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Original Article

Splenectomy in living donor liver transplantation and risk factors of portal vein thrombosis

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ABSTRACT

Background: Graft inflow modulation (GIM) during adult-to-adult living donor liver transplantation (LDLT) is a common strategy to avoid small-for-size syndrome, and some transplant surgeons attempt small size graft strategy with frequent GIM procedures, which are mostly performed by splenectomy, in LDLT. However, splenectomy can cause serious complications such as portal vein thrombosis and overwhelming postsplenectomy infection.

Methods: Forty-eight adult-to-adult LDLT recipients were enrolled in this study and retrospectively reviewed. We applied the graft selection criteria, which routinely fulfill graft-to-recipient weight ratio $\geq$ 0.8%, and consider GIM as a backup strategy for high portal venous pressure (PVP).

Results: In our current strategy of LDLT, splenectomy was performed mostly due to hepatitis C and splenic arterial aneurysms, but splenectomy for GIM was intended to only one patient (2.1%). The final PVP values $\leq$ 20 mmHg were achieved in all recipients, and no significant difference was observed in patient survival or postoperative clinical course based on whether splenectomy was performed or not. However, 6 of 18 patients with splenectomy (33.3%) developed postsplenectomy portal vein thrombosis (PVT), while none of the 30 patients without splenectomy developed PVT after LDLT. Splenectomy was identified as a risk factor of PVT in this study ($P < 0.001$). Our study revealed that a lower final PVP could be risk factor of postsplenectomy PVT.

Conclusions: Using sufficient size grafts was one of the direct solutions to control PVP, and allowed GIM to be reserved as a backup procedure. Splenectomy should be avoided as much as possible during LDLT because splenectomy was found to be a definite risk factor of PVT. In splenectomy cases with a lower final PVP, a close follow-up is required for early detection and treatment of PVT.

Introduction

Liver transplantation is an established procedure for treating patients with end-stage liver disease. Since the indications for living donor liver transplantation (LDLT) were successfully extended from pediatric to adult cases, adult-to-adult LDLT has been widely accepted as an effective treatment for liver failure diseases [1,2]. As a partial graft is inevitable in LDLT, transplant surgeons often face problems related to the insufficient liver graft volume for the recipient's metabolic requirement. In general, liver grafts with graft-to-recipient weight ratio (GRWR) less than 0.8% or graft weight/standard liver volume ratio less than 40% have been considered as small-for-size grafts. Critical adverse events related to graft size-mismatching are collectively termed small-for-size syndrome (SFSS); these result in higher mortality and morbidity [3–5].

Previous reports have shown that sustained portal hypertension after liver transplantation is one of the important etiological factors of SFSS; higher portal venous pressure (PVP) at the end of LDLT results in a poor outcome for the recipients [5,6]. Clinical relevance of PVP modulation during LDLT has been recognized thereafter [7], and some transplant surgeons chose small grafts to opt for donor safety by performing concurrent graft inflow modulation (GIM) to avoid SFSS in LDLT. In the setting of LDLT with small grafts, more than 50% cases required GIM procedures, which were mostly performed by splenectomy [8,9]. However, splenectomy can

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Table 1
Demographic data of recipients and donors ($n = 48$).

Variables	Value
Recipient factors	
Sex (male/female)	23/25
Age (yr)	48.7 ± 13.2
MELD score	19.1 ± 8.7
Child-Pugh (A/B/C)	4/10/34
Etiology	
Viral hepatitis (HBV/HCV)	16 (5/11)
Cholestatic (PBC/PSC/BA)	11 (5/3/3)
Fulminant hepatic failure	3
Alcoholic cirrhosis	3
Autoimmune hepatitis	2
Graft dysfunction after LDLT	2
Other	11
HCC (beyond Milan criteria)	9 (3)
Donor factors	
Sex (male/female)	25/23
Age (yr)	41.5 ± 12.3
Graft factors	
Graft type (right/left)	38/10
Graft weight (g)	610.9 ± 145.2
Estimated GRWR (%)	1.02 ± 0.22
Actual GRWR (%)	1.08 ± 0.24
ABO blood type compatibility (identical/compatible/incompatible)	25/11/12
Pre-formed donor specific antibody (HLA class I/class II)	2/3

Unless stated otherwise, data are shown as average ± standard deviation.
BA: biliary atresia; GRWR: graft/recipient weight ratio; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; HLA: human leukocyte antigen; LDLT: living donor liver transplantation; MELD: model for end-stage liver disease; PBC: primary biliary cholangitis; PSC: primary sclerosing cholangitis.

cause serious complications such as portal vein thrombosis (PVT) and severe infections. While many studies have reported PVT risk factors after deceased donor liver transplantation [10,11], there are few studies that describe complications related to splenectomy and their risk factors in LDLT. Therefore, in this study, we examined our adult-to-adult LDLT cases to evaluate the impact of splenectomy during LDLT on the clinical outcomes of liver transplant recipients and further analyzed postsplenectomy PVT cases to investigate their risk factors.

