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Superior Outcomes and Reduced Wait Times in Pediatric Recipients of Living Donor Liver Transplantation

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Background. Living donor liver transplantation (LDLT) is increasingly used to bridge the gap between the current supply and demand imbalance for deceased donor organs to provide lifesaving liver transplantation. **Methods.** Outcomes of 135 children who underwent LDLT were compared with 158 recipients of deceased donor liver transplantation (DDLT) at the largest pediatric liver transplant program in Canada. **Results.** Recipients of LDLT were significantly younger than deceased donor recipients ($P \leq 0.001$), less likely to require dialysis pretransplant ($P < 0.002$) and had shorter wait time duration when the primary indication was cholestatic liver disease ($P = 0.003$). The LDLT donors were either related genetically or emotionally (79%), or unrelated (21%) to the pediatric recipients. One-, 5-, and 10-year patient survival rates were significantly higher in LDLT (97%, 94%, and 94%) compared with DDLT (92%, 87%, and 80%; log-rank $P = 0.02$) recipients, as were graft survival rates (96%, 93%, and 93% for LDLT versus 89%, 81.4%, and 70%, respectively, for DDLT; log-rank $P = 0.001$). Medical and surgical complications were not statistically different between groups. Graft failure was higher in recipients of DDLT (odds ratio, 2.60; 95% confidence interval, 1.02, 6.58) than in the LDLT group after adjustment for clinical characteristics and propensity score. **Conclusions.** Living donor liver transplantation provides superior outcomes for children and is an excellent and effective strategy to increase the chances of receiving a liver transplant.

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Liver transplantation (LT) is an established lifesaving treatment for children with a spectrum of etiologies including biliary atresia (BA), pediatric acute liver failure

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(PALF), metabolic liver conditions, tumors, autoimmune liver diseases, and other cholestatic diseases.[1-3] As overall outcomes have improved, expanding indications for pediatric LT include metabolic liver conditions,[4] underscoring the need for programs to address the shortage of donor organs as an impedance to access for patients requiring LT. Given an aging population and the rising incidence of obesity, it is sobering to acknowledge that the rate of high quality deceased donors (DD) organs is not anticipated to be on the increase.[5] Waiting times for pediatric LT are growing worldwide.[6] In Asia, live donation was developed to alleviate the lack of access to deceased organs.[7] Although deceased donor liver transplantation (DDLT) remains the standard of care in North America, the supply imbalance remains problematic. Living donor liver transplantation (LDLT) is an important option for centers to meet the needs of patients requiring LT.[8]

The practical and theoretical advantages of LDLT include preemptive and earlier timing of hepatic replacement surgery before serious clinical decompensation, facilitation of high-quality grafts via thorough live donor (LD) evaluations, and minimization of preservation injury to the graft with decreased cold ischemia times (CITs).[9-13] Potential immunological benefits for recipients of organs from genetically related donors have also been reported.[14] Challenges faced by LDLT programs include reducing donor morbidity without compromise to recipient outcomes, as well as ensuring the live donation process remains voluntary, altruistic, and noncoercive.[15]

Published pediatric experience with LDLT in North America is limited to small patient cohorts,[16-19] and do not address the many clinical variables that may impact the outcomes of LDLT compared to DDLT. The aims of this study were to determine the short- and long-term outcomes of pediatric LDLT performed in the largest pediatric LT program in Canada, to compare these outcomes with a contemporaneous cohort of pediatric recipients of DDLT, and to identify variables that predict patient and graft outcomes.

PATIENTS AND METHODS

Study Design

This was a retrospective cohort study of all consecutive patients undergoing isolated LT between 2000 and 2015 at The Hospital for Sick Children (SickKids) in Toronto, Canada. This study was approved by the SickKids Research Ethics Board. The first pediatric recipient of LDLT occurred in October 1996; however, due to program restructuring, the LDLT program was not operational until 2000 and a formal collaboration was developed with the Living Donor Office and the adult LT program at the Toronto General Hospital, University Health Network (UHN).[8]

