Clinical Implications of Donor Warm and Cold Ischemia Time in Donor After Circulatory Death Liver Transplantation

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The use of donation after circulatory death (DCD) liver allografts has been constrained by limitations in the duration of donor warm ischemia time (DWIT), donor agonal time (DAT), and cold ischemia time (CIT). The purpose of this study is to assess the impact of longer DWIT, DAT, and CIT on graft survival and other outcomes in DCD liver transplants. The Scientific Registry of Transplant Recipients was queried for adult liver transplants from DCD donors between 2009 and 2015. Donor, recipient, and center variables were included in the analysis. During the study period, 2107 patients underwent liver transplant with DCD allografts. In most patients, DWIT and DAT were <30 minutes. DWIT was <30 minutes in 1804 donors, between 30 and 40 minutes in 248, and >40 minutes in 37. There was no difference in graft survival, duration of posttransplant hospital length of stay, and readmission rate between DCD liver transplants from donors with DWIT <30 minutes and DWIT between 30 and 40 minutes. Similar outcomes were noted for DAT. In the multivariate analysis, DAT and DWIT were not associated with graft loss. The predictors associated with graft loss were donor age, donor sharing, CIT, recipient admission to the intensive care unit, recipient ventilator dependence, Model for End-Stage Liver Disease score, and low-volume transplant centers. Any CIT cutoff >4 hours was associated with increased risk for graft loss. Longer CIT was also associated with a longer posttransplant hospital stay, higher rate of primary nonfunction, and hyperbilirubinemia. In conclusion, slightly longer DAT and DWIT (up to 40 minutes) were not associated with graft loss, longer posttransplant hospitalization, or hospital readmissions, whereas longer CIT was associated with worse outcomes after DCD liver transplants.

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Because of the shortage of liver allografts, mortality rates for patients on the liver transplantation waiting list are still significant.[1,2] Donation after circulatory death (DCD) allografts have been used to mitigate organ shortage and death on the waiting list.[3] However, DCD liver allografts have been considered increased-risk organs because of posttransplant complications and slightly worse outcomes compared with organs from brain-dead donors.[4-9] Many transplant centers have been selective in the evaluation of DCD donors in order to improve their outcomes. One of the criteria used in the selection of DCD donors is the donor warm ischemia time (DWIT), which has been defined as the time from the withdrawal of life support to the in situ aortic cold perfusion. Many centers consider the donor agonal time (DAT) a better predictor of clinical outcomes after DCD liver transplantation.[5] DAT (also called functional DWIT) has been defined as the time starting at a specific donor blood pressure or oxygen saturation (SaO_2) after withdrawal of support and ending at the in situ aortic cold perfusion. However, different centers proposed different donor

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; CIT, cold ischemia time; DAT, donor agonal time; DCD, donation after circulatory death; DRI, donor risk index; DWIT, donor warm ischemia time; GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; ICU, intensive care unit; IQR, interquartile range; MELD, Model for End-Stage Liver Disease; NASH, nonalcoholic steatohepatitis; PNF, primary nonfunction; SaO_2, oxygen saturation; SBP, systolic blood pressure; SRTR, Scientific Registry of Transplant Recipients.

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hemodynamic values to define the start of DAT.[5,10-12] In the United Network for Organ Sharing data, the agonal phase starts when the donor systolic blood pressure (SBP) drops below 80 mm Hg and/or donor SaO_2 drops below 80% (Fig. 1).[13] A DWIT or DAT longer than 30 minutes has been considered an increased risk for graft loss.[7,14-16] In a recent survey, the majority of liver transplant centers in the United States reported that their maximal acceptable DWIT or DAT was within 30 minutes.[4] Cold ischemia time (CIT) is another relevant factor with potential effects on clinical outcomes after liver transplantation.[8] As this is a modifiable factor depending on donor allocation policies and donor/recipient management, it is important to assess its specific impact on DCD liver transplant outcomes and identify a significant cutoff.

The purpose of this study is to evaluate the clinical implications of DWIT, DAT, and CIT on graft survival after liver transplantation with DCD grafts. The primary clinical endpoint evaluated in this study is graft survival. Secondary outcomes include posttransplant hospital length of stay and posttransplant readmission rate, as these metrics are relevant in influencing hospital costs and health care resource use. The analysis will also include transplant center volume and will be adjusted per transplant center in order to account for variations in donor and patient care between different transplant centers.

