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ORIGINAL ARTICLE

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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 al[2] 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 induction[9] 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 Yerdel 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%),

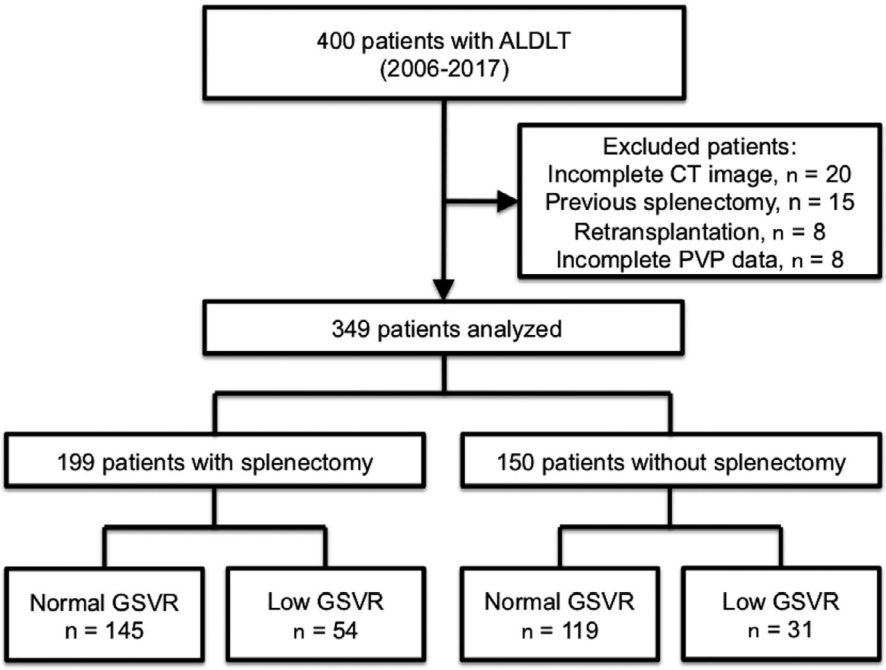

FIGURE 1 Patient population flow diagram. ALDLT, adult-to-adult living donor liver transplantation; CT, computed tomography; GSVR, graft-to-spleen volume ratio; PVP, portal venous pressure

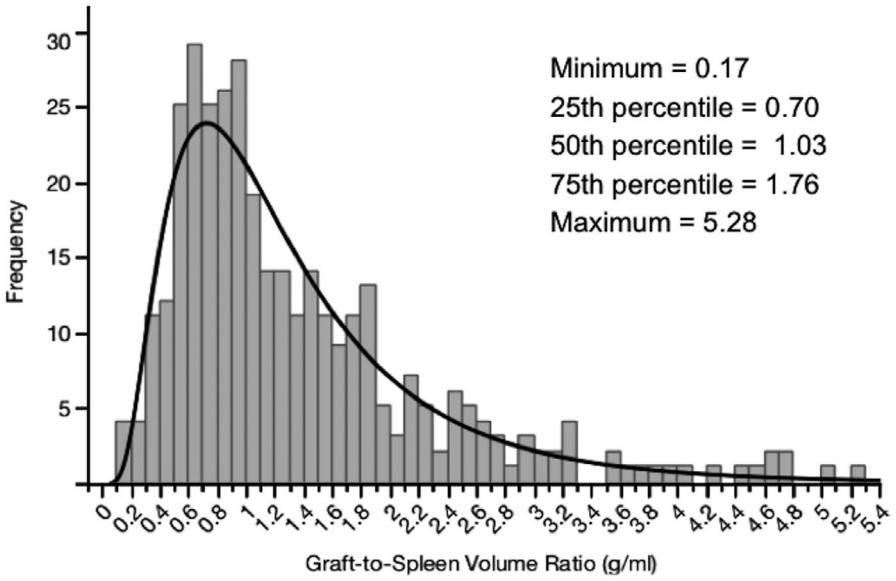

FIGURE 2 Distribution of the pretransplant graft-to-spleen volume ratio among all recipients

