Outcome and challenges of left-lobe living-donor liver transplantation in adults

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Background
Left-lobe (LL) liver grafts have become once again the preferred option during the process of graft selection in many transplant centers worldwide. Minimizing donor morbidity, which has been reported to be higher with donation of the larger right-lobe (RL) graft, was the principal motivation. The aim of this work was to evaluate the outcome of living-donor liver transplantation (LDLT) using LL grafts in adults.
Patients and methods
A single-center retrospective study that included all adult patients who underwent LDLT between July 2018 and June 2020. Thirty-eight patients underwent LDLT, 13 patients received LL grafts, while 25 patients received RL grafts. The two groups were compared in terms of patient and graft survival, incidence of various posttransplant complications, and incidence of small-for-size syndrome. Donor morbidity was evaluated as well.
Results
There was no difference between LL and RL graft recipients regarding patient and graft survival. The incidence of posttransplant complications also did not differ significantly between both groups. Only one LL recipient with a graft-to-recipient weight ratio of 0.56 experienced small-for-size syndrome, however, the outcome in this patient did not differ from that of other patients. RL donors had a statistically significant higher postdonation peak total serum bilirubin ($P<0.001$).
Conclusion
LL grafts are a feasible option for adult LDLT. Transplant surgeons should always consider selecting LL as their primary graft according to a clear graft-selection algorithm. RL grafts can carry more risk to the healthy donors and should be selected only when LL grafts are deemed unsuitable.

Keywords:
adults, left lobe, living donor

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Introduction

Living-donor liver transplantation (LDLT) has become a legitimate treatment modality for patients with end-stage liver disease [1]. The first successful adult LDLT (ALDLT), using a left-lobe (LL) graft, was reported in 1993 [2]. After that, the early series of ALDLT were exclusively centered on LL grafts to avoid posthepatectomy liver failure in the living donors [3]. However, the rising concern of small-for-size syndrome (SFSS) with its associated inferior outcomes came to the surface [4].

Since the introduction of ALDLT, several reports from different centers worldwide had documented the use of both graft types with a current predominant use of the larger right-lobe (RL) grafts in the majority of those centers. The Vancouver forum reported a global donor mortality rate of 0.5% with RL grafts versus 0.1% with LL grafts [5]. Moreover, a preceding report from the Japanese Liver Transplantation Society survey showed a higher donor's morbidity with RL than with LL grafts (19 vs. 12%, respectively) [6].

The emergence of portal venous-pressure (PVP) modulation strategies that were introduced to protect against the detrimental effects of portal hypertension and consequently prevent SFSS, particularly early posttransplant, allowed more effective use of the smaller LL grafts in ALDLT [7].

Moreover, the accumulation of surgical experiences and the continuous refinements of the surgical techniques employed during LT have also allowed the gradual shifting from RL back to LL grafts

[8,9]. The recent shift from RL to LL grafts aims at shifting the risk from the healthy donors back to the recipients [10].

Safety limits for the effective use of the smaller LL grafts should be determined to know how far we can go during the process of graft selection in order to create a favorable balance between achieving acceptable recipients' outcomes – through maximizing the function of the small grafts – while maximizing donor safety [11]. The aim of this work was to evaluate the efficacy and outcomes of the ALDLT using LL grafts in terms of patient and graft survival and posttransplant complications and management. Donors' morbidity will be evaluated as well.

Patients and methods

Study population and design

This was a single-center retrospective study that included all adult patients (≥18 years), who underwent LDLT at Kyoto University Hospital, Japan, between July 2018 and June 2020. The authors give their consent for publishing this material. During this period, 38 patients underwent LDLT, 13 patients received LL grafts, and 25 patients received RL grafts. Patients who received grafts from deceased donors were excluded. Recipients of LL and RL grafts were compared in terms of patient and graft survival, early graft loss, incidence of various posttransplant complications, and incidence of SFSS.

Similarly, donors of LL and RL grafts were compared in terms of blood loss, operative duration, hospital stay, and incidence of postdonation complications including posthepatectomy hepatic insufficiency. All the procedures were conducted in accordance with the Declaration of Helsinki of 1996.

Data collection

Patients' data were retrieved from the medical records and were analyzed. Retrieved data included demographic data of recipients and donors; preoperative data of the recipients included ABO-compatibility status, indications for LT, Child–Turcotte–Pugh scores, classes, and Model for End Stage Liver Disease scores. Donors' data included expected graft and residual liver volumes and hepatic vascular and biliary anatomy. Various intraoperative data, including operative time, blood-loss volume, graft type and characteristics, and PVP-modulation strategies, were collected. Postoperative outcomes both for donors and recipients were evaluated.