Methods

Patients

Between August 2012 and January 2017, a total of 79 patients underwent LDLT at Nagoya University Hospital. Forty-eight adult-to-adult LDLT recipients (age ≥ 18 years) were enrolled in this study and retrospectively reviewed. Eighteen of the 48 LDLT recipients who underwent splenectomy during LDLT were further examined to investigate the risk factors of postsplenectomy PVT. The study protocol was approved by the Nagoya University Ethics Committee (Ethics Committee Approval No. 2016–0512).

The detailed demographic data of 48 LDLT recipients and donors are summarized in Table 1. The mean age of the recipients was 48.7 ± 13.2 years. Of 48 patients, 23 were men and 25 women. The mean model for end-stage liver disease score calculated for the liver recipients before LDLT was 19.1 ± 8.7. In 12 ABO-blood type incompatible combinations and 5 pre-formed donor-specific antibody transplants, a total of 500 mg of rituximab was administered before LDLT according to our desensitization protocol for the prevention of antibody-mediated rejection. The liver graft types were 38 (79.2%) right lobe grafts without the middle hepatic vein and 10 (20.8%) left lobe grafts with or without the caudate lobe.

Graft selection criteria

Dynamic contrast-enhanced computed tomography was performed to construct three-dimensional images for the hepatic artery, portal vein, and hepatic vein phase. Volumetric assessments of the hepatic graft and remnant liver were further analyzed with the imaging software HepaVision (MeVis, Bremen, Germany). Graft selection was decided based on volumetric analyses. We applied the selection criteria which fulfill GRWR ≥ 0.8% in order to avoid small-for-size grafts, in addition to the condition that the remnant liver for the living donors should be more than 30% after donation. The estimated graft weight was calculated using the imaging software before LDLT, and the actual graft weight was measured after graft perfusion on the back table in the operating room.

Surgical procedures

Donor hepatectomy and recipient liver transplantation were performed as described previously [12,13]. Briefly, a graft type was decided according to our graft selection criteria. In the case of a right lobe graft, significant drainage veins from the anterior segment, such as V5 or V8, were preserved in the liver graft and prepared for anastomosis on the back table to minimize hepatic venous congestion. In the case of left lobe graft, the graft contains the middle hepatic vein. The caudate lobe was included in the left lobe graft if the estimated GRWR of the left lobe graft without the caudate lobe was less than 0.8%.

After the recipient underwent total hepatectomy, reconstruction of the hepatic vein between the recipient and the liver graft was performed in an end-to-end fashion. The graft portal vein was anastomosed to the recipient portal vein. Anastomosis of the hepatic artery was performed using higher surgical loupe magnification. After reconstruction of all vessels, good triphasic hepatic venous outflow and sufficient portal and intrahepatic arterial flow were confirmed using intraoperative Doppler ultrasound.

Intraoperative PVP was monitored with an 18-gauge antithrombotic catheter inserted via a small jejunal venous branch and measured at three time points: (i) initial PVP, at the time of PVP monitoring catheter insertion; (ii) PVP after reflow of the liver graft; and (iii) final PVP, before abdominal closure. The optimal PVP was set below 20 mmHg after completion of all vessel anastomoses of the liver graft [6,14]. Portosystemic collateral vessels with a diameter larger than approximately 1 cm, e.g., gastric/esophageal varices, inferior mesenteric venous varices, and spleno-renal shunts, were clamped temporally to check the elevation of PVP, and then ligated.

Indications for splenectomy

Splenectomy was performed regardless of PVP levels in patients with hepatitis C (to prevent thrombocytopenia during posttransplant ribavirin/interferon combination therapy) and splenic arterial aneurysm (to prevent rupture with fatal hemorrhage). In recipients with PVP > 20 mmHg after all vessel anastomoses, splenectomy was also performed as a backup procedure to control PVP.

