Expanding the Donor Pool: Donation After Circulatory Death and Living Liver Donation Do Not Compromise the Results of Liver Transplantation

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Because of the shortfall between the number of patients listed for liver transplantation (LT) and the available grafts, strategies to expand the donor pool have been developed. Donation after circulatory death (DCD) and living donor (LD) grafts are not universally used because of the concerns of graft failure, biliary complications, and donor risks. In order to overcome the barriers for the implementation of using all 3 types of grafts, we compared outcomes after LT of DCD, LD, and donation after brain death (DBD) grafts. Patients who received a LD, DCD, or DBD liver graft at the University of Toronto were included. Between January 2009 through April 2017, 1054 patients received a LT at our center. Of these, 77 patients received a DCD graft (DCD group); 271 received a LD graft (LD group); and 706 received a DBD graft (DBD group). Overall biliary complications were higher in the LD group (11.8%) compared with the DCD group (5.2%) and the DBD group (4.8%; $P < 0.001$). The 1-, 3-, and 5-year graft survival rates were similar between the groups with 88.3%, 83.2%, and 69.2% in the DCD group versus 92.6%, 85.4%, and 84.7% in the LD group versus 90.2%, 84.2%, and 79.9% in the DBD group ($P = 0.24$). Furthermore, the 1-, 3-, and 5-year patient survival was comparable, with 92.2%, 85.4%, and 71.6% in the DCD group versus 95.2%, 88.8%, and 88.8% in the LD group versus 93.1%, 87.5%, and 83% in the DBD group ($P = 0.14$). Multivariate Cox regression analysis revealed that the type of graft did not impact graft survival. In conclusion, DCD, LD, and DBD grafts have similar longterm graft survival rates. Increasing the use of LD and DCD grafts may improve access to LT without affecting graft survival rates.

Liver Transplantation 24 779–789 2018 AASLD.
Received December 5, 2017; accepted March 13, 2018.

Liver transplantation (LT) using a donation after brain death (DBD) organ is the standard of care for patients with decompensated liver disease. Over the last 3 decades, the outcomes of LT have improved and the indications have been extended.[1] The success of LT has increased the demand, resulting in a severe organ shortage.[1] Currently, almost 15,000 patients are waiting for a liver graft in the United States.[2] Because of the growing gap between the number of patients on the waiting list and a relatively static donor organ supply, mortality while on the waiting list now averages 20%-25% in most centers.[3]

Living donor liver transplantation (LDLT) or donation after circulatory death (DCD) grafts have been proposed to increase the donor pool. However, many centers are reluctant to embrace these options. Adoption of LDLT has been limited by concerns about the risk for living donors (LDs) and early reports on high rates of technical complications.[4] Likewise,

Abbreviations: ALP, alkaline phosphatase; AST, aspartate aminotransferase; BMI, body mass index; CCI, comprehensive complication index; CI, confidence interval; CIT, cold ischemia time; DBD, donation after brain death; DCD, donor after circulatory death; ERCP, endoscopic retrograde cholangiopancreatography; FFP, fresh frozen plasma; FHF, fulminant hepatic failure; HAT, hepatic artery thrombosis; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HJ, hepaticojejunostomy Roux-en-Y; HR, hazard ratio; HRS, hepatorenal syndrome; ICU, intensive care unit; INR, international normalized ratio; LD, living donor; LDLT, living donor liver transplantation; LT, liver transplantation; MELD, Model for End-Stage Liver Disease;

adoption of DCD LT has been limited by reports on higher rates of poor immediate graft function and longterm biliary strictures.[5,6] Currently, only 6% and 4% of the LTs in the United States are adult DCD LT or LDLT, respectively.[2,7] In contrast, at the University of Toronto, the usage of these grafts has steadily grown over time and accounts for 15%-25% of patients. This growth was facilitated by efforts to expand the donor pool using LDLT and DCD LT. The LDLT program of the University of Toronto started in the year 2000. This option is now used in approximately 25% of our adult recipients.[8] Furthermore, the DCD program started in 2007, and these grafts now comprise 10%-15% of our program volume.

This review was undertaken to determine the impact of using a high proportion of these alternative types of grafts. We hypothesize that current short-term and longterm results would be equivalent for these procedures, providing further evidence that it is appropriate to promote all graft types to maximize access to LT.

Patients and Methods

STUDY DESIGN

Cases for this retrospective study are from a large prospectively collected database from the University of Toronto. The study population was composed of patients who received a first LT from a DCD graft (DCD group), a LDLT graft (LD group, right lobe liver grafts), or a DBD graft (DBD group) at the University of Toronto. Patients who received a multiorgan transplant were excluded. The patient and graft survival rates were compared between the 3 groups, as were the operative and postoperative complications. The study period went from January 2009 to April 2017. This study period was chosen because we only included patients in the DCD group where the contemporary protocol was used, which was initiated in 2009.[9] The median follow-up from the time of transplant was 35 months (range, 0.7-99) for the DCD group, 46 months (range, 0.06-99) for the LD group, and 40 months (range, 0-99) for the DBD group. Approval for this study was obtained from the ethical committee of the Toronto General Hospital.

