Factors affecting persistent splenomegaly after adult-to-adult living donor liver transplantation using a left lobe

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F.K. and Y.I. collected and analyzed data, and wrote the article. Y.I and S.K. designed this study. Y.I., J.Y., N.F., and S.K. performed operations on donors and recipients.

Disclosure

The authors declare no conflicts of interest to disclose as described by Transplantation.

Abbreviations

spleen volume, SV; adult to adult living donor liver transplantation, A2LDLT; computed tomography, CT; portal vein pressure, PVP; cadaveric donor liver transplantation, CDLT; portal vein flow, PVF; graft volume, GV; standard liver volume, SLV; one-way analysis of variance, ANOVA; central venous pressure, CVP; fresh-frozen plasma, FFP; model for end-stage live disease score, MELD score; graft-recipient weight ratio, GRWR;

Abstract

Background.

The aim of the present study was to evaluate spleen volume (SV) and the factors influencing it after adult-to-adult living donor liver transplantation (A2LDLT) using a left lobe.

Methods.

Pre-transplant computed tomography (CT) and post-transplant CT two years after A2LDLT were examined by volumetric analysis in 24 patients. The factors affecting the change in post-transplant SV were analyzed.

Results.

The mean pre-transplant SV (692±483 mL) decreased significantly to 420±292 mL after A2LDLT (p=0.001). Post-transplant SV was >500 mL in 9 patients (Group A) and ≤500 mL in 15 (Group B). Pre-transplant SV, platelet count, anhepatic time, operative time, intraoperative blood loss, post-transplant portal vein pressure >20 mmHg and post-transplant portal vein flow >250 mL/min/100 g graft weight showed significant differences between the two groups.

Actual GV and GV/standard liver volume ratio showed no inter-group differences. The only significant factor related to a post-transplant SV of >500 mL was the pre-transplant SV. Post-transplant platelet counts were significantly increased from the pre-transplant values in both Group A ($p=0.004$) and Group B ($p<0.001$).

Conclusions.

Pre-transplant SV is the only significant factor predicting a SV of >500 mL after A2LDLT using a left lobe. However, even in patients with a SV of >500 mL, the platelet count increased significantly from the pre-transplant value.

Liver transplantation is the ideal treatment for end-stage liver disease. Most patients who undergo orthotopic liver transplantation show a decrease in spleen volume (SV)[1,2]. However, it has been reported that the spleen remains significantly enlarged in some patients, and that splenomegaly may persist for up to 2-4 years after cadaveric donor liver transplantation (CDLT)[3]. It is anticipated that in patients who undergo partial liver transplantation such as split liver transplantation or living donor liver transplantation (LDLT), graft hyper-perfusion may cause more persistent splenomegaly. It is said that use of a left lobe graft may cause small for size syndrome[4-6]. To overcome this complication, various types of portal inflow modulation have been applied [7-9]. At our institution we have been performing adult-to-adult LDLT (A2LDLT) using left lobe grafts without splenectomy or portocaval shunts in many patients[10,11]. In the present study, we investigated SV at 2 years after A2LDLT using left lobe grafts and evaluated the factors affecting SV.

Patients and Methods

Between September 2003 and February 2018, 86 consecutive LDLTs were performed at Juntendo University Hospital after obtaining approval from the University Ethics and Indications Committee. The recipients comprised 65 adults (aged ≥18 years) and 21 children (aged <18 years). We used only left lobe grafts without the caudate lobe for adult recipients and did not perform right lobe LDLT. Standard liver volume (SLV) of the recipients was calculated according to the formula of Urata et al.[12]. Estimated graft volume (GV) was calculated by CT volumetric analysis, and actual GV was measured on the back table. Our general selection criteria for grafts in A2LDLT included a preoperatively estimated GV/SLV ratio equal to or greater than 30%[11].

