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ORIGINAL ARTICLE

Impact of imbalanced graft-to-spleen volume ratio on outcomes following living donor liver transplantation in an era when simultaneous splenectomy is not typically indicated

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The impact of an imbalanced graft-to-spleen volume ratio (GSVR) on posttransplant outcomes other than postreperfusion portal hypertension remains unknown. The importance of GSVR might vary according to whether simultaneous splenectomy (SPX) is performed. This retrospective study divided 349 living donor liver transplantation (LDLT) recipients from 2006 to 2017 into 2 groups: low GSVR (≤ 0.70 g/mL) and normal GSVR (> 0.70 g/mL). The cutoff value of GSVR was set based on the first quartile of the distributed data. Graft survival and associations with various clinical factors were investigated between the groups according to whether SPX was performed. Low GSVR did not affect outcomes when SPX was performed. In contrast, it was associated with an increased incidence of early graft loss (EGL) and poor graft survival by presenting posttransplant thrombocytopenia, cholestasis, coagulopathy, and massive ascites when the spleen was preserved. Among patients with a preserved spleen, the multivariable analysis results revealed that older donor age and low GSVR were independent risk factors for graft loss. In conclusion, low GSVR was an independent predictor of graft loss after LDLT when the spleen was preserved. Preserved spleen with extremely low GSVR may be related to persistent hypersplenism, impaired graft function, and consequent EGL.

KEYWORDS

clinical research/practice, complication: medical/metabolic, graft survival, liver allograft function/dysfunction, liver transplantation/hepatology, patient characteristics, risk assessment/risk stratification

1 | INTRODUCTION

In cirrhotic recipients of liver transplantation (LT), spleen volume reflects the portal hemodynamic status. In addition to pre-LT

conditions, the spleen volume is also associated with excessive portal venous flow after reperfusion during LT; a low graft-to-spleen volume ratio (GSVR) has been reported to predict postreperfusion portal hypertension (PHT).¹ Recently, Gyoten et al² suggested that preoperative assessment of GSVR can be used to indicate the need for splenectomy (SPX) before reperfusion to prevent PHT. However, these previous studies were conducted with a relatively small sample size of <100 patients, and the clinical impact of GSVR on post-LT outcomes other than postreperfusion PHT has never been investigated.

Abbreviations: CI, confidence interval; CT, computed tomography; DAA, direct-acting antiviral agent; EGL, early graft loss; GRWR, graft-to-recipient weight ratio; GSVR, graft-to-spleen volume ratio; GW, graft weight; HCV, hepatitis C virus; HR, hazard ratio; IFN, interferon; INR, international normalized ratio; IQR, interquartile range; LDLT, living donor liver transplantation; LT, liver transplantation; PHT, portal hypertension; POD, postoperative day; PT-INR, prothrombin time-international normalized ratio; PVP, portal venous pressure; SPX, splenectomy; TB, total bilirubin.

In partial LT, the reduction in the liver vasculature increases portal venous pressure (PVP) in the early phase, but in the later phase, the liver graft regenerates to adapt to the persistent recipient hemodynamic environment with a gradual improvement of splenomegaly.³ Therefore, simultaneous SPX during LT is not necessarily performed, and its validity remains controversial. While the positive aspects of SPX, in particular, preventing PHT and improving hepatic vascular compliance, have often been reported,^{4,5} it may negatively affect some surgical outcomes, such as operative time, blood loss, portal venous thrombosis formation, and infectious complications.^{6,7} Additionally, recent advances in interferon (IFN)-free direct-acting antiviral agents (DAAs)⁸ and rituximab induction⁹ have made SPX unnecessary for hepatitis C virus (HCV)-positive recipients and ABO-incompatible patients. Based on these findings, the clinical meaning of GSVR should be discussed differently with patients in whom SPX is indicated or planned and with patients in whom SPX is not planned; in other words, the importance of GSVR might vary according to whether SPX is performed or not.

To elucidate these clinical questions, we conducted a retrospective study reviewing our 12-year experience of living donor LT (LDLT). The aim of the present study was to evaluate the clinical impact of imbalanced GSVR on outcomes in LT recipients in an era when SPX is not necessarily indicated.

2 | MATERIALS AND METHODS

2.1 | Study population

A single-center retrospective analysis was performed including all patients aged ≥ 18 years who underwent initial LDLT at Kyoto University Hospital, Japan between April 2006 and September 2017. Among 400 consecutive patients, 349 were enrolled after excluding the following cases: 20 without whole spleen imaging by preoperative computed tomography (CT), 15 with prior SPX before LT, 8 with retransplantation, and 8 with incomplete PVP data.

All study protocols were approved by the Ethics Committee of Kyoto University (Approval number: R1473), and all procedures were conducted in accordance with the Declaration of Helsinki of 1996.

2.2 | Indications of SPX

According to our PVP modulation strategy, SPX was mainly performed if PVP remained >15 mm Hg after reperfusion.¹⁰ SPX was also performed in the following patients: (1) patients with HCV, regardless of PVP, to prevent thrombocytopenia during the post-LT viral treatment before DAAs were available; (2) patients with ABO incompatibility who underwent emergent LT in addition to rituximab administration; and (3) patients with splenic arterial aneurysms.

Ligation of portosystemic shunts was performed only after graft implantation, regardless of whether PVP modulation was indicated. Only large spontaneous portosystemic shunts, such as splenorenal shunts and gastric/esophageal varices (collateral

vessels), were ligated if the PVP was ≤ 15 mm Hg upon temporary clamping of the collateral vessels to improve the portal flow and prevent the portal venous steal phenomenon.¹¹⁻¹³ If the PVP was >15 mm Hg upon temporary clamping, the shunts were left untreated.

2.3 | Evaluation of GSVR

GSVR was calculated by dividing the actual graft weight (GW) in grams by the estimated spleen volume in milliliters, as referenced in a previous study.¹ The actual GW was used as the graft volume in determining the liver GSVR, because the actual GW is more precise than the estimated graft volume based on imaging. Three-dimensional images of the recipient's spleen were created using SYNAPS VINCENT software (Fujifilm Medical Co. Ltd, Tokyo, Japan). All preoperative CT imaging was obtained within 2 months before the LT.

2.4 | Definitions

Bacterial infection was identified according to the Centers for Disease Control and Prevention's National Healthcare Safety Network surveillance definitions.¹⁴ Portal vein thrombosis was categorized according to Yerdell classification grade.¹⁵ Early graft loss (EGL) was defined as retransplantation or mortality during the first 90 days after LT.