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	Total n = 349	Patients with splenectomy n = 199			Patients without splenectomy n = 150		
		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	*P* value	Normal GSVR n = 119	Low GSVR n = 31	*P* value
Operation time, min	819 (727-946)	825 (743-960)	863 (766-973)	.337	775 (708-890)	829 (721-938)	.422
CIT, min	92 (58-148)	100 (61-147)	89 (61-135)	.669	82 (56-150)	102 (60-174)	.426
WIT, min	43 (36-51)	43 (36-53)	44 (37-52)	.854	43 (35-51)	42 (35-47)	.388
Collateral ligation	99 (28.4)	55 (37.9)	15 (27.8)	.182	22 (18.5)	7 (23.3)	.549
Spleno-renal shunt ligation	67 (19.3)	29 (20.0)	12 (22.2)	.730	22 (18.5)	4 (13.3)	.506
Final PVP, mm Hg	13 (11-15)	13 (11-15)	14 (12-16)	.172	12 (11-15)	14 (12-15)	.025
Immunosuppressant							
Tacrolimus + MMF	235 (67.3)	95 (65.5)	35 (64.8)	.926	87 (73.1)	18 (58.1)	.104
Postoperative outcomes							
Blood loss, mL	6290 (3660-10 675)	7263 (4243-12 163)	6798 (4678-10 600)	.681	4630 (2700-7790)	6400 (3420-10 820)	.053
Transfused red blood cells, U	10 (6-20)	12 (4-22)	11 (6-46)	.718	8 (4-28)	10 (2-22)	.849
Transfused platelets, U	20 (10-30)	20 (10-30)	20 (10-40)	.561	15 (0-25)	15 (0-30)	.884
Transfused fresh-frozen plasma, U	10 (6-16)	12 (6-19)	12 (6-17)	.853	8 (4-12)	10 (6-18)	.065
Portal vein or splenic vein thrombosis[a]	24 (6.9)	12 (8.3)	8 (14.8)	.189	3 (2.5)	1 (3.2)	1.000
Acute rejection	142 (40.1)	59 (40.7)	25 (46.3)	.476	41 (34.5)	17 (54.8)	.038
Bacterial infection	170 (48.7)	75 (51.7)	27 (50.0)	.829	50 (42.0)	18 (58.1)	.110
Bacteremia	108 (30.9)	42 (29.0)	20 (37.0)	.274	31 (26.1)	15 (48.4)	.016
Pneumonia[a]	18 (5.2)	7 (4.8)	3 (5.6)	1.000	6 (5.0)	2 (6.5)	.700
Cholangitis	52 (14.9)	28 (19.3)	9 (16.7)	.670	9 (7.6)	6 (19.4)	.051
Early graft loss[a]	39 (11.1)	15 (10.3)	8 (14.8)	.455	8 (6.7)	8 (25.8)	.006
Infection[a]	23 (6.6)	10 (6.9)	3 (5.6)	1.000	5 (4.2)	5 (16.1)	.032
Acute rejection[a]	5 (1.4)	1 (0.7)	2 (3.7)	.180	0	2 (6.5)	.042
Cerebral hemorrhage[a]	5 (1.4)	3 (2.1)	1 (1.9)	1.000	1 (0.8)	0	1.000
Hepatic artery complication[a]	1 (0.3)	0	1 (1.9)	.271	0	0	—
Others[a]	5 (1.4)	1 (0.7)	1 (1.9)	.470	2 (1.7)	1 (3.2)	.503

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.

[a]Fisher exact test was applied. Other comparisons were performed using the Pearson χ^2 test for categorical variables.

