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(Article begins on next page)

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Liver Transplantation Using Grafts From Donors After Circulatory Death: A Propensity Score–Matched Study From a Single Center

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The use of livers from donation after circulatory death (DCD) is increasing, but concerns exist regarding outcomes following use of grafts from "marginal" donors. To compare outcomes in transplants using DCD and donation after brain death (DBD), propensity score matching was performed for 973 patients with chronic liver disease and/or malignancy who underwent primary whole-liver transplant between 2004 and 2014 at University Hospitals Birmingham NHS Foundation Trust. Primary end points were overall graft and patient survival. Secondary end points included postoperative, biliary and vascular complications. Over 10 years, 234 transplants were carried out using DCD grafts. Of the 187 matched DCDs, 82.9% were classified as marginal per British Transplantation Society guidelines. Kaplan–Meier analysis of graft and patient survival found no significant differences for either outcome between the paired DCD and DBD patients (p = 0.162 and p = 0.519, respectively). Aspartate aminotransferase was significantly higher in DCD recipients until 48 h after transplant (p < 0.001). The incidences of acute kidney injury and ischemic cholangiopathy were greater in DCD recipients (32.6% vs. 15% [p < 0.001] and 9.1% vs. 1.1% [p < 0.001], respectively). With appropriate recipient selection, the use of DCDs, including those deemed marginal, can be safe and can produce outcomes comparable to those seen using DBD grafts in similar recipients.

Abbreviations: AKI, acute kidney injury; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BAR, balance of risk; BTS, British Transplantation Society; CIT, cold ischemic time; CMV, cytomegalovirus; DBD, donation after brain death; DCD, donation after

Introduction

Liver transplantation is the only curative option for patients with end-stage liver disease, regardless of etiology. Liver disease is the fifth leading cause of death in the United Kingdom, and the mortality rate continues to increase (1). In the past decade, the number patients on the active U.K. liver transplant register has more than doubled (253 in 2004 to 611 patients in 2015) (2, 3), and in response, there has been a 10-fold increase in the number of transplants using grafts from donation after circulatory death (DCD) (13 in 2003 to 177 in 2015) (2,3). In the United Kingdom between April 1, 2014, and March 31, 2015, 15% of patients died or were removed from the liver transplant waiting list (3); a proportion of these patients might have been saved if an appropriate donor had become available.

Donation after brain death (DBD) has been the preferred practice in countries that use deceased donation since the Harvard criteria were introduced in 1968 because the criteria permit oxygenation of the organ until the point of preservation (4). In the late 1980s, interest in DCDs grew because of the increasing demand for organs. Following long-term success with kidney transplants using DCD grafts (5), specialists turned their attention to the use of DCD liver grafts, with outcomes benefiting from decades of improved preservation methods, immunosuppression and surgical techniques. DCD organs, however, are still used judiciously, and many factors are taken into account to minimize the likelihood of an adverse outcome.

In the United Kingdom, virtually all DCD retrievals are from controlled donors (Maastricht III) (6), enabling the retrieval team to closely monitor the functional warm ischemic time (FWIT)—the point at which oxygen saturation falls below 80% or systolic blood pressure falls below 50 mmHg until aortic perfusion occurs (7). Organ ischemia triggers a complex cascade of cellular and molecular events, including the release of proinflammatory mediators and chemotaxis of cell types that initiate progressive immunological processes. During the reperfusion phase, "the reflow paradox" promotes infiltration of the tissues by leukocytes, and cellular injury occurs through a series of pathways that include lipid peroxidation and the creation of reactive oxygen species (8). The FWIT increases the recipient's risk of postreperfusion syndrome (9), primary nonfunction, delayed graft function (10–12), ischemic cholangiopathy (IC) (13–16), and acute and chronic kidney disease (17). The cost of DCD transplants can also be 50% higher; IC, for example, is associated with a higher readmission rate, multiple invasive procedures and, in some cases, retransplantation (18–21).

Between April 2013 and March 2014, University Hospitals Birmingham NHS Foundation Trust (UHB) performed 189 liver transplants in 171 patients, and 44 of these transplants were performed using DCD grafts. The hospital has a very active DCD program and uses >80% of the DCD grafts that are offered (22). In 2014, a meta-analysis by O'Neill et al concluded that DCD transplantation was associated with an increase in biliary complications, IC, graft loss and mortality (23). Our aim was to investigate whether this statement was applicable to our patient population and, as such, to present the largest single-center study of its kind.

Materials and Methods

UHB approved this study (CARMS-02246). Adult patients (aged >16 years) who underwent primary orthotopic liver transplantation between July 2004 and July 2014 were initially included. Pediatric transplants and recipients of grafts from living donors, split livers, machine-perfused grafts, domino grafts or multiple organs were excluded, as were patients with a primary etiology of acute liver failure (they would be less likely to receive a DCD graft). The hospital transplant database is maintained prospectively and contains information on the donor, the recipient, the retrieval process, the perioperative period, complications, and follow-up.

