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# Long-Term Outcomes of Early Experience in Donation After Circulatory Death Liver Transplantation: Outcomes at 10 Years

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Data Interpretation D  
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\* Khalid Khwaja was able to review the manuscript but tragically died before submission of this manuscript. This manuscript was his original idea, which is why he remains senior author, and we submit this research in his honor

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**Background:** Donation after circulatory death (DCD) livers remain an underutilized pool of transplantable organs due to concerns of inferior long-term patient survival (PS) and graft survival (GS), which factors greatly into clinician decision-making and patient expectations.

**Material/Methods:** This retrospective study used SRTR data to assess 33 429 deceased-donor liver transplants (LT) and compared outcomes between DCD and donation after brain death (DBD) LT recipients in the United States. Data were collected from 2002 to 2008 to obtain 10 years of follow-up (2012-2018) in the era of MELD implementation. Propensity scores for donor type (DCD vs DBD) were estimated using logistic regression, and the association of donor type with 10-year outcomes was evaluated after adjustment using stabilized inverse probability of treatment weights.


**Results:** After adjusting for confounders, patient survival for DBD recipients at 10 years was 60.7% versus 57.5% for DCD recipients ( $P=0.24$ ). Incorporating retransplants, 10-year adjusted patient survival was 60.2% for DBD recipients versus 55.5% for DCD recipients ( $P=0.07$ ). Adjusted 10-year graft survival for DBD recipients was 56.4% versus 45.4% for DCD recipients ( $P<0.001$ ). Surprisingly, however, 1 year after LT, DBD and DCD graft failure rates converged to 7.5% over the remaining 9 years.

**Conclusions:** These data reveal inferior 10-year DCD graft survival, but only in the first year after LT, and similar 10-year patient survival in DCD LT recipients compared to DBD recipients. Our results show the stability and longevity of DCD grafts, which should encourage the increased utilization of these livers for transplantation.

**Keywords:** **Graft Survival • Liver Transplantation • Outcome Assessment (Health Care) • Tissue and Organ Procurement • Tissue Survival • Transplantation Conditioning**

**Abbreviations:** **ASTS** – American Society for Transplant Surgeons; **CI** – confidence interval; **CIT** – cold ischemic time; **DBD** – donation after brain death; **DCD** – donation after circulatory death; **DHOPE** – dual hypothermic oxygenation machine perfusion; **GS** – graft survival; **HOPE** – hypothermic oxygenated perfusion; **IC** – ischemic cholangiopathy; **LT** – liver transplant; **MELD** – model for end-stage liver disease; **NMP** – normothermic machine perfusion; **OPTN** – Organ Procurement and Transplantation Network; **PS** – patient survival; **sIPW** – stabilized inverse probability of treatment weights; **SRTR** – Scientific Registry of Transplant Recipients; **SDs** – standardized differences; **SCS** – static cold storage; **WIT** – warm ischemic time

**Full-text PDF:** <https://www.annalsoftransplantation.com/abstract/index/idArt/930243>

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## Background

In the United States, over 13 000 patients are on the waiting list for a liver transplant (LT), while only 8896 LTs are performed annually [1]. This discrepancy between the supply and demand for organs continues to increase, and as a result, efforts to expand the donor pool are a central focus of the field. One solution to mitigate the liver organ shortage is the increased utilization of donation after circulatory death (DCD) livers [2,3].

DCD livers are procured for transplantation after diagnosed and confirmed cardio-respiratory death. In contrast to donation after brain death (DBD), in which donor organs are perfused via mechanical ventilation throughout the organ recovery process, DCD organs are procured under either controlled or uncontrolled donation conditions. In the former, the anticipated death of a donor prompts planned removal of life-sustaining measures, while in the latter, unexpected cardiopulmonary arrest followed by failed resuscitation leads to subsequent organ procurement [4]. In DCD organ donation, the lengthened time period from withdrawal of cardiopulmonary support until organ cooling via flush during the procurement operation – referred to as warm ischemic time (WIT) – is thought to decrease the quality of procured livers, causing higher rates of early allograft dysfunction and primary nonfunction [4].

Currently in the United States, only 12.1% of all LTs come from DCDs [5]. This practice is largely due to evidence that DCD livers may have worse long-term patient and graft survival compared to DBD livers, attributed to higher rates of biliary complications and ischemic cholangiopathy (IC) [2,6-9]. In addition, DCD grafts have increased rates of retransplantation and prolonged waitlist time for patients needing retransplants [10]. DCD LT has also been linked to end-stage renal disease [11].

However, recent evidence suggests that carefully selected DCD livers from younger donors have excellent outcomes, including better GS compared to DBD livers from older donors [10]. Outcomes may be comparable to DBD LT recipients, especially when IC can be prevented in DCD recipients [12]. In recent years, strategies have been developed to improve DCD LT outcomes, including minimizing cold ischemic time (CIT) and WIT, infusion of tissue plasminogen activator into the hepatic artery, and rapid donor organ removal protocols [10,13].

