Portal vein pressure modulation in adult living donor liver transplant: a necessity for achieving better outcomes

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Background
Living donor liver transplantation was first introduced as an alternative to deceased donor liver transplantation. In adult living donor liver transplantation (ALDLT), it is inevitable that the graft would be smaller than the native liver. However, if the graft function is not sufficient to satisfy the metabolic needs of the recipient, small-for-size syndrome (SFSS) can be encountered. Elevated portal vein pressure (PVP) is believed to be a main contributor in the pathophysiology of the SFSS. Therefore, we analyzed the potential effect of PVP on the outcomes in ALDLT in this study.
Patients and methods
Data were gathered prospectively for patients who underwent ALDLT with PVP monitoring during the period between June 30, 2018, and June 30, 2020, in Kyoto University Hospital. As a result, 36 patients were enrolled in our study. Modulation was done by splenectomy (SPX) when graft weight-to-recipient spleen volume ratio was less than or equal to 0.7 g/ml or PVP after graft reperfusion was more than 15 mmHg when graft was obtained from older or ABO incompatible donors.
Results
With this modulation strategy, SFSS was not encountered, and overall survival was 100%. High final PVP tended to be encountered in smaller graft weight, lower donor BMI, and left lobe grafts. Graft weight-to-spleen volume ratio less than 0.64 g/ml was an independent risk factor for high PVP after graft reperfusion. SPX was safely done with no difference in complications, postoperative platelet count was higher, and daily ascites amount was lower in patients who underwent SPX.
Conclusion
PVP monitoring and modulation is a necessity for good outcomes after ALDLT.

Keywords:
graft-to-spleen volume ratio, living donor liver transplantation, portal vein pressure, small-for-size, splenectomy

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Introduction

Living donor liver transplantation (LDLT) was first introduced as an alternative to deceased donor liver transplantation for treatment of end-stage liver diseases [1,2]. LDLT indication was extended to include both adult and pediatric age groups [3,4]. In adult living donor liver transplantation (ALDLT), it is inevitable that the graft would be smaller than the native liver. However, if the graft function is not sufficient to satisfy the metabolic needs of the recipient, the small-for-size syndrome (SFSS) can be encountered. Elevated portal vein pressure (PVP) is believed to be a main contributor in the pathophysiology of the SFSS. Therefore, we analyzed the potential effect of PVP on the outcomes in ALDLT in this study.

Patients and methods

Study population

Data were gathered prospectively for patients who underwent ALDLT with PVP monitoring during the period between June 30, 2018 and June 30, 2020, in Kyoto University Hospital. An adult recipient was defined as a patient aged more than 18 years old. Patients who underwent deceased donor liver transplantation, as pediatric recipients, and patients with no PVP were excluded from the study. As a result, 36 patients were enrolled in our study (Fig. 1). This research was performed in the Hepatobiliary, Pancreatic, Transplantation Surgery Department, Kyoto University Hospital. Ethical Committee approval and written informed consent were obtained from all participants.

Selection criteria for donors and recipients and middle hepatic vein reconstruction strategy

All donors were examined for liver/spleen ratio through noncontrast computed tomography scan

by CTW3000 (Hitachi Medical Systems, Tokyo, Japan) to assess the degree of hepatic steatosis. Only donors with liver/spleen ratio more than 1.1 (<30% macrovesicular steatosis) were accepted for donation [5]. In the left lobe graft (LLG), middle hepatic vein (MHV) was procured within the graft, whereas in the right lobe graft without MHV, a segmental vein (such as V5 and V8) was considered significant when the drained area represented more than 10% of the graft and then it was preserved for reconstruction. SYNAPSE VINCENT software (Fujifilm Medical Co. Ltd, Tokyo, Japan) was the software tool used for measuring the congested volume of the graft as well as the volume of the whole graft [6]. The lower limit of graft-to-recipient weight ratio (GRWR) was planned to be 0.6%.

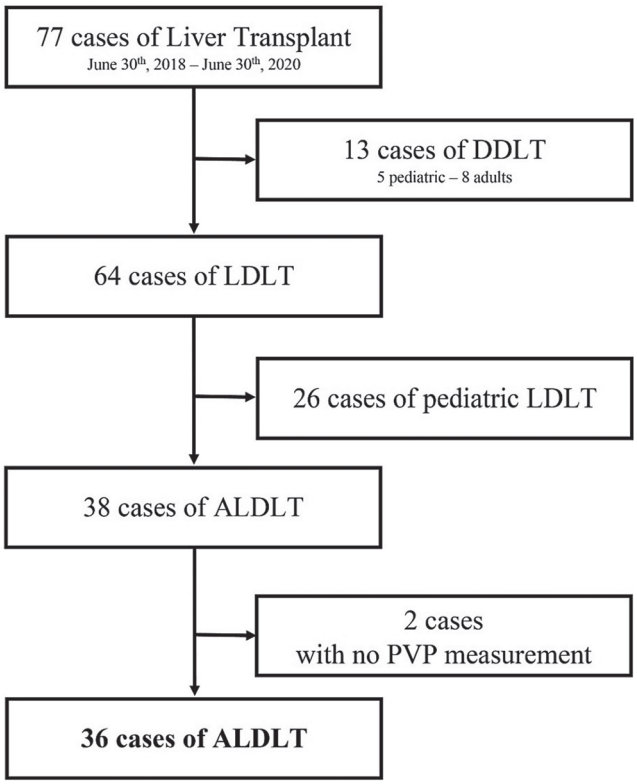
Portal vein pressure modulation: preoperative indication 'graft weight-to-spleen volume ratio'

Spleen volume was calculated in milliliters by creating three-dimensional image of the recipient's spleen. Graft weight-to-spleen volume ratio (GSVR) was calculated by dividing the graft weight in grams by the estimated spleen volume in milliliters. In February 2019, an indication for splenectomy (SPX) was proposed when the estimated GSVR was less than or equal to 0.7 g/ml, regardless of the intraoperative PVP measurements. All preoperative computed tomgraphy imaging was obtained within 2 months before the LT. Spleen volume measurement was performed using SYNAPS VINCENT software (Fujifilm Medical Co. Ltd) [7].

