and binary multiple logistic regression analysis was performed. A *P* value of < 0.05 was considered statistically significant. Usefulness of significant risk factors to predict the development of PSVT was estimated using the analysis of receiver operating characteristic (ROC) curves. These statistical analyses were completed using SPSS statistic version 21 software (IBM, Tokyo, Japan).

Results

Risk factor analysis of the development of PSVT

The incidence and location of PSVT are shown in Table 1. Twenty-eight of the 50 patients (56.0%) developed PSVT after splenectomy: PVT in 9 (18.0%) and SVT alone in 19 (38%). Among the 28 patients with thrombosis, 2 patients without any prophylactic treatment started receiving warfarin, and 3 patients receiving aspirin switched to warfarin after the onset of thrombosis. Other patients with thrombosis continued to receive administered anticoagulants, which was received before detecting thrombosis. After anticoagulant therapy for 2 to 8 months, disappearance rates of PVT and SVT were 100% and 88.2%, respectively.

Comparison of clinical characteristics between the patients with or without PSVT are shown in Table 2. The patients with PSVT demonstrated significantly higher age ($P = 0.01$) and higher SV ($P = 0.001$) compared to those without PSVT. Although hospital stay was significantly longer in the patients with PSVT than in those without PSVT, the incidence of the complication of Clavien-Dindo grade 2 and more except for PSVT did not differ between the 2 groups.

Multiple logistic regression analysis demonstrated that higher age (odds ratio: 1.115, 95% confidence interval: 1.020-1.219, $P = 0.017$) and larger SV (odds ratio: 1.005, 95% CI: 1.001-1.008, $P = 0.004$) were selected as the significant predictive factors for PSVT (Table 3). Of the 2 predictive factors by multiple logistic regression analysis, SV was found to have the larger areas under the ROC curve (AUC), which was 0.757, in comparison with age in

Table 2 Comparison of clinical characteristics of the patients with or without PSVT

	PSVT (-) (n = 22)	PSVT (+) (n = 28)	P value
Sex ratio (M:F)	17:5	16:12	0.13
Age (years)	54.6 ± 7.2	60.4 ± 8.1	0.01
Aetiology			0.59
HBV	1	3	
HCV	20	21	
Alch	0	4	
Others	1	0	
Albumin (g/dL)	3.46 ± 0.46	3.57 ± 0.53	0.43
Total bilirubin (mg/dL)	1.06 ± 0.64	1.38 ± 0.89	0.15
PT-INR	1.16 ± 0.13	1.21 ± 0.12	0.17
Creatinine (mg/dL)	0.76 ± 0.22	0.80 ± 0.19	0.53
Total cholesterol (mg/dL)	137.6 ± 20.9	132.4 ± 27.9	0.54
Cholinesterase (ΔPh)	0.50 ± 0.16	0.51 ± 0.18	0.73
White blood count (×10 ³ /uL)	3.22 ± 1.28	2.87 ± 1.45	0.37
Hemoglobin (g/dL)	12.1 ± 1.5	11.3 ± 1.7	0.10
Platelet count (×10 ³ /uL)	57.1 ± 23.6	45.6 ± 17.6	0.06
Child-Pugh score			0.39
A	18	18	
B	3	10	
C	1	0	
Spleen volume (mL)	472.9 ± 205.1	725.3 ± 303.7	0.001
Preoperative liver volume (mL)	1,276.7 ± 329.6	1,122.4 ± 394.9	0.14
Operation			0.99
LS	19	25	
OS	1	0	
Conv	2	3	
The other operation ^a	6 (27.3%)	2 (7.1%)	0.12
Operation time (min)	171.6 ± 48.9	152.8 ± 40.8	0.16
Blood loss (mL)	455 ± 565	794 ± 1093	0.16
Prophylactic treatment			0.99
AC	9	14	
AP	6	6	
Both	2	3	
Non	5	5	
Hospital stay (days)	10.2 ± 3.6	15.9 ± 6.1	0.001
Other complications ^b	4 (18.8%)	6 (21.4%)	0.94

AC, anticoagulant therapy; AP : antiplatelet therapy; Conv, laparoscopic conversion to open surgery; LS, laparoscopic splenectomy; OS, open splenectomy; PT-INR, prothrombin time international ratio.