DCD GRAFTS

All DCD grafts in the current study are Maastricht category 3 DCD donors.[10] Trillium Gift of Life Network coordinated the allocation of organs from DCD donors at the Toronto General Hospital. Recipient allocation was based on the calculated Model for End-Stage Liver Disease (MELD) score, with the exception of patients listed for hepatocellular carcinoma (HCC) who received exception points. Furthermore, the selection of candidates for DCD grafts was based on trying to keep the cold ischemia time (CIT) at <8 hours, therefore avoiding recipients with complicated hepatectomies (retransplantation or need for vascular reconstructions) and/or diagnosed portal vein thrombosis.

The organ procurement for DCD grafts at the University of Toronto has been described previously.[9] Briefly, an intensive care physician at the donor hospital who was completely independent from the recovery and recipient teams identified potential DCD donors and organized the process of withdrawal of life support and the declaration of donor death. Heparin (1000 U/kg) was administered prior to withdrawal of life support. Warm ischemia time (WIT) for DCD grafts is defined as the time from withdrawal of life support of the donor to organ perfusion, regardless of the mean arterial pressure or the partial pressure of oxygen levels. The maximum tolerated WIT at our center is 30 minutes. In some exceptional circumstances, the WIT was slightly expanded at the surgeons' discretion (a maximum WIT of 33 minutes). All DCD graft recipients included in the current study received an injection of tissue plasminogen activator (tPA) through the hepatic artery.[9,11] The tPA dose used was 100 μg/kg (donor weight) and was administered before the portal

MRCP, magnetic resonance cholangiography; PBC, primary biliary cirrhosis; PNF, primary nonfunction; pRBC, packed red blood cell; PSC, primary sclerosing cholangitis; PTC, percutaneous transhepatic cholangiography; tPA, tissue plasminogen activator; UNOS, United Network for Organ Sharing.

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View this article online at wileyonlinelibrary.com.

DOI 10.1002/lt.25068

Potential conflict of interest: Nothing to report.

vein anastomosis (5-10 minutes before portal reperfusion). DCD grafts with >10% of estimated steatosis are currently declined for transplantation.

LD GRAFTS

Only right lobe adult-to-adult LDLT patients were included in the current study, in order to represent a homogeneous cohort. When donors are selected for living donation, they have to be in good health and fulfill several criteria as reported elsewhere.[8,12] The accepted donor age ranges between 18 and 60 years, and donors are not accepted if they have underlying medical conditions or comorbidities, underlying liver disease, abnormal liver tests, or vascular and biliary anomalies. Steatosis of >10% in the donor is a contraindication for living donation at our program. In order to evaluate graft and donor remnant liver volumes and the vascular anatomy, all potential donors undergo triphasic computerized tomography. For the evaluation of biliary anatomy, they undergo magnetic resonance cholangiography (MRCP).[13] We aim to provide recipients with a graft that has an estimated graft-to-recipient weight ratio $\geq$ 0.8% and leave donors with a residual liver volume of $\geq$30%.

LT TECHNIQUES

The preferred recipient transplant procedure for DCD and DBD grafts has been a caval replacement technique. The preferred biliary anastomosis in all transplant procedures has been a duct-to-duct anastomosis. Some patients in the DCD and DBD group required a hepaticojejunostomy Roux-en-Y (HJ) due to underlying liver disease or unfavorable anatomical conditions to perform a duct-to-duct anastomosis. Within the LD group, the preferred technique is a duct-to-duct anastomosis. An HJ is performed in cases where there is more than 1 bile duct orifice that cannot be reconstructed together. Intra-abdominal drains are not placed routinely. Furthermore, no venovenous bypass was used during LT at our center.

POSTTRANSPLANT OUTCOMES

Graft function and acute reperfusion injury were assessed in the early postoperative period (48 hours) by peak serum aspartate aminotransferase (AST). The posttransplant graft function was assessed by total serum bilirubin, alkaline phosphatase (ALP), and the international normalized ratio (INR). Graft failure was determined by the time of listing for retransplantation or patient death.

General Postoperative Complications

All complications during patient admission were collected. Complications were classified according to the Clavien-Dindo classification into grades 0-5.[14] Examples for complications classified with the respective Clavien-Dindo grade include the following: grade 1—nausea and vomiting or generalized edema; grade 2—pneumonia, urinary tract infection, or rejection; grade 3a—radiological or endoscopic treatment, eg, pneumothorax, gastric ulcer bleeding; grade 3b—surgical treatment, eg, laparotomy because of bleeding or bile duct revision; grade 4a—acute renal failure or respiratory failure; grade 4b—multiorgan failure; and grade 5—patient death. Furthermore, the comprehensive complication index (CCI) was calculated for all complications that occurred during hospital admission.[15,16] The CCI is a validated metric system integrating all recorded complications into a formula, resulting in a score with a range of 0-100 (CCI of 100 equals death) and is based on the Clavien-Dindo classification.[16-18]

Biliary Complications

Biliary complications occurring at any time during follow-up were collected. These complications were identified by abnormal liver function tests or a clinical presentation consistent with cholangitis. Diagnosis of biliary complications was confirmed with cholangiography.