Portal vein pressure modulation: intraoperative indication 'portal vein pressure measurement'

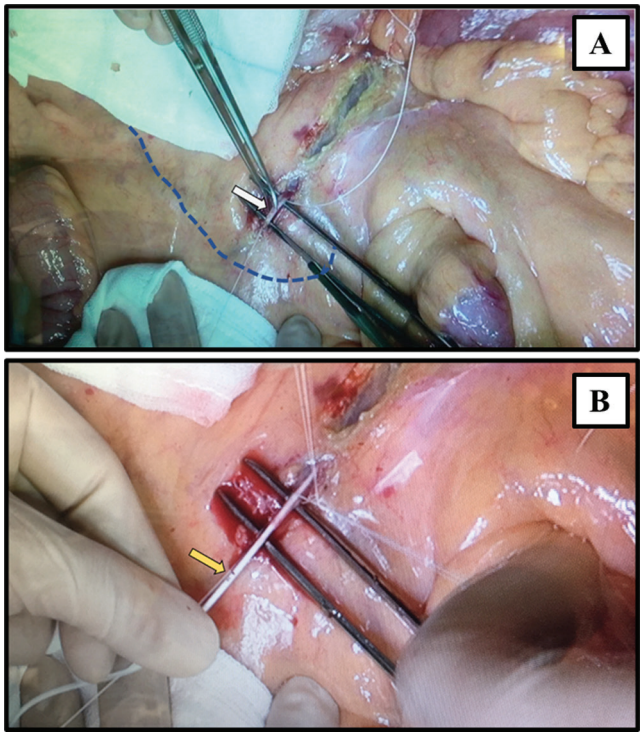
An 18-G catheter was inserted via a small jejunal vein branch to monitor the PVP. The tip of the catheter was positioned in the recipient's superior mesenteric vein or a jejunal vein (Fig. 2). The portal vein catheter was removed before abdominal closure to prevent infection or thrombosis. Decision for modulation was taken when PVP was persistently more than 15 mmHg after hepatic graft arterial flow reconstruction. Modulation was indicated only for recipients receiving grafts from donors with at least one risk factor, older donors (>45 years old) and/or ABO incompatible donors, after updating the policy in 2018 [8]. PVP modulation was performed by SPX. Large spontaneous portosystemic shunts, for example, splenorenal shunt or coronary vein, were ligated to prevent steal phenomenon, after PVP monitoring while shunt test clamping. If PVP was more than 15 mmHg on temporary shunt clamping and the graft had one of the mentioned risk factors, SPX was done first with the shunt open, and then the shunt was ligated.

Figure 1



Study population.

Figure 2



PVP catheter insertion. (a) Jejunal vein (white arrow). Caution not to injure marginal vessels (blue dashed line), (b) 18-G catheter (yellow arrow) inserted for 7-cm length. PVP, portal vein pressure.

Immunosuppression

Immunosuppressant drugs, consisting of tacrolimus or cyclosporine and mycophenolate mofetil, were started within 24 h after ALDLT in all patients. All ABO-incompatible recipients were administered rituximab (500 mg/body) more than 2 weeks before transplantation as well as tacrolimus and mycophenolate mofetil one week before transplantation [9].

Study design and statistical analysis

The study population was divided according to the final PVP into 'high final PVP' and 'low final PVP' with a cut-off value of 15 mmHg. The whole study population was also divided, according to PVP modulation by SPX, into two different groups: SPX group and no SPX group. All variables were presented and tested for difference between each pair of groups. Categorical variables were presented as numbers and percentages, whereas continuous data were presented as a median with range or interquartile range. Although categorical variables were tested using Pearson's χ^2 test, continuous variables were tested using Mann–Whitney *U* test. Risk factor analyses for both high PVP after reperfusion and high final PVP were conducted. Risk factor analyses were made by logistic regression fit model. Variables with a *P* value less than 0.1 by logistic regression univariate analysis were considered candidates for multivariate analysis. When a continuous variable was a candidate for multivariate analysis, a cutoff value was created using the receiver operating characteristic (ROC) curve, and this variable was re-entered as a categorical variable. Odds ratio and 95% confidence interval were calculated for each variable. Statistical significance was considered when the *P* value was less than 0.05. The overall survival analysis was analyzed using Kaplan–Meier survival curve. All statistics were calculated using JMP Pro 16 software (SAS Institute, Cary, North Carolina, USA).

Results

Baseline characteristics and posttransplantation outcome

Final portal vein pressure groups

Baseline characteristics: distribution of variables and differences between the two groups of high and low final PVP as well as the whole population are shown in Table 1. Median final PVP in the low and high final PVP groups were 11 and 17 mmHg, respectively. High-grade PVT, donor BMI, graft weight, and LLG type were significantly different across the two groups. GRWR% tended to be lower in the high PVP group; however, statistical significance could not be reached.

Outcomes and graft function: there was no significant difference between the two final PVP groups regarding outcomes (Table 1). Chronological changes in graft function tests across the two groups of final PVP are shown in Figure 3. Although ascites amount per day tended to be higher in the high final PVP group in the first 14 days after transplantation, statistically significant differences were not achieved. Other graft functions showed almost no differences between the two groups (Fig. 3).

Splenectomy and no splenectomy groups

Baseline characteristics: distribution of variables and differences between the two groups of SPX and no SPX are shown in Table 2. Preoperative spleen volume, GSVR, and warm ischemia time (WIT) had a significant difference across the two groups. High PVP after reperfusion and high final PVP were significantly more prevalent in the SPX group.

Outcomes and graft function: patients in the SPX group had a significantly longer operative time and shorter postoperative hospital length of stay with no difference regarding postoperative complications. Graft function tests showed no significant difference between the SPX groups except for the aspartate transaminase on postoperative day (POD)1, which showed significant elevation in the SPX group (*P*=0.02). Daily ascites amounts were significantly less in the SPX group from POD7 to POD28. Platelet counts were significantly higher in the SPX group all along the early postoperative course (Fig. 4).

Logistic regression risk factor analysis

Risk factors for high final portal vein pressure

By univariate analysis, graft weight, LLG, and donor BMI were candidates for multivariate risk factor analysis (*P*<0.1). The cutoffs for graft weight and donor BMI were determined with the ROC curve with association to high final PVP. Graft weight cutoff was set at 400 g [area under the curve (AUC) was 0.78, sensitivity=72%, and specificity 83%]. Similarly, donor BMI cutoff was determined at 23.2 kg/m^2 (AUC=0.77, sensitivity=100%, and specificity 55%). Although graft weight less than 400 g, LLG, and donor BMI less than 23.2 kg/m^2 were significant risk factors for high final PVP by univariate analysis, none of the three variables were an independent risk factor by multivariate analysis (Table 3).

