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ORIGINAL ARTICLE

Donation after cardiac death liver transplantation is associated with increased risk of end-stage renal disease

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Summary

Limited organ supply has led to greater use of liver allografts with higher donor risk indices (DRI) and/or donated after cardiac death (DCD). DCD status is associated with acute kidney injury after liver transplantation; however, less is known about the association between donor quality and end-stage renal disease (ESRD). Using SRTR data, we assembled a cohort of liver transplant recipients from 2/2002 to 12/2010. We fit multivariable Cox regression models for ESRD. Model 1 included total DRI; model 2 included components of DRI, including DCD, as separate variables. Forty thousand four hundred and sixty-three liver transplant recipients were included. Median DRI was 1.40 (IQR 1.14, 1.72); 1822 (5%) received DCD livers. During median follow-up of 3.93 years, ESRD occurred in 2008 (5%) and death in 11 075 (27%) subjects. There was a stepwise increase in ESRD risk with higher DRI (DRI ≥1.14 and <1.40: HR 1.17, $P = 0.06$; DRI ≥1.40 and <1.72: HR 1.29, $P = 0.003$; DRI ≥1.72: HR 1.39, $P < 0.001$, compared with DRI <1.14). Adjusting for DRI components separately, DCD status was most strongly associated with ESRD (HR 1.40, $P = 0.008$). Higher DRI is associated with ESRD after liver transplantation, driven in part by DCD status. Donor quality is an important predictor of long-term renal outcomes in liver transplant recipients.

Introduction

Renal dysfunction after liver transplantation (LT) significantly impacts recipient morbidity and survival [1]. The aetiology of kidney disease after LT is multifactorial including baseline recipient attributes such as pretransplant renal dysfunction, diabetes, hypertension and hepatitis C, and the postoperative utilization of calcineurin inhibitor-based immunosuppression. Acute kidney injury (AKI) in the peri-transplant period from a variety of insults, including hepatorenal syndrome and sepsis, is also recognized as a risk factor for future chronic kidney disease (CKD) [2]. Identification of modifiable risk factors for CKD and end-stage renal disease (ESRD) could lead to interventions to improve recipient outcomes. Previous research on CKD after LT has focused primarily on recipient attributes or perioperative events. An examination of associations between donor graft quality and ESRD could lead to additional opportunities to improve renal outcomes after LT.

Donor graft quality is known to be associated with graft and patient outcomes, in part related to ischaemia reperfusion injury after LT due to the release of a variety of molecular products and cytokines from the donor hepatocytes and resident Kupffer cell [3,4]. These injuries can range from mild transaminase elevation to a systemic inflammatory response with hemodynamic collapse. The severity of these injuries is associated with inferior organ quality as assessed by a variety of measures including the Donor Risk Index (DRI) and may reflect older donor age, ischaemic events in the donor or at the time of transplant, prolonged

organ storage or allograft steatosis [5]. Early hepatocellular dysfunction after transplant decreases graft survival, and the severity of the preservation injury is associated with an increased risk of AKI [6–9]. In particular, donation after cardiac death (DCD) liver allografts are exposed to an obligatory period of donor warm ischaemia, demonstrate an increased incidence of peri-transplant hepatocellular injury, and are associated with diminished graft and patient survival [10–14]. Hepatic ischaemia reperfusion injury has been associated with peri-operative AKI [15,16], and recipients of DCD livers have been shown to have a higher risk of post-transplant AKI compared with recipients of livers from donors with brain death [15,17].

While allograft quality appears to be associated with AKI in the peri-transplant period, an understanding of the relationship between allograft quality and CKD or ESRD is currently evolving [18,19]. Given known associations with AKI on long-term renal outcomes, we hypothesize that recipients of lower quality liver allografts will have an increased risk of CKD and ESRD. The aim of this study was to examine the association between allograft quality, assessed through DRI and DCD status, and post-transplant ESRD in a national cohort of LT recipients.