During the retrieval process, most teams in the United Kingdom use aortic and portal perfusion to flush the graft effectively (with the only exception being DBD retrievals in which the pancreas and small bowel are also being procured). The preferred preservation fluid regimen for procurement without pancreas is 3–4 L of heparinized Marshall's solution (a low-viscosity solution) via the aorta under 200 mmHg pressure (which results in superior organ washout than gravity-alone perfusion) (24,25), 1 L of UW solution under gravity via the portal vein, and an additional back-table flush through the artery and portal vein with UW solution. During DCD procurement, the gallbladder is opened after vascular perfusion, and the bile duct is divided and then flushed via the gallbladder opening as well as on the back table. Donor FWIT is generally limited within the United Kingdom to 30 min for DCD liver procurement. Cold ischemic time (CIT) is defined as the time between cold aortic perfusion and reperfusion at implantation via either the portal vein or hepatic artery.

Primary end points were overall graft and patient survival. Secondary end points included relevant postoperative complication rates within 90 days, incidence of postoperative acute kidney injury (AKI), ventilator duration, length of intensive treatment unit (ITU) stay, length of hospital stay, biliary complications (cholangitis, leak, IC, anastomotic stricture) and vascular complications (hepatic artery stenosis and hepatic artery thrombosis [HAT]) over the follow-up period. AKI was defined as peak serum creatinine 2.0–2.9 times baseline and thus was included the "risk, injury, failure, loss and end-stage kidney disease," or RIFLE, categories. IC was defined as nonanastomotic biliary strictures in the presence of a patent hepatic artery confirmed on magnetic resonance cholangiopancreatography (MRCP) or endoscopic retrograde cholangiopancreatography by one of two consultant specialist radiologists. The donor risk index (DRI) and balance of risk (BAR) score were also calculated for the matched recipients.

Propensity score matching (PSM) was used to match patients receiving DCD livers to those receiving DBD livers. PSM is a recognized method of balancing covariates in two groups to reduce selection bias (26). In our analysis, we included all donor and recipient variables of clinical relevance to the posttransplant outcome measures in the propensity score model, namely, donor age and BMI, days on ventilator, CIT, recipient age and BMI, recipient primary diagnosis and Model for End-Stage Liver Disease (MELD) score (Table S1). A total of 187 DCD recipients were successfully matched to DBD recipients using these criteria, with the remaining 47 DCD recipients excluded from the matched analysis. Year of transplant was not used as a variable because its inclusion reduced the number of matched pairs. Additional information regarding the PSM process can be found in the Supplementary Methods.

Comparisons between organ types in the unmatched data were performed using t-tests for continuous factors and Fisher exact tests for categorical variables. After matching, normally distributed continuous variables and nonparametric continuous variables were compared using the paired t-test and Wilcoxon signed rank test, respectively. The McNemar test was used to compare categorical data. Survival was estimated using Kaplan–Meier plots with log-rank tests for differences, and adjusted survival was determined using Cox proportional hazards analyses. Data were analyzed using SPSS v21 (IBM Corp, Armonk, NY). Continuous variables were expressed as mean and standard deviation (SD) or median and interquartile range, as appropriate.

Results

Donor and recipient characteristics
A total of 973 patients underwent primary whole-liver transplantation for chronic liver disease between July 2004 and July 2014; 234 (24.0%) received DCD organs, and 739 (76.0%) received DBD organs (Tables 1). All patients had at least 90 days of follow-up. The mean donor age was 50.1 years, 52.4% were male and mean BMI was 26.6. Donor cause of death was consistent with national data (22). The mean recipient age was 53.1 years, 65.3% were male and mean BMI was 27.5. The most common causes of chronic disease were alcoholic cirrhosis (25.9%), hepatitis C cirrhosis (21.2%), primary biliary