All pediatric LT recipient care and follow-up take place exclusively at SickKids, as previously described.[20] LT surgeons with appointments at both SickKids and UHN perform the donor and recipient surgeries. Briefly, at the time of candidate listing, all parents are provided with LD information, including contact information for the UHN Living Donor Office. Prospective donors are fully informed of their rights to terminate donor evaluation at any stage in the process. Evaluations, investigations, consultations, operations, perioperative care, and subsequent follow-up of all live liver donors are centralized at and provided by, the UHN adult LT program. All recipients were required to meet our criteria for DDLT, be formally listed and maintained on the DD waitlist until the day of LDLT. Since 2006, the UHN Living Donor office has also evaluated anonymous donors for both directed and nondirected donation,[21] preferentially recommending pediatric patients when available due to the lower reported risk with left or left lateral lobe compared with right lobe resection surgery, and prioritization to those with the highest medical need (pediatric end-stage liver disease [PELD] or Model for End-Stage Liver Disease [MELD] score).[8,22] An anonymous donor was defined as one who had no biological connection and whose identity was unknown to the recipient when starting the assessment and until the LT surgical date.[22] When evaluating anonymous donor candidates, particular attention is paid to motivation, decision-making, prior altruism, consideration of other forms of community service, and social support. Donors are reminded that Canadian law prohibits profiting in any material way from the donation. All recipients and donors were Canadian citizens.

Study Population

Inclusion criteria included all recipients younger than 18 years at the time of first isolated LT between May 1, 2000, and December 31, 2015. Recipients of multiorgan transplants and liver retransplant recipients were excluded.

Data Collection

Information from institutional electronic patient record included demographics, clinical data (primary diagnosis, time on the waitlist, comorbid events, prior organ availability, PELD or MELD scores at the time of transplant), and targeted laboratory values. For subjects receiving LDLT, the relationship between the donor (mother, father, other genetic relatives, emotionally related [friends or neighbors], or anonymous) and recipients was recorded.

Perioperative data collected included allograft type, type of biliary anastomosis, CIT, warm ischemia time (WIT), and key immediate post-LT complications (for definitions **Table S1, SDC**, http://links.lww.com/TXD/A178),[23] the number of days intubated, duration of stay in the pediatric intensive care unit (PICU), time to first discharge from the hospital, acute cellular rejection (ACR), chronic rejection (CR), site and histopathology of posttransplant lymphoproliferative disease (PTLD), immunosuppression details and concomitant medications were also collected. Kidney function at 1 year after LT was assessed by calculated glomerular filtration rate using the modified Schwartz formula (based on serum creatinine) and recorded utilization of antihypertensive agents.[24,25]

Clinical Protocols

The techniques of LD hepatectomy performed at our institution have been described previously.[26-28] All study patients followed institutional protocols for immunosuppression, which were unchanged during the study duration.[29,30] Briefly, standard induction immunosuppression was comprised of dual therapy including tacrolimus and corticosteroids, with steroid taper over 3 months to discontinuation. Patients with clinically noted oliguria, hepatorenal syndrome, or dialysis requirement before LT received a kidney-sparing protocol comprised of corticosteroids, either antithymocyte globulin or 2 doses of basiliximab (Simulect; Novartis, Basel, Switzerland), until

normalization of creatinine or improving urine output at which time tacrolimus would be started. Mycophenolate mofetil as adjunctive therapy was also added once these patients with pre-LT renal dysfunction were eating well. For recipients with a primary diagnosis of hepatoblastoma, tacrolimus was replaced by sirolimus starting at postoperative day 30.[29,30] Diagnosis of ACR required a liver biopsy for histopathological confirmation, with treatment initiated with a biopsy interpretation of Rejection Activity Index of 4 or greater of 9.[31] Chronic rejection was diagnosed as per the updated Banff criteria.[32]

Statistical Analyses

Descriptive statistics were calculated for demographic and clinical variables. Continuous data were reported as medians and interquartile ranges (IQR). Categorical variables were reported as count and proportions. Comparisons of data between LDLT and DDLT groups were performed using χ^2, *t* tests, and Fisher exact or rank-sum tests as appropriate. For calculation of ACR-free survival, data were censored at the first episode of biopsy-proven rejection. Patient and graft survival rates were evaluated using the Kaplan-Meier methods with censoring at the time of death or retransplantation/death and compared using the log-rank test. Multivariable Cox proportional hazard regression models were built with important clinical variables that reached a significance of $P < 0.2$ by univariable analysis.