Additionally, the arrival of machine perfusion in the field of liver transplantation has greatly expanded the avenues to rescue marginal DCD livers for transplantation. Several normothermic machine perfusion (NMP) clinical trials have proven the benefits of recreating ex-vivo normothermic conditions for liver allografts, which are reflected in lower peak transaminase levels, reduced incidence of early allograft dysfunction, less hepatocellular graft injury, and equivalent clinical outcomes. The

magnitude of these benefits have been significantly greater for DCD liver allografts compared to DBD grafts [14-18].

Based on the current debate on DCD versus DBD LT outcomes (especially long-term) and the changing landscape of marginal allograft modification with machine perfusion, we conducted a large retrospective cohort study using national SRTR data to assess long-term outcomes from the early experience in DCD versus DBD liver transplantation. In February 2002, the use of the MELD score was implemented by UNOS nationwide to improve LT allocation, and as a result, we chose to assess 10-year DCD LT outcomes in the era of MELD implementation (2002-2008) to obtain follow-up data from 2012-2018.

Because studies have shown the majority of DCD LT graft failure occurs within the first year after transplant [2,8,19], we hypothesized that long-term follow-up data would reveal equivalent graft survival (GS) rates at 1 year after LT. Our second hypothesis was that as rates of retransplantation of DCD allografts decreased and clinical experience with DCD LT increased, long-term patient survival (PS) between DCD and DBD LT recipients would be comparable. Both these hypotheses assess the longevity and stability of DCD liver allografts in a large national cohort and have major implications for their increased utilization in clinical decision-making to mitigate the organ shortage in the United States.

## Material and Methods

### Patient Inclusion Criteria and Data Acquisition

This study used data from the SRTR. The SRTR data system includes data on all donors, wait-listed candidates, and transplant recipients in the United States, submitted by the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration, United States Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors. Transplant recipient baseline data were linked with deceased-donor data and recipient follow-up data within the SRTR database.

We identified adults ( $\geq 18$  years of age) who underwent a deceased donor, first-time, liver-only transplant between March 2002 and December 2008 to capture MELD score data with 10-year follow-up. Those who were missing data in the SRTR database on DCD versus DBD status (our main exposure), were excluded from our study cohort. The institutional review board at Beth Israel Deaconess Medical Center determined that the study met criteria for exempt status (Protocol #2019P000434).

## Statistical Analysis

We stratified the study cohort into DCD versus DBD recipients. Donor baseline characteristics were summarized as mean (standard deviation) or median (1<sup>st</sup> quartile and 3<sup>rd</sup> quartile) for continuous variables and counts (percentages) for categorical variables. To compare characteristics, we performed chi-squared tests for categorical variables, and *t* tests and Wilcoxon rank sum tests for normally and non-normally distributed data, respectively. To adjust for confounding, we utilized propensity score methods [20]. A propensity score was estimated using logistic regression with donor type as the outcome and all potential confounders as predictors. All covariates in the logistic regression were selected *a priori* and are presented in **Table 1**. Continuous variables were modeled flexibly using restricted cubic splines, which allows the model to fit non-linear relationships between predictor and outcome. We used the estimated probabilities from our logistic regression model to calculate stabilized inverse probability of treatment weights (sIPWs) [21]. The sIPWs were used to weight each patient's contribution to the survival analyses described below. Baseline characteristics in our reweighted cohort were evaluated using standardized differences (SDs) to assess for balance between DCD and DBD groups. After satisfactory covariate balance was determined, treatment effects were estimated. Our primary outcome was overall PS and our secondary outcome was GS.

## Patient Survival

To assess differences in overall PS, recipients were followed from date of first liver transplant until death from any cause. Retransplants and those lost to follow-up were initially censored. However, this approach potentially violated the assumption of non-informative censoring; therefore, we performed a sensitivity analysis in which recipients were followed until death from any cause, including retransplantation. Both analyses with retransplants censored and retransplants incorporated were reported. Finally, LT recipients lost to follow-up were censored in the analysis.

## Graft Survival

In this analysis, we only assessed graft failure for first-time liver transplantation. SRTR defines graft failure as failure from any cause, including need for retransplantation or death, even with a functioning graft [22]. Those lost to follow-up were censored.

Patients with greater than 10 years of follow-up data were administratively censored in all analyses. Overall survival, stratified by donor type, was estimated using the Kaplan-Meier method and after reweighting using sIPWs. Donor types were compared using the log-rank test. The association between

DCD and DBD with overall PS and GS was estimated using Cox proportional hazards regression models with reweighting using sIPWs; results were summarized using hazard ratios (HRs) with 95% confidence intervals (95% CIs). We used a robust variance estimator to account for the weights used during estimation [23]. Patients were excluded from survival analyses when missing recipient or donor characteristic information for any continuous variable. All tests were 2-sided and *P* values <0.05 were considered statistically significant. R version 3.6.3 (R Development Core Team, 2020) was used for all statistical analyses.

