

Henry Ford Health

## Henry Ford Health Scholarly Commons

---

Surgery Articles

Surgery

---

12-6-2021

### Superior Long-Term Outcomes of Adult Living Donor Liver Transplantation: A Cumulative Single-Center Cohort Study With 20 Years of Follow-Up

Toru Goto

Tommy Ivanics

Henry Ford Health, tivanic1@hfhs.org

Mark S. Cattral

Trevor Reichman

Anand Ghanekar

*See next page for additional authors*

Follow this and additional works at: [https://scholarlycommons.henryford.com/surgery\\_articles](https://scholarlycommons.henryford.com/surgery_articles)

---

#### Recommended Citation

Goto T, Ivanics T, Cattral MS, Reichman T, Ghanekar A, Sapisochin G, McGilvray ID, Sayed B, Lilly L, Bhat M, Selzner M, and Selzner N. Superior long-term outcome of Adult Living Donor Liver Transplantation A cumulative single-center cohort study with 20 years follow-up. Liver Transpl 2021.

This Article is brought to you for free and open access by the Surgery at Henry Ford Health Scholarly Commons. It has been accepted for inclusion in Surgery Articles by an authorized administrator of Henry Ford Health Scholarly Commons.

---

**Authors**

Toru Goto, Tommy Ivanics, Mark S. Cattral, Trevor Reichman, Anand Ghanekar, Gonzalo Sapisochin, Ian D. McGilvray, Blayne Sayed, Les Lilly, Mamatha Bhat, Markus Selzner, and Nazia Selzner

# Superior Long-Term Outcomes of Adult Living Donor Liver Transplantation: A Cumulative Single-Center Cohort Study With 20 Years of Follow-Up

Toru Goto,<sup>1,2,\*</sup> Tommy Ivanics ,<sup>1,3,4,\*</sup> Mark S. Cattral,<sup>1</sup> Trevor Reichman,<sup>1</sup> Anand Ghanekar,<sup>1</sup> Gonzalo Sapisochin,<sup>1</sup> Ian D. McGilvray,<sup>1</sup> Blayne Sayed ,<sup>1</sup> Les Lilly,<sup>1</sup> Mamatha Bhat,<sup>1</sup> Markus Selzner,<sup>1</sup> and Nazia Selzner <sup>1</sup>

<sup>1</sup>Multiorgan Transplant Program, Toronto General Hospital, University of Toronto, Toronto, ON, Canada; <sup>2</sup>Department of Surgery, Division of Hepato-Biliary-Pancreatic Surgery & Transplantation, Kyoto University Graduate School of Medicine, Kyoto, Japan; <sup>3</sup>Department of Surgery, Henry Ford Hospital, Detroit, MI; and <sup>4</sup>Department of Surgical Sciences, Uppsala University, Akademiska Sjukhuset, Uppsala, Sweden

Living donor liver transplantation (LDLT) is an attractive alternative to deceased donor liver transplantation (DDLT). Although both modalities have similar short-term outcomes, long-term outcomes are not well studied. We compared the 20-year outcomes of 668 adults who received LDLT with 1596 DDLTs at the largest liver transplantation (LT) program in Canada. Recipients of LDLT were significantly younger and more often male than DDLT recipients ( $P < 0.001$ ). Autoimmune diseases were more frequent in LDLT, whereas viral hepatitis and alcohol-related liver disease were more frequent in DDLT. LDLT recipients had lower Model for End-Stage Liver Disease scores ( $P = 0.008$ ), spent less time on the waiting list ( $P < 0.001$ ), and were less often inpatients at the time of LT ( $P < 0.001$ ). In a nonadjusted analysis, 1-year, 10-year, and 20-year patient survival rates were significantly higher in LDLT (93%, 74%, and 56%, respectively) versus DDLT (91%, 67%, and 46%, respectively; log-rank  $P = 0.02$ ) as were graft survival rates LDLT (91%, 67%, and 50%, respectively) versus (90%, 65%, and 44.3%, respectively, for DDLT; log-rank  $P = 0.31$ ). After multivariable adjustment, LDLT and DDLT were associated with a similar hazard of patient and graft survival. Our data of 20 years of follow-up of LDLT from a single, large Western center demonstrates excellent long-term outcomes for recipients of LDLT.

*Liver Transplantation 0 1–9 2022 AASLD.*

Received July 28, 2021; accepted November 17, 2021.