We also constructed models adjusting for the propensity score using covariate analysis. The propensity score for each subject was calculated based on variables that differed between LDLT and DDLT recipients at baseline and included age, diagnosis, weight, and height at LT, dialysis requirement, wait time and serum gamma-glutamyltransferase level. Separate multiple regression models were subsequently developed with graft or patient outcome serving as the dependent variable, and allograft (DDLT vs LDLT) type as the main predictor variable while adjusting for propensity score and other variables which were significant on univariate analysis. This allowed us to estimate the graft or patient outcome associated with the allograft type of interest while reducing confounding effects by adjusting for the propensity score, the probability of receiving either DDLT or LDLT. Statistical analyses were conducted using SAS, and a P value <0.05 was considered significant.

RESULTS

Study Population

Among 293 consecutive pediatric LT recipients, 46% received LDLT (n = 135) and 54% underwent DDLT (n = 158) (Table 1). LDLT recipients were significantly younger than DDLT recipients ($P \leq 0.001$). Recipients of LDLT were less likely (n = 1, 0.7%) to require dialysis pre-LT than DDLT (n = 9, 5.6% ($P < 0.002$). The most common indication for pediatric LT was BA (39%), occurring twice as frequently in recipients of LDLT (53%) than DDLT (26%, $P = 0.001$). Children presenting with PALF underwent LT with a graft from a LD less often (6/41, 10%) than from a DD (35/41, 90%). Wait times were not statistically different between DDLT (median, 61 d; IQR, 9, 213 d) and LDLT (median, 76 d; IQR, 37, 135 d; $P = 0.3$) recipients. However, among patients with a primary etiology of chronic cholestatic liver disease, median wait time duration was statistically shorter among those in receipt of LDLT (75 days) compared to DDLT (132 d, $P = 0.003$). The majority of LD were genetically related to the recipient; however, approximately 16% of children in our LDLT cohort received an allograft from an anonymous donor. Calculated PELD and MELD scores at the time of LT were not statistically significant between LDLT and DDLT groups. The median duration of follow-up was 2.2 years for LDLT and 3.5 years for DDLT recipients.

TABLE 1.

Clinical characteristics of 293 pediatric LT recipients by allograft

Characteristics	LDLT (n = 135)	DDLT (n = 158)	P
	Median (IQR) or mean (± SD) or n (%)		
Recipient demographics			
Male sex	71 (52%)	86 (54%)	0.8
Age, mo	13 (7–55)	56.5 (12–137)	<0.001
Etiology of liver disease			<0.001
BA	72 (53%)	41 (26%)	
Other cholestatic diseases[a]	9 (6.6%)	14 (8.8%)	
Metabolic disease[b]	23 (17%)	29 (18.3%)	
PALF	6 (4.4%)	35 (22%)	
Tumor	8 (5.9%)	12 (7.5%)	
Others[c]	17 (12.5%)	27 (17%)	
Clinical status at LT			
Weight, kg	9.1 (7.4–18)	17.8 (8.8–35)	<0.002
Height, cm	73 (65–105)	100.6 (69.4–138)	<0.001
Height Z score	–1.12 (± 1.61)	–0.59 (± 1.67)	0.008
PELD score	11 (1–18)	7.2 (–2 to 13)	0.97
MELD score	12.5 (8.5–21)	13 (11–23)	0.1
Dialysis pretransplant	1 (0.7%)	9 (5.6%)	0.02
Overall wait time, d	76 (37–135)	61 (9–213)	0.3
Wait time in cholestatic diseases,[d] d	75 (42–135)	132 (47–295)	0.003
Laboratory variables at LT			
Conjugated bilirubin, μmol/L	78 (0–155)	51 (0–179)	0.5
Albumin level, g/L	30.5 (27–36)	31 (27–37)	0.5
ALT, IU/L	104.5 (62–167)	94.5 (36–217)	0.4
GGT, IU/L	137 (64–306)	78.5 (44–158)	0.007
Calculated GFR[e]	140.2 (110–164.1)	125.2 (99.1–155.15)	0.016
Intraoperative variables			
CIT, h	2 (1.3–2.5)	7.38 (6.29–9)	<0.001
WIT, min	0.47 (0.43–0.56)	0.59 (0.48–1.05)	0.002
Biliary reconstruction method			
Roux-en-Y	130 (96%)	102 (64%)	<0.001
Duct to duct anastomosis	5 (4%)	59 (37%)	

[a] Includes Alagille syndrome, Byler disease, progressive intrahepatic cholestatic syndromes, total parenteral nutrition cholestasis, sclerosing cholangitis, and idiopathic cholestasis.