Graft-selection criteria

The upper-age limit for donor selection was 65 years. All donors were examined for the liver-to-spleen attenuation ratio through noncontrast computed tomographic scan by CTW3000 (Hitachi Medical Systems, Tokyo, Japan) to assess the degree of hepatic steatosis as an alternative to liver biopsy by comparing liver attenuation against splenic attenuation. Only donors with an liver-to-spleen ratio more than 1.1, which is equivalent to no-to-mild steatosis (<30% macrovesicular steatosis), were accepted for donation.

Graft selection was based mainly on the estimated preoperative graft-to-recipient weight ratio (GRWR) and the donor future liver-remnant volume. LL graft with the middle hepatic vein was always the first choice when GRWR was more than or equal to 0.6%, which is the minimum accepted GRWR limit. The graft-selection flow-chart is shown in Fig. 1.

Portal venous-pressure measurement and modulation

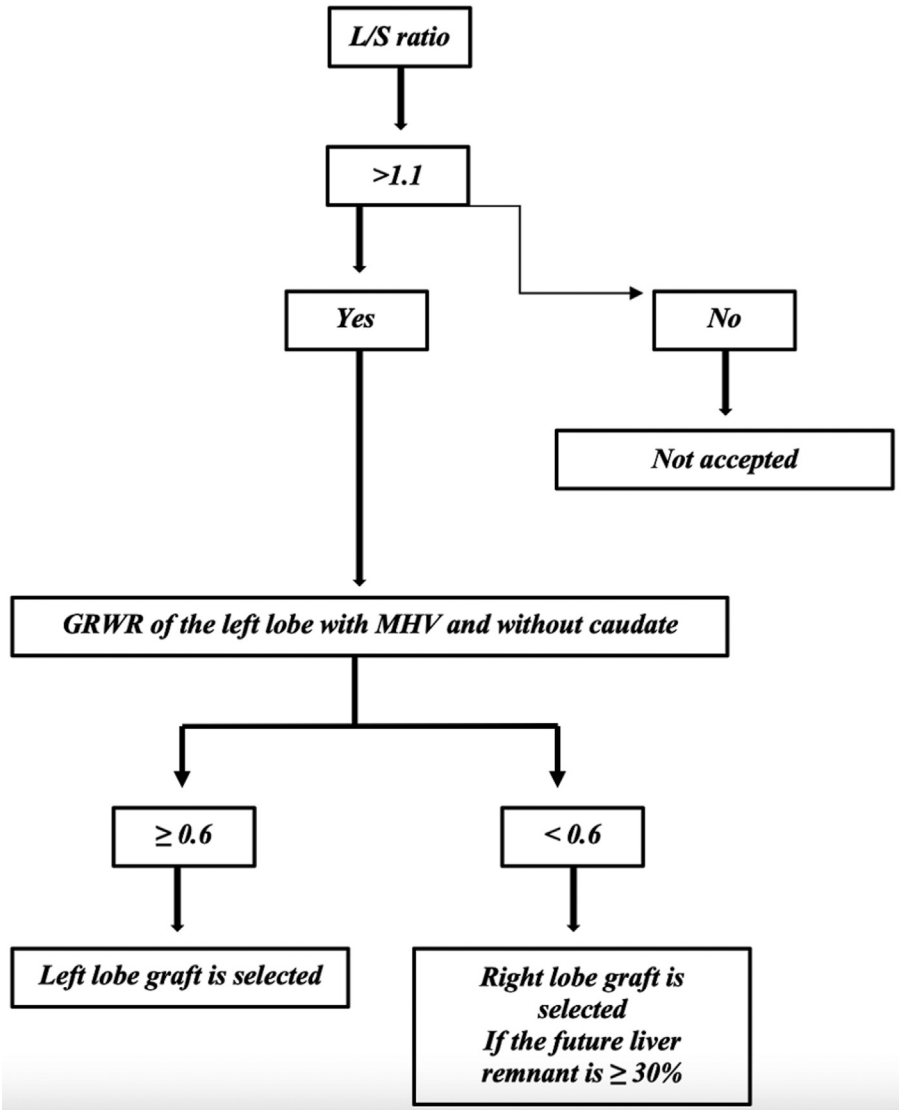
PVP was monitored through insertion of an 18-G catheter in a small jejunal vein branch. The tip of the catheter was positioned in the recipient's SMV or a jejunal vein. The PV catheter was removed before abdominal closure to prevent infection. The current PVP-modulation strategy reserves splenectomy for grafts coming from older (≥45 years old) or ABO-incompatible donors if the PVP was more than 15 mmHg after graft reperfusion [12]. One more indication for splenectomy is a graft-to-spleen volume ratio (GSVR) less than or equal to 0.7. This indication was applied after low GSVR was reported to be an independent risk factor for graft loss after LDLT when the spleen was preserved, which was attributed to persistent hypersplenism and impaired graft function [13].