## Results

Our study cohort consisted of 33 429 deceased donors, of which 32 021 were identified as DBD donors and 1408 as DCD donors. DCD donors were younger (35.9 versus 41.5 years, *P*<0.001), more likely to be male (66.5% versus 59.5%, *P*<0.001), non-Hispanic white (85.9% versus 68.3%, *P*<0.001), non-smokers (70.1% versus 65.7%, *P*=0.003), had lower BMI (25.3 versus 25.7, *P*=0.022), and less likely to have a history of diabetes (7.3% versus 9.2%, *P*=0.049), hypertension (20.3% versus 32.1%, *P*<0.001), or prior myocardial infarction (2.7% versus 3.4%, *P*<0.001) compared to DBD donors. DCD donors were more likely to be CDC high risk (6.9% versus 5.5%, *p*<0.001), anti-cytomegalovirus negative (48.8% versus 33.9%, *P*<0.001), and hepatitis C negative (67% versus 60.7%, *P*<0.001) compared to their DBD donor counterparts (**Table 2**).

Regarding LT recipients, DCD LT recipients were more likely to be older (53.8 versus 52.7 years, *P*<0.001), non-Hispanic White (75.7% versus 72.5%, *P*=0.015), and anti-cytomegalovirus positive (60.7% versus 59.7%, *P*=0.001) and had lower INR (1.5 versus 1.6, *P*<0.001), creatinine (1.0 mg/dl versus 1.1 mg/dl, *P* = 0.01), and total bilirubin (3.0 mg/dl versus 3.5 mg/dl, *P*<0.001). The recipient groups did not have statistically significant differences in sex (30.8% female in DCD versus 32.3% female in DBD, *P*=0.22), BMI (27.6 kg/m<sup>2</sup> in DCD versus 27.4 kg/m<sup>2</sup> in DBD, *P*=0.65), or primary diagnosis of liver disease (encompassing all acute hepatic necrosis, cirrhosis, and hepatitis) (**Table 2**).

Of the 33 429 recipients who met the inclusion criteria, 4752 were excluded from subsequent analyses due to missing data. Following reweighting using sIPWs, the DCD and DBD groups were well-balanced. Compared to DBD donors, the reweighted DCD donor group was younger (mean donor age 40.3 years versus 41.4 years, SD 0.06), more likely to be female (43.2% versus 40.0%, SD 0.067), and had shorter mean CITs (6.7 h versus 7.0 h, SD 0.044). Compared to DBD recipients, the reweighted DCD recipient group was slightly younger (mean recipient age 52.7 years versus 52.9 years, SD 0.016). Both reweighted

**Table 1.** Liver transplant donor and recipient characteristics.

Characteristic	DBD (n=32 021)	DCD (n=1408)	P value
<b>Donor</b>			
Age in years, mean (standard deviation)	41.5 (17.5)	35.9 (14.9)	<0.001
Sex, Female, n (%)	12 963 (40.5)	472 (33.5)	<0.001
Race, n (%)			<0.001
Non-Hispanic white	21 866 (68.3)	1209 (85.9)	
Black	4 979 (15.6)	102 (7.2)	
Other	5 176 (16.2)	97 (6.9)	
BMI in kg/m <sup>2</sup> , median (q1-q3)	25.7 (22.7-29.4)	25.3 (22.3-29.3)	0.022
Cause of death, n (%)			<0.001
Anoxia	4 314 (13.5)	442 (31.4)	
Cerebrovascular/stroke	14 232 (44.4)	292 (20.7)	
Head trauma	12 677 (39.6)	592 (42.0)	
Other	798 (2.5)	82 (5.8)	
History of smoking, n (%)			0.003
Yes	10 639 (33.2)	406 (28.8)	
No	21 050 (65.7)	986 (70.1)	
Unknown	332 (1.0)	16 (1.1)	
History of diabetes, n (%)			0.049
Yes	2 954 (9.2)	103 (7.3)	
No	28 937 (90.4)	1 300 (92.3)	
Unknown	130 (0.4)	5 (0.4)	
History of hypertension, n (%)			<0.001
Yes	10 287 (32.1)	287 (20.3)	
No	21 511 (67.2)	1 119 (79.3)	
Unknown	223 (0.7)	5 (0.4)	
History of previous MI, n (%)			<0.001
Yes	1 087 (3.4)	38 (2.7)	
No	25 603 (80.0)	1 186 (84.2)	
Unknown	5 331 (16.6)	184 (13.1)	
Total cold ischemic time in hours, median (q1-q3)	7.0 (5.3-9.0)	7.0 (5.3-9.0)	0.33
CDC high risk			<0.001
Yes	1 867 (5.8)	98 (6.9)	
No	20 611 (64.4)	1093 (77.6)	
Unknown	9 550 (29.8)	217 (15.5)	
Anti-CMV status			<0.001
Positive	21 055 (65.8)	711 (50.5)	
Negative	10 816 (33.8)	687 (48.8)	
Unknown	150 (0.5)	10 (0.7)	
HCV antibody status			<0.001
Positive	928 (2.9)	15 (1.1)	
Negative	19 445 (60.7)	944 (67.0)	
Unknown	11 648 (36.4)	4 (32.0)	

