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ORIGINAL ARTICLE

Impact of graft thickness reduction of left lateral segment on outcomes following pediatric living donor liver transplantation

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Reducing graft thickness is essential to prevent large-for-size graft problems in pediatric living donor liver transplantation (LDLT). However, long-term outcomes of LDLT using reduced-thickness left lateral segment (LLS) grafts are unclear. In 89 patients who underwent LDLT using reduced LLS grafts between 2005 and 2017, short-term and long-term outcomes were compared between a nonanatomically reduced LLS (NAR-LLS) graft group and a reduced-thickness LLS graft group. Estimated blood loss was lower and abdominal skin closure was less needed in the recipient operation in the reduced-thickness LLS graft group. Postoperatively, portal vein (PV) flow was significantly decreased in the NAR-LLS graft group, and there was shorter intensive care unit (ICU) stay and fewer postoperative complications, especially bacteremia, in the reduced-thickness LLS graft group. Graft survival at 1 and 3 years after LDLT using reduced-thickness LLS grafts was 95.2% and 92.4%, respectively, which was significantly better than for NAR-LLS grafts. Multivariate analysis revealed that fulminant liver failure, hepatofugal PV flow before LDLT, and NAR-LLS graft were associated with poor graft survival. In conclusion, LDLT using reduced-thickness LLS grafts is a safe and feasible option with better short- and long-term outcomes in comparison with NAR-LLS grafts.

KEYWORDS
clinical research/practice, graft survival, liver transplantation/hepatology, liver transplantation: living donor, patient survival

1 | INTRODUCTION

Split, reduced, and living donor liver transplantation (LDLT) techniques have developed over the past 2 decades because of a shortage of size-matched liver grafts for pediatric recipients. These technical innovations have expanded the donor pool and decreased waiting-list mortality for children.[1] However, when the graft-to-recipient weight ratio (GRWR) exceeds 4.0% in neonates and smaller infants receiving a left lateral segment (LLS) graft from an adult donor, the graft may be too large, which carries risks of morbidity.[2] To overcome this critical large-for-size graft problem, advanced techniques have been developed to further reduce the size of LLS grafts in pediatric LDLT, especially for neonates or smaller infants.[2-8] However, the anteroposterior thickness of grafts remains a problem, particularly in smaller children without portal hypertension, hepatomegaly, or ascites, most of whom do not have sufficient abdominal space to

Abbreviations: ACR, acute cellular rejection; BW, body weight; CT, computed tomography; FHF, fulminant hepatic failure; GRWR, graft-to-recipient weight ratio; GV, graft volume; ICU, intensive care unit; LDLT, living donor liver transplantation; LLS, left lateral segment; NAR-LLS, nonanatomically reduced left lateral segment; PELD, pediatric end-stage liver disease; PT-INR, international normalized ratio of prothrombin time; PV, portal vein; SLV, standard liver volume; S2, Segment 2; S3, Segment 3.

allow a thick graft to settle, because these techniques use nonanatomical reduction of the lateral or caudal part of the LLS, which cannot adequately reduce graft thickness.[9]

Anatomically reduced LLS grafting has been reported as an alternative method for smaller infants and is known as a subsegment 2 graft or conventional reduced-thickness LLS graft.[10] Although this graft can reduce graft thickness, there are some technical disadvantages, mainly the risk of injury to the portal pedicle because of the need for dissection at the base of the umbilical fissure. Therefore, since 2014, we have introduced a modified reduction technique of the LLS, which we refer to as the modified segment 2 (S2) graft.[9,11] However, there have been no studies to date of the long-term outcomes of pediatric LDLT patients who received reduced-thickness LLS grafts or large-scale studies of the effectiveness of the grafts.

In this retrospective study, we assessed short-term and long-term outcomes of LDLT using reduced-thickness LLS grafts compared with conventional nonanatomically reduced LLS (NAR-LLS) grafts. We also examined the prognostic factors affecting graft survival and assessed graft regeneration rate in smaller children.

2 | PATIENTS AND METHODS

2.1 | Patients

From November 2005 to January 2017, a total of 403 consecutive pediatric patients (< 18 years old) underwent LDLT at the National Center for Child Health and Development, Tokyo, Japan. Of these, 261 patients received an LLS graft and 96 patients received a reduced LLS graft. After excluding 7 recipients who required graft reduction in situ during the recipient operation, 89 patients were enrolled in this study: 47 in the NAR-LLS graft group and 42 in the reduced-thickness LLS graft group (13 subsegment 2 grafts and 29 modified S2 grafts; Figure 1).

Immunosuppressive therapy consisted of tacrolimus and low-dose steroids.[12] Informed consent was obtained from all donors and recipients before enrollment and their anonymity was preserved. The study was approved by the Ethics Committee of the National Center for Child Health and Development and conducted in accordance with the Declaration of Helsinki (2008).

2.2 | Graft selection

Until December 2012, we had selected NAR-LLS grafts as the only option for small infants when the estimated graft-to-recipient weight ratio (GRWR) exceeded 4.0%.[6,7] Between January 2013 and July 2014, we accounted for the size and shape of the graft and considered using a reduced-thickness LLS graft when the ratio of the maximum thickness of the LLS to the anteroposterior diameter of the recipient's abdominal cavity was ≥ 1.0. When the ratio was < 1.0, we considered using the NAR-LLS graft. The algorithm during this period has been described previously.[9] Since September 2014, we have used the modified S2 graft as the first option although we have used NAR-LLS grafts when the donor grafts were extremely thin and adequate volume reduction could be achieved by NAR-LLS rather than modified S2 grafts. The current algorithm is shown in Figure 2A and the number of cases of each graft type over time is shown in Figure 2B.

