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Donation after Cardiac Death Liver Transplantation: Predictors of Outcome

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We aimed to identify recipient, donor and transplant risk factors associated with graft failure and patient mortality following donation after cardiac death (DCD) liver transplantation. These estimates were derived from Scientific Registry of Transplant Recipients data from all US liver-only DCD recipients between September 1, 2001 and April 30, 2009 (n = 1567) and Cox regression techniques. Three years post-DCD liver transplant, 64.9% of recipients were alive with functioning grafts, 13.6% required retransplant and 21.6% died. Significant recipient factors predictive of graft failure included: age ≥ 55 years, male sex, African–American race, HCV positivity, metabolic liver disorder, transplant MELD ≥ 35, hospitalization at transplant and the need for life support at transplant (all, $p \leq 0.05$). Donor characteristics included age ≥ 50 years and weight >100 kg (all, $p \leq 0.005$). Each hour increase in cold ischemia time (CIT) was associated with 6% higher graft failure rate (HR 1.06, $p < 0.001$). Donor warm ischemia time ≥ 35 min significantly increased graft failure rates (HR 1.84, $p = 0.002$). Recipient predictors of mortality were age ≥ 55 years, hospitalization at transplant and retransplantation (all, $p \leq 0.006$). Donor weight >100 kg and CIT also increased patient mortality (all, $p \leq 0.035$). These findings are useful for transplant surgeons creating DCD liver acceptance protocols.

Key words: DCD liver transplant, graft failure, outcomes, prognosis, risk factors

Abbreviations: SRTR, Scientific Registry of Transplant Recipients; OPTN, Organ Procurement and Transplantation Network; CIT, cold ischemia time; DWIT, donor warm ischemia time; DCD, donation after cardiac death; HRSA, Health Resources and Services Administration

Introduction

The continued critical shortage of donor liver allografts has prompted innovative strategies to increase the donor pool. In addition to the proliferation of organ donor recruitment initiatives, transplant providers have been encouraged by the Institute of Medicine and the Health Resources and Services Administration (HRSA) to use grafts from higher risk donors to decrease the burden of a growing waiting list (1–3). The utilization of liver allografts from donors after cardiac death (DCD) has increased over the last decade, and now comprises more than 5% of all liver transplants (4).

It is well known that outcomes after DCD liver transplantation are inferior to transplantation using livers from brain dead donors (4–19), and these differences have been ascribed to organ injury related to the pathophysiology of donor death and subsequent graft-related morbidity (6,8,10,13,14,19). The inferior graft survival related to DCD liver transplantation could potentially be mitigated by recognizing the presence of extraordinary donor risk factors and by optimizing donor–recipient matching. Several authors have identified ischemic cholangiopathy as a main driver of inferior DCD liver graft outcomes (6,8,10,13,14,19). Clinical decision-making in the donor selection process would be enhanced by knowing whether risk factors for ischemic cholangiopathy also predict graft failure and/or death following DCD liver transplantation. This would enable transplant surgeons to determine degrees of 'high risk' for a given transplant candidate–donor pair, and provide for a more informed prediction of a recipient's clinical course.

The intent of this study was to determine recipient and donor risk factors associated with inferior DCD outcomes using comprehensive data from the Scientific Registry of Transplant Recipients (SRTR). Additionally, we sought to better understand posttransplant outcomes following DCD liver transplantation including retransplantation and mortality rates. We hypothesized that factors demonstrated in prior single-center studies to be associated with ischemic cholangiopathy including donor weight, donor age and cold

ischemia time (CIT) would also be associated with graft failure and posttransplant mortality.

Methods

Using liver transplant recipient and donor data from the SRTR, a retrospective cohort was constructed of DCD liver transplant recipients who received liver-only grafts from September 1, 2001 to April 30, 2009. All patient-level transplant candidate, recipient and donor data are submitted by all transplant centers and organ procurement organizations to the Organ Procurement and Transplantation Network (OPTN), which subsequently transfers these data to the SRTR. The SRTR uses several methods to ascertain and verify recipient outcomes by cross validating against other data sources, such as the Social Security Death Master File for candidate and recipient mortality (20,21). SRTR data are the most comprehensive national data on candidate, recipient and donor demographics, comorbidities, disease progression, clinical risk factors and posttransplant outcomes including graft failure and recipient death (21).