Materials and methods

Sources of data

This study used a linked dataset from the Scientific Registry of Transplant Recipients (SRTR) and the United States Renal Data System (USRDS). The SRTR data system includes data on all donors, wait-listed candidates and transplant recipients in the United States, submitted by the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration, US Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors. Outcomes of death in SRTR are determined through centre reports as well as through linkage to the Social Security Death Master File. ESRD outcomes were ascertained through SRTR data on kidney transplantation as well as submission of Centers for Medicare and Medicaid Services (CMS) form 2728 for chronic dialysis to the USRDS.

Study subjects

The study population included adult (≥18 years of age) LT recipients in the US between February 27, 2002 (when the MELD system was implemented) and December 31, 2010. The end date was chosen so that all recipients had at least 1 year of follow-up. We excluded subjects with known ESRD before LT (defined as dialysis for greater than 3 months or kidney transplant before LT) and subjects who received a transplant from a living donor. We also excluded liver recipients with human immunodeficiency virus because their workup and treatment were likely to be substantially different from other recipients. Finally, we excluded subjects who received a liver in combination with another solid organ transplant, as they may have different peri-transplant AKI risks.

Analytic approach

We described baseline demographic and clinical characteristics of the study population using median and interquartile range (IQR) for continuous variables and distributions for categorical variables. The primary exposures were DRI and DCD status. The primary endpoints were death and ESRD, defined as initiation of chronic dialysis or receipt of a kidney transplant. Date of ESRD was considered the first date reported on CMS form 2728 submitted to USRDS or date of kidney transplant reported in SRTR. Outcomes were ascertained from the date of LT until ESRD, death or 1 March 2012, whichever occurred first.

We fit multivariable Cox regression models for the outcome of ESRD, censored at death. We inspected graphical displays and statistical tests of proportionality of hazards to confirm that the proportional hazards assumption was satisfied. On the basis of prior studies and our clinical judgment about clinical risks for ESRD after LT, we identified independent variables for these models [20–22]. We calculated DRI using the algorithm described by Feng *et al.* [5] incorporating the following donor variables: age (categorized as <40, ≥40 and <50, ≥50 and <60, ≥60 and <70, and ≥70 years), cause of death (trauma, anoxia, cerebrovascular accident and other), race (white, black, or other), DCD status, partial/split liver, height, share type (local, regional, or national) and cold ischaemia time. In the first multivariable model, composite DRI was included, categorized in quartiles (<1.14, ≥1.14 and <1.40, ≥1.40 and <1.72, ≥1.72). To determine which components of DRI were associated with post-transplant ESRD, individual components of DRI were included as independent variables in a second multivariable model.

In addition to these donor characteristics, recipient variables were assessed at transplant and included: age (<40, ≥40 and <50, ≥50 and <60, and ≥60 years), sex, race (black or nonblack), diabetes, hypertension, primary cause of liver disease (hepatitis C, hepatitis B, alcohol, nonalcoholic steatohepatitis, cholestatic, autoimmune, hepatocellular carcinoma, cryptogenic cirrhosis and other), location prior to transplant (intensive care unit, hospitalized in nonintensive care unit or not hospitalized), international normalized ratio (INR) of prothrombin time (<1.4, ≥1.4 and <1.9, ≥1.9), total bilirubin (<2.3, ≥2.3 and <5.9, ≥5.9 mg/dl) serum albumin (<2.6, ≥2.6 and <3.2, ≥3.2 g/dl) and serum

sodium (<135, ≥135 and <138, ≥138 mEq/l). Recipient pre-transplant GFR was estimated according to the Modification of Diet in Renal Disease Study (MDRD) equation using creatinine at the time of transplant. Recipient estimated glomerular filtration rate (eGFR) was categorized as ≥60, 30–59, 15–29, and <15 ml/min/1.73 m^2 or acute dialysis at the time of transplant.

Analyses were conducted using STATA 12.0 (Stata Corporation, College Station, TX, USA). All reported *P* values are two-sided, and a *P* value <0.05 was the threshold for statistical significance.