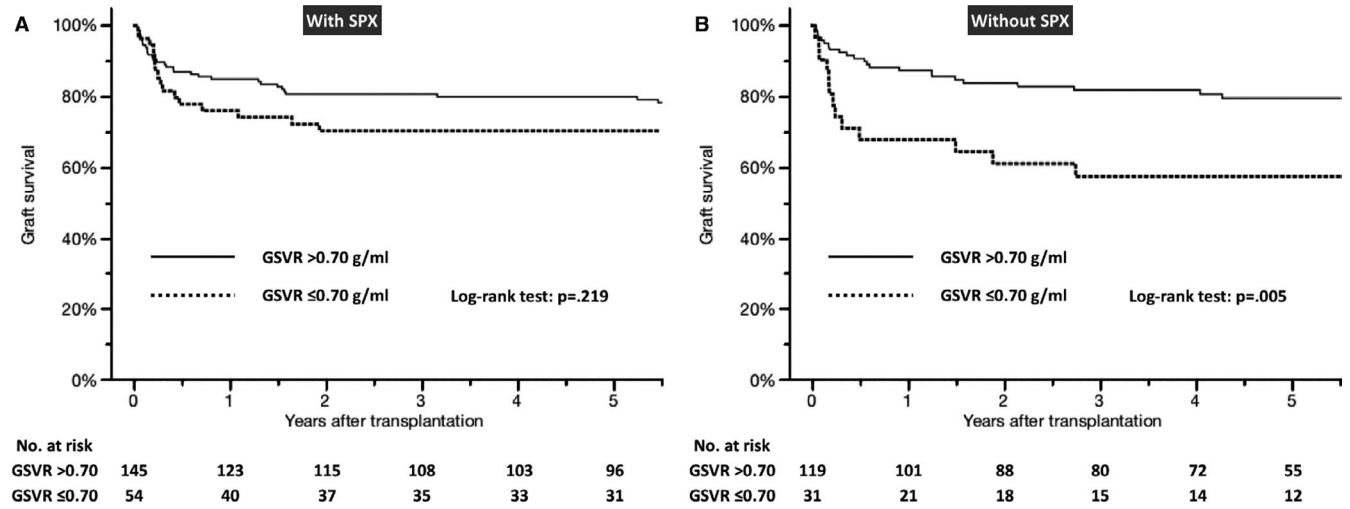

FIGURE 3 Graft survival according to graft-to-spleen volume ratio. A, In the subgroup with simultaneous splenectomy (n = 199). B, In the subgroup without simultaneous splenectomy (n = 150). GSVR, graft-to-spleen volume ratio; SPX, splenectomy

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 100×10^3/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.