**Table 1 continued.** Liver transplant donor and recipient characteristics.

Characteristic	DBD (n=32 021)	DCD (n=1408)	P value
<b>Recipient</b>			
Age in years, mean (standard deviation)	52.7 (10.0)	53.8 (9.6)	<0.001
Sex, Female, n (%)	10 354 (32.3)	433 (30.8)	0.22
Race, n (%)			0.015
Non-Hispanic white	23 204 (72.5)	1 066 (75.7)	
Black	2 887 (9.0)	123 (8.7)	
Other	5 930 (18.5)	219 (15.6)	
BMI in kg/m <sup>2</sup> , median (q1-q3)	27.4 (24.1-31.5)	27.6 (24.0-31.3)	0.65
Primary diagnosis			0.25
Biliary disease	2 803 (8.7)	109 (7.7)	
Liver disease	22 953 (71.6)	1 044 (74.0)	
Metabolic	872 (2.7)	29 (2.2)	
Tumor	4 405 (13.7)	185 (13.1)	
Other	988 (3.1)	41 (3.0)	
Blood type			<0.001
A	11 926 (37.2)	559 (39.7)	
B	4 304 (13.5)	153 (10.9)	
AB	1 684 (5.3)	46 (3.3)	
O	14 107 (44.1)	650 (46.1)	
INR, median (q1-q3)	1.6 (1.3-2.0)	1.5 (1.2-1.9)	<0.001
Serum creatinine in mg/dl, median (q1-q3)	1.1 (0.8-1.6)	1.0 (0.8-1.5)	0.01
Total bilirubin in mg/dl, median (q1-q3)	3.5 (1.8-8.1)	3.0 (1.6-6.0)	<0.001
Calculated model for end-stage liver disease (MELD) score, median (q1-q3)	17 (12-27)	15 (10-24)	
HCC exception			0.99
Yes	7 519 (23.5)	331 (23.5)	
No	24 502 (76.5)	1 077 (76.5)	
Anti-CMV status			0.001
Positive	19 129 (59.7)	854 (60.7)	
Negative	8 721 (27.2)	415 (29.5)	
Unknown	4 171 (13.0)	139 (9.9)	
Follow-up time in days, median (q1-q3)	3 477 (1068-3650)	3 053 (758-3650)	<0.001

recipient groups had the same frequency of primary diagnosis of liver disease (71.5%, SD 0.088) and median lab MELD score of 17 (Table 1).

### Patient Survival (PS)

Median follow-up time for recipients with complete data was 3250 (q1=839, q3=3650) days. During follow-up, a total 10 141 recipients died of any cause. Kaplan-Meier survival analysis of post-LT PS with 10-year follow up was conducted with both

unadjusted and reweighted data. With retransplants censored, the unadjusted overall PS for DBD liver recipients at 10 years was 60.1% (95% CI: 59.5%, 60.7%) versus 54.7% (95% CI: 51.9%, 57.7%) for DCD liver recipients ( $P=0.002$ ) (Figure 1A).

After reweighting by sIPW, the overall adjusted PS for DBD liver recipients with retransplants censored at 1, 3, 5, and 10 years was 88.6% (95% CI: 88.2%, 89.0%), 80.2% (95% CI: 79.7%, 80.7%), 74.1% (95% CI: 73.6%, 74.7%), and 60.7% (95% CI: 60.1%, 61.3%), respectively. The overall adjusted PS for DCD

**Table 2.** Liver transplant donor and recipient characteristics reweighted using stabilized inverse probability of treatment weights (sIPWs).

