American Journal of Transplantation 2009; 9: 773–781
Wiley Periodicals Inc.

doi: 10.1111/j.1600-6143.2009.02560.x

Liver Transplantation Using Donation After Cardiac Death Donors: Long-Term Follow-Up from a Single Center

M. E. de Vera*, R. Lopez-Solis, I. Dvorchik, S. Campos, W. Morris, A. J. Demetris, P. Fontes and J. W. Marsh

Thomas E. Starzl Transplantation Institute, University of Pittsburgh Medical Center, Pittsburgh, PA
Presented in part at the 2008 American Transplant Congress, Toronto, Canada
**Corresponding author: Michael E. de Vera, deverame@upmc.edu*

There is a lack of universally accepted clinical parameters to guide the utilization of donation after cardiac death (DCD) donor livers and it is unclear as to which patients would benefit most from these organs. We reviewed our experience in 141 patients who underwent liver transplantation using DCD allografts from 1993 to 2007. Patient outcomes were analyzed in comparison to a matched cohort of 282 patients who received livers from donation after brain death (DBD) donors. Patient survival was similar, but 1-, 5- and 10-year graft survival was significantly lower in DCD (69%, 56%, 44%) versus DBD (82%, 73%, 63%) subjects ($p < 0.0001$). Primary nonfunction and biliary complications were more common in DCD patients, accounting for 67% of early graft failures. A donor warm ischemia time >20 min, cold ischemia time >8 h and donor age >60 were associated with poorer DCD outcomes. There was a lack of survival benefit in DCD livers utilized in patients with model for end-stage liver disease (MELD) ≤30 or those not on organ-perfusion support, as graft survival was significantly lower compared to DBD patients. However, DCD and DBD subjects transplanted with MELD >30 or on organ-perfusion support had similar graft survival, suggesting a potentially greater benefit of DCD livers in critically ill patients.

Key words: Extended donor criteria, graft failure, graft outcome, MELD score

Abbreviations: LTx, liver transplantation; DCD, donation after cardiac death; DBD, donation after brain death; HCV, hepatitis C virus; CMV, cytomegalovirus; MV, mechanical ventilation; HD, hemodialysis.

Received 08 October 2008, revised 16 December 2008 and accepted for publication 20 December 2008

Introduction

The critical shortage of organs has prompted a marked increase in the use of donation after cardiac death (DCD) donors in liver transplantation (LT) (1). Studies, however, have shown that graft survival of DCD livers are inferior to that of donation after brain death (DBD) donor livers (2–5), with one study estimating a relative risk of graft failure of 1.85 times higher in DCD patients compared to DBD recipients (3). The incidence of primary nonfunction (PNF) using DCD livers has ranged from 0% to 5.5%, while biliary complication rates have been reported to be higher compared to DBD allografts (13–37% vs. 1–20%) (2,6,7). There are currently a number of issues pertaining to the use of DCD livers that remain unresolved, as the majority of studies on DCD outcomes have come from reviews of the United Network of Organ Sharing (UNOS) data base (3–5) or single-center studies that have reported on relatively small numbers of patients (2,6–10). For instance, there are no widely accepted DCD donor parameters predictive of good outcomes that could guide surgeons on whether or not to use or discard a DCD liver. In addition, it is unclear and controversial as to which patients would benefit the most from the use of these allografts (3,5). In this study, we attempt to address these issues and report our experience and the long-term outcomes of patients who received DCD livers at the University of Pittsburgh Medical Center (UPMC). This study follows a description in 1995 of our initial DCD LT experience from 1989 to 1993 (11).

Patients and Methods

Following Institutional Review Board approval, a retrospective review from a prospectively established data base was performed in 2845 adult patients who underwent LT at the Starzl Transplantation Institute at UPMC between March 1993 and October 2007. Donor and recipient characteristics were reviewed and 141 (5%) patients who underwent 142 liver transplants from DCD donors (one patient was transplanted twice with a DCD liver) were identified. Twenty-one DCD LT were performed from 1993 to 1999 and 120 were performed from 2000 to 2008. Each DCD patient was randomly matched to two DBD subjects according to time of transplant (within 0.2 ± 1 years), patient age (within 0.6 ± 8 years), model for end-stage liver disease (MELD) score (within 0.3 ± 3 points), donor age (within 1.9 ± 8.7 years) and retransplant status (i.e. patients undergoing retransplantation were matched accordingly to control patients), with each variable

being given similar importance. In addition, patients with hepatitis C and/or hepatocellular carcinoma were matched to corresponding patients as were patients on mechanical ventilation (MV) and hemodialysis (HD) prior to transplantation in >90% of cases. The MELD score utilized was the physiologic or 'native' MELD based on laboratory values obtained immediately prior to transplantation, and not from MELD upgrades or exception points, assuring an accurate analysis of patients' severity of illness at the time of transplant.

The DCD procurement protocol of our local organ procurement organization follows the 1997 Institute of Medicine Guidelines (12), and the donor technique utilized for the procurement of DCD donor livers has been previously described in detail (11). Briefly, patients are withdrawn from organ-perfusion support inside the operating room and systemic heparin (50 000 units) is administered prior to extubation, with another 10 000 units mixed into the first bag of preservation solution. Following pronouncement of the donor by an independent physician and after a prescribed time ranging from 2 min to 5 min, rapid cannulation of the abdominal aorta and cold perfusion of organs with either University of Wisconsin (UW) solution (3,000–5,000 mL) or Histidine–Tryptophan–Ketoglutarate (HTK) solution (10 000–15 000) is performed, with portal perfusion accomplished in the back table. The common bile duct is also infused directly gently with several injections of cold preservation solution. Donor warm ischemia time (DWIT) was defined as the time interval between extubation of the donor to the perfusion of organs, and cold ischemia time (CIT) was defined as the time interval from perfusion of organs during the recover to reperfusion of the liver in the recipient. A liver biopsy was performed in select cases wherein the donor surgeon felt it was necessary to assist in the decision-making process to utilize the organ; 72 (51%) of the DCD versus 112 (40%) of the DBD livers were biopsied. Beginning in 2002, our center began accepting DCD livers procured by other centers.