During splenectomy procedures, a vessel sealing system and an end-stapling device were used to avoid any injuries of fragile collateral vessels that could result in massive uncontrollable bleeding [15].

Evaluation of vascular patency and PVT diagnosis

Blood flow of liver grafts (hepatic vein, hepatic artery, and portal vein) was evaluated routinely twice a day using Doppler ultrasound until postoperative day (POD) 7 and once a day from POD 7 to 14 following LDLT. After POD 14, Doppler ultrasound was performed as required, approximately once a week. If recipients

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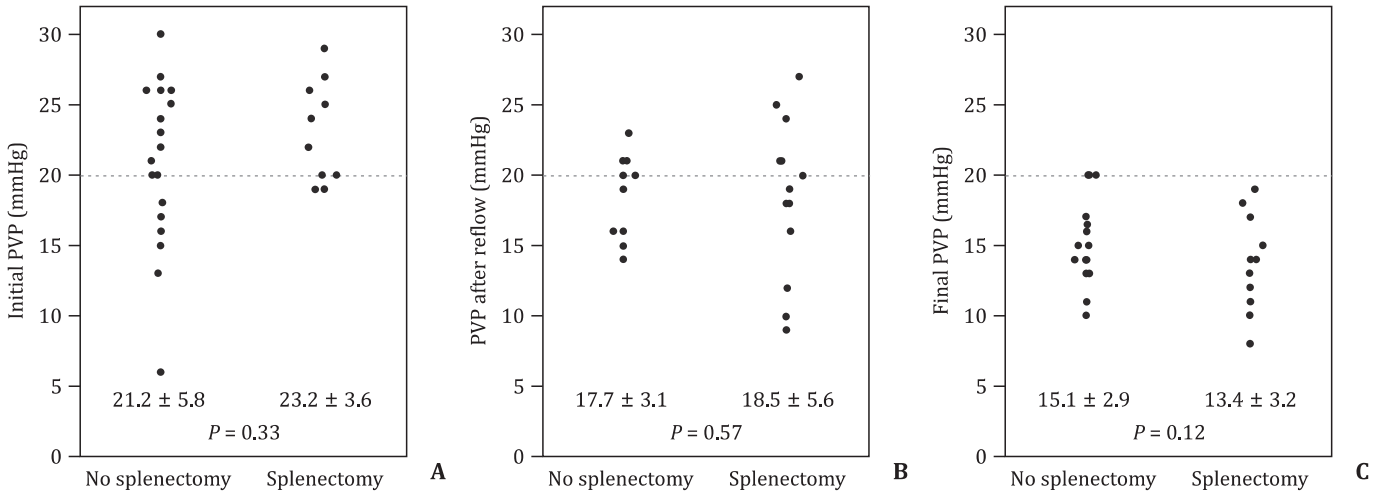

Fig. 1. Actual changes of portal venous pressure (PVP) during living donor liver transplantation. **A**: Initial PVP; **B**: PVP after reflow; **C:** Final PVP. Though PVP values > 20 mmHg after reflow were observed in 9 cases, final PVP values of ≤ 20 mmHg were achieved in all patients. The final PVP values were not significantly associated splenectomy performance (Mann–Whitney *U* test).

showed abnormal clinical courses (e.g., high fever, prolonged massive ascites, or elevated liver enzymes/hyperbilirubinemia in laboratory tests), dynamic contrast-enhanced computed tomography was performed to check biliary leakage, intraabdominal abscess, or vascular thrombosis. All the PVT cases in this study were diagnosed with either Doppler ultrasound or enhanced computed tomography.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation, mean ± standard error of the mean, or medians and ranges. Statistical analyses of continuous variables were performed with either Mann–Whitney's *U* test or repeated measure analysis of variance for repeated blood sample tests. Categorical variables were analyzed using the Chi-squared test or Fisher's exact test. The patient survival rates were calculated using the Kaplan–Meier method, and the log-rank test was used for between-group comparisons. Statistical calculations were performed with statistical software (JMP 13.0, SAS Institute Inc., Cary, NC, USA). Values of $P < 0.05$ were considered statistically significant.

