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Abbreviations:

ANZDATA _ Australia and New Zealand Dialysis and Transplant

ANOVA - analysis of variance

BMI – body mass index

CAD – coronary artery disease

CI – Confidence interval

CNI – calcineurin-inhibitor

DCGL – death-censored graft loss

DBD – donation after brain death

DCD – donation after cardiac death donor

DGF – delayed graft function

eGFR – Estimated glomerular filtration rate

ESKD – end-stage kidney disease

HLA – human leukocyte antigen

HR – hazard ratio

LD – live-donor

PRA – panel reactive antibody

Abstract

Background and objective: Delayed graft function (DGF) is an established complication after donation after cardiac death (DCD) kidney transplants, but the impact of DGF on graft outcomes is uncertain. To minimize donor variability and bias, a paired donor kidney analysis was undertaken where one kidney developed DGF and the other did not develop DGF using data from the Australia and New Zealand Dialysis and Transplant Registry. **Methods:** Using paired DCD kidney data from the Australia and New Zealand Dialysis and Transplant Registry, we examined the association between DGF, graft and patient outcomes between 1994-2012 using adjusted Cox regression models. **Results:** Of the 74 pairs of DCD kidneys followed for a median of 1.9 years (408 person-years), a greater proportion of recipients with DGF had experienced overall graft loss and death-censored graft loss at 3 years compared to those without DGF (14% vs. 4%, p=0.04 and 11% vs. 0%, p<0.01 respectively). Compared to recipients without DGF, the adjusted hazard ratio for overall graft loss at 3 years for recipients with DGF was 4.31 (95%CI 1.13, 16.44). The adjusted HR for acute rejection and all-cause mortality at 3 years in recipients who have experienced DGF were 0.98 (95%CI 0.96, 1.01) and 1.70 (95%CI 0.36, 7.93) respectively, compared to recipients without DGF. **Conclusions:** Recipients of DCD kidneys with DGF experienced a higher incidence of overall and death-censored graft loss compared to those without DGF. Strategies aim to reduce the risk of DGF could potentially improve graft survival in DCD kidney transplants.

Introduction

Donation after cardiac death (DCD) is an important source of donor kidneys worldwide. In Australia, the number of DCD kidney transplants has increased by at least four times between 2007 and 2013, with similar trend being observed in other countries [1]. The initial concerns that DCD kidneys are associated with poorer graft outcomes compared to donation after brain death (DBD) kidney transplants have largely been allayed, with large registry analyses from the United Kingdom and United States showing similar short and medium-term graft outcomes in recipients of DCD and DBD kidneys[2-4]. Whilst the influence of the mechanisms of donor death on longer-term graft outcomes is unclear, there is now evidence showing the incidence of other short term adverse effects such as delayed graft function (DGF) is substantial and is increasing, owing to the use of more marginal donor kidneys and DCD kidneys for transplantation.

DGF is an established risk factor for adverse graft outcomes in DBD kidney transplants, with a recent meta-analysis showing that the presence of DGF is associated with a 38% and 41% relative increase in the risk of acute rejection and graft loss at 3.2 years follow-up respectively [5]. By contrast, the association between DGF and graft outcomes in DCD kidney transplants is less clear, with several studies suggesting similar graft outcomes between recipients of DCD kidneys who had experienced DGF and no DGF [6,7]. Although DCD kidneys are more susceptible to the deleterious effects of cold ischaemic injury compared to DBD kidneys, it has been shown that brain death induces a greater up-regulation of inflammatory gene expression profile in the DBD kidneys compared to DCD kidneys, which may to some extent explain why DGF in DCD kidneys may not have the same deleterious effects on graft survival as DBD kidneys [8]. Nevertheless, the impact of DGF on graft outcomes remains uncertain as multiple donor and recipient characteristics often modify graft outcomes despite being adjusted for in statistical models. Taking into consideration

that within pair donor kidney analysis may be a more accurate and reliable method of assessing the association between the study factor of interest and graft outcomes, the aim of this study was to examine the association between DGF and graft and patient outcomes using paired kidney data.