[b] Includes α-1-antitrypsin deficiency, Crigler-Najjar syndrome, cystic fibrosis, glycogen storage disease, inborn errors in bile acid metabolism, neonatal hemochromatosis, primary hyperoxaluria, tyrosinemia, urea cycle defects, and Wilson disease.

[c] Includes congenital hepatic fibrosis, Budd-Chiari syndrome, autoimmune hepatitis cirrhosis, drug toxicity, hepatitis c cirrhosis, and unknown cirrhosis.

[d] Cholestatic diseases include BA and other cholestatic diseases.

[e] Using modified Schwarz formulae.

ALT, alanine transaminase; BA, biliary artresia; CB, conjugated bilirubin; CIT, cold ischemia time; DDLT, deceased donor liver transplantation; GFR, glomerular filtration rate; GGT, gamma-glutamyl transpeptidase; IQR, interquartile range; LDLT, living donor liver transplantation; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; PALF, pediatric acute liver failure; PELD, pediatric end-stage liver disease; WIT, warm ischemia time.

TABLE 2.

Posttransplantation course and complications

Variables	LDLT (n = 135)	DDLT (n = 158)	
Posttransplant variables	**Median (IQR) or n (%)**		***P***
Duration of PICU stay, d	4 (2–8)	4 (2–8)	0.8
Duration of intubation, d	2 (1–5)	2 (1–6)	0.8
Length of hospital stay after LT, d	23.5 (17–36)	27 (17.2–46)	0.2
Biliary complications			
Biliary leak	4 (31%)	9 (69%)	0.2
Biliary stricture	14 (48%)	15 (52%)	0.7
PTLD	14 (48%)	15 (52%)	0.7
Kidney dysfunction at 1 y post-LT			
Total recipients with cGFR [a]	14 (36%)	25 (64%)	0.2
Recipient on at least 1 antihypertensive	13 (33%)	27 (67%)	0.06

[a] Calculated glomerular filtration rate expressed as mL/min per 1.73 m^2 body surface area.

DDLT, deceased donor liver transplantation; cGFR, calculated glomerular filtration rate; IQR, interquartile range; LDLT, living donor liver transplantation; LT, liver transplantation; PICU, pediatric intensive care unit; PTLD, posttransplant lymphoproliferative disease.

Intraoperative and Perioperative Courses

Grafts from live donors provided left lateral (n = 112, 82.8%), left (n = 5, 3.7%) and right (n = 18, 13.4%) lobes to our pediatric recipients. Genetically related donors were most frequently parents (n = 63, 61%) with allografts from mothers (n = 52/83, 63%) most frequently used. DD organs provided whole (n = 76, 48%), reduced (n = 49, 31%) and split (n = 33, 21%) allografts. CIT was significantly lower in LDLT (median, 2 h; IQR, 1.3, 2.5 h) than in DDLT (median, 7.38 h; IQR, 6.29, 9 h; $P < 0.001$) recipients. WIT was also significantly shorter in recipients of LDLT (47 min; IQR, 43, 56 min) than DDLT (59 min; IQR, 48, 65 min; $P = 0.002$). Time to extubation after LT, duration of PICU stay, as well as time to first discharge from the hospital, were not statistically different between recipients of LDLT and DDLT. Key posttransplant characteristics and complications noted during the intraoperative and perioperative course are provided in Table 2.

Surgical Complications

There were a total of 42 biliary complications identified among all LT recipients (Table 2). No difference in the prevalence of biliary or vascular complications was noted between recipients of DDLT versus LDLT. There were a total 38 vascular complications, inclusive of hepatic artery thrombosis (HAT) (LDLT n = 5; DDLT n = 5, $P = 0.8$), portal vein complications (LDLT, n = 12; DDLT, n = 6, $P = 0.07$), and hepatic vein complications (LDLT, n = 5; DDLT, n = 5, $P = 0.8$).

Immunosuppressive Use at 1 Year Posttransplantation

By 1 year after LT, the majority of patients have prescribed either tacrolimus (84%) or sirolimus (16%). All hepatoblastoma patients (6%) transitioned from tacrolimus over to sirolimus after postoperative day 30 as per our program practice.[30] Mycophenolate mofetil was used as adjuvant therapy in 10%. Nine percent of recipients were still on steroids, with the indication being the treatment of recently diagnosed ACR. There was no statistically significant difference in immunosuppressive agent utilization at 1 year after LDLT and DDLT.