2.5 | Statistical analysis

Continuous variables are presented as medians with ranges or interquartile ranges (IQRs) as appropriate. Categorical variables are presented as numbers and percentages. Comparisons were performed using the Mann-Whitney *U* test for continuous variables and the χ^2 test or Fisher exact test for categorical variables as appropriate. Significant factors that predicted graft loss were analyzed with a Cox proportional hazards model. Any variable with a *P* value $< .05$ in the univariable analysis was considered a candidate for multivariable analysis. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for each variable. Graft survival was estimated with the Kaplan-Meier method and compared with the log-rank test. A *P* value of $< .05$ was considered to indicate statistical significance. JMP 12.0 (SAS Institute, Cary, NC) was used for all statistical analyses.

3 | RESULTS

The patient population is summarized in Figure 1. There were 176 men (50.4%) and 173 women (49.6%), and their median age was 54 years (range, 18-69). The median donor age was 45 years (range, 20-67). The causes for LDLT were as follows: HCV (32.7%), autoimmune hepatitis (21.2%), hepatitis B virus (14.9%), alcohol abuse (9.2%), biliary atresia (6.3%), nonalcoholic steatohepatitis (3.7%),

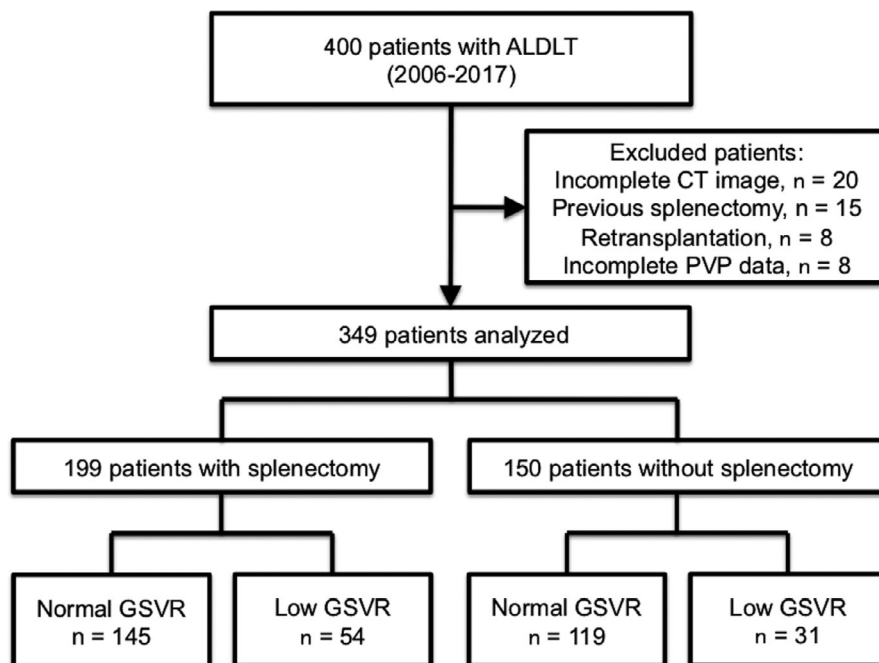


FIGURE 1 Patient population flow diagram. ALDLT, adult-to-adult living donor liver transplantation; CT, computed tomography; GSVR, graft-to-spleen volume ratio; PVP, portal venous pressure

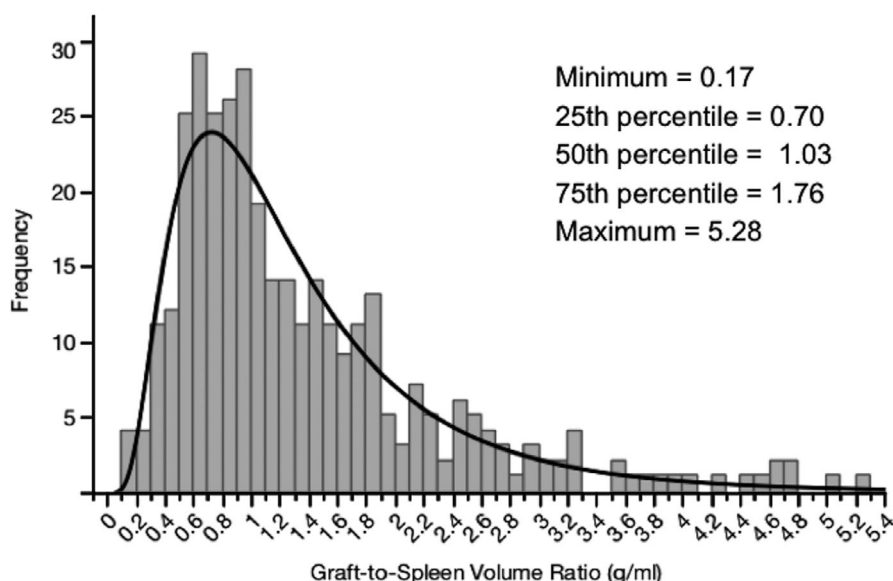


FIGURE 2 Distribution of the pretransplant graft-to-spleen volume ratio among all recipients

acute liver failure (3.4%), metabolic disorders (2.3%), Budd-Chiari syndrome (2.0%), and cryptogenic hepatitis (4.3%). Simultaneous SPX was performed on 199 (57.0%) patients. The main indications for SPX were PVP modulation (n = 128), HCV-related disease (n = 46), splenic arterial aneurysm (n = 13), accidental hemorrhage (n = 5), ABO incompatibility (n = 3), Hassab's operation (n = 1), and unmentioned (n = 3). There were 37 patients who presented with persistent PHT despite SPX. No patient underwent additional SPX after initial LT. The median follow-up period was 75.7 months (range, 0.3-148.9).

3.1 | Cutoff value for GSVR

The distribution of pre-LT GSVR is presented in Figure 2. The median GSVR in the whole cohort was 1.03 g/mL (range, 0.17-5.28). The first and third quartiles were 0.70 and 1.76 g/mL, respectively. Because no working definition of GSVR has yet been established in the clinical setting, we set the cutoff value according to the IQR, which was considered to be objective based on 349 measured values. We intended to elucidate the impact of extremely low GSVR on graft survival; thus, we chose the first quartile as the threshold,

TABLE 1 Clinical characteristics of recipients, donors, and posttransplant outcomes according to graft-to-spleen volume ratio