Sensitivity analyses

We assessed degree and distribution of missing data on recipient and donor characteristics. To estimate the maximum effect of missing data on outcomes, we performed sensitivity analyses in which extreme values were assigned to individuals with missing data. For example, cold ischaemia time was missing in 3055 (8%) subjects. In a sensitivity analysis, we applied the 5th and 95th percentiles of cold ischaemia time from the remainder of the cohort to those with missing data. Diabetes status was missing in 273 (2%) subjects. In the primary analysis, subjects with missing diabetes status were categorized as not have diabetes and then categorized as having diabetes in a sensitivity analysis. Results were similar to primary analyses and are not shown.

Results

Baseline characteristics

A total of 46 004 adults underwent LT between 27 February, 2002 and 31 December, 2010, of which 40 463 subjects met inclusion criteria. As shown in Fig. 1, the overall cohort comprised 38 641 (95%) transplants from non-DCD donors and 1822 (5%) from DCD donors.

Table 1 shows baseline subject characteristics at the time of LT by DCD status. The overall median age at LT was 54 years [IQR 48, 60], and recipients of DCD organs were slightly older than non-DCD recipients. Hepatitis C was the most common indication for LT in both groups. There was no difference in prevalence of pre-LT diabetes between DCD and non-DCD recipients. DCD recipients had lower median Model for End-Stage Liver Disease (MELD) score at transplant than non-DCD recipients (17 vs. 19, $P < 0.001$). DCD recipients were more likely to have eGFR ≥60 ml/min/1.73 m^2 at the time of LT. Donor characteristics included in the DRI are shown in Table 2. The overall median DRI was 1.40 (IQR 1.14, 1.72); the DRI of DCD donors was higher than that of non-DCD donors. A greater proportion of DCD donors was young, white and died from trauma compared with non-DCD donors. Therefore, the higher DRI in these donors was primarily driven by DCD status, and these DCD livers otherwise had generally favourable donor characteristics.

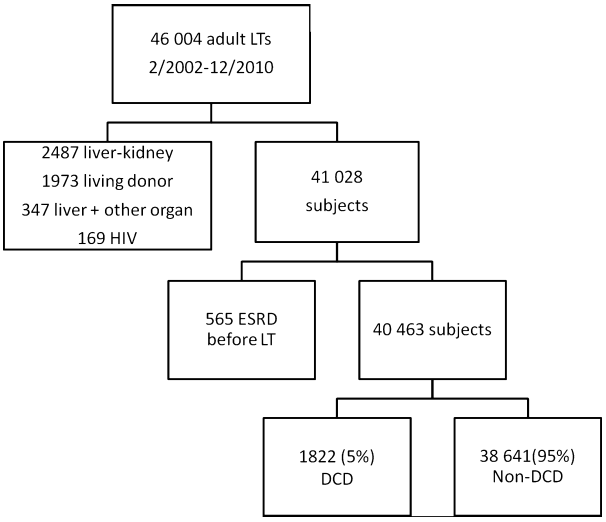

Figure 1 Cohort generation.

Outcomes of relisting, end-stage renal disease and death

During a median follow-up of 3.93 years (IQR 1.85, 6.42), a total of 3666 (9%) subjects were relisted for a second LT, at a median of 73 days (IQR 6, 449) after first transplant. A greater percentage of DCD recipients were relisted for another LT compared with non-DCD recipients (20% vs. 9%, $P < 0.001$), although median time to relisting was not significantly different between the two groups. A total of 2008 (5%) subjects developed ESRD after LT. Among non-DCD recipients, 1909 (4.9%) developed ESRD; among DCD recipients, 99 (5.4%) developed ESRD. DCD recipients developed ESRD sooner after transplant than non-DCD recipients: median time to ESRD was 0.55 years (IQR 0.10, 2.72) for DCD recipients compared with 1.63 years (IQR 0.22, 3.92) for non-DCD recipients, $P = 0.002$. Death occurred in 11 075 (27%) subjects. Mortality was higher in DCD recipients (29%) compared with non-DCD recipients (27%), $P = 0.039$, and death occurred earlier after transplant among DCD recipients: median time to death was 0.89 years (IQR 0.18, 2.46) for DCD recipients compared with 1.29 years (IQR 0.33, 3.33) for non-DCD recipients, $P < 0.001$.