In all donors, we assessed vascular anatomy and volumetry of the liver by using 3-dimensional computer models (Fraunhofer MEVIS, Bremen, Germany).

2.3 | Surgical procedure

2.3.1 | Conventional NAR-LLS grafts (Figure 3A)

These grafts have been referred to as monosegment grafts or hyperreduced LLS grafts.[2,7,8] The donor LLS was reduced in situ as described previously.[2,7] Both the caudal and lateral parts of the LLS were resected in situ while preserving the medial branch of the left hepatic vein.

2.3.2 | Reduced-thickness LLS grafts

Subsegment 2 grafts (Figure 3B)

After isolation of the LLS graft, portal vein (PV) feeding segment 3 ([S3] P3) was exposed, and the relevant PV branches feeding the reduced part of S3 were occluded to make demarcation lines on the surface between S2 and S3.[9] The portal venous flow to the graft

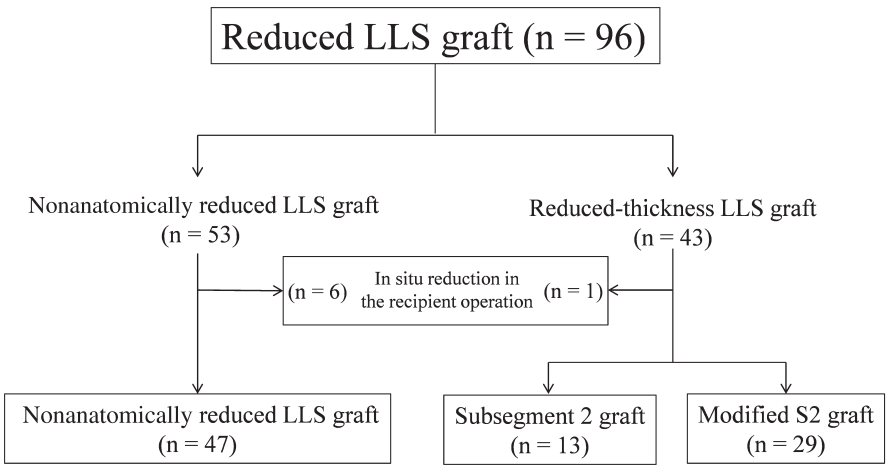

FIGURE 1 Flow diagram of the patients included in this study.

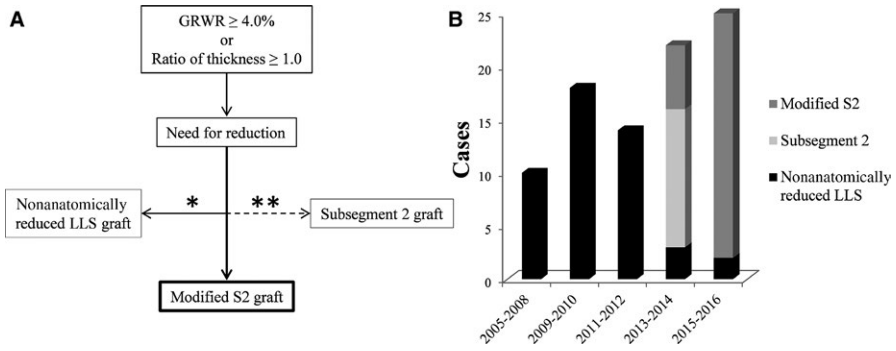

FIGURE 2 Graft selection at National Center for Child Health and Development. (A) Current algorithm used for the preoperative assessment for graft type selection. Asterisk indicates that use of the NAR-LLS graft is considered when donor grafts are extremely thin and adequate volume reduction could be achieved with NAR-LLS rather than modified S2 grafts. Double asterisk indicates that the use of the subsegment 2 graft is considered when the recipient is an extremely small infant (< 1 month old) where the donor graft is relatively bigger compared to the size of the recipient's abdominal cavity. (B) LDLT using reduced LLS graft. GRWR, graft-to-recipient weight ratio; LLS, left lateral segment; S2, segment 2

was routinely confirmed using intraoperative Doppler ultrasonography in order to preserve it inside the liver. The further parenchymal transection was performed following the demarcation lines.[9]

Modified (P3-preserved) S2 grafts (Figures 3C and 4)

After isolation of the LLS graft, the ventral part of S3 was removed in situ while preserving the main Glisson's pedicle of S3 on the graft side (Figure 4A,B). Parenchymal transection was performed along the boundary between the ventral and dorsal parts of S3 without extensive dissection at the base of the umbilical fissure. The thickness of the graft was reduced sufficiently and the main portal venous branch perfusing the dorsal part of S3 and the drainage hepatic veins could be preserved.

In all recipient operations, hepatic artery reconstruction was performed under microscopy. Biliary reconstruction was performed using Roux-en-Y hepaticojejunostomy. LDLT was performed by 3 experienced surgeons (M.K., S.S., and A.F.) following a standardized surgical procedure.