Graft survival and adverse outcomes

The primary outcome measures in the study were patient survival, graft survival and the occurrence or development of PNF, delayed graft function (DGF), biliary complications or retransplantation. Graft survival was defined as the time from transplantation to either retransplantation or patient death, with 'early' and 'late' graft failure occurring within 1 year and greater than 1 year posttransplantation, respectively. PNF was defined as primary graft failure within 7 days after transplantation requiring retransplantation or leading to patient death, while DGF was defined as primary graft failure characterized by cholestasis within 6 months of transplantation in the absence of hepatic artery thrombosis (HAT) or biliary complications, also leading to retransplantation or patient death. The following donor and recipient variables were tested for their association with the primary outcome measures: Donor age >60 versus ≤60 years, CIT >8 versus ≤8 h, DWIT >20 versus ≤20 min, male donor to female recipient transplants, donor body mass index (BMI) >30 versus ≤30 kg/m^2, recipient age >60 versus ≤60 years, MELD score >30 versus ≤30, use of MV pretransplantation, use of HD pretransplantation, recipient BMI >30 versus ≤30 kg/m^2 and recipient male gender. These variables were chosen as they have been shown in other studies to be predictive of poor outcomes after LT (4,5,7,13). In addition, since these factors are known at the time of transplant, they may potentially serve as clinical parameters that could be utilized to determine whether a DCD liver should be used or discarded at the time of procurement. The total and ICU cost per patient were estimated costs and were obtained from hospital records and reported as relative units (RU).

Statistical analysis

Patient and graft survival analysis was performed using the Kaplan–Meier method, and survival between groups was compared using the log-rank test. Multivariate analyses to identify variables independently associated with graft survival were performed using Cox proportional-hazards analysis. Continuous variables were analyzed using the Student's *t*-test or Mann–Whitney U test when appropriate, and categorical variables were analyzed using Pearson's chi-square test or Fisher's exact test when appropriate. Variables found to be significant or approaching significance ($p \leq 0.08$) in the univariate analyses looking at the development of PNF, DGF, biliary complications and retransplantation were entered into a stepwise multivariate binary logistic regression analysis. Statistical significance was defined as a p-value of <0.05. All analyses were performed using SPSS 15.0 or 16.0 statistical software (SPSS Inc, Chicago, IL).

Results

The DCD (141 patients) and DBD (282 patients) groups were well matched in recipient and donor demographics (Table 1). Total bilirubin and serum transaminases 1 week posttransplantation were similar between both groups; however, DCD patients had significantly higher INR at 1 week. Peak AST and ALT as well as total bilirubin levels at 1 month posttransplantation were significantly higher in the DCD patients. There was no difference in the total hospital length of stay (LOS) per patient between the groups but there was a trend to a longer ICU LOS per patient in DCD patients. In addition, the ICU cost and the total hospitalization cost per patient was significantly higher in the DCD group by 1.7 RU and 1.2 RU, respectively. The mean DWIT in the DCD group was 19.8 ± 8.8 min (range, 7–53 min); data were unavailable in seven donors. There was no significant difference between the DCD and DBD groups in their cumulative 1-, 5- and 10-year patient survival (DCD, 79%/70%/57% vs. DBD, 85%/76%/64%, $p = 0.08$ by log-rank analysis) (Figure 1). Graft survival, however, was significantly worse in the DCD group compared to the DBD cohort (69%/56%/44% vs. 82%/73%/63%, respectively, $p < 0.0001$ by log-rank analysis). When compared to DBD patients, DCD subjects had a significantly higher incidence of PNF (12% vs. 3%, $p < 0.001$), biliary complications (25% vs. 13%, $p < 0.001$) and retransplantation (18% vs. 7%, $p < 0.001$), whereas no difference was noted in HAT rates (6% vs. 6%, $p = 1.00$). We found no differences in the outcomes of locally procured versus imported DCD livers with respect to 1-, 5- and 10-year graft survival rates (65%/57%/42% vs. 75%/55%/48%, respectively, $p = 0.42$ by log-rank test) or the incidence of PNF (14% vs. 9%, $p = 0.43$), bile duct complications (31% vs. 17%, $p = 0.08$) and retransplantation (22% vs. 14%, $p = 0.27$). In addition, of 75 patients transplanted after 2000 in whom data regarding the type of preservation solution utilized was available (61 patients with HTK vs. 14 patients with UW solution), no significant differences were found in graft survival ($p = 0.54$ by log-rank analysis), PNF/DGF (0.25), retransplantation ($p = 1.00$), bile duct complications ($p = 0.32$) and HAT rates ($p = 0.34$) between recipients of either preservation solution.

Causes of graft failure in DCD patients

We examined the impact of several donor and recipient characteristics on graft survival and the occurrence of PNF,