Variables	Patients with splenectomy n = 199			Patients without splenectomy n = 150			
	Total n = 349	Normal GSVR n = 145	Low GSVR n = 54	P value	Normal GSVR n = 119	Low GSVR n = 31	P value
Recipient factors							
Age, y	54.9 (46.7-60.3)	57 (50-62)	53 (38-58)	<.001	54 (45-60)	51 (37-58)	.176
Female	173 (49.6)	71 (49.0)	28 (51.9)	.717	59 (49.6)	15 (48.4)	.906
Liver disease							
Hepatitis B	52 (14.9)	18 (12.4)	6 (11.1)	.802	24 (20.2)	4 (12.9)	.355
Hepatitis C	114 (32.7)	85 (58.6)	14 (25.9)	<.001	13 (10.9)	2 (6.5)	.460
AIH/PBC/PSC	74 (21.2)	18 (12.4)	22 (40.7)	<.001	23 (19.3)	11 (35.5)	.056
Biliary atresia ^a	22 (6.3)	2 (1.4)	6 (11.1)	.006	9 (7.6)	5 (16.1)	.167
Alcoholic ^a	32 (9.2)	6 (4.1)	1 (1.9)	.677	23 (19.3)	2 (6.5)	.108
Acute liver failure ^a	12 (3.4)	1 (0.7)	0	1.000	11 (9.3)	0	.121
Child-Pugh C	231 (66.2)	88 (60.7)	41 (75.9)	.045	83 (69.8)	19 (61.3)	.369
MELD score	18 (14-23)	17 (14-21)	19 (16-22)	.019	19 (14-26)	16 (14-20)	.153
Portal vein thrombosis							
Grades I-II	46 (13.2)	21 (14.5)	7 (13.0)	.784	13 (10.9)	5 (16.1)	.427
Grades III-IV ^a	13 (3.7)	7 (4.8)	2 (3.7)	1.000	3 (2.5)	1 (3.2)	1.000
Spleen volume, mL	515 (331-782)	461 (324-604)	1003 (750-1358)	<.001	377 (225-564)	1055 (893-1389)	<.001
Donor factors							
Age, y	45 (32-55)	40 (30-54)	51 (35-56)	.098	33 (20-56)	49 (36-55)	.334
Graft weight, g	565 (448-674)	565 (453-678)	515 (425-631)	.036	575 (455-700)	550 (413-670)	.306
GRWR, %	0.90 (0.75-1.04)	0.90 (0.76-1.07)	0.86 (0.75-0.98)	.159	0.92 (0.77-1.09)	0.89 (0.70-0.99)	.153
ABO incompatibility	84 (24.1)	34 (23.5)	16 (29.6)	.371	28 (23.5)	6 (19.4)	.621
Surgical factors							
Splenectomy							
For PVP modulation	128 (36.7)	91 (62.8)	37 (68.5)	.451	—	—	—
For HCV-related disease	46 (13.2)	40 (27.6)	6 (11.1)	.014	—	—	—
For splenic arterial aneurysm ^a	13 (3.7)	7 (4.8)	6 (11.1)	.119	—	—	—
For accidental hemorrhage ^a	5 (1.4)	4 (2.8)	1 (1.9)	1.000	—	—	—
For ABO incompatibility ^a	3 (0.9)	1 (0.7)	2 (3.7)	.180	—	—	—
For Hassab ^a	1 (0.3)	0	1 (1.9)	.271	—	—	—
For unmentioned reasons ^a	3 (0.9)	2 (1.4)	1 (1.9)	1.000	—	—	—

(Continues)

TABLE 1 (Continued)

Variables	Total n = 349	Patients with splenectomy n = 199		Patients without splenectomy n = 150	
		Normal GSVR n = 145	Low GSVR n = 54	Normal GSVR n = 119	P value
Operation time, min	819 (727-946)	825 (743-960)	863 (766-973)	775 (708-890)	.337
CIT, min	92 (58-148)	100 (61-147)	89 (61-135)	82 (56-150)	.669
WIT, min	43 (36-51)	43 (36-53)	44 (37-52)	42 (35-47)	.854
Collateral ligation	99 (28.4)	55 (37.9)	15 (27.8)	22 (18.5)	.182
Spleno-renal shunt ligation	67 (19.3)	29 (20.0)	12 (22.2)	22 (18.5)	.730
Final PVP, mm Hg	13 (11-15)	13 (11-15)	14 (12-16)	14 (12-15)	.172
Immunosuppressant					
Tacrolimus + MMF	235 (67.3)	95 (65.5)	35 (64.8)	87 (73.1)	.926
Postoperative outcomes					
Blood loss, mL	6290 (3660-10 675)	7263 (4243-12 163)	6798 (4678-10 600)	4630 (2700-7790)	.681
Transfused red blood cells, U	10 (6-20)	12 (4-22)	11 (6-46)	8 (4-28)	.718
Transfused platelets, U	20 (10-30)	20 (10-30)	20 (10-40)	15 (0-25)	.561
Transfused fresh-frozen plasma, U	10 (6-16)	12 (6-19)	12 (6-17)	8 (4-12)	.853
Portal vein or splenic vein thrombosis ^a	24 (6.9)	12 (8.3)	8 (14.8)	3 (2.5)	.189
Acute rejection	142 (40.1)	59 (40.7)	25 (46.3)	41 (34.5)	.476
Bacterial infection	170 (48.7)	75 (51.7)	27 (50.0)	50 (42.0)	.829
Bacteremia	108 (30.9)	42 (29.0)	20 (37.0)	31 (26.1)	.274
Pneumonia ^a	18 (5.2)	7 (4.8)	3 (5.6)	6 (5.0)	1.000
Cholangitis	52 (14.9)	28 (19.3)	9 (16.7)	9 (7.6)	.670
Early graft loss ^a	39 (11.1)	15 (10.3)	8 (14.8)	8 (6.7)	.455
Infection ^a	23 (6.6)	10 (6.9)	3 (5.6)	5 (4.2)	1.000
Acute rejection ^a	5 (1.4)	1 (0.7)	2 (3.7)	0	.180
Cerebral hemorrhage ^a	5 (1.4)	3 (2.1)	1 (1.9)	1 (0.8)	1.000
Hepatic artery complication ^a	1 (0.3)	0	1 (1.9)	0	.271
Others ^a	5 (1.4)	1 (0.7)	1 (1.9)	2 (1.7)	.470

Data are presented as the medians (interquartile range) or n (%).

AIH, autoimmune hepatitis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; MELD, Model for End-stage Liver Disease; MMF, mycophenolate mofetil; GRWR, graft-to-recipient weight ratio; HCV, hepatitis C virus; CIT, cold ischemia time; WIT, warm ischemia time; PVP, portal venous pressure; GSVR, graft-to-spleen volume ratio.

^aFisher exact test was applied. Other comparisons were performed using the Pearson χ^2 test for categorical variables.