Table 1: Demographics of whole data and associated standardized differences

	Total	DCD	DBD	Difference
n	973	234	739	
Donor factors				
Age	50.1 (14.9)	49.1 (16.6)	50.4 (14.3)	0.084
Sex[1]				
Male	510 (52.4%)	132 (56.4%)	378 (51.2%)	0.104
Female	463 (47.6%)	102 (43.6%)	361 (48.8%)	0.104
BMI[1]	26.6 (4.9)	25.2 (4.0)	27.0 (5.0)	0.398
Virology				
CMV +ve	477 (49.0%)	113 (48.3%)	364 (49.3%)	0.020
Hepatitis B +ve	27 (2.8%)	4 (1.7%)	23 (3.1%)	0.092
Hepatitis C +ve	13 (1.3%)	2 (0.9%)	11 (1.5%)	0.055
Days on ventilator[1]	2.4 (3.5)	2.1 (3.4)	2.5 (3.5)	0.116
Cause of death				
Cerebrovascular accident	636 (65.4%)	124 (53.0%)	512 (69.3%)	0.339
Head injury	115 (11.8%)	38 (16.2%)	77 (10.4%)	0.171
Cardiac arrest	67 (6.9%)	28 (12.0%)	39 (5.3%)	0.240
Malignancy	23 (2.4%)	4 (1.7%)	19 (2.6%)	0.062
Other	132 (13.6%)	40 (17.1%)	92 (12.4%)	0.133
Location of donor				
Local	129 (13.3%)	33 (14.1%)	96 (13.0%)	0.032
Regional	213 (21.9%)	60 (25.6%)	153 (20.7%)	0.116
National	631 (64.9%)	141 (60.3%)	490 (66.3%)	0.125
Retrieval team				
Birmingham	696 (71.5%)	149 (63.7%)	547 (74.0%)	0.224
Other	277 (28.5%)	85 (36.3%)	192 (26.0%)	0.224
DCD FWIT (min)	21 (15–25)	20.6 (6.8)	–	–
CIT (h)[1]	8.3 (2.3)	7.1 (1.6)	8.7 (2.4)	0.784
Marginal DCD[2]		201 (83.8%)		
>1 Marginal feature		127 (41.0%)		
Recipient factors				
Age[1]	53.1 (10.6)	55.3 (9.3)	52.5 (10.9)	0.276
Sex[1]				
Male	635 (65.3%)	148 (63.2%)	487 (65.9%)	0.056
Female	338 (34.7%)	86 (36.8%)	252 (34.1%)	0.056
BMI[1]	27.5 (5.1)	26.7 (4.9)	27.7 (5.2)	0.198
MELD[1]	16 (5.7)	13.8 (4.7)	16.2 (5.8)	0.455
HCC present	266 (27.3%)	88 (37.6%)	178 (24.1%)	0.295
Recipient diagnosis[1]				
Alcohol-related cirrhosis	252 (25.9%)	63 (26.9%)	189 (25.6%)	0.030
Hepatitis C cirrhosis	206 (21.2%)	54 (23.1%)	152 (20.6%)	0.061
Primary biliary cirrhosis	126 (12.9%)	41 (17.5%)	85 (11.5%)	0.171
PSC	102 (10.5%)	22 (9.4%)	80 (10.8%)	0.046
NASH	61 (6.3%)	17 (7.3%)	44 (6.0%)	0.052
Hepatitis B cirrhosis	42 (4.3%)	11 (4.7%)	31 (4.2%)	0.024
Other	184 (18.9%)	26 (11.1%)	158 (21.4%)	0.282

Values expressed as mean (standard deviation) or number (percentage), as appropriate. +ve, positive test result; CIT, cold ischemic time; CMV, cytomegalovirus; DBD donation after brain death; DCD, donation after circulatory death; FWIT, functional warm ischemic time; HCC, hepatocellular carcinoma; MELD, Model for End-Stage Liver Disease; NASH, nonalcoholic steatohepatitis; PSC, primary sclerosing cholangitis.
[1]Variables used in propensity score–matching process.
[2]"Marginal" as described by the British Transplantation Society guidelines (27).

cirrhosis (12.9%) and primary sclerosing cholangitis (PSC; 10.5%). The mean MELD score was 16, which is in keeping with previous results from our center (17). The number of transplants using DCD grafts increased from 1 in 2004 to 49 in 2014 (Figure 1). Overall, 83.8% of the 234 DCD grafts were classified as "marginal," and 41.0% fulfilled two or more of the following criteria that define marginal-

ity, according to the British Transplantation Society (BTS) guidelines (2013): age >50 years, weight >100 kg, intensive care unit stay >5 days, FWIT >20 min, CIT >8 h and >15% steatosis (27).

Following PSM, 187 pairs of patients were closely matched, with the majority of variables found to have

Table 2: Demographics of propensity score–matched groups and associated standardized differences