Characteristic	DBD (n=27 483)	DCD (n=1194)	SD*
<b>Donor</b>			
Age in years, mean (standard deviation)	41.4 (17.5)	40.3 (17.4)	0.06
Sex, Female, n (%)	10 977 (40.0)	515 (43.2)	0.067
Race, n (%)			0.078
Non-Hispanic white	18 918 (68.9)	812 (68.2)	
Black	4 228 (15.4)	213 (17.9)	
Other	4 293 (15.6)	166 (13.9)	
BMI in kg/m <sup>2</sup> , median (q1-q3)	25.7 (22.7-29.5)	25.3 (22.3-29.7)	0.035
Cause of death, n (%)			0.093
Anoxia	3 966 (14.5)	209 (17.6)	
Cerebrovascular/stroke	11 854 (43.2)	479 (40.3)	
Head trauma	10 892 (39.7)	467 (39.2)	
Other <sup>6</sup>	727 (2.6)	36 (3.0)	
History of smoking, n (%)			0.008
Yes	9020 (32.9)	395 (33.2)	
No	18 131 (66.1)	783 (65.8)	
Unknown	288 (1.1)	13 (1.1)	
History of diabetes, n (%)			0.048
Yes	2 542 (9.3)	94 (7.9)	
No	24 784 (90.3)	1 091 (91.6)	
Unknown	112 (0.4)	6 (0.5)	
History of hypertension, n (%)			0.039
Yes	8 753 (31.9)	375 (31.5)	
No	18 513 (67.5)	804 (67.5)	
Unknown	173 (0.6)	12 (1.0)	
History of previous MI, n (%)			0.091
Yes	937 (3.4)	59 (4.9)	
No	22 282 (81.2)	930 (78.1)	
Unknown	4 220 (15.4)	202 (17.0)	
Total cold Ischemic Time in hours, median (q1-q3)	7.0 (5.3-9.0)	6.7 (5.2-9.0)	0.044
CDC high risk			0.062
Yes	1 679 (6.1)	90 (7.5)	
No	18 294 (66.7)	795 (66.7)	
Unknown	7 465 (27.2)	306 (25.7)	
Anti-CMV status			0.046
Positive	17 867 (65.1)	773 (64.9)	
Negative	9 439 (34.4)	408 (34.2)	
Unknown	133 (0.5)	10 (0.9)	
HCV antibody status			0.037
Positive	792 (2.9)	38 (3.2)	
Negative	17 027 (62.1)	718 (60.3)	
Unknown	9 620 (35.1)	435 (36.5)	

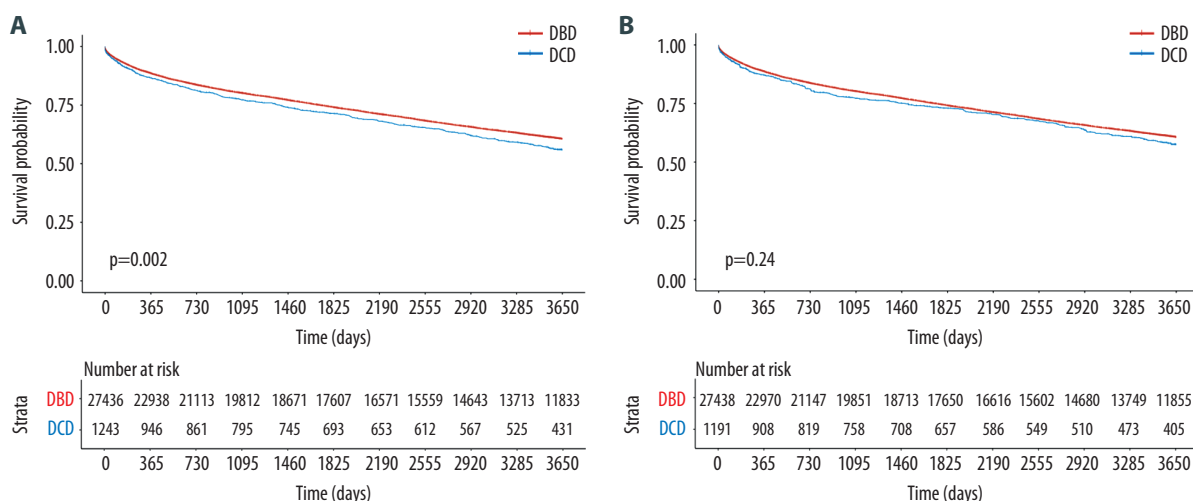
**Table 2 continued.** Liver transplant donor and recipient characteristics reweighted using stabilized inverse probability of treatment weights (sIPWs).

Characteristic	DBD (n=27 483)	DCD (n=1194)	SD*
<b>Recipient</b>			
Age in years, mean (standard deviation)	52.9 (10.0)	52.7 (9.8)	0.016
Sex, female, n (%)	8 820 (32.1)	417 (35.1)	0.062
Race, n (%)			0.029
Non-Hispanic White	20 001 (72.9)	883 (74.2)	
Black	2 433 (8.9)	102 (8.6)	
Other	5 005 (18.2)	205 (17.3)	
BMI in kg/m <sup>2</sup> , median (q1-q3)	27.4 (24.1-31.5)	27.1 (23.9-30.7)	0.079
Primary diagnosis			0.088
Biliary disease	2 416 (8.8)	126 (10.5)	
Liver disease	19 609 (71.5)	851 (71.5)	
Metabolic	724 (2.6)	29 (2.5)	
Tumor	3 914 (14.3)	145 (12.1)	
Other	776 (2.8)	40 (3.4)	
Blood type			0.099
A	10 224 (37.3)	431 (36.2)	
B	3 633 (13.2)	127 (10.6)	
AB	1 393 (5.1)	75 (6.3)	
O	12 118 (44.4)	558 (46.8)	
INR, median (q1-q3)	1.6 (1.3-2.0)	1.6 (1.3-2.0)	0.002
Serum creatinine in mg/dl, median (q1-q3)	1.1 (0.8-1.6)	1.1 (0.8-1.6)	0.002
Total bilirubin in mg/dl, median (q1-q3)	3.4 (1.7-7.9)	3.6 (1.8-7.7)	0.019
Calculated model for end-stage liver disease (MELD) score, median (q1-q3)	17 (11-27)	17 (12-26)	
HCC exception			0.068
Yes	6 504 (23.7)	248 (20.9)	
No	20 934 (76.3)	942 (79.1)	
Anti-CMV status			0.045
Positive	16 566 (60.4)	741 (62.2)	
Negative	7 660 (27.9)	323 (27.2)	
Unknown	3 212 (11.7)	126 (10.6)	