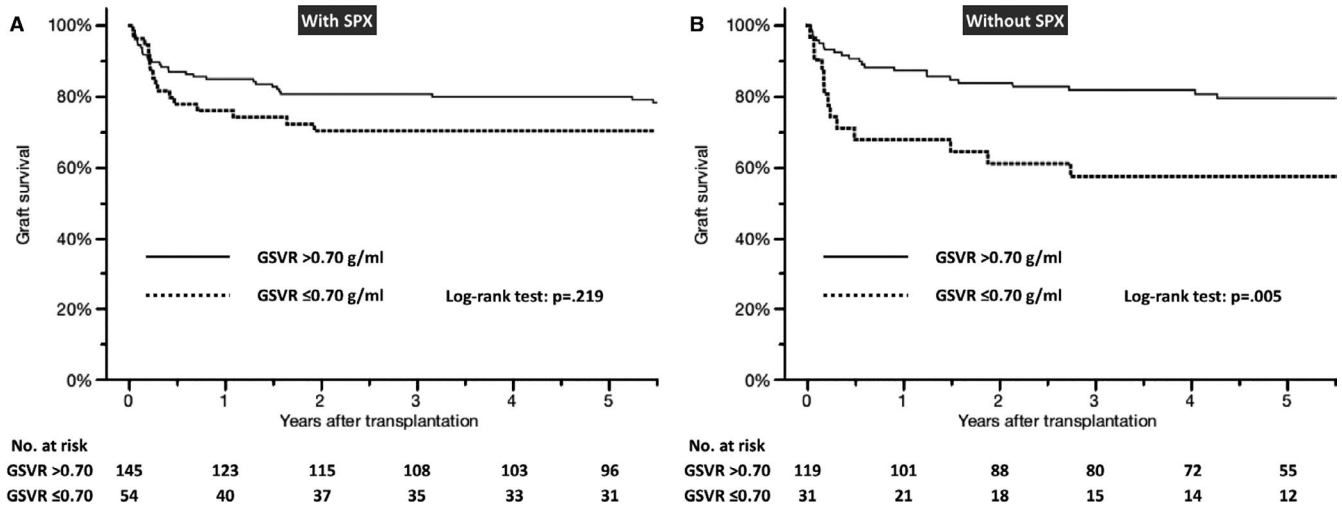


FIGURE 3 Graft survival according to graft-to-spleen volume ratio. A, In the subgroup with simultaneous splenectomy ($n = 199$). B, In the subgroup without simultaneous splenectomy ($n = 150$). GSVR, graft-to-spleen volume ratio; SPX, splenectomy

and patients were assigned to 1 of 2 groups: low GSVR (≤ 0.70 g/mL, $n = 85$) or normal GSVR (> 0.70 g/mL, $n = 264$).

3.2 | Baseline characteristics and post-LT outcomes

After classifying by the presence or absence of simultaneous SPX, the clinical characteristics and post-LT outcomes were compared between the low GSVR and normal GSVR groups (Table 1). In the subgroup with SPX ($n = 199$), there were variations in recipient age, background liver disease, Child-Pugh score, Model for End-Stage Liver Disease score, and GW between the 2 groups. However, there were no differences in postoperative outcomes. In contrast, in the subgroup without SPX ($n = 150$), while recipient factors, donor factors, surgical factors, and immunosuppressant regimen were similar between the groups, the low GSVR group had a higher incidence of acute rejection ($P = .040$), bacteremia ($P = .019$), and EGL ($P = .006$). As the cause of EGL, infection ($P = .032$) and acute rejection ($P = .042$) occurred at a higher rate in the low GSVR group.

Kaplan-Meier plots in Figure 3A show that the survival rate of the low GSVR group was comparable to that of the normal GSVR group ($P = .219$) if SPX was performed. Cumulative graft survival by group was as follows: normal GSVR, 84.8% and low GSVR 74.0% at 1 year; normal GSVR, 79.9% and low GSVR, 70.2% at 5 years. In contrast, Kaplan-Meier plots in Figure 3B show that the low GSVR group demonstrated significantly worse graft survival compared with the normal GSVR group ($P = .005$) if the spleen was preserved. Cumulative graft survival by group was as follows: normal GSVR, 87.3% and low GSVR, 67.7% at 1 year; normal GSVR, 79.5% and low GSVR, 57.4% at 5 years.

3.3 | Changes in laboratory values and ascites after LDLT

To investigate the detailed cause of inferior outcomes in patients with low GSVR whose spleen was preserved, chronologic changes

in the platelet count, prothrombin time-international normalized ratio (PT-INR), total bilirubin (TB), and ascites in the first month after LT are presented in Figure 4. The transition differed depending on whether SPX was performed. In the subgroup with SPX, there were no remarkable differences in the platelet count, PT-INR, TB, and the amount of ascites between the normal GSVR and low GSVR groups (Figure 4A-D). The platelet count remained low until postoperative days (PODs) 5 to 7 and rapidly increased during post-LT weeks 1 to 4 (Figure 4A). Although TB was significantly higher than the pre-LT value until POD 7 in the low GSVR group, the difference diminished afterward (Figure 4C). In contrast, low GSVR was associated with unfavorable data in the subgroup without SPX. While the platelet count in the normal GSVR group gradually increased after post-LT week 1, recovery was not observed for more than 1 month in the low GSVR group, and it remained very low with a median value that never exceeded $100 \times 10^3/\text{mL}$ (Figure 4E). The low GSVR group also presented significantly higher PT-INR, TB, and amount of ascites from the period immediately following LT, and the difference lasted for 1 month (Figure 4F-H).

Other values, including white blood cell count, hemoglobin, aspartate aminotransferase, and alanine aminotransferase, are presented in Figure S1. The transitions of these values were very similar between the groups.

3.4 | Risk factors for graft loss

Risk factors were assessed among the subgroups with and without SPX. In the subgroup with SPX ($n = 199$), 20 variables, including recipient factors, donor factors, and surgical factors, were analyzed with Cox proportional hazards models (Table 2). Multivariable analysis revealed that donor age (HR, 1.183; 95% CI, 1.057-1.330; $P = .004$) and final PVP > 15 mm Hg (HR, 2.262; 95% CI, 1.191-4.097; $P = .014$) independently affected graft survival after LDLT among recipients on whom simultaneous SPX was performed.