Liver transplantation (LT) is the only curative treatment for patients with end-stage liver disease. However, the limited availability of deceased donors denies access to this lifesaving treatment to many

recipients: approximately 25% to 30% of patients die each year while waiting for a liver graft. To reduce waitlist mortality, many programs initiated living donor LT (LDLT) 2 decades ago as an alternative to deceased donor LT (DDLT). LDLT provides many advantages over DDLT, including timely access that enables transplantation when the recipient is in a better state of health, planned elective surgery, higher quality grafts from younger donors, and shorter cold ischemia times (CITs).<sup>(1)</sup> A recent meta-analysis of controlled trials revealed that LDLT showed a comparable perioperative mortality rate with DDLT despite a higher rate of surgical complications.<sup>(2)</sup>

The Toronto adult LDLT program began in April 2000<sup>(3–10)</sup> to decrease waitlist mortality for adults with end-stage liver disease. We reported previously that in

*Abbreviations:* A2ALL, Adult-to-Adult Living Donor Liver Transplantation Cohort Study; AIH, autoimmune hepatitis; BMI, body mass index; CI, confidence interval; CIT, cold ischemia time; DDLT, deceased donor liver transplantation; EBL, estimated blood loss; FFP, fresh frozen plasma; GRWR, graft-to-recipient weight ratio; HAT, hepatic artery thrombosis; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; ICU, intensive care unit; INR, international normalized ratio; IQR, interquartile range; LDLT, living donor liver transplantation; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; NASH, nonalcoholic steatohepatitis; OPTN, Organ Procurement

a matched cohort study, hospital stay and short-term survival were comparable for LDLT and DDLT recipients.<sup>(11)</sup> Herein, we report the cumulative 20-year experience of LDLT at the Toronto General Hospital, University Health Network. The main purposes of this study were to compare the long-term patient and graft survival rates between LDLT and DDLT and analyze detailed longitudinal data on causes of death and graft loss. This study represents the longest follow-up of LDLT recipients from a single Western center.

## Patients and Methods

### STUDY DESIGN

This study was a retrospective cohort study, which was reviewed and approved by the Research Ethics Board at Toronto General Hospital/University Health Network (no. 18-6045). All clinical investigations were conducted in accordance with the Declaration of Helsinki principles (2000) for medical research in human participants. All cumulative data of donors and recipients who underwent primary LT from April 2000 to April 2020 at Toronto General Hospital were collected using electronic patient records and analyzed. LT from donors after cardiocirculatory death, pediatric recipients (younger than age 18 years) at transplantation, patients with fulminant hepatic failure, and patients who received combined solid organ transplantations were excluded (Fig. 1).

and Transplantation Network; OR, operating time; PRBC, packed red blood cells; PSC, primary sclerosing cholangitis; PVT, portal vein thrombosis; WIT, warm ischemia time.

Address reprint requests to Nazia Selzner, M.D., Ph.D., Multiorgan Transplant Program, Toronto General Hospital, University of Toronto, 700 University Avenue, Toronto, ON, Canada. Telephone: 416-340-5166; FAX: 416-340-3378; E-mail: Nazia.Selzner@ubn.ca

\*These authors are co-first authors.

The database that supports the findings of this study is available from the corresponding author. Restrictions apply to the availability of the data.

Additional supporting information may be found in the online version of this article.

© 2021 by the American Association for the Study of Liver Diseases.

View this article online at [wileyonlinelibrary.com](http://wileyonlinelibrary.com).

DOI 10.1002/lt.26386

Potential conflict of interest: Nothing to report.

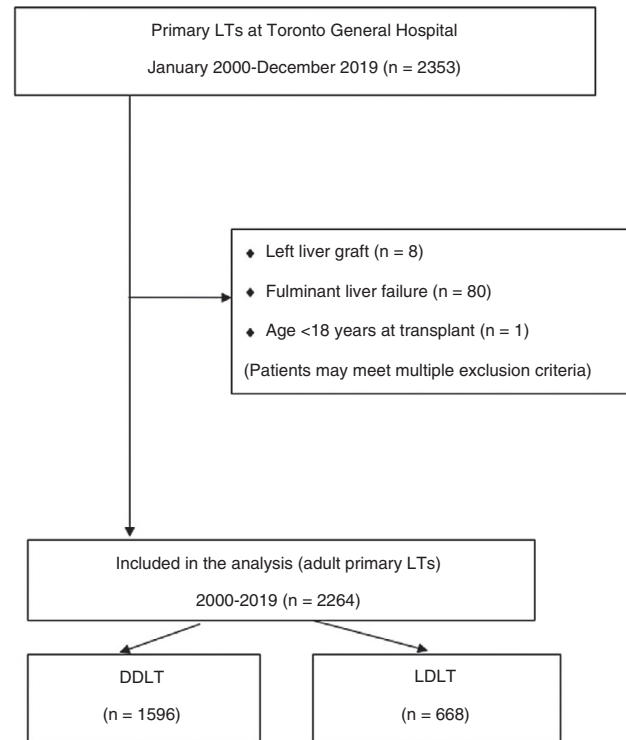


FIG. 1. Flowchart of patient inclusion and exclusion.

### OUTCOMES

The primary endpoint was the long-term patient and graft survival during 20 years of follow-up. The secondary endpoint was the incidence of causes of graft loss or patient death in both groups.