Operative management and measurement of portal flow

The authors' techniques for left lobe graft and recipient total hepatectomy in A2LDLT have been described in detail previously[10,11]. The graft consists of the left lobe with inclusion of the middle hepatic vein. Intraoperative blood flow measurements were taken with an ultrasonic transit time flow meter (Transonic System,

Ithaca, NY) in the recipient. After anastomosis of all the vessels and 15 min of equilibration, but before biliary reconstruction, portal vein flow (PVF) was measured. The portal vein pressure (PVP) was measured by direct puncture with a 25-gauge needle and pressure tubing attached to a normal central venous pressure (CVP) monitoring transducer.

Postoperative care

The initial immunosuppressive regimen consisted of FK 506 and prednisone. Intensive anticoagulant treatment, carried out for more than 2 weeks after LDLT, included administration of low-dose low-molecular-weight heparin (50U/kg/day for 4 weeks), antithrombin III (target of 100% antithrombin activity for 2 weeks), 1nafamostat mesilate 0.1 mg/kg/hr for one week), prostaglandin E_1 (0.01 μg/kg/min for one week), gabexate mesilate (1 mg/kg/h for one week).

Volumetry of the recipient spleen and graft

Since 2008 we have routinely performed pre- and post-transplant CT of the abdomen in 34 consecutive recipients. Of these

34 patients, 10 were excluded from the study for one of the following reasons: Absence of portal hypertension before LDLT (n=4), a history of splenectomy (n=1), death within 1 month after LDLT (n=2), follow-up interval <1 year (n=1), and inability to perform post-transplant CT because of patient migration (n=2). The remaining 24 patients were enrolled in the present study. CT studies were performed using multislice CT. GV and SV were measured using a Synapse Vincent volumetric analysis system ver.4 (Fujifilm, Tokyo)[13]. The time point of CT assessment of SV and GV was two years after A2LDLT. We divided the recipients into two groups according to the post-transplant SV: >500 mL (Group A) and ≤500 mL (Group B). To identify the possible factors related to persistent splenomegaly, the following variables were compared between the two groups: pre-transplant recipient variables, including age, sex, liver disease, history of ascites, presence of collateral circulation, model for end-stage live disease (MELD) score, Child-Pugh score, and liver and renal function test results; graft-related data, including actual GV, GV/SLV ratio, and SV; perioperative data, including cold

ischemia time, operation time, and intraoperative blood loss; hemodynamic factors including post-transplant PVP, and PVF; postoperative factors including surgical complications, post-transplant GV, post-transplant GV/SLV, liver function, and hospital stay.

Statistical analysis

Continuous variables were expressed as mean ± SD or the median with range, and statistical analysis of data was performed using one-way analysis of variance (ANOVA). A paired *t*-test was conducted to examine the differences in SV and GV. Qualitative variables were compared by chi-squared test. Variables were also compared by multivariate analysis using a logistic regression model. The variables that were ultimately used for a logistic regression analysis were chosen on the basis of clinical importance. Calculations were performed using the JMP 11.2.0 software package (SAS Institute Inc., NC). Differences at $p < 0.05$ were considered to be statistically significant.

Results

The primary liver disease was viral liver cirrhosis in nine patients, primary biliary cirrhosis in seven, biliary atresia in three, alcoholic cirrhosis in two, cryptogenic cirrhosis in two and primary sclerosing cholangitis in one. The mean pre-transplant SV (692±483 mL) decreased significantly to 420±292 mL after A2LDLT (paired t-test, p=0.001, Figure 1). Platelet counts after LDLT increased significantly relative to the pre-transplant values (from 8.4±5.0 /10^4μL to 17.0±7.8 /10^4μL, paired t-test, p<0.001, Figure 2). The actual GV (445±84 mL) increased significantly to 1,195±337 mL after LDLT (paired t-test, p<0.001, Figure 3). Nine patients (37.5%) were placed into Group A and fifteen (62.5%) into Group B.