^aThe other operation simultaneously performed: cholecystectomy in 7; partial gastrectomy in 1.

^bClavien-Dindo grade II and more except for PSVT (postoperative bleeding in 8, surgical site infection in 1, disseminated intravascular coagulation in 1).

which AUC was 0.709 (Fig. 3). The optimal cut-off value of spleen volume was determined by ROC curve analysis as 520 mL, showing sensitivity of 71.4% and specificity of 72.7%.

Hepatic functional change after splenectomy according to spleen volume

Because SV was determined as the most useful predictor of PSVT, we further divided the 50 patients into the 2 groups according to SV: small volume group (SVG: SV less than 520 mL, n = 24) and large volume group (LVG: SV 520 mL or more, n = 26).

Comparison of pre-, intra-, and post-operative clinical features between SVG and LVG is shown in Table 4. In the preoperative features, TB, and MELD score were significantly higher in LVG than in SVG. White blood cell count, hemoglobin concentration, and platelet count were significantly lower in LVG

Table 3 Multivariate analysis of the risk factor for postoperative PSVT

	Odds ratio	95% confidence interval	P value*
High age	1.115	1.020–1.219	0.017
Large spleen volume	1.005	1.001–1.008	0.004

*Significant at $P < 0.05$.

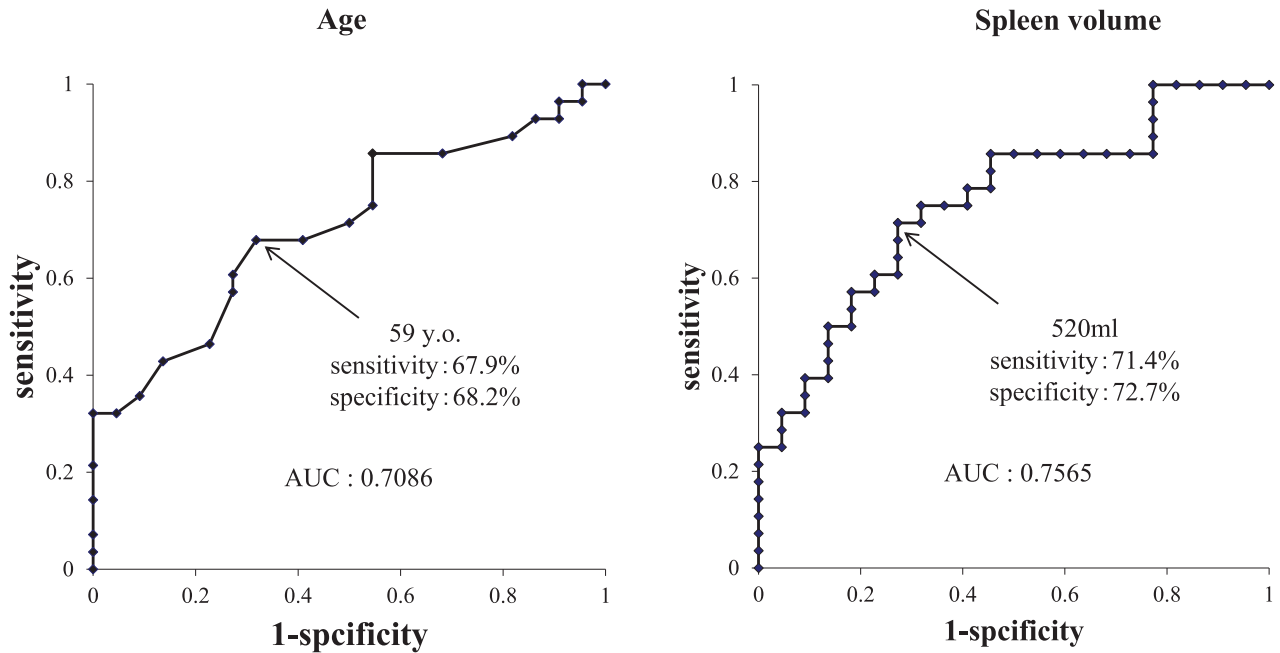


Fig. 3 ROC curves of age and spleen volume for predicting postoperative PSVT.