### TRANSPLANTATION PROTOCOL AND FOLLOW-UP

The selection criteria and operative procedure of LDLT and DDLT were described previously.<sup>(3,4,8,9,10,11)</sup> At Toronto General Hospital, all patients were registered on the waiting list for DDLT and were also offered the option of LDLT, regardless of their original diseases and their severity. To ensure donor safety, we have incorporated standard operating procedures and policies developed by a collaborative multidisciplinary team.<sup>(9,10)</sup> Living donation is voluntary and altruistic, and donors and recipients are informed of the complications and survival rates in our program before surgery. Right lobe grafts with or without the middle hepatic vein were transplanted; the

graft-to-recipient weight ratio (GRWR) was  $\geq 0.8$  in most LDLT recipients.

For immunosuppressive therapy, all patients received steroid induction as per our program protocol.<sup>(5,11)</sup> In addition, all LDLT recipients received an additional induction agent, either thymoglobulin or basiliximab (Simulect; Novartis Pharmaceuticals Company, East Hanover, NJ). Basiliximab or thymoglobulin was used selectively in DDLT patients if renal dysfunction or neurologic impairment was present at the time of transplant. Steroids were rapidly tapered to a low dose of prednisone in the first few months and stopped within 3 to 6 months if there was no evidence of rejection; only a minority of patients continued on low-dose maintenance prednisone. Calcineurin inhibitors were also used for maintenance therapy: cyclosporine (Neoral; Novartis Pharmaceuticals Company) for patients with chronic hepatitis C virus (HCV) infection and tacrolimus (Prograf; Astellas Pharma US, Inc., Deerfield, IL) for all other patients. Mycophenolate mofetil (Cellcept; Hoffman-La Roche, Inc, Nutley, NJ) was used selectively at the attending physician's discretion at doses up to 2000 mg/day.

## COVARIATES

We retrieved clinical characteristics from our electronic database, including recipient age, recipient sex (male or female), recipient location at LT (home, intensive care unit [ICU], rehabilitation, ward, and unknown), Model for End-Stage Liver Disease (MELD) score at transplant, original liver disease etiology (autoimmune hepatitis [AIH], alcohol-related cirrhosis, hepatitis B virus [HBV], HCV, hepatoma, metabolic disorder, nonalcoholic steatohepatitis [NASH], primary biliary cholangitis, primary sclerosing cholangitis [PSC], and other), donor age, donor sex (male or female), graft type, type of biliary anastomosis (duct-to-duct, Roux-en-Y), CIT (minutes), warm ischemia time (WIT) (minutes), operation time (minutes), estimated blood loss (EBL; mL), and intraoperative transfusion type (units; packed red blood cells [PRBC], fresh frozen plasma [FFP], platelets).

## CAUSES OF DEATH/GRAFT LOSS

Causes of death or graft loss were categorized as follows: biliary complications, recurrence of primary

diseases, hepatocellular carcinoma (HCC) recurrence, de novo cancer, cardiovascular events, stroke, hepatic artery thrombosis (HAT), portal vein thrombosis (PVT), infections, and others. Cases where the cause of death could not be determined were categorized as "others." The causes of graft loss were analyzed in 2 periods: the first 5 years and after 5 years.

## STATISTICAL ANALYSIS

Descriptive data for continuous variables were expressed as median with interquartile range (IQR). These were compared using the Mann-Whitney U test. Categorical variables were expressed as numbers and percentages and were compared using chi-square and Fisher's exact test. Graft loss was defined as patient death or retransplantation. Patient and graft survival were analyzed from the time of LT using Kaplan-Meier curve analysis with log-rank tests. An additional Kaplan-Meier curve analysis was performed to compare the 2 groups from the time of listing. A sensitivity analysis of survival from LT was performed for patients with MELD scores greater than 25 at LT. The proportional hazard assumption was assessed using Schoenfeld residuals against the transformed time. Graft type (DDLT and LDLT) was not a time-dependent covariate. Cox proportional hazard regression models were constructed to evaluate the association of graft type on post-LT patient and graft survival. The effect of the exposure of interest (graft type) was assessed by multivariable adjustment of clinically deemed confounding variables. A total of 4 separate Cox proportional hazard models were constructed to evaluate the association between graft type on patient and graft survival, which evaluated events in the full follow-up time of the study cohort. In the first model, hazard ratios (HRs) comparing posttransplant mortality and graft loss hazards were estimated without adjustment for donor and recipient characteristics. In the second model, HRs were estimated with adjustment for recipient factors only (recipient age at transplant, etiology of liver disease, HCC, location of recipient at the time of transplant, MELD score). In the third model, HRs were estimated with adjustment for donor factors and ischemia times only (CIT, WIT, and donor age). In the fourth model, HRs were estimated with adjustment for donor and recipient factors. Models for patients without HCC were built separately as a sensitivity analysis. All statistical analyses were

performed using R (R version 4.0.3 [2020-10-10], R Foundation for Statistical Computing, Vienna, Austria; <http://www.R-project.org/>).