Large spontaneous portosystemic shunts were ligated in place to prevent portal steal phenomenon if the PVP was less than or equal to 15 mmHg on temporary shunt clamping.

Immunosuppression

Tacrolimus or cyclosporine and mycophenolate mofetil were started within 24 h after ALDLT in all patients. Steroids were reserved for patients with autoimmune diseases and as pulse-steroid therapy in patients with suspected rejection. All ABO-incompatible recipients were routinely administered a single dose of Rituximab (500 mg) around 2 weeks before transplantation. They were also given tacrolimus and mycophenolate mofetil 1 week before transplantation.

Figure 1



Donor evaluation and graft-selection process. GRWR, graft-to-recipient weight ratio; L/S ratio, liver-to-spleen attenuation ratio; MHV, middle hepatic vein.

Definitions

The Kyushu group criteria for defining SFSS are the current criteria used for diagnosing SFSS. These include the presence of both total bilirubin more than 10 mg/dl at postoperative day (POD) 14 without any other definitive cause for cholestasis and a daily ascite production of more than 1 l at POD14 or more than 500 ml at POD28 [14]. Early graft loss was defined as graft loss during the first 90 days after transplantation.

Statistical analysis

Continuous data were expressed as the mean±SD and were nonparametrically compared using the Mann–Whitney *U* test. Categorical data were expressed in numbers and percentages and were compared using the χ^2 or Fisher's exact test, as appropriate. Patient and graft survival were evaluated using Kaplan–Meier survival curves, and the difference between curves was assessed using the log-rank test. *P* values of less than 0.05 were considered to indicate statistical significance. All statistical analyses were performed using the JMP 15 software program (SAS Institute, Cary, North Carolina, USA).

Results

Patient characteristics

Thirteen patients received LL grafts, while 25 patients received RL grafts. Table 1 demonstrates recipients' and donors' characteristics. The mean age of the donors of RL grafts was higher than that of the donors of LL grafts (43.0±12.6 vs. 34.8±10.2, respectively) with a *P* value that approached but did not reach statistical significance (0.064).

Table 1 Recipients and donors' characteristics

Recipients' parameters	Recipients of RL grafts (*N*=25)	Recipients of LL grafts (*N*=13)	*P* value
Age	52.3±12.2	52.1±17.4	0.580
Sex (M/F)	16/9	2/11	**0.006**
BMI (kg/m^2)	24.0±3.5	21.7±3.2	0.077
ABO compatibility (identical/compatible/incompatible)	16/6/3	7/2/4	0.353
Child–Pugh class (A/B/C)	1/7/17	0/3/10	0.707
MELD score	12.8±6.1	17.2±8.4	0.062
Preoperative PVT (no/I/II/III/IV)	23/0/1/1/0	9/2/2/0/0	0.098
Expected graft weight (g)	633.4±146.0	407.6±66.7	<**0.001**
Expected GRWR	0.99±0.23	0.73±0.1	**0.001**
Expected GSVR*	1.1±0.6	1.0±0.4	0.840
Operative time (min)	824.6±168.1	741.6±186.3	0.140
Blood loss (ml)	6566.3±5838.8	5190.5±4305.5	0.442
Simultaneous splenectomy (yes/no/Hx)	7/17/1	2/10/1	0.640
Cold ischemia time	122.4±67.2	80.6±65.7	**0.016**
Warm ischemia time	49.0±28.1	45±28.1	0.180
Actual graft weight	677.9±93.1	383.8±66.9	<**0.001**
Actual GRWR	1.1±0.2	0.70±0.1	<**0.001**
Actual GSVR*	1.2±0.7	1.0±0.4	0.671
Final PVP•	11.7±3.0	14.3±2.9	**0.011**
Type of biliary anastomosis (D–D/HJ)	21/4	8/5	0.226
Donors' characteristics	Donors of LL	Donors of RL	*P* value
Age	43.0±12.6	34.8±10.2	0.064
Sex (M/F)	6/19	6/7	0.270
BMI (kg/m^2)	22.7±2.4	21.5±3.0	0.415
Operative time (min)	389.6±57.3	350.7±60.0	**0.041**
Blood loss (ml)	325.3±223.1	282.4±313.6	0.181
Number of graft's HAs (1/2/3)	25/0/0	6/6/1	<**0.001**
Number of graft's BDs (1/2)	12/13	11/2	**0.039**

BDs, bile ducts; D–D, duct-to-duct anastomosis; F, female; GRWR, graft-to-recipient weight ratio; GSVR, graft-to-spleen volume ratio; HAs, hepatic arteries; Hx, past history of splenectomy; LL, left lobe; M, male; MELD, Model for End Stage Liver Disease; PVP, portal venous-pressure; PVT, portal vein thrombosis; RL, right lobe. *Four patients who did not have a preoperative spleen volumetry were excluded from analysis. •PVP was not assessed in two patients who underwent LT post-Kasai procedure for biliary atresia due to technical difficulty. Bold values refer to *P*-values that were found to be of statistical significance.