Results

Overall survival and SFSS cases

The overall 5-year patient survival rate was 93.8% during a median follow-up period of 35 months (range 7–60 months). We have experienced three deceased cases due to shock liver after gastric ulcer bleeding, multiple organ failure, and chronic cholangitis, respectively, although the GRWR ≥ 0.8% and PVP ≤ 20 mmHg had been achieved in all these 3 cases. Our target GRWR values were set more than 0.8%, but there were 4 cases with actual GRWR values < 0.8% unexpectedly. However, these four patients did not show poor clinical outcomes.

According to the Clavien's criteria, graft dysfunction due to SFSS was defined as the presence of 2 of the following on 3 consecutive days: serum total bilirubin level (T-Bil) > 5.84 mg/dL (100 μmol/L), prothrombin time international normalized ratio (PT-INR) > 2, and encephalopathy grade 3 or 4 during the first operative week after exclusion of technical, immunological, and infectious causes [5]. While 4 cases fulfilled the Clavien's SFSS criteria, the overall 5-year patient survival rates of these 4 patients were 100%.

Splenectomy and PVP during LDLT

Splenectomy was performed in 18 cases (37.5%); the indication was hepatitis C in 12 cases, splenic arterial aneurysms in 4 cases, and removal of the spleno-renal shunt around the spleen in one case. Only in one remaining case, splenectomy was conducted for PVP modulation. In this patient, the PVP value was above 20 mmHg even after all vascular reconstructions.

Actual changes in the PVP during LDLT are shown in Fig. 1. PVP during LDLT was monitored in 14 of 18 patients with splenectomy (77.8%), and in 23 of 30 patients without splenectomy (76.7%). The mean initial PVP values were 21.2 ± 5.8 mmHg in patients without splenectomy and 23.2 ± 3.6 mmHg in patients with splenectomy ($P = 0.33$). Though PVP values > 20 mmHg after reflow were observed in 9 cases, final PVP values of ≤ 20 mmHg were eventually achieved in all patients. The final PVP values were 15.1 ± 2.9 mmHg in patients without splenectomy, and 13.4 ± 3.2 mmHg in patients with splenectomy ($P = 0.12$; Fig. 1C). There were no statistically significant differences of PVP values between patients with and without splenectomy in each corresponding PVP measure point.

Median postoperative follow-up periods in LDLT recipients with splenectomy were 37 months (9–57 months), and those without splenectomy were 32 months (7–60 months). The 4-year patient survival rates in patients with splenectomy were 94.4%, and those without splenectomy were 93.3%, which did not show significant difference (Fig. 2A). Comparison of immediate postoperative changes of total bilirubin level and prothrombin time-international normalized ratio (PT-INR) after LDLT were analyzed by repeated measure analysis of variance (Fig. 2B and C). This analysis didn't show any significant differences in both total bilirubin level and PT-INR between recipients with splenectomy and recipients without splenectomy group. Although PT-INR in patients with splenectomy on POD 28 seemed to be elongated, it was due to anticoagulant treatment by warfarin for prophylaxis of portal vein thrombosis.

Postsplenectomy PVT in recipients

Enhanced computed tomography after LDLT revealed postsplenectomy PVT in 6 of 18 patients who underwent splenectomy. The perioperative clinical features of the six patients are shown in Table 2. Three of six patients required thrombectomy by laparotomy on POD 1, 2, and 14, respectively, because PVT occurred in