## Results

### PATIENT CHARACTERISTICS

A total of 2264 recipients met the inclusion criteria for the study: 668 LDLTs and 1596 DDLTs. The median follow-up duration was 4.7 years (IQR, 1.5-10.1 years). Patient and operation characteristics are displayed in Table 1. LDLT recipients were significantly younger and more often male compared with DDLT recipients. Significant differences were observed in the etiology of the underlying liver diseases ( $P < 0.001$ ), with LDLT recipients having more autoimmune diseases, including PSC (5.8% versus 15.6%), primary biliary cholangitis (3.1% versus 8.8%), AIH (3.1% versus 4.9%), whereas DDLT showed more patients with viral hepatitis (HBV, 14.6% versus 5.1%; HCV, 32.7% versus 27.8%) and alcohol-related cirrhosis (19.7% versus 14.7%). A higher proportion of patients also received a transplant for HCC (either a known diagnosis or incidental findings) in the DDLT group (46.6% versus 27.4%;  $P < 0.001$ ). LDLT recipients had significantly lower medical MELD scores at transplant (median [IQR], 16 [11-25] versus 15 [12-20];  $P = 0.008$ ), with shorter waiting time from listing to transplantation (median [IQR], 183 [37-365] versus 110 [73-219];  $P < 0.001$ ) and were less often inpatients (17% versus 30%;  $P < 0.001$ ). As expected, donor age was significantly lower in the LDLT group when compared with DDLT (50 years versus 38 years;  $P < 0.001$ ), with slightly more female donors in the LDLT group. Both CIT (median minutes [IQR], 450 [353-549] versus 95 [61-129];  $P < 0.001$ ) and WIT (median minutes [IQR], 50 [42-59] versus 47 [39-60];  $P = 0.015$ ) were shorter in LDLT, but EBL volumes were similar. Intraoperative transfusions of PRBC, platelets, and FFP in LDLT were significantly lower (Table 1). In the LDLT group, 54.5% had a bilioenteric anastomosis with a Roux-en-Y compared with 12.7% in the DDLT group ( $P < 0.001$ ). The LDLT group had a significantly higher rate of HAT (2.2%) versus DDLT (0.8%;  $P = 0.005$ ) and a higher proportion of retransplantations (6.1% versus 2.4%;  $P < 0.001$ ). No difference was seen in the rate of PVT between both groups. These results indicate

higher frequencies of LDLT in younger recipients with lower MELD scores and autoimmune diseases.

### PATIENT SURVIVAL

Patient survival at 1 year, 5 years, 10 years, 15 years, and 20 years (95% confidence interval [CI]) for LDLT versus DDLT were as follows: 1-year LDLT, 93.3% (95% CI, 91.4%-95.2%) versus DDLT, 91.3% (95% CI, 89.9%-92.7%;  $P = 0.13$ ); 5-year LDLT, 83.8% (95% CI, 80.9%-86.9%) versus DDLT, 79.0% (95% CI, 76.8%-81.3%;  $P = 0.03$ ); 10-year LDLT, 73.6% (95% CI, 69.5%-78.0%) versus DDLT, 67.2% (95% CI, 64.2%-70.2%;  $P = 0.01$ ); 15-year LDLT, 59.7% (95% CI, 53.1%-67.1%) versus DDLT, 54.7% (95% CI, 50.7%-58.9%;  $P = 0.02$ ); and 20-year LDLT, 56.3% (95% CI, 58.9%-64.9%) versus DDLT, 46.3% (95% CI, 40.8%-52.7%;  $P = 0.02$ ). Overall posttransplant survival is shown in Fig. 2. The median survival was 17.8 years (95% CI, 16.2-Not applicable [NA]) in the DDLT group and was not reached in the LDLT group (survival >50%). In the sensitivity analysis, evaluating the survival from the time of listing comparing the 2 groups favored LDLT, although this was not statistically significant (Supporting Fig. 1).

In the unadjusted analysis from the time of transplant, LDLT was associated with an improved patient survival overall relative to DDLT (HR, 0.80; 95% CI, 0.67-0.97;  $P = 0.02$ ). Compared with DDLT, the overall patient and graft survival was similar between the graft types on risk-adjusted analysis, after adjustment for donor characteristics, and after adjustment for recipient and donor characteristics (Table 2).

### GRAFT SURVIVAL

Graft survival at 1 year, 5 years, 10 years, 15 years, and 20 years (95% CI) for LDLT versus DDLT were as follows: 1-year LDLT, 90.6% (95% CI, 88.4%-92.8%) versus DDLT, 89.9% (95% CI, 88.4%-91.5%;  $P = 0.73$ ); 5-year LDLT, 80.7% (95% CI, 77.6%-84.0%) versus DDLT, 77.3% (95% CI, 75.1%-79.7%;  $P = 0.18$ ); 10-year LDLT, 67.4% (95% CI, 63.0%-72.1%) versus DDLT, 65.1% (95% CI, 62.1%-68.2%;  $P = 0.27$ ); 15-year LDLT, 53.0% (95% CI, 46.1%-60.9%) versus DDLT, 52.7% (95% CI, 48.8%-57.0%;  $P = 0.32$ ); and 20-year LDLT, 49.8% (95% CI, 42.2%-58.7%) versus DDLT, 44.3% (95% CI, 38.7%-50.7%;  $P = 0.32$ ). Overall posttransplant graft survival is shown in Fig. 3. The median graft survival was 16.9 years (95% CI, 14.5-20.2) in the DDLT group and 15.7 years (95% CI, 14.7-NA) in the LDLT group.