Risk factors for ESRD

Table 3 shows the results of multivariable Cox regression for ESRD, censored at death, adjusting for recipient risk factors and quartiles of composite DRI. There was a stepwise increase in the risk of ESRD with increasing quartiles

Table 1. Baseline subject characteristics and serologic data for liver transplant recipients by DCD status.

Baseline attributes	All (n = 40 463)	Non-DCD (n = 38 641)	DCD (n = 1822)	P
Age, years, med (IQR)	54 (48, 60)	54 (48, 60)	55 (50, 60)	<0.001
Male, *n* (%)	27 397 (68)	26 132 (68)	1265 (69)	0.11
Race, *n* (%)				
White	29 470 (73)	28 095 (73)	1375 (75)	0.002
Black	3585 (9)	3425 (9)	160 (9)	
Asian	1922 (5)	1870 (5)	52 (3)	
Hispanic ethnicity	5099 (13)	4879 (13)	220 (12)	
Other or Multiracial	387 (1)	372 (1)	15 (1)	
Cause of Liver Disease, *n* (%)				
Hepatitis C	13 594 (34)	12 960 (34)	634 (35)	0.002
Hepatocellular carcinoma	6038 (15)	5747 (15)	291 (16)	
Alcohol	5150 (13)	4888 (13)	262 (14)	
Cholestatic	3193 (8)	3063 (8)	130 (7)	
Cryptogenic cirrhosis	2784 (7)	2659 (7)	125 (7)	
Autoimmune	1925 (5)	1858 (5)	67 (4)	
Nonalcoholic steatohepatitis	1806 (4)	1711 (4)	95 (5)	
Hepatitis B	1087 (3)	1050 (3)	37 (2)	
Other	4886 (12)	4705 (12)	181 (10)	
Diabetes, n (%)	8688 (21)	8287 (21)	401 (22)	0.57
Hypertension, n (%)	7213 (18)	6854 (18)	359 (20)	0.032
Location at time of transplant, n (%)				
Intensive care unit	4251 (11)	4115 (11)	136 (7)	<0.001
Hospitalized not in ICU	6304 (16)	6070 (16)	234 (13)	
Not hospitalized	29 908 (74)	28 456 (74)	1452 (80)	
Length of stay (days) after transplant, med (IQR)	10 (7, 16)	10 (7, 16)	10 (7, 17)	0.22
MELD Score at transplant, med (IQR)	18 (13, 26)	19 (13, 26)	17 (13, 23)	<0.001
Creatinine at transplant, mg/dl, med (IQR)	1.0 (0.8, 1.5)	1.0 (0.8, 1.5)	1.0 (0.8, 1.4)	0.005
eGFR at transplant, ml/min/1.73 m^2, n (%)				
≥60	24 102 (60)	22 938 (59)	1164 (64)	<0.001
30–59	10 363 (26)	9921 (26)	442 (24)	
15–29	3148 (8)	3049 (8)	99 (5)	
<15 or dialysis	2850 (7)	2733 (7)	117 (6)	
INR, INR units	1.6 (1.3, 2.1)	1.6 (1.3, 2.1)	1.5 (1.3, 1.9)	<0.001
Total Bilirubin, mg/dl, med (IQR)	3.6 (1.8, 8.4)	3.6 (1.8, 8.5)	3.0 (1.7, 6.0)	<0.001
Serum albumin, g/dl, med (IQR)	2.9 (2.5, 3.4)	2.9 (2.5, 3.4)	3.0 (2.5, 3.4)	0.005
Serum sodium, mEq/l, med (IQR)	136 (133, 139)	136 (133, 139)	136 (133, 139)	0.91