Materials and Methods

Study population

Of the 201 paired primary DCD kidney transplant recipients identified between 1994-2012 using Australia and New Zealand Dialysis and Transplant (ANZDATA) registry, 74 pairs were included in this study because of differences in the presence of DGF (i.e. only one of the two recipients from the same DCD donor experienced DGF, defined as requiring dialysis after transplantation). We excluded recipients of multiple organ grafts and DCD kidney transplants where both recipients from the same DCD donor experienced either no DGF or DGF. ANZDATA registry does not collect the reason for DGF and therefore, we were unable to differentiate between DGF (and therefore requiring dialysis) secondary to hyperkalaemia or other reasons.

Data collection

Baseline data included recipient characteristics of age, gender, cause of end stage kidney disease (ESKD), race, body mass index (BMI, in kg/m^2), waiting time (in years), presence of comorbidities (diabetes, coronary artery disease [CAD]) and smoking history; and transplant-related characteristics included the use of induction antibody therapy, human leukocyte antigen (HLA)-mismatches, percentage peak panel reactive antibody (PRA), total ischaemic time and type of initial immunosuppressive agents (categorised as calcineurin-inhibitor [CNI], antimetabolite and prednisolone).

Clinical Outcomes

The primary clinical outcomes of this study were overall graft loss, death-censored graft loss (DCGL), acute rejection in the first 6 months after transplant, graft function (estimated glomerular

filtration rate [eGFR]), all-cause mortality and death with functioning graft. Graft loss, eGFR and death were examined at 1 and 3 years post-transplant.

Statistical analyses

Comparisons of the baseline characteristics between recipients who had experienced no DGF or DGF were made by chi-square test, Mann-Whitney U test and analysis of variance (ANOVA) for categorical and continuous variables respectively where appropriate. Overall graft loss, DCGL, acute rejection at 6 months, all-cause mortality and death with functioning graft were examined using the adjusted Cox proportional hazard regression analysis. In addition, random effects (shared frailty) Cox proportional hazard regression models, accounting for the potential intra-cluster correlation within transplant states and country were undertaken for analysis involving graft loss. Linear regression was used to examine the association between DGF and eGFR at 1 and 3 years. Graft loss censored for death was coded as 0ml/min/1.73m^2. The proportional hazard assumptions of all Cox regression models were checked graphically by plotting the Schoenfield residuals, with no evidence of departures from proportional hazards for overall graft loss, DCGL, all-cause mortality and death with functioning graft. The covariates included in the Cox and linear regression models were recipient and transplant-related characteristics outlined above. Results were expressed as hazard ratio (HR) or mean differences with 95% confidence interval (95% CI). Potential effect modification was tested between the study factor and other covariates using two-way interaction terms in the adjusted models. Only covariates which were associated with outcomes with p-values of <0.10 in the unadjusted analyses were included in the multivariable-adjusted analyses. Recipient age was included in all models given its “biological” relationship with outcomes. All analyses were undertaken using SPSS V10 statistical software program (SPSS Inc., North Sydney, Australia) and SAS statistical software 9.4.

Results

Study population

The mean (SD) age of the 74 donors was 45.2 (16.3) years. Fifty (67.6%) donors were males, 13 (17.8%) had a history of hypertension and 25 (33.8%) whose death were attributed to cerebrovascular accident. Table 1 shows the baseline recipient and transplant-related characteristics of the study population stratified by presence of DGF. The median (IQR) follow-up time of the 148 recipients was 1.94 (0.86-3.38) years resulting in 408 patient-years, with similar median (IQR) follow-up period between recipients without DGF (1.96 [0.90-3.38] years) and with DGF (1.93 [0.83-3.44] years, p=0.78). Recipients who had experienced DGF had a higher mean BMI compared to those without DGF (27.7 vs. 24.9kg/m^2, p<0.01) but other recipient characteristics, total ischaemic time, baseline immunological status and initial immunosuppression were similar between groups. Median (IQR) duration of dialysis in recipients who had experienced DGF was 9 (5-14) days.