Predictors of inferior DCD outcomes

We used a cumulative incidence function to ascertain the competing risk rates of various post-DCD liver transplant outcomes over time, including the proportions alive with a functioning graft, retransplanted and dead. Multivariable Cox proportional hazards models were used to determine donor, recipient and transplant predictors of inferior DCD outcomes, with separate models for graft failure and for posttransplant mortality. Graft failure was defined as the earlier of retransplantation or death. In the mortality model, retransplantation was treated as a time-varying covariate, meaning the effect of a repeat transplant was not exerted on post-DCD liver transplant mortality until it occurred. Follow-up time at risk was censored at the end of follow-up (October 31, 2009) in both models. All patients had at least 6 months of follow-up. For each model, we evaluated all clinically relevant covariates available in the SRTR data, and focused particularly on those that were predictive of ischemic cholangiopathy in previous single center studies (6,16,22,23). Donor variables tested in the models included donor age, race, body mass index, weight and donor cause of death. Investigated recipient characteristics included age, race, sex, medical condition, prior liver transplantation, diagnosis, preexisting candidate malignancy, diabetes, prior abdominal surgery and portal vein thrombosis. Transplant characteristics included local versus shared donor, partial or split liver, ABO compatibility, donor warm ischemia time (DWIT)(from cessation of cardiopulmonary support to *in situ* cold perfusion) and CIT. In order to explore the effects of warm and CIT, the functional form of each of these variables was determined by assessing lowess plots of martingale residuals and statistical significance of the covariates in the graft failure model. Various categorizations, cut-points and splines were tested during the model building process. Indicators were used for missing data, as fewer than 10% of the total data across all variables were missing.

Additional analyses focused on the potential association of interactions among risk factors for ischemic cholangiopathy with rates of graft failure and patient death. Chan et al. (22) have previously shown that older donor age, high donor weight and long ischemia times were associated with the development of ischemic cholangiopathy. Interaction terms were created by combining the individual covariate effects that were thought to have the most clinical impact on ischemic cholangiopathy. These terms were then tested in the graft loss and survival models.

This study was approved by the US HRSA SRTR project officer. HRSA has determined that this study satisfies the criteria for the nstitutional Review Board exemption described in the 'Public Benefit and Service Program'provisions of 45 Code of Federal Regulations 46.101(b)(5) and HRSA Circular 03. All statistical analyses were performed using SAS v9.2 (SAS Institute, Cary, NC, USA). Statistical significance was defined by $p < 0.05$.

Results

There were 1567 DCD liver transplants identified over the time period. More than 80% of patients had greater than 1 year of follow-up, with minimum follow-up of 182 days. The demographic and clinical characteristics of DCD liver transplant recipients and donors are displayed in Table 1. Nearly 5% of DCD liver transplant recipients had previously undergone a liver transplant. More than 20% of DCD liver transplant recipients were hospitalized at the time of transplant. Approximately 5% of DCD liver recipients were listed as Status 1. The average age of DCD liver donors was 35.2 ± 15.4 years and two-thirds were male. Average donor body weight was 77.3 ± 20.8 kg. Traumatic injury was the most common cause of death. Mean CIT was 7.5 ± 3.7 h, and mean DWIT was 16 min. More than 60% of the DCD livers were procured locally. Only 2.5% of the DCD donors were uncontrolled.

In the 3 years following DCD liver transplant, there was a substantial incidence of graft failure, retransplantation and mortality (Figure 1). The cumulative probability of being alive with a functioning DCD graft at 3 years was higher than 64%. However, the probability of death was 21.6% within 3 years, with the highest rate during the first year. Relisting occurred in 19.9% of DCD liver transplant recipients ($n = 312$), at a median of 73.5 days following transplant (interquartile range 6–209 days). Median lab Model for End-Stage Liver Disease (MELD) at relisting was 21 (interquartile range 16–29). However, the cumulative probability of retransplantation was only 13.6% by 3 years, likely reflecting attrition of relisted candidates due to death or low transplant rates. The majority of retransplants occurred in the first few months following DCD liver transplantation.