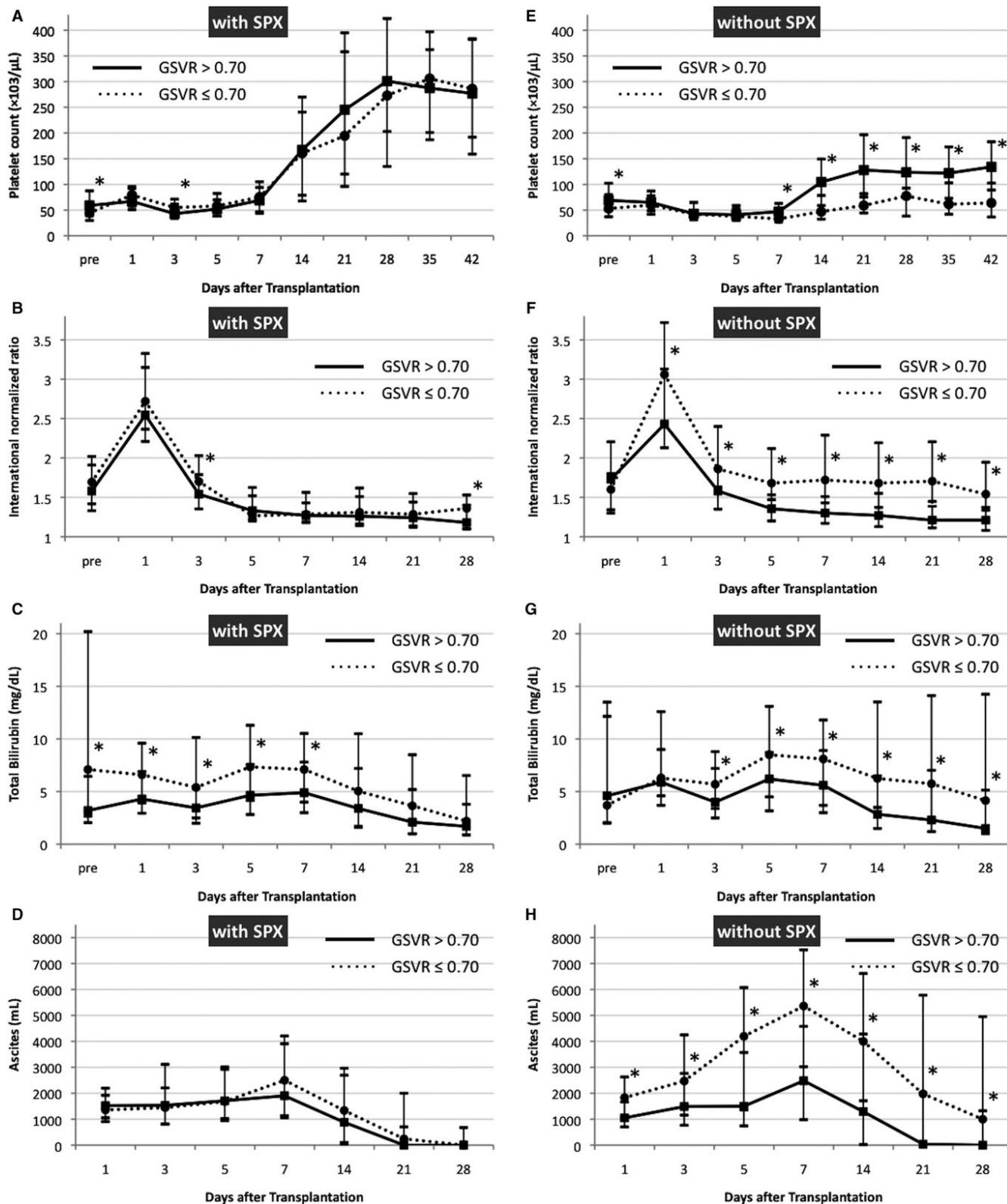


FIGURE 4 Chronologic changes in the laboratory values and ascites according to graft-to-spleen volume ratio. A-D, The results of analyses in the subgroup with simultaneous splenectomy ($n = 199$). A, Platelet counts. B, International normalized ratio. C, Total bilirubin. D, Ascites (E-H) show the results of analyses in the subgroup without simultaneous splenectomy ($n = 150$). E, Platelet counts. F, International normalized ratio. G, Total bilirubin. H, Ascites. * $P < .05$. GSVR, graft-to-spleen volume ratio; SPX, splenectomy

TABLE 2 Cox proportional hazards model assessing risk factors for graft loss in the subgroups with and without simultaneous splenectomy

Variables	Subgroup with splenectomy (n = 199)				Subgroup without splenectomy (n = 150)			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Recipient factors								
Age by 5 y	0.946 (0.844-1.073)	.844			0.970 (0.862-1.103)	.634		
Sex, female	1.273 (0.734-2.229)	.390			0.881 (0.456-1.682)	.700		
Liver disease								
Hepatitis B	1.100 (0.634-1.918)	.735			1.095 (0.326-2.755)	.866		
Hepatitis C	0.740 (0.257-1.693)	.506			0.790 (0.297-1.764)	.588		
AIH/PBC/PSC	1.540 (0.789-2.815)	.196			1.234 (0.549-2.516)	.590		
Child-Pugh C	1.281 (0.721-2.377)	.406			0.995 (0.510-2.053)	.989		
MELD score > 25	1.197 (0.600-2.216)	.593			1.273 (0.603-2.513)	.509		
High-grade PVT ^a	1.495 (0.363-4.076)	.524			0.960 (0.054-4.437)	.967		
Spleen volume, by 100 mL	0.997 (1.065-1.003)	.936			1.068 (0.989-0.937)	.090		
Donor factors								
Age by 5 y	1.142 (1.026-1.276)	.015	1.183 (1.057-1.330)	.004	1.198 (1.052-1.380)	.006	1.187 (1.041-1.368)	.010
Left lobe graft	2.183 (1.256-3.863)	.006	1.702 (0.805-3.526)	.161	1.258 (0.631-2.416)	.504		
Graft weight <450 g	2.573 (1.462-4.466)	.001	1.951 (0.966-4.043)	.063	1.800 (0.872-3.516)	.108		
GRWR <0.8%	1.128 (0.705-2.242)	.410			1.135 (0.538-2.239)	.727		
ABO incompatibility	1.787 (0.985-3.135)	.056			1.527 (0.723-3.011)	.254		
Surgical factors								
GSVR ≤0.70 g/mL	1.310 (0.706-2.327)	.380			2.434 (1.202-4.706)	.015	2.257 (1.113-4.373)	.025
Bleeding >10 L	0.978 (0.527-1.736)	.941			1.191 (0.507-2.486)	.667		
Transfused platelets								
Final PVP >15 mm Hg	2.192 (1.161-3.939)	.017	2.262 (1.191-4.097)	.014	—	—		
Collateral ligation	0.916 (0.500-1.616)	.768			1.945 (0.891-3.921)	.092		
CIT >150 min	0.979 (0.491-1.813)	.949			1.130 (0.534-2.241)	.737		
WIT >60 min	0.973 (0.372-2.110)	.950			0.454 (0.074-1.491)	.221		

AIH, autoimmune hepatitis; CI, confidence interval; CIT, cold ischemia time; GRWR, graft-to-recipient weight ratio; GSVR, graft-to-spleen volume ratio; HR, hazard ratio; MELD, Model for End-Stage Liver Disease; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; PVP, portal venous pressure; PVT, portal venous thrombosis; WIT, warm ischemia time.

—, Not available.

^aYerdel classification grades III-IV.

In the subgroup without SPX (n = 150), the same variables, excluding final PVP, were analyzed with Cox proportional hazards models. Multivariable analysis revealed that both donor age (HR, 1.187; 95%

CI, 1.041-1.368; *P* = .010) and GSVR ≤ 0.70 g/mL (HR, 2.257; 95% CI, 1.113-4.373; *P* = .025) independently affected graft survival after LDLT among recipients in whom the spleen was preserved.