Risk factors for high portal vein pressure after reperfusion

By univariate analysis, GSVR, older donor age, and WIT were candidates for multivariate risk factor analysis (*P*<0.1). The cutoffs for graft weight and donor BMI were determined with the ROC curve with association to high PVP after reperfusion. The GSVR cutoff was set at 0.64 g/ml (AUC=0.70, sensitivity=63%, and specificity 87%). Similarly, WIT was determined

Table 1 Characteristic distributions in the whole population and between the two groups of final portal vein pressure

	Whole (*N*=36)	Low final PVP (*N*=29)	High final PVP (*N*=7)	*P* value
Recipient age (years)	56.5 (21.0–69.9)	56.7 (22.6–69.9)	55.8 (21.0–69.9)	0.47
Recipient sex (female)	20 (55.6)	14 (48.3)	6 (85.7)	0.07
Recipient's body composition				
BMI (kg/m^2)	23.6 (15.8–33.6)	23.9 (15.8–33.6)	20.5 (16.5–26.4)	0.15
Primary disease				
HCC	13 (36.1)	11 (37.9)	2 (28.6)	0.64
PSC/PBC/BA	9 (25.0)	8 (27.6)	1 (14.3)	0.47
HCV	5 (13.9)	5 (17.3)	0	0.24
HBV	5 (13.9)	4 (13.8)	1 (14.3)	0.97
Alcoholic	5 (13.9)	4 (13.8)	1 (14.3)	0.97
Liver function status				
MELD score	13 (3–40)	13 (3–40)	13 (9–20)	0.92
Child–Pugh class				
A	1 (2.8)	1 (3.5)	0	0.62
B	10 (27.8)	9 (31.0)	1 (14.3)	0.37
C	25 (69.4)	19 (65.5)	6 (85.7)	0.30
History of GI bleeding	15 (42.9)	11 (37.9)	4 (66.7)	0.20
Ascites amount				
Nil	9 (25.0)	8 (27.6)	1 (25.0)	0.47
Mild	11 (30.6)	8 (27.6)	3 (42.9)	0.43
Moderate to massive	16 (44.4)	13 (44.8)	3 (42.9)	0.93
Preoperative PVT	6 (16.7)	4 (13.8)	2 (28.6)	0.35
Grades 1 and 2	5 (13.9)	4 (13.8)	1 (14.3)	0.97
Grade 3	1 (2.8)	0	1 (14.3)	0.04
Preoperative spleen volume (ml)	562 (202–1777)	553 (202–1777)	630 (288–1085)	0.87
Massive splenomegaly (>1000 ml)	5 (15.6)	4 (15.4)	1 (16.7)	0.94
GSVR (g/ml)	1.00 (0.32–3.35)	1.04 (0.32–3.35)	0.79 (0.42–1.16)	0.24
GSVR <0.7 g/ml	8 (25.0)	5 (19.2)	3 (50.0)	0.12
Preoperative platelet count (×10^3/μl)	60 (26–233)	61 (29–233)	58 (26–162)	0.39
Graft-related variables				
ABO incompatible	7 (19.4)	5 (17.2)	2 (28.6)	0.50
Donor age (years)	37.7 (20.7–60.2)	41.6 (20.7–60.2)	34.0 (22–50.2)	0.25
Older >45 years	15 (41.7)	13 (44.8)	2 (28.6)	0.43
Donor BMI (kg/m^2)	22.6 (16.1–28.7)	23.5 (18.1–28.7)	20.6 (16.1–23.2)	0.03
Donor L/S ratio	1.26 (1.1–1.68)	1.24 (1.10–1.68)	1.27 (1.17–1.32)	0.76
Graft type (left lobe)	13 (36.1)	8 (27.6)	5 (71.4)	0.03
Graft weight (g)	592 (310–880)	610 (320–880)	335 (310–740)	0.03
GRWR (%)	0.88 (0.54–1.58)	0.76 (0.56–1.43)	0.69 (0.54–1.58)	0.09
GRWR <0.8%	13 (36.1)	9 (31.0)	4 (57.1)	0.20
Operation-related variables				
CIT (min)	85.5 (29–267)	83 (29–267)	102 (37–233)	0.95
WIT (min)	40.5 (21–176)	39 (21–60)	53 (29–176)	0.21
PVP measurements				
Initial PVP (mmHg)	19.5 (6–32)	19 (6–32)	25 (14–31)	0.17
PVP after reperfusion (mmHg)	14 (7–28)	13 (7–19)	20.5 (15–28)	0.01
PVP after reperfusion >15 mmHg	9 (25.0)	4 (13.8)	5 (71.4)	<0.01
Final PVP (mmHg)	12 (7–21)	11 (7–15)	17 (16–21)	<0.01
Simultaneous splenectomy	8 (22.2)	4 (13.8)	4 (57.1)	0.01
Presence of collaterals	28 (77.8)	22 (75.8)	6 (85.7)	0.57
Ligation of collaterals	23 (85.2)	17 (81.0)	6 (85.7)	0.25
Blood loss (l)	5.0 (0.78–15.9)	5.0 (0.8–15.9)	6.9 (1.3–12.3)	0.41
Blood loss/body weight (ml/kg)	82.9 (12.5–306.7)	79.3 (12.5–192.1)	139.3 (21.7–306.7)	0.23
Packed RBCs transfusion (U)	9 (0–52)	10 (0–52)	8 (0–30)	0.86
FFP transfusion (U)	10 (0–36)	8 (0–36)	10 (0–36)	0.43
Operative time (h)	12.3 (7.8–18.2)	12.1 (7.8–18.1)	15.0 (9.9–18.2)	0.13
Outcome				
ICU stay (days)	14 (7–34)	14 (7–33)	14 (12–34)	0.45
Hospital LOS (days)	52 (23–125)	52 (23–125)	42 (30–107)	0.75