Patients and Methods

Donor and recipient data were obtained from the Scientific Registry of Transplant Recipients (SRTR) Standard Analysis File. The cohort study included all adult primary liver transplants from DCD donors performed in the United States from January 2009 to December 2015. The primary response variable of this study was graft survival. Other outcomes analyzed were posttransplant hospital stay, rate of primary nonfunction (PNF), 30-day mortality rate, readmission rate at 6 months, and serum total bilirubin at 6-month follow-up. PNF was obtained from the SRTR database entry for PNF graft failure, and it was defined as immediate graft failure causing patient death or requiring retransplantation without any apparent cause. The serum total bilirubin at 6 months after transplant was obtained from the follow-up data of the SRTR database. The actual date of this laboratory test was confirmed and was at a median of 6.1 months after the date of the transplant (interquartile range [IQR], 5.8-6.7 months). The SRTR data on 6-month posttransplant follow-up were available for 1854 patients (the remaining 233 patients died or underwent retransplant before 6 months). The readmission status was missing in 24 patients (1.2%), and the serum total bilirubin at 6-month follow-up was not reported in 16 patients (0.8%). Independent variables included the following donor characteristics: age, sex, ethnicity, body mass index (BMI), terminal serum aspartate aminotransferase (AST), terminal serum alanine aminotransferase (ALT), organ sharing (local versus shared), and donor cause of death. Recipient variables were age, sex, ethnicity, BMI, laboratory Model for End-Stage Liver Disease (MELD) score, medical condition (admission to intensive care unit [ICU], hospitalized without ICU admission, or not hospitalized at time of transplant), ventilator dependence at time of transplant, and diagnosis of liver disease. Other predictors included DWIT, DAT, CIT, and center volume for DCD liver transplants. Transplant centers were stratified into 3 tertiles based on the number of DCD liver transplants performed. The high-volume tertile included centers that performed more than 21 DCD liver transplants during the whole observation time, the middle-volume tertile included centers that performed between 6 and 21 transplants, and the low-volume tertile included centers that performed fewer than 6 transplants.

DWIT was defined as the time from the withdrawal of life-sustaining measures (donor extubation) until the in situ aortic cold perfusion (Fig. 1). DAT started after the withdrawal of life support when the donor SBP dropped below 80 mm Hg or the SaO_2 dropped below 80% until the in situ aortic cold perfusion. This definition was based on the data collection for the agonal phase in the SRTR database. The cutoff of 30 minutes for both DWIT and DAT was chosen based on previous studies that indicated this cutoff as a marker of increased risk for complications after DCD liver transplantation.[7,14-16]

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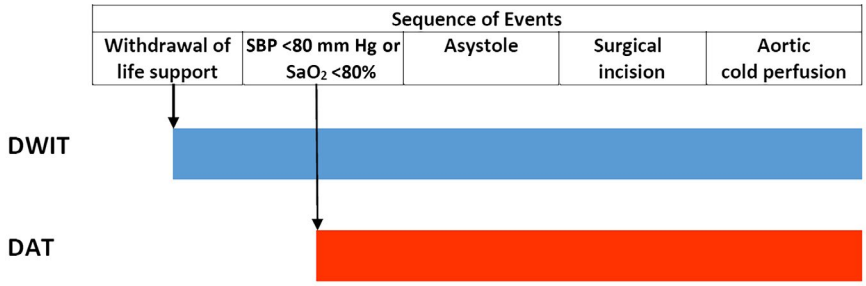

FIG. 1. Definition of DWIT and DAT. DWIT was defined as the time from the withdrawal of life-sustaining measures until the in situ aortic cold perfusion. DAT started after the withdrawal of life support when donor SBP dropped below 80 mm Hg or the SaO_2 dropped below 80% until the in situ aortic cold perfusion.

As of 2009, the SRTR database has reported complete data on DCD DWIT and DAT with a minimization of missing values, which is why that year was chosen as the start of the study period (Table 1). Because of missing data, DWIT could not be calculated in 18 patients who were excluded from the final analysis. This study was approved by the Institutional Review Board of the University of Cincinnati College of Medicine.

Categorical variables were analyzed with chi-square and Fisher's exact tests when appropriate and continuous variables with the Wilcoxon test. Patient and graft survival were estimated with Kaplan-Meier survival curves and compared with the log-rank test. A Cox proportional hazards regression model was used to assess the effects of DWIT and DAT on graft loss controlling for recipient and donor characteristics. All the variables with *P* values <0.20 in the univariate analysis were included in the multivariate model. A frailty (random effects) model was used in the multivariate analysis to account for the clustering effects of the transplant center where the recipient underwent liver transplant. All *P* values reported were 2-sided, and only *P* values <0.05 were considered significant. Statistical analysis was performed with SAS, version 9.4 (SAS Institute, Cary, NC).