BILIARY STRICTURES

Strictures were characterized by imaging with percutaneous transhepatic cholangiography (PTC), endoscopic retrograde cholangiopancreatography (ERCP), or MRCP. For the purpose of this study, biliary strictures were divided into diffuse intrahepatic strictures and focal strictures. Diffuse intrahepatic strictures were those that were not amenable to definitive management with endoscopic or radiographic stenting, and more often progressed to graft failure. Focal strictures included those that involved anastomotic strictures and focal extrahepatic strictures.

BILIARY LEAKS

Leaks were diagnosed clinically and with imaging (ultrasound, computerized axial tomography, or magnetic resonance imaging).

TABLE 1. Recipient and Donor Characteristics Summarized and Compared Between the 3 Donor Types

	DCD Group (n = 77)	LD Group (n = 271)	DBD Group (n = 706)	*P* Value
Recipient characteristics				
Age, years	57 (19-71)	38 (18-61)	58 (18-75)	0.01
Sex (male)	54 (70)	160 (59)	524 (74)	<0.001
BMI, kg/m^2	25.8 (15-42)	26 (15-47)	27 (14-53)	0.01
HCV positive	29 (37.7)	66 (24.4)	229 (32.4)	0.02
HCC	41 (53.2)	76 (28)	319 (45.2)	<0.001
FHF	3 (3.9)	6 (2.2)	31 (4.4)	0.28
PBC or PSC	3 (3.9)	66 (24.4)	56 (7.9)	<0.001
ICU prior to transplant	3 (3.9)	15 (5.5)	52 (7.4)	0.36
HRS prior to transplant	7 (9.1)	6 (2.2)	31 (4.4)	0.03
Calculated medical MELD	19.7 (6-40)	17.2 (6-46)	20.2 (6-56)	<0.001
Donor characteristics				
Age, years	40 (11-64)	36 (12-61)	51 (9-86)	<0.001
Sex, male	51 (66)	113 (42)	398 (56)	<0.001
Median BMI, kg/m^2	24.4 (17-33)	26.6 (15-44)	26.3 (14-46)	0.003
Cause of death				0.02
Trauma	9 (11.7)	—	59 (8.4)	
Anoxia	21 (27.3)	—	146 (20.7)	
Cerebrovascular accident	25 (32.5)	—	408 (57.8)	
Other	8 (10.4)	—	70 (9.9)	
Warm ischemia time DCD, minutes	22.5 (9-33)	—	—	—
Warm ischemia time recipient, minutes	54 (24-86)	44 (15-148)	49 (12-556)	0.01
CIT, hours	5.7 (0.7-11.8)	1.4 (0.4-6)	7.3 (0.9-18.6)	<0.001
Intraoperative characteristics				
Blood loss, L	4 (0-19)	2.8 (0-16)	3 (0-44)	0.01
Transfusion of pRBC, units	4.7 (0-23)	4 (0-25)	4.1 (0-30)	0.52
Transfusion of >5 units of pRBC	23 (29.9)	62 (22.9)	189 (26.8)	0.32
Transfusion of cellsaver blood, mL	1000 (200-9280)	726 (139-7700)	519 (45-7500)	<0.001
Transfusion of FFP, units	7 (0-32)	5.3 (0-31)	6 (0-34)	0.02
Transfusion of platelets, units	5.5 (0-20)	3.2 (0-54)	3.8 (0-50)	0.01

NOTE: Data are given as n (%) or median (range).

Biliary complications were also classified as early-onset (within the first year after LT) and late-onset (≥1 year after LT) biliary complications.

STATISTICAL ANALYSIS

Data were expressed as mean ± standard deviation when a normal distribution of data was identified or median (range) in the case of a nonnormal distribution. The analysis of variance test was used to compare numerical variables between the 3 study groups. The chi-square test was used for categorical variables to compare groups. Survival rates were estimated by the Kaplan-Meier method and compared by log-rank test. $P < 0.05$ was considered statistically significant. Patient and graft survival was calculated from the time of LT. Cox survival analysis was performed to assess the effect of type of donor adjusted for the following confounders: recipient sex and age, disease-specific parameters, MELD score, donor sex and age, and parameters related to the transplantation procedure. Possible effects from the type of donor were tested by including interaction terms between type of donor with confounders. In addition, a sensitivity analysis was performed in the subgroups of high-risk patients. Statistical analysis was performed with SPSS, version 23.0 (SPSS, Chicago, IL).