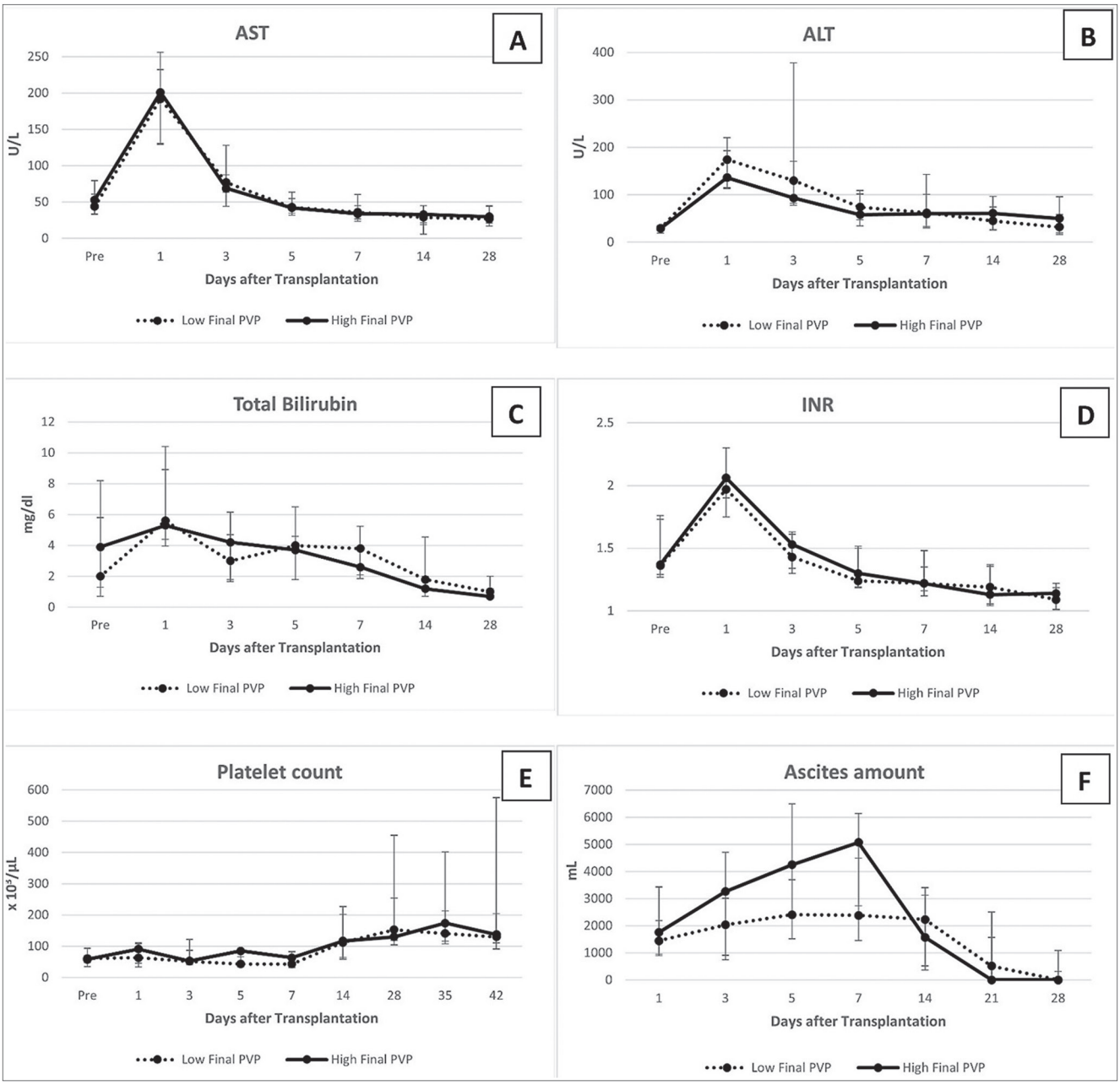
(*Continued*)

Table 1 (Continued)

	Whole (*N*=36)	Low final PVP (*N*=29)	High final PVP (*N*=7)	*P* value
SFSS	0	0	(0.0)	
30-day reoperation	6 (17.1)	5 (17.2)	1 (14.3)	0.85
30-day rejection	12 (33.3)	10 (34.5)	2 (28.6)	0.77
30-day bacterial infection	19 (52.8)	15 (51.7)	4 (57.1)	0.80
Vascular complications	5 (13.9)	5 (17.2)	0	0.24
Biliary complication	10 (27.8)	9 (31.0)	1 (14.3)	0.37

Data are presented as median (range) or *n* (%).
BA, biliary atresia; CIT, cold ischemia time; FFP, fresh frozen plasma; GI, gastrointestinal; GRWR, graft-to-recipient weight ratio; GSVR, graft-to-spleen volume ratio; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; L/S ratio, liver/spleen CT attenuation ratio; LOS, length of stay; MELD, model of end-stage liver disease; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; PVP, portal vein pressure; PVT, portal vein thrombosis; RBCs, red blood cells; SFSS, small-for-size syndrome; WIT, warm ischemia time.

Figure 3



Chronological changes in graft function tests between the high and low final PVP groups. Data are presented as median and interquartile range. ALT, alanine transaminase; AST, aspartate transaminase; INR, international normalized ratio; PVP, portal vein pressure.

Table 2 Characteristic distributions in the whole population and between the two groups, with and without splenectomy