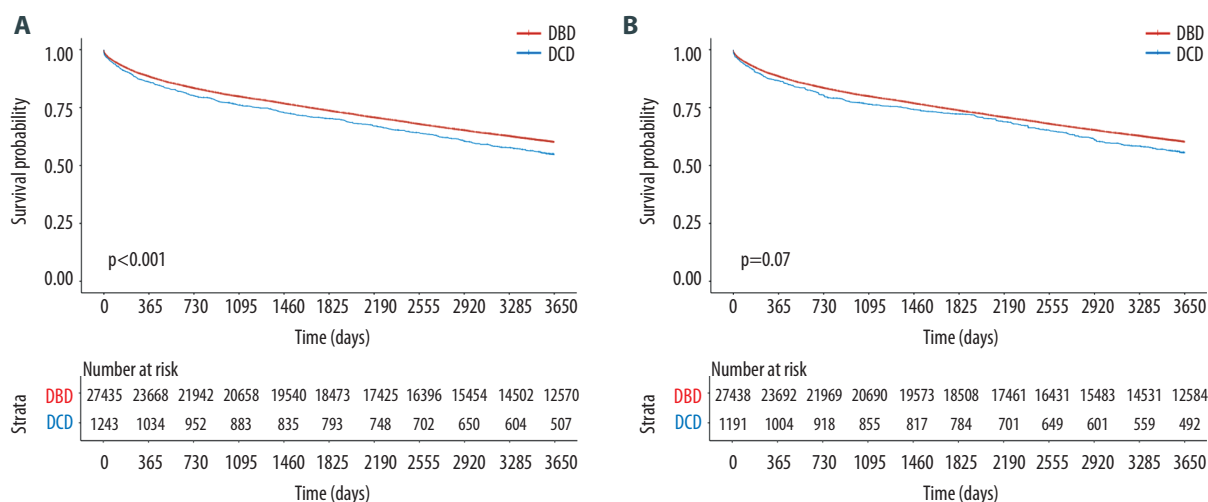
SD – standardized difference, \* a value <0.10 is considered well-balanced.

liver recipients with retransplants censored at 1, 3, 5, and 10 years was 87.1% (95% CI: 84.1%, 90.2%), 77.2% (95% CI: 73.3%, 81.3%), 73.0% (95% CI: 68.9%, 77.3%), and 57.5% (95% CI: 52.8%, 62.6%), respectively. Notably, there was no statistically significant difference in 10-year PS after reweighting by sIPW between DBD and DCD liver recipients ( $p=0.24$ ) (Figure 1B). In this analysis, the hazard ratio comparing overall PS between donor type was 1.11 (95% CI: 0.95, 1.29).

This analysis was repeated including all follow-up time and whether or not recipients were retransplanted. With retransplants incorporated, the unadjusted PS for DBD liver recipients at 10 years was 60.5% (95% CI: 59.9%, 61.1%) compared to 55.8% (95% CI: 52.8%, 59.0%) for DCD liver recipients ( $P<0.001$ ) (Figure 2A). After reweighting with sIPW, the overall adjusted PS for DBD liver recipients with retransplants incorporated at 1, 3, 5, and 10 years was 88.5% (95% CI: 88.1%, 88.8%), 79.8% (95% CI: 79.4%, 80.3%), 73.7% (95% CI: 73.2%, 74.2%), and 60.2% (95% CI: 59.6%, 60.8%), respectively. The overall adjusted PS for



**Figure 1.** Kaplan-Meier curves of patient survival stratified by DCD vs DBD liver transplant with retransplants censored in (A) unadjusted groups ( $P=0.002$ ) and (B) sIPW reweighted groups ( $P=0.24$ ).



**Figure 2.** Kaplan-Meier curves of patient survival stratified by DCD vs DBD liver transplant with retransplants incorporated in (A) unadjusted groups ( $P<0.001$ ) and (B) sIPW reweighted groups ( $P=0.07$ ).