Results

Between January 2009 and April 2017, 1054 patients who fulfilled the inclusion criteria underwent transplantation at the University of Toronto. Of these, 77 patients received a DCD graft (DCD group); 271 received a LD graft (LD group); and 706 received a DBD graft (DBD group).

Recipient and donor characteristics are presented in Table 1. Patients in the LD group were more likely female and younger. Primary sclerosing cholangitis (PSC) and primary biliary cirrhosis (PBC) as the indication for transplantation were less common in the DCD group ($P < 0.001$). The calculated MELD at transplant was slightly lower in the LD group, and similar numbers of patients were admitted to the intensive care unit (ICU) prior to transplantation in all 3 groups ($P = 0.36$). The median (range) of WIT for the DCD group was 22 minutes (9-33 minutes).

TABLE 2. Posttransplant Outcomes Were Compared Between Recipients From the DCD Group, LD Group, and DBD Group

	DCD Group (n = 77)	LD Group (n = 271)	DBD Group (n = 706)	*P* Value
Length of hospital stay, days	13 (6-140)	11 (4-161)	13 (2-384)	0.13
Length of stay the ICU, days	1 (0-21)	1 (0-66)	1 (0-45)	0.69
Peak AST (U/L)	1782 (125-25,387)	444 (30-2529)	1041 (30-19,614)	<0.001
AST at 7 days	54 (14-1239)	59 (12-974)	55 (10-3525)	0.79
Total bilirubin, μmol/L				
7 days	35 (9-354)	50 (4-380)	37 (7-565)	0.30
6 months	14 (4-460)	10 (0.3-522)	10 (0.5-471)	0.35
12 months	13 (4-313)	11 (3-675)	11 (2-339)	0.30
ALP (U/L)				
6 months	128 (28-2094)	150 (48-2728)	112 (38-1374)	<0.001
12 months	118 (30-1152)	139 (42-1186)	115 (23-1632)	0.001
INR at 12 months	1 (0.9-3.2)	1 (0.8-4.6)	1 (0.12-3.6)	0.60
Postoperative complications				
Any complication	54 (70)	176 (65)	447 (63)	0.48
More than 1 complication	30 (39)	85 (31.4)	232 (32.9)	0.46
Postoperative CCI, mean ± standard deviation	28.2 (± 24)	22 (± 22)	22.6 (± 23)	0.09
Postoperative CCI >60	6 (7.8)	15 (5.5)	37 (5.2)	0.65
Clavien-Dindo classification				
3a	3 (3.9)	23 (8.5)	52 (7.4)	0.40
3b	19 (24.7)	48 (17.7)	91 (12.9)	0.01
4a	9 (11.7)	22 (8.1)	71 (10.1)	0.54
4b	2 (2.6)	5 (1.8)	20 (2.8)	0.68
5	3 (3.9)	6 (2.2)	19 (2.7)	0.72
Complication grade ≥3b	32 (42)	78 (29)	199 (28)	0.049
Acute renal failure	7 (9.1)	9 (3.3)	35 (5)	0.11
Rejection within 1 month	7 (9)	29 (11)	83 (12)	0.73
Rejection follow-up	17 (22)	67 (25)	185 (26)	0.69
Retransplantation	3 (3.9)	10 (3.7)	8 (1.1)	0.02
Early <30 days	2 (2.6)	5 (1.8)	2 (0.3)	0.01
Late ≥30 days	1 (1.3)	5 (1.8)	6 (0.8)	0.42
Causes of retransplantation				0.42
HAT	0 (0.0)	6 (60)	3 (37.5)	
Biliary complications	1 (33.3)	2 (20)	1 (12.5)	
Chronic rejection	1 (33.3)	1 (10)	2 (25)	
PNF	1 (33.3)	1 (10)	2 (25)	

NOTE: Data are given as n (%) or median (range), unless otherwise noted.

OPERATIVE CHARACTERISTICS

Significant differences were observed in the type of biliary anastomosis performed in each group: DCD group with 93.4% duct-to-duct and 6.6% HJ versus the LD group with 48% duct-to-duct and 52% HJ versus the DBD group with 87.1% duct-to-duct and 12.9% HJ ($P < 0.001$).

Intraoperative administration of blood products and blood loss at the time of LT is shown in Table 1. There was a significantly higher intraoperative blood loss and transfusion of blood products in the DCD group compared with the LDLT and DBD groups.

Posttransplant Outcomes

The median follow-up after LT was longer in the LD group (46 months; range, 0.06-99 months) versus the DBD group (40 months; range, 0-99 months) versus the DCD group (35 months; range, 0.6-99 months; $P = 0.04$). The posttransplant outcomes are summarized in Table 2. The length of hospital stay was similar between the groups. The median peak AST levels were higher in the DCD group (DCD versus LD versus DBD = 1782 versus 444 versus 1041 U/L, respectively; $P < 0.001$). However, the AST levels at day 7 as well as the total bilirubin levels after 7 days, after 6 months, and after 12 months were comparable between the 3 groups. ALP values at 6 months were higher in the LD group and remained higher at 12 months.