There were various indications for LT in our series. These are demonstrated in Fig. 2.

The mean operative time for recipients of RL grafts was higher than that of recipients of LL grafts (824.6 ±168.1 vs. 741.6±186.3 min, respectively), however, it did not reach statistical significance (*P*=0.140).

The cold ischemia time in the recipients of LL grafts was significantly shorter with a *P* value of 0.016. No statistically significant difference was detected between the two groups regarding the amount of intraoperative blood loss. Nine patients underwent simultaneous splenectomy as a part of PVP modulation.

Six patients had preoperative portal vein thrombosis (PVT). The two patients with grade I underwent eversion thrombectomy. Similarly, two out of three patients with grade II PVT underwent eversion thrombectomy, while the third one needed an interposition vein graft between the graft and the recipient PV stumps. The patient with grade III PVT needed an interposition vein graft between the graft PV and a large left gastric vein collateral for restoration of PV flow. Vein grafts were obtained from autologous external iliac veins.

The mean operative time of the donors of LL grafts was significantly shorter with a *P* value of 0.041.

Arterial anastomosis was single in all RL recipients. In LL recipients, although six grafts had two hepatic arteries, only one artery was reconstructed, and the other artery was ligated after confirmation of adequate back flow. A patient who received LL graft with three hepatic arteries required reconstruction of the largest two arteries and the third one was ligated.

Portal venous-pressure modulation

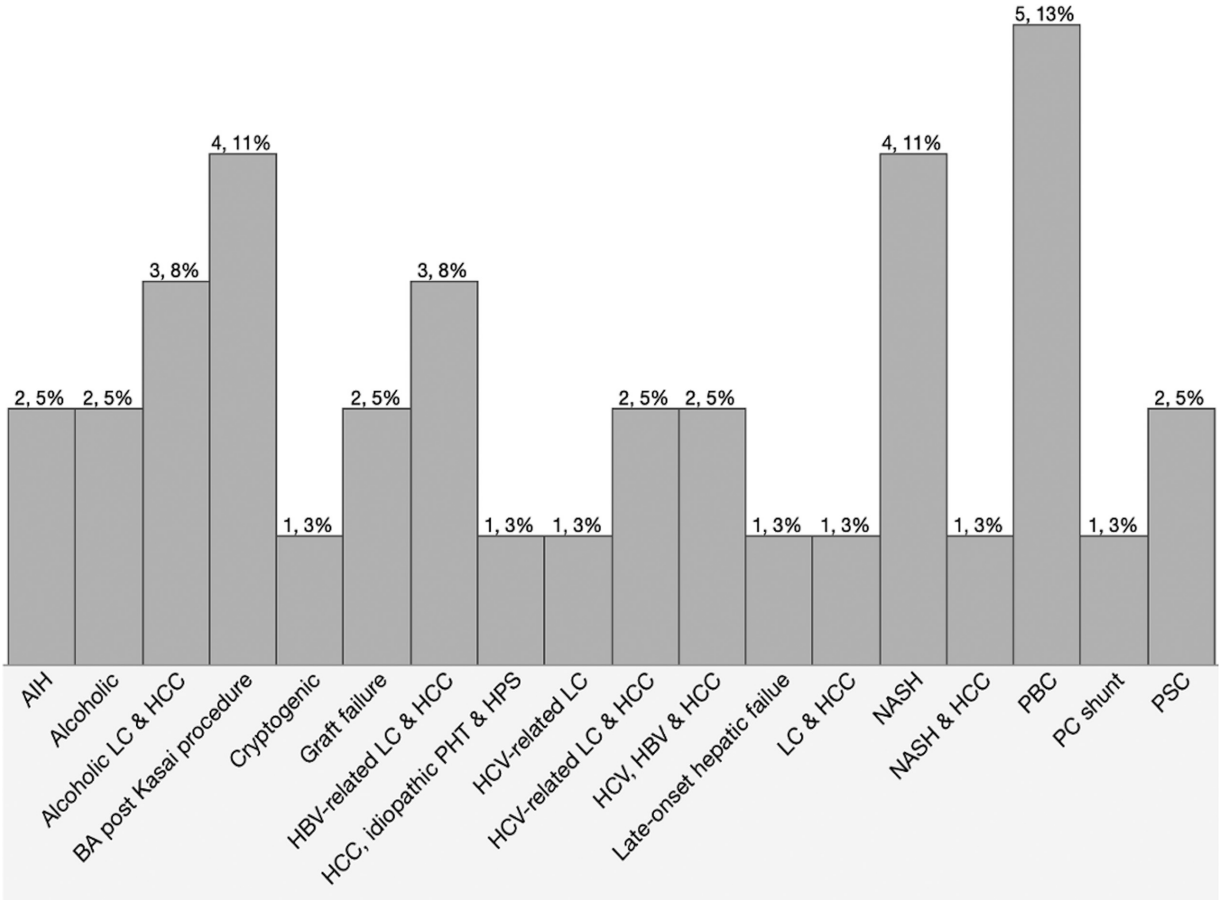
Twenty-four patients underwent PVP modulation, nine patients in the LL cohort versus 15 patients in the RL cohort (*P*=0.728). The final PVP was