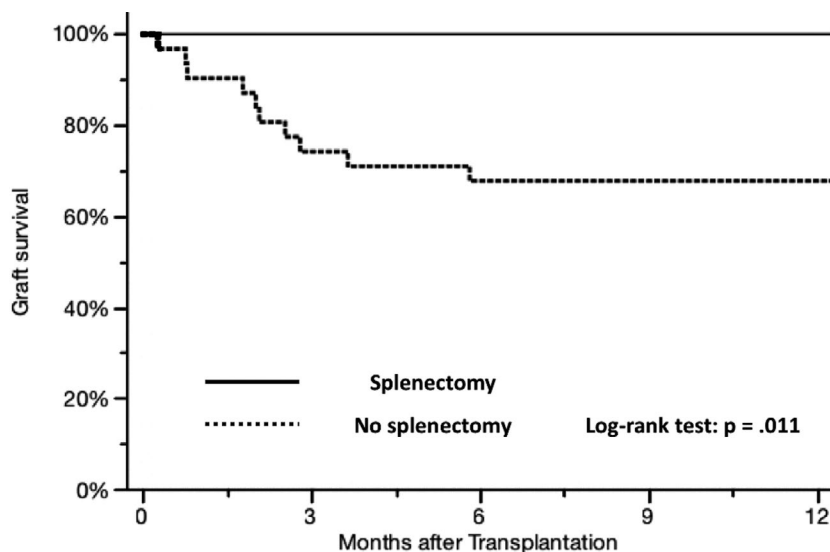


FIGURE 5 The effect of splenectomy on graft survival in patients with both low GSVR and PVP ≤ 15 mm Hg after reperfusion. GSVR, graft-to-spleen volume ratio; PVP, portal venous pressure

No. at risk						
Splenectomy	17	17	17	17	17	17
No splenectomy	31	23	21	21	21	21

3.5 | Possible positive effect of SPX on graft survival in patients with low GSVR

To elucidate a prophylactic method against poor prognosis in recipients with low GSVR, we investigated the effect of SPX on graft survival. Patients presenting with PHT after reperfusion and requiring SPX for modulation ($n = 37$) were excluded from the analysis, because SPX is performed to prevent small-for-size syndrome or EGL, and it might have improved the survival curve of those who had spleen preservation with low GSVR by shifting these high-risk patients to the SPX group. PHT is the absolute indication for SPX at our institution and should be reserved only for necessary cases in the future.¹⁶ Therefore, comparison excluding PVP-modulated cases may provide information closer to the true effect of SPX in recipients with normal PVP, namely, in recipients in whom it was not necessary or planned.

Survival analysis revealed that among patients with low GSVR ($n = 48$), those with SPX presented better graft survival (100% vs 71.0% at 90 days, 100% vs 67.7% at 1 year, $P = .011$) (Figure 5). The backgrounds of patients are shown in the Supplementary Table. Chronologic changes in platelet count, PT-INR, TB, and ascites after LT are presented in Figure S2.

4 | DISCUSSION

We demonstrated that an imbalanced GSVR could be an important prognostic factor in LDLT and that it had different meanings according to whether simultaneous SPX was performed. Particularly in recipients with spleen preservation, low GSVR ≤ 0.70 g/mL was related to post-LT thrombocytopenia, impaired graft function, and associated EGL. The valuable strength of this study is the new insight into the potential risk of low GSVR in the population without

PHT after reperfusion, that is, in whom SPX or PVP modulation was not indicated, while the only existing evidence regarding GSVR was its effect on postreperfusion PHT.^{1,2} These data enabled us to determine the high-risk population for whom the PVP modulation strategy could not save and assisted us in establishing a new surgical strategy.

A low GSVR was associated with a poor prognosis; it has been associated with post-LT thrombocytopenia, hyperbilirubinemia, coagulopathy, and massive ascites when the spleen was preserved. In particular, the negative impact of thrombocytopenia on LDLT has been frequently cited; Chang et al¹⁷ found that thrombocytopenia preceded infections and could be used to predict morbidity and mortality. Lesurtel et al¹⁸ and Akamatsu et al¹⁹ set the platelet count cutoff at $50 \times 10^9/L$ to $60 \times 10^9/L$ on POD 5. While the predominant mechanism of thrombocytopenia in the early phase following LT is increased consumption,²⁰ the platelet count normally reaches a nadir at post-LT day 5 but returns to preoperative levels by day 14.²¹ Surprisingly, in recipients with low GSVR and a preserved spleen, the platelet count did not increase from the pre-LT level for over a 1-month period. Given that consumption was higher in patients with low GSVR than in patients with normal GSVR or SPX, the involvement of sequestration by persistent splenomegaly and hypersplenism cannot be excluded. Other parameters in the early post-LT period have been reported for predicting poor outcomes in LDLT. Peak TB level >27 mg/dL within 28 days,²² hyperbilirubinemia >20 mg/dL for >7 consecutive days after POD 7,²³ and PT-INR >1.6 on POD 5¹⁹ have been identified as significant predictors of mortality. However, the mechanisms of these abnormalities are not completely understood. Our analyses showed that these abnormalities were less frequently observed when the GSVR was normal or SPX was performed, implying that a preserved spleen with an extremely imbalanced GSVR could be an important underlying cause.