GENERAL COMPLICATIONS

There were no significant differences in the proportion of patients with any complications, with more

TABLE 3. Biliary Complications, Type of Biliary Complications, and Treatment of Biliary Complications Compared Between Recipients From the DCD Group, LD Group, and DBD Group

	DCD Group (n = 77)	LD Group (n = 271)	DBD Group (n = 706)	*P* Value
Any biliary complication	4 (5.2)	32 (11.8)	34 (4.8)	<0.001
Biliary leak	0 (0)	17 (6.3)	7 (1)	<0.001
Leak alone	0 (0)	10 (3.7)	7 (1)	
Leak and stricture	0 (0)	7 (2.6)	—	
Treatments of biliary leaks alone				0.62
No treatment	—	1 (0.4)	—	
Percutaneous drainage	—	3 (1.1)	2 (0.3)	
Laparotomy (drain or HJ)	—	6 (2.2)	5 (0.7)	
Biliary stricture	4 (5.2)	22 (8.1)	27 (3.8)	0.02
Focal stricture	2 (2.6)	21 (7.7)	14 (2)	<0.001
Diffuse strictures	2 (2.6)	1 (0.4)	13 (1.8)	0.18
Early-onset stricture (<1 year)	4 (5.2)	15 (5.5)	23 (3.3)	0.42
Late-onset stricture (≥1 year)	—	7 (2.6)	4 (0.6)	
Treatments of biliary strictures				0.03
No treatment	1 (1.3)	—	4 (0.6)	
ERCP	1 (1.3)	6 (2.2)	15 (2.1)	
PTC	—	6 (2.2)	5 (0.7)	
Laparotomy (HJ)	1 (1.3)	8 (3)	1 (0.1)	
Retransplantation	1 (1.3)	2 (0.7)	2 (0.3)	

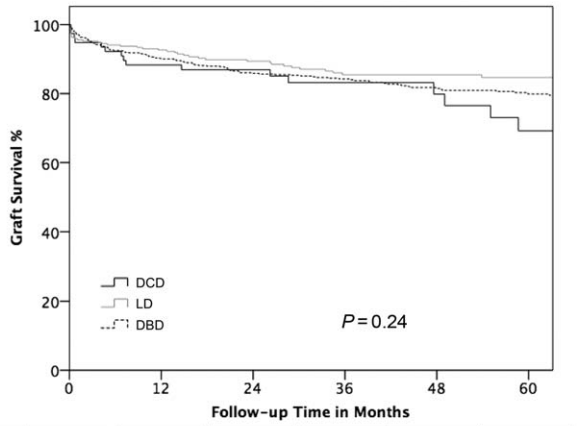
NOTE: Data are given as n (%).

than 1 complication, or with complications classified as Clavien-Dindo ≥3a between groups (Table 2). However, there were significantly more complications classified as Clavien-Dindo 3b in the DCD group (24.7%) compared with the LD group (17.7%) and the DBD group (12.9%; $P = 0.01$). Severe complications (classified as Clavien-Dindo ≥3b) were more common in the DCD group (42%) versus the LD and the DBD group (29% and 28%, respectively; $P = 0.049$). Nevertheless, analyzing the CCI revealed a similar score for the 3 groups (DCD versus LD versus DBD = 28.2 versus 22 versus 22.6; $P = 0.09$) and a comparable rate of patients with a CCI > 60 ($P = 0.65$) during hospital admission. Additionally, the rate of patients with acute renal failure and postoperative rejection was comparable between the groups. The proportion of patients needing retransplantation in the first 30 days after transplantation was higher in the DCD group (n = 2, 2.6%) and the LD group (n = 5, 1.8%) than in the DBD group (n = 2, 0.3%; $P = 0.01$). There was no difference between the groups in the retransplantation rate 30 days after transplantation ($P = 0.42$). The cause of retransplantation was mostly hepatic artery thrombosis (HAT) in the LD group (n = 6 out of 10) and the DBD group (n = 3 out of 8), whereas the reasons for retransplantation in the DCD group were biliary complication, chronic rejection, and primary nonfunction (PNF; n = 1 each).

BILIARY COMPLICATIONS

Overall biliary complications were higher in the LD group (11.8%) compared with the DCD group (5.2%) and to the DBD group (4.8%; $P < 0.001$; Table 3). The rate of leaks was higher in the LD group (6.3%) compared with the DBD group (1%) and the DCD group (0%; $P < 0.001$). Only 4 (5.2%) patients in the DCD group developed biliary strictures compared with 22 (8.1%) patients in the LD group and 27 (3.8%) patients in the DBD group ($P = 0.02$). Treatment of biliary complications is reported in Table 3. One patient in the LD group had a bile leak that was not treated due to the fact that the patient had a drain in place at the time of surgery.