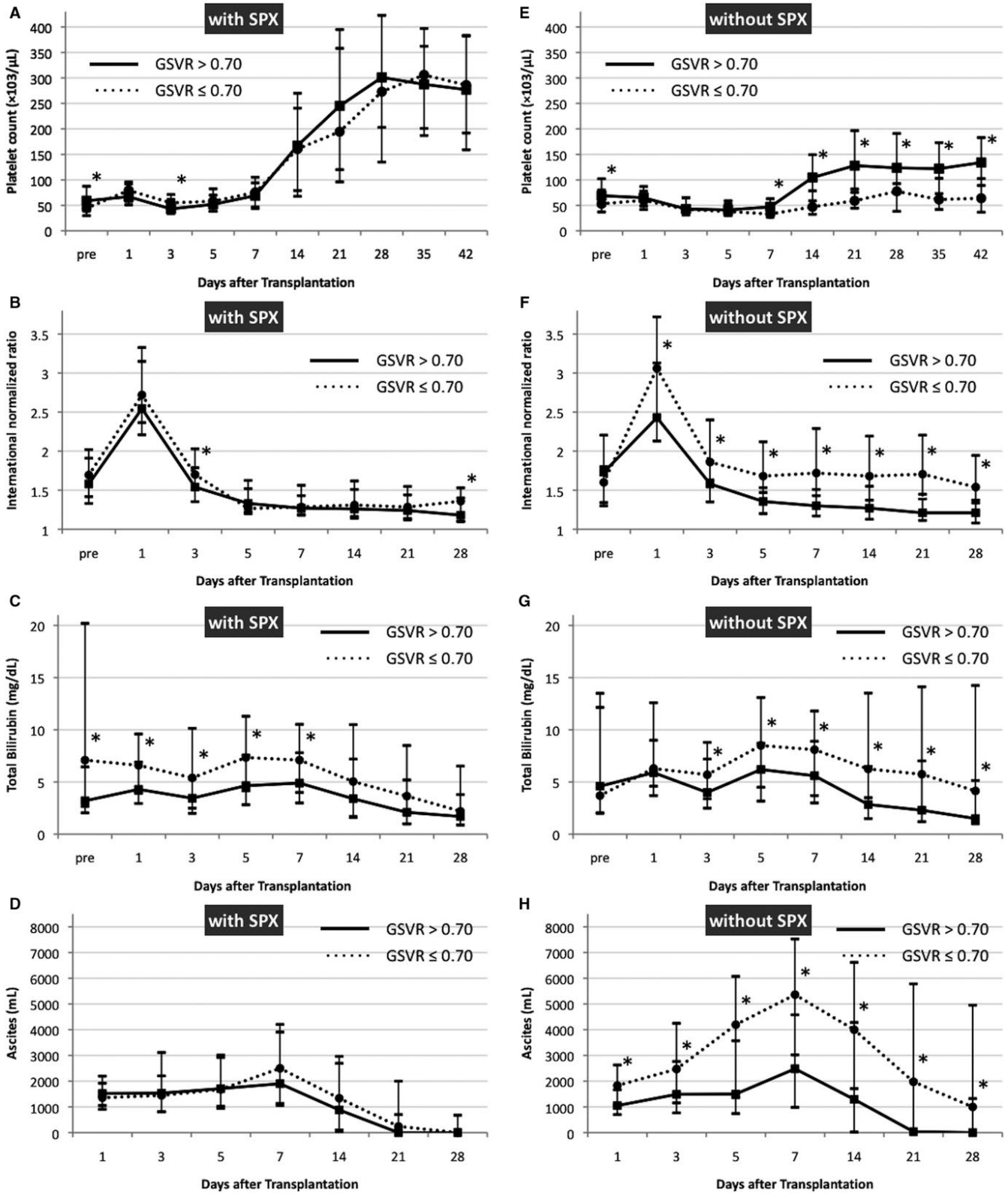

FIGURE 4 Chronologic changes in the laboratory values and ascites according to graft-to-spleen volume ratio. A-D, The results of analyses in the subgroup with simultaneous splenectomy (n = 199). A, Platelet counts. B, International normalized ratio. C, Total bilirubin. D, Ascites (E-H) show the results 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

	Subgroup with splenectomy (n= 199)				Subgroup without splenectomy (n = 150)			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
Variables	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.

[a]Yerdel 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.