	DCD	DBD	Difference	Unmatched DCD
n	187	187		47
Donor factors				
Age	49.4 (16.2)	47.7 (14.7)	0.110	48.3 (18.0)
Sex[1]				
Male	102 (54.5%)	106 (56.7%)	0.044	30 (63.8%)
Female	85 (45.5%)	81 (43.3%)	0.044	17 (36.2%)
BMI[1]	25.5 (4.1)	25.4 (4.7)	0.023	24.1 (3.6)
Virology				
CMV +ve	94 (50.3%)	105 (56.1%)	0.116	19 (40.4%)
Hepatitis B +ve	3 (1.6%)	6 (3.2%)	0.105	1 (2.1%)
Hepatitis C +ve	2 (1.1%)	3 (1.6%)	0.043	–
Days on ventilator[1]	2.2 (3.5)	2.3 (2.5)	0.033	2.1 (3.2)
Cause of death				
Cerebrovascular accident	100 (53.5%)	115 (61.5%)	0.162	24 (51.1%)
Head injury	30 (16.0%)	31 (16.6%)	0.016	8 (17.0%)
Cardiac arrest	22 (11.8%)	7 (3.7%)	0.306	6 (12.8%)
Malignancy	4 (2.1%)	4 (2.1%)	0.000	–
Other	31 (16.6%)	30 (16.0%)	0.016	9 (19.1%)
Location of donor				
Local	24 (12.8%)	30 (16.0%)	0.091	9 (19.1%)
Regional	49 (26.2%)	35 (18.8%)	0.178	11 (23.4%)
National	114 (61.0%)	122 (65.2%)	0.087	27 (57.4%)
Retrieval team				
Birmingham	115 (61.5%)	160 (85.6%)	0.568	34 (72.3%)
Other	72 (38.5%)	27 (14.4%)	0.568	13 (27.7%)
DCD FWIT (min)	20 (7)			22 (7)
CIT (h)[1]	7.3 (1.6)	7.4 (2.0)	0.094	6.3 (1.4)
Marginal DCD	155 (82.9%)			41 (87.2%)
>1 Marginal feature	75 (40.1%)			23 (48.9%)
Recipient factors				
Age[1]	54.8 (9.7)	55.2 (10.0)	0.041	57.5 (7.6)
Sex[1]				
Male	119 (63.6%)	188 (59.9%)	0.076	29 (61.7%)
Female	68 (36.4%)	75 (40.1%)	0.076	18 (38.3%)
BMI[1]	26.9 (4.9)	26.9 (4.8)	0.000	26.1 (4.7)
MELD[1]	14.0 (4.8)	13.7 (4.4)	0.065	10.7 (5.4)
HCC present	67 (35.8%)	57 (30.5%)	0.113	21 (44.7%)
Recipient diagnosis[1]				
Alcohol-related cirrhosis	47 (25.1%)	43 (23.0%)	0.049	16 (34.0%)
Hepatitis C cirrhosis	48 (25.7%)	42 (22.5%)	0.075	6 (12.8%)
Primary biliary cirrhosis	29 (15.5%)	38 (20.3%)	0.125	12 (25.5%)
PSC	17 (9.1%)	17 (9.1%)	0.000	5 (10.6%)
NASH	12 (6.4%)	10 (5.3%)	0.047	5 (10.6%)
Hepatitis B cirrhosis	9 (4.8%)	9 (4.8%)	0.000	2 (4.3%)
Other	25 (13.4%)	28 (15.0%)	0.046	1 (2.1%)
Risk stratification			p-value[2]	
DRI	2.82 (0.64)	1.80 (0.34)	<0.001	2.72 (0.61)
DRI minus donor type	1.87 (0.42)	1.80 (0.34)	0.077	1.81 (0.41)
BAR score	4.88 (2.66)	4.40 (2.49)	0.053	3.7 (2.7)

+ve, positive test result; BAR, balance of risk; CIT, cold ischemic time; CMV, cytomegalovirus; DBD donation after brain death; DCD, donation after circulatory death; DRI, donor risk index; FWIT, functional warm ischemic time; HCC, hepatocellular carcinoma; MELD, Model for End-Stage Liver Disease; NASH, nonalcoholic steatohepatitis; PSC, primary sclerosing cholangitis.
[1]Variables used in propensity score–matching process.
[2]Paired t-test.

standardized differences <0.100 (Table 2). In addition, 82.9% of matched DCD grafts were classified as marginal, as described. There was a trend toward a higher BAR score in the DCD group (4.88 vs. 4.40, p = 0.053), and DRI was significantly higher for these recipients (2.82 vs. 1.80, p < 0.001). This difference was lost when graft type was removed from the DRI equation (factor of 0.411), resulting in means of 1.87 versus 1.80
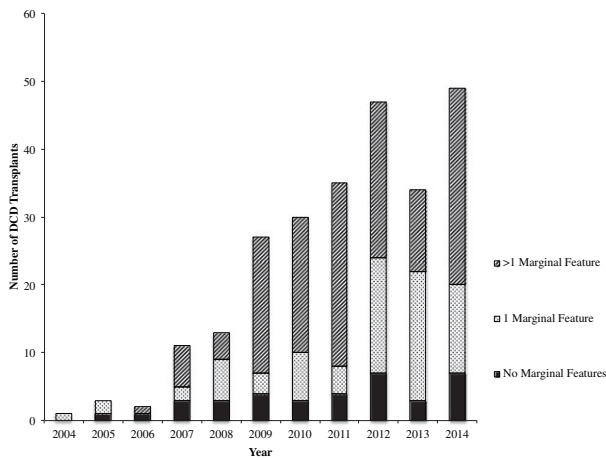
Figure 1: Number of transplants using DCD donors at University Hospitals Birmingham NHS Foundation Trust and proportions of marginal donors. AST, aspartate aminotransferase; DBD, donation after brain death; DCD, donation after circulatory death.

(p = 0.077). A total of 47 DCD recipients were not matched to DBD recipients. Their demographics and outcomes are presented in Tables 2–4 for comparison. The PSM process does not specify why a match cannot be performed for a particular case; however, in analysis of all unmatched DCD recipients, it is likely that a lower MELD score prohibited a successful match to a DBD recipient. The demographics of these particular subsets were very similar otherwise (Table 2).