Several recipient, donor and transplant factors were identified as predictors of graft failure following DCD liver transplantation (Table 2). Recipients $\geq$ age 55 years had a significant 26% higher adjusted graft failure rate compared to recipients age 18–55 years. Pediatric recipients (less than 18 years old) had a lower graft failure rate (hazard ratio [HR] 0.33; $p = 0.04$). Female sex was significantly protective from graft failure, whereas African–American race was associated with a 38% higher graft failure rate compared to white race. Compared to recipients with noncholestatic liver disorders, those with metabolic liver diseases had a twofold higher adjusted risk of graft failure. Previous liver transplantation trended toward a 45% higher DCD liver graft failure rate compared to those who underwent primary liver transplant (HR 1.45, $p = 0.063$). Although Status 1 medical urgency was not significantly associated with graft failure, other metrics of disease severity had notable effects. Those with MELD scores greater than 35 at transplant had a significant 47% higher graft

Table 1: Recipient, donor and transplant characteristics for 1567 DCD liver transplants

Recipient characteristics			
		Mean	**SD**
Age (mean)(SD)		52.9	11.4
BMI (kg/m^2)		28.1	5.8
Lab MELD/PELD at transplant		17[1]	13–24[2]
		Frequency	**Percent**
Male sex		1062	67.8
Race/ethnicity	White	1179	75.2
	Hispanic	194	12.4
	Black	137	8.7
	Other	57	3.6
Recipient diagnosis	Noncholestatic	1039	66.3
	Malignant neoplasm	203	13.0
	Cholestatic	124	7.9
	Other	90	5.7
	AHN	69	4.4
	Metabolic	42	2.7
Previous liver transplant		75	4.8
Status 1 medical urgency		70	4.5
Medical condition at transplant	Ambulatory	1193	76.1
	Non-ICU hospitalized	210	13.4
	ICU hospitalized	164	10.5
Donor characteristics			
		Mean	**SD**
Age (mean)(SD)		35.2	15.4
Weight (kg)		77.3	20.8
		Frequency	**Percent**
Male sex		1034	66.0
Race/ethnicity	White	1340	85.5
	Black	118	7.5
	Hispanic	81	5.2
	Other	28	1.8
Cause of death	Trauma	662	42.2
	Anoxia	492	31.4
	Stroke	320	20.4
	Other	93	5.9
Uncontrolled DCD donor		39	2.5
Transplant characteristics			
		Mean	**SD**
Cold ischemia time (h)		7.5	3.7
Donor warm ischemia time (mins)		16.1	9.2
		Frequency	**Percent**
Donor location	Shared	550	35.1
	Local	1017	64.9
ABO incompatible		10	0.6

[1]Median MELD score.
[2]Interquartile range of MELD scores. PELD = Pediatric End-Stage Liver Disease.

failure rate than those with MELD scores 15–25. Hospitalization and the requirement of life support, respectively, were also significant independent predictors of graft failure. Older donor age (>50 years) was associated with a 39%–88% higher adjusted risk of graft failure compared to donors age 18–50 years (donor age 50–60 years, HR 1.39, $p = 0.0047$; donor age ≥60 years, HR 1.88, $p = 0.0011$). Donor body weight greater than 100 kg was associated with a significant 56% higher adjusted risk of graft failure compared to those less than 100 kg. Donor cause of death was not significantly associated with risk of graft failure.

DWIT and CIT were independently associated with graft failure. The distribution of DWIT is displayed in Figure 2. As shown in Figure 3, DCD liver grafts with DWIT 35 min or greater (3.8% of cases) had a significant 1.8-fold higher graft loss rate compared to those with DWIT less than 15 min ($p = 0.0028$). Graft failure rates were not significantly different for those with DWIT of 15–35 min compared to those less than 15 min. Each hour of CIT was associated with a 6% increase in the relative rate of graft failure when analyzed continuously ($p < 0.001$). When analyzed categorically, even moderate CIT (6–10 h) was associated with a significant 64% higher graft failure risk (compared to