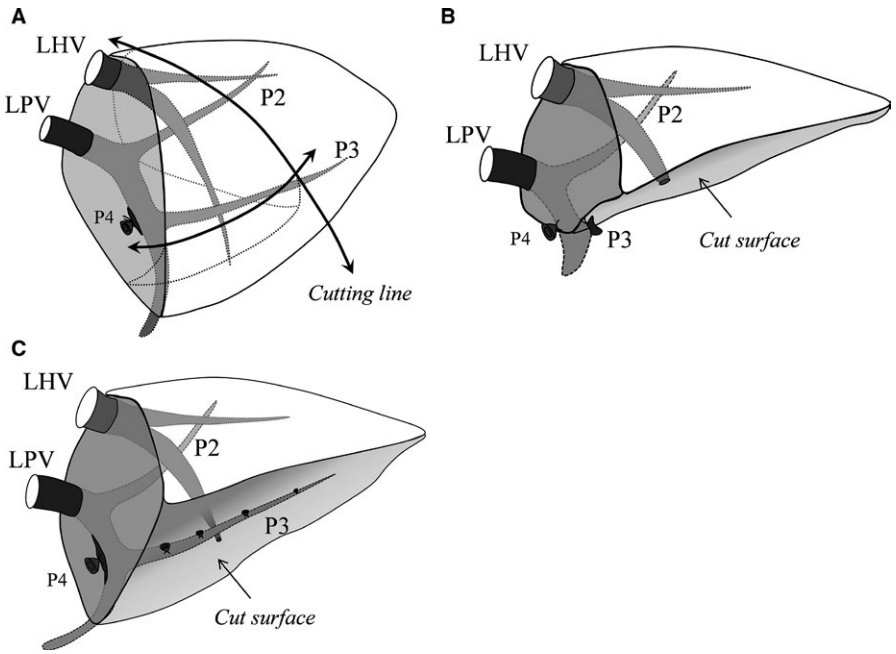

FIGURE 3 Schema of the reduction method for each type of reduced left lateral segment (LLS) graft. (A) Nonanatomically reduced LLS (NAR-LLS) graft. (B) Subsegment 2 graft. Each portal vein (PV) branch feeding S2 and Segment 3 (S3) was separately exposed and the relevant PV branches feeding the reduced part of S3 were occluded to make demarcation lines on the surface between S2 and S3. (C) Modified S2 graft. The anterior surface of S3 was removed without extensive dissection at the base of umbilical fissure. The transection line should be located horizontally on the level of the P3. Ventral branches of P3 that emerged on the cutting plane were ligated. This transection line can preserve the drainage vein of the graft and P3 was preserved. LHV, left hepatic vein; LPV, left portal vein; P2, portal vein branch feeding S2; P3, portal vein branch feeding S3

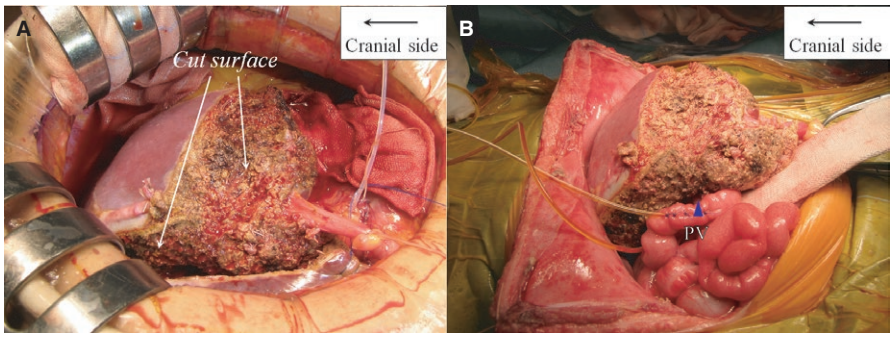

FIGURE 4 Example of an LDLT with modified segment 2 graft. Recipient is a 38-day-old girl, weighing 3.6 kg. (A) After isolation of the LLS graft, the ventral part of S3 was removed in situ. The main Glisson's pedicle of S3 was preserved on the graft side. (B) During the recipient operation, the modified S2 graft was implanted in the abdominal cavity. Primary abdominal closure was achieved. This graft (weight 137 g) has a thickness of 2.4 cm. PV, portal vein

2.4 | Study variables

The following clinical data were collected from electronic medical records: age, sex, body weight (BW), original disease, pretransplant patient condition, pediatric end-stage liver disease (PELD) score, blood type, PV flow detected by Doppler ultrasonography, serum bilirubin, international normalized ratio of prothrombin time (PT-INR), duration of ventilator weaning, duration of ICU stay, duration of hospital stay, and presence of infections or vascular complications. Surgical data were collected from operation records. Postoperative complications among recipients were graded according to the Clavien–Dindo classification system.[13] PV flow after abdominal closure was measured immediately postoperatively by Doppler ultrasonography in the ICU. Percent change in PV flow rate was calculated for each patient as (PV flow after closure − PV flow before closure) × 100/PV flow before closure. Pretransplant laboratory parameters were collected during the week before LDLT in all cases.

2.5 | Assessment of the graft regeneration

The percent ratio of graft volume (GV) to standard liver volume (SLV) (GV/SLV [%]) was assessed at 1 month, 3 months, and 1 year after LDLT. A volume of 1 cm^3 of the liver was assumed to be 1 g.[14] Volumetry was performed by one of the authors (R.I.).

2.6 | Statistical analysis

Continuous variables were summarized as medians and ranges and then compared with Wilcoxon rank-sum test. Categorical variables were summarized as frequencies and percentages and compared using the chi-square test. Overall and graft survival curves were estimated using the Kaplan–Meier method and compared with the log-rank test. Areas under receiver operating characteristic curves for mortality were used to determine the optimal cutoff values for PELD score, recipient age, and BW. Prognostic factors for graft loss were identified using univariate and multivariate Cox proportional hazards models and only pretransplant factors were included in the multivariate analyses. Significant confounding factors were selected by multivariate Cox regression analyses with backward elimination ($P < .05$), keeping the variable of interest (graft type) in the model. All reported P values are 2-sided, with a value of 0.05 considered statistically significant. All analyses were done using SPSS software ver. 21 (IBM SPSS, Chicago, IL).