Results

DWIT, DAT, AND GRAFT SURVIVAL

During the study period, 2107 patients underwent liver transplant with DCD allografts. Donor and recipient characteristics are summarized in Table 1. The median DWIT (time from donor extubation to aortic cold perfusion) was 22 minutes (IQR, 18-26 minutes). The DWIT was <30 minutes in 1804 donors, between 30 and 40 minutes in 248 donors, and more than 40 minutes in 37 donors (Fig. 2A). As shown in Table 2, the 3 subgroups (DWIT <30 minutes, DWIT 30-40 minutes, and DWIT >40 minutes) were similar for most of the variables except for slight differences in donor sex, recipient MELD score, and recipient medical condition. Patients transplanted with allografts from DCD donors with DWIT <30 minutes presented slightly lower MELD scores and were less likely to be admitted to the ICU at time of transplant. There was no difference in the graft survival curves between DWIT <30 minutes and DWIT between 30 and 40 minutes (Fig. 3A). The median DAT (time measured from the moment when the donor SBP drops below 80 mm Hg or SaO_2 below 80% until the beginning of aortic cold perfusion) was 19 minutes (IQR, 15-23 minutes). The DAT was less than 30 minutes in 1970 donors, between 30 and 40 minutes in 101 donors, and more than 40 minutes in 17 donors. As shown in Fig. 3B, there was no difference in liver transplant graft survival between DCD donors with DAT <30 minutes and donors with DAT between 30 and 40 minutes.

The results of univariate and multivariate proportional hazards regression models for graft loss are reported in Table 3. In the multivariate model, DWIT was not associated with graft loss (hazard ratio [HR], 1.00; 95% confidence interval [CI], 0.99-1.02; $P = 0.50$). We also compared DWIT <30 minutes versus DWIT 30-40 minutes and found that DWIT 30-40 minutes was not associated with graft loss (HR, 0.99; 95% CI, 0.76-1.30; $P = 0.97$). When we tested DAT in the multivariate model, it was not associated with graft loss (HR, 1.00; 95% CI, 0.99-1.02; $P = 0.73$). In the multivariate proportional hazards model, the predictors associated

TABLE 1. Donor and Recipient Characteristics in 2107 DCD Liver Transplants

Variables	Value (n = 2107)
Donor age, years	32.4 (22.7-44.0)
Donor sex, male	1441 (68.4)
Donor ethnicity	
White	1719 (81.6)
African American	198 (9.4)
Other	190 (9.0)
Donor BMI, kg/m^2	25.7 (22.5-29.6)
Donor AST, IU/L	56 (35-90)
Donor ALT, IU/L*	42 (26-73)
Donor sharing, local	1494 (70.9)
Donor cause of death	
Anoxia	910 (43.2)
Trauma	782 (37.1)
Stroke	333 (15.8)
Other	82 (3.9)
DWIT, minutes†	22 (18-26)
DAT, minutes‡	19 (15-23)
CIT, hours†	5.7 (4.6-7.0)
Recipient age, years	58.3 (52.4-63.3)
Recipient sex, male	1469 (69.7)
Recipient ethnicity	
White	1558 (73.9)
African American	181 (8.6)
Other	368 (17.5)
Recipient BMI, kg/m^2§	27.8 (24.5-31.6)
Laboratory MELD score	18 (12-24)
Recipient portal vein thrombosis‖	219 (10.4)
Recipient medical condition	
Not hospitalized	1673 (79.4)
Hospitalized, not in ICU	287 (13.6)
Hospitalized, in ICU	147 (7.0)
Recipient on ventilator at time of transplant	65 (3.1)
Recipient diagnosis	
HCV	745 (35.4)
HBV	52 (2.5)
Alcohol	360 (17.1)
NASH	202 (9.6)
HCC	336 (15.9)
Cholestatic disease	106 (5.0)
Autoimmune	59 (2.8)
Cryptogenic	97 (4.6)
Other	150 (7.1)
Center volume	
High (>21 liver transplants)	1652 (78.4)
Medium (6-21 liver transplants)	374 (17.8)
Low (<6 liver transplants)	81 (3.8)

NOTE: Data are given as median (IQR) and n (%).
*1 missing observation.
†18 missing observations.
‡19 missing observations.
§14 missing observations.
‖6 missing observations.

with graft loss were donor age, donor sharing (versus local allocation), CIT, recipient admission to ICU at time of transplant, and recipient ventilator dependence at time of transplant (Table 3). Recipient ICU admission at time of transplant, recipient ventilator dependence, and laboratory MELD score were markers of disease severity. In order to explore the impact of MELD score and eliminate possible effects of an interaction with other markers of disease severity, we reran the multivariate model by excluding recipient medical condition and recipient ventilator dependence. When we ran such multivariate analyses, recipient laboratory MELD score was associated with increased risk for graft loss (HR, 1.01; 95% CI, 1.01-1.02; $P = 0.007$).

Transplant centers were stratified into 3 tertiles based on the number of DCD liver transplants performed. In the multivariate proportional hazards model, transplantation at high- and medium-volume centers was protective against graft loss (HR, 0.38; 95% CI, 0.27-0.55; $P < 0.01$; HR, 0.42; 95% CI, 0.29-0.63; $P < 0.01$, respectively). We also investigated whether the center volume had an interaction effect with DWIT on graft failure. When we assessed the interaction between the transplant center volume of DCD liver transplants and DWIT in the multivariate Cox regression, we found that this interaction was not significant (HR, 1.01; 95% CI, 0.99-1.03; $P = 0.34$).