	Whole (*N*=36)	SPX (*N*=8)	No SPX (*N*=28)	*P* value
Recipient age (years)	56.5 (21.0–69.9)	50.5 (21.0–61.2)	58.8 (22.6–69.9)	0.11
Recipient sex (female)	20 (55.6)	3 (37.5)	17 (60.7)	0.24
Recipient's body composition				
BMI (kg/m^2)	23.6 (15.8–33.6)	22.4 (19.3–26.4)	23.9 (15.8–33.6)	0.31
Primary disease				
HCC	13 (36.1)	2 (25.0)	11 (39.3)	0.46
PSC/PBC/BA	9 (25.0)	3 (37.5)	6 (21.4)	0.35
HCV	5 (13.9)	0	5 (17.9)	0.20
HBV	5 (13.9)	2 (25.0)	3 (10.7)	0.30
Alcoholic	5 (13.9)	0	5 (17.9)	0.20
Liver function status				
MELD score	13 (3–40)	11.5 (6–16)	15 (3–40)	0.06
Child–Pugh class				
A	1 (2.8)	0	1 (3.6)	0.59
B	10 (27.8)	3 (37.5)	7 (25.0)	0.49
C	25 (69.4)	5 (62.5)	20 (71.4)	0.63
History of GI bleeding	15 (42.9)	4 (50.0)	11 (39.3)	0.59
Ascites amount				
Nil	9 (25.0)	1 (12.5)	8 (28.6)	0.35
Mild	11 (30.6)	3 (37.5)	8 (28.6)	0.63
Moderate to massive	16 (44.4)	4 (50.0)	112 (42.9)	0.72
Preoperative PVT	6 (16.7)	1 (12.5)	5 (17.9)	0.72
Grade 1 and 2	5 (13.9)	0	5 (17.9)	0.20
Grade 3	1 (2.8)	1 (12.5)	0	0.06
Preoperative spleen volume (ml)	562 (202–1777)	1038.5 (624–1777)	464.5 (202–1117)	<0.01
Massive splenomegaly (>1000 ml)	5 (15.6)	4 (50.0)	1 (3.6)	<0.01
GSVR (g/ml)	1.00 (0.32–3.35)	0.54 (0.37–1.16)	1.12 (0.32–3.35)	<0.01
GSVR <0.7 g/ml	8 (25.0)	7 (87.5)	1 (4.2)	<0.01
Graft-related variables				
ABO incompatible	7 (19.4)	3 (37.5)	4 (14.3)	0.14
Donor age (years)	37.7 (20.7–60.2)	47.9 (20.7–58.0)	36.8 (21.0–60.2)	0.54
Older >45 years	15 (41.7)	5 (62.5)	10 (35.7)	0.18
Donor BMI (kg/m^2)	22.6 (16.1–28.7)	23.2 (19.0–24.0)	22.0 (16.1–28.7)	0.89
Donor L/S ratio	1.26 (1.1–1.68)	1.28 (1.14–1.57)	1.24 (1.10–1.68)	0.70
Graft type (left lobe)	13 (36.1)	2 (25.0)	11 (39.3)	0.46
Graft weight (g)	592 (310–880)	625 (310–820)	577.5 (320–880)	0.62
GRWR (%)	0.88 (0.54–1.58)	0.92 (0.62–1.58)	0.85 (0.54–1.43)	0.70
GRWR <0.8%	13 (36.1)	2 (25.0)	11 (39.3)	0.46
Operation-related variables				
CIT (min)	85.5 (29–267)	109 (37–223)	78.5 (29–267)	0.16
WIT (min)	40.5 (21–176)	53 (33–176)	38 (21–131)	0.02
WIT >45 min	14 (38.9)	5 (62.5)	9 (32.1)	0.12
PVP measurements				
Initial PVP (mmHg)	19.5 (6–32)	22 (14–31)	19 (6–32)	0.33
PVP after reflow (mmHg)	14 (7–28)	18 (15–28)	13 (7–21)	<0.01
Final PVP (mmHg)	12 (7–21)	14 (9–21)	12 (7–20)	0.54
High final PVP	7 (19.4)	4 (50.0)	3 (10.7)	0.01
Presence of collaterals	28 (77.8)	7 (87.5)	21 (75.0)	0.45
Ligation of collaterals	23 (85.2)	5 (62.5)	18 (64.3)	0.93
Blood loss (l)	5.0 (0.78–15.9)	6.3 (2.3–12.1)	4.4 (0.78–15.9)	0.31
Blood loss/body weight (ml/kg)	82.9 (12.5–306.7)	95.1 (30.5–187.2)	65.1 (12.5–306.7)	0.30
Packed RBCs transfusion (U)	9 (0–52)	8 (4–30)	10 (0–52)	0.95
FFP transfusion (U)	10 (0–36)	10 (0–28)	9 (0–36)	0.80
Operative time (h)	12.3 (7.8–18.2)	15.4 (13.6–18.2)	12.0 (7.8–17.4)	<0.01
Outcome				
ICU stay (days)	14 (7–34)	13 (9–17)	14 (7–34)	0.54
Hospital LOS (days)	52 (23–125)	34 (29–60)	55 (23–125)	0.01

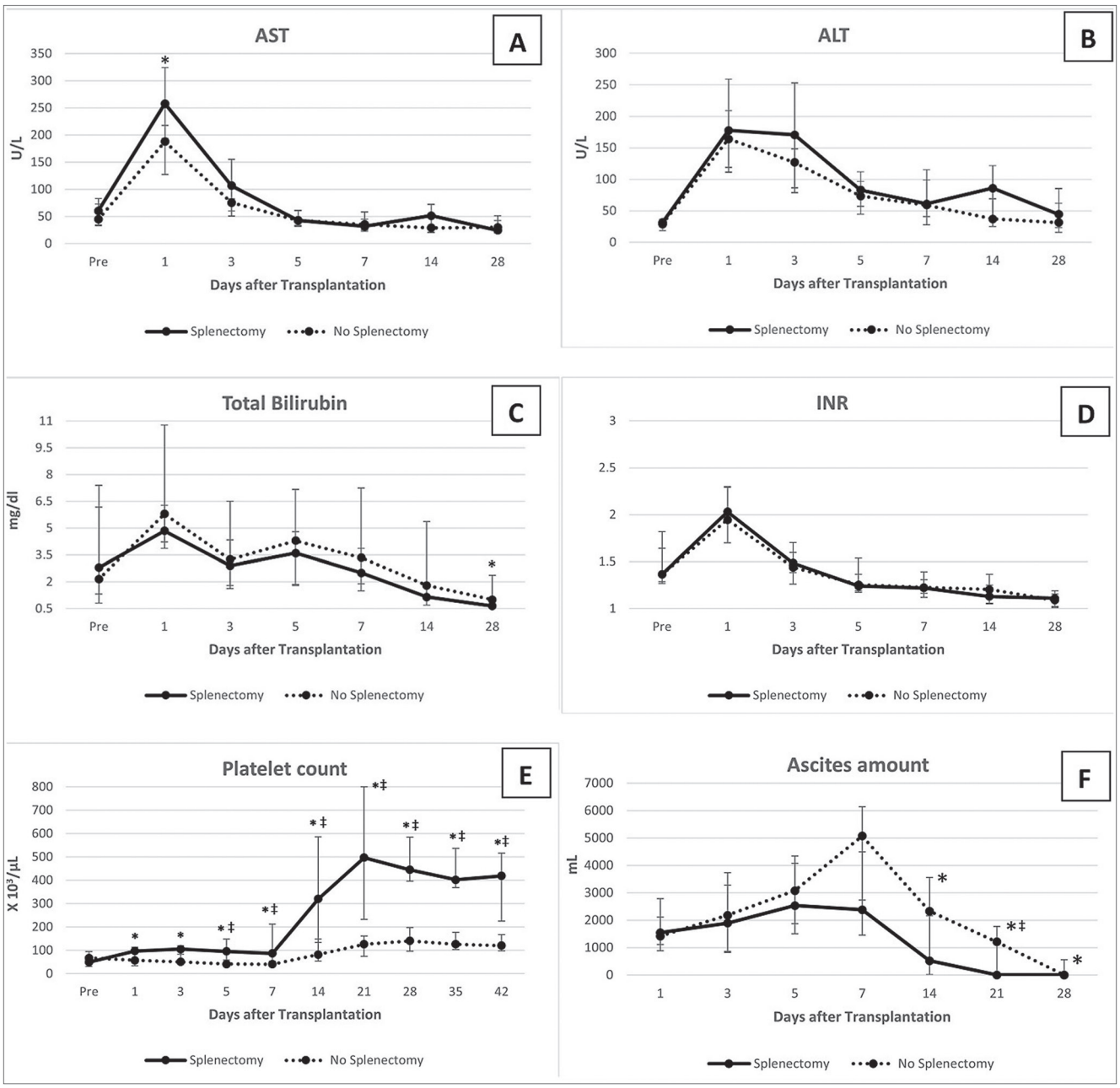
(*Continued*)