3 | RESULTS

3.1 | Patient characteristics

Table 1 shows the characteristics of the 89 LDLT patients who received a reduced LLS graft. Median age at LDLT was 7.3 (range 1.0-18.5) months, median BW was 5.9 (range 2.4-9.4) kg, and median PELD score was 18.4 (range 0-52.0). Median estimated and actual GRWR were 4.8 (range 2.4-15.6) and 2.9 (1.3-4.7), respectively. Common indications for LDLT with a reduced LLS graft included biliary atresia (56.2%) and fulminant hepatic failure (FHF; 19.1%). Twenty-eight patients (31.5%) were managed in the ICU at the time of LDLT. Of them, 23 patients received mechanical ventilation support and/or apheresis therapy due to respiratory or renal impairment, coagulopathy, hepatic encephalopathy, and hyperammonemia. The median follow-up period was 42.1 (range 0.3-124.3) months.

Table 2 summarizes the pretransplant characteristics of the NAR-LLS group and the reduced-thickness LLS graft group. Median age, BW, PELD score, weight-for-age z-score, serum bilirubin, and PT-INR were not significant between the 2 groups.

3.2 | Surgical outcomes and postoperative complications

Table 2 summarizes the surgical outcomes in the 2 groups. The reduced-thickness LLS graft group had a significantly lower median amount of blood loss than the NAR-LLS graft group (71.7 g/kg vs 136.1 g/kg, $P = .003$) and also tended to have shorter median warm ischemic time (26 vs 30 minutes, $P = .088$) and cold ischemic time (22 vs 31 minutes, $P = .051$). Significantly fewer patients needed abdominal skin closure in the reduced-thickness LLS graft

TABLE 1 Patient characteristics

Characteristics	Value
Age, mo	7.3 (1.0-18.5)
Sex, M/F	29/60
Body weight, kg	5.9 (2.4-9.4)
Original disease, n (%)	
Biliary atresia	50 (56.2)
Fulminant hepatic failure	17 (19.1)
Metabolic diseases	8 (9.0)
Alagille syndrome	6 (6.7)
Hepatoblastoma	1 (1.1)
Other	7 (7.9)
Preoperative status, n (%)	
At home	3 (3.4)
Hospitalized	58 (65.1)
ICU-bound	28 (31.5)
PELD score	18.4 (0-52.0)
Estimated GRWR, %	4.8 (2.4-15.6)
Actual GRWR, %	2.9 (1.3-4.7)
Graft type, n (%)	
Nonanatomically reduced LLS graft	
Reduced LLS	5 (5.6)
HRLLS	42 (47.2)
Reduced-thickness LLS graft	
Subsegment 2	13 (14.6)
Modified segment 2	29 (32.6)
Blood type combination, n (%)	
Identical	48 (53.9)
Compatible	20 (22.5)
Incompatible	21 (23.6)
Follow-up (mo)	42.1 (0.3-124.3)

ICU, intensive care unit; PELD, pediatric end-stage liver disease; GRWR, graft-to-recipient weight ratio; LLS, left lateral segment; HRLLS, hyperreduced left lateral segment.

group than in the NAR-LLS graft group (2.4% vs 27.7%, $P = .001$). Median percent change in the PV flow rate was significantly lower in the NAR-LLS graft group than in the reduced-thickness LLS graft group (−26.9% vs 23.5%, $P = .003$). Operation time, estimated GRWR, and actual GRWR did not differ significantly between the groups.

Table 3 shows the incidence of postoperative complications between the reduced-thickness LLS graft group and the NAR-LLS group. Incidence of these complications was significantly lower in the reduced-thickness LLS graft group than in the NAR-LLS graft group (23.8% vs 48.9%, $P = .017$). Incidence of biliary and vascular complications did not differ significantly between the groups, whereas incidence of postoperative bacteremia was significantly lower in the reduced-thickness LLS graft group (11.9% vs 44.7%, $P = .001$). Regarding the serum parameters, bilirubin and PT-INR on postoperative day (POD) 14 and 28 were significantly lower in the reduced-thickness LLS graft group than in the NAR-LLS graft group. In addition, the reduced-thickness LLS graft group had shorter median duration of ventilator weaning (1 day vs 8 days, $P = .001$), ICU stay (11.5 days vs 28 days, $P < .001$), and hospital stay (45 days vs 57 days, $P = .024$). There were no cases of hepatic arterial thrombosis or hepatic venous outflow obstruction in either group.

In donors, perioperative parameters did not differ significantly between the groups.

3.3 | Details of cases with mortality or graft loss with a reduced LLS graft

Table 4 shows the clinical details of 16 patients with mortality or graft loss with a reduced LLS graft (17.8%). In deceased patients (n = 11), the primary original disease was FHF (n = 4) and biliary atresia (n = 4). Seven of 8 patients who died within 90 days after LDLT received an NAR-LLS graft, and the remaining patient received a modified S2 graft. The primary cause of death was sepsis in all 7 of the patients who received an NAR-LLS graft and viral pneumonia in the patient who received a modified S2 graft. In patients 1 and 8, sepsis was caused by jejunal perforation. Two of 3 patients who died beyond 90 days after LDLT received an NAR-LLS graft and the remaining patient received a modified S2 graft. The cause of death was pulmonary hypertension in 2 patients and graft failure due to acute cellular rejection (ACR) in 1 patient. In 6 patients who required retransplantation, the cause of graft loss was progression of intrapulmonary shunt in patient 11, ACR with veno-occlusive change in 3 patients, and antibody-mediated rejection in 2 patients.

3.4 | Long-term outcomes after LDLT using a reduced LLS graft

During a median follow-up of 4.3 years, patient survival rate was 97.6% in the reduced-thickness LLS graft group and 83.0% in the NAR-LLS graft group at 1 year and 95.1% and 80.9%, respectively, at 3 years. The corresponding graft survival rate was 95.2% and 74.5% at 1 year and 92.4% and 72.3% at 3 years. Patient survival ($P = .045$, Figure 5A) and graft survival ($P = .014$, Figure 5B) were significantly better in the reduced-thickness LLS graft group than in the NAR-LLS graft group.