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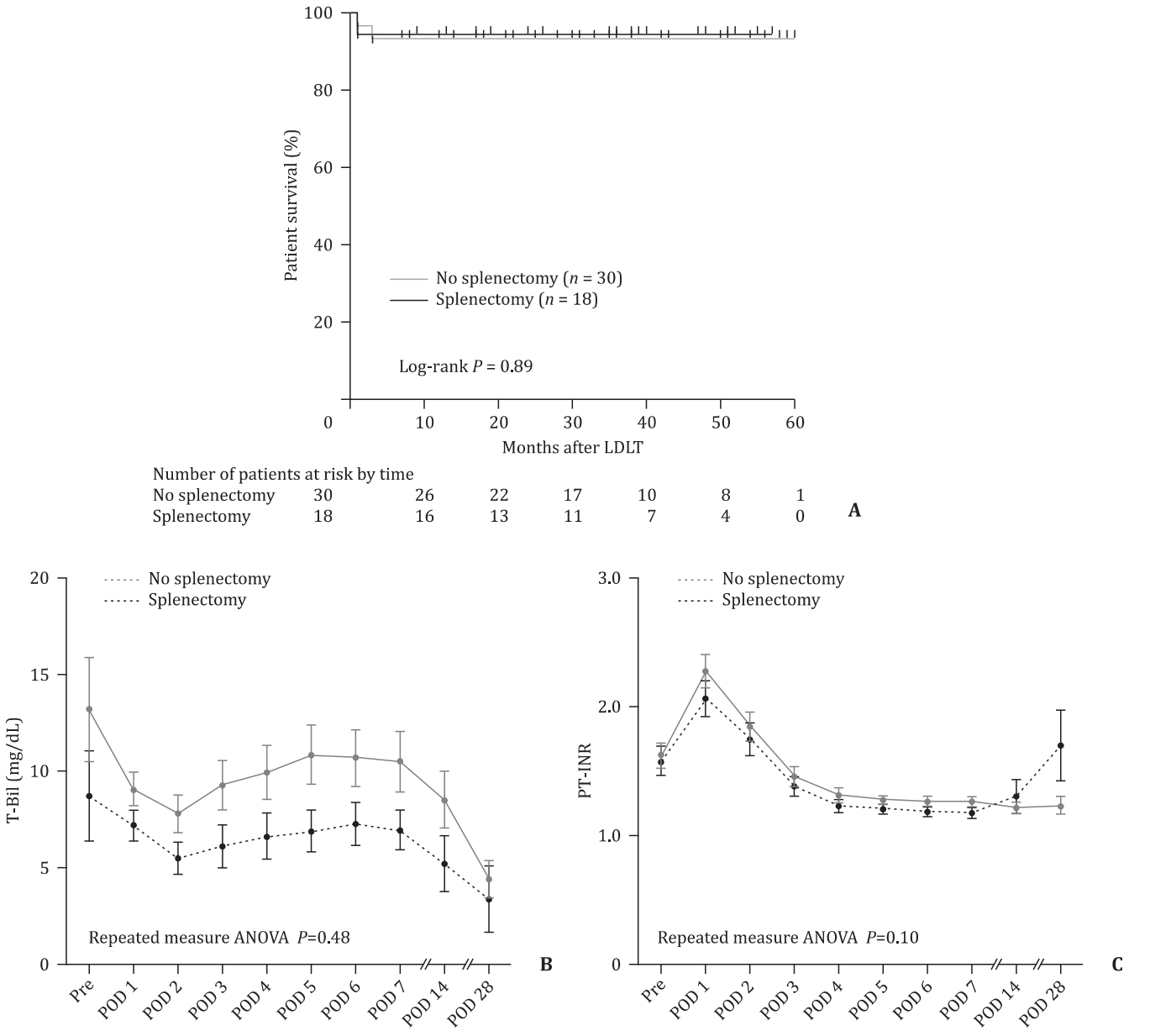

Fig. 2. **A**: Survival curves after living donor liver transplantation based on splenectomy; **B**: Posttransplant mean total bilirubin (T-Bil) plot with the standard error of the mean; **C**: Posttransplant mean prothrombin time international normalized ratio (PT-INR) plot with the standard error of the mean. No significant difference between the two groups was found in patient survival (Log-rank test) and serum levels of T-Bil and PT-INR (repeated measure analysis of variance).

Table 2
Profiles of 6 postsplenectomy PVT cases.

Case	Age (yr)	Sex	Etiology	Graft types	Actual GRWR	Indication for splenectomy	Final PVP (mmHg)	Location of PVT	Date of diagnosis	Treatment for PVT
1	62	Male	HCV-LC, HCC	Right	1.02%	HCV	14	P6	POD 58	Warfarin
2	54	Male	HCV-LC, HCC	Right	1.39%	HCV	NR	P7	POD 16	Warfarin
3	58	Female	HCV-LC	Right	1.33%	HCV	12	PV trunk	POD 1	Surgical thrombectomy Heparin→Warfarin
4	34	Male	HCV-LC	Right	1.26%	HCV	8	P6	POD 14	Warfarin
5	54	Female	HCV-LC	Right	1.09%	HCV	10	Posterior branch	POD 2	Surgical thrombectomy Heparin→Warfarin
6	45	Male	HBV-LC, HCC	Right	0.73%	SAA	11	PV trunk	POD 14	Surgical thrombectomy Heparin→Warfarin

GRWR: graft-to-recipient weight ratio; HBV-LC: hepatitis B virus-related liver cirrhosis; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; HCV-LC: hepatitis C virus-related liver cirrhosis; SAA: splenic arterial aneurysm; POD: postoperative day; PVP: portal venous pressure; PVT: portal vein thrombosis.