Table 1: Demographics of DCD and DBD donor liver transplant patients

Characteristics	DCD	DBD	p-Value
Number of patients	141	282	
Recipient age (Years)	53.1 ± 10.7	53.7 ± 9.3	0.55
Recipient gender (M:F)	90 (64%):51 (36%)	172 (61%):110 (39%)	0.60
Recipient BMI	27.8 ± 5.5	28.4 ± 5.5	0.25
MELD score	18.3 ± 9	18.5 ± 8	0.78
MV prior to LTx	22 (15%)	33 (12%)	0.35
HD prior to LTx	17 (12%)	34 (12%)	0.76
Liver transplant: Primary	125 (89%)	250 (89%)	0.95
Second	14 (10%)	29 (10%)	
Third	2 (1%)	3 (1%)	
Donor age (Years)	37.1 ± 15.9	39.1 ± 16.1	0.23
Donor gender (M:F)	95 (67%):46 (33%)	166 (59%):116 (41%)	0.11
Donor BMI	26.3 ± 5.9	26.6 ± 7.2	0.70
CIT (Min)	657 ± 170	636 ± 177	0.25
T. Bili 1 week	7.0 ± 6.2	6.1 ± 6.4	0.18
T. Bili 1 month	3.2 ± 4.6	2.3 ± 3.7	0.05
ALT 1 week	162 ± 223	164 ± 250	0.93
AST 1 week	120 ± 552	78 ± 223	0.30
INR 1 week	1.3 ± 0.3	1.2 ± 0.2	0.003
Peak ALT	1774 ± 1546	1331 ± 1750	0.01
Peak AST	4694 ± 4088	2464 ± 2721	<0.001
ICU LOS per patient (days)	21.5 ± 25.6	16.6 ± 25.3	0.07
Total LOS per patient (days)	34.6 ± 30.6	31.3 ± 33.2	0.35
ICU Cost per patient (estimated)	1.7 RU	RU	<0.001
Total cost per patient (estimated)	1.2 RU	RU	0.05

development of biliary complications and retransplantation in DCD patients, as well as contrasted the timing and incidence of these complications to DBD patients. Overall, 62/141 (44%) DCD grafts failed compared to 76/282 (27%) DBD grafts ($p = 0.001$). In order to more accurately assess and compare the causes of graft failure between cohorts, patients who died with functioning grafts (12 [19%] DCD vs. 42 [55%] DBD patients, $p < 0.001$) were censored, resulting in an adjusted number of 50 DCD livers and 34 DBD livers that failed. Forty (80%) of the DCD livers and 25 (73%) of the DBD grafts failed within the first year of transplant ($p = 0.8$). PNF/DGF and biliary complications were the major causes of early graft failure, cumulatively accounting for 67% of early graft failures in the DCD group versus 48% in the DBD patients ($p = 0.001$), demonstrating a significant difference in graft failure patterns between both groups. Other causes of early graft failure in DCD patients included HAT (10%) and deaths from sepsis/multiorgan failure (19%), while DBD patients also lost their grafts from intraoperative deaths from cardiovascular complications (28%), HAT (8%), humoral rejection (4%), HCV recurrence (8%) and deaths from sepsis and multiorgan failure (4%). Causes of late graft failure (greater than 1-year posttransplantation) in the DCD group included recurrent disease (PBC and HCV, 30%), biliary complications (20%), deaths from sepsis and multiorgan failure (20%) and vascular complications (20%) (one patient was lost to follow-up and died of unknown causes), whereas late graft failure etiologies in the DBD cohort included chronic rejection (11%), biliary complications (11%), recurrent disease (67%) and vascular complications (11%). There were 43 (30%) HCV+, DCD patients versus 81/282 (29%) ($p = 0.73$). Of note, we did not utilize any HCV+, DCD allografts but had 16 HCV+, DBD livers ($p = 0.002$). Graft loss from HCV recurrence was not significantly different between the DCD (1/43 [2.3%]) and DBD (7/81 [8.6%]) groups ($p = 0.73$).

Univariate analysis with the log-rank test revealed that in DCD patients, poor graft survival was associated with a DWIT >20 min ($p = 0.07$), recipient MELD score >30 ($p = 0.08$), use of MV pretransplantation ($p = 0.05$) and recipient BMI >30 ($p = 0.05$). Multivariate analysis using a Cox proportional hazard model showed that a MELD >30 ($p = 0.04$) was an independent predictor of poor graft survival in DCD LT, while DWIT >20 min ($p = 0.08$) and recipient BMI >30 ($p = 0.07$) were factors that approached significance (Table 2). Univariate analysis in DBD recipients showed that inferior graft survival was associated with transplantation of patients with MELD >30 ($p = 0.02$), use of MV pretransplantation ($p = 0.001$) and the use of HD pretransplantation ($p = 0.002$). Multivariate analysis revealed that only the use of MV pretransplantation was an independent predictor of poor graft survival in DBD patients.

Comparison of DCD patients who underwent LT before or after 2000 showed no significant differences in graft survival ($p = 0.31$ by log-rank test). Prior to 2000, the majority of DCD grafts were lost within 3 months of transplantation, and although not statistically significant, there was a

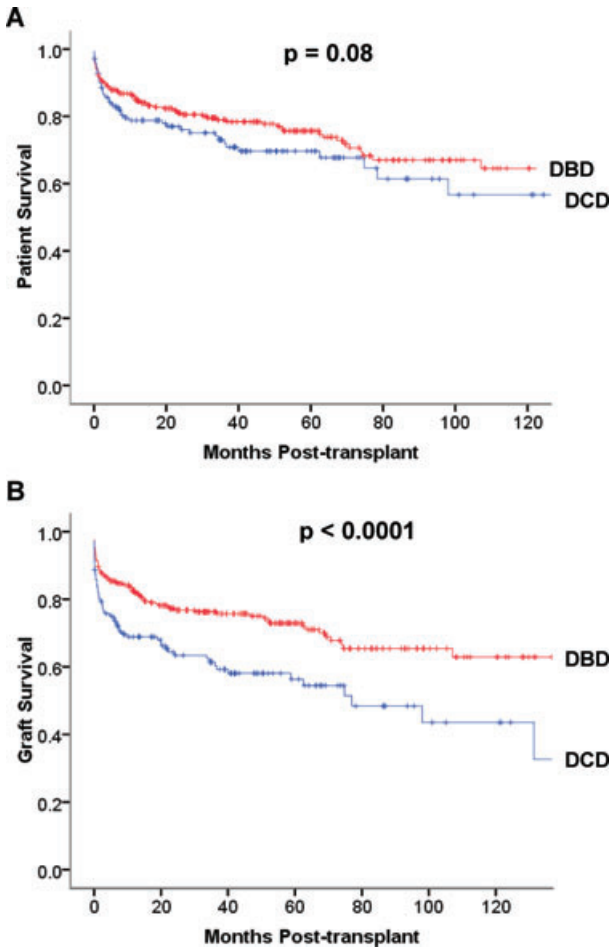


Figure 1: Kaplan–Meier (A) Patient and (B) graft survival curves of DCD and DBD patients with survival comparison using the log-rank test.