Within the group of patients with longer DWIT, other predictors associated with graft loss were shared allocation of liver allograft outside the local donor service area (HR, 1.88; 95% CI, 1.13-3.15; $P = 0.02$) and recipient dependent on mechanical ventilation at time of transplant (HR, 2.67; 95% CI, 1.09-6.56; $P = 0.03$).

The subgroups of patients with DWIT >40 minutes and DAT >40 minutes included 37 and 17 patients, respectively. As these subgroups were small, the analysis and interpretation of the results is limited. In the subgroup of patients with DWIT >40 minutes, the graft survival rates at 1 and 5 years were 83.3% and 56.2%, whereas patients with shorter DWIT exhibited graft survival rates of 84.8% and 67.9%, respectively

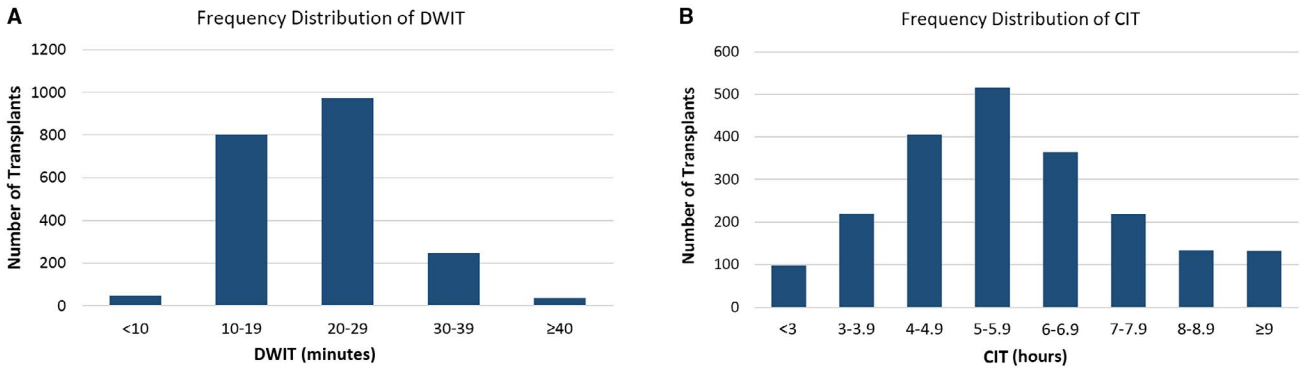

FIG. 2. (A) Histograms built by dividing liver transplants into groups based on the duration of DWIT. (B) Histograms representing the frequency distribution of DCD liver transplants based on the duration of CIT in hours.

TABLE 2. Donor and Recipient Characteristics in DCD Liver Transplant Subgroups Based on DWIT

Characteristics	DWIT <30 Minutes (n = 1804)	DWIT 30-40 Minutes (n = 248)	DWIT >40 Minutes (n = 37)	*P* Value
Donor age, years	32.2 (22.7-44.0)	33.8 (22.8-44.0)	30.0 (22.7-38.7)	0.67
Donor sex, male	1253 (69.5)	159 (64.1)	18 (48.7)	0.008
Donor ethnicity				0.99
White	1473 (81.6)	202 (81.4)	31 (83.8)	
African American	166 (9.2)	24 (9.7)	3 (8.1)	
Other	165 (9.2)	22 (8.9)	3 (8.1)	
Donor BMI, kg/m^2	25.8 (22.5-29.9)	25.2 (22.4-28.9)	23.7 (20.9-27.7)	0.06
Donor ALT/GPT, IU/L	42 (26-73)	39 (23-75)	44 (31-72)	0.65
Donor AST/GOT, IU/L	57 (36-91)	52 (31-81)	50 (37-77)	0.08
Donor sharing, local	1290 (71.5)	162 (65.3)	29 (78.4)	0.09
Donor cause of death				0.16
Anoxia	768 (42.6)	117 (47.2)	19 (51.4)	
Trauma	686 (38.0)	75 (30.2)	11 (29.7)	
Stroke	283 (15.7)	45 (18.2)	4 (10.8)	
Other	67 (3.7)	11 (4.4)	3 (8.1)	
Donor CIT, hours	5.7 (4.6-7.0)	5.5 (4.4-7.0)	5.2 (4.0-7.8)	0.61
DRI	1.87 (1.66-2.16)	1.94 (1.69-2.24)	1.77 (1.65-2.16)	0.08
Recipient age, years	58.3 (52.3-63.3)	58.1 (52.5-62.2)	58.9 (54.0-65.0)	0.36
Recipient sex, male	1263 (70.0)	171 (68.9)	21 (56.8)	0.21
Recipient ethnicity				0.22
White	1338 (74.2)	187 (75.4)	23 (62.2)	
African American	158 (8.8)	19 (7.7)	2 (5.4)	
Other	308 (17.1)	42 (16.9)	12 (32.4)	
Recipient BMI, kg/m^2	27.8 (24.6-31.7)	27.4 (23.8-31.3)	27.2 (24.6-30.2)	0.62
Laboratory MELD score	17 (12-24)	19 (13-27)	20 (16-31)	0.009
Recipient medical condition				0.03
Not hospitalized	1443 (79.9)	186 (75)	29 (78.4)	
Hospitalized, not in ICU	248 (13.8)	33 (13.3)	4 (10.8)	
Hospitalized in ICU	113 (6.3)	29 (11.7)	4 (10.8)	
Recipient on ventilator	51 (2.8)	13 (5.2)	1 (2.7)	0.12
Recipient HCV diagnosis	631 (34.9)	94 (37.9)	16 (43.2)	0.40
Recipient portal vein thrombosis	189 (10.5)	23 (9.3)	4 (10.8)	0.83