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Table 3
Comparison of perioperative variables between PVT and non-PVT cases among the 18 splenectomized recipients.

Variables	PVT ($n=6$)	Non-PVT ($n=12$)	P value
Recipient age (yr)	54 (34–62)	56 (19–65)	0.82
Recipient male sex	4 (66.7%)	6 (50.0%)	0.39
Donor age (yr)	38 (26–55)	32 (23–54)	0.45
Graft type, right lobe	6 (100%)	11 (91.7%)	0.47
GRWR	1.18% (0.73%–1.06%)	0.99% (0.84%–1.76%)	0.44
HCC	3 (50.0%)	4 (33.3%)	0.49
Preoperative PVT	0	0	–
Preoperative PT-INR	1.32 (1.15–1.94)	1.50 (1.07–3.15)	0.29
Preoperative platelet count ($\times 10^3/\mu$L)	38.5 (19.0–71.0)	49.5 (31.0–260.0)	0.29
Diameter of SPV (mm)	15 (10–20)	10 (8–15)	0.07
Surgical time (min)	745 (711–869)	689 (632–980)	0.21
Blood loss (mL)	10,141 (5073–17,090)	6535 (2734–24,317)	0.34
CIT (min)	86 (70–120)	60 (35–168)	0.15
WIT (min)	49 (35–67)	38 (28–55)	0.18
Interposition grafting	1 (16.7%)	1 (8.3%)	0.60
Ligation of collateral veins	4 (66.7%)	6 (50.0%)	0.50
HCV for splenectomy	5 (83.3%)	7 (58.3%)	0.29
Initial PVP (mmHg)	20 (19–29)	25 (19–27)	0.52
PVP after reflow (mmHg)	15 (9–21)	14 (10–19)	0.20
Final PVP (mmHg)	11 (8–14)	14 (10–19)	**0.04**
Portal venous flow (cm/s)	57 (30–117)	60 (35–168)	0.75

Data are given as n (%) or median (range).
CIT: cold ischemic time; GRWR: graft-to-recipient weight ratio; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; PT-INR: prothrombin time-international normalized ratio; PVP: portal venous pressure; PVT: portal vein thrombosis; SPV: splenic vein; WIT: warm ischemic time.

the main branch of the portal vein and the occlusion involved the entire lumen of main portal vein. After the PVT removal operation, the patients were maintained on a heparin infusion that was later converted to warfarin. In the other three patients, PVTs were located in the peripheral branches of the portal vein and the portal flow into the liver graft was mostly preserved. As the patients were asymptomatic and laboratory tests showed no elevation of transaminase levels, we treated them with oral administration of warfarin. None of the 30 patients without splenectomy developed PVT after LDLT. Splenectomy was identified as a risk factor for postoperative PVT based on a comparison between splenectomized and non-splenectomized recipients (33.3% vs 0, $P < 0.001$).

Risk factors for postsplenectomy PVT

The comparison of perioperative variables between PVT and non-PVT cases among the 18 splenectomized patients is shown in Table 3. Although the differences between PVT and non-PVT patients were not statistically significant at initial PVP or PVP at reflow, the final PVP values were significantly lower in PVT patients compared with non-PVT patients ($P=0.04$). On the other hand, the portal venous flow, measured with ultrasonographic examination at the time of intensive care unit admission immediately after LDLT, showed no statistically significant difference. In the PVT cases, preoperative diameter of the splenic vein was marginally larger than in non-PVT cases ($P=0.07$). There were no significant differences in the age, sex, and other preoperative and surgical variables.

Discussion

Donor safety is of paramount importance in LDLT, and some transplant surgeons have attempted LDLT with a smaller graft to reduce the risk to healthy volunteer living donors [16,17]. When applying the small graft strategy, frequent GIM procedures are inevitable to control excessive portal inflow in the recipient. However, there are some risks in GIM if splenectomy is performed or portosystemic shunts are created. First, it is necessary to control hepatofugal collateral pathways during LDLT to increase the postoperative portal inflow and reduce ischemic damage to the graft, but GIM might have the opposite effect to adequate portal inflow, which is essential for rapid regeneration of liver grafts after LDLT [18]. Moreover, two major concerns after splenectomy are vascular complications and severe infections, so-called overwhelming postsplenectomy infection caused by *Streptococcus pneumoniae* [19]. As the sequelae of PVT and *S. pneumoniae* sepsis are serious in LDLT recipients [19,20], unnecessary splenectomy should be avoided in liver transplantation.