trend to a higher rate of PNF/DGF (19% vs. 11%, p = 0.18) and HAT (14% vs. 4%, p = 0.1) when DCD patients transplanted prior to and after 2000 were compared. Relative to DBD patients, DCD subjects transplanted before or after 2000 had lower 1- and 5-year graft survival rates irrespective of the era (before 2000—73%/65% vs. 52%/48%, respectively, p = 0.02; after 2000—84%/74% vs. 72%/56%, respectively, p = 0.002).

Retransplantation

Twenty-six (18%) DCD patients underwent retransplantation, 21 (81%) within the first year of transplant. Similarly, 16 DBD patients were retransplanted, 12 (75%) within the first year (p = 1.00 vs. DCD). Reasons for early retransplantation in the DCD group included PNF/DGF (76%), biliary complications (9%), HAT (9%) and hepatic vein outflow obstruction (5%), while PNF/DGF (66%), ischemic cholangiopathy (17%) and HAT (17%) were early retransplant etiologies in DBD patients. Univariate analyses showed that the use of donors >60 years (p = 0.08) and the transplantation of recipients >60 years (p = 0.001) were associated with retransplantation in DCD patients; only the latter (p = 0.02) was found in multivariate analyses to be an independent predictor of retransplantation (Table 2). Causes of late retransplantation (greater than 1-year post-transplantation) in the DCD group included recurrent PBC (20%), ischemic cholangiopathy with bile casts (40%) and vascular complications (40%), while recurrent HCV (75%) and chronic rejection (25%) were etiologies for late retransplantation in DBD patients. None of the donor or recipient variables by univariate analysis were found to be associated with the development of PNF in DBD patients.

Table 2: Multivariate analyses of DCD and DBD donor and recipient risk factors for poor outcomes after liver transplantation

Variable	HR/RR (95% C.I.)	p-Value
DCD patients		
Inferior graft survival	HR	
DWIT >20 min	1.63 (0.94–2.81)	0.08
MELD >30	2.00 (1.03–3.90)	0.04
Recipient BMI >30	1.69 (0.96–2.98)	0.07
Retransplantation	RR	
Recipient age >60	12.19 (1.58–94.1)	0.02
Occurrence of bile duct complications	RR	
Donor age >60	5.61 (0.98–32.2)	0.05
Occurrence of PNF/DGF	RR	
Male donor to female recipient	3.72 (1.28–10.8)	0.02
Recipient age >60	5.71 (1.16–28.0)	0.03
Recipient BMI >30	3.68 (1.31–10.3)	0.01
DBD patients		
Inferior graft survival	HR	
Use of MV pretransplant	2.33 (1.36–4.00)	0.002
Retransplantation		
No risk factors identified		
Occurrence of bile duct complications		
No risk factors identified		
Occurrence of PNF/DGF		
No risk factors identified		

PNF

PNF occurred in 17 DCD patients, and 14 (82%) underwent retransplantation. Seven patients died, including 3 who were too sick to be retransplanted. Three other patients had DGF requiring retransplantation within 3 months after the initial LTx. Univariate analysis revealed that both PNF/DGF was associated with transplantation of male donors to female recipients (p = 0.06), recipients >60 years (p = 0.06) and recipients with BMI >30 (p = 0.03). Multivariate analysis using step-wise logistic regression showed that these three variables—transplantation of male DCD donors to female recipients (p = 0.02), recipients >60 years (p = 0.03) and recipients with BMI >30 (p = 0.01), were all independent predictors of PNF/DGF (Table 2). In the DBD cohort, 6 (2%) patients developed PNF and 4 (1%)

developed DGF. All PNF patients and 2 DGF subjects were retransplanted, and overall, 6 of the 10 patients expired. None of the donor or recipient variables by univariate analysis were found to be associated with the development of PNF in DBD patients.

Biliary complications

Biliary complications occurred in 36 (25%) patients; 18 (50%) developed graft failure, including 9 (25%) who underwent retransplantation and 13 (36%) patients died. Bile duct complications consisted of intrahepatic strictures (ischemic cholangiopathy with or without bile casts) along with a concomitant anastomotic stricture (23 patients), isolated anastomotic strictures (10 patients) and bile leaks (3 patients). Biliary problems were diagnosed in 33 patients using endoscopic retrograde cholangiopancreatography (ERCP) and percutaneous transhepatic cholangiography in three subjects. All 18 patients whose grafts did not fail were managed with ERCP and stenting. Univariate analysis showed that biliary complications were associated with the use of donors >60 years ($p = 0.08$) and transplantation of patients on HD at the time of transplant ($p = 0.001$). Multivariate analysis revealed that only transplantation of donors >60 years ($p = 0.05$) was an independent predictor of the development of bile duct complications (Table 2). Indeed, 4 out of 6 (67%) DCD patients who received grafts from donors >60 years developed biliary complications, with half requiring retransplantation. In marked contrast to DCD patients, 75% of bile duct complications in DBD subjects were due to anastomotic strictures (21/28 patients), the majority of which was managed with ERCP. Of the remaining 7 patients, 3 had bile leaks, 2 had biliary complications because of hepatic artery stenosis and 1 patient had PSC recurrence. Only 2 DBD subjects developed and underwent retransplantation for ischemic cholangiopathy with bile casts ($p < 0.01$ compared to DCD patients). None of the donor or recipient variables tested by univariate analysis were found to be associated with the development of bile duct complications in DBD patients.