TABLE 1. Recipient and Transplant Characteristics Stratified by Graft Type

Recipient Characteristics	DDLT (n = 1596)	LDLT (n = 668)	P Value
Recipient age at transplant, years	57 (50-62)	54 (47-61)	<0.001 <sup>†</sup>
Male sex	1181 (74.0)	402 (60.2)	<0.001 <sup>‡</sup>
BMI	28 (24-30)	27 (23-29)	<0.008
Total bilirubin at transplant, $\mu\text{mol/L}$	44 (21-128)	46 (25-97)	0.94
INR at transplant	1.5 (1.2-2.0)	1.4 (1.2-1.7)	<0.001
Creatinine at transplant, $\mu\text{mol/L}$	84 (67-118)	76 (64-104)	<0.001
MELD score at transplant*	16 (11-25)	15 (12-20)	0.008 <sup>†</sup>
MELD score at transplant without HCC*	22 (16-29)	16 (20-22)	<0.001
MELD score at transplant greater than 25	370 (23.3)	65 (9.7)	<0.001
Recipient location at transplant			<0.001 <sup>‡</sup>
Home	1120 (70.2)	554 (82.9)	
ICU	87 (5.5)	5 (0.7)	
Rehabilitation	1 (0.1)	0 (0.0)	
Ward	387 (24.2)	109 (16.3)	
Unknown	1 (0.1)	0 (0.0)	
Time on waitlist, days	183 (37-365)	110 (73-219)	<0.001 <sup>†</sup>
Etiology of original liver disease			
AIH	50 (3.1)	33 (4.9)	
Alcohol-related cirrhosis	314 (19.7)	98 (14.7)	
HBV	233 (14.6)	34 (5.1)	
HCV	522 (32.7)	186 (27.8)	
Hepatoma (non-HCC)	21 (1.3)	12 (1.8)	
Metabolic disorder	40 (2.5)	15 (2.2)	
NASH	180 (11.3)	69 (10.3)	
Others	94 (5.9)	58 (8.7)	
Primary biliary cholangitis	50 (3.1)	59 (8.8)	
PSC	92 (5.8)	104 (15.6)	
HCC	743 (46.6)	183 (27.4)	<0.001 <sup>‡</sup>
Donor age, years	50 (36-62)	38 (29-49)	<0.001 <sup>†</sup>
Donor male sex	937 (58.7)	300 (44.9)	<0.001 <sup>‡</sup>
Biliary anastomosis			<0.001 <sup>‡</sup>
Duct to duct	1377 (86.3)	303 (45.4)	
Roux-en-Y	203 (12.7)	364 (54.5)	
Unknown	16 (1.0)	1 (0.1)	
CIT, minutes	450 (353-549)	95 (61-129)	<0.001 <sup>†</sup>
WIT, minutes	50 (42-59)	47 (39-60)	0.015 <sup>†</sup>
OR time, minutes	449 (385-517)	540 (460-630)	<0.001 <sup>†</sup>
EBL, mL	2350 (1400-4000)	2000 (1325-4000)	0.352 <sup>†</sup>
PRBC, units	4 (1-6)	2 (1-6)	<0.001 <sup>†</sup>
Platelets, units	1 (0-4)	1 (0-3)	<0.001 <sup>†</sup>
FFP, units	6 (2-10)	5 (2-8)	0.040 <sup>†</sup>
Retransplantation	39 (2.4)	41 (6.1)	<0.001 <sup>‡</sup>
HAT	13 (0.8)	15 (2.2)	0.005 <sup>‡</sup>
PVT	3 (0.2)	2 (0.3)	0.607 <sup>‡</sup>

NOTE: Data are provided as median (IQR) or n (%).

\*The MELD score represents medical MELD and not exception points.

<sup>†</sup>Kruskal-Wallis rank sum test.

<sup>‡</sup>Pearson chi-square test.

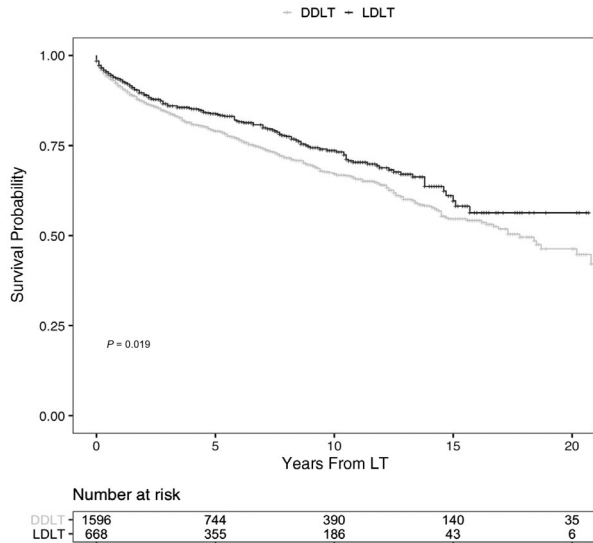


FIG. 2. Posttransplant patient survival stratified by graft type.