Preoperative factors affecting the post-transplant SV are listed in Table 1. There were significant differences in the pre-transplant SV (p<0.001) and the platelet count (p=0.008) between the two groups. Post-transplant SV was significantly correlated with pre-transplant SV (r^2=0.45, Y=138+0.407X, p<0.001, Figure 4). Table 2 shows the perioperative factors affecting spleen size. There

were significant differences in anhepatic time (p=0.003), operation time (p=0.002), and intraoperative blood loss (p=0.004). The number of patients with a post-transplant PVP of >20 mmHg was significantly larger in Group A than in Group B (p=0.009). The number of patients with a post-transplant PVF of >250 mL/min/100 g graft weight was significantly larger in Group A than in Group B (p=0.005). The only variable associated with persistent splenomegaly that remained significant after application of the logistic regression model was pre-transplant SV (p=0.046) (Table 3).

Postoperative factors affecting spleen size are shown in Table 4. Post-transplant GV was significantly greater in Group A than in group B (p=0.003). Post-transplant SV was significantly correlated with post-transplant GV (r^2=0.30, Y=-145+0.473X, p=0.006, Figure 5). Post-transplant platelet count was significantly lower in Group A than in Group B (p=0.001). However, post-transplant platelet counts were significantly increased from the pre-transplant values in both Group A (p=0.004) and Group B (p<0.001).

Discussion

In the present study, after A2LDLT using a left lobe, a significant reduction of SV was observed. However, the mean post-transplant SV (420±292 mL) was greater than the normal range (219±76 mL) and 15 (62.5%) patients still had splenomegaly. Nine out of 24 recipients showed a large SV of >500 mL two years after transplantation. Persistent splenomegaly and portosystemic collaterals have been reported after CDLT and LDLT[3, 14,15]. In the present study, the post-transplant SV clearly demonstrated a statistically significant linear relationship with the pre-transplant SV, and the pre-transplant SV was a significant factor predictive of a post-transplant SV of >500 mL.

Even after CDLT, the spleen remains significantly enlarged in 56% of patients[3]. The rate of reduction of SV may be significantly greater in patients receiving total liver grafts than in those with partial liver grafts. Chen et al. analyzed 87 recipients who underwent A2LDLT using a right lobe. The recipients were grouped according to the graft weight-to-recipient weight ratio (GRWR>1 vs. GRWR>1).

There were no significant differences in the mean postoperative SV and the changes in mean SV ratio between the two groups[16]. Kim et al. reported that although the type of transplantation (CDLT vs. LDLT) did not affect the degree of change in varices or splenic volume, the rate of reduction of SV in LDLT was weakly but significantly correlated with the weight of the transplanted liver (Pearson's correlation coefficient, $r=0.401$; $p<0.0001$)[14]. The hemodynamic patterns after left lobe LDLT can be predicted on the basis of graft size and spleen size. In the present study, GV and the GV/SLV ratio were important but insufficient parameters predictive of persistent splenomegaly after A2LDLT. Therefore, the relationship between spleen size and graft size remains controversial.

In patients with massive splenomegaly, the structural changes in the spleen, including fibrosis, do not allow for complete return to a normal size even after portal hypertension has been relieved by liver transplantation[3]. Splenic and retroperitoneal varices remain even several years after liver transplantation. Although graft hyperperfusion may improve gradually, splenic and retroperitoneal

varices frequently have a large systemic draining route and persistent collaterals may be maintained for a long time because of increased flow through the persistently enlarged spleen[14,18].

Whereas actual graft size at the time of LDLT was similar between the patients with a SV of ≥500 mL and those with a SV of <500 mL, it was significantly larger in the former than in the latter at two years after LDLT. The prolonged excessive post-transplant portal blood flow related to persistent splenomegaly may accelerate regeneration of the transplanted partial liver graft[19, 20]. In patients with a SV of ≥500 mL, the average post-transplant GV/SLV ratio was more than 100% and hyperkinetic portal hemodynamics was suspected in recipients with a large spleen. However, portal hypertension may improve gradually because of a markedly increased GV and decreasing intrahepatic resistance. In fact, even in patients with a SV of ≥500 mL, the average platelet count increased to 10.3±4.0/10^4μL. The detection of splenomegaly or persistent portosystemic shunt in the absence of other clinical findings does not necessarily mean recurrence of liver disease with

portal hypertension.