DCD donor determinants

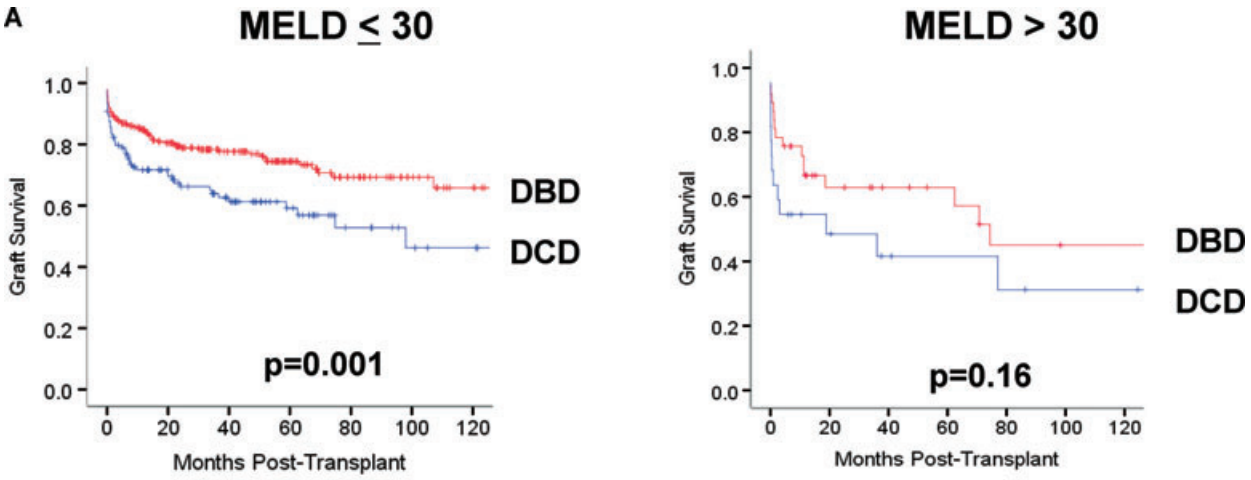
There are currently no universally accepted donor parameters to guide surgeons on whether or not a DCD liver procured should be used for transplantation. Perhaps the most significant parameter is the DWIT, as by definition, this is the major factor that distinguishes DCD from DBD donors. A DWIT >20 min was associated in this study with poorer graft survival, with a RR of 1.63 (95% CI, 0.94–2.81, $p = 0.08$) (Table 2). Surprisingly, CIT was not found to be significantly associated with poor outcomes in DCD patients; however, the incidence of PNF was 2.5 times less in patients with a CIT ≤8 h versus those with a CIT >8 h (1/20 [5%] versus 16/121 [13%] patients, respectively, $p = 0.47$). Patients who underwent LT from DCD donors >60 years had a markedly high rate of biliary complications (67%), with a RR of 5.61 (95% CI, 0.98–32.2, $p = 0.05$) (Table 2). Therefore, based on these data, our donor criteria for utilizing DCD livers for transplantation at UPMC are: DWIT ≤20 min, donor age ≤60 years and CIT ≤8 h (Table 3).

Effect of MELD score on graft survival of DCD and DBD patients

Because the use of DCD livers is associated with poorer graft survival, there is no consensus and it is unclear as to which patients would benefit the most from the use of these organs (3,5). There is evidence that sicker patients may benefit the most from the use of livers from 'extended criteria donors' (14,15). We thus examined the impact of the MELD score and the use of pretransplant organ-perfusion support (MV or HD) on graft survival of DCD and DBD patients. Patients with a MELD score ≤30 had significantly lower 1-, 5- and 10-year graft survival rates when transplanted with DCD compared to DBD livers (72%/59%/46% vs. 85%/74%/66%, respectively, $p = 0.001$) (Figure 2A), with a HR of 1.88 (95% CI [1.29–2.75]). At MELD scores >30, however, DCD recipients had graft survival rates that were lower, but not statistically significant, than DBD patients (54%/42%/31% vs. 67%/63%/45%, respectively, $p = 0.16$). DCD and DBD patients in both MELD groups had comparable donor and recipient characteristics (Figure 2A). On a similar note, we found that DCD and DBD patients on MV and/or HD at the time of transplant had similar 1-, 5- and 10-year graft survival rates (DCD, 66%/52%/32% vs. DBD, 68%/59%/41% [$p = 0.59$]) whereas patients not on either MV or HD had significantly worse graft survival when they received DCD allografts (DCD, 70%/58%/47% vs. DBD, 86%/76%/68% [$p < 0.001$]), with a HR of 2.15 (95% CI, 1.45–3.19). Both DCD and DBD patients on or off pretransplant HD and/or MV were also well matched in donor and recipient variables (Figure 2B). The 1-, 5- and 10-year patient survival in DCD and DBD patients with MELD >30 (68%/55%/46% and 67%/63%/45%, respectively, $p = 0.82$) or on MV and/or HD (74%/60%/41% and 70%/61%/42%, respectively, $p = 0.96$) were similar. Patient survival rates in DCD and DBD patients with MELD ≤30 (81%/72%/58% and 88%/78%/68%, respectively, $p = 0.09$) was similar but trending toward inferior outcomes in DCD patients, while patients not on MV and/or HD had worse patient survival when they received DCD versus DBD livers (80%/72%/61% and 88%/79%/70%, respectively, $p = 0.04$). Overall, these data demonstrate that 'sicker', high-risk recipients have a greater patient and graft survival benefit from the transplantation of DCD livers compared to patients who are not as critically ill.