than in SVG. However, there were no significant differences between the 2 groups in terms of sex, age, etiology, AST, ALT, ALP, Alb, PT-INR, creatinine, T-cho, Ch-E, Child-Pugh classification, and preoperative liver volume. In the intra- and postoperative features, blood loss, hospital stay, and incidence of PSVT were significantly higher in LVG than in SVG, while there were no significant differences in operation time and postoperative complications other than PSVT.

Furthermore we analyzed the changes in platelet count, AST, ALT, ALP, TB, Alb, Ch-E, T-cho, and liver volume before and after splenectomy according to SV. Platelet count in LVG, in which preoperative value was significantly lower compared to SVG, was remarkably increased after splenectomy, showing significantly higher values at 1 and 3 months after splenectomy than those in SVG. Δ Plt was also significantly higher in LVG than in SVG (Fig. 4A). AST levels in both groups did not show significant changes after splenectomy (Fig. 4B). There was no significant difference in preoperative and at 3 months after splenectomy ALT levels and Δ ALT between the 2 groups; however, ALT in LVG was significant lower than in SVG at 1 month after splenectomy (Fig. 4C). There was no significant difference in preoperative ALP between the 2 groups; however, ALP in LVG was significantly higher than in SVG at 3 months after splenectomy.

Δ ALP in LVG was greater than in SVG (Fig. 4D). TB in LVG, in which preoperative value was significantly higher compared to SVG, was significantly decreased after splenectomy, showing the values at 1 and 3 months after splenectomy, which were similar to those in SVG. Δ TB in LVG was bigger than that in SVG, although not statistically significant ($P = 0.09$) (Fig. 4E). Alb levels in both groups did not show significant changes after splenectomy; however, Δ Alb in LVG was bigger than that in SVG, although not statistically significant ($P = 0.06$) (Fig. 4F). Ch-E in LVG was significantly increased at 3 months after splenectomy. Δ Ch-E was significantly higher in LVG than in SVG (Fig. 4G). T-cho in LVG was significantly increased at 3 months after splenectomy, showing significantly higher values at 3 months after splenectomy than those in SVG. Δ T-cho was significantly higher in LVG than in SVG (Fig. 4H). There was no significant difference in liver volume between SVG and LVG at preoperative and 3 months after splenectomy. Δ liver volume in LVG did not show a significant difference compared to that in SVG (Fig. 4I).

Discussion

The results of our study in evaluating the risk of PSVT and improvement of liver function after splenectomy for the patients with chronic liver

Table 4 Comparison of pre-, intra-, and post-operative features between patients with small spleen volume group (SVG) and large spleen volume group (LVG)