In summary, although post-transplant SV was significantly decreased from the pre-transplant SV, 9 of the present 24 recipients showed a SV of >500 mL after A2LDLT using a left lobe. Pre-transplant SV is the sole significant factor predicting a post-transplant SV of >500 mL. However, even in patients with a SV of >500 mL, the platelet count was increased significantly from the pre-transplant value.

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Table 1 Preoperative variables

Variables	Group A (n=9)	Group B (n=15)	*P*
Age (year)	47±15	52±10	0.33
Gender			
Male	5	4	0.16
Female	4	11	
Disease			
Cholestatic disease	3	8	0.34
Hepatocellular disease	6	7	
Presence of ascites			
Yes	6	11	0.73
No	3	4	
Presence of collateral circulation			
Yes	4	3	0.20
No	5	12	
MELD score	17.1±3.6	17.0±4.0	0.95
Child-Pugh score	10.1±0.6	10.7±1.5	0.56
Spleen volume (mL)	1097±496	450±271	<0.001
Platelet (/10^4 μL)	5.0±2.0	10.4±5.2	0.008
Bilirubin (mg/dL)	10.6±13.9	8.38±6.83	0.60
Total protein (g/dL)	6.96±1.15	6.71±0.82	0.55
Albumin (g/dL)	2.78±0.49	2.47±0.43	0.12
A/G ratio	0.72±0.23	0.61±0.18	0.20
Prothrombin time (%)	64±10	60±15	0.52
Creatinine (mg/dL)	0.76±0.42	0.64±0.35	0.46

Table 2 Perioperative variables

	Variables	Group A (n=9)	Group B (n=15)	*P*
Graft factor	Actual graft volume (mL)	480±53	427±92	0.14
	Graft volume / standard liver volume ratio (%)	42.0±7.2	39.9±6.5	0.46
Surgical factor	Anhepatic time (min)	122±51	70±26	0.003
	Operative time (min)	1116±202	902±94	0.002
	Intraoperative blood loss (min)	2167±1712	653±550	0.004
Hemodynamic factor	Post-transplant portal vein pressure (mmHg)>20mmHg			
	Yes	7	8	0.009
	No	0	7	
	Post-transplant portal vein flow (mL/min/100g graft weight)>250mL/min/100g graft weight)			
	Yes	7	7	0.005
	No	0	6	

Table 3. Final model: factors associated with postoperative splenomegaly by logistic regression analysis

Factor	Parameter estimate	Standard error	95% Confidence interval	P
Graft volume (mL)	-0.010	0.013	-0.044 - 0.009	0.43
Pre-transplant spleen volume (mL)	-0.005	0.002	-0.011- -0.001	0.046
Portal vein pressure after LDLT (mmHg)	0.102	0.223	-0.290 - 0.635	0.45
portal vein flow after LDLT (mL/min/100g graft weight)	-0.001	0.007	-0.016 - 0.012	0.92

Table 4 Postoperative variables

Variables	Group A (n=9)	Group B (n=15)	*P*
Acute cellular rejection			
Yes	1	5	0.20
No	8	10	
Re-operation			
Yes	3	1	0.09
No	6	14	
Post-transplant graft volume (mL)	1463±313	1061±265	0.003
Post-transplant GV/SLV (%)	126±15	97±21	0.002
Prothrombin time (%)	82±9	89±11	0.11
Bilirubin (mg/dL)	2.92±4.07	1.19±0.62	0.10
Platelet (/10^4 μL)	10.3±4.0	20.3±7.1	0.001
Post-transplant average daily amount of ascites for 14 days (mL)	1979±1150	1602±875	0.38
Hospital stay (day)	139±112	81±53	0.10

Figure legend

Fig. 1

The mean pre-transplant SV (692±483 mL) decreased significantly to 420±292 mL after A2LDLT (paired t-test, p=0.001)

Fig. 2

Platelet counts after LDLT increased significantly relative to the pre-transplant values (from 8.4±5.0 /10^4μL to 17.0±7.8 /10^4μL, paired t-test, p<0.001).