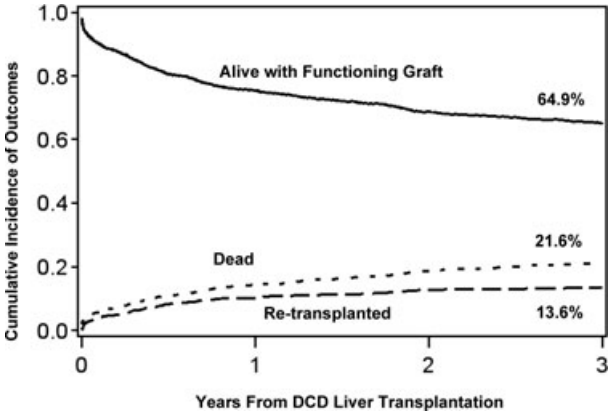

Figure 1: Cumulative incidence of post-DCD liver transplant outcomes. Three years after undergoing DCD liver transplantation, nearly 65% of recipients were alive with a functioning graft. However, more than 20% of these recipients were dead at 3 years, and 13.6% required a subsequent liver transplant.

those less than 6 h). Compared to those with CIT less than 6 h, CITs greater than 10 h (16% of cases) were associated with at least a twofold risk of graft failure, but this relative risk approached a fourfold increase when CIT was greater than 13 h (4% of cases) (HR 3.84, $p < 0.0001$). Missing CIT, which may be a proxy for longer CITs, was also associated with significantly higher adjusted graft failure and patient mortality rates (Table 2). Local and shared organs did not have significantly different risks of graft failure after adjusting for CIT time.

Several recipient, donor and transplant factors were predictive of posttransplant mortality (Table 3). Older recipient age (≥55 years) was associated with a significant 60% higher mortality risk compared to those aged 18–55 years. Retransplantation was associated with a 2.4-fold higher mortality rate compared to those whose grafts remained functional following the index DCD transplant. Notably, several of the recipient factors associated with graft failure in Table 2 were not significant predictors of mortality after adjusting for retransplantation. Patients who were hospitalized at the time of DCD transplant had a 48% higher risk of dying compared to the ambulatory liver transplant recipients. Compared to low MELD scores (<15), higher MELD scores were not significantly associated with posttransplant mortality. Status 1 medical urgency was not predictive of posttransplant mortality.

Previously identified risk factors for ischemic cholangiopathy (donor age, donor weight and CIT) were highly associated with poor outcomes following DCD liver transplantation, which prompted testing of interactions between these terms in graft failure and mortality models. Several interaction terms between advanced donor age (age >60 years), long CIT (>10 h) and donor body weight (>100 kg) were created and their effects on graft failure and patient mortality were modeled. These interactions were not significantly associated with graft failure or mortality (data not shown).

Discussion

As utilization of DCD liver grafts has increased over the past decade, outcomes following transplantation of these grafts have been compared to outcomes of grafts from brain dead donors (4,8,10–12,24). These comparisons are important, but they do not help transplant providers understand which DCD liver grafts may be associated with acceptable long-term outcomes and which may not. Few studies have attempted to identify risk factors for poor outcomes among the DCD liver transplant population (15,16). We have demonstrated that a number of recipient, donor and transplant factors are independently associated with graft failure and post-DCD transplant mortality. Factors that have been previously identified to be associated with ischemic cholangiopathy, including donor age, donor weight and CIT were independently associated with post-DCD transplant graft failure, but, of these factors, only donor weight and CIT were also shown to affect post-DCD transplant mortality after adjusting for retransplantation.

Authors from several single-center studies have described outcomes following DCD liver transplantation, but these smaller cohorts are generally underpowered to demonstrate significant differences in patient mortality and graft failure risks among DCD recipients. These studies are also difficult to generalize, because individualized center practices and allocation-related issues may affect donor selection (6,8,9,11,14,17,18). Further, these studies do not provide transplant surgeons with information on longer term prognosis. Lee et al. (15) and Mateo et al. (16) previously studied retrospective cohorts derived from OPTN data to create DCD liver risk profiles. Each was driven by transplant factors including CIT greater than 10 h, donor factors including age over 60 years and recipient factors including the need for life support at transplant and previous liver transplant. Our study improves upon the existing literature using an updated cohort of 1567 patients with at least 6 months of posttransplant follow-up. Growing utilization of DCD liver allografts and increasing scrutiny of transplant outcomes warrants the use of robust clinical data from clinical registries to assist providers in assessing individual patient risk. We have demonstrated that more than one-third of DCD liver transplant recipients die or require a subsequent liver transplant 3 years after the initial transplant. This may improve the informed consent process, and help assist providers in providing recommendations to patients given their individual needs and the particular organ availability constraints locally.