Postoperative course, outcomes, and complications

There was no significant difference between the paired DCD and DBD recipients with respect to the postoperative course (Table 3). Aspartate aminotransferase (AST) was

not normally distributed, thus the values were logged and reported as geometric means. The resulting values were significantly higher in DCD recipients until 48 h after transplant (two-tailed t-test, p < 0.001), returning to a level similar to that seen in DBD recipients at day 5 (Figure 2).

Kaplan–Meier analysis of overall graft and patient survival found no significant differences for either outcome between the paired DCD and DBD recipients (p = 0.162 and p = 0.519, respectively) (Figures 3 and 4). A stratified Cox regression returned a hazard ratio for mortality of 1.16 (95% confidence interval 0.68–2.01, p = 0.579) for DCD relative to DBD recipients. Table S2 contains the etiology of retransplantation (regraft) and death for matched DCD and DBD recipients as well as unmatched DCD recipients. For all matched recipients, the most common causes of death were recurrence of hepatocellular carcinoma (HCC; 23.5%), sepsis (18.0%), pulmonary complications (13.5%), HAT (11.2%), and cardiac complications (10.1%). The primary causes of graft loss and death within the first 30 days were primary nonfunction (DCD, n = 5 [2.6%] resulting in two deaths; DBD, n = 2 [1.1%]) and HAT for all matched recipients. After 1 year, recurrence of HCC accounted for most deaths.

The incidence of AKI was significantly greater in DCD recipients (32.6% vs. 15.0%, p < 0.001), and there was a trend in the same group toward higher incidence of postoperative bleeding (12.8% vs. 7.0%, p = 0.080). On further analysis of renal function, there was no difference in urea or creatinine between matched recipients at 1 year after transplant (Table 4); however, regardless of graft type, patients who required short-term filtration went on to have elevated levels of urea and creatinine at 1 year (filtration vs. no filtration; urea 10.2 [SD 3.3] vs. 8.0 [SD 2.5], p < 0.001; creatinine 124.6 [SD 33.1] vs. 105.6 [SD 27.7], p < 0.001). There was a significantly

Table 3: Postoperative course and outcomes for matched groups and unmatched DCDs

	DCD	DBD	p-value	Unmatched DCD
Postoperative course[1]				
Operating time (h)	4.8 (4.0–5.7)	4.9 (4.3–6.0)	0.104	4.9 (4.1–5.9)
Days ventilated	1 (1–2)	1 (1–2)	0.331	1 (1–2)
Days in ITU	3 (2–6)	2 (2–4)	0.066	3 (1–5)
Length of stay (days)	10 (7–15)	10 (7–15)	0.870	7 (9–17)
Estimated graft survival				
<30 days	90.4% (0.022)	93.6% (0.018)		95.7% (0.029)
<1 year	82.7% (0.028)	86.1% (0.025)		95.7% (0.029)
Overall graft survival[2]			0.166	
Estimated patient survival				
<30 days	94.1% (0.017)	96.3% (0.014)		97.9% (0.021)
<1 year	87.6% (0.025)	88.8% (0.023)		95.6% (0.030)
Overall patient survival[2]			0.519	

Values expressed as median (interquartile range), number (percentage) or percentage (standard error), as appropriate. Graft survival includes all deaths as well as patients who required retransplantation. DBD donation after brain death; DCD, donation after circulatory death; ITU, intensive treatment unit.
[1]Wilcoxon signed rank test.
[2]Log-rank (Mantel–Cox).

Table 4: Postoperative complications for matched groups and unmatched DCDs

	DCD	DBD	p-value	Unmatched DCD
<90-day postoperative complications[1]				
Cardiac complication	16 (8.6%)	11 (5.9%)	0.405	2 (4.3%)
Postoperative bleeding	24 (12.8%)	13 (7.0%)	0.080	1 (2.1%)
Respiratory complication	20 (10.7%)	29 (15.6%)	0.188	3 (6.4%)
Posttransplant diabetes	11 (5.9%)	18 (9.6%)	0.230	2 (4.3%)
Acute kidney injury	61 (32.6%)	28 (15.0%)	**<0.001**	5 (10.6%)
Renal function 1 year after transplant				
Urea (mmol/L)	8.0 (2.6)	8.7 (3.0)	0.847	8.2 (2.2)
Creatinine (mmol/L)	105 (48)	115 (30)	0.763	102 (25)
Biliary complications[2]				
Cholangitis	8 (4.3%)	9 (4.8%)	0.791	–
Bile leak	9 (4.8%)	5 (2.6%)	0.270	1 (2.1%)
Ischemic cholangiopathy	17 (9.1%)	2 (1.1%)	**<0.001**	5 (10.6%)
Anastomotic stricture	27 (14.4%)	23 (12.2%)	0.289	6 (12.8%)
Vascular complications[2]				
Hepatic artery stenosis	5 (2.7%)	2 (1.1%)	0.180	–
Hepatic artery thrombosis	9 (4.8%)	6 (3.2%)	0.416	3 (6.4%)
Combined	14 (7.5%)	8 (4.3%)	0.148	3 (6.4%)