Fig. 3

he actual GV (445±84 mL) increased significantly to 1,195±337 mL after LDLT (paired t-test, p<0.001).

Fig. 4

Post-transplant SV was significantly correlated with pre-transplant SV (r^2=0.45, Y=138+0.407X, p<0.001).

Fig. 5

Post-transplant SV was significantly correlated with post-transplant GV (r^2=0.30, Y=-145+0.473X, p=0.006).

Figure 1. Changes of spleen volume

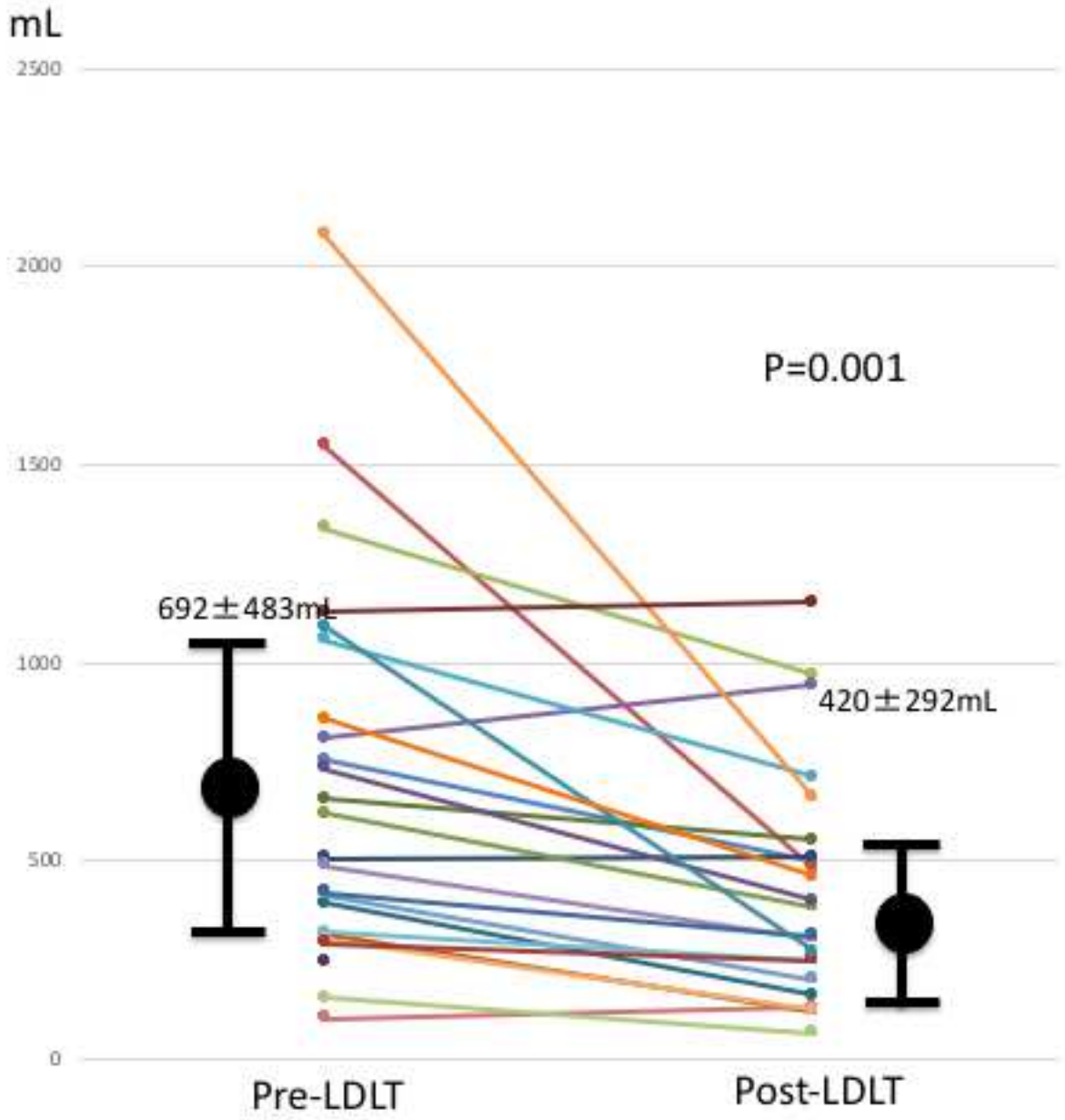

Figure 2. Changes of platelet count