3.5 | Subgroup analysis in the reduced-thickness LLS graft group

Table 5 summarizes the perioperative outcomes between the subsegment 2 graft group and the modified S2 graft group. In recipients, pretransplant characteristics and posttransplant outcomes did not differ significantly between the groups. In donors, the modified S2 graft group had heavier graft weight (138 g vs 192 g, $P = .001$), lower reduction rate (47.5% vs 22.1%, $P < .001$), and higher GRWR (2.7% vs 3.3%, $P = .004$) than the subsegment 2 graft group. There were no

TABLE 2 Comparison of characteristics and surgical outcomes between patients with nonanatomically reduced LLS graft and reduced-thickness LLS graft

	Nonanatomically reduced LLS graft (n = 47)	Reduced-thickness LLS graft (n = 42)	*P* value
Pretransplant characteristics			
Age, mo (range in d)	7.5 (32-554)	7.1 (29-434)	.769
Sex, M/F	14/33	15/27	.652
Body weight, kg	5.9 (2.4-8.5)	5.9 (2.8-9.4)	.622
Patient condition, n (%)			
ICU	17 (36.2)	11 (26.2)	.365
Hospitalized	28 (59.6)	30 (71.4)	.272
At home	2 (4.2)	1 (2.4)	1.000
PELD score	18.6 (0-52.0)	18.2 (2.2-36.0)	.235
Hepatofugal PV flow, n (%)	10 (21.3)	5 (11.9)	.270
Weight-for-age z-score	−1.9 (−4.3-4.5)	−2.0 (−4.9-0.6)	.990
Bilirubin, mg/dL	12.5 (0.1-46.1)	11.0 (0.1-31.5)	.106
PT-INR	1.4 (0.9-4.4)	1.4 (0.9-4.9)	.393
Surgical outcomes			
Operation time, min	497 (352-1558)	504 (348-1085)	.840
Blood loss, g/kg	136.1 (15.8-896.7)	71.7 (12.8-426.8)	**.003**
WIT, min	30 (19-60)	26 (21-67)	.088
CIT, min	31 (8-160)	22 (7-136)	.051
Interposition vein graft for PV reconstruction, n (%)	11 (23.4%)	10 (23.8%)	1.000
Estimated GRWR (%)	4.9 (3.5-15.6)	4.7 (2.4-9.7)	.755
Actual GRWR (%)	2.8 (1.3-4.7)	3.1 (1.5-4.7)	.061
Abdominal closure (Primary/partial skin)	34/13	41/1	**.001**
PV flow before closure, cm/s	31.7 (8.4-134.6)	24.5 (8.2-142.7)	.117
PV flow after closure, cm/s	25.3 (6.8-90.4)	26.6 (7.3-79.8)	.395
Percent change in PV flow rate (%)	−26.9 (−73.5-353.6)	23.5 (−75.0-206.5)	**.003**

Bold type indicates statistically significant differences.
ICU, intensive care unit; PELD, pediatric end-stage liver disease; WIT, warm ischemic time; CIT, cold ischemic time; GRWR, graft-to-recipient weight ratio; PV, portal vein.

significant differences in patient survival ($P = .309$) or graft survival ($P = .863$) between the groups.

3.6 | Graft regeneration in CT volumetry after LDLT

Figure 6 shows serial changes of GV/SLV in recipients after LDLT. Volumetric data of grafts were available for 13 recipients (NAR-LLS graft: 8; subsegment 2 graft: 3; modified S2 graft: 2) at 1 month, 27 recipients (NAR-LLS graft: 14; subsegment 2 graft: 4; modified S2 graft: 9) at 3 months, and 8 recipients (NAR-LLS graft: 4; subsegment 2 graft: 2; modified S2 graft: 2) at 1 year after LDLT. GV/SLV increased rapidly within 1 month, and GV converged toward the SLV at 1 year after LDLT (Figure 6).

3.7 | Prognostic factors for graft survival following LDLT using a reduced LLS graft

Table 6 shows the results of univariate analysis of risk factors for graft loss after LDLT using a reduced LLS graft. Significant risk factors for graft loss (n = 16) after LDLT were FHF, high PELD score, ICU bound, hepatofugal PV flow prior to LDLT, use of NAR-LLS graft, presence of PV complication, and reoperation. Multivariate analysis with pretransplant candidate variables revealed that the independent risk factors for graft loss after LDLT were FHF (HR 3.998, 95% CI 1.421-11.253, $P = .009$), hepatofugal PV flow (HR 4.296, 95% CI 1.478-12.489, $P = .007$), and use of NAR-LLS graft (HR 3.541, 95% CI 1.006-12.465, $P = .049$).

TABLE 3 Comparison of postoperative complications, parameters, and donor data between patients with nonanatomically reduced LLS graft and reduced-thickness LLS graft