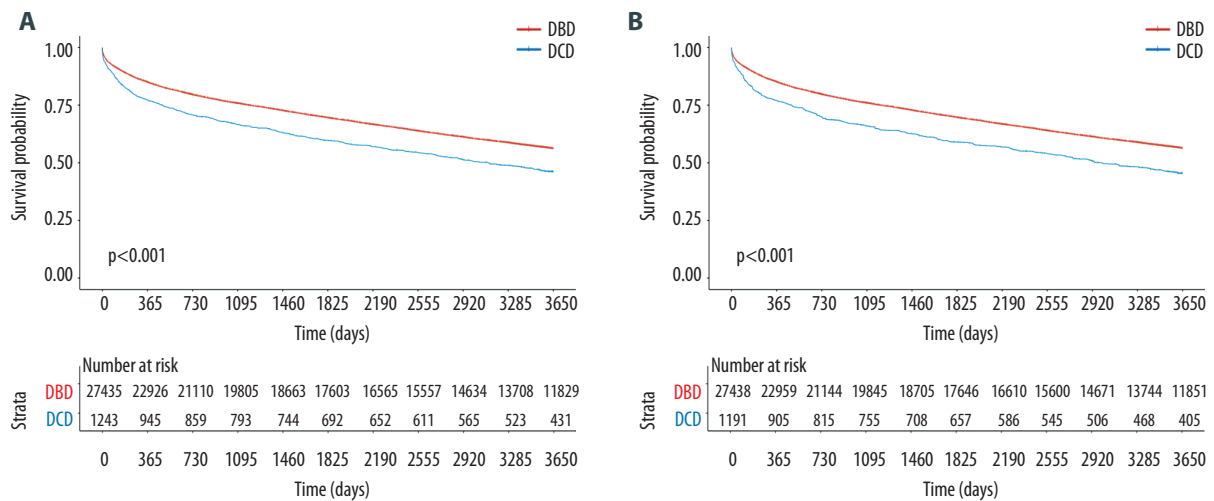
DCD liver recipients with retransplants incorporated at 1, 3, 5, and 10 years was 86.6% (95% CI: 83.7%, 89.6%), 76.4% (95% CI: 72.7%, 80.3%), 72.2% (95% CI: 68.3%, 76.3%), and 55.5% (95% CI: 51.1%, 60.4%), respectively. Notably, there was no statistically significant difference in 10-year PS after reweighting by sIPW, even with retransplants incorporated, between DBD and DCD liver recipients ( $P=0.07$ ) (Figure 2B). Similar to the primary overall PS analysis, the hazard ratio was 1.15 (95% CI: 1.00, 1.33).

### Graft Survival (GS)

Median follow-up time was 3246 (q1=838, q3=3650) days and a total of 11 996 patients had graft failure. The unadjusted

GS for DBD liver recipients at 10 years was 56.2% (95% CI: 55.6%, 56.8%) versus 46.1% (95% CI: 43.3%, 49.0%) for DCD liver recipients ( $P<0.001$ ) (Figure 3A). Following reweighting with sIPW, the adjusted GS for DBD livers at 1, 3, 5, and 10 years was 85.1% (95% CI: 84.7%, 85.5%), 76.0% (95% CI: 75.5%, 76.5%), 69.7% (95% CI: 69.2%, 70.3%), and 56.4% (95% CI: 55.8%, 57.0%), respectively. The adjusted GS for DCD livers at 1, 3, 5, and 10 years was 77.0% (95% CI: 73.4%, 80.8%), 65.9% (95% CI: 61.7%, 70.4%), 59.0% (95% CI: 54.5%, 63.8%), and 45.4% (95% CI: 40.9%, 50.4%), respectively. There was a statistically significant difference in 10-year GS between DCD and DBD livers ( $P<0.001$ ) (Figure 3B). The hazard ratio for this analysis was 1.42 (95% CI: 1.24, 1.62). However, reweighted GS





**Figure 3.** Kaplan-Meier curves of graft survival stratified by DCD vs DBD liver transplant in (A) unadjusted groups ( $p < 0.001$ ) and (B) sIPW reweighted groups ( $P < 0.001$ ).

Kaplan-Meier curves revealed that 36% of DCD and 29% of DBD graft failure cases occurred within the first year of LT. At 1 year after LT, the percentage of DBD and DCD graft failure cases converged at 7% and 8%, respectively, per year.

## Discussion

In 2019, there were 4000 fewer LTs than patients on the LT waitlist in the United States [1]. As the liver organ shortage persists, efforts to expand the organ pool must continue. Recent data have shown that DCD livers are a potential source of acceptable but underutilized organs [3], with evidence showing comparable graft and patient survival in well-selected recipients [10,12]. The arguments against these conclusions are that they derive from small, single-center cohort studies, or that the follow-up time of 1-5 years is insufficient. Our study addressed this gap by assessing long-term (10-year) DCD liver allograft stability on a national scale. We showed that 10-year PS was not statistically different based on early DCD LT experience compared to DBD LTs. It was previously thought that DCD LT recipients had higher rates of retransplantation, and retransplanted patients had worse outcomes [24]. While the latter remains true, the rate of DCD retransplantation drastically decreased over the years [25]. Thus, as the rates of retransplantation in DCD LT recipients decreased, overall PS of this group rose.