The selective utilization of DCD liver grafts by transplant surgeons is based on several factors, which involve judging donor quality before and after organ procurement. Our

Table 2: Predictors of graft failure following DCD liver transplantation[1]

	Variable	Hazard ratio	95% CI		p-Value
Recipient characteristics					
Age at transplant	<18 years (reference 18–55 years)	0.33	0.11	0.95	0.040
	≥55 years (reference 18–55 years)	1.26	1.05	1.52	0.014
Sex	Female (reference male)	0.73	0.59	0.91	0.004
Race	African American (reference white)	1.38	1.02	1.87	0.038
Diagnosis	Metabolic disorders (reference noncholestatic cirrhosis)	2.13	1.31	3.47	0.003
MELD Score	≥35 (reference 15–25)	1.47	1.00	2.16	0.048
Hospitalization status	ICU or non-ICU hospitalization at transplant (reference ambulatory)	1.39	1.09	1.78	0.008
Medical condition at transplant	On life support (reference no life support)	1.46	1.01	2.13	0.045
Hepatitis C virus serology	Positive (reference no, unknown, missing)	1.23	1.01	1.51	0.041
Donor characteristics					
Donor age	<18 years (reference 18–50 years)	0.71	0.50	1.00	0.0498
	50–60 years (reference 18–50 years)	1.39	1.11	1.75	0.0047
	≥60 years (reference 18–50 years)	1.88	1.29	2.74	0.0011
Donor weight	>100 kg	1.56	1.20	2.04	0.0010
Transplant characteristics					
Donor warm ischemia time[2]	≥35 mins (reference <35 mins)	1.84	1.23	2.74	0.0028
Cold ischemia time	6–10 h (reference <6 h)	1.64	1.29	2.08	<0.0001
	10–13 h (reference <6 h)	2.04	1.50	2.78	<0.0001
	≥13 h (reference <6 h)	3.84	2.57	5.74	<0.0001
	Missing (reference <6 h)[3]	2.42	1.77	3.30	<0.0001

[1]Also adjusted for: donor cause of death, race, sex and height, recipient BMI, diabetes, diagnosis, status 1/1A/1B, on dialysis, previous liver transplant, previous malignancy, previous abdominal surgery, history of portal vein thrombosis at transplant, HBV serology and ABO compatibility.
[2]Warm ischemia time was missing in 8.6% of DCD liver recipients.
[3]Cold ischemia time was missing in 10.3% of DCD liver recipients.

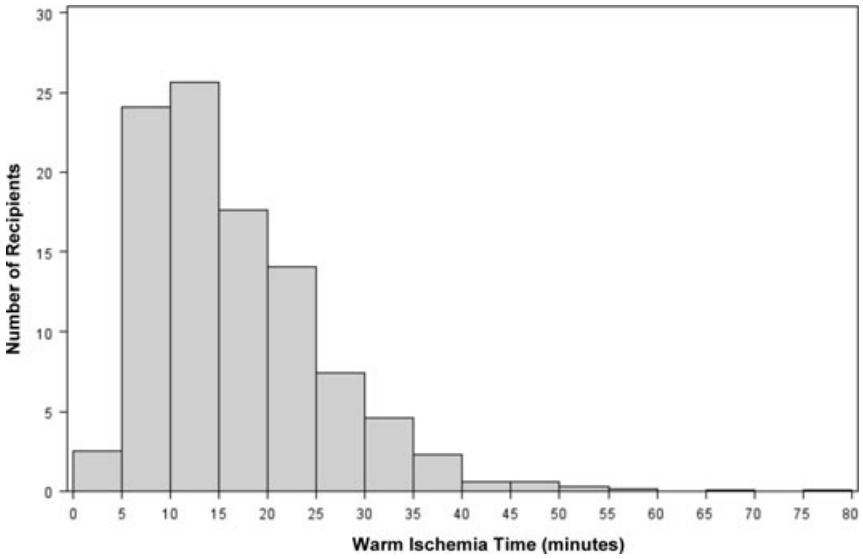

Figure 2: Donor warm ischemia time distribution among 1567 DCD liver transplant recipients. Donor warm ischemia time, defined as the time from cessation of cardiopulmonary support to aortic cannulation and core cooling, was widely dispersed among all DCD liver transplant recipients. The distribution is somewhat leftward shifted, owing to the utilization of some grafts with very long donor warm ischemia times. Notably, 3.8% of DCD liver transplant recipients had grafts implanted with donor warm ischemia times greater than 35 min.

