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ORIGINAL ARTICLE

The beneficial role of simultaneous splenectomy in living donor liver transplantation in patients with small-for-size graft

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Summary

Small-for-size (SFS) graft syndrome is one of the major causes of graft loss in living donor liver transplantation (LDLT). We examined whether splenectomy is beneficial for overcoming SFS graft syndrome in LDLT. The patients were classified into two groups: the Sp (−) group ($n = 69$), in which splenectomy was not performed, and the Sp (+) group ($n = 44$), in which it was. The incidence of SFS graft syndrome was investigated. Risk factors of SFS graft syndrome were identified by univariate- and multivariate analysis. To clarify whether splenectomy is beneficial for patients with a SFS graft, subgroup analysis was performed for patients who had a graft weight-to-standard liver weight (GW-SLW) ratio of 40% or less ($n = 50$). Thirty-one of 113 patients developed SFS graft syndrome. A multivariate analysis identified that having a male donor was an independent risk factor of SFS graft syndrome. SFS graft syndrome occurred in 11 of 50 patients with a GW-SLW ratio <40%, and Sp (−) was an independent risk factor for the occurrence of SFS graft syndrome in patients ($P = 0.014$). Simultaneous splenectomy is favorable for overcoming SFS graft syndrome in LDLT patients with a GW-SLW of 40% or less.

Introduction

Size mismatch is a major obstacle in living donor liver transplantation (LDLT) between adults, and small-for-size (SFS) graft syndrome after LDLT remains a major complication of the procedure. It is often catastrophic and therefore should be avoided [1]. A greater understanding of the technical factors relating to the transplant surgery and innovations, including venous outflow reconstruction, have solved some of the problems associated with this procedure [2]; however, the occurrence of SFS graft syndrome appears to depend on multiple factors related to both donors and recipients [3]. Most surgeons believe that SFS graft syndrome can induce postoperative hyperbilirubinemia, intractable ascites and prolonged coagulopathy, which may ultimately lead to liver failure [4].

One of the major causes of graft loss in SFS graft syndrome is considered to be excessive portal venous flow to the graft [5], and Boillot *et al.* [6] report that a reduction of portal venous flow to the graft brought about a good outcome when using a SFS graft. We previously reported the impact of splenectomy to improve hypersplenism and avoid graft congestion on account of excessive portal venous flow on the outcome of six cases of LDLT using a left lobe graft [5]. None of the patients who underwent splenectomy experienced hyperbilirubinemia or intractable ascites and, in the majority of the cases, both portal pressure and portal vein flow after splenectomy decreased in comparison to that before splenectomy. We therefore believe that splenectomy is beneficial in improving the outcome in LDLT [7].

Splenectomy in liver transplantation, however, has been reported to have an adverse effect on the outcome of the liver transplantation on account of post-splenectomy septic complications [8,9]. On the other hand, splenectomy for patients with hepatitis C virus was recently reported to have significantly improved platelet counts soon after LDLT [10]. Moreover, there was no significant difference in the frequency of morbidity between patients who did and did not undergo splenectomy. Nonetheless, the role of simultaneous splenectomy in LDLT remains undetermined.

Therefore, the aim of the present study was to clarify whether simultaneous splenectomy can preclude SFS graft syndrome and thereby improve the outcome in LDLT.

Patients and methods

Patients

Between April 2003 and March 2007, 128 adult patients underwent LDLT at Kyushu University Hospital; the data of 126 of these patients were available. Splenic artery ligation was performed in six cases intraoperatively [5], and six cases had undergone splenectomy prior to LDLT for portal hypertension. One case underwent LDLT using dual grafts from two donors. These 13 cases were excluded from the present study. Therefore, a total of 113 patients (58 females and 55 males) were enrolled in the study. Graft types included left lobe with caudate lobe graft ($n = 63$), right lobe graft without the middle hepatic vein (MHV) ($n = 46$), right lobe graft with MHV ($n = 2$), left lobe graft ($n = 1$) and posterior sector graft ($n = 1$). The indications for LDLT were liver cirrhosis on account of hepatitis C ($n = 52$), primary biliary cirrhosis ($n = 17$), fulminant hepatic failure (FHF) ($n = 12$), liver cirrhosis on account of hepatitis B ($n = 11$), cryptogenic cirrhosis ($n = 4$), liver cirrhosis on account of alcohol abuse ($n = 4$), primary sclerosing cholangitis ($n = 3$), biliary atresia ($n = 3$), autoimmune hepatitis ($n = 2$) and others ($n = 5$) (Table 1).

Table 1. Indications for living donor liver transplantation with or without splenectomy.