Other reasons for improved long-term DCD LT patient survival were better recipient and organ selection. In 2009, the American Society for Transplant Surgeons (ASTS) released guidelines for DCD LT, which included CIT less than 8 h, total WIT less than 30 min, and donor age younger than 55 years [26]. Adherence

to these guidelines leading to stricter allograft selection improved PS, decreased rates of graft nonfunction, and shortened post-operative hospital courses [27-29]. These clinical improvements were reflected in the results of this study, as incorporating retransplanted patients into survival analysis only decreased 10-year DCD PS by 2.0% compared to the retransplant-censored group.

Despite comparable PS, DCD livers were shown to have lower 10-year GS compared to DBD livers. However, the differences in 10-year GS between DCD and DBD livers were due to events in the first year after LT. We showed that DCD allografts that survived the first year had similar 10-year graft failure rates compared to their DBD counterparts, at 7-8% (Figure 3B). This result underscores the importance of assessing long-term outcomes in DCD liver allografts, as the problems with longevity are actually upfront. Additionally, the incorporation of machine perfusion technology in liver transplantation provides a platform to reduce graft failure in these organs. Schlegel et al demonstrated that hypothermic oxygenated perfusion (HOPE)-treated DCD liver allografts had significantly less biliary cirrhosis and fibrosis at 4 weeks after LT due to less reperfusion injury after machine perfusion [30]. The same group demonstrated HOPE livers had longer 5-year GS due to less primary nonfunction and IC compared to static cold storage (SCS) DCD allografts [31]. Dual hypothermic oxygenation machine perfusion (DHOPE)-treated DCD livers also had similar improvements in 6 and 12 month GS and biliary complications [32]. Finally, NMP has been shown to improve GS in DCD allografts. Op Den Dries et al revealed that NMP provided superior preservation of bile duct endothelial cell function in DCD livers compared to allografts preserved with SCS [33]. Additionally, Liu et al indicated that NMP reduced biliary complications after LT by

enhancing regeneration of biliary epithelial cells [34]. These studies signify that machine perfusion has the potential to address the Achilles heel of DCD LT: high rates of graft failure within the first year of LT secondary to IC and biliary complications. Our data shows that if the recent assimilation of machine perfusion in clinical practice can alleviate these early biliary problems within the first year of transplant, the long-term stability of DCD allografts is comparable to DBD livers.

The findings of this study have major clinical and policy implications. This analysis of the early experience with DCD liver transplantation revealed that DCD donors were younger and healthier, with fewer comorbidities, than DBD donors. DCD LT recipients were older and had lower median MELD scores (15 versus 17). Thus, the clinical practice trend was transplanting DCD livers in older but relatively healthy recipients, and transplanting DBD livers (which comprise the majority of LTs) into younger patients who had longer life expectancies, or sicker recipients who could not physiologically tolerate DCD liver allografts [35,36]. Our data suggest that this clinical practice can be expanded with increased utilization of DCD livers in well-selected LT patients without compromising long-term PS. Additionally, machine perfusion of DCD liver allografts can now mitigate the high rates of graft failure in these organs. Thus, while the field of LT has gained tremendous clinical experience with DCD livers over the past decade, currently only 12.1% of all LTs come from DCD donors [5], suggesting that transplantable DCD livers are being underutilized.

This study is not without limitations. Despite using a large national transplant database, analysis of biliary tract complications and graft failure reasons were limited due to missing data. Biliary complications were unknown in 82% of DCD LT recipients and 90% of DBD LT recipients, and graft failure reason was unknown in 93% of LTs. Thus, despite the statistical significance of differences between these 2 recipient pools, the large percentages of unknown data due to lack of a United Network for Organ Sharing reporting requirement made these findings null. As a result, the majority of literature on IC and graft failure reasons in DCD versus DBD LT is confined to single-center studies. Statistical issues with lack of power in SRTR data have prompted a call for standardization of transplantation metrics nationwide [37].

## Conclusions

In conclusion, our study demonstrated long-term stability of DCD liver allografts. Results showed that 10-year PS was comparable between the early experience in DCD LTs compared to DBD LTs, even after incorporating retransplants. We suspect these findings were due to the decreased rate of retransplantation in DCD LTs secondary to improved organ and patient selection and shorter ischemic times. DCD liver recipients had an 11% lower 10-year GS compared to DBD LTs, but at 1 year after LT, the long-term graft failure rates were equivalent. These data show that clinical experience with DCD LT has increased and with the advent of machine perfusion technology to tackle early biliary complications, the time for increased DCD liver utilization yielding good long-term patient outcomes has arrived.

## SRTR Disclaimer

The data reported here have been supplied by the Hennepin Healthcare Research Institute as the contractor for the Scientific Registry of Transplant Recipients (SRTR). The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy of or interpretation by the SRTR or the U.S. Government.

## Data Availability

The authors declare that the data supporting the findings in this paper are available and if needed, can be provided upon request.

## Conflict of Interest

None.

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