significantly higher in LL recipients (14.3±2.9 vs. 11.7 ±3.0, *P*=0.011). However, the mean final PVP for both groups was less than the target final PVP (15 mmHg).

Posttransplant outcomes

To assess early graft function, we compared the two groups in terms of posttransplant international normalized ratio (INR) values and daily ascite production. There was no statistically significant difference regarding the amount of ascite production on POD7, POD14, and POD28. The mean INR value was significantly higher with LL recipients on POD7 (1.35±0.16 vs. 1.22±0.15) with a *P* value of 0.017. However, the mean INR values on POD14 and POD28 did not significantly differ across the two groups. Table 2 demonstrates some of the early graft-function parameters.

Figure 2



Distribution of liver-transplantation indications. AIH, autoimmune hepatitis; BA, biliary atresia; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; LC, liver cirrhosis; NASH, nonalcoholic steatohepatitis; PBC, primary biliary cirrhosis; PC, portocaval; PSC, primary sclerosing cholangiopathy.

Table 2 Parameters of early graft function

Recipients' variables	Recipients of RL grafts (*N*=25)	Recipients of LL grafts (*N*=13)	*P* value
POD7			
INR	1.22±0.15	1.35±0.16	**0.017**
Ascites' amount (ml)•	3369.7±2977.8	4272.6±3392.9	0.246
POD14			
INR	1.12±0.19	1.27±0.23	0.324
Ascites' amount (ml)•	1980.5±2101.6	2502.6±1527.9	0.187
POD28			
INR	1.14±0.18	1.13±0.20	0.579
Ascites amount (ml)	601.7±1638.1	698.6±2058.3	0.941

INR, international normalized ratio; LL, left lobe; POD, postoperative day; RL, right lobe. •One patient was excluded from the analysis due to lack of information regarding the amount of ascites on this day. Bold values refer to *P*-values that were found to be of statistical significance.

The incidence of biliary and vascular complications did not differ significantly based on the graft type (P=0.457 and 1.000, respectively). Tables 3 and 4 demonstrate the incidence and management of biliary and vascular complications, respectively.

Seven patients received grafts from ABO-incompatible donors. Antibody-mediated rejection was suspected in two patients only and measures to manage antibody-mediated rejection were implied with favorable outcome. Acute cellular rejection was suspected in 13 patients and steroid full-pulse therapy or lower doses of steroids were given, depending on the suspicion index. The incidence of immunological complications as well as bacterial infections did not differ significantly between recipients of RL graft and LL graft (P=0.728 and 0.495, respectively).

Seven patients needed emergent reoperation during the first month posttransplant. Two patients were LL recipients, while the other five patients were RL recipients. The causes for reoperation included control of bleeding and biliary leakage, among others.

The distribution of recipients based on their GRWR is demonstrated in Fig. 3. Two patients in this series had a GRWR less than 0.6 (0.56 and 0.54), however, only the one with GRWR of 0.56 experienced posttransplant SFSS based on the definition employed in Kyoto University. This patient had interactable ascites (daily production >1 l) and prolonged cholestasis (total bilirubin >10 mg/dl) with no other definite cause on POD14. However, only with supportive treatment, the amount of ascites was controlled, and cholestasis improved, and by POD28, the total bilirubin level was 2.7 mg/dl and there was no more ascitic drainage.