	SVG (<520 mL) n = 24	LVG (≥520 mL) n = 26	P value
Sex ratio (M:F)	15:9	18:8	0.62
Age (years)	57.5 ± 7.6	58.1 ± 8.8	0.82
Etiology			0.29
HBV	1	3	
HCV	22	19	
Alcohol	1	3	
Other	0	1	
Aspartate aminotransferase (IU/L)	66.7 ± 23.0	52.9 ± 24.5	0.08
Alanine aminotransferase (IU/L)	61.9 ± 28.0	42.9 ± 23.7	0.09
Alkaline phosphatase (IU/L)	348 ± 182	397 ± 192	0.45
Albumin (g/dL)	3.61 ± 0.51	3.44 ± 0.48	0.22
Total bilirubin (mg/dL)	0.99 ± 0.42	1.47 ± 0.99	0.03
PT-INR	1.15 ± 0.10	1.22 ± 0.14	0.06
Creatinine (mg/dL)	0.75 ± 0.13	0.81 ± 0.25	0.28
Total cholesterol (mg/dL)	140.8 ± 22.0	129.0 ± 26.5	0.09
Cholinesterase (ΔPh)	0.52 ± 0.18	0.50 ± 0.16	0.71
White blood count (×10³/μL)	3.41 ± 1.24	2.66 ± 1.42	0.05
Hemoglobin (g/dL)	12.5 ± 1.5	10.9 ± 1.5	<0.01
Platelet count (×10³/μL)	59.7 ± 23.4	42.3 ± 14.6	<0.01
Child-Pugh score			0.29
A	20	17	
B	4	8	
C	0	1	
MELD score	8.17 ± 1.71	9.73 ± 2.76	0.02
Liver volume (mL)	1,210 ± 321	1,186 ± 420	0.72
Operation			0.55
LS	21	23	
OS	1	0	
Conv	2	3	
Operation time (min)	155.8 ± 48.8	166.0 ± 41.8	0.43
Blood loss (mL)	344.8 ± 445.5	922.2 ± 1125.3	0.02
Hospital stay (days)	11.7 ± 5.0	15.0 ± 6.1	0.04
Complication			
Postoperative bleeding	4	4	1.00
PSVT	8 (33%)	20 (77%)	<0.01
Other	1	0	0.31

Conv, laparoscopic conversion to open surgery; HBV, hepatitis B virus; HCV, hepatitis C virus; PT-INR, prothrombin time international ratio; LS, laparoscopic splenectomy; MELD, model for end-stage liver disease; OS, open splenectomy; PSVT, portal/splenic vein thrombosis.

diseases, demonstrated the following: (1) more than half of the patients (56.0%), which was higher than we expected, developed PSVT, (2) risk factors of PSVT were higher age and higher SV, (3) of the 2 risk factors, SV was proven to be the most reliable predictor for PSVT and optimal cut-off value of SV was determined as 520 mL, (4) compared to the preoperative features between LVG and SVG, LVG had significantly higher TB and MELD score, and significantly lower white blood cell count, hemoglobin concentration, and platelet count than SVG, (5) in LVG, compared to SVG, Δplatelet count, ΔChE and ΔT-cho were significantly increased after splenectomy, suggesting that splenectomy for large spleen contributed to improve in liver function.

The reported incidence of PSVT after splenectomy is significantly different between the patients with or without chronic liver diseases. The incidence for hematologic disorders, splenic tumor, and splenomegaly was reported to be 7% to 10%.^{1,18} On the other hand, its incidence in patients with chronic liver diseases, who had low platelet counts, was significantly higher, 34.2% to 52.5%.^{7,11,19} Zhang *et al* reported that the incidence of postoperative PVT was 47.8% (33/69) in open surgery for patients with liver dysfunction due to hepatitis B virus.⁷ Incidence of PSVT in our reports was comparable to previous reports. Therefore, we did not consider laparoscopic surgery as the cause of high incidence of PSVT; however, further examination is required.