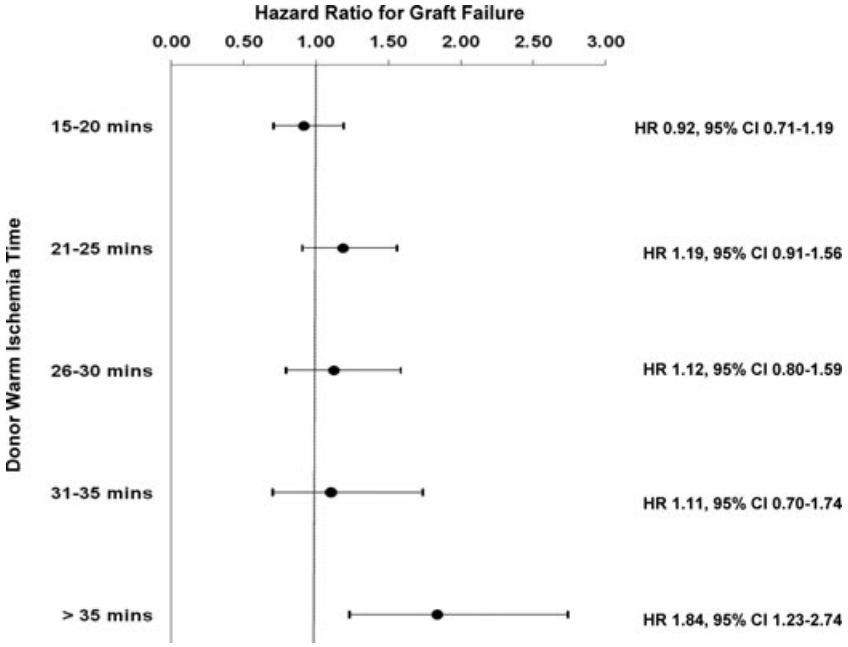

Figure 3: The effect of donor warm ischemia time on graft failure following DCD liver transplantation. Using a multivariable Cox regression approach, we determined that donor warm ischemia time has a significant effect on graft failure risk, defined as requiring retransplantation or death. After several sensitivity analyses, donor warm ischemia time of 35 min or greater was identified as a threshold associated with a significantly increased adjusted rate of graft failure.

study provides a framework from which to judge clinical risk of a DCD liver at the time of organ acceptance. Our data suggest that DCD liver grafts from older, heavier donors with long CIT should be used with caution, given the increased graft failure risk associated with these factors. DWIT was also highly associated with graft failure. However, the relationship between DWIT and graft failure was nonlinear. Instead, an apparent threshold effect was noted at 35 min. We speculate that this may reflect selective discard of poor quality organs with lower warm ischemia time on the basis of surgical judgment, and only limited use (less than 5% of cases) of organs with DWIT longer than 35 min. The duration of DWIT is weighed heavily in the decision to use a DCD liver; its effects are influenced by donor hemodynamics during the agonal phase and by variations in DCD organ recovery practices. Our models are limited by the level of detail available in the DCD donor data submitted to the OPTN. Future analyses will benefit from additional data now being collected during the agonal period, including serial hemodynamic measurements at regular intervals and other physiological parameters (25). The inability to account for variations from standard DCD organ procurement practices is a confounding factor (26), thus reducing the direct applicability of our observational data analyses to individual organ donation events. However, the results presented here may help

Table 3: Predictors of mortality following DCD liver transplantation[1]

Variable		Hazard ratio	Confidence interval		p-Value
Recipient characteristics					
Age at transplant	≥55 years (reference = age 18–55 years)	1.60	1.28	1.99	<0.0001
Retransplant[2]		2.35	1.75	3.17	<0.0001
Hospitalization status	ICU or non-ICU hospitalization at transplant (reference ambulatory)	1.48	1.12	1.97	0.006
Donor characteristics					
Donor weight	>100 kg	1.39	1.02	1.89	0.035
Transplant characteristics					
Cold ischemia time[3]	6–10 h (reference <6 h)	1.49	1.12	1.98	0.0058
	10–13 h (reference <6 h)	1.95	1.36	2.78	0.0003
	≥13 h (reference <6 h)	2.26	1.39	3.69	0.0011
	Missing (reference <6 h)	2.02	1.39	2.92	0.0002