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

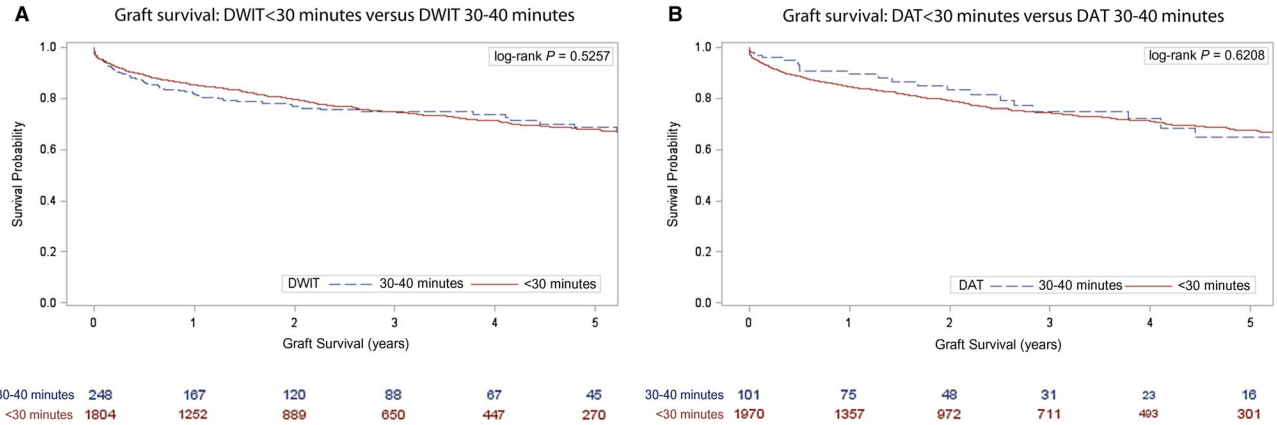

FIG. 3. Kaplan-Meier graft survival estimates. (A) Graft survival in DCD liver transplants with DWIT <30 minutes compared with graft survival for DCD liver transplants with DWIT between 30 and 40 minutes. (B) Graft survival curves of DCD liver transplants with DAT <30 minutes versus DAT 30-40 minutes.

(P = 0.31). There were 17 patients with DAT >40 minutes. Their graft survival rates at 1 and 5 years (82.3% and 74.1%) were not different from patients with shorter DAT (84.8% and 67.7%, P = 0.88). The interpretation of these data needs to be careful because of the limitations related to the small sample size.

When we treated donor BMI as a continuous numeric variable, it was not a significant predictor for graft failure in the multivariate analysis for the entire cohort. We then looked at donor BMI as a categorized variable by checking different cutoffs of BMI and found that a donor BMI >27 kg/m^2 was actually associated with graft loss in both univariate and multivariate analyses (HR, 1.21; 95% CI, 1.01-1.45; P = 0.04). We also looked at the subgroup with very high BMI to evaluate their outcomes. We identified 167 transplant recipients from donors with BMI >35 kg/m^2. Their rates of graft survival at 1 and 5 years were 83.8% and 57.2%, respectively, and were significantly lower than the other patients with donor BMI ≤35 kg/m^2 (85.0% and 68.6%, respectively; P = 0.04).

CIT AND GRAFT SURVIVAL

In the whole cohort, the median CIT was 5.7 hours (IQR, 4.6-7.0 hours). The frequency distribution of CITs is displayed in Fig. 2B. In the multivariate proportional hazards model, CIT was associated with increased risk for graft loss (HR, 1.1; 95% CI, 1.1-1.2; P < 0.01). Using the same multivariate model, we calculated the adjusted HR for graft loss associated with each cutoff of CIT. The highest adjusted HR for graft loss was noted with a CIT cutoff of 8 hours. Liver transplantations from DCD donors with a CIT of ≥8 hours were associated with an adjusted HR for graft loss of 1.7 (95% CI, 1.4-2.2; P < 0.01). Every cutoff value of CIT above 4 hours was associated with a significant HR for graft loss. The HR associated with a cutoff of 4 hours was 1.5 (95% CI, 1.2-2.1; P < 0.01). Figure 4 shows Kaplan-Meier survival curves in which DCD liver transplants with CIT >8 hours were associated with worse graft survival when compared with those with shorter CIT.