DCD, donation after cardiac death; eGFR, estimated glomerular filtration rate.

of DRI, adjusted for recipient risk factors [DRI ≥1.14 and <1.40: hazard ratio (HR) 1.17, $P = 0.06$; DRI ≥1.40 and <1.72: HR 1.29, $P = 0.003$; DRI ≥1.72: HR 1.39, $P < 0.001$, all compared with reference DRI <1.14]. The strongest recipient risk factors for ESRD were lower eGFR at the time of LT (eGFR 30–59: HR 3.25, $P < 0.001$; eGFR 15–29: HR 6.13, $P < 0.001$, eGFR<15 or acute dialysis: HR 9.30, $P < 0.001$, all compared with reference eGFR≥60 ml/min/1.73 m^2), liver failure due to hepatitis C compared with reference of cholestatic liver disease (HR 2.06, $P < 0.001$), diabetes (HR 2.04, $P < 0.001$) and black race compared with other races (HR 1.88, $P < 0.001$).

Table 4 shows the results of multivariable Cox regression for ESRD, censored at death, adjusting for components of DRI as separate variables. DCD status was the strongest donor risk factor for ESRD (HR 1.40, $P = 0.008$). Recipients of livers from donors ages 50–59 years (HR 1.29, $P = 0.003$) and ages 60–69 years (HR 1.32, $P = 0.01$) had an increased risk of post-transplant ESRD compared with younger donors (reference age < 40 years). Donor age ≥70 years was not significantly associated with ESRD, although this represented a small proportion of donors. Cold ischaemia time was also independently associated with increased risk of post-transplant ESRD (HR 1.02, $P = 0.002$ for each additional hour of cold ischaemia time). Donor cause of death, split liver, height and share type was not associated with ESRD. Similar to the first multivariable model, the strongest recipient risk factors for ESRD were

Table 2. Donor characteristics, by DCD status.

Donor factor	All (n = 40 463)	Non-DCD (n = 38 641)	DCD (n = 1822)	P
Donor age years, *n* (%)				
<40	17 778 (44)	16 715 (43)	1063 (58)	<0.001
40–49	7941 (20)	7537 (20)	404 (22)	
50–59	7831 (19)	7540 (20)	291 (16)	
60–69	4708 (12)	4650 (12)	58 (3)	
≥70	2205 (5)	2199 (6)	6 (1)	
Donor cause of death, *n* (%)				
Cerebrovascular accident	17 602 (44)	17 244 (45)	358 (20)	<0.001
Trauma	15 343 (38)	14 584 (38)	759 (42)	
Anoxia	6453 (16)	5856 (15)	597 (32)	
Other	1065 (3)	957 (2)	108 (6)	
Donor race, *n* (%)				
White	27 694 (68)	26 147 (68)	1547 (85)	<0.001
Black	6441 (16)	6298 (16)	143 (8)	
Other	6328 (16)	6196 (16)	132 (7)	
Partial/split liver, *n* (%)				
Yes	597 (1)	596 (2)	1 (0.1)	<0.001
No	39 866 (99)	38 045 (98)	1921 (99)	
Donor height (cm), med (IQR)	173 (165, 180)	173 (165, 180)	175 (165, 180)	<0.001
Share type, *n* (%)				
Local	28 867 (71)	27 679 (72)	1188 (65)	<0.001
Regional	9060 (22)	8625 (22)	435 (24)	
National	2536 (6)	2337 (6)	199 (11)	
Cold ischaemia time (h), med (IQR)	7.0 (5.1, 9.0)	7.0 (5.1, 9.0)	6.8 (5.2, 8.6)	0.16
Donor Risk Index, med (IQR)	1.40 (1.14, 1.72)	1.38 (1.13, 1.69)	1.85 (1.60, 2.17)	<0.001

DCD, donation after cardiac death.

lower eGFR at transplant, hepatitis C, diabetes and black race.