Bold values indicate statistically significant results. DBD donation after brain death; DCD, donation after circulatory death.
[1]Reported as rates at 90 days, with p-values from the McNemar test.
[2]Reported as Kaplan–Meier estimated overall rates with p-values from log-rank (Mantel–Cox) tests of all available follow-up.

higher incidence of IC in DCD recipients (9.1% vs. 1.1%, p < 0.001), with similar rates of cholangitis, bile leak, anastomotic biliary stricture, hepatic artery stenosis, and HAT (Table 4).

Discussion

This retrospective propensity score–matched study using data from the largest single-center DCD cohort in the literature demonstrated similar graft and patient survival following transplant with DCD and DBD grafts. With the exception of IC and AKI, we also demonstrated similar postoperative complication rates.

PSM is an accepted method of estimating the effect of a treatment by attempting to reduce bias from confounding variables (26,28). We performed a 1:1 match because this is the most commonly accepted form of this technique, which allowed us to determine the impact of receiving a DCD graft. Despite supposedly resulting in increased precision, cohort studies matching at ratios of 1:>1 have been shown to result in somewhat higher levels of bias (29,30). Any bias introduced by year of transplant, which was excluded from the PSM process, is expected to be minimized by the fact that the number of DCD transplants performed during the early years of the DCD program were small, and as techniques for the use of DCDs improved, numbers increased.

Despite the use of DCD grafts remaining controversial, the transplant community must continue to maximize the pool of DCD grafts to respond to the increasing inci-

dence of chronic liver disease. The literature presents a mixed picture, with studies arising from early registry data showing up to 30% graft failure (10,11) but smaller high-volume single-center studies demonstrating similar graft and patient survival (9,31,32). A recent meta-analysis demonstrated higher incidence of biliary complications, decreased 1-year graft survival and 3-year patient survival in DCD recipients; however, the authors commented on significant unexplained differences in effect size between centers (23), a sentiment echoed by Callaghan et al in 2013 in their U.K. cohort study (33). Our data demonstrate similar graft and patient survival in a matched cohort of "low-risk" recipients, albeit with a weak trend toward reduced graft survival in the DCD cohort.

AST levels within the first 5 days following transplant reflect damage at a hepatocellular level. In 2012, UHB's biochemistry department changed its policy on the testing of AST and began using alanine aminotransferase (ALT) as the standard transaminase in transplant patients. This meant that 46% of our DCD cohort was excluded from the AST analysis (compared with 9% of the DBD cohort). Despite this, we were able to demonstrate a significant difference between AST levels within the first 48 h after transplant (Figure 2). Of note, average peak ALT was also higher in DCD recipients. Leithead et al were the first to show that peak AST was the only variable associated with the development of AKI (17). They also demonstrated that ischemia–reperfusion injury was strongly related to postoperative AKI in DBD recipients (34). Although AST is also released from damaged renal tissue, peak AST has been shown to correlate strongly
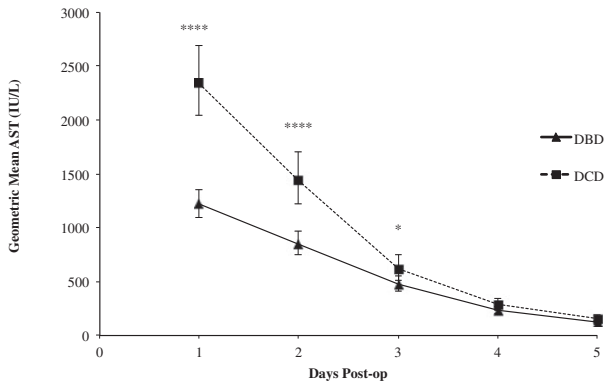
Figure 2: Chart of geometric mean postoperative AST. There were 187 patients in each matched group (number available for analysis: DCD, n = 101; DBD, n = 173). *p = 0.030, ****p < 0.001. AST, aspartate aminotransferase; DBD, donation after brain death; DCD, donation after circulatory death.
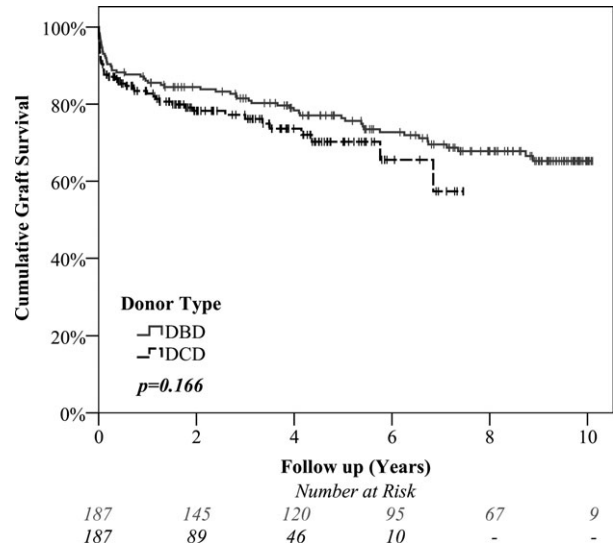