Table 3 Biliary complications, incidence, and management

Case no.	Graft type	Type of complication	Management
1	Left lobe	Anastomotic stricture	ERC and stenting
2	Right lobe	Anastomotic stricture	ERC and stenting
3	Left lobe	Anastomotic stricture and recurrent cholangitis	Repeated ERCs and stenting
4	Right lobe	Anastomotic stricture	ERC and stenting
5	Left lobe	Cholangitis	AMR measures and antibiotics
6	Right lobe	Biliary leak	Laparotomy, lavage, and anterior wall repair over external stents
7	Right lobe	Anastomotic stricture	ERC>failed>PTBD>ERC and stenting
8	Left lobe	Repeated cholangitis, no obvious anastomotic or intrahepatic stricture	Antibiotics
9	Right lobe	Right posterior segmental duct stricture	ERC and ENBD >>stenting
10	Right lobe	Cholangitis	Antibiotics
11	Left lobe	Cholangitis	Antibiotics

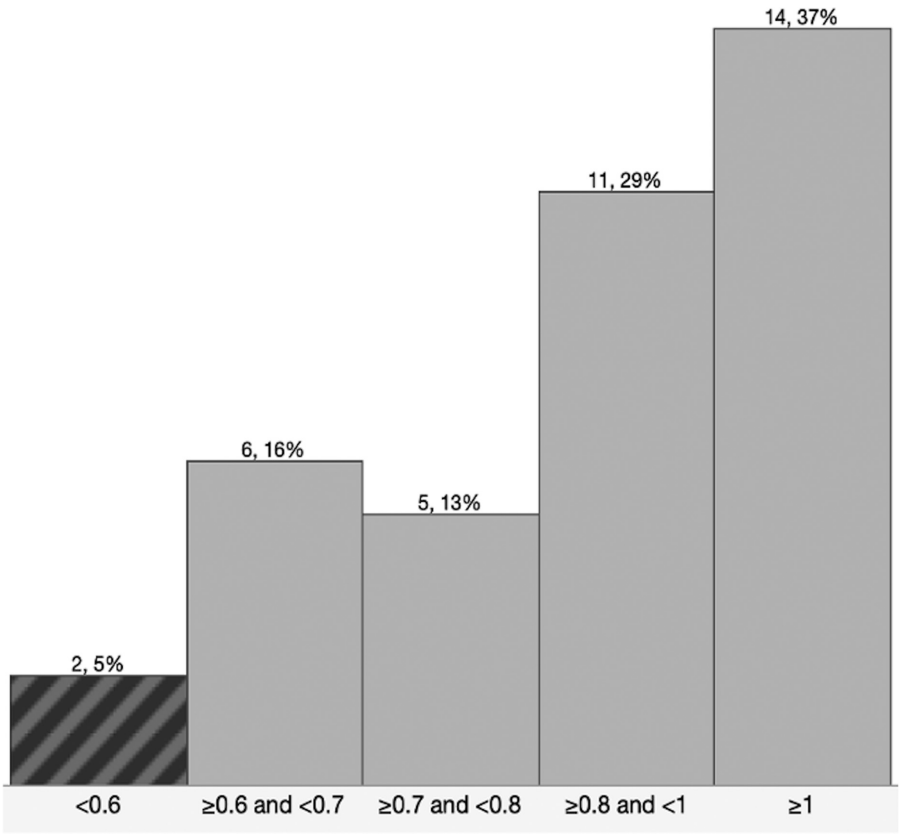
AMR, antibody-mediated rejection; ENBD, endoscopic nasobiliary drainage; ERC, endoscopic retrograde cholangiography; PTBD, percutaneous transhepatic biliary drainage.

Table 4 Vascular complications posttransplant, incidence, and management

Case no.	Graft type	Type of complication	Management
1	Left lobe	Venous outflow obstruction that resulted in diminished portal flow	Interventional dilatation
I	Left lobe	MHV stenosis	MHV stenting
3	Right lobe	HV stenosis	HV stenting
4	Right lobe	Partial thrombosis of the HV and PV	Anticoagulants
5	Right lobe	Poor HV flow on POD0	HV reconstruction on POD0

HV, hepatic vein; MHV, middle hepatic vein; POD, postoperative day; PV, portal vein

Figure 3



Distribution of the recipients based on their graft-to-recipient weight ratio (GRWR).

Patients and graft survival

The mean follow-up time was 356.8±169.1 days. Patient and graft-survival rates were 100%. Figure 4 demonstrates Kaplan–Meier survival curves for patient and graft survival.

Postdonation outcomes

Postdonation liver function tests, including peak serum total bilirubin and peak serum transaminases, were better in donors of LL grafts, however, it only reached statistical significance with a *P* value less than 0.001 with peak total serum bilirubin (Table 5).

Eight donors (four donors of LL and four donors of RL grafts) experienced postdonation complications. These were classified as grade I in six donors. Two donors had grade III complications. One donor (grade IIIa) had a keloid scar that was excised under local anesthesia 11 months postdonation. The other donor (grade IIIb) was explored on POD15 for a perforated duodenal stress ulcer. Upon exploration, there was omental creeping that sealed the perforation. Peritoneal lavage and drainage were performed. Grading was based on Clavien–Dindo classification of postoperative surgical complications [15].