In a subanalysis, we focused on the 1822 DCD recipients to determine whether there is a subgroup of DCD recipients at higher risk for ESRD based on other donor characteristics. In a multivariable Cox analysis, we did not identify other donor characteristics including donor age, estimated warm ischaemia time, or cold ischaemia time that were independently associated with ESRD in DCD recipients. Similar to the primary analysis, recipient risk factors for post-transplant ESRD in this subgroup included lower eGFR at the time of transplant, diabetes and black race.

Discussion

In a national cohort of liver transplant recipients, higher DRI and DCD status were associated with an increased risk of post-transplant ESRD. We found a 40% increased risk of ESRD in recipients of DCD livers in multivariable analysis adjusting for known recipient risk factors for long-term renal disease. When DCD livers were used, the donors tended to have otherwise favourable characteristics including younger donor age, death less likely caused by cerebrovascular accident, white race and shorter cold ischaemia time. In addition, the recipients of DCD and higher DRI livers tended to have lower MELD scores and higher eGFR at the time of LT. Despite these favourable donor and recipient characteristics, higher DRI and DCD status remained independently associated with an increased risk of ESRD after LT. These findings contribute to the current knowledge that donor quality is associated with short and long-term clinically meaningful outcomes and provide new insights into the association between donor quality and kidney injury. ESRD is as an important complication after LT that should be considered when utilizing hepatic allografts from higher risk donors.

Considerations about expanding the use of lower quality allografts are pertinent given the ongoing organ shortage. In 2012, 11 000 adults were added to the LT waitlist, but only 6000 received a transplant [23]. National efforts to increase the organ supply initially led to a steady increase in the percentage of organs transplanted from DCD donors [24–26]. DCD liver grafts have previously been shown to have an increased rate of graft loss primarily related to biliary complications due to ischaemic cholangiopathy in the setting of ischaemia reperfusion injury [10,12,13,27–29]. Ischaemia reperfusion injury is thought to be more severe

Table 3. Multivariable cox regression analysis of end-stage renal disease after liver transplant, adjusting for composite Donor Risk Index.*

Characteristic	Hazard ratio	95% Confidence interval	*P*
Donor Risk Index			
DRI lowest quartile (<1.14)	Reference	Reference	Reference
DRI second quartile (≥1.14 and <1.40)	1.17	0.99, 1.39	0.06
DRI third quartile (≥1.40 and <1.72)	1.29	1.09, 1.52	0.003
DRI highest quartile (≥1.72)	1.39	1.18, 1.64	<0.001
Estimated GFR at transplant			
≥60 ml/min/1.73 m^2	Reference	Reference	Reference
30–59 ml/min/1.73 m^2	3.25	2.80, 3.78	<0.001
15–29 ml/min/1.73 m^2	6.13	5.03, 7.46	<0.001
<15 ml/min/1.73 m^2 or acute dialysis	9.30	7.57, 11.44	<0.001
Cause of liver disease			
Cholestatic	Reference	Reference	Reference
Hepatitis B	1.10	0.64, 1.90	0.72
Autoimmune	1.46	0.96, 2.22	0.07
Nonalcoholic steatohepatitis	1.51	1.03, 2.20	0.033
Other	1.57	1.10, 2.24	0.013
Cryptogenic cirrhosis	1.60	1.11, 2.30	0.013
Alcohol	1.61	1.14, 2.27	0.007
Hepatocellular carcinoma	1.83	1.29, 2.59	0.001
Hepatitis C	2.06	1.49, 2.84	<0.001
Pretransplant diabetes	2.04	1.80, 2.31	<0.001
Black race versus other	1.88	1.58, 2.22	<0.001
Male	1.20	1.06, 1.37	0.004
Pretransplant hypertension	1.07	1.00, 1.15	0.046
Serum sodium			
Lowest tertile (<135 mEq/l)	Reference	Reference	Reference
Middle tertile (≥135 and <138 mEq/l)	1.49	1.29, 1.72	<0.001
Highest tertile (≥138 mEq/l)	1.55	1.33, 1.80	<0.001
Total bilirubin			
Lowest tertile (<2.3 mg/dl)	Reference	Reference	Reference
Middle tertile (≥2.3 and <5.9 mg/dl)	0.80	0.69, 0.94	0.007
Highest tertile (≥5.9 mg/dl)	0.73	0.60, 0.88	0.001
Serum albumin			
Lowest tertile (<2.6 g/dl)	Reference	Reference	Reference
Middle tertile (≥2.6 and <3.2 g/dl)	0.92	0.80, 1.06	0.25
Highest tertile (≥3.2 g/dl)	0.77	0.66, 0.89	<0.001