Table 2 (Continued)

	Whole (*N*=36)	SPX (*N*=8)	No SPX (*N*=28)	*P* value
30-day reoperation	6 (17.1)	1 (14.3)	5 (17.9)	0.82
30-day rejection	12 (33.3)	4 (50.0)	8 (28.6)	0.26
30-day bacterial infection	19 (52.8)	4 (50.0)	15 (53.6)	0.86
Vascular complications	5 (13.9)	1 (12.5)	4 (14.3)	0.90
Biliary complication	10 (27.8)	2 (25.0)	8 (28.6)	0.84

Data are presented as median (range) or *n* (%).
BA, biliary atresia; CIT, cold ischemia time; FFP, fresh frozen plasma; GI, gastrointestinal; GRWR, graft-to-recipient weight ratio; GSVR, graft-to-spleen volume ratio; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; L/S ratio, liver/spleen CT attenuation ratio; LOS, length of stay; MELD, model of end-stage liver disease; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; PVP, portal vein pressure; PVT, portal vein thrombosis; RBCs, red blood cells; SPX, splenectomy; WIT, warm ischemia time.

Figure 4



Chronological changes in graft function tests between the splenectomy and no splenectomy groups. Data are presented as median and interquartile range. **P* value less than 0.05, ‡*P* value less than 0.01. ALT, alanine transaminase; AST, aspartate transaminase; INR, international normalized ratio.

Table 3 Logistic regression risk factor analysis for high final portal vein pressure

	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P* value	OR	95% CI	*P*
Recipient age (years)	0.97	0.91–1.02	0.26			
Recipient sex (female)	6.43	0.69–60.3	0.10			
Recipient BMI (kg/m^2)	0.83	0.64–1.07	0.13			
Primary disease						
HCC	0.65	0.11–3.97	0.65			
PSC/PBC/BA	0.44	0.05–4.23	0.48			
Viral	0.52	0.06–05.13	0.58			
Alcoholic	1.04	0.10–11.09	0.97			
Liver function status						
MELD score	0.98	0.86–1.11	0.72			
Child–Pugh class C	3.16	0.33–30.0	0.32			
Portal hypertension surrogate markers						
History of GI bleeding	2.18	0.41–11.64	0.36			
Moderate to massive ascites	0.92	0.17–4.89	0.93			
Preoperative PVT	2.50	0.36–17.57	0.36			
Preoperative spleen volume (ml)	1.00	0.99–1.0	0.85			
Massive splenomegaly (>1000 ml)	1.04	0.10–11.10	0.97			
GSVR (g/ml)	0.21	0.02–2.11	0.19			
GSVR <0.7 g/ml	3.60	0.61–21.35	0.16			
Preoperative PLT count	0.99	0.97–1.01	0.49			
Graft-related variables						
ABO incompatible	1.92	0.29–12.86	0.50			
Donor age (years)	0.96	0.89–1.03	0.25			
Older donor age >45 years	0.49	0.08–2.97	0.44			
Donor BMI <23.2 kg/m^2	8.50	0.90–80.03	0.06	4.98	0.44–56.47	0.20
Donor L/S ratio	0.09	0.01–59.10	0.46			
Graft type (left lobe)	5.56	1.05–40.95	0.04	2.81	0.18–43.48	0.46
Graft weight <400 g	11.56	1.70–78.46	0.01	3.47	0.20–58.96	0.39
GRWR (%)	0.10	0.01–4.93	0.25			
GRWR <0.8%	2.96	0.55–16.08	0.21			
Operation-related variables						
CIT (min)	1.00	0.99–1.01	0.89			
WIT (min)	1.04	0.99–1.10	0.10			
Presence of collaterals	1.91	0.19–18.69	0.58			
Ligation of collaterals	4.24	0.45–39.87	0.21			
Blood loss (l)	1.0	0.99–1.00	0.35			
Blood loss/body weight (ml/kg)	1.01	1.00–1.02	0.10			
Packed RBCs transfusion (U)	1.00	0.93–1.07	0.91			
FFP transfusion (U)	1.04	0.96–1.12	0.38			

BA, biliary atresia; CI, confidence interval; CIT, cold ischemia time; FFP, fresh frozen plasma; GI, gastrointestinal; GRWR, graft-to-recipient weight ratio; GSVR, graft-to-spleen volume ratio; HCC, hepatocellular carcinoma; L/S ratio, liver/spleen CT attenuation ratio; MELD, model of end-stage liver disease; OR, odds ratio; PBC, primary biliary cirrhosis; PLT, platelet; PSC, primary sclerosing cholangitis; PVT, portal vein thrombosis; RBCs, red blood cells; WIT, warm ischemia time.

at 45 min (AUC=0.83, sensitivity=89%, and specificity 74%). By multivariable analysis using the three variables, GSVR less than 0.64 g/ml and WIT more than 45 min were independent risk factors for high PVP after reperfusion (Table 4).