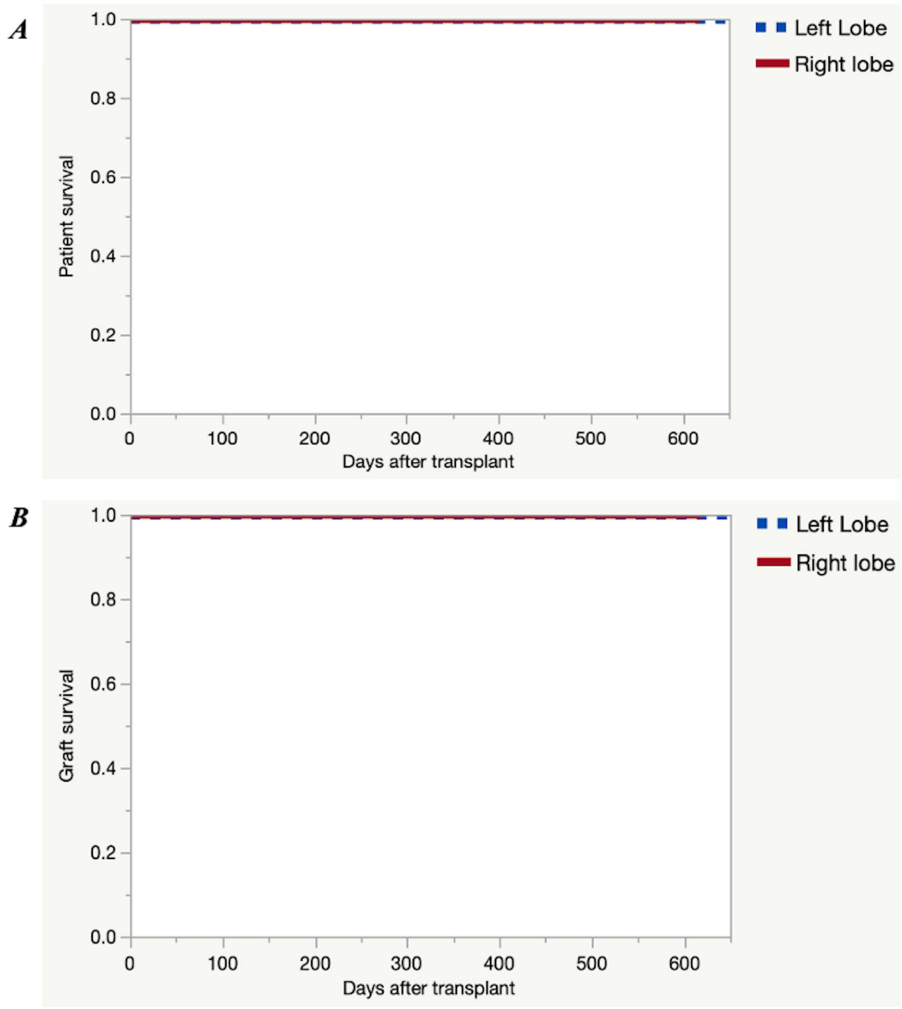
Discussion

The initial reports of ALDLT were exclusively using LL grafts in order to assure donors' safety. However, with the emergence of the SFSS concern, RL grafts gradually replaced LL grafts in most transplant centers [16].

Recently, a renewed interest in obtaining smaller grafts has emerged to minimize donor risk [10]. In this study, we evaluated the outcomes of LDLT using LL grafts in comparison with the larger RL grafts. We also evaluated donors' outcomes in terms of safety and postdonation morbidity.

Graft-selection process has undergone continuous modification over the years. At Kyoto University, LL grafts constituted the majority of grafts donated during the early ALDLT era. Then based on reported lower survival rates in patients with GRWR of less than 1%, selection of RL grafts took the upper hand to minimize the risk of SFSS [17]. A subsequent report from the same group in 2014 [18] reported a superior recovery of postoperative liver functions and lower morbidity in LL donors. Moreover, LL and RL recipients had comparable survival rates even in

Figure 4



(a) Patient survival Kaplan–Meier curve. (b) Graft survival Kaplan–Meier curve.

Table 5 Postdonation liver function tests

Donors' variables	Donors of RL grafts (*N*=25)	Donors of LL grafts (*N*=13)	*P* value
Peak total bilirubin (mg/dl)	3.8±1.4	2.0±0.9	<**0.001**
Peak serum AST (IU/l)	349.8±252.9	252.8±62.8	0.094
Peak serum ALT (IU/l)	362.2±203.0	340.9±100.6	0.724

LL, left lobe; RL, right lobe. Bold values refer to *P*-values that were found to be of statistical significance.

recipients deemed to be a high-risk group with Model for End Stage Liver Disease scores more than 20.

These findings were consistent with a preceding report from a multicentric study from 46 LDLT centers across Japan [6], which reported a higher complication rate in RL donors.