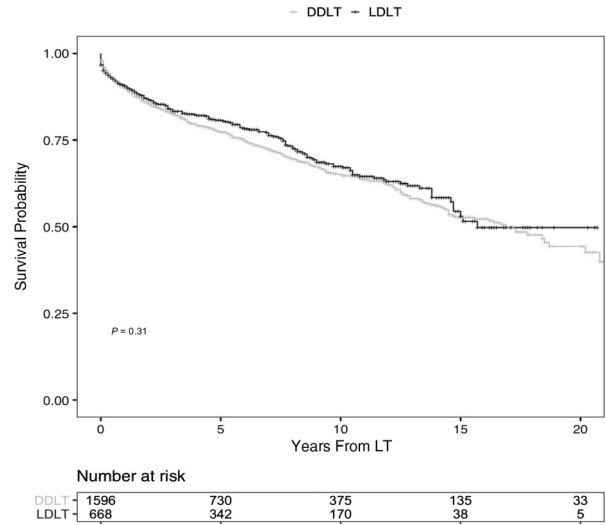


FIG. 3. Posttransplant graft survival stratified by graft type.

TABLE 2. Impact of Graft Type (LDLT versus DDLT) on Posttransplant Outcomes

Posttransplant Survival	Compared With DDLT	
	Overall HR (95% CI)	P Value
Unadjusted analysis		
Patient survival	0.80 (0.67-0.97)	0.02
Graft survival	0.91 (0.77-1.09)	0.30
Adjusted for recipient characteristics*		
Patient survival	1.16 (0.86-1.57)	0.33
Graft survival	1.35 (1.03-1.77)	0.03
Adjusted for donor characteristics†		
Patient survival	0.94 (0.70-1.27)	0.68
Graft survival	1.12 (0.85-1.47)	0.43
Adjusted for recipient and donor characteristics‡		
Patient survival	1.00 (0.72-1.38)	0.99
Graft survival	1.17 (0.87-1.57)	0.29

\*Adjusted for recipient age at transplant, etiology of liver disease, location of recipient at the time of transplant, and MELD score at transplant.

†Adjusted for CIT, WIT, type of biliary anastomosis (Roux-en-Y or duct-to-duct), and donor age.

‡Adjusted for CIT, WIT, recipient age at transplant, etiology of liver disease, location of recipient at the time of transplant, type of biliary anastomosis, MELD score at transplant, and donor age.

Compared with DDLT, the overall hazard of graft loss was similar between the graft types in the unadjusted analysis and after adjustment for donor

characteristics alone. After adjustment for recipient characteristics alone, LDLT was associated with a higher hazard of graft mortality (reference, DDLT; HR, 1.35; 95% CI, 1.03-1.77;  $P = 0.03$ ; Table 2) This effect was attenuated after adjustments for both donor and recipient characteristics, with no statistically significant difference noted in the hazard of graft loss with LDLT (reference, DDLT).

### CAUSES OF DEATH/GRAFT LOSS

The cause of graft loss was classified into 10 different categories in Tables 3 and 4. For patients who experienced graft failure in the first 5 years after LT, the LDLT group had a higher rate of biliary complications (5% versus 2%;  $P = 0.04$ ) and HAT (11% versus 3%;  $P = 0.003$ ), whereas the DDLT group has a significantly higher rate of graft loss from de novo cancer (Table 3). For patients who experienced graft failure/death 5 years or more after LT, cardiovascular events were higher in the LDLT group (21% versus 8%;  $P = 0.008$ ; Table 4).

### Discussion

This is the largest single-center experience with the longest follow-up period of LDLT in adults reported by a single Western country LT program. Currently, LDLT constitutes approximately one-third of the



TABLE 3. Cause of Graft Loss: First 5 Years After LT Stratified by Graft Type

Cause of Graft Loss	DDLT (n = 303)	LDLT (n = 114)	P Value*
Biliary complications	5 (2)	6 (5)	0.040
Recurrence of primary disease	32 (11)	9 (8)	0.415
HCC recurrence	36 (12)	8 (7)	0.150
De novo cancer	63 (21)	14 (12)	0.046
Cardiovascular events	23 (8)	5 (4)	0.244
Stroke	7 (2)	5 (4)	0.261
Infections	45 (15)	25 (22)	0.085
HAT	10 (3)	12 (11)	0.003
PVT	1 (0)	2 (2)	0.125
Others	80 (26)	25 (22)	0.348

NOTE: Data are provided as n (%).

\*Pearson chi-square test.