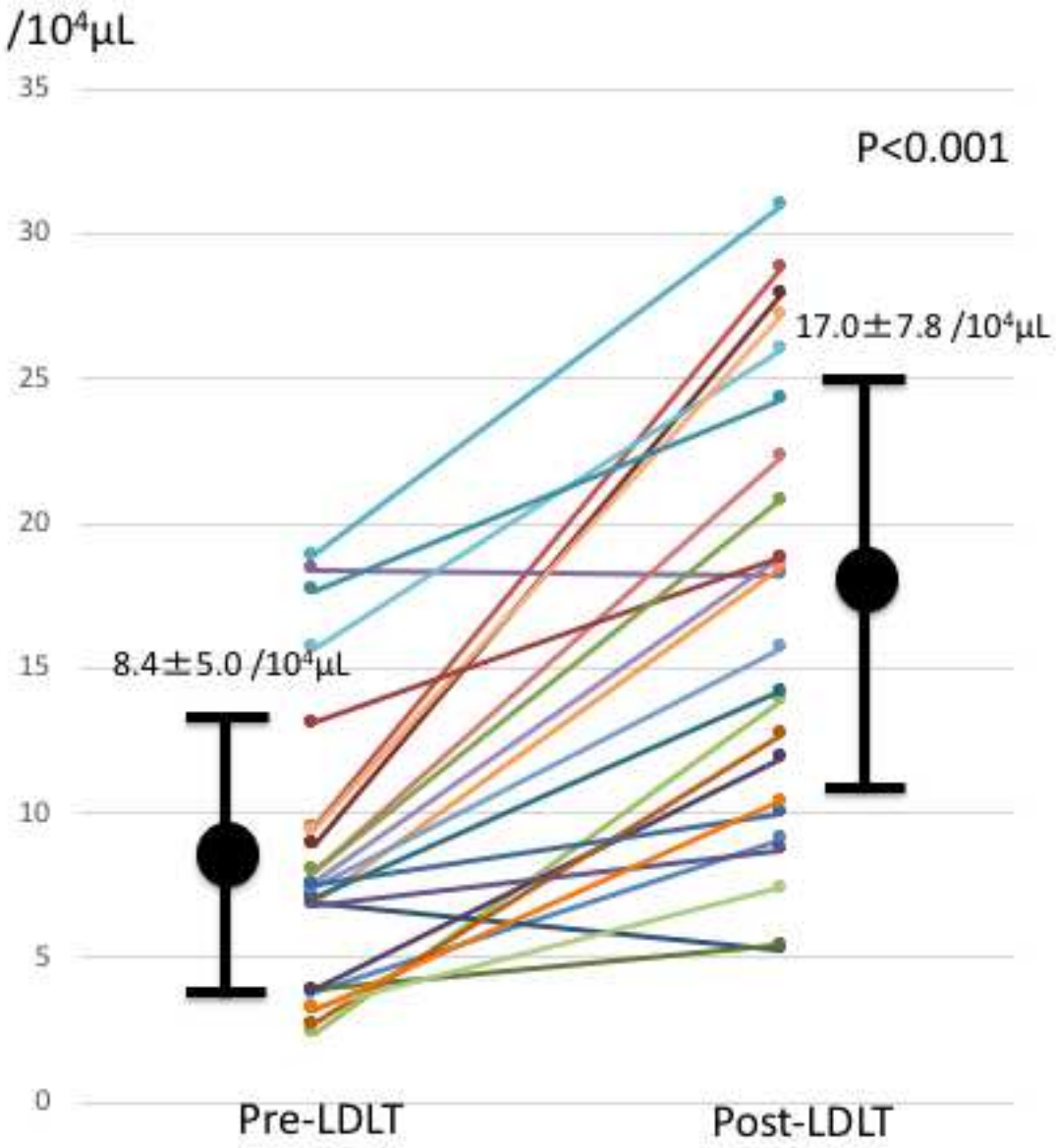

Figure 3. Chages of graft volume

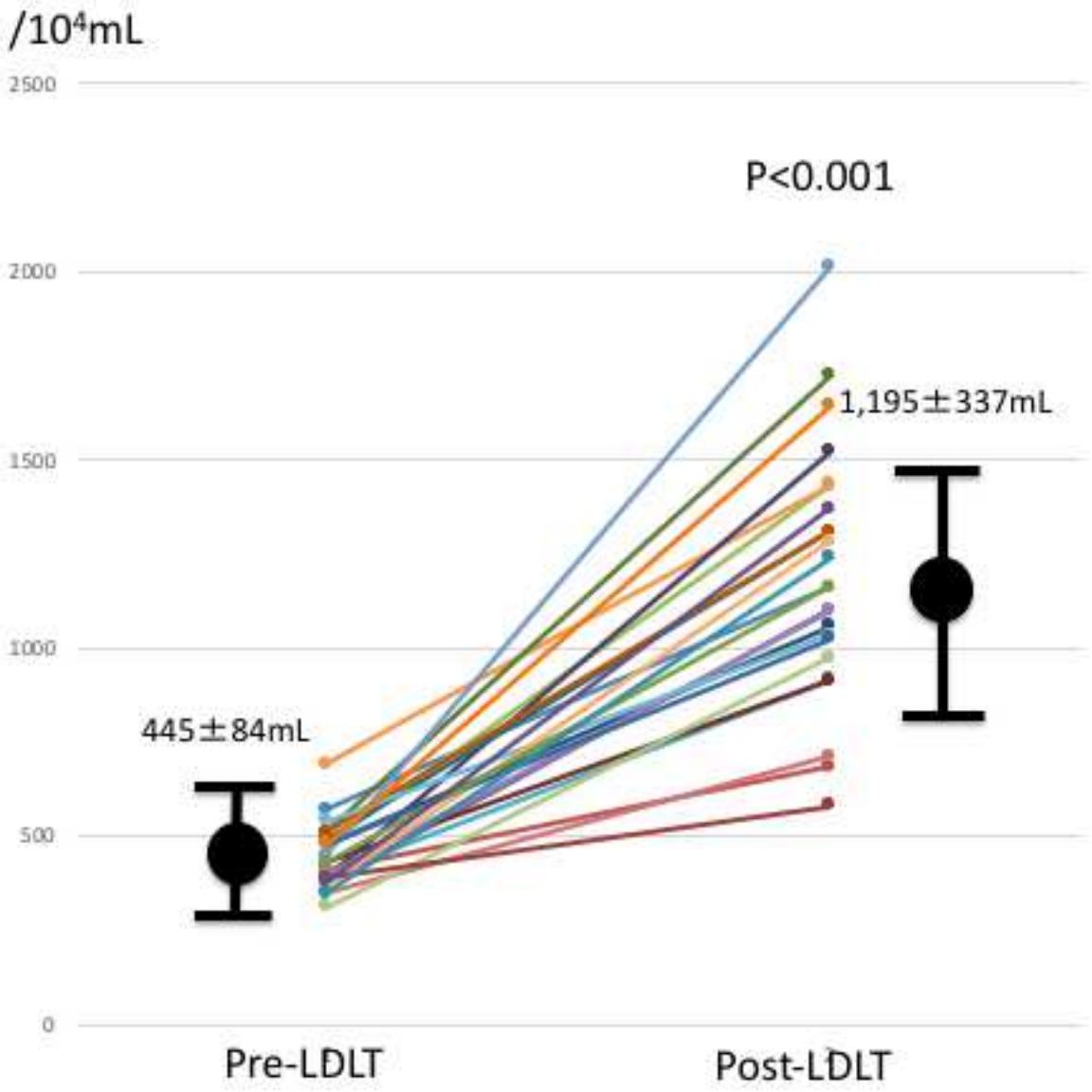

Fig. 4. Correlation between Pre-transplant spleen volume and post-transplant spleen volume