We assessed the effects of the combination of long and short CIT with long and short DWIT. In the subgroup with DWIT <30 minutes, a CIT ≤6 hours was associated with 1- and 5-year graft survival rates of 87.6% and 71.1%, which were higher when compared with CIT >6 hours (81.9% and 63.2%; P < 0.001). In the subgroup with DWIT between 30 and 40 minutes, 1- and 5-year graft survival rates for CIT ≤6 hours were 83.6% and 72.3%, respectively, whereas the graft survival rates for CIT >6 hours were 80.3% and 64.8%, respectively. Although a short CIT was associated with higher survival rates, the difference was not significant (P = 0.45) for the last subgroup.

OTHER OUTCOMES

The median posttransplant hospital stay was 9 days in both DCD liver transplants with DWIT <30 minutes and DWIT between 30 and 40 minutes (Table 4). There was no difference in 30-day mortality rates and PNF rates between the 2 groups. The readmission rate during the first 6 months after transplant was 45.2%

TABLE 3. Univariate and Multivariate Proportional Hazards Model Predicting Graft Loss

	Univariate Analysis		Multivariate Analysis	
Variables	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Donor age (per 1-year increase)	1.01 (1.01-1.02)	<0.01	1.01 (1.01-1.02)	<0.01
Donor sex	1.01 (0.84-1.21)	0.94		
Donor ethnicity				
African American versus white	0.86 (0.63-1.18)	0.36		
Other versus white	0.99 (0.73-1.36)	0.99		
Donor BMI (per 1-unit increase)	1.01 (1.00-1.03)	0.05	1.01 (0.99-1.02)	0.33
Donor AST	1.00 (1.00-1.01)	0.18	1.00 (0.99-1.00)	0.78
Donor ALT	1.00 (1.00-1.01)	0.07	1.00 (1.00-1.00)	0.08
Donor sharing (shared versus local)	1.39 (1.16-1.67)	<0.01	1.27 (1.04-1.55)	0.02
Donor cause of death				
Anoxia versus trauma	0.84 (0.69-1.02)	0.08	0.79 (0.65-0.98)	0.03
Stroke versus trauma	1.23 (0.99-1.61)	0.05	1.13 (0.88-1.47)	0.34
Other versus trauma	1.21 (0.80-1.83)	0.37	1.14 (0.75-1.74)	0.53
DWIT (per 1-minute increase)	1.01 (0.99-1.02)	0.29	1.00 (0.99-1.02)	0.50
DAT (per 1-minute increase)*	1.00 (0.99-1.02)	0.51		
CIT (per 1-hour increase)	1.10 (1.06-1.15)	<0.01	1.11 (1.06-1.15)	<0.01
Recipient age (per 1-year increase)	1.00 (0.99-1.01)	0.38		
Recipient sex	1.05 (0.87-1.26)	0.63		
Recipient ethnicity				
African American versus white	1.29 (0.97-1.71)	0.08	1.33 (0.99-1.78)	0.06
Other versus white	1.08 (0.86-1.35)	0.53	1.10 (0.87-1.39)	0.45
Recipient BMI	1.00 (0.99-1.01)	0.76		
Recipient laboratory MELD score (per 1-unit increase)	1.01 (1.00-1.02)	0.02	1.0 (0.99-1.01)	0.70
Recipient portal vein thrombosis	0.87 (0.66-1.14)	0.31		
Recipient medical condition				
ICU versus home	1.97 (1.49-2.59)	<0.01	1.80 (1.15-2.84)	0.01
Hospitalized not ICU versus home	1.17 (0.90-1.50)	0.23	1.23 (0.92-1.64)	0.17
Recipient ventilator	2.51 (1.74-3.63)	<0.01	1.77 (1.05-2.97)	0.03
Recipient HCV	0.96 (0.80-1.15)	0.63		
Center volume				
High versus low	0.46 (0.32-0.64)	<0.01	0.38 (0.27-0.55)	<0.01
Medium versus low	0.50 (0.34-0.73)	<0.01	0.42 (0.29-0.63)	<0.01
High versus medium	0.92 (0.73-1.15)	0.44	0.90 (0.70-1.16)	0.42

*When DAT was tested in the multivariate model, it was not associated with graft loss (HR, 1.00; 95% CI, 0.99-1.02; $P = 0.73$).

for patients who received DCD livers with DWIT <30 minutes and 46.2% for DWIT between 30 and 40 minutes ($P = 0.94$). There was no difference in the serum total bilirubin levels and rate of hyperbilirubinemia (defined as serum total bilirubin >2 mg/dL) at 6 months after transplant between the 2 DWIT groups (Table 4). We also looked at these metrics for DAT, and there was no difference in the length of posttransplant hospital stay, 30-day mortality rate, PNF rate, readmission rate, and serum bilirubin levels between DAT <30 minutes and DAT >30 minutes. We also looked at relisting rates for liver retransplant after DCD liver transplant. We found the relisting rates for liver retransplant were 8.9% and 11.6% at 1 and 3 years in the group with DWIT <30 minutes and 9.4% and 11.3% for patients with DWIT between 30 and 40 minutes ($P = 0.65$).