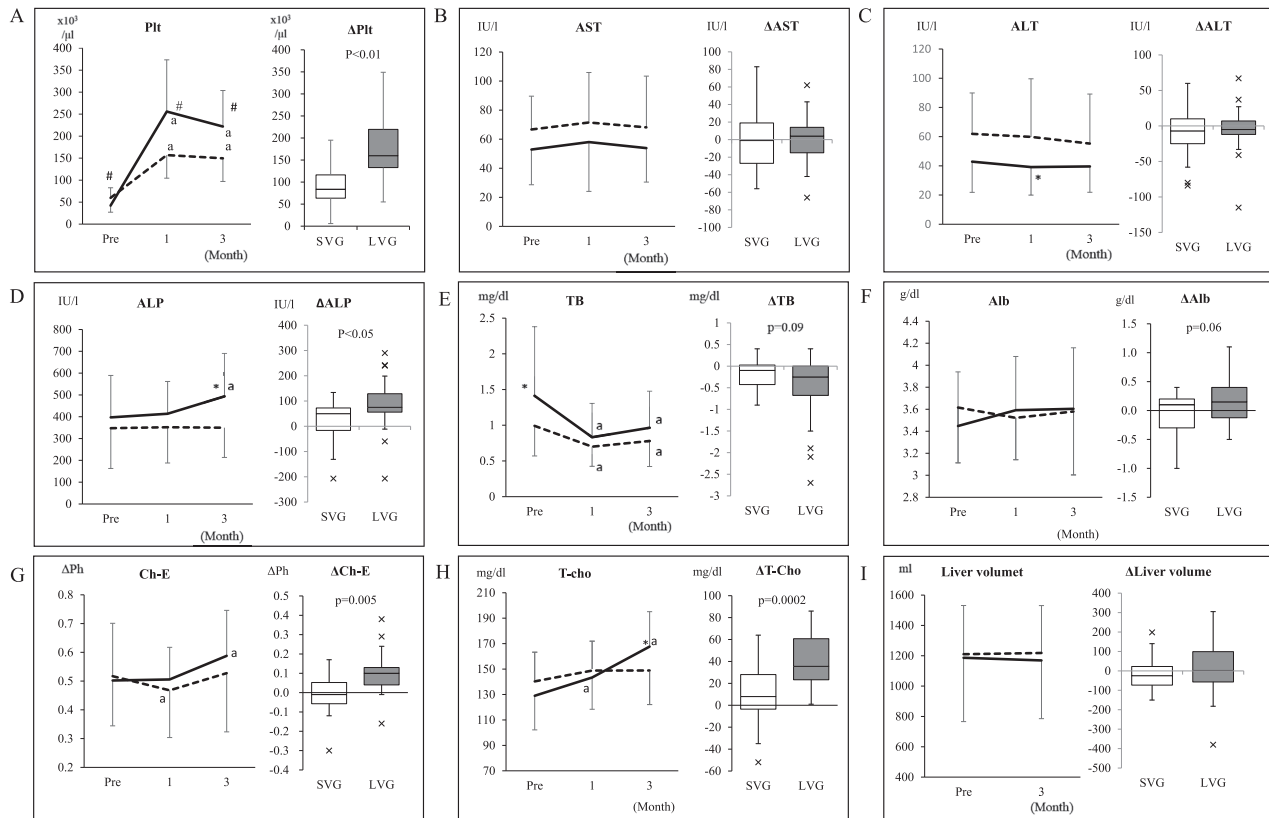


Fig. 4 Changes of serum markers for liver functions and liver volume after splenectomy between the patients with small spleen volume group (SVG; dotted line) and large spleen volume group (LVG; solid line). Data are presented as mean \pm SD. a: $P < 0.05$ versus preoperative values; #: $P < 0.05$ versus SVG; #: $P < 0.01$ versus SVG. In each box and whisker plots the median is indicated as the center line, and the box indicates the interquartile range (first to third quartiles). Box and whiskers encompass 95% of the range of the data associated with each sample and outliers is indicated as \times marks.

It is generally accepted that decreased portal venous flow is the primary factor leading to the development of PVT in patients with liver cirrhosis.¹ Additionally, the coagulation disorder is also regarded as an important factor of PVT.²⁻⁴ Interestingly, there was no difference in the development of PSVT whether thromboprophylaxis was performed in our study. We speculated that conventional thromboprophylaxis could not prevent PSVT. It was considered urgent to establish new postoperative thromboprophylaxis.

As risk factors of PSVT after splenectomy, splenomegaly,⁵ large splenic vein diameter,⁶ low preoperative white blood cell counts,⁶ high ratio of portal venous velocity before and after operation,⁷ and low antithrombin-III activity⁸ had been reported. In our study, large spleen and high age were the independent risk factor of PSVT after splenectomy. Previous studies reported that splenomegaly was considered a risk factor of PSVT after splenectomy,

because a large stump of splenic vein causes blood turbulence, which in turn can result in a local increase in coagulability and enhanced thrombus formation.^{6,9,10} The large spleen has abundant portal venous flow compared with the small spleen, and thus decrease of portal venous flow after splenectomy is much higher. The risk of PSVT might rise with increasing age, because of an age-related hemostatic imbalance. Several reports showed that the incidence of venous thromboembolism rose markedly with increasing age.²⁰⁻²²