Indications	Sp (–) group ($n = 69$)	Sp (+) group ($n = 44$)	*P*-value
Liver cirrhosis			
HCV(with HCC)	29 (26)	23 (19)	
HBV (with HCC)	6 (4)	5 (3)	
Alcohol (with HCC)	2 (0)	2 (1)	
Cryptogenic (with HCC)	3 (2)	1 (0)	
Primary biliary cirrhosis	9	8	N.S.
Fulminant hepatic failure	8	4	
Primary sclerosing cholangitis	3	0	
Biliary atresia	3	0	
Autoimmune hepatitis	1	1	
Acute on chronic HBV hepatitis	2	0	
Wilson's disease	1	0	
Epithelioid hemangioendothelioma	1	0	
Hemangioma	1	0	

Sp (–) Group: control group in which splenectomy was not performed; Sp (+) Group: group in which splenectomy was performed. HCV: hepatitis virus type C; HBV: hepatitis virus type B; HCC: hepatocellular carcinoma.

Donor and graft selection

Donors were selected from among the candidates who initiatively hoped to be living donors [1,11]. Donors were required to be within a third degree of consanguinity with recipients or spouses, and were aged between 20 and 65 years of age. For a donor without a third degree of consanguinity with the recipient, individual approval was obtained from the Ethics committee of Kyushu University Hospital. Good Samaritan donation was not used. Potential donors were evaluated for blood-group compatibility; evaluated also with liver function test, human leukocyte antigen crossmatch, and serological tests for hepatitis B, hepatitis C, human immunodeficiency viruses, human T-cell lymphotropic virus type 1 and other transmittable viruses. Electrocardiography and a pulmonary function test were performed as well.

Abdominal ultrasound was routinely carried out for all donors and percutaneous liver biopsy was performed for candidates with a suspected fatty liver, *i.e.* with more than a moderate degree of fat by an ultrasound [11]. Such donor candidates were admitted to Kyushu University Hospital overnight to undergo the liver biopsy. In this protocol, when the biopsy specimen revealed macro-vesicular steatosis in more than 10% of hepatocytes, donor candidates were not accepted as living donors.

For the evaluation of donor candidates older than 50 years, an ultrasound echocardiography and an exercise stress electrocardiography were routinely performed to rule out any asymptomatic heart disease. Donors with an abnormal value of tumor markers underwent chest CT, and upper and lower fiber-optic endoscopies of the gastrointestinal tract and colon to rule out malignant disease. Such candidates with heart disease or malignant disease were eliminated as candidates, and did not undergo further evaluation described below.

Eligible donors proceeded for the imaging studies including chest and abdominal X-rays, and 3-mm slice computed tomography scan for graft volumetric analysis. Three-dimensional CT was introduced for volumetric analysis and delineation of vascular anatomy [12]. Standard liver weight (SLW) of recipients was calculated according to the formula of Urata [13]. Graft weight

(GW) was predicted by CT volumetric analysis. Our decision about graft type for recipients was based upon the preoperatively predicted GW to SLW (GW-SLW) ratio. Left lobe graft was used when the preoperatively predicted GW-SLW ratio was more than 35%.

Postoperative management

With regard to graft harvesting technique, recipient surgery and perioperative patient management of the recipients, including immunosuppression regimens, the conditions have been described elsewhere [1,5,11]. Immunosuppression was initiated with a protocol based on either tacrolimus (Prograf; Astellas Pharma Inc., Tokyo, Japan) or cyclosporine A (Neoral; Novartis Pharma K.K., Tokyo, Japan). Aspirin was indicated when the patient's platelet count reached more than 300 000/mm^3 after LDLT. Warfarin, which was initiated at a dose of 1 mg daily, was indicated when portal thrombus was noted by postoperative CT scan. The target INR was set at 1.8–2.0. Heparin was not routinely used even when prothrombin time recovered early after LDLT. Pneumococcal immunization was not administered before or after LDLT.

All patients had monthly follow-ups, and the median follow-up period was 632 days, with 274 days and 962 days as the 25th and 75th percentiles, respectively. Patient survival was defined as the time period between LDLT and patient's death.

Comparison of portal hemodynamics and postoperative graft function

The patients were classified into two groups: the Sp (−) group ($n = 69$), in which splenectomy was not performed, and the Sp (+) group ($n = 44$), in which splenectomy was performed. Splenectomy was performed for patients with hepatitis C ($n = 15$), portal pressure after portal reperfusion above 20 mmHg at the time of the LDLT ($n = 12$), hepatocellular carcinoma beyond the Milan criteria [14] ($n = 7$), severe hypersplenism defined as preoperative white blood cell (WBC) count less than 2,000/mm^3 and platelet count less than 30 000/mm^3 ($n = 5$), an ABO blood type-incompatible donor ($n = 3$) [15], accidental injury ($n = 1$) and/or a splenic artery aneurysm ($n = 1$).