DRI, Donor Risk Index.

*Censored for death. Model also adjusted for recipient age-strata, patient location at the time of transplant and international normalized ratio of prothrombin time at transplant. None of these variables was significantly associated with the outcome.

in DCD livers due to an obligatory warm ischaemia period during organ procurement. These complications have been associated with decreased graft [5,29–31] and patient survival after DCD liver transplantation [11]. Similar to these previous reports, we found that recipients of DCD and higher DRI livers had an increased incidence of relisting for second LT and death.

Recently, DCD status has also been shown to contribute to kidney injury after liver transplant. Leithead *et al.* showed an increased risk of post-LT AKI in a single-centre cohort of 88 recipients of DCD livers compared with propensity-matched recipients of non-DCD livers (53% vs 32%, $P < 0.001$). DCD recipients were also more likely to have severe AKI, as determined by RIFLE criteria, and require renal replacement therapy [15]. The authors postulate that the increased risk of AKI is related to extrahepatic complications of a systemic inflammatory response that occurs with ischaemia reperfusion injury, supported by the fact that DCD recipients had significantly higher median peak aspartate aminotransferase (AST) levels compared with non-DCD recipients, and peak AST was strongly associated with AKI in DCD recipients [15]. These authors found a similar relationship between hepatic ischaemia reperfusion injury, as assessed through peak AST, and AKI in a cohort of donation after brain death LT recipients [16]. This same centre has also demonstrated a temporal trend

Table 4. Multivariable cox regression analysis of end-stage renal disease after liver transplant, adjusting for separate components of Donor Risk Index.*

Characteristic	Hazard ratio	95% Confidence interval	*P*
Donation after cardiac death	1.40	1.09, 1.80	0.008
Donor age (years)			
<40	Reference	Reference	Reference
40–49	1.07	0.90, 1.27	0.44
50–59	1.29	1.09, 1.54	0.003
60–69	1.32	1.07, 1.63	0.01
≥70	1.13	0.84, 1.53	0.42
Cold ischaemia time (h)	1.02	1.01, 1.04	0.002
Donor race			
White	Reference	Reference	Reference
Black	0.92	0.77, 1.08	0.30
Other	1.20	1.02, 1.40	0.025
Estimated GFR at transplant			
≥60 ml/min/1.73 m^2	Reference	Reference	Reference
30–59 ml/min/1.73 m^2	3.17	2.71, 3.71	<0.001
15–29 ml/min/1.73 m^2	6.03	4.92, 7.38	<0.001
<15 ml/min/1.73 m^2 or acute dialysis	9.13	7.37, 11.31	<0.001
Cause of liver disease			
Cholestatic	Reference	Reference	Reference
Hepatitis B	1.15	0.67, 2.00	0.61
Autoimmune	1.37	0.89, 2.11	0.16
Nonalcoholic steatohepatitis	1.48	1.00, 2.18	0.048
Other	1.50	1.04, 2.16	0.029
Cryptogenic cirrhosis	1.58	1.08, 2.30	0.017
Alcohol	1.55	1.09, 2.21	0.015
Hepatocellular carcinoma	1.81	1.27, 2.59	0.001
Hepatitis C	2.00	1.44, 2.79	<0.001
Pretransplant diabetes	2.00	1.76, 2.27	<0.001
Black race versus other	1.82	1.52, 2.18	<0.001
Male	1.19	1.04, 1.35	0.012
Serum sodium			
Lowest tertile (<135 mEq/l)	Reference	Reference	Reference
Middle tertile (≥135 and <138 mEq/l)	1.46	1.26, 1.69	<0.001
Highest tertile (≥138 mEq/l)	1.49	1.28, 1.74	<0.001
Total bilirubin			
Lowest tertile (<2.3 mg/dl)	Reference	Reference	Reference
Middle tertile (≥2.3 and <5.9 mg/dl)	0.80	0.68, 0.95	0.008
Highest tertile (≥5.9 mg/dl)	0.73	0.60, 0.89	0.001
Serum albumin			
Lowest tertile (<2.6 g/dl)	Reference	Reference	Reference
Middle tertile (≥2.6 and <3.2 g/dl)	0.91	0.79, 1.05	0.21
Highest tertile (≥3.2 g/dl)	0.77	0.67, 0.90	<0.001