Table 3: University of Pittsburgh donor criteria for the utilization of DCD livers

DWIT ≤20 min
Donor age ≤60
CIT ≤8 h

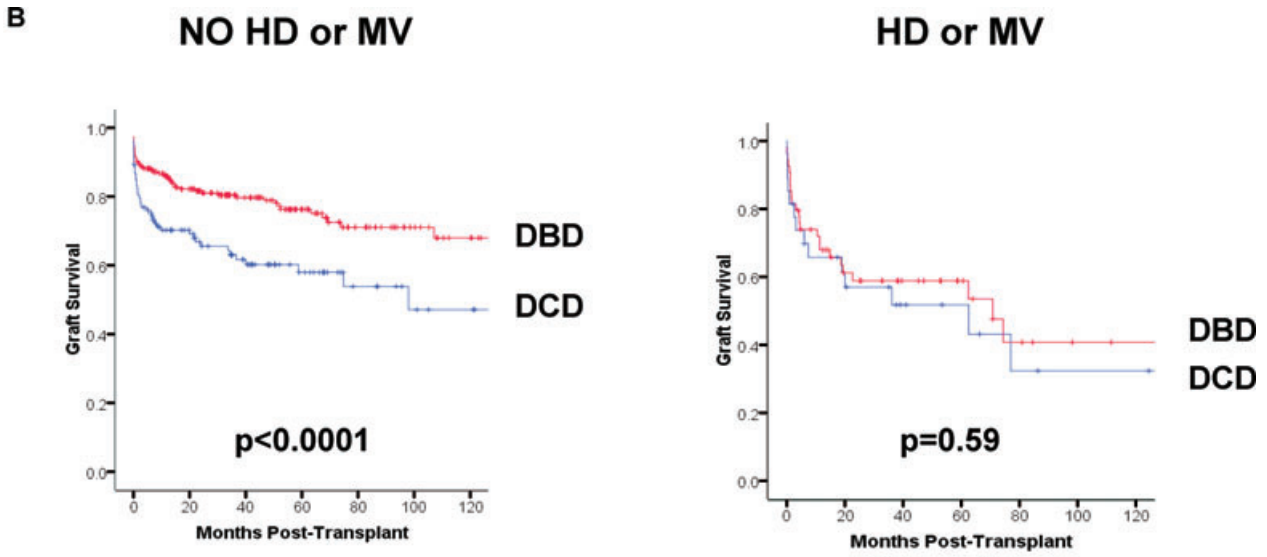


	MELD ≤ 30			MELD > 30		
	DCD (119 pts)	DBD (245 pts)	*p*	DCD (22 pts)	DBD (37 pts)	*p*
Recipient age	53.7 ± 10.1	54.1 ± 9.2	0.66	50 ± 13.4	59.8 ± 9.3	0.78
Recipient M:F	66%/34%	62%/38%	0.42	50%/50%	57%/43%	1.00
Recipient BMI	27.8 ± 5.5	28.2 ± 5.4	0.57	27.4 ± 5.1	30 ± 6.5	0.12
# on MV or HD	12 (10%)	29 (12%)	0.72	15 (68%)	25 (68%)	1.00
Donor age	38.3 ± 16	40.2 ± 16.1	0.30	30.4 ± 13.8	31.6 ± 13.8	0.76
Donor BMI	26.6 ± 5.8	27.1 ± 7.5	0.52	25.2 ± 6.6	23.6 ± 4	0.25
CIT	670 ± 171	649 ± 174	0.29	588 ± 153	548 ± 179	0.39
Male donor to female recipient	32 (27%)	45 (18%)	0.08	6 (27%)	11 (30%)	1.00

Figure 2: Effect of (A) MELD score and (B) pretransplant organ-perfusion support (HD, hemodialysis; MV, mechanical ventilation) on graft survival of patients assessed by Kaplan–Meier analysis and Cox proportional-hazards analysis. Tables demonstrate that groups in each stratum were well-matched.

Discussion

This report describes a large single-center experience utilizing DCD liver allografts with a follow-up of over 10 years. Compared to a well-matched cohort of DBD subjects, DCD patients had poorer graft survival and also had a trend to worse patient survival (Figure 1). These results are consistent with other reports on DCD outcomes (2–5) and also supports the recent study of Feng et al., which assigned DCD livers a relatively high donor risk index (DRI) (16). DCD recipients also had significantly higher ICU and total costs per patient and there was a trend to longer ICU LOS per patient compared to DBD subjects. Multivariate analysis showed that poorer graft survival in DCD transplants was independently associated with the transplantation of patients with MELD >30 or BMI >30 or the use of allografts with DWIT >20 min (Table 2), whereas inferior graft survival in DBD transplants was associated with pretransplant MV. The attrition in DCD grafts occurred early within the first year of transplant and was due to the high incidence of PNF/DGF and biliary complications, which also led to a higher retransplantation rate in the DCD group. Of note, the survival curves of both cohorts became parallel after the first year, suggesting that therapeutic interventions to decrease the occurrence of these complications will significantly impact and improve the utility of these grafts. PNF/DGF were the leading causes of early graft failure in the DCD group, accounting for 50% of the cases, and by multivariate analyses were found to be associated with the transplantation of male donor livers to female recipients and of recipients >60 years or with a BMI >30. We also found that a CIT ≤8 h was associated with a much lower incidence of PNF, though this did not reach statistical significance likely because of low patient numbers. Biliary



	No HD or MV			HD or MV		
	DCD (113 pts)	DBD (228 pts)	*p*	DCD (27 pts)	DBD (54 pts)	*p*
Recipient age	53.7 ± 9.6	54 ± 9.4	0.76	50.8 ± 14.8	52.5 ± 8.7	0.51
Recipient M:F	67%/33%	61%/39%	0.34	48%/52%	59%/41%	0.36
Recipient BMI	27.8 ± 5.2	28 ± 5.1	0.74	27.4 ± 6.6	30 ± 6.9	0.11
MELD	15 ± 7	16 ± 7	0.37	15 (68%)	25 (68%)	0.35
Donor age	38 ± 16	40 ± 16	0.27	30.3 ± 7.5	28.6 ± 7.3	0.55
Donor BMI	26.6 ± 5.9	27.2 ± 7.5	0.51	25.2 ± 5.8	24.4 ± 5.5	0.55
CIT	667 ± 160	651 ± 176	0.39	619 ± 205	575 ± 173	0.31
Male donor to female recipient	27 (24%)	42 (18%)	0.25	11 (41%)	14 (26%)	0.21