The variables related to the donors, recipients and grafts were compared between the two groups. Portal pressure was monitored through a mesenteric vein during surgery. An electromagnetic blood flowmeter (MVF-3100; Nihon Koden Corp., Tokyo, Japan) was used for blood flowmetry. All measurements were performed under stable hemodynamic conditions. Changes in portal pressure and portal flow were investigated using the data for patients for whom both portal pressure and portal vein flow before and after splenectomy had been recorded. Post-transplant liver function on postoperative day (POD) 14 based on serum total bilirubin or the amount of daily drainage of ascites was recorded. Post-transplant hyperbilirubinemia was defined as a serum total bilirubin level of more than 10 mg/dl on POD 14, and intractable ascites was defined as a level of more than 1000 ml on POD 14. SFS graft syndrome was defined by the development of hyperbilirubinemia or intractable ascites [1]. The incidence of sepsis and acute cellular rejection (ACR), as well as cause of death were compared between the groups. Complications associated with splenectomy were recorded. Additionally, WBC or platelet counts at 3 or 6 months after LDLT were compared.

Univariate and multivariate analyses were performed to identify the factors associated with the occurrence of SFS graft syndrome, and with the improvement of WBC and platelet counts. Improvement of WBC and platelet counts was identified when WBC count reached more than 4,000/mm^3 and platelet count more than 100 000/mm^3 3 months after LDLT.

Analysis of cases with a graft weight-to-standard liver weight (GW-SLW) ratio of 40% or less

To clarify whether splenectomy is beneficial for transplant patients with a SFS graft, subgroup analysis was performed for patients with a GW-SLW ratio [13] of 40% or less. The mean value of the GW-SLW ratio was 42% in this series. The cut-off GW-SLW value for a SFS graft was set at 40% because Sugawara *et al.* demonstrated that grafts with a GW-SLW ratio more than 40% had better prognosis in living donor liver transplantation [16]. Fifty of 113 transplant patients had a GW-SLW ratio of 40% or less. Univariate- and multivariate analysis were performed to identify the factors associated with the occurrence of SFS graft syndrome, and with the improvement of WBC and platelet counts in this subgroup.

Statistical analysis

The significance of differences between the groups was determined by the Chi-squared test, the paired or unpaired Student *t*-test or the Mann–Whitney *U*-test. Logistic regression analysis was applied to the univariate- and the multivariate analysis. Survival was calculated by the Kaplan–Meier product-limited method, and differences in survival between the groups were then compared using the log-rank test. Data were expressed as mean ± standard deviation. All statistical analyses were performed using Stat View 5.0 software (SAS Institute, Inc., Cary, NC, USA). A P-value of <0.05 was considered significant.

Results

The indications of LDLT in this series are shown in Table 1. There was no significant difference between the Sp (+) and Sp (−) groups.

The characteristics of the present patients are shown in Table 2. GW, GW-SLW ratio and GW-to-recipient body weight (RW) ratio in the Sp (+) group were smaller than those in the Sp (−) group. With regard to the recipients' variables, portal pressure at laparotomy in the Sp (+) group was significantly higher than that in the Sp (−) group. The pretransplant platelet counts in the Sp (+) group were significantly lower than those in the Sp (−) group.

Figure 1 is a comparison of portal pressure and portal vein flow before and after splenectomy in both groups. The portal pressure before splenectomy of the Sp (+) group was 19.2 ± 3.9 mmHg, which was higher than that of the Sp (−) group (17.5 ± 4.1 mmHg, $P < 0.05$), and significantly decreased after splenectomy (16.5 ± 3.6 mmHg, $P < 0.01$). The portal pressure in the Sp (+) group after splenectomy decreased to the same level as that of the Sp (−) group. The portal vein flow in the Sp (+) group decreased after splenectomy ($P < 0.05$). Therefore, the portal vein flow after splenectomy in the Sp (+) group was significantly lower than that in the Sp (−) group ($P < 0.05$). With respect to the spleen size, data on 40 spleens were available in this study. The mean weight was 480 g (range, 95–1260 g). Forty-four patients underwent splenectomy, of whom 20 patients had portal vein pressure >20 mmHg after reperfusion. The data of portal vein flow was available in 13 patients in the Sp (+) group and 46 patients in the Sp (−) group. The portal flow/100 gram liver tissue in the Sp (+) group was 464 ml/100 g tissue, and tended to be higher than that in the Sp (−) group (373 ml/g tissue, $P = 0.14$).