Figure 4: Kaplan–Meier curve of graft survival. DBD, donation after brain death; DCD, donation after circulatory death.
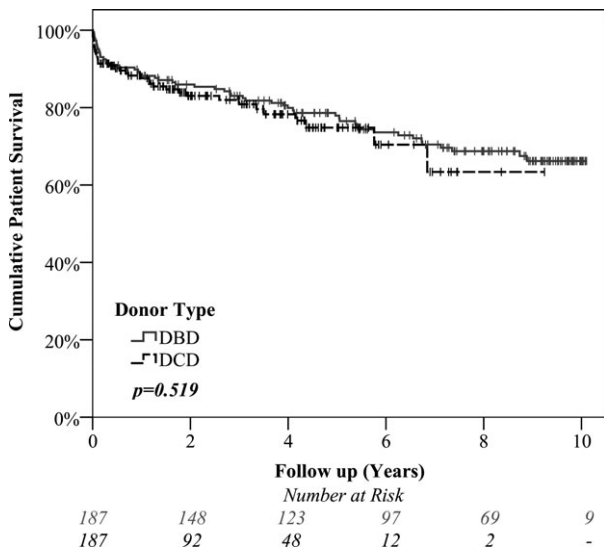

Figure 3: Kaplan–Meier curve of patient survival. DBD, donation after brain death; DCD, donation after circulatory death.

with histological grading of hepatic injury (35). Peak AST was higher in DCD recipients, and in terms of early complications, AKI was the only complication found to differ significantly between the two organ types (p < 0.001). There was a trend toward more postoperative bleeding in DCD recipients, which could be an indicator of inferior graft function and disordered clotting cascades (p = 0.080). Transplants for HCC or PSC in recipients with lower MELD scores tend to take less time than transplants in patients with higher MELD scores (e.g. those with alcoholic liver disease and recurrent spontaneous bacterial peritonitis). In these cases, the full extent of postreperfusion coagulopathy may occur following abdominal closure; therefore, we advo-

cate a hemostatic pause before completing the biliary anastomosis to allow for this in such situations.

When considering late complications, De Olivera et al demonstrated levels of IC not seen previously in the literature (2.5% incidence in DCD cohort) and hypothesized that it was due to a policy of only accepting grafts exposed to <30 min of warm ischemia and restricting CIT to 8 h (36). A balance must be reached because stringent selection criteria will significantly reduce the number of available organs. Our data show a rate of IC in DCD recipients of 9.1% compared with 1.1% in DBD recipients (p < 0.001) and anastomotic biliary stricture rates of 14.4% and 12.2% for DCD and DBD recipients, respectively (p = 0.289). These findings are consistent with a large body of literature (13–15,36,37). Patients with symptoms or liver function tests indicative of IC were imaged using MRCP. If confirmed, patients were managed conservatively (most patients maintained acceptable biochemistry), and if their symptoms or biochemistry warranted, patients were relisted for transplantation. In this matched cohort, no patients required relisting, and one patient with IC developed biliary sepsis and died suddenly as a result.

Our PSM used CIT as a confounding variable, hence the mean times were similar between the groups (mean of 7.3 h for DCD and 7.4 h for DBD recipients, standardized difference 0.094). The mean FWIT for DCD grafts was 20 min, which lies just within the marginal range for FWIT, according to BTS guidelines. When using standard procurement and preservation techniques, limiting the FWIT in DCD retrievals is crucial in reducing the development of IC. Compared with other determinants of marginality, it is likely FWIT has the greatest impact

on graft function after transplantation. It has been calculated that 1 min of additional warm ischemia can increase the risk of IC or hepatic necrosis by up to 16% (38). Normothermic machine liver perfusion (NMLP) has shown promise in terms of *in situ* normothermic regional perfusion (39), preservation (40), viability testing (41) and reconditioning of liver grafts. Our center performed the first transplantation of a discarded liver graft after viability testing using NMLP (42). In the future, cellular therapy may also offer some benefit in terms of reducing the immunological insults triggered by warm ischemia (43, 44).