	Nonanatomically reduced LLS graft (n = 47)	Reduced-thickness LLS graft (n = 42)	*P* value
Complications ≥ 3b, n (%)	23 (48.9)	10 (23.8)	**.017**
Biliary complications, n (%)	2 (4.3)	1 (2.4)	1.000
leak/stricture	0/2	1/0	
PV complication, n (%)	3 (6.4)	1 (2.4)	.619
HAT, n (%)	0 (0)	0 (0)	1.000
HVOO, n (%)	0 (0)	0 (0)	1.000
Reoperation, n (%)	14 (29.8)	6 (14.3)	.126
Ascites > 1 L on POD 30, n (%)	5 (10.6)	2 (4.8)	.434
Bacteremia, n (%)	21 (44.7)	5 (11.9)	**.001**
Acute cellular rejection, n (%)	19 (40.4)	18 (42.9)	.830
Bilirubin, mg/dL			
POD 14	2.2 (0.2-25.6)	0.6 (0.1-5.5)	**<.001**
POD 28	0.8 (0.1-21.2)	0.4 (0.1-3.5)	**.003**
PT-INR			
POD 14	1.5 (1.0-4.3)	1.2 (0.9-2.0)	**.001**
POD 28	1.3 (1.0-2.2)	1.2 (0.9-1.8)	**.045**
Duration of ventilator weaning, d	8 (0-307)	1 (0-242)	**.001**
ICU stay, d	28 (5-104)	11.5 (4-72)	**<.001**
Hospital stay, d	57 (9-560)	45 (9-373)	**.024**
Retransplantation, n (%)	4 (8.5)	2 (4.8)	.680
Mortality, n (%)	9 (19.1)	2 (4.8)	.054
Donor data			
Age, mo	32 (20-62)	34 (21-43)	.562
Sex, M/F	23/24	21/21	1.000
BMI, kg/m^2	21.3 (16.9-29.0)	21.5 (17.1-26.6)	.490
Graft weight, g	155 (72-245)	177 (106-280)	.050
Reduction rate, %	38.3 (15.4-81.9)	36.9 (15.1-71.3)	.083
Operation time, min	330 (202-470)	318 (199-535)	.291
Blood loss, g	190 (10-1448)	233 (50-710)	.308
Complications ≥ 3b, n (%)	0 (0)	0 (0)	1.000

Bold type indicates statistically significant differences.
PV, portal vein; HAT, hepatic arterial thrombosis; HVOO, hepatic venous outflow obstruction; POD, postoperative day; PT-INR, international normalized ratio of prothrombin time; ICU, intensive care unit.

4 | DISCUSSION

In this study of our 10-year experience with 89 pediatric LDLT recipients who received a reduced LLS graft at a high-volume Japanese institution, we found that LDLT using the reduced-thickness LLS graft for small babies was associated with better short-term outcomes and better patient and graft survival than LDLT using the conventional NAR-LLS graft. Furthermore, our modified thickness reduction technique leads to satisfactory long-term outcomes because of the safer surgical approach. The results of this first study describing the long-term outcomes of small children with reduced-thickness LLS graft received from living donors indicates that this graft is a valuable option that offers advantages over the NAR-LLS graft.

Adequate reduction of graft thickness is important for preventing major problems related to large-for-size grafts, such as

TABLE 4 Details of cases with mortality or graft loss who received a reduced LLS graft

No.	Sex	Age at LDLT (mo)	Body weight (kg)	Original disease	Graft type	Actual graft weight (g)	Actual GRWR (%)	Reduction rate (%)	Complications and cause of death or graft loss
Cases within 90-d mortality									
1	F	3	4.0	FHF	NAR	119	3.0	58.1	Sepsis due to jejunal perforation (POD 52)
2	F	6	8.0	FHF	Modified S2	280	3.5	17.9	RSV pneumonia (POD 9)
3	M	7	4.1	Cryptogenic LC	NAR	115	2.8	22.8	Sepsis (POD 10)
4	F	7	5.8	Alagille syndrome	NAR	125	2.2	61.7	ACR, Sepsis (POD 54)
5	F	7	5.8	BA	NAR	181	3.1	36.5	ACR, Sepsis (POD 51)
6	F	9	5.7	BA	NAR	202	3.5	42.5	ACR, Sepsis (POD 36)
7	F	10	6.2	BA	NAR	219	3.5	15.4	ACR, Sepsis (POD 18)
8	M	14	6.0	Alagille syndrome	NAR	139	2.3	52.7	Sepsis due to jejunal perforation (POD 24)
Cases beyond 90-d mortality or graft loss									
9	F	1	3.5	FHF	NAR	72	2.1	81.9	ACR, Graft failure (POM 6)
10	M	4	4.5	FHF	NAR	139	3.1	36.8	Pulmonary hypertension (POM 18)
11[a]	M	7	5.2	BA	Modified S2	180	3.5	42.7	Pulmonary hypertension (POM 13)
12	M	6	6.4	FHF	NAR	192	3.0	21.0	Graft loss due to ACR with VOC (POM 10)
13	F	7	7.0	BA	NAR	146	2.1	39.7	Graft loss due to AMR (POD 49)
14	M	7	7.3	FHF	Subsegment 2	124	1.7	71.3	Graft loss due to ACR with VOC (POM 19)
15	F	8	7.2	BA	NAR	91	1.3	63.2	Graft loss due to AMR (POD 60)
16	M	10	8.0	FHF	NAR	137	1.7	54.8	Graft loss due to ACR with VOC (POM 9)

ACR, acute cellular rejection; AMR, antibody-mediated rejection; BA, biliary atresia; FHF, fulminant hepatic failure; GRWR, graft-to-recipient weight ratio; LC, liver cirrhosis; LDLT, living donor liver transplantation; LLS, left lateral segment; NAR, nonanatomically reduced LLS graft; POD, postoperative day; RSV, respiratory syncytial virus; VOC, veno-occlusive change.

[a]Patient 11 underwent retransplantation due to graft loss caused by portal vein occlusion and progression of intrapulmonary shunt on POM 8.