Of the 2 risk factors, SV was found to have the largest AUC, and the optimal cut-off value of SV determined by ROC curve analysis was 520 mL, corresponding to sensitivity of 71.4% and specificity of 72.7% in this study. To the best of our knowledge, only 2 previous studies examined the cut-off value of SV for high risk of PSVT after splenectomy in patients with cirrhosis. Ushitora *et al* retrospectively examined the medical records of the 38 cirrhotic

patients who underwent splenectomy and reported that its cut-off value was 450 mL by ROC curve analysis, corresponding to sensitivity of 85% and specificity of 56%.¹¹ Iida *et al* also retrospectively analyzed 28 patients with severe cirrhosis who underwent splenectomy and reported that its cut-off value was 450 mL, corresponding to sensitivity of 90% and specificity of 73%.²³ Because SV was determined as the most useful predictor of PSVT, we classified the 50 patients into SVG and LVG according to cut-off value of SV to clarify the characteristics of LVG and how splenectomy between SVG and LVG influences postoperative liver function.

Interestingly, our present study revealed that LVG showed the paradoxical relationship between the characteristics during perioperative period and those during the late postoperative period: LVG was characterized by impaired preoperative liver function, greater amount of blood loss, and higher incidence of PSVT during the perioperative period, while during late postoperative period it was characterized by significant improvements in platelet counts and in liver functions. Platelet count in LVG, in which preoperative value was significantly lower compared to SVG, was remarkably increased after splenectomy, showing significantly higher values at 1 and 3 months after splenectomy than those in SVG. Δ Plt was also significantly higher in LVG than in SVG. TB in LVG, whose preoperative value was significantly higher compared to SVG, was significantly decreased after splenectomy and Δ TB in LVG was bigger than that in SVG although not statistically significant. Δ Alb in LVG was bigger than that in SVG. Ch-E indicating hepatic synthetic ability and T-cho indicating hepatic metabolic capacity in LVG were significantly increased at 3 months after splenectomy, and Δ Ch-E and Δ T-cho were significantly higher in LVG than in SVG. In the previous small cohort study on 12 patients with liver cirrhosis, it was reported that splenectomy improved liver function such as the value of Alb, Ch-E, and T-cho.¹² According to the previous retrospective study on 38 consecutive cirrhotic patients who underwent splenectomy or simultaneous hepatectomy and splenectomy,¹¹ serum levels of TB and prothrombin time were significantly improved at 1 year after splenectomy. The other prospective study on 70 patients with liver cirrhosis and portal hypertension showed that the Child-Pugh score was significantly improved at 3 months after laparoscopic splenectomy.²⁴ However, these previous studies did not examine the improvement

in liver function and platelet counts after splenectomy according to the degree of SV.

There are 2 possible reasons for thrombocytopenia in patients with liver disease. Platelet dynamics in chronic liver disease with thrombocytopenia showed that splenic platelet pooling and increased destruction were the main causes of thrombocytopenia in previous studies.²⁵ It was also reported that decreased plasma thrombopoietin (TPO), caused by its reduced production in the liver, contributed to thrombocytopenia in patients with chronic liver failure.²⁶ Therefore, it was considered that greater amounts of platelets were pooling and destroyed in the large spleen compared as in the small spleen, resulting a greater improvement in platelet count after splenectomy had shown in LVG than in SVG. Additionally, by examining plasma TPO levels before and after splenectomy, new mechanisms may be obtained. Future research is expected.