[1]Also adjusted for: donor cause of death, race, sex and height, recipient race, sex, BMI, diabetes, status 1/1A/1B, lab MELD score at transplant, on dialysis, previous malignancy, previous abdominal surgery, recipient BMI, history of portal vein thrombosis at transplant, HBV serology, HCV serology, ABO compatibility, local/shared organ and warm ischemia time.
[2]Time-varying covariate.
[3]Cold ischemia time was missing in 10.3% of DCD liver recipients.

surgeons create better evidence-based DCD acceptance protocols and assist in informing patients of the risks associated with specific types of DCD liver grafts.

MELD-based liver allocation has facilitated improved clinical decision-making in liver transplantation, but the MELD system was not specifically designed to predict posttransplant outcomes (27–31). Nonetheless, in our mortality model, DCD liver recipients with MELD scores greater than 35 at transplant were at significantly higher graft failure risk than those with MELD scores of 15–25. We did not see a similar relationship between MELD and the risk of posttransplant mortality. Any causal relationship between higher recipient MELD at transplant and inferior outcomes among DCD liver transplants could not be derived from our current study, but deserves scrutiny in future work.

The development of ischemic biliary strictures is a major source of morbidity after DCD liver transplant. This injury is very difficult to treat, and although endoscopic and percutaneous biliary drainage may provide symptomatic relief, the underlying pathology in some cases is progressive, ultimately requiring retransplantation or leading to death. We could not calculate the attributable risk of ischemic cholangiopathy in relation to long-term graft or patient outcome, because neither its definition nor time of onset is uniform or reported to the OPTN. Factors associated with ischemic cholangiopathy including older donor age, high donor weight, CIT and DWIT were significant predictors of graft failure in our study (16). Further studies are clearly needed to identify clinical tools that ameliorate the risk of biliary injury in DCD grafts, such as improvements in organ preservation. Progressive DCD liver graft dysfunction causes significant patient morbidity and leads to substantial clinical resource utilization, which may warrant relisting for transplant. Retransplantation was associated with significantly higher mortality risk compared to those whose original grafts survived, but further study is warranted to determine whether modification of allocation rules is necessary to increase access to retransplantation for those with failing DCD liver grafts. Retransplantation of patients with ischemic cholangiopathy and progressive graft dysfunction and/or cholangitis may be challenging, depending on their waiting list priority as measured by lab MELD. Clearly, further clinical and policy investigations are necessary to reduce the incidence and improve outcomes for recipients who develop ischemic cholangiopathy after DCD liver transplant.

Our study has some additional limitations, primarily related to the depth and quality of data available to the SRTR. We observed a significant association between longer DWIT and worse graft outcome. However, this variable is subject to bias related to variation in the practice of DCD organ recovery and volatile hemodynamics following cessation of cardiopulmonary support (26). An additional weakness is related to missing data, as patients who had no recorded CIT had significantly higher risks of graft failure and patient death. Precise interpretation of this finding is impossible. It is possible that the true values for missing CITs are very long, and may be a broader marker of poor organ quality resulting in delayed placement by the organ procurement organization. Alternatively, missing data may be a surrogate for the quality of patient care. Both of these explanations must be considered speculative (32).

In summary, DCD liver transplantation remains an important effort to expand organ availability with 3-year graft survival rates greater than 60%. However, donor, recipient and transplant factors all may be associated with incrementally poorer outcomes following DCD liver transplantation. Further study is needed to refine our understanding of these risk factors, and the events that define the impact of DWIT, such that donor and recipient selection may be modified in the hopes of allowing optimal selective use of livers from DCD donors.

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This study was approved by the US HRSA SRTR project officer. HRSA has determined that this study satisfies the criteria for the IRB exemption described in the 'Public Benefit and Service Program' provisions of 45 CFR 46.101(b)(5) and HRSA Circular 03.

Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

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