Acute Cellular Rejection and Chronic Rejection

The 1-, 3- and 5-year ACR-free survival rates were 64.4%, 61.1%, and 61.1%, respectively, in the LDLT group compared with 55%, 44.4%, and 43.4% in the DDLT group (hazard ratio [HR], 0.73; 95% confidence interval [CI], 0.51-1.04; $P = 0.08$) (Figure 1A). Histologically confirmed CR was diagnosed in two DDLT recipients and recorded as the indication for retransplantation at 5.4 years and 13.9 years after initial LT. There were no histologically confirmed CR episodes reported in the LDLT group.

Posttransplant Lymphoproliferative Disease

PTLD was diagnosed in 15 DDLT and 14 LDLT recipients. Tonsils and adenoids were the commonest PTLD sites in

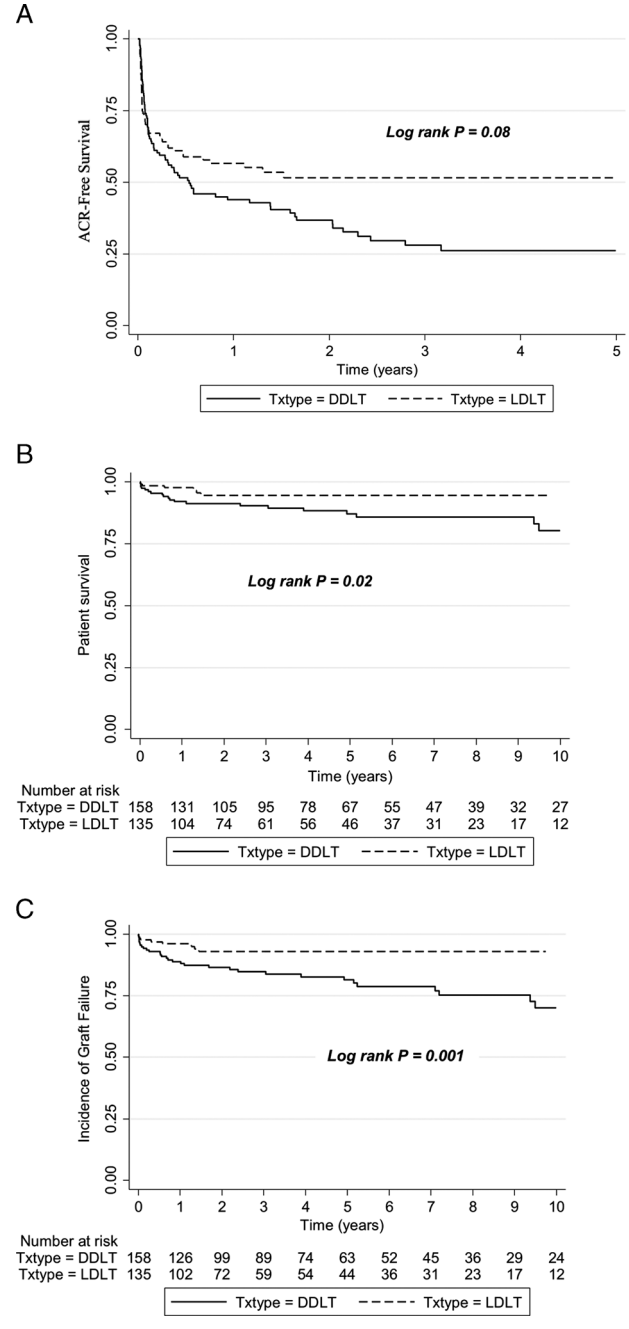

FIGURE 1. A, ACR-free survival in recipients of LDLT and DDLT at The Hospital for Sick Children, 2000 to 2015. B, Patient survival after pediatric LDLT and DDLT at The Hospital for Sick Children, 2000 to 2015. C, Graft survival after pediatric LDLT and DDLT at The Hospital for Sick Children, 2000 to 2015. ACR, acute cellular rejection; DDLT, deceased donor liver transplantation; LDLT, living donor transplantation.