TABLE 4. Cause of Graft Loss: 5 Years or More After LT Stratified by Graft Type

Cause of Graft Loss	DDLT (n = 155)	LDLT (n = 66)	P Value*
Biliary complications	2 (1)	3 (5)	0.136
Recurrence of primary disease	15 (10)	11 (17)	0.140
HCC recurrence	11 (7)	3 (5)	0.476
De novo cancer	35 (23)	11 (17)	0.322
Cardiovascular events	13 (8)	14 (21)	0.008
Stroke	3 (2)	1 (2)	0.830
Infections	24 (16)	8 (12)	0.516
HAT	3 (2)	2 (3)	0.616
PVT	2 (1)	0 (0)	0.352
Others	46 (30)	14 (21)	0.195

NOTE: Data are provided as n (%).

\*Pearson chi-square test.

adult LTs performed each year at our center. We report LDLT outcomes with a 20-year patient survival rate exceeding 60%. The post-LT mortality hazard of LDLT recipients was similar to DDLT after risk adjustment for DDLT. This report demonstrates the success of the LDLT procedure with excellent long-term outcomes of a well-characterized cohort in a single center and endorses the benefit of LDLT to decrease mortality on the waiting list for adult recipients with low MELD scores and long waiting times.

Although similar short-term patient survival results were reported by several retrospective and prospective studies with large registry data, to our knowledge, our study is the only study reporting on 20 years of follow-up data from LDLT recipients from a large, single-center Western country. Hoehn et al.<sup>(12)</sup> retrospectively evaluated the data of

715 LDLT patients at 35 centers and 14,282 DDLT patients at 62 centers from 2007 to 2012 collected by the Scientific Registry of Transplant Recipients and the Organ Procurement and Transplantation Network (OPTN). Unadjusted analysis demonstrated that LDLT showed superior survival rates of LDLT ( $P = 0.04$ ) at 2 years after LT, but propensity score matching for 708 LDLT recipients showed no difference in recipient ( $P = 0.41$ ) and graft ( $P = 0.72$ ) survival rates. Gordon et al.<sup>(6)</sup> presented a retrospective cohort study that included 2103 LDLT and 46,674 DDLT patients of the national OPTN/United Network for Organ Sharing data from 2002 to 2012.<sup>(6)</sup> Unadjusted survival analysis showed that LDLT had significantly higher survival rates compared with DDLT patients (excluding the first 15 LDLT cases performed in each transplant center:

5-year survival rate, 77.8% in LDLT versus 71.0% in DDLT;  $P < 0.001$ ). The Adult-to-Adult Living Donor Liver Transplantation Cohort Study (A2ALL) study,<sup>(13)</sup> which was a multicenter prospective study in North America, demonstrated that LDLT recipients had significantly better survival probability compared with DDLT (70% versus 64% at 10 years;  $P = 0.02$ ) in unadjusted analysis and was comparable in adjusted analysis by lower MELD score and nonsevere renal dysfunction. These large database series with short-term outcomes and our study with long-term follow-up indicate that the better survival rate in LDLT is based on favorable patient backgrounds, such as lower MELD scores, higher rates of autoimmune diseases, fewer transplant patients from ICU and inpatient wards, and lower rates of de novo malignancy in LDLT recipients may be attributed to the presence of fewer risk factors based on the underlying etiologies, such as more autoimmune diseases in this group.

However, the cause of death during the entire study period showed no significant differences between the 2 groups in our study, similar to the A2ALL study. We analyzed causes of graft loss at 2 different time points: early term (from 0 to 5 years after transplantation) and late term (from 5 to 20 years). Within the group of patients experiencing a graft loss within the first 5 years, LDLT recipients had more biliary complications and more often HAT. Consequently, the rate of retransplantation was higher in the LDLT group, presumably attributed to a higher rate of early HAT. Of note, despite a significantly higher rate of graft loss attributed to HAT in the LDLT group, the overall rate of HAT in our study is low (2% in LDLT versus <1% in DDLT), indicating center expertise. Similarly, the overall impact of graft loss attributed to biliary complications in our cohort of LDLT is low (5%) compared with previously reported higher incidence of biliary<sup>(2,11,14,15,16,17,18,19,20)</sup> complications. Furthermore, no differences in graft loss attributed to biliary or vascular complications were observed between 5 to 20 years of follow-up between both groups. Surprisingly, a higher proportion of LDLT recipients in our study had graft loss from cardiovascular complications such as myocardial infarction in the long term. Finally, our data showed no difference in infection, recurrence of original diseases, and graft rejection as causes of graft loss.

In this study, we performed an unadjusted and detailed survey of 2 different donor types in our

cumulative history and evaluated the risk factor for long-term outcomes in LDLT recipients. As this study is neither prospective nor a matched cohort study, we recognize that it may be limited by the different characteristics of each group and potential donor and recipient selection biases.

In conclusion, LDLT is an effective therapeutic option that provides significant long-term benefits with similar posttransplant patient and graft survival rates as with DDLT. Our results demonstrate LDLT's benefits of less waiting times for transplantation and overall equal long-term survival rates when performing LDLTs in patients with lower MELD scores.

*Acknowledgments:* The authors thank Audrey Kim, a clinical research technician, for valuable assistance with the collection of data.