The 4-year patient survival rate in all patients was 85.8%, while that of the Sp (−) and Sp (+) groups were 84.4% and 92.1%, respectively (Fig. 2, P = NS). The survival rate between the groups was not significantly different even though significantly smaller grafts were transplanted in the Sp (+) group. The causes of death in the Sp (−) group were sepsis in four subjects, tumor recurrence in three, brain herniation on account of FHF in one, subcapsular hematoma after percutaneous liver biopsy in one and adult T-cell leukemia in one [17]. All

Table 2. Comparison of variables between donors, grafts and recipients between the Sp (−) and the Sp (+) groups.

Variables	Sp (−) group (n = 69)	Sp (+) group (n = 44)	P-value
Donor variables			
Age (years)	33.7 ± 10.9	36.5 ± 11.6	0.2
Gender (F/M)	17/52	18/26	0.07
ABO blood type (identical/compatible/incompatible)	54/15/0	30/11/3	0.07
Graft variables			
Graft type (LL/RL/posterior segment)	38/31/0	26/17/1	0.39
Reconstruction of segment V/VIII vein (Y/N)	18/13	10/5	0.58
Graft weight (g)	523 ± 95	456 ± 103	<0.01
GW-SLW ratio	43.6 ± 7.6	39.4 ± 7.2	<0.01
GW-RW ratio	0.88 ± 0.20	0.77 ± 0.18	<0.01
Warm ischemic time (min)	37.5 ± 9.5	39.4 ± 10.7	0.32
Cold ischemic time (min)	67.8 ± 36.7	79.6 ± 51.1	0.16
Recipient variables			
Age (years)	52.7 ± 12.4	50.9 ± 11.3	0.45
Gender (F/M)	32/37	26/18	0.19
MELD	13.0 ± 7.0	14.3 ± 7.1	0.32
Portal pressure at laparotomy	22.4 ± 6.7	25.9 ± 4.4	<0.01
Operation time (min)	766 ± 168	814 ± 175	0.16
Blood loss (g)	4872 ± 3210	5789 ± 4571	0.21
Platelet count ($\times 10^4$/ml)	8.7 ± 6.4	5.2 ± 2.2	<0.0l
WBC count (/ml)	4793 ± 2775	3977 ± 592	0.12

Sp (−) Group: control group in which splenectomy was not performed; Sp (+) Group: group in which splenectomy was performed. Data are expressed mean ± S.D. LL: left lobectomy with or without caudate lobectomy; RL: right lobectomy; SP(+) Group contained two cases transplanted RL with middle hepatic vein; GW: graft weight; SLW: standard liver weight calculated by 706.2 × body surface area plus 2.4; RW: recipient body weight; MELD: model for end-stage liver disease score; WBC: white blood cell.

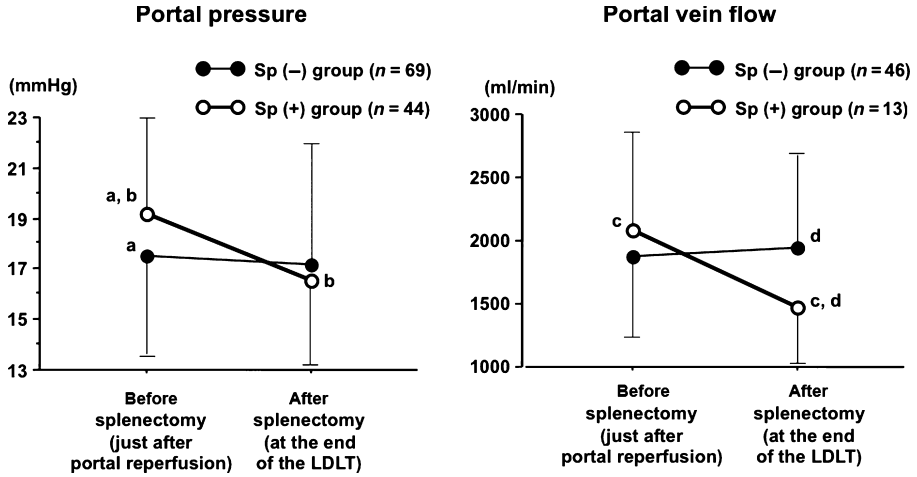

Figure 1 Portal pressure and portal vein flow before and after splenectomy. a, c, d: $P < 0.05$, b: $P < 0.01$. ●: Sp (–) group; ○: Sp (+) group.