DDLT (40%) and LDLT (43%) recipients, representing our program's practice of preemptive otolaryngology consultation with any clinical note of snoring or clinically detected tonsillar enlargement.[33] PTLD was also diagnosed in the gastrointestinal tract (n = 5, 33% DDLT and 57% LDLT) and others (27% DDLT). The prevalence of PTLD was not statistically different between DDLT versus LDLT ($P = 0.7$) groups.

Kidney Dysfunction

Evaluation of renal function at 1 year post-LT revealed stage 2 chronic kidney disease in 39 (13%) patients, with no statistically significant difference between those receiving LD (n = 14, 10.3%) or DD (n = 25, 16%; $P = 0.2$) allografts. At least one antihypertensive medication was being taken by 40 (13.6%) patients at 1 year post-LT follow-up, with no statistical difference by LDLT (n = 13) and DDLT status (n = 27; $P = 0.06$).

Patient and Graft Survival

Overall 1-, 5-, and 10-year patient survivals for the entire cohort was 95%, 90%, and 86%, respectively. A total of 6 (4.4%) deaths were noted among LDLT recipients, with sepsis being the most common (n = 3) cause. Among DDLT recipients, there were 21 (13.2%) deaths, with sepsis (n = 5, 24%) being again the most common cause, followed by hepatoblastoma recurrence in 3 (14%).

Overall 1-, 5-, and 10-year graft survivals for the whole cohort was 92%, 86%, and 79%, respectively. A total of 42 graft failure events occurred, in 8 (6%) LDLT and 34 (22%) DDLT subjects, leading to retransplantation in 17 (40%) and death in 24 (57%). Median time to graft failure was 9 (IQR, 0.8, 47) months. Retransplantation occurred in a total of 17 (LDLT n = 2, DDLT n = 15) subjects. Among LD recipients, graft failure was due to primary nonfunction and HAT occurring at a median 93.5 days posttransplantation. In the DDLT group, indications for retransplantation included HAT (n = 4), CR (n = 2), disease recurrence (n = 2), ischemic cholangiopathy (n = 2), and one each for primary nonfunction, de novo autoimmune hepatitis, Budd-Chiari, recurrence of hemophagocytic lymphohistiocytosis, and intestinal failure-associated liver disease.

Risk Factors for Patient and Graft Survivals

One-, 5-, and 10-year patient survival rates after LDLT (97%, 94%, and 94%) were significantly higher than after DDLT (92%, 87%, and 80%) ($P = 0.02$) (Figure 1B). Univariate Cox proportional hazard regression models identified allograft type (DD), higher PELD score at the time of LT, and etiology of primary liver disease (diagnosis other than BA) as risk factors for poor patient survival. In multiple regression analysis, with propensity score covariate adjustment, higher PELD score at the time of LT remained the only significant risk factor for decreased patient survival ($P < 0.0001$) (Table 3).

Graft survival at 1, 5, and, 10 years for LDLT recipients was 96.1%, 93%, and 93%, respectively, which was significantly higher than 88.8%, 81%, and 70% in recipients of a DD allograft ($P = 0.001$) (Figure 1C). We also analyzed the impact of DD allograft (whole, reduced, and split) type and LD allograft. In comparison to DD whole graft recipients, children who underwent LDLT had better graft survival (HR, 0.31; 95% CI, 0.15-0.76). There was no difference in graft survival between DD whole graft and technical variant (neither reduced [HR, 1.1; 95% CI, 0.52-2.4] nor split [HR, 1.1; 95% CI, 0.45-2.7]) allografts. Univariate analyses revealed allograft type (DD), higher PELD score, etiology of primary liver disease (diagnosis other than BA), and HAT to be closely associated with decreased graft survival. Allograft type, PELD scores, and HAT were determined to be independent factors associated with graft survival in multiple regression analysis after propensity score covariate adjustment (Table 3). The propensity score was generated using variables which were significantly different at baseline between DDLT and LDLT, including indication for pediatric LT.

Outcomes of Anonymous LDLT

A total of 22 (16%) children underwent LT with an organ from a live anonymous donor (LAD), with a median follow-up of 14 months (IQR, 3, 51 mo). Biliary atresia was the most common (n = 10, 42%) indication. Median recipient age at the time of anonymous LDLT was 14 months (IQR, 9, 55 mo). Patient and graft survival rates at 1 and 5 years after anonymous LDLT were 95% and 95%.