We then assessed CIT and divided the DCD liver transplants into 2 groups with a CIT of 6 hours as the cutoff because it was the closest to the median CIT of the entire cohort. As shown in Table 4, a CIT longer than 6 hours was associated with longer posttransplant

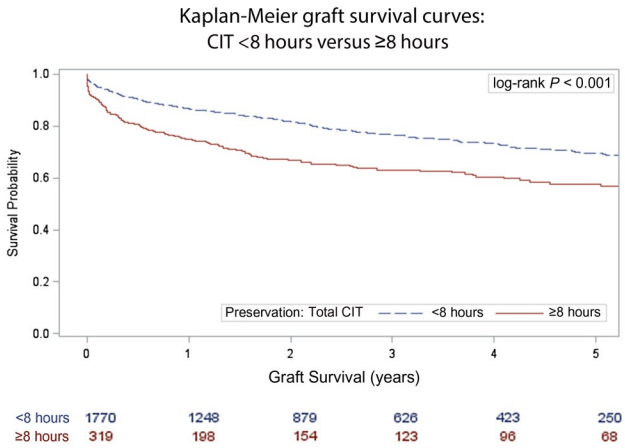

FIG. 4. Kaplan-Meier graft survival curves in DCD liver transplants with CIT <8 hours versus CIT ≥8 hours.

hospital stay, higher rates of PNF, and higher serum bilirubin at 6 months after transplant.

Discussion

In this study, we analyzed the data from a large cohort including all patients transplanted with DCD liver allografts in the United States in recent years with the aim to assess outcomes reflecting the most recent changes in donor management and recipient care for DCD liver transplants.[11,17] Complete SRTR data on DWIT and DAT for DCD donors are available only for transplants performed in recent years; data on transplants performed in the previous eras (before 2009) are affected by several missing values for DAT and DWIT. The analysis of this large cohort of DCD liver transplants showed that the majority of liver allografts came from DCD donors with a DWIT and DAT shorter than 30 minutes. In a previous survey, most transplant centers declared that they would avoid the use of DCD liver allografts with DWIT and DAT longer than 30 minutes.[4] However, in our study, DWIT and DAT were not associated with graft loss. DCD liver transplants from donors with DAT and DWIT between 30 and 40 minutes displayed similar graft survival compared with DCD donors with DAT and DWIT <30 minutes. It seems therefore reasonable to consider the use of DCD organs from donors with DWIT and DAT slightly longer than 30 minutes in properly selected recipients in order to expand the donor pool and increase access to transplantation.

We also looked at readmissions during the first 6 months after transplant, serum bilirubin at 6 months, PNF rates, and 30-day mortality rates in order to capture possible effects of the complications from DCD liver transplants. We did not find any difference in readmission rates, PNF rates, early mortality, and hyperbilirubinemia between shorter and longer DAT and DWIT. Moreover, DWIT and DAT did not affect the duration of posttransplant hospitalization and readmission rates that are relevant in terms of hospital costs and resource use in health care.[18,19] A previous large single-center study (215 patients) evaluated the impact of DWIT and DAT on biliary complications after liver transplant. In that study, DWIT and DAT did not affect the rates of posttransplant intrahepatic bile duct strictures and overall biliary complications; only the time from asystole to aortic cross-clamp was associated with increased risk for biliary complications.[20]

TABLE 4. Posttransplant Outcomes in Recipients After DCD Liver Transplants Stratified by DWIT and Donor CIT

	DWIT			CIT		
Outcome	<30 Minutes (n = 1804)	30-40 Minutes (n = 248)	*P* Value	≤6 Hours (n = 1239)	>6 Hours (n = 850)	*P* Value
Posttransplant hospital stay, days	9 (7-15)	9 (7-17)	0.07	9 (6-14)	10 (7-17)	<0.01
Graft failure due to PNF	26 (1.4)	4 (1.6)	0.78	12 (1.0)	19 (2.2)	0.03
30-day mortality	59 (3.3)	8 (3.2)	0.86	32 (2.6)	35 (4.1)	0.06
Readmission at 6 months*	721 (45.2)	97 (46.2)	0.94	494 (44.4)	345 (47.6)	0.09
Serum total bilirubin at 6 months, mg/dL†	0.6 (0.4-0.9)	0.6 (0.4-0.9)	0.74	0.6 (0.4-0.9)	0.7 (0.5-1.0)	<0.01
Patients with bilirubin >2 mg/dL at 6 months†	121 (7.6)	14 (6.7)	0.77	63 (5.7)	71 (9.8)	<0.01

NOTE: Data are given as median (IQR) or n (%).
*Readmission data were not reported in 24 patients.
†Serum total bilirubin at 6-month follow-up was missing in 16 patients.