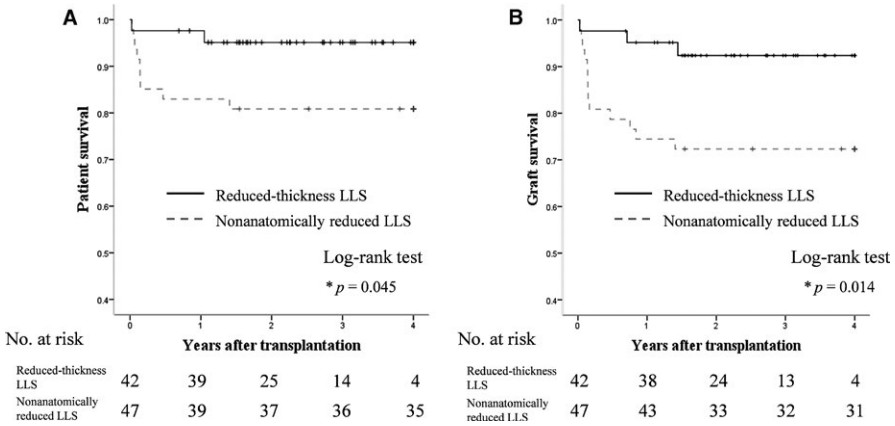

FIGURE 5 Comparison of long-term patient and graft survival between use of a reduced-thickness LLS graft and a NAR-LLS graft. (A) Patient survival (P = .045) and (B) graft survival (P = .014) are significantly better in the reduced-thickness LLS graft group than in the NAR-LLS graft group. LLS, left lateral segment

TABLE 5 Comparison of perioperative outcomes between subsegment 2 graft and modified S2 graft groups

	Subsegment 2 graft (n = 13)	Modified S2 graft (n = 29)	*P* value
Pretransplant characteristics			
Age, mo (range in d)	6.2 (34-434)	7.6 (29-407)	.451
Sex, M/F	6/7	9/20	.488
Body weight, kg	6.2 (3.5-9.4)	5.9 (2.8-8.8)	.957
PELD score	11.0 (4.0-36.0)	16.5 (2.2-33.0)	.108
Posttransplant outcomes			
Complications ≥ 3b, n (%)	5 (38.5)	5 (17.2)	.238
Biliary complications, n (%)	0 (0)	1 (3.4)	1.000
Leak/stricture	0/0	1/0	
PV complication, n (%)	0 (0)	1 (3.4)	1.000
Reoperation, n (%)	4 (30.8)	2 (6.9)	.063
Hospital stay, d	51 (32-373)	43 (9-242)	.268
Retransplantation, n (%)	1 (7.7)	1 (3.4)	.528
Mortality, n (%)	0 (0)	2 (6.9)	1.000
Donor data			
Graft weight, g	138 (106-213)	192 (122-280)	**.001**
Reduction rate, %	47.5 (36.7-71.3)	22.1 (15.1-60.7)	**<.001**
Operation time, min	333 (280-438)	312 (199-535)	.060
Blood loss, g	240 (50-525)	220 (60-710)	.872
WIT, min	28 (23-46)	25 (21-67)	.053
CIT, min	18 (10-52)	25 (7-136)	.072
Actual GRWR (%)	2.7 (1.5-3.8)	3.3 (1.9-4.7)	**.004**

Bold type indicates statistically significant differences.
PELD, pediatric end-stage liver disease; WIT, warm ischemic time; CIT, cold ischemic time; GRWR, graft-to-recipient weight ratio; PV, portal vein.

vascular complications and graft dysfunction due to graft compression or inadequate blood flow.[2] The thickness of an NAR-LLS graft cannot be reduced adequately for LDLT because the thick portion remains in the umbilical fissure.[15] In contrast, S2 is more likely to be suitable for small infants or neonates with a narrow abdominal cavity. In this study, the incidence of primary abdominal closure was lower and PV flow after abdominal closure was significantly decreased in the NAR-LLS graft group than in the reduced-thickness LLS graft group. We consider that the thinness of the S2 graft itself or using the modified S2 graft reduction technique enabled us to perform primary abdominal closure without graft or vascular compression.

Another expected advantage of using the reduced-thickness LLS graft is to decrease infections, including abdominal wall

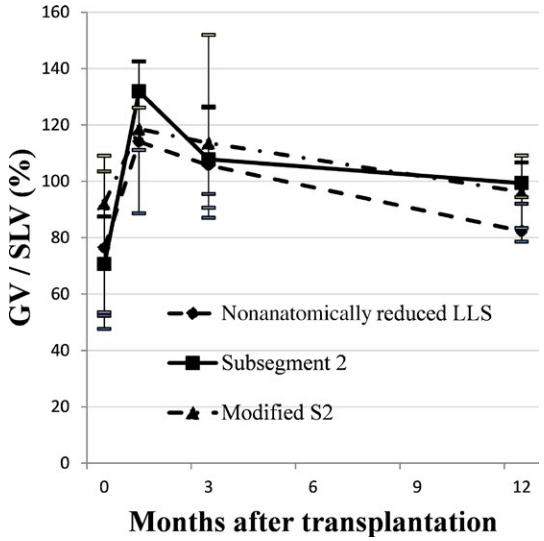

FIGURE 6 Serial changes in GV/SLV (%) in recipients with reduced left lateral segment (LLS) graft after LDLT. GV, graft volume; SLV, standard liver volume; LLS, left lateral segment

infections and respiratory complications leading to delayed extubation.[9,11] In this study, the lower incidence of abdominal skin closure and shorter duration of ventilator weaning in patients with the reduced-thickness LLS graft is consistent with these reported findings. Moreover, we believe that ensuring PV flow is essential to avoid systemic infections. In all 7 of the patients with an NAR-LLS graft who died within 90 days after LDLT in this study, the cause of death was sepsis (subsequent to steroid pulse therapy for ACR in 5 cases and jejunal perforation in 2 cases), and most of these cases had reduced PV flow after abdominal closure. PV flow can be susceptible to intravascular volume depletion caused by increased vascular permeability in the early postoperative phase. Moreover, this fluid shift can cause abdominal compartment syndrome via systemic edema or ascites. Further decrease in PV flow could result in poor synthetic capability, leading to worsened immune function or fragility of tissues such as the bowel wall. This vicious cycle is easily accelerated in the presence of coexisting ACR or bacterial infection and is potentially lethal for pediatric LDLT recipients. Improvement of these factors by adequate graft thickness reduction may have resolved this cycle and contributed to significantly better graft survival in patients who received a reduced-thickness LLS graft.