Figure 2: Continued

complications were the second leading cause of graft failure in DCD subjects and occurred in 25% of patients, an incidence comparable to other studies (2,6,7). We rigorously analyzed all bile duct complications and categorized occurrences of ischemic cholangiopathy with or without bile casts, anastomotic strictures and bile leaks in the analyses. Although there was a high rate of biliary complications associated with DCD livers, 50% of the patients with bile duct problems did not progress to graft failure and were successfully managed endoscopically, including some patients with ischemic cholangiopathy, demonstrating that the occurrence of biliary complications in DCD patients in our experience was not necessarily synonymous with graft loss. Biliary complications were highly associated with the use of donors >60 years (RR, 5.61 [95% CI, 0.98–32.2, p = 0.05]) (Table 2). Although the hepatic arterial system is relatively 'atheroresistant' compared to some other organs, it is still susceptible to age-related fibrointimal hyperplasia that can limit the arterial end-organ circulation of the biliary tree. Ischemic cholangiopathy in DCD livers is thought to be related to the warm ischemia time incurred during the procurement process while waiting for the donor to be pronounced. In addition to the hypoxic injury, this period of DWIT results in sludging of blood components (e.g. platelets) in the peribiliary plexus and leads to suboptimal reperfusion and ischemic injury to the biliary tree (17). The

lack of a standard definition of the DWIT, however, has been problematic (18), making studies that utilize UNOS data difficult to interpret, confounding comparisons of individual DCD studies, and preventing valid recommendations of a DWIT ceiling above which would predict poor outcomes. Our definition of DWIT was unambiguous—from time of extubation to complete organ perfusion, and we did not use a blood pressure threshold below which would define the beginning of the DWIT as others have (7,10), as tissues are still hypoxic in a DCD donor who maintains a blood pressure but has ceased to ventilate. Taking all of these data into consideration, our current donor guidelines and recommendations for utilizing DCD liver allografts at UPMC are: DWIT $\leq$20 min, donor age $\leq$60 and CIT $\leq$8 h (Table 3). Although CIT $\leq$8 h was not statistically significantly associated with inferior outcomes, the incidence of PNF in our experience was much lower compared to DCD allografts with CIT $>$8 h (5% vs. 13%), consistent with the findings of Abt et al. wherein the incidence of graft loss decreased from 30.4% to 10.8% in patients with CIT $<$8 h (4). Slight variations of these parameters have been suggested in other studies (4–7,18); however, the current report is the first from a large single-center experience to verify these donor determinants.

Because of the overall poorer outcomes associated with DCD LT, there has been controversy as to which patients would be the most appropriate to receive these allografts (3,19,20). Addressing this matter is of particular importance, as the number of DCD donors has increased significantly in the last several years. Multivariate analyses revealed that recipients of DCD livers with age $>$60 and BMI $>$30 had worse outcomes, as did subjects with a MELD $>$30 (Table 2), suggesting that the use of DCD allografts should be avoided in patients with these characteristics. Two recent UNOS data base reviews have, indeed, advocated utilizing DCD livers in 'low-risk' recipients, as 'high-risk' patients on MV ('organ-perfusion support') or on HD were shown to have higher rates of graft loss compared to DBD patients (5,20). However, an important caveat is that neither of these reports stratified DBD patients into risk categories that matched the low- and high-risk DCD patients. By contrast, our analysis revealed that in DCD and DBD patients that were well matched across all risk groups (Figure 2), DCD recipients with MELD $\leq$30 had significantly worse graft survival compared to DBD control patients ($p = 0.001$), whereas DCD and DBD patients with MELD scores $>$30 had graft survival rates that were not significantly different ($p = 0.16$). One can argue that there was a recognizable trend toward worse graft survival rates in DCD patients with MELD scores $>$30 compared to DBD subjects, and it is possible that there may be an associated type II error because of the relatively low patient numbers. However, our analysis also showed that critically ill DCD and DBD patients on MV and/or HD had comparable graft survival rates (Figure 2B), altogether suggesting that sicker, high-risk patients may benefit more from, and thus be more appropriate recipients of DCD livers. Although multivariate analysis of the DCD cohort alone showed better graft survival when DCD livers were utilized in patients with MELD scores $\leq$30 (Table 2), this 'advantage' was not enough to offset the poorer graft outcomes of DCD patients in comparison to matched DBD patients in this MELD score category, demonstrating an apparent lack of survival benefit of DCD livers in this subgroup of patients. In addition, patient survival also paralleled graft survival in that sicker DCD and DBD patients (MELD $>$30 or patients on MV and/or HD) had similar patient survival rates while those not as critically ill (not on MV and/or HD) had significantly lower patient survival. Extended criteria donor livers can be safely and suitably transplanted into sick and critically ill patients with relatively good outcomes (14,15), and our findings are consistent with a recent report that demonstrated a failure to maximize survival benefit when high DRI deceased donor livers (e.g. DCD allografts) were transplanted into lower-MELD patients (21).