The time to the development of biliary strictures was longer in the LD group (median 7 months, range 0.8-71) compared with the DCD group (median, 4 months; range, 2.4-10) and to the DBD group (median, 4 months; range, 0.1-19) without reaching statistical significance ($P = 0.08$). The rate of late-onset biliary strictures (≥1 year) was 31.8% in the LD group (7/22) compared with 0% in the DCD group and 14.8% in the DBD group (4/27; $P = 0.42$). The 1-, 3-, and 5-year cumulative risk of developing biliary strictures was 5.5%, 5.5%, and 5.5% in the DCD group compared with 5.8%, 11.1%, and 13.3% in the LD group and 3.7%, 4.4%, and 4.7% in the DBD group, respectively ($P = 0.001$).



DCD	77	66	50	36	23	16
LD	271	243	200	154	126	86
DBD	706	602	471	370	297	215

FIG. 1. Graft survival rates as analyzed by Kaplan-Meier estimation and compared between recipients who have received a DCD graft (black line) versus a LD graft (gray line) versus a DBD graft (black dotted line). Patients at risk are shown in the table below the graph.

DONOR OUTCOMES

Within the LD group, 271 hepatectomies were performed in 271 healthy donors. Postoperative mortality was 0. The overall morbidity rate in these patients was 15.7% (36 patients). Only 4.8% (11 patients) suffered a serious complication classified as Clavien-Dindo $\geq$3b.

PATIENT AND GRAFT SURVIVAL

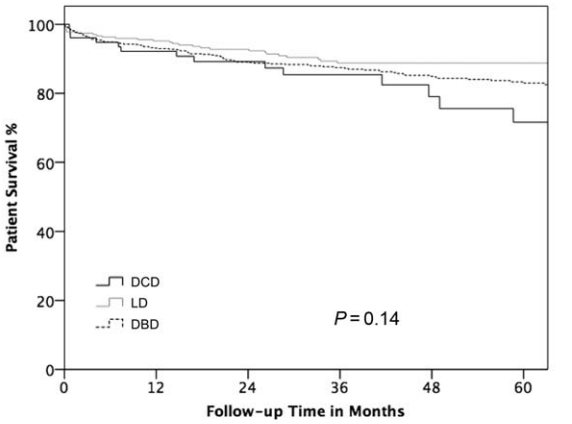
The 1-, 3-, and 5-year graft survival was 88.3%, 83.2%, and 69.2% in the DCD group versus 92.6%, 85.4%, and 84.7% in the LD group versus 90.2%, 84.2%, and 79.9% in the DBD group ($P = 0.24$; Fig. 1). The 1-, 3-, and 5-year patient survival was 92.2%, 85.4%, and 71.6% in the DCD group versus 95.2%, 88.8%, and 88.8% in the LD group versus 93.1%, 87.5%, and 83% in the DBD group ($P = 0.14$; Fig. 2).

Multivariate Cox regression analysis for graft survival was performed adjusting for factors with differences in the basic recipient and donor characteristics: donor age, sex, body mass index (BMI), and CIT and recipient age, sex, BMI, indication for LT, and MELD score. Furthermore, pretransplant ICU stay, WIT, intraoperative use of blood products, peak AST, biliary complication, posttransplant acute renal failure, CCI, and year of transplant were included in the analysis. The type of graft did not show a significant impact on posttransplant graft survival in the multivariate regression analysis (DCD versus LD: hazard ratio [HR], 0.79; 95% confidence interval [CI], 0.42-1.47; $P = 0.45$; DCD versus DBD: HR, 0.86; 95% CI, 0.48-1.5; $P = 0.59$). The only factors that showed significant influence on graft survival were the posttransplant CCI (HR, 1.02; 95% CI, 1.01-1.03; $P < 0.001$) and a categorized posttransplant CCI of more than 60 (HR, 3.59; 95% CI, 2.05-6.2; $P < 0.001$). Furthermore, this finding was not affected after testing for effect modification of type of graft via MELD score, peak AST and CCI of >60 and CCI as a continuous variable (all P values > 0.05). Sensitivity analyses of the subgroups of high-risk patients (patients with a CCI of >60 and patients with complications $\geq$3b) showed similar results.

Discussion

This study compares outcomes following orthotopic LT using DCD, DBD, and LD grafts. Our analysis indicates that carefully selected LDLT, DCD LT, and DBD LT provide similar results in a single-center academic institution. The proportion of patients being transplanted with DCD and LDLT grafts has been steady but low in North America.[19] Our data suggest that access to LT could be improved without compromising recipient outcomes by increasing the use of these alternatives to DBD LT.