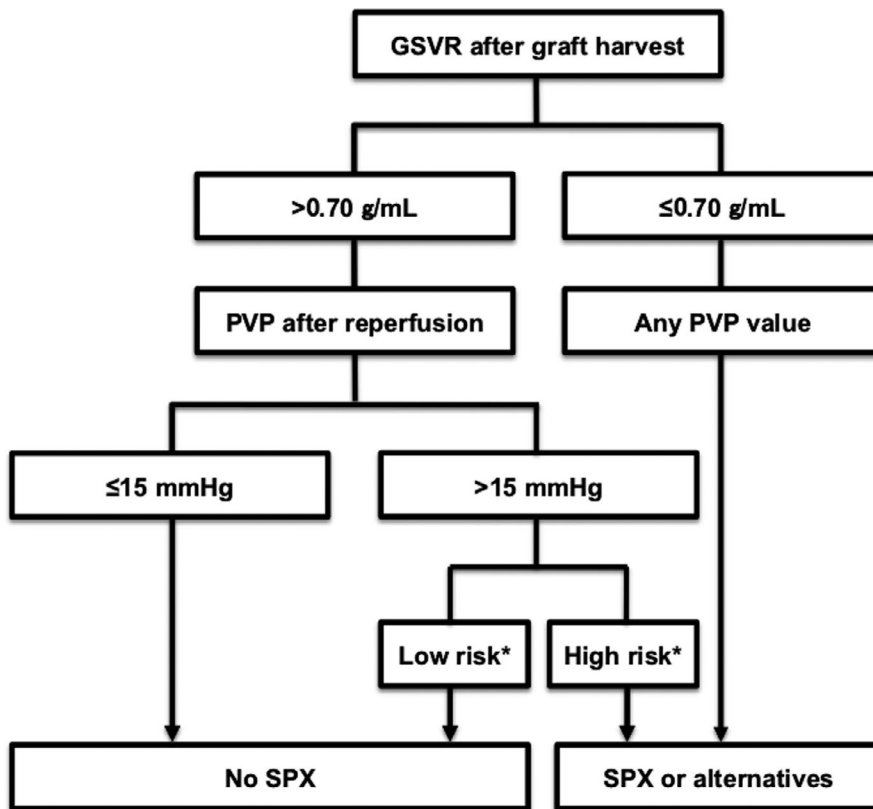


FIGURE 6 Proposed algorithm for managing patients with low GSVR combined with a PVP modulation strategy. *The low-risk group includes grafts from both ABO-compatible/identical donors and young donors aged <45 years, and the high-risk group includes grafts from either ABO-incompatible donors or older donors aged ≥45 years. GSVR, graft-to-spleen volume ratio; PVP, portal venous pressure; SPX, splenectomy

Severe infection and rejection could be fatal in these patients. Platelets have been found to mediate liver regeneration²⁴; thus, thrombocytopenia could prevent liver regeneration. Poor graft regeneration and resulting impaired graft function due to hypersplenism may account for the intolerance to severe infection. The secretion of specific cytokines such as IFN- γ and tumor necrosis factor- α is elevated in cirrhotic patients with hypersplenism.²⁵ These cytokines have been identified as markers of acute cellular rejection after LT in humans.^{26,27} We presume that the overexpression of these specific substances due to persistent hypersplenism may induce rejection after LT.

Two possible solutions can be raised to avoid these adverse events. First, selecting a larger graft can increase GSVR. While meticulous strategies and surgical performance have recently enabled satisfactory LDLT outcomes with a graft-to-recipient weight ratio (GRWR) as low as 0.6%,²⁸ our results suggest that GSVR is a better predictor of graft survival than the GRWR for selected recipients, especially when SPX is not scheduled. Second, SPX could prevent thrombocytopenia and improve graft function. SPX has been performed to correct the effects of low blood cell and platelet counts in severe cases of splenomegaly and hypersplenism.²⁹ Additionally, SPX may be beneficial for graft function by reducing portal hyperflow and ischemia/reperfusion injury in LDLT.³⁰⁻³² Therefore, it should be reserved for only necessary cases.³³ While PVP modulation is well known,^{10,16} our results indicate that low GSVR may be another indication for SPX in terms of curing hypersplenism. However, the validity of other options must also be discussed. Splenic artery embolization, including partial embolization, is a minimally invasive

treatment that can be performed as an additional treatment after LT to treat PHT^{34,35}; however, its efficacy in platelet recovery was inferior to that of SPX,³⁶ and the efficacy in graft function has never been evaluated. Although Han et al³⁷ recently demonstrated that a graded increase in the amount of transfused platelets and higher postreperfusion platelet counts during surgery increased graft regeneration for 2 weeks after LT, the graft survival was not affected. Further research is needed to discover more reliable interventions.

The true effect of graft selection and SPX in the targeted population should be verified in a prospectively accumulated cohort, combined with the PVP modulation strategy. Grafts for LDLT should meet both GRWR ≥ 0.6% and GSVR > 0.70 g/mL in Kyoto University Hospital. However, spleen volume represents individual portal hemodynamic status and does not necessarily correlate with body weight; thus, using smaller grafts in cases of low GSVR is inevitable on some occasions. Here, we propose an algorithm for managing patients with low GSVR (Figure 6). In this strategy, SPX will be limited to (1) the high-risk patients with a high PVP,¹⁶ even a GSVR > 0.70 g/mL; and (2) patients with a GSVR ≤ 0.70 g/mL regardless of PVP. In institutions where simultaneous SPX has been abandoned, other alternative interventions such as splenic artery ligation/embolization or platelet transfusion should be applied. The high risk patients here indicate the recipients who receive grafts from either ABO-incompatible donors or donors age ≥45 years.¹⁶

The current study has several limitations. First, this analysis included a single institution at which intentional PVP modulation is routinely applied. In this cohort, because SPX was performed on all patients with PHT after reperfusion, the subgroup without SPX included only patients with normal PVP. The impact of low GSVR

may change if the spleen is preserved at institutions at which PVP is not measured; thus, the data should be interpreted with caution. However, as mentioned previously, graft survival in those with spleen preservation and low GSVR should be even less likely if all patients with PHT after reperfusion are included because of their poor outcome. Second, SPX is performed for miscellaneous reasons, which is a confounding bias. However, considering that the indications for SPX vary according to the institutions in clinical settings,^{4,7,16,38} the results represent real-world experience. Finally, hypersplenism is not caused solely by spleen preservation with a low GSVR. Undiagnosed PHT might contribute to the pathogenesis of hypersplenism and impaired graft function in these patients even if the PVP was ≤ 15 mm Hg after reperfusion, as post-LT monitoring of the PVP was not available for most of the enrolled patients. Even so, the fact would not change that some kind of intervention is needed.

In conclusion, low GSVR was an independent predictor of graft loss after LDLT in patients when the spleen was preserved. Spleen preservation with extremely low GSVR may be related to persistent hypersplenism, impaired graft function, and consequent EGL even when postreperfusion PVP is not elevated. Although selecting larger grafts based on GSVR or performing SPX could be an effective option for preventing these adverse events, further research is warranted to investigate optimal interventions.

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DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