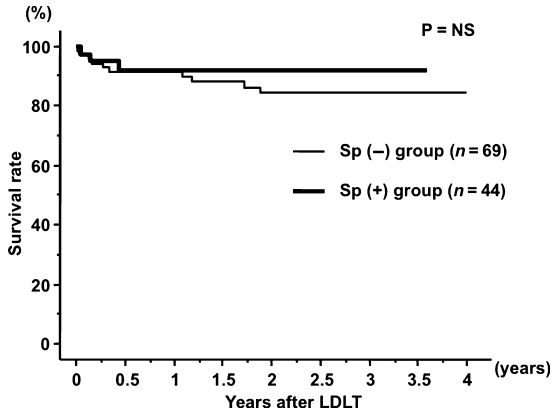

Figure 2 Four-year survival rate after LDLT. The 4-year patient survival rate of the Sp (–) group was 84.4% and that of the Sp (+) group was 92.1%. The difference was not significant.

three deaths in the Sp (+) group were on account of sepsis. One patient had obstructive suppurative cholangitis on account of bile duct stones before the LDLT. The patient had sepsis on account of *S. maltophilia* 4 days after the LDLT and died 18 days after the LDLT. The second patient was very sick before the LDLT. The pretransplant MELD score of the patient was 29. The patient had sepsis on account of methicillin-resistant *S. aureus* (MRSA) 10 days after the LDLT and died 54 days after the LDLT. The last patient had had hydrocephalus and had intracranial hemorrhage after the LDLT. The patient was very sick after that event and developed sepsis. The patient had sepsis on account of *S. maltophilia* 7 days after the LDLT and died 159 days after the LDLT.

Septic complications occurred in 13 patients in the present study, five in the Sp (+) group and eight in the Sp (−) group; the incidence of sepsis was not significantly different between the two groups. The incidence of ACR in the Sp (+) group was 16.3%, and 18.6% in the Sp (−) group (P = NS).

With respect to liver function after LDLT, 31 patients developed SFS graft syndrome. Univariate analysis revealed that being a female recipient, having a male donor, being a gender-mismatched recipient, donor age >40 years, recipient age <55 years and preoperative

Table 3. Predictive factors identified by the univariate Logistic regression analysis in all patients.

	SFS graft syndrome		Improvement of cell count	
Variables	Hazard ratio	*P*-value	Hazard ratio	*P*-value
Gender mismatch (+)	4.60	0.002	0.92	0.84
Male donor	3.00	0.042	0.37	0.038
Female recipient	2.55	0.035	0.92	0.84
Donor age >40 years	3.30	0.007	1.63	0.28
Recipient age <55 years	3.28	0.009	1.66	0.21
MELD >13	2.47	0.036	1.42	0.40
Blood loss >2000 ml	3.79	0.088	0.63	0.43
Operative time >750 min	1.88	0.14	1.02	0.96
Left lobe graft	1.57	0.30	1.13	0.77
GW-SLW ratio >40%	1.14	0.76	0.52	0.12
GW-RW ratio >0.85%	1.57	0.31	0.45	0.053
Splenectomy (–)	1.22	0.64	0.10	<0.0001
Portal flow before closure >1700(ml/min)	1.49	0.46	0.81	0.70
Portal pressure before closure >20 (mmHg)	1.27	0.66	0.46	0.16

GW: graft weight; SLW: standard liver weight calculated by 706.2 × body surface area plus 2.4; RW: recipient body weight; MELD: model for end-stage liver disease score.

Table 4. Multivariate analysis for risk factors of small-for-size graft syndrome in all patients.

Variables	Hazard ratio	95% CI	*P*-value
Male Donor	4.34	1.14–16.6	0.032
Gender mismatch (+)	3.64	0.97–13.7	0.057
Recipient age <55 years	2.41	0.83–7.04	0.11
Donor age >40 years	2.35	0.81–6.77	0.11
MELD >13	2.19	0.82–5.85	0.12
Female recipient	1.10	0.29–4.18	0.89

MELD score >13 were predictive factors for the incidence of SFS graft syndrome (Table 3). A multivariate analysis identified that having a male donor was an independent risk factor of SFS graft syndrome in the present study (Table 4).

Other complications possibly associated with splenectomy occurred in four patients: leakage of pancreatic juice, which was treated with short-term fasting, occurred in two patients, intra-abdominal hemorrhage, which required rel-aparotomy, occurred in 1, and portal vein thrombosis occurred in one patient and disappeared spontaneously.