Several possible mechanisms for improvement of liver function after splenectomy were reported. First, transforming growth factor- β 1 (TGF- β 1), which plays a crucial role in the matrix production during liver fibrosis, is an inhibitory factor regarding the regeneration of hepatocytes.^{27,28} Akahoshi *et al*²⁸ investigated the TGF- β 1 production in the spleen of cirrhotic rats and the effects of splenectomy on the healing process from liver fibrosis. The plasma concentration of TGF- β 1 of the portal vein after splenectomy was significantly lower than that of non-splenectomy. Therefore splenectomy may improve liver function by reducing the levels of spleen-derived TGF- β 1. Second, platelets and platelet-derived factors has assumed to have a central role in liver regeneration by growing experimental evidence.²⁹ Using a 70% hepatectomy model in mice, Murata *et al* demonstrated that thrombocytosis, which was produced by pegylated recombinant human megakaryocyte growth and development factor significantly promoted liver regeneration compared to the control mice.³⁰ In contrast, it was also reported that thrombocytopenia induced by injecting busulfan in a partial hepatectomy model of mice impaired the initiation of hepatocyte proliferation.³¹ Taken together with the previously reported results, higher platelet counts in LVG may contribute to greater improvement of liver function in LVG compared to SVG in our study. Third, decreasing portal flow by removal of large spleen may ameliorate liver function. In the previous study, splenectomy in the cirrhotic patients resulted in a significant reduction in mean portal venous pressure and improvements in liver function tests.³² In

another study on cirrhotic patients with portal hypertension who underwent splenectomy, portal venous flow evaluated by ultrasonography before splenectomy significantly correlated with the spleen size, and splenectomy significantly reduced portal venous flow as well as pressure, resulting in reduction of intrahepatic vascular resistance.³³ Our previous experimental study using a rat small-for-size liver transplantation model demonstrated that splenectomy exerted dual cytoprotective effects by preventing excessive portal venous inflow and eliminating splenic inflammatory cell recruitment into the liver, which in turn inhibited hepatocellular apoptosis and improved liver regeneration.³⁴ It was therefore considered that splenectomy in LVG may have greater influence in attenuation of portal pressure than that in SVG, resulting in significant improvement of liver function in LVG compared with SVG.

ALP in LVG, in which preoperative value was not significant difference compared to SVG, was significantly increased after splenectomy, and Δ ALP in LVG was significantly higher than in SVG. High ALP levels can show that the bile ducts are obstructed. Also, elevated ALP could occur for various reasons such as active bone formation occurring, a disease that affects blood calcium level, vitamin D deficiency, or damaged liver cells.³⁵ It is unclear why ALP levels were significantly elevated in the LVG compared to SVG despite improvements in liver function such as Alb, Ch-E, and T-cho levels.

Although portal vein thrombosis (PVT) used to be a critical complication, its outcomes have been improving in recent years. In the retrospective study of the 174 patients with PVT in 2001, only 46 patients (23.4%) received anticoagulation and a 5-year survival rate in 37 of the 174 patients who had nonmalignant cirrhotic PVT was only 45%.³⁶ In the retrospective multicenter question cohort study of current status of portal vein thrombosis in Japan in 2016, 315 (77.6%) of 406 cirrhotic patients with PVT received anticoagulation therapy and 77% patients who received anticoagulation achieved partial or complete recanalization. Moreover, 75% survival time was 39.5 months in patients who achieved complete recanalization and 50% survival time was 60.2 months in patients who achieved partial recanalization, while 50% survival time was 20.1 months in patients who exacerbated PVT.³⁷ In contrast, there have been few studies on the treatment of PSVT after splenectomy and only Kawanaka *et al* reported the results of a small cohort

study: 8 (88.9%) of 9 patients with PSVT were found to have complete recanalization after anticoagulation therapy.⁸ In our study, 22 (88.0%) of 25 patients who developed PSVT had the thrombus dissolved by anticoagulant therapy (Table 2) and there was no mortality. Therefore, splenectomy could be safely applied even in LVG by early induction of anticoagulant therapy after surgery, although large SV was the risk factor of postoperative PSVT in splenectomy for patients with chronic liver dysfunction.

In conclusion, large spleen (520 mL and greater) is an independent risk factor for PSVT after splenectomy in patients with chronic hepatitis or liver cirrhosis, with a clear benefit from splenectomy in improving liver function, as long as PSVT is properly diagnosed and managed.

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