Effect of Donor-Recipient Relationship on Outcomes After LDLT

Amongst recipients of a LD graft from parent (n = 83), non-parent/genetically related (n = 24), and non parent/genetically unrelated emotionally related and anonymous, (n = 28) donors, no statistical differences in patient survival ($P = 0.4$) or graft survival ($P = 0.4$) were found between these three subgroups. There was also no statistically significant difference in the likelihood of ACR developing in recipients of an

TABLE 3.

Risk factors for graft and patient survival after pediatric LT multivariate analyses

Outcome	Multivariable analysis unadjusted for propensity score HR (95% CI)	*P*	Multivariate analysis adjusted for propensity score HR (95% CI)	*P*
Graft survival				
DDLT vs LDLT	3.54 (1.46-8.55)	0.005	2.60 (1.02,6.58)	0.04
PELD	1.03 (1.02-1.05)	<0.0001	1.04 (1.02,1.05)	<0.0001
HAT	8.9 (2.5-31.24)	0.0006	9.31 (2.97,29.22)	0.0001
Patient survival				
DDLT vs LDLT	2.64 (0.99-7.04)	0.05	2.39 (0.93, 6.15)	0.07
PELD	1.04 (1.02-1.06)	<0.0001	1.04 (1.02, 1.06)	<0.0001

CI, confidence interval; DDLT, deceased donor liver transplantation; HAT, hepatic artery thrombosis; HR, hazard ratio; LDLT, living donor liver transplantation; LT, liver transplantation; PELD, pediatric end-stage liver disease.

LDLT organ compared with any of the 3 graft types from a DD ($P = 0.5$).

DISCUSSION

This is the largest single-center experience of LDLT in children reported by a single North American LT program. Currently, LDLT constitutes approximately half of the pediatric LT performed each year at our center. We report LDLT outcomes with 10-year patient survival rate of greater than 94%, higher than previously reported survival rates after adjustment for confounding factors.[34] There were no differences in surgical or medical complications after LDLT in comparison with a contemporaneous cohort of consecutive DDLT performed in the same period. In comparison to DD whole graft recipients, children who underwent LDLT had better graft survival. This experience suggests that access to LT with superior outcomes are achievable if more centers in the Western world in regions with prolonged wait times uniformly and vigorously embraced the option of LDLT.

Excellent outcomes after LDLT in children have previously been reported from the Japanese and Eurotransplant registry data, and single-center experiences from large pediatric programs in Europe and Asia.[34-37] Graft survival at 3 years post pediatric LDLT have been reported as 90.7% and patient survival at 3 years have been reported at 91.4%.[19] Data from Japanese Liver Transplant Society, the largest pediatric LDLT cohort in the world, demonstrate 5- and 20-year patient survival rates of 85.4% and 79.6%, respectively.[34] We extend these findings by demonstrating significantly higher 1-, 5-, and 10-year patient survival rates in pediatric recipients of LDLT compared to DDLT in children with similar characteristics. This contrasts to findings of no difference in overall 1- and 3-year patient survival rates reported in recipients of pediatric LDLT and DDLT performed in Turkey and Wisconsin.[19]

The similarly excellent 1- and 5-year LDLT graft survival rates of 92% and 89%, respectively, compared with the lower 80% and 77%, respectively, among a Belgium cohort undergoing DDLT were also attributed to lower ischemic time in LDLT recipients.[38] In the Scientific Registry of Transplant Recipients cohort, graft outcomes for children younger than 1 year who underwent LDLT were higher than those who underwent DDLT.[39] We also found no differences in perioperative vascular and biliary or medical complications between patients receiving LDLT or DDLT. This is consistent with our center's report of an overall biliary complication rate of 16.7% with no differences between those receiving LDLT versus DDLT[40] but contrasts with the published literature reporting a higher risk of biliary complications associated with LDLT in adults.[41] The reason for this difference might be due to the refinement of surgical techniques, different indications for LT in children, superior vascularization of the biliary plate in left lateral segment grafts, and the predominant use of Roux-en-Y reconstruction in pediatric LDLT.