The DRI introduced by Feng et al focused on donor factors as well as CIT and retrieval location (which is closely linked to CIT) and has been reported to be predictive of graft survival (45). The mean DRI of 2.82 for our DCD recipient cohort would ordinarily predict 1-year graft survival of 71.4%. In this cohort, 1-year graft survival was 87.6% (the predicted graft survival rate for a DRI score of <1). After removing DCD as a determining factor of graft survival, the mean DRI reduced to 1.87 (vs. 1.80 DBD, which remains unchanged, p = 0.077). The BAR score was devised in 2011 based on 37 255 patients in the United Network for Organ Sharing database (46). Given that neither warm ischemia nor donor type are taken into account in BAR scoring, the mean BAR score was 4.88 for DCD recipients and 4.40 for DBD recipients. The survival rates of our matched cohorts (1-year 87.6% DCD and 88.8% DBD) are in keeping with published data suggesting that a score of 4–5 predicts 1-year patient survival to be 89–92%. Our mean BAR score is low because no patients underwent retransplant or were on preoperative life support, and our mean MELD score was 16 (±5.7). This is <20, the average MELD of patients in the United States prior to transplant. Perhaps the MELD score is low across the cohort because of the exclusion of acute liver failure and retransplant patients from our analysis. Patients with HCC also generally had lower MELD scores than those with end-stage chronic liver disease: 27.3% of the whole cohort had HCC with a mean MELD score of 14. The mean MELD scores within the matched groups were even lower (14.0 DCD and 13.7 DBD). DCD recipients are generally chosen because they have lower MELD scores than the typical chronic liver disease patient, and DBD recipients were matched to them. Because of the size of the DCD cohort, it was not possible to perform any meaningful matched analysis on a higher scoring MELD subset. With the introduction of machine perfusion, it may be possible in the future to safely transplant marginal donors into higher risk recipients and compare outcomes in such a cohort.

There are several reasons why we believe we can achieve such results. Other than being simply a high-volume center, we use a number of strategies. At our hospital, the decision to choose a recipient for a DCD graft is made between the transplant surgeon and a hepatology consultant, and low-risk recipients are chosen for DCD grafts on the basis that they can better cope with a reperfusion insult that can occur using marginal grafts. They are also usually easier to explant, which helps keep CIT to a minimum. Low risk in terms of etiology usually means patients with low MELD scores and/or those with HCC (thus the 37.6% incidence of HCC in DCD recipients compared with 24.1% in DBD recipients in the whole cohort) (Table 1). In addition, when transplanting marginal grafts, our consultant surgeons are acutely aware of the importance of keeping the second period of warm ischemia at implantation to a minimum. Recipients aged >50 years are chosen only if they do not have diabetes or cardiovascular disease, and DCD grafts are rejected if the are moderately steatotic or stiff following preservation. CIT is kept strictly under 8 h, and we accept livers that have been exposed to FWIT of up to 40 min (but only if other criteria are within normal range). To extend into the category of marginal donors, donor age is the boundary that we invariably push, frequently accepting DCD grafts from donors aged >50 years.

A number of the consultants have started to use the technique of hepatic artery-first (HA-first) reperfusion when utilizing marginal grafts because they believe it reduces the risk of postreperfusion cardiovascular instability. A matched study of 40 DCD transplants performed at our center showed that HA-first reperfusion increased intraoperative stability and reduced the incidence of postreperfusion syndrome and peak posttransplant bilirubin (47). A much larger study is required to further investigate the benefits of HA-first reperfusion. In addition to what has already been discussed in the methods in terms of procurement, DCD donors are ordinarily withdrawn on the ITU as long as it is not situated too far from the operating room, in which case they are withdrawn in the adjacent anesthetic room. Following asystole, there is a 5-min stand-down period prior to bringing the patient to the operating room. Overall, 38.5% of DCD retrievals were performed by teams from other centers (compared with 14.4% of DBD retrievals)— another indication of our willingness to accept and transplant marginal donors that have been rejected by other centers. We are happy to do so because of the understanding that all U.K. retrieval teams follow the same rigorous procurement guidelines laid out by the BTS. We do not use thrombolytics or other specific techniques to target the microcirculation. Vendrell et al demonstrated that there was no role for the use of exogenous fibrinolysis (48). A study by Simon et al demonstrated no formation of microthrombi in DCD biopsies at different stages of cold storage, and they felt that made it less likely that microthrombi are involved in the pathophysiology of nonanastomotic strictures after liver transplantation (49). Time from extubation to arrest (even if oxygen saturation or blood pressure remain stable) is generally limited to

60 min, after which a liver would not normally be procured even if a patient arrested following a subsequently acceptable FWIT while waiting the remaining 2–3 h for kidney procurement. This group, however, could be a target for the viability testing of livers using NMLP (42).

In conclusion, this propensity score–matched single-center cohort study supports the notion that with appropriate recipient selection and other techniques, the use of DCDs, including those deemed marginal as per national guidelines, can be used safely and produce outcomes comparable to those seen using DBD grafts in similar recipients. Despite accepted risks such as AKI and IC, they remain a crucial source of donors at a time when the demand for liver transplantation is increasing.

Acknowledgments

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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Supporting Information

Additional Supporting Information may be found in the online version of this article.

Table S1: Logistic regression model used to generate the propensity score.

Table S2: Causes of regraft and death in matched recipients and unmatched donation after circulatory death donors.

Data S1: Supplementary Methods.