CIT was a significant risk factor for graft loss: Every CIT longer than 4 hours carried an increased risk for graft loss with the highest HR noted for a cutoff of 8 hours of CIT. In our study, we found that longer CIT was also associated with a higher PNF rate, longer posttransplant hospitalization, and higher serum total bilirubin levels at 6 months after transplant. The negative effect of CIT on outcomes after DCD liver transplants was also reported in a large study from the United Kingdom that prompted the inclusion of CIT among the predictors of graft loss and PNF in the UK DCD risk score.[21] These considerations are also relevant in terms of future donor allocation policies in order to minimize the organ transport time that may prolong the CIT with negative implications on patient outcomes. A very short CIT of <4 hours was obtained in only 318 patients (15.2%), and it is probably not feasible in every DCD liver transplant. Although such a short CIT cannot be achieved in every liver transplant, it is reasonable to maximize all efforts in policy, donor allocation, organ transportation, recipient selection, and surgery timing to keep the duration of CIT as short as possible.

Both donor and recipient selection are critical to optimize outcomes in DCD liver transplantation.[17,22] In our study, donor age, cause of death, and organ sharing were donor predictors for graft loss. Anoxia as cause of donor death showed a protective effect with lower risk for graft loss compared with other causes of death. It is possible that the initial anoxic event preconditioned the allograft, resulting in a mitigation of the oxidative effects from the second ischemic hit, which occurred at the time of cardiac arrest after the withdrawal of care. A previous study underlined that DCD donors from anoxia have been historically underused despite the fact that they were not associated with worse outcomes.[23] The findings of our study are reassuring that DCD donors with a history of anoxia can be used without increased risk for graft loss.

We also assessed donor BMI, as it has been previously identified as a risk factor for graft loss in DCD liver transplants.[21,24] When we treated donor BMI as a continuous variable, it was not significant in the multivariate model despite a borderline effect in the univariate analyses. We then looked at donor BMI as a categorized variable by checking different cutoffs of BMI and found that a donor BMI >27 kg/m^2 was actually associated with increased risk for graft loss in both univariate and multivariate analysis. Moreover, patients with very high donor BMI (>35 kg/m^2) exhibited lower graft survival.

Recipient selection is also an important step in liver transplantation, especially in the allocation of marginal organs.[25-27] The recipients of DCD liver allografts presented a relatively low laboratory MELD score with a median equal to 18 (IQR, 12-24), whereas in the same period, the median MELD score for brain-dead donor allograft recipients was 21 (IQR, 14-31). Similar findings with lower MELD score in DCD allografts were reported in previous studies.[11,22] In the multivariate analysis, sicker recipients, such as patients admitted to the ICU at time of transplant, patients on mechanical ventilator at time of transplant, and those with a high MELD score, were associated with worse outcomes.

In many complex surgical procedures, including liver transplantation, hospitals performing a high volume of these procedures achieved better outcomes.[28,29] In our cohort, we found that transplant centers performing a high or medium volume of DCD liver transplants were associated with better graft survival when compared with centers performing a low volume of DCD liver transplants. There is probably a learning curve in both donor management and recipient care that relates to specific problematic issues involved in DCD donation, which can explain the impact of the case volume on outcomes. Moreover, some high-volume centers developed protocols that are effective in optimizing the outcomes in DCD liver transplants.[11] Future strategies such as the use of machine perfusion can be considered to increase the use of DCD liver allografts by mitigating ischemia/reperfusion injuries, including the effects of prolonged cold ischemia.[30,31] In a previous report, machine perfusion was effective in improving outcomes of marginal liver allografts.[32]

A limitation related to the SRTR database is the lack of detailed granular data on some donor and recipient characteristics, for example, donor liver biopsy or administration of tissue plasminogen activator.[33-35] Moreover, the SRTR database provides data on the total duration of DWIT and DAT but does not include information on the specific trajectory of blood pressure and SaO_2 values. Another missing outcome measure is the ischemic cholangiopathy that is a specific complication observed more often after DCD liver transplants. However, this large data set provides valuable information on the experience with DCD liver transplants in the most recent transplant era with the advantage of a large sample size and the possibility to include in the analysis several donor, recipient, and transplant center factors.

In conclusion, longer DWIT and DAT (up to 40 minutes) were not associated with worse graft survival, PNF, longer posttransplant hospitalization, or hospital readmissions. It is reasonable to consider transplantation liver allografts from DCD donors even when the DWIT and DAT are slightly longer than 30 minutes in selected cases with the potential benefit of an expansion of the donor pool. Longer CIT was associated with worse graft survival and outcomes in DCD liver transplants. Donor allocation policies, organ transportation, and management of recipient surgery should aim to achieve short CIT in order to optimize clinical outcomes from DCD liver transplants.

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