Survival analysis for the whole population

During the period of follow-up of our study, no mortality was encountered in our population. Median follow-up period was 15 months (range, 1.25–23.9 months). Kaplan–Meier overall survival curve is shown in Fig. 5.

Discussion

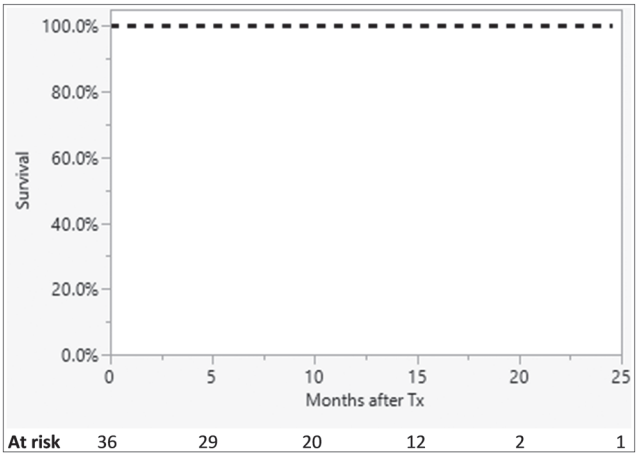
In the current study, with the described strategy of PVP modulation, high final PVP was more encountered with lower donor BMI, lower graft weight, and LLGs. Neither of the enrolled variables was an independent risk factor by multivariate analysis. In a case of advanced PVT (grade 3), persistent high PVP was seen till the end of operation. Complication rates and graft outcomes showed no significant differences across the groups of final PVP with the current modulation strategy.

Table 4 Logistic regression risk factor analysis for portal vein pressure after reperfusion

	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Recipient age (years)	0.96	0.91–1.02	0.15			
Recipient sex (female)	0.55	0.12–2.52	0.44			
Recipient BMI (kg/m^2)	0.93	0.75–1.15	0.51			
Primary disease						
HCC	0.85	0.17–4.17	0.84			
PSC/PBC/BA	0.82	0.14–4.90	0.82			
Viral	1.00	0.16–6.14	1.00			
Alcoholic	0.72	0.07–7.42	0.78			
Liver function status						
MELD score	0.91	0.79–1.05	0.21			
Child–Pugh class C	1.75	0.30–10.21	0.53			
Portal hypertension surrogate markers						
History of GI bleeding	4.00	0.81–19.82	0.09	10.5	0.63–175.86	0.10
Moderate to massive ascites	1.00	0.22–4.56	1.00			
Preoperative PVT	1.64	0.25–10.95	0.61			
GSVR <0.64 g/ml	6.4	1.08–37.96	0.04	62.34	1.89–2060.69	0.02
Preoperative PLT count	0.99	0.97–1.01	0.40			
Graft-related variables						
ABO incompatible	1.26	0.20–7.97	0.81			
Donor age (years)	1.06	0.99–1.14	0.12			
Older donor age >45 years	4.00	0.81–19.82	0.09	6.85	0.50–93.53	0.15
Donor BMI (kg/m^2)	0.86	0.64–1.15	0.31			
Donor L/S ratio	4.97	0.05–531.15	0.50			
Graft type (left lobe)	0.85	0.17–4.17	0.84			
GRWR (%)	0.46	0.02–9.90	0.62			
GRWR <0.8%	0.85	0.17–4.17	0.84			
Operation-related variables						
CIT (min)	1.01	1.00–1.02	0.11			
WIT >45 min	10.00	1.67–60.00	0.01	28.67	1.58–521.65	0.02
Presence of collaterals	1.00	0.16–6.14	1.00			
Ligation of collaterals	0.63	0.13–2.91	0.55			

BA, biliary atresia; CI, confidence interval; CIT, cold ischemia time; FFP, fresh frozen plasma; GI, gastrointestinal; GRWR, graft-to-recipient weight ratio; GSVR, graft-to-spleen volume ratio; HCC, hepatocellular carcinoma; L/S ratio, liver/spleen CT attenuation ratio; MELD, model of end-stage liver disease; OR, odds ratio; PBC, primary biliary cirrhosis; PLT, platelet; PSC, primary sclerosing cholangitis; PVT, portal vein thrombosis; RBCs, red blood cells; WIT, warm ischemia time.

Figure 5



Kaplan–Meier overall survival curve of the whole population.

Graft weight was previously thought to be the only determinant of SFSS development. Kiuchi *et al.* [10] reported that the use of grafts with GRWR less than 1% led to worse graft survival. Tanaka and Ogura [11] also reported that in the early experience of Kyoto University, early graft survival was significantly poorer when the GRWR was less than 0.8%. Our department also reported that the main factor for occurrence of SFSS after ALDLT is the use of SFSG (GRWR <0.8%) leading to poor outcome and suggested SPX as a way to modulate portal inflow to prevent catastrophic outcome [12]. However, the concept of SFSS has shifted from being exclusively dependent upon the graft weight only to be a multifactorial process that includes not only graft factors but also recipient factors [13]; the most important of which is the PVP and shear stress. Such concept was supported when Boillot *et al.* [14] reported successful partial graft liver transplantation using a LLG with a GRWR of 0.61% after constructing a side-to-side meso-caval shunt and ligating the SMV downstream the shunt, keeping the PVP at 10 mmHg.