Although there were no significant differences in the graft regeneration rate within each graft type, the technique of modified reduction of LLS graft thickness that we have been using at our center has some advantages. First, the ventral part of S3 can be removed without extensive dissection at the umbilical fissure. Srinivasan et al reported that liver transplantation with an S2 graft appears to be more technically challenging and riskier than that with an S3 graft,[4] and thus the major concern of living donor hepatectomy involving an S2 graft is injury to the portal pedicle because of the need for dissection at the base of the umbilical fissure.[16] To prevent injury due to misunderstanding of the vessel branches, routine precise preoperative planning using 3-dimensional fusion CT images is needed.[17] Second, we never compromise outflow of the graft as long as P3 is preserved: we do this by keeping the cutting plane horizontally just above P3, because the main left hepatic vein normally runs between the S2 branch of the PV (P2) and P3 (Figure 3C). In contrast, during transection of the subsegment 2 graft, surgeons must take care to avoid injury to the left hepatic vein. Third, in case of biliary stricture after LDLT, preservation of P2 and P3 makes accessibility for radiological intervention easier.[18] The present study shows outcomes in the modified S2 group comparable with those in the subsegment 2 graft group. Especially in the LDLT setting, it is essential to avoid potential risks of graft injury without compromising donor safety. We believe that our modified reduction technique is a safer and more feasible procedure for transplant surgeons than the segment 2 graft and has the potential to provide improved outcomes with lower vascular and biliary complication rates.

In this study, GV in reduced LLS grafts increased rapidly within 1 month after LDLT and converged toward the SLV of recipients with time. Our findings are comparable with those reported in a previous study.[19] It has also been reported that a significant decrease in Glisson density as well as an increase in hepatic acinus area was found in biopsy specimens from noncirrhotic individuals with 2 consecutive hepatectomies.[20] Although it is difficult to show that these findings of remnant liver after hepatectomy are applicable to liver transplantation settings, this study suggests that the number of Glissonian sheaths may not increase after monosegmental graft transplantation, which may compromise future bile excretion capacity. From this point of view, we therefore believe that our modified reduction technique, with preservation of P3, is a rational approach. Further accumulation of cases with reduced-thickness LLS graft and longer observation periods is necessary to clarify these clinical impacts.

This study had certain limitations. First, although the sample size for LDLT using reduced LLS grafts was large, all patients were from a single institution, leading to potential selection biases including race, graft type, indications for surgery, and surgical techniques. Second, this study was retrospective in design, and thus perioperative data should be interpreted with caution. Specifically, we must admit that the lower amount of blood loss in the NAR-LLS graft group compared with the reduced-thickness LLS graft might be partially because of the initial learning curve of surgical techniques. In addition, the period performed LDLT may partially affect outcomes because of retrospective study design. Ideally, a well-defined, nationwide, prospective study is needed to accurately evaluate independent risk factors for outcomes after LDLT.

In conclusion, this study demonstrated that LDLT using the reduced-thickness LLS graft is a safe and feasible option with better short- and long-term outcomes for small children compared with using the conventional NAR-LLS graft. Although longer-term observation is needed to collect further data, we believe that this technical innovation will extend the applicability of LDLT and offer improved outcomes.

TABLE 6 Univariate and multivariate analysis of risk factors for graft loss following LDLT using a reduced LLS graft

			Univariate analysis		Multivariate analysis	
Variables		**n**	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**
FHF	+	17	3.50 (1.30-9.41)	**.013**	3.40 (1.42-11.25)	**.009**
	–	72	Ref.		Ref.	
PELD score	> 23	21	3.80 (1.42-10.15)	**.008**		
	≤ 23	67	Ref.			
ICU-bound	+	28	4.17 (1.51-11.45)	**.006**		
	–	61	Ref.			
Weight-for-age z-score	< −2	38	2.58 (0.94-7.12)	.067		
	≥ −2	51	Ref.			
Recipient age, mo	< 6	33	0.36 (0.10-1.25)	.106		
	≥ 6	56	Ref.			
Recipient body weight, kg	< 5	20	1.21 (0.39-3.74)	.745		
	≥ 5	69	Ref.			
Hepatofugal PV flow	+	15	3.64 (1.32-10.08)	**.013**	4.30 (1.48-12.49)	**.007**
	–	74	Ref.		Ref.	
Nonanatomically reduced graft	+	47	4.09 (1.17-14.34)	**.028**	3.54 (1.01-12.47)	**.049**
	–	42	Ref.		Ref.	
Interposition vein graft for PV reconstruction	+	21	0.69 (0.20-2.43)	.566		
	–	68	Ref.			
PV complication[a]	+	4	16.16 (4.75-54.95)	**<.001**		
	–	85	Ref.			
Reoperation[a]	+	20	4.09 (1.53-10.91)	**.005**		
	–	69	Ref.			
Bacteremia[a]	+	34	2.04 (0.76-5.49)	.158		
	–	55	Ref.			

Bold type indicates statistically significant differences.
CI, confidence interval; HR, hazard ratio; FHF, fulminant hepatic failure; ICU, intensive care unit; PELD, pediatric end-stage liver disease; PV, portal vein.
[a]Postoperative factors (PV complication, reoperation, and bacteremia) were excluded from multivariate analysis.

DISCLOSURE

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

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