We apply the graft selection criteria, which routinely fulfill GRWR $\geq$ 0.8%, and consider GIM as a backup strategy for high PVP after the reflow. In our current strategy of adult-to-adult LDLT, splenectomy intended for GIM was performed only for one recipient out of 48 adult recipients. Based on our graft selection criteria, all patients in this study could achieve the final PVP of $<$ 20 mmHg without a frequent GIM procedure, and with excellent consequences. Recently, hepatitis C has not been an indication for splenectomy in our institution because treatment for hepatitis C has changed from ribavirin/interferon combination therapy to interferon-free direct-acting antiviral therapy. Considering our result that splenectomy was performed mostly due to hepatitis C (in 12 of 18 splenectomy cases), much less cases will require splenectomy in the future. Our graft selection criteria with large grafts (GRWR $\geq$ 0.8%) made it possible to control PVP and minimize the indication for splenectomy as GIM during LDLT.

Our selection criteria of GRWR $\geq$ 0.8% denotes higher demand for right lobe grafts, as has been the case for approximately 80% of our living donors. This leaves concerns regarding the risks for living donors. However, the mortality risk did not vary significantly between left and right lobe donations, as seen in a recent worldwide survey [21]. In our study, no living donors experienced severe life-threatening complications (Clavien's grading system Grade IIIb or higher). These results suggested that the risk of right lobectomy was comparable to that of left lobectomy and right lobe donation could be performed safely.

None of our recipients experienced overwhelming postsplenectomy infection in the present study, while enhanced computed tomography after LDLT demonstrated that 6 of 18 (33.3%) patients with splenectomy developed postsplenectomy PVT. Splenectomy was identified as a risk factor associated with the development of PVT in this study. However, splenectomy has the benefit of

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avoiding SFSS [7,9]. What we found in LDLT with sufficient graft size was that high PVP could still be observed, and in that particular patient, GIM functioned to avoid SFSS. In addition, splenectomy is a necessary procedure for LDLT recipients with splenic arterial aneurysm to prevent rupture. Because a certain number of LDLT recipients should undergo splenectomy during LDLT, it is important to identify the risk factors of postsplenectomy PVT.

This study revealed that a lower final PVP could be risk factor of postsplenectomy PVT in LDLT. It is interesting to note that the final PVP values of patients with splenectomy were significantly lower in PVT patients than in non-PVT patients; on the contrary, the portal venous flow was not significantly different between the two groups. In splenectomy cases with lower final PVP and larger diameter of the splenic vein, frequent Doppler ultrasound will be required for early detection of PVT after LDLT.

Although the larger diameter of the splenic vein didn't reach the statistical significance, previous reports have shown that the preoperative diameter of the splenic vein is a useful predictor of PVT after laparoscopic splenectomy [22,23]. Data was not shown in this paper, but we found various numbers of thrombosis inside the large diameter of the splenic vein, which should be monitored carefully for its extension towards the portal vein.

A limitation of our study is that multivariate analysis was not performed because this is a single-institution study with a small number of patients who underwent splenectomy ($n = 18$). It remains unclear whether a lower final PVP or larger diameter of the splenic vein are directly relevant to postsplenectomy PVT. Nevertheless, the possible influence of these factors on the pathogenesis of PVT cannot be excluded and will require further study. When the risk factors of postsplenectomy PVT are determined in a large sample size study, splenectomy cases with such risk factors would need intensive anticoagulation treatment for several weeks after LDLT to prevent PVT.

In conclusion, using sufficient size grafts was one of the direct solutions to control PVP, and allowed GIM to be reserved as a backup procedure. Splenectomy should be avoided as much as possible during LDLT because splenectomy was found to be a definite risk factor of PVT. However, splenectomy is still an effective GIM procedure in some LDLT cases. In splenectomy cases with a lower final PVP, a close follow-up is required for early detection and treatment of PVT.

Contributors

Ogura Y proposed the study. KN and Ogura Y performed the research and wrote the first draft. KN, Ogura Y, OS, Onishi Y and KH collected the data and analyzed the data. All authors contributed to the design and interpretation of the study and to further drafts. KY is the guarantor.

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Ethical approval

The study protocol received an approval by the Nagoya University Ethics Committee (Ethics Committee Approval No. 2016-0512).

Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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