Graft weight has then been less accused to be the main contributor to the SFSS, whereas the portal hyperperfusion and persistent portal hypertension have gained much popularity [11]. Kelly *et al.* [15] reported that 20% of partial liver graft cases in a porcine model showed sinusoidal congestion and hemorrhage, which were evident as early as 5 min after graft reperfusion, and these changes were less severe in larger liver grafts. In the same context, Asakura *et al.* [16] reported that patients with PVP modulation using portacaval shunts achieved significantly better outcomes than the ones without modulation after LT using extremely small grafts in pigs. In the clinical setting, Yagi *et al.* [17] reported that PVP less than or equal to 20 mmHg in the early phase after LDLT was associated with more graft dysfunction than the ones with PVP less than 20 mmHg. Shortly later, Yagi *et al.* [18] also reported another case series where they implemented the PVP modulation techniques aiming to render the final PVP less than 20 mmHg. They stated that the PVP depended on not only PV flow volume but also graft compliance (depending on graft quality and outflow) [18]. Ogura *et al.* [19] reported that the overall survival in the era with PVP modulation was significantly better than survival in the era without PVP modulation. Moreover, the patients with final PVP less than 15 mmHg had significantly better survival rates, better graft function (less cholestasis and less coagulopathy), and less daily ascites amount than the ones with high final PVP in the era of PVP modulation. In relation with the GRWR, they reported that the final PVP was well controlled despite the various GRWR ranges, and they indicated that the PVP could have been controlled by not only the GRWR but also other factors [19]. Therefore, the Kyoto group managed to decrease the lower limit of GRWR, then to 0.7%, and then to 0.6% assisted by the PVP modulation strategy by SPX [19–21]. In a recent study, Macshut *et al.* [22] reported that older donor age (>45 years) was an independent risk factor for negative outcomes after ALDLT using SFSGs; however, grafts with GRWR less than 0.6% were not yet advised to be used even with younger donors.

After application of PVP modulation strategies, LLG selection regained popularity after previous standardization of right lobe graft (RLG) selection, with actively increased LLG selection for the sake of donor safety as the larger remaining liver volume [19–21]. Although about 70% of the patients with high final PVP in our study received LLG, the use of LLG was not an independent risk factor for high final PVP and it was not associated with any inferior outcomes to RLGs. Soejima *et al.* [23] reported that LLGs were feasible without affection of patient and graft survival. Similarly, Ikegami *et al.* [24] reported the selection of LLG when the graft volume to standard liver volume was basically less than or equal to 35%, but they reported LLGs should be obtained from younger donors (<48 years) and transplanted to recipients with MELD scores less than 19. Iida *et al.* [6] also reported a lower survival outcome of LLG when transplanted to patients with several risk factors of preoperative recipient status; therefore, they recommended RLG to be used in such patients. Recently, Yagi *et al.* [25] recommended a left-lobe first graft selection algorithm keeping the donor safety as a first priority, using GRWR cutoff less than or equal to 0.6% with recommendation to use quite a larger graft whenever available in situations related to recipient status and graft quality. Yagi *et al.* [18] reported that compliance per unit graft weight in LLGs was as high as RLGs with MHV due to the complete drainage, which was significantly higher than RLG without MHV.

Simultaneous SPX with LDLT is always a matter of debate; however, with the current strategy of PVP modulation by SPX, the incidence of SFSS was nil in our study. Moreover, patients in the SPX group had lower hospital length of stay, despite longer operative time. Graft function tended to be better in the SPX group, regarding cholestasis and ascites amount especially after POD7, and platelet count was significantly higher in the SPX group from the first day after transplant. On the contrary, the SPX group showed no difference regarding blood loss, complications, or reoperation rates in comparison with the no SPX group. A recent study reported that simultaneous SPX improved the survival outcome of LDLT and graft function regarding cholestasis, coagulopathy, and ascites and prevented SFSS [26]. They performed SPX for SFSGs, significant portal hypertension, and high PVP more than 20 mmHg after reperfusion [26]. Badawy *et al.* [27] from the Kyoto group reported that SPX could be safely performed when indicated with recommendation of preoperative vaccination and short-term postoperative anticoagulant. Although thrombotic complications and blood loss were higher in the SPX group, which was also reported by Macshut *et al.* [28] about Kyoto University experience, these complications were no more higher in the SPX group in the recent era reported in our study. On the contrary, Ito *et al.* [29] warned of simultaneous SPX in LDLT, because of the high risk of postoperative hemorrhage and lethal infectious complication. However, they never performed SPX for portal inflow modulation but for other indications. A meta-analysis reported by Coker *et al.* [30] stated that simultaneous SPX during LT was efficient in increasing platelet count and decreasing portal pressure. However, it tended to increase complication rates and perioperative mortality. However, that study analyzed data from whole graft as well as LDLT.

One of the indications of SPX in our study was low GSVR which is considered a reflection of the relationship between the graft size and the degree of portal hypertension. The cutoff value used in our study was 0.7 g/ml [7]. GSVR less than 0.64 g/ml was an independent risk factor for high PVP after graft reperfusion in our study. Cheng *et al.* [31] included spleen size providing graft-to-recipient spleen size ratio, which would reflect posttransplant hyperperfusion better if it was less than 0.60. In the same context, Gyoten *et al.* [32] reported that spleen volume-to-graft volume ratio of more than 0.95 predicted portal hypertension of more than 20 mmHg. Another study from Kyushu University reported that GSVR was significantly correlated with portal hyperperfusion and persistent thrombocytopenia and hyperbilirubinemia after LDLT even in children and young adults (<30 years) transplanted for biliary atresia [33]. They reported that GSVR less than 0.88 predicted persistent thrombocytopenia and hyperbilirubinemia less than or equal to 30 days after LDLT [33]. A recent study from China reported that low GSVR (<1.03 g/ ml) was an important predictor of portal hypertension and impaired graft function after LDLT [34]. However, they did not recommend SPX but consideration of partial SPX in such cases [34].

In light of our current study, the outcome of ALDLT was superb when applying the current strategy of PVP modulation. However, this study has a few limitations. The first limitation was the small study population, which was reflected in the small number of patients in each of the study groups. Second, almost all the patients (recipients and donors) in our study were Japanese, and differences between races and lifestyles may lead to different outcomes even among patients with similar characteristics. Lastly, this was a retrospective single-center study; therefore, a prospective, multicenter or a nationwide study should be performed to confirm our results.

In conclusion, PVP monitoring and modulation using the objective parameters mentioned in this study is a necessity for good outcomes after ALDLT. PVP modulation by SPX can be safely performed when indicated. GSVR less than 0.64 g/ml was an independent risk factor for high PVP after graft reperfusion.

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Conflicts of interest

There are no conflicts of interest.

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