Controversy exists in the literature regarding whether ACR rates are lower in children who undergo LDLT. Studies exist showing both ACR rates to be lower,[19,42] higher,[38] or no difference between recipients of LDLT and DDLT.[43,44] Among our patients, we did not identify any differences in rejection episodes between recipients of LDLT and DDLT. In addition, we did not find a difference in ACR-free survival rates among children who receive LD grafts from parents, from genetically related versus nongenetically related, nor anonymous donors. This perhaps suggests that HLA matching may not have an added benefit. However, limited power may be contributory due to the small sizes of our 2 subgroups. It has been postulated that the favorable effect of improved HLA matching in LDLT could be nullified by unknown effects including possible lower secretion of donor-soluble HLA antigens by the LDLT graft with a consequent lower tolerogenic effect.[45] More work on the role of donor-soluble HLA and exploring the donor-recipient relationship effect on rejection is needed to address these questions in the future.

Retransplant rates among LDLT recipients were lower than among those receiving DDLT. Our higher retransplant rates amongst DDLT recipients may be the result of multiple factors including higher quality grafts from the meticulous LD work-up, as well as to lower CIT feasible in the journey to LDLT. Similar to results shown in other studies, retransplantation rates were higher in our recipients of pediatric DDLT,[12] likely a result of multiple factors including increased postischemic injury from longer ischemic times, graft edema and parenchymal resistance occurring after revascularization.[46,47] In our cohort, WIT and CIT were longer in DDLT as compared with LDLT. The additional WIT is most likely related to an additional venous anastomosis that is required in many DDLT. While LDLT involves a hepatic vein anastomosis and portal vein anastomosis prior to reperfusion, DDLT with whole grafts or full left lobe grafts include the IVC and require suprahepatic IVC, infrahepatic IVC, and portal vein anastomoses. The additional anastomosis adds approximately 10-15 minutes, accounting for the longer WIT in DDLT recipients.

Although DDLT remains the standard of care for LT in most jurisdictions across the world including Canada, the demand for feasible DD organs far exceeds the available supply. A recent analysis from the United States highlighted that there was an 8% wait-time mortality among children with infants being disproportionately affected.[39] Yet, in the United States, despite growing waiting lists and significant waitlist mortality, only 11% of children receive a live donor graft.[48,49] When considering replication of our experience at other centers in North America and Europe, we acknowledge many healthcare system advantages in Toronto. First, we candidly advise all recipient families that this is the best option to avoid the risks of death or disqualification on the waiting list, to regain better health more quickly, and to enlarge the donor poor for all children waiting for a LT. Second, our pediatric and adult LT programs have high case volumes and are tightly integrated which facilitates technology transfer, coordination of care between sites, and a strong record of donor safety.[50] Third, Canada has a generous social and legal system that provides publically funded healthcare, protects employment for donors when they take time off work and reimburses the direct costs of donation. Fourth, we are prepared to accept anonymous donors who have contributed 16% of our donor population.[21,22,51,52]

The strengths of our study include the analysis of a contemporaneous well-characterized cohort of pediatric LDLT recipients receiving protocolized immunosuppression and clinical care that was largely unchanged over the entire study period in North America. Our excellent outcomes are

reflective of the collaborative partnership with a highly experienced high-volume adult transplant program committed to addressing the unique surgical and ethical challenges in children, rigorous and comprehensive documentation of complications and long-term follow-up to minimize donor-risk and enhance donor safety, and a commitment to advance the field to ensure the continued provision of high-quality donor grafts with outcomes that are superior to our reported outcomes with DDLT. Although we used propensity score covariate analysis with a variety of variables to attempt to reduce the bias of choice of DDLT versus LDLT based on characteristics of the recipients, residual confounding may remain. We also acknowledge several limitations with our study. These include the relatively short median study follow-up when considering the expected long-life expectancy of pediatric LT recipients. Although rare, graft versus host disease has been reported as a complication occurring after LDLT.[53-56] There have been no cases clinically concerning for graft versus host disease in our study cohort. However, we could not evaluate for HLA matching, because we did not have donor serum or recipient serum available for HLA typing or donor-specific antibodies estimation for LDLT.

In conclusion, LDLT is an effective lifesaving therapeutic option for children with end-stage liver disease and other selected pediatric liver conditions. Our data suggest there is an opportunity to use LDLT more widely by pediatric transplant programs to reduce or eliminate waitlist deaths, improve time to transplant, and ultimately improve longterm outcomes for children in need of LT.

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Supporting Information: Additional Supporting Information may be found in the online version of this article.

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