In this series, LL graft with the middle hepatic vein and without the caudate lobe was considered if the GRWR was more than or equal to 0.6. Ikegami *et al.* [11] considered the LL graft with the caudate lobe as their primary graft if the graft volume/standard liver volume was more than or equal to 35%.

In this study, we could not detect any statistically significant difference in the morbidity rate between RL and LL donors with a *P* value of 0.407, which could be attributed to the small number of the study population. Soejima *et al.* [1] demonstrated that postoperative liver function tests, including peak total bilirubin and peak aminotransferases, were significantly better in LL donors. In this series, postoperative liver function tests were significantly different between LL and RL donors only with peak serum total bilirubin level ($P<0.001$).

PVP-modulation strategies have undergone continuous modification over the past years in order to mitigate the issue of SFSS. The current PVP-modulation strategy adopted by Kyoto group includes performing splenectomy only in grafts

coming from high-risk donors (≥45 years old or ABO-incompatible) if the PVP was more than 15 mmHg after graft reperfusion. In this series, large spontaneous portosystemic shunts was ligated in place to prevent portal steal phenomenon if the PVP was less than or equal to 15 mmHg on temporary shunt clamping. Splenectomy is currently also performed with GSVR less than 0.7, regardless of any other factors.

Braun *et al.* [19] compared graft function between RL and LL recipients through evaluating both INR and total bilirubin. They reported significantly higher INR and total bilirubin in LL recipients (1.5 vs. 1.2, $P<0.001$ and 4.6 vs. 2.7, $P=0.001$, respectively) at POD7, which remained significantly higher at POD14. In our series, we also evaluated the graft function on POD7, POD14, and POD28 through evaluating INR levels and the amount of ascite production. INR levels were higher in LL recipients at POD7 ($P=0.017$), however, the levels were comparable at POD14 and 28. The amount of ascite production did not differ between RL and LL recipients at POD7, POD14, and POD28. We did not use serum total bilirubin level for evaluation of graft function because it is more liable to be affected in response to various types of complications.

According to Kyushu definition of SFSS, only one patient in this study experienced posttransplant SFSS diagnosed on POD14. This patient received a LL graft and his GRWR was 0.56. Although this patient's actual GRWR proved to be less than the minimum limit for donor selection, this was not the only recipient who received a graft with a GRWR below this limit. There was also another patient with a GRWR of 0.54 who did not develop SFSS.

This finding supports the notion that SFSS is not solely determined by the graft size. Hill *et al.* [20] reported a comparable incidence of SFSS between the two cohorts, which they defined based on the GRWR (<0.8 vs. ≥0.8%). In the GRWR less than 0.8% group, the incidence was 13.9 versus 9.4% in the larger graft-size group with a P value of 0.69. In a recent report from Kyoto University, Macshut *et al.* [21] performed multivariate analyses to explore the risk factors for poor outcomes after LT using small-for-size grafts. Older donor age (≥45 years) was an independent risk factor for SFSS, early graft loss, and 1-year mortality after ALDLT. Interestingly, GRWR was not proved to be an independent risk factor for any of these poor posttransplant outcomes. This finding may in part explain the single incidence of SFSS in our series with a GRWR of 0.56, while it did not occur in another patient with a GRWR of 0.54. The recipient who developed SFSS received a graft from a donor who was 55 years old, while the other patient received a graft from a young donor who was 36 years old. Moreover, zero liver biopsy from the graft transplanted in the recipient with SFSS revealed the highest steatosis % in our cohort (10%). Steatotic grafts have been linked to poor graft function due to decreased sinusoidal lumen by the fat droplets, inefficient anaerobic metabolism of the hepatocytes with steatosis, and increased free radicals by the lipid peroxidation after reperfusion [22].

The incidence of various posttransplant complications, including biliary, vascular, and immunological complications, did not differ significantly between LL and RL recipients. These results are consistent with the results reported by Soejima *et al.* [1] who reported comparable incidence of posttransplant vascular, immunological, and biliary complications between RL and LL recipients.

In this series, both patient and graft survival were excellent with no single graft or patient loss among both recipients of LL and RL grafts during the follow-up period. Although the follow-up period was not long enough to give accurate conclusions regarding patient and graft long-term survival, the comparable outcomes of LL and RL recipients are promising.

Conclusion

In conclusion, LL grafts are a feasible and safe option for ALDLT. Transplant surgeons should always consider selecting LL as their primary graft according to a clear graft-selection algorithm. RL grafts can carry more risk to the healthy donors and should be selected only when LL grafts are deemed unsuitable. It has been proven that graft size is not the only determinant for the incidence of SFSS. Factors like donor age, graft quality, and severity of liver disease among others have been also correlated with the outcomes after LT.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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