## REFERENCES

- 1) Abu-Gazala S, Olthoff KM. Current status of living donor liver transplantation in the United States. *Annu Rev Med* 2019;70:225-238.
- 2) Wan P, Yu X, Xia Q. Operative outcomes of adult living donor liver transplantation and deceased donor liver transplantation: a systematic review and meta-analysis. *Liver Transpl* 2014;20:425-436.
- 3) Linares I, Goldaracena N, Rosales R, Maza LDL, Kathis M, Kollmann D, et al. Splenectomy as flow modulation strategy and risk factors of de novo portal vein thrombosis in adult-to-adult living donor liver transplantation. *Liver Transpl* 2018;24:1209-1220.
- 4) Kollmann D, Goldaracena N, Sapisochin G, Linares I, Selzner N, Hansen BE, et al. Living donor liver transplantation using selected grafts with 2 bile ducts compared with 1 bile duct does not impact patient outcome. *Liver Transpl* 2018;24:1512-1522.
- 5) Goldaracena N, Barbas AS, Galante A, Sapisochin G, Al-Adra D, Selzner N, et al. Live donor liver transplantation with older donors: Increased long-term graft loss due to HCV recurrence. *Clin Transplant* 2018;32:e13304.
- 6) Gordon FD, Goldberg DS, Goodrich NP, Lok ASF, Verna EC, Selzner N, et al. Recurrent primary sclerosing cholangitis in the Adult-to-Adult Living Donor Liver Transplantation Cohort Study: comparison of risk factors between living and deceased donor recipients. *Liver Transpl* 2016;22:1214-1222.
- 7) Aravinthan AD, Doyle AC, Issachar A, Dib M, Peretz D, Cattral MS, et al. First-degree living-related donor liver transplantation in autoimmune liver diseases. *Am J Transplant* 2016;16:3512-3521.
- 8) Shah SA, Grant DR, McGilvray ID, Greig PD, Selzner M, Lilly LB, et al. Biliary strictures in 130 consecutive right lobe living donor liver transplant recipients: results of a Western center. *Am J Transplant* 2007;7:161-167.
- 9) Shah SA, Grant DR, Greig PD, McGilvray ID, Adcock LD, Girgrah N, et al. Analysis and outcomes of right lobe hepatectomy in 101 consecutive living donors. *Am J Transplant* 2005;5:2764-2769.
- 10) Hemming AW, Cattral MS, Reed AI, Van Der Werf WJ, Greig PD, Howard RJ. Liver transplantation for hepatocellular carcinoma. *Ann Surg* 2001;233:652-659.

- 11) Reichman TW, Katchman H, Tanaka T, Greig PD, McGilvray ID, Cattral MS, et al. Living donor versus deceased donor liver transplantation: a surgeon-matched comparison of recipient morbidity and outcomes. *Transplant Int* 2013;26:780-787.
- 12) Hoehn RA, Wislon GC, Wima K, Hohmann SF, Midura EF, Woodle SE, et al. Comparing Living donor and deceased donor liver transplantation 2007–2012. *Liver Transpl* 2014;20:1347–1355.
- 13) Olthoff KM, Smith AR, Abecassis M, Baker T, Emond JC, Berg CL, et al. Defining long-term outcomes with living donor liver transplantation in North America. *Ann Surg* 2015;262:465–475; discussion 473–465.
- 14) Dahm F, Georgiev P, Clavien PA. Small-for-size syndrome after partial liver transplantation: definition, mechanisms of disease and clinical implications. *Am J Transplant* 2005;5:2605–2610.
- 15) Lai JC, Pichardo EM, Emond JC, Brown RS, Jr. Resource utilization of living donor versus deceased donor liver transplantation is similar at an experienced transplant center. *Am J Transplant* 2009;9:586–591.
- 16) Macías Gómez C, Dumonceau J-M, Marcolongo M, de Santibañes E, Ciardullo M, Pekolj J, et al. Endoscopic management of biliary complications after adult living-donor versus deceased-donor liver transplantation. *Transplantation* 2009;88:1280–1285.
- 17) Al-Sebayel M, Khalaf H, Al-Sofayan M, Al-Saghier M, Abdo A, Al-Bahili H, et al. Experience with 122 consecutive liver transplant procedures at King Faisal Specialist Hospital and Research Center. *Ann Saudi Med* 2007;27:333–338.
- 18) Liu CL, Fan ST, Lo CM, Wei WI, Chan SC, Yong BH, et al. Operative outcomes of adult-to-adult right lobe live donor liver transplantation: a comparative study with cadaveric whole-graft liver transplantation in a single center. *Ann Surg* 2006;243:404–410.
- 19) Garcia-Retortillo M, Forns X, Llovet JM, Navasa M, Feliu A, Massaguer A, et al. Hepatitis C recurrence is more severe after living donor compared to cadaveric liver transplantation. *Hepatology* 2004;40:699–707.
- 20) Freise CE, Gillespie BW, Koffron AJ, Lok AS, Pruett TL, Emond JC, et al. Recipient morbidity after living and deceased donor liver transplantation: findings from the A2ALL Retrospective Cohort Study. *Am J Transplant* 2008;8:2569–2579.