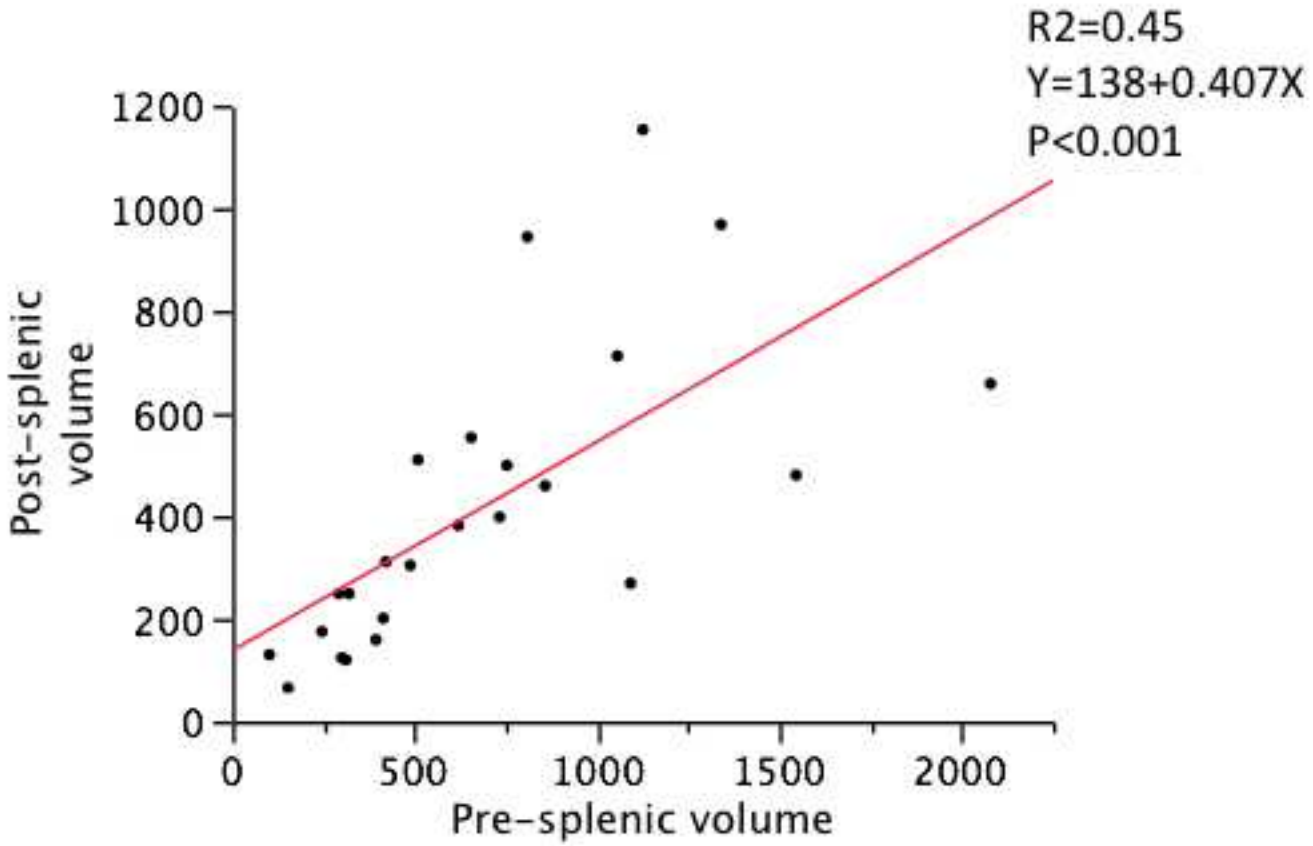

Fig. 5 Correlation between post-transplant splenic volume and post-transplant graft volume