Figure 3 shows a comparison of WBC and platelet counts before and after LDLT. The WBC counts in the Sp (+) group increased remarkably after LDLT compared to those before LDLT ($P < 0.005$). Moreover, the WBC counts in the Sp (+) group at 3 and 6 months after LDLT were significantly higher than those in the Sp (−) group ($P < 0.001$). The platelet counts in the Sp (+) group increased remarkably after LDLT compared to those before LDLT ($P < 0.001$). Additionally, the platelet counts in the Sp (+) group at 3 and 6 months after LDLT were twice as high as those in the Sp (−) group ($P < 0.001$). Both WBC and platelet counts improved in 61 patients 3 months after LDLT. The univariate analysis revealed that splenectomy and having a female donor were predictive factors for the improvement of WBC and platelet counts (Table 3). Multivariate analysis identified that splenectomy was an independent predictive factor for the improvement of WBC and platelet counts 3 months after LDLT (Hazard ratio: 9.21; 95% CI: 3.1–27.0; $P < 0.0001$).

The characteristics of transplant patients with a GW-SLW ratio ≤40% are shown in Table 5. GWs in the Sp (+) group were smaller than those in the Sp (−) group; however, the GW-SLW ratio or GW-RW ratio did not differ between the two groups. With regard to the recipients' variables, portal pressure at laparotomy in the Sp (+) group was significantly higher than that in the Sp (−) group. The pretransplant platelet counts in the Sp (+) group were significantly lower than those in the Sp (−) group.

Among the 50 transplant patients with a GW-SLW ratio ≤40%, 11 patients developed SFS graft syndrome. Two patients in the Sp (+) group and nine patients in the Sp (−) group developed SFS graft syndrome ($P < 0.005$). The univariate analysis revealed that splenectomy (−) was a risk factor for the occurrence of SFS graft syndrome (Table 6). Both WBC and platelet counts improved in 29 transplant patients with GW-SLW ratio ≤40% 3 months after LDLT. The univariate analysis identified that splenectomy was a predictive factor for the improvement of WBC and platelet counts (Table 6). No other factors were associated with the occurrence of SFS graft syndrome or with the improvement of cell count in the present study.

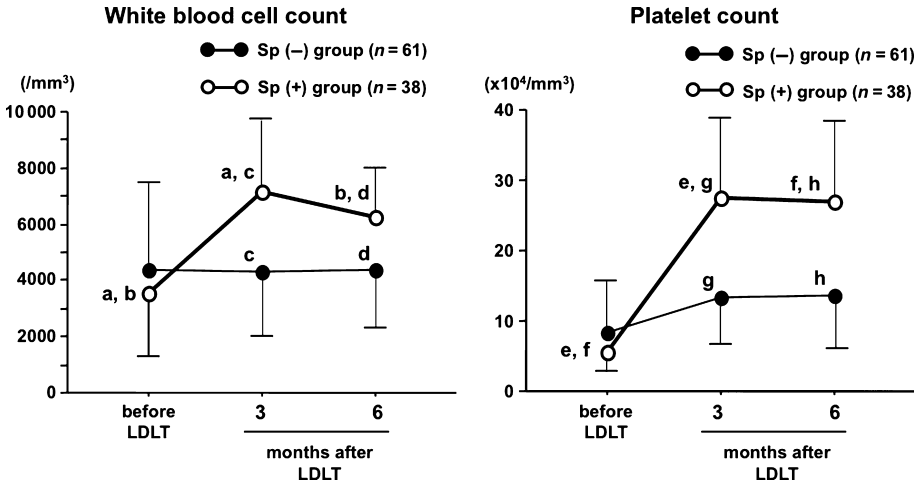

Figure 3 WBC and platelet counts before and after LDLT. a, b: $P < 0.005$, c, d: $P < 0.001$. e, f: $P < 0.001$, g, h: $P < 0.001$. ●: Sp (–) group; ○: Sp (+) group.

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Table 5. Comparison of variables for the patients with SFS graft between the Sp (–) and the Sp (+) groups.