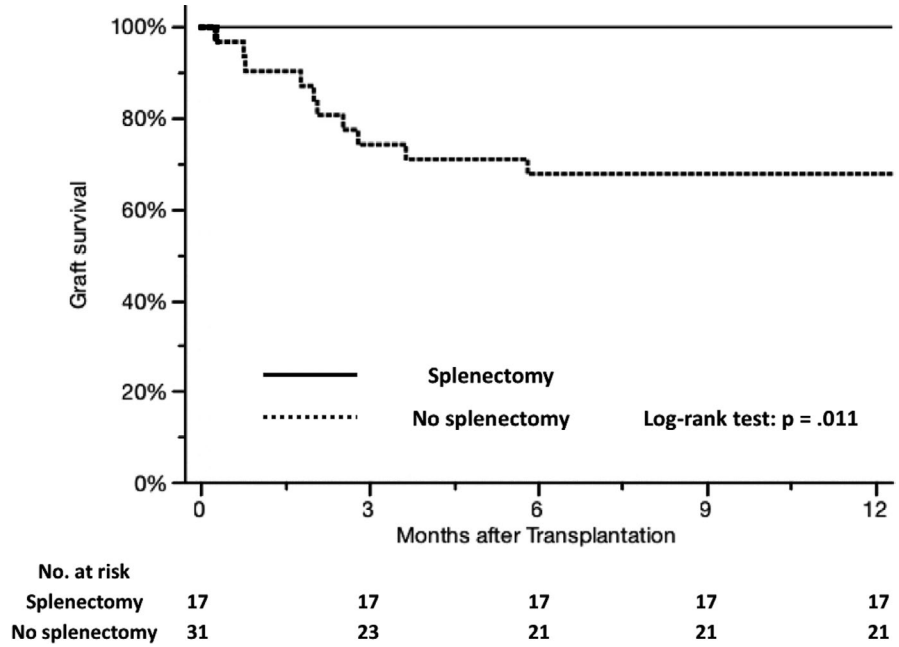

FIGURE 5 The effect of splenectomy on graft survival in patients with both low GSVR and PVP ≤15 mm Hg after reperfusion. GSVR, graft-to-spleen volume ratio; PVP, portal venous pressure

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 al [17] found that thrombocytopenia preceded infections and could be used to predict morbidity and mortality. Lesurtel et al[18] and Akamatsu et al[19] set the platelet count cutoff at 50×10/L to 60 × 10/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 5[19] 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.

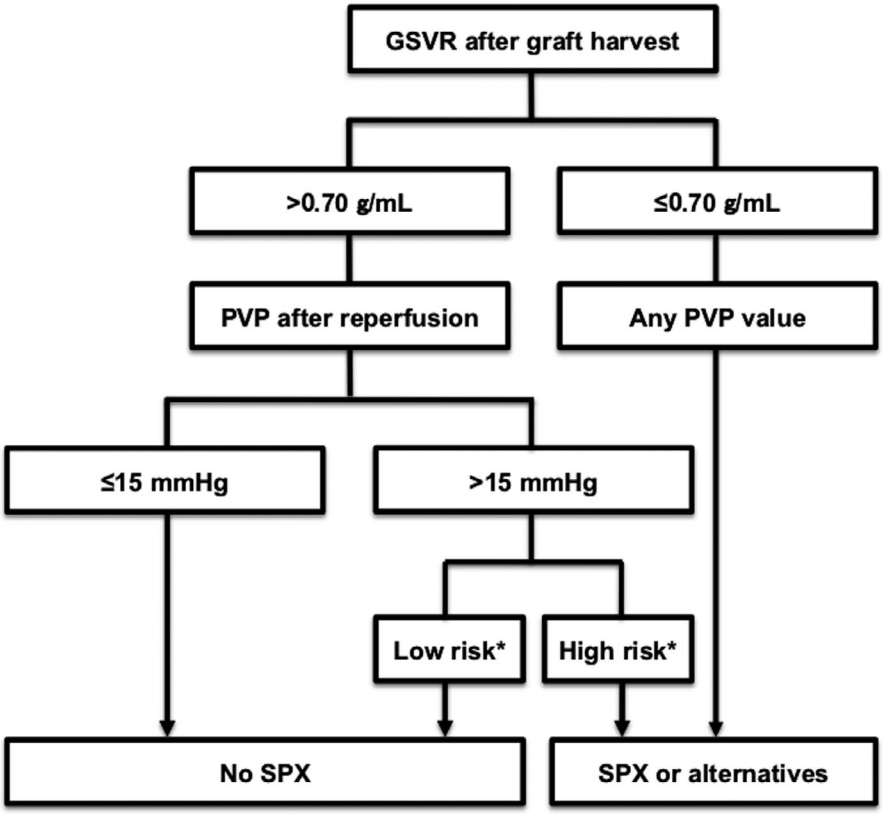

FIGURE 6 Proposed algorithm for managing patients with low GSVR combined with a PVP modulation strategy. *The low-risk group includes grafts from both ABO-compatible/identical donors and young donors aged <45 years, and the high-risk group includes grafts from either ABO-incompatible donors or older 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 generation[24]; 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 al[37] 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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SUPPORTING INFORMATION

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

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