The proportion of patients transplanted with DCD grafts varies widely between transplant centers,[9,20-23] currently accounting for 6% for all of the programs in the United States. At the University of Toronto, 15% of all LTs are performed using DCD grafts. Our main concern when starting our programs was the potential for increased rates of PNF and ischemic-type biliary strictures compared with DBD grafts.[5,6] Early studies had reported poorer outcomes of DCD grafts, with 3- and 5-year graft survival rates of only 50% and 40%, respectively.[23,24] However, with some refinements of the surgical management,[9,25] we are now achieving longterm graft survival rates between 70% and 80%, which are identical to our outcomes using DBD grafts. In a recently published study, Laing et al. used a propensity score–matched analysis to compare outcomes after LT with DCD versus DBD grafts (n = 187, each).[26] They reported comparable graft and patient survival in both groups, however, with significantly higher rates of ischemic cholangiopathy in DCD



DCD	77	68	50	36	23	16
LD	271	249	206	158	128	87
DBD	706	609	474	373	300	217

FIG. 2. Patient survival rates have been analyzed by Kaplan-Meier estimation and compared between recipients who have received a DCD graft (black line) versus a LD graft (gray line) versus a DBD graft (black dotted line). Patients at risk are shown in the table below the graph.

recipients (9.1% versus 1.1%; $P < 0.001$).[26] Notably, since implementing a DCD protocol including donor heparinization, minimization of CIT, and administration of intrahepatic tPA around the time of portal reperfusion, we have observed only 1 case of diffuse ischemic cholangiopathy leading to graft failure and only 1 case of PNF in 77 DCD LT recipients. Blok et al. recently published on longterm outcomes of DCD versus DBD LT in the Eurotransplant region.[27] With 126 DCD and 1264 DBD LTs performed between 2003 and 2007, the authors reported comparable long-term patient survival ($P = 0.59$).[27] Nevertheless, graft survival at 5 years was significantly lower in DCD recipients (54.4%) compared with DBD recipients (65.6%; $P = 0.02$).[27] Similar results were recently reported by a group in the Netherlands, evaluating DCD versus DBD LT from 2001 to 2015 (n = 115 and 326, respectively).[17] The authors of this series reported similar patient survival but lower graft survival in the DCD group compared with the DBD group at 5 years (60% versus 75%; $P = 0.002$).[17] Additionally, this group evaluated the CCI as a measure of the entire burden of postoperative morbidity up to 6 months after LT. They found a significantly higher median CCI at 6 months after LT in DCD recipients, and they additionally reported a higher number of patients undergoing retransplantation because of ischemic-type biliary strictures in the DCD group.[17] The DCD group in the currently presented study cohort reached a graft survival of 69.2% at 5 years, and there was no difference comparing the graft survival between the DCD, the LD, and the DBD group ($P = 0.24$). Furthermore, all 3 groups compared in this study showed similar CCI scores ($P = 0.09$). The CCI in our cohort during patient admission was lower compared with the CCI reported from the group in the Netherlands (posttransplant CCI during hospital admission: Toronto, DCD 28.2 versus DBD 22.6; Netherlands, DCD 38.2 versus DBD 36.7).[17] Nevertheless, in our cohort, recipients of DCD grafts experienced more often a Clavien-Dindo grading $\geq$3b complication compared with the LD and the DBD group (42% versus 29% versus 28%, respectively; $P = 0.049$). It is also important to highlight that the overall risk in DCD transplantation might be lower in our center because of strict recipient selection policies looking for uncomplicated hepatectomies. Muller et al. recently defined benchmark cutoffs for morbidity parameters in LT by selecting low-risk cases with an ideal donor-recipient match and comparing the results to higher-risk groups.[28] Comparing our results with the described benchmark values revealed a CCI at discharge and proportion of patients with complications $\geq$3b within the cutoffs for LT in all 3 groups (reported cutoffs: CCI at discharge $\leq$29.6 and grade III complications $\leq$42%).[28]

Centers performing LDLT have generally reported excellent outcomes with 5-year graft survival rates of 80%-90%.[8,29,30] LDLT has been extensively used in Asia but currently only accounts for 3.7% of adult LTs in the United States. The widespread adoption of LDLT has been hindered by concerns about morbidity and mortality in a healthy donor.[30] Our data show, however, that this option can be offered with low rates of donor morbidity. In over 650 patients, we have had no donor deaths and no major permanent morbidity while achieving transplant outcomes similar to the results of deceased donor grafts. In the LD group, 12% of the patients experienced biliary complications, and only 8% developed a biliary stricture during follow-up. This low rate is probably explained by the growing experience at our center with more than 500 adult-to-adult LDLTs performed since 2000.[8] In a previous report of patients receiving LDLT between 2000 and 2010, we diagnosed a biliary stricture rate of 19.5%. Therefore, the rate of strictures has decreased since then.[31] Overall, the biliary complication rate at our center is low compared with results reported in the Adult-to-Adult Living Donor Liver Transplantation

Cohort Study (probability for leaks 26% and for strictures 32%).[32] Additionally, the rates are comparable to those of large Asian centers, where biliary complications have been described in a range between 15%[33] and 35%.[34-36]

Recipient characteristics were slightly different between recipients of different types of grafts. The MELD score was lower in the LD group compared with the other groups. We offer LDLT to all patients on the waiting list,[37,38] but those with a lower MELD—with lower chance of attracting a deceased donor organ offer—get transplanted with a LD graft more often. DBD grafts, in contrast, are always offered to the patients with the highest MELD score on the list. We generally decline DCD graft offers to recipients with an expected prolonged hepatectomy time, such as retransplantations. The latter policy probably explains why the CIT within the DCD group was shorter compared with the CIT for DBD grafts in our series.