Variables	Sp (–) group (n = 22)	Sp (+) group (n = 28)	P-value
Donor variables			
Age (years)	32.5 ± 10.7	33.5 ± 9.5	0.75
Gender (F/M)	7/15	12/16	0.42
ABO blood type (identical/compatible)	18/4	21/7	0.56
Graft variables			
Graft type (LL/RL/posterior segment)	17/5/0	22/5/1	0.58
Reconstruction of segment V/VIII vein (Y/N)	2/3	3/1	0.29
Graft weight (g)	447 ± 79	396 ± 56	<0.01
GW-SLW ratio	35.2 ± 3.7	35.0 ± 4.1	0.90
GW-RW ratio	0.72 ± 0.11	0.70 ± 0.11	0.57
Warm ischemic time (min)	38.8 ± 9.3	37.6 ± 9.4	0.65
Cold ischemic time (min)	62.0 ± 27.3	72.6 ± 38.9	0.28
Recipient variables			
Age (years)	49.4 ± 11.0	53.6 ± 9.2	0.14
Gender (F/M)	8/14	15/13	0.23
MELD	11.5 ± 5.7	15.3 ± 8.2	0.08
Portal pressure at laparotomy	20.7 ± 5.7	25.9 ± 4.8	<0.005
Operation time (min)	773 ± 151	779 ± 139	0.87
Blood loss (g)	5412 ± 4168	5110 ± 3679	0.79
Platelet count ($\times 10^4$/ml)	9.6 ± 7.1	5.1 ± 2.3	<0.005
WBC count (/ml)	4420 ± 2157	3840 ± 2501	0.39

Sp (–) Group: control group in which splenectomy was not performed; Sp (+) Group: group in which splenectomy was performed. Data are expressed mean ± S.D. LL: left lobectomy with or without caudate lobectomy; RL: right lobectomy; SP(+) Group contained one case transplanted RL with middle hepatic vein; GW: graft weight; SLW: standard liver weight calculated by 706.2 × body surface area plus 2.4; RW: recipient body weight; MELD: model for end-stage liver disease score; WBC: white blood cell.

Table 6. Predictive factors identified by the univariate Logistic regression analysis in patients with a GW-SLW ratio ≤40%.

	SFS graft syndrome		Improvement of cell count	
Variables	Hazard ratio	P-value	Hazard ratio	P-value
Gender mismatch (+)	0.71	0.62	2.43	0.14
Male donor	3.48	0.14	1.19	0.77
Female recipient	0.97	0.97	0.78	0.68
Donor age >40 years	1.09	0.91	2.41	0.24
Recipient age <55 years	2.81	0.17	1.95	0.27
MELD >13	2.52	0.19	1.28	0.68
Blood loss >4500 ml	2.27	0.25	1.28	0.68
Operative time >750 min	1.75	0.43	0.86	0.80
Left lobe graft	1.35	0.73	1.72	0.45
Splenectomy (–)	9.01	0.010	0.26	0.032
Portal flow before closure >1700(ml/min)	0.57	0.43	0.76	0.66
Portal pressure before closure >20 (mmHg)	0.58	0.50	0.72	0.67

GW: graft weight; SLW: standard liver weight calculated by 706.2 × body surface area plus 2.4; RW: recipient body weight; MELD: model for end-stage liver disease score.

Discussion

It is of great interest that simultaneous splenectomy decreased the risk of SFS graft syndrome for transplant patients with a GW-SLW ratio of 40% or less. A comparison of portal pressure and portal vein flow before and after splenectomy showed that both pressure and flow did decrease after splenectomy. Several LDLT techniques using SFS grafts have been proposed in order to avoid graft congestion and failure on account of over-perfusion [6,18]. Additionally, it has been reported that early postoperative portal pressure elevation to 20 mmHg or more results in a poor graft outcome in LDLT [19]. It is very hard to hypothesize which contributes more to post-transplant outcome, portal pressure or portal flow, because even univariate analysis did not reveal any relation between portal flow or pressure and graft function in the present study.

A multivariate analysis identified that having a male donor was an independent risk factor of SFS graft syndrome. The result seemed to be inconsistent with a previous report, which suggested an increased risk of graft failure in male recipients of female livers or in gender-

mismatched patients in cadaveric liver transplantation [20]. The sample size of this study was small; therefore, further study is needed to clarify how gender affects the outcome of liver transplantation, especially the outcome of LDLT.

As the splenic component accounts for up to 52% of the total portal venous flow [21], its contribution to portal hypertension cannot be ignored. Cheng *et al.* recently reported that the size of the spleen was in linear correlation with the amount of the portal flow [22]. Therefore, it makes sense that removal of the spleen reduces the portal flow. In the present study, spleen size was not associated with portal pressure, total portal flow or portal flow per 100 g of liver tissue. The size ratio of the liver graft to the recipient spleen size was not correlated with portal flow or portal pressure in the present study, contrary to the findings of a previous report [22].