*Censored for death. Model also adjusted for the following recipient risk factors: age-strata, pretransplant hypertension, patient location at the time of transplant and international normalized ratio of prothrombin time at transplant. Model adjusted for the following donor risk factors: cause of death, split liver, height and share type. None of these variables was significantly associated with the outcome.

for increased incidence of AKI with the use of higher risk, primarily DCD, allografts [17]. We found that the median time to ESRD after LT was shorter among DCD recipients, potentially supporting the hypothesis that AKI early after transplant related to ischaemia reperfusion injury drives the increased risk of ESRD in DCD recipients. Similarly, in a recent study by Israni *et al.* [18] DRI was included in a risk prediction equation for ESRD occurring within 6 months after LT but not significant in the prediction equation for ESRD occurring between 6 months and 5 years post-LT.

Previous studies have shown that there may be a subgroup of younger DCD donors with shorter ischaemia time that have improved graft outcomes compared with other

DCD donors [26,32]. We analysed the subcohort of DCD recipients to determine whether there are other donor characteristics that modify the risk of ESRD. We did not find that other donor characteristics alter the risk of ESRD among DCD recipients, although in the overall cohort, older donor age and prolonged cold ischaemia time were associated with increased risk of ESRD.

Our study has a number of limitations. The primary outcome in this study was ESRD; given limited follow-up time, it is possible that more LT recipients had advanced CKD that had not yet progressed to dialysis or kidney transplant. We hypothesize that the increased risk of ESRD in recipients of DCD organs is related to AKI after transplant, but with limitations of this dataset, we had limited information about post-transplant renal function or dialysis. We also postulate that DCD recipients had increased ischaemia reperfusion injury after transplant based on prior literature, although no laboratory or biopsy results were available in this registry dataset to confirm this hypothesis. A single creatinine at the time of transplant was used to estimate GFR using the MDRD equation, which does not necessarily accurately characterize duration or degree of pretransplant renal dysfunction. Finally, there was missing data on key factors such as diabetes and cold ischaemia time, but sensitivity analyses imputing extreme values for these variables yielded similar results to primary analyses.

In summary, in this national cohort of LT recipients, recipients of livers from DCD donors or donors with higher DRI had an increased risk of ESRD after LT. This may reflect an increased risk of AKI after transplant related to a systemic inflammatory response in the setting of ischaemia reperfusion injury. Recipients of DCD organs are already known to have increased risk of graft loss and mortality. ESRD is another important complication that should be considered and discussed with patients when deciding about allocation of DCD or high DRI organs, particularly in candidates who have other risk factors for long-term renal dysfunction such as pretransplant CKD, diabetes and hepatitis C. Further research should focus on the pathogenesis of kidney injury after DCD liver transplantation and the effect on long-term renal outcomes.

Authorship

RLR: participated in research design, performed data analysis, and participated in writing the manuscript. PPR: participated in research design, participated in data analysis, and participated in writing the manuscript. PLA: participated in research design, participated in data analysis, and participated in writing the manuscript.

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