- Cheng YF, Huang TL, Chen TY, et al. Liver graft-to-recipient spleen size ratio as a novel predictor of portal hyperperfusion syndrome in living donor liver transplantation. *Am J Transplant*. 2006;6(12):2994-2999.
- Gyoten K, Mizuno S, Kato H, et al. A novel predictor of post-transplant portal hypertension in adult-to-adult living donor liver transplantation: increased estimated spleen/graft volume ratio. *Transplantation*. 2016;100(10):2138-2145.
- Jiang SM, Zhang QS, Zhou GW, Huang SF, Lu HM, Peng CH. Differences in portal hemodynamics between whole liver transplantation and living donor liver transplantation. *Liver Transpl*. 2010;16(11):1236-1241.
- Wang H, Ikegami T, Harada N, et al. Optimal changes in portal hemodynamics induced by splenectomy during living donor liver transplantation. *Surg Today*. 2015;45(8):979-985.
- Badawy A, Hamaguchi Y, Satoru S, Kaido T, Okajima H, Uemoto S. Evaluation of safety of concomitant splenectomy in living donor liver transplantation: a retrospective study. *Transpl Int*. 2017;30:914-923.
- Lusebrink R, Blumhardt G, Lohmann R, et al. Does concomitant splenectomy raise the mortality of liver transplant recipients? *Transpl Int*. 1994;7(Suppl 1):S634-S636.
- Ito K, Akamatsu N, Ichida A, et al. Splenectomy is not indicated in living donor liver transplantation. *Liver Transpl*. 2016;22(11):1526-1535.
- Gane EJ, Agarwal K. Directly acting antivirals (DAAs) for the treatment of chronic hepatitis C virus infection in liver transplant patients: "a flood of opportunity". *Am J Transplant*. 2014;14(5):994-1002.
- Egawa H, Teramukai S, Haga H, et al. Impact of rituximab desensitization on blood-type-incompatible adult living donor liver transplantation: a Japanese multicenter study. *Am J Transplant*. 2014;14(1):102-114.
- Ogura Y, Hori T, El Moghazy WM, et al. Portal pressure < 15 mm Hg is a key for successful adult living donor liver transplantation utilizing smaller grafts than before. *Liver Transpl*. 2010;16(6):718-728.
- Lee SG, Moon DB, Ahn CS, et al. Ligation of left renal vein for large spontaneous splenorenal shunt to prevent portal flow steal in adult living donor liver transplantation. *Transpl Int*. 2007;20(1):45-50.
- Sadamori H, Yagi T, Matsukawa H, et al. The outcome of living donor liver transplantation with prior spontaneous large portosystemic shunts. *Transpl Int*. 2008;21(2):156-162.
- Reddy MS, Rela M. Portosystemic collaterals in living donor liver transplantation: what is all the fuss about? *Liver Transpl*. 2017;23(4):537-544.
- Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control*. 2008;36(5):309-332.
- Yerdel MA, Gunson B, Mirza D, et al. Portal vein thrombosis in adults undergoing liver transplantation: risk factors, screening, management, and outcome. *Transplantation*. 2000;69(9):1873-1881.
- Yao S, Kaido T, Uozumi R, et al. Is portal venous pressure modulation still indicated for all recipients in living-donor liver transplantation? *Liver Transpl*. 2018;24(11):1578-1588.
- Chang FY, Singh N, Gayowski T, et al. Thrombocytopenia in liver transplant recipients: predictors, impact on fungal infections, and role of endogenous thrombopoietin. *Transplantation*. 2000;69(1):70-75.
- Lesurtel M, Raptis DA, Melloul E, et al. Low platelet counts after liver transplantation predict early posttransplant survival: the 60-5 criterion. *Liver Transpl*. 2014;20(2):147-155.
- Akamatsu N, Sugawara Y, Kanako J, et al. Low platelet counts and prolonged prothrombin time early after operation predict the 90 days morbidity and mortality in living-donor liver transplantation. *Ann Surg*. 2017;265(1):166-172.
- Richards EM, Alexander GJ, Calne RY, Baglin TP. Thrombocytopenia following liver transplantation is associated with platelet consumption and thrombin generation. *Br J Haematol*. 1997;98(2):315-321.
- McCaughan GW, Herkes R, Powers B, et al. Thrombocytopenia post liver transplantation. Correlations with pre-operative platelet count, blood transfusion requirements, allograft function and outcome. *J Hepatol*. 1992;16(1-2):16-22.

22. Marubashi S, Dono K, Nagano H, et al. Postoperative hyperbilirubinemia and graft outcome in living donor liver transplantation. *Liver Transpl*. 2007;13(11):1538-1544.
23. Ikegami T, Shirabe K, Yoshizumi T, et al. Primary graft dysfunction after living donor liver transplantation is characterized by delayed functional hyperbilirubinemia. *Am J Transplant*. 2012;12(7):1886-1897.
24. Lesurtel M, Graf R, Aleil B, et al. Platelet-derived serotonin mediates liver regeneration. *Science*. 2006;312(5770):104-107.
25. Ren S, Zhang S, Li M, et al. NF- κ B p65 and c-Rel subunits promote phagocytosis and cytokine secretion by splenic macrophages in cirrhotic patients with hypersplenism. *Int J Biochem Cell Biol*. 2013;45(2):335-343.
26. Bathgate AJ, Lee P, Hayes PC, Simpson KJ. Pretransplantation tumor necrosis factor- α production predicts acute rejection after liver transplantation. *Liver Transpl*. 2000;6(6):721-727.
27. Millán O, Rafael-Valdivia L, Torrademé E, et al. Intracellular IFN- γ and IL-2 expression monitoring as surrogate markers of the risk of acute rejection and personal drug response in *de novo* liver transplant recipients. *Cytokine*. 2013;61(2):556-564.
28. Uemura T, Wada S, Kaido T, et al. How far can we lower graft-to-recipient weight ratio for living donor liver transplantation under modulation of portal venous pressure? *Surgery*. 2016;159(6):1623-1630.
29. Zhan XL, Ji Y, Wang YD. Laparoscopic splenectomy for hypersplenism secondary to liver cirrhosis and portal hypertension. *World J Gastroenterol*. 2014;20(19):5794-5800.
30. Yoshizumi T, Taketomi A, Soejima Y, et al. The beneficial role of simultaneous splenectomy in living donor liver transplantation in patients with small-for-size graft. *Transpl Int*. 2008;21(9):833-842.
31. Soejima Y, Shirabe K, Taketomi A, et al. Left lobe living donor liver transplantation in adults. *Am J Transplant*. 2012;12(7):1877-1885.
32. Akamatsu N, Sugawara Y, Satou S, et al. Hemodynamic changes in the hepatic circulation after the modulation of the splenic circulation in an *in vivo* human experimental model. *Liver Transpl*. 2014;20(1):116-121.
33. Athanasiou A, Moris D, Damaskos C, Spartalis E. Splenectomy is not indicated in living donor liver transplantation. *Liver Transpl*. 2017;23(4):561-562.
34. Presser N, Quintini C, Tom C, et al. Safety and efficacy of splenic artery embolization for portal hyperperfusion in liver transplant recipients: a 5-year experience. *Liver Transpl*. 2015;21(4):435-441.
35. Rysmakhanov M, Doskali M, Taganova A, et al. Splenic artery embolization in patients after orthotopic liver transplant. *Exp Clin Transplant*. 2015;13(Suppl 3):52-54.
36. Tomikawa M, Akahoshi T, Sugimachi K, et al. Laparoscopic splenectomy may be a superior supportive intervention for cirrhotic patients with hypersplenism. *J Gastroenterol Hepatol*. 2010;25(2):397-402.
37. Han S, Park HW, Song JH, et al. Association between intraoperative platelet transfusion and early graft regeneration in living donor liver transplantation. *Ann Surg*. 2016;264(6):1065-1072.
38. Emond JC, Goodrich NP, Pomposelli JJ, et al. Hepatic hemodynamics and portal flow modulation: the A2ALL experience. *Transplantation*. 2017;101(10):2375-2384.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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