With respect to previously reported results on splenectomy, some authors have stated that splenectomy in liver transplantation is closely associated with septic complications and a poorer prognosis [8,9,23]. Lusebrink *et al.* therefore recommended that splenectomy be performed only in very selected cases [24]. The incidence of septic complications in the present study, however, did not differ significantly between the two groups. We thus speculate that a whole graft has sufficient liver mass compared to a partial liver graft, and may not lead to excessive portal vein flow into the graft. It has been suggested that splenectomy may lead to insufficient portal flow, which induces hepatic atrophy and liver failure in whole liver graft transplantation [25]. This inadequate portal flow might lead to septic complications. Improvements in post-transplant care may also have contributed to a decrease in the occurrence of sepsis [26]. Further immunological study is required to determine how splenectomy affects the incidence of septic complications in liver transplantation.

Splenic artery ligation (SAL) as an alternative to splenectomy was performed in six cases in our institute. Although portal flow and portal pressure before closure in the SAL group did not differ from those in the Sp (+) group, SAL patients failed to recover their WBC ($2860 \pm 727/mm^3$) and platelet ($8.2 \pm 2.4 \times 10^4/mm^3$) counts 3 months after LDLT. Both counts were significantly lower than those of Sp (+) group ($P = 0.02$ and $P = 0.004$, respectively). Furthermore, serum total bilirubin (mg/dl) on POD 14 in the SAL group was higher than that in the Sp (+) group (14.4 ± 14.4 vs. 6.4 ± 7.3, $P = 0.03$). Umeda *et al.* recently reported the impact of preoperative splenic artery embolization [27]. This interventional radiology may become another alternative approach for portal decompression. Furthermore, there are reports in the literature that describe the salvage of small grafts by performing porto-systemic shunts [6,18]. Our basic strategy is to close any shunts as much as possible when performing LDLT. Portal flow is often diverted away when a huge shunt is kept patent, and if portal flow decreases too much, graft function will be impaired. We experienced a case in which the patient had to undergo re-laparotomy to close a large portocaval shunt [28]. Therefore, we attempt to close any shunts at the time of the LDLT and perform splenectomy as an inflow modification.

The splenectomy itself did not affect the operation time or the extent of blood loss during the LDLT in our series. Since October 2006, we have been using a vessel sealing system, LigaSure Atlas^{TM} (Valleylab, Boulder, CO, USA), for dissection around the spleen, which has made splenectomy safer and easier, even when the patient has severe portal hypertension [29]. The data on 13 patients were available regarding blood loss during splenectomy, and the mean blood loss was only 80 ml in all cases. We experienced intra-abdominal bleeding in 1 case after splenectomy, however, this patient was treated before the vessel sealing system had been adopted.

Some institutions recommend pre-emptive interferon therapy for patients with hepatitis C viremia after LDLT [30], however, one of the obstacles for introducing or continuing interferon therapy is pancytopenia. Kishi *et al.* recently published a preliminary report regarding the usefulness of splenectomy in maintaining platelet and WBC counts with respect to inducing and continuing pre-emptive interferon therapy [10]. We found that a partial graft could not correct portal hypertension with hypersplenism early after LDLT [5], therefore, we have decided to perform simultaneous splenectomy for all patients with hepatitis C in order to facilitate early IFN induction after LDLT since July 2005. In fact, only splenectomy was found to associate with improving WBC and platelet counts 3 months after LDLT in the present study.

The spleen has recently been the focus of other basic studies. Lesurtel *et al.* [31] recently reported that serotonin, which was mostly carried and released by platelets in the blood, is involved in the initiation of liver regeneration in a mouse hepatectomy model. Serotonin knock out mouse impaired hepatocyte proliferation after 70% hepatectomy, and was recovered after the replacement of serotonin precursor. Furthermore, transforming growth factor beta, which is a major antiproliferative factor for hepatocytes, was produced and secreted by the spleen during the early phase of liver regeneration in a rat two-thirds hepatectomy model [32]. These findings suggest therefore that the spleen may jeopardize the regenerative capacity of the liver, and that splenectomy may be recommended especially in patients with SFS graft, which requires extensive liver regeneration. Furthermore, a

basic study revealed that platelets, which significantly increased after the LDLT in the Sp (+) group in our study, promote liver regeneration after 70% hepatectomy in mice [33]. This result means that improving pancytopenia may be important in overcoming SFS graft syndrome, as well.

In conclusion, simultaneous splenectomy is favorable for overcoming SFS graft syndrome in LDLT patients with a GW-SLW ratio of 40% or less. Furthermore, splenectomy was an independent predictive factor for improving WBC and platelet counts after LDLT.

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Authorship

TY, AT, YS: designed study. TY, AT, YS, HU, TI, NH, Y-IY, HK: performed study. TY, YS, HK: collected data. TY, YM, TN: analyzed data. TY, YM: wrote the paper.

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