Additionally, donor characteristics were slightly different between groups: the DCD and LD groups were younger. When selecting LD candidates, we will choose a younger donor when there are multiple applicants.[13] Our current upper age limit for living liver donation is 60 years. Over time, the DCD donor age has increased (data not shown). A study analyzing the impact of DCD donor age on outcome after LT has reported that DCD grafts from >45-year-old donors can be used safely, resulting in comparable outcome after LT with DBD grafts.[25] Nevertheless, according to an analysis of the United Network for Organ Sharing (UNOS) database by Scalea et al., DCD organs from donors <50 years of age with <6 hours CIT show significantly superior graft survival compared with recipients from DBD donors ≥60 years old.[39] Interestingly, besides a reported increase of LT performed with DCD livers according to the UNOS database, 133 (27%) of DCD grafts were discarded in 2014, with the majority of donors being <50 years old.[39] The main reason for the discard of those livers was the WIT. Our current upper age limit for DCD donors is 65 years. However, the risks and benefits for transplanting a DCD organ are evaluated on a recipient-by-recipient basis. A recently published study on older DCD donors supports this strategy.[40] Schlegel et al. analyzed the outcomes of 315 patients with DCD LT, comparing donors with >60 years to those with ≤60 years, and found no impact of donor age on patient and graft survival.[40]

Compared with DBD and LD grafts, DCD grafts had evidence of an increased ischemia/reperfusion injury due to the warm ischemic injury suffered by the graft from withdrawal of life support until perfusion of the organs and cooling.[41] In our series, we observed 2 possible consequences of increased preservation injury. First, the peak AST level within 24 hours was higher in this group of patients, even though it normalized within the early postoperative period. It has been previously reported that high AST levels after transplantation can correlate with worse patient and graft outcome.[42,43] Second, there was a higher rate of blood loss in the DCD group. This might be explained either by the inhibition of the clotting cascade during reperfusion injury and the injection of tPA at the time of reperfusion to prevent microvascular thrombosis or a low-grade disseminated intravascular coagulation.[11] Transfusion rates of fresh frozen plasma (FFP), platelets, and autologous blood were higher in the DCD group compared with the LDLT and DBD groups. Furthermore, the rate of patients with postoperative complications rated Clavien-Dindo 3b was higher in the DCD group versus the LDLT and DBD groups (22% versus 14% versus 12%; $P = 0.045$). Besides those drawbacks, the type of graft used did not negatively impact the overall graft and patient survival. Similarly, there was no influence of the type of graft on graft survival investigated in a multivariate Cox regression model adjusted for confounding factors. In contrast to reports from other centers, DCD grafts did not have higher rates of biliary complications.[20,41,44-46] In our study, <3% of the DCD recipients developed diffuse biliary strictures, and only 1 patient required a liver retransplantation for biliary complications.

In our series, the outcomes of DCD and LDLT groups were both comparable to the DBD control group. Accordingly, we believe that institutions with a LDLT program should also have a DCD program in place to optimize the donor pool and minimize potential harm to LDs. Nevertheless, there are several scenarios when LDLT offers advantages over DCD and DBD LT. In particular, patients with a low MELD score are unlikely to attract a graft from DCD or DBD donors and often can only proceed with living donation. Similarly, LDLT can be offered to recipients before they become critically ill and the chances of a successful transplantation decline or they are delisted for disease progression. We also believe that LDLT is an excellent option for patients with fulminant liver failure, when LDLT can be performed after a rapid donor evaluation with minimal waiting time.[38] When comparing these 3 types of transplantation, there is a selection bias as patients are different between groups.

Nevertheless, these data provide "real-world" data indicating that all these grafts may have adequate outcomes in recipients who are adequately selected.

This study has several limitations. First, this study is based on a retrospective data analysis. Furthermore, we have not compared the costs of the different types of grafts with their slightly different resource requirements and complication profiles. However, only a few centers worldwide perform LT with grafts from DBD, LD, as well as DCD donors, and we therefore believe that our study cohort represents relevant information on excellent outcome using all 3 types of grafts.

In conclusion, DCD, LD, and DBD grafts result in similar patient and graft survival rates in the modern era. Increasing the use of LD and DCD grafts could improve access to LT without affecting longterm graft survival rates.

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