We currently have not practiced a strict policy of transplanting DCD livers only to critically ill patients. A perfect match between the DCD donor and high-risk recipient and the performance of an uncomplicated transplant is crucial as these critical patients must be able to survive a potential rocky reperfusion and overcome the severe fibrinolysis and coagulopathy that typically occur with these allografts. More importantly, it is striking to note that the 5- and 10- year graft survival rates in patients with MELD $>$30 or those on organ-perfusion support was quite inferior in comparison to less critically ill subjects, making the utilization of DCD allografts less than ideal in the former group of patients. However, these outcomes were irrespective of the type of graft utilized (DCD or DBD) and most likely reflect the generally poorer long-term outcomes of LT in the critically ill. We firmly believe that there are other groups of patients that may have a true survival benefit from DCD liver transplants, such as MELD 'disadvantaged' patients (e.g. subjects with hepatocellular carcinoma who are beyond the Milan criteria or patients with low MELD scores that do not adequately reflect their level of illness and their critical need for a transplant) or HCC patients who are listed in areas with long waiting times. Unfortunately, because of the lack of accurate wait list mortality rates across a broad spectrum of patients with defined risks, retrospective studies such as ours are limited in the ability to provide more meaningful recommendations on which patient population will truly benefit from DCD livers, and must primarily gauge the benefit (or the lack thereof) of these grafts by assessing posttransplant outcomes relative to DBD recipients (22). This report, therefore, underscores the need for further studies to solidly define this subgroup of patients as well as validate our findings and critically address the overall utility of DCD livers. Therapeutic maneuvers are also desperately needed to decrease the incidence of PNF/DGF and biliary complications, and several promising interventions such as novel preservation solutions and agents as well as machine perfusion of the liver should hopefully be available for clinical use in the near future (23). The infusion

of tissue plasminogen activator into the hepatic artery after portal reperfusion (24) or the injection of HTK preservation solution into the bile duct during the procurement process have been anecdotally reported to decrease the incidence of biliary complications. Whatever the means, improving DCD outcomes will make a true impact on the shortage of donor livers.

Acknowledgment

We thank Mary Amanda Dew and Andrea DiMartini for critical reading of the article.

References

1. Available from: http://www.unos.org
2. Foley DP, Fernandez LA, Leverson G et al. Donation after cardiac death: The University of Wisconsin experience with liver transplantation. Ann Surg 2005; 242:724–731.
3. Merion RM, Pelletier SJ, Goodrich N, Englesbe MJ, Delmonico FL. Donation after cardiac death as a strategy to increase deceased donor liver availability. Ann Surg 2006; 244: 555–562.
4. Abt PL, Desai NM, Crawford MD et al. Survival following liver transplantation from non-heartbeating donors. Ann Surg 2004; 239: 87–92.
5. Mateo R, Cho Y, Stapfer M et al. Risk factors for graft survival after liver transplantation from donation after cardiac death donors: An analysis of OPTN/UNOS data. Am J Transplant 2006; 6: 791–796.
6. Fujita S, Mizuno S, Fujikawa T et al. Liver transplantation from donation after cardiac death: A single center experience. Transplantation 2007; 84: 46–49.
7. Chan EY, Olson LC, Kisthard JA, Perkins JD, Bakthavatsalam R, Halldorson JB. Ischemic cholangiopathy following liver transplantation from donation after cardiac death donors. Liver Transpl 2008; 14: 604–610.
8. Fukumori T, Kato T, Levi D et al. Use of older controlled non-heartbeating donors for liver transplantation. Transplantation 2003; 75: 1171–1174.
9. Reich DJ, Munoz SJ, Rothstein KD et al. Controlled non-heartbeating donor liver transplantation. Transplantation 2000; 70: 1159–1166.
10. Muiesan P, Girlanda R, Jassem W et al. Single-center experience with liver transplantation from controlled non-heartbeating donors. Ann Surg 2005; 242: 732–738.
11. Casavilla A, Ramirez C, Shapiro R et al. Experience with liver and kidney allografts from non-heartbeating donors. Transplantation 1995; 59: 197–203.
12. Institute of Medicine, National Academy of Sciences. Non-Heartbeating Organ Transplantation: Medical and Ethical Issues in Procurement. Washington, DC: National Academy Press, 1997.
13. Cameron AM, Ghobrial RM, Yersiz H, Farmer DG, Lipsutz GS, Gordon SA. Optimal utilization of donor grafts with extended criteria. Ann Surg 2006; 243: 748–755.
14. Maluf DG, Edwards EB, Kauffman HM. Utilization of extended donor criteria liver allograft: Is the elevated risk of failure independent of the model for end-stage liver disease score of the recipient? Transplantation 2006; 82:1653–1657.
15. Amin MG, Wolf MP, TenBrook JA Jr. et al. (Expanded criteria donor grafts for deceased donor liver transplantation under the MELD system: A decision analysis. Liver Transpl 2004; 10;1468–1475.
16. Feng S, Goodrich NP, Bragg-Gresham JL et al. Characteristics associated with liver graft failure: The concept of a donor risk index. Am J Transpl 2006; 6: 783–790.
17. Demetris AJ, Fontes P, Lunz JG, Specht S, Murase N, Marcos A. Wound healing in the biliary tree of liver allografts. Cell Transplant 2006; 15(S1):S57–S65.
18. Bernat JL, D'Alessandro AM, Port FK et al. Report of a national conference on donation after cardiac death. Am J Transplant 2006; 6: 281–291.
19. Freeman RB. Utility is not just posttransplant outcome! Am J Transplant 2006; 6: 2817.
20. Lee K-W, Simpkins CE, Montgomery RA, Locke JE, Segev DL, Maley WR. Factors affecting graft survival after liver transplantation from donation after cardiac death donors. Transplantation 2006; 82: 1683–1688.
21. Schaubel DE, Sima CS, Goodrich NP, Feng S, Merion RM. The survival benefit of deceased donor liver transplantation as a function of candidate disease severity and donor quality. Am J Transplant 2008; 8: 419–425.
22. Mateo R, Singh G, Sher L, Selby R, Genyk Y. Utility versus utilization of DCD liver allografts. Am J Transplant 2007; 7: 263.
23. Guarrera JV, Karim NA. Liver preservation: Is there anything new yet? Curr Opin Organ Transplant 2008; 13: 148–154.
24. Fung JJ, Eghtesad B, Patel-Tom K. Using livers from donation after cardiac death donors—A proposal to protect the true Achilles heel Liver Transpl 2007; 13: 1633–1636.