Proportion of recipients who had experienced rejection or had died were similar between those with and without DGF. A greater proportion of recipients with DGF had experienced DCGL compared to those without DGF, with the majority of the DCGL occurring within the first 3 years post-transplant (Table 1).

Delayed graft function, overall and death-censored graft loss

The unadjusted cumulative overall graft survivals at 1 and 3 years for recipients without DGF were 95% and 95% respectively; and were 90% and 83% respectively for recipients with DGF (log-rank p=0.04). Compared to recipients without DGF, the adjusted hazard ratio for 1-year overall graft

loss for recipients with DGF was 2.75 (95%CI 0.68, 11.01); and was 4.31 (95%CI 1.13, 16.44) for 3-year overall graft loss, adjusted for HLA-mismatches, waiting time, recipient age and smoking status (Figure 1). The adjusted HR in the random effects models for 1 and 3-year overall graft loss were 2.39 (95%CI 0.62, 9.28; p=0.200) and 3.40 (95%CI 0.94, 12.4; p=0.060) respectively. Adjusted Kaplan Meier curves for overall graft survivals according to DGF status are shown in Figure 2A. Causes of graft loss at 3 years by DGF status are shown in Table 1. Median (IQR) time to overall graft loss was similar between recipients with and without DGF (3.8 [1.9-12.6] months vs. 2.0 [-] months respectively, p=0.47).

The unadjusted cumulative death-censored graft survivals at 1 and 3 years for recipients without DGF were 100% and 100% respectively; and were 91% and 86% respectively for recipients with DGF (log-rank p-value 0.03). Recipients without DGF did not experienced DCGL in the first 3 years after transplantation. Adjusted Kaplan Meier curves for death-censored graft survivals according to DGF status are shown in Figure 2B.

Delayed graft function, acute rejection and graft function

There were no associations between DGF and acute rejection at 6 months in the unadjusted and adjusted models. The adjusted hazard ratio for acute rejection for recipients with DGF was 0.98 (95%CI 0.96, 1.01), adjusted for recipient age, initial immunosuppression and PRA (Figure 1).

The mean (SD) eGFR at 1 and 3 years for recipients with and without DGF are shown in Table 1. Compared to recipients without DGF, the mean eGFR was 14.98mL/min/1.73m^2 (95%CI -28.83,

-0.77, p=0.04) lower at 3 years, but not at 1 year (-5.93mL/min/1.73m^2, 95%CI -16.99, 4.49, p=0.25) in recipients with DGF; adjusted for gender, recipient age and BMI.

Delayed graft function and mortality

The cumulative patient survivals at 1 and 3 years for recipients with and without DGF were 96% and 96% respectively. Compared to recipients without DGF, the adjusted hazard ratios for all-cause mortality and death with functioning graft at 1 year for recipients with DGF were 1.26 (95%CI 0.25, 6.49) and 0.41 (95%CI 0.04, 4.21) respectively; and at 3 years were 1.70 (95%CI 0.36, 7.93) and 0.80 (95%CI 0.12, 5.18) respectively, adjusted for recipient age, diabetes, smoking status and waiting time (Figure 1).

Discussion

In our study involving 74 paired DCD kidney transplants with a median follow-up time of 1.9 years, we have shown that DGF is associated with a higher incidence of overall graft loss and DCGL at 3 years. At 3 years after transplantation, 14% of kidney transplant recipients who had experienced DGF experienced death-censored graft loss, compared to no patients who did not experience DGF.

DGF is a frequent complication of DCD kidney transplants, with reported incidence of almost 50% compared to 20% for DBD kidney transplants, attributed to the greater susceptibility of DCD kidneys to the deleterious effects of cold ischaemia [9]. DGF occurs at a result of ischaemia-reperfusion injury. In the ensuing ischaemic injury following organ procurement, there is osmotic injury to cells in addition to an accumulation of reactive oxygen species [10,11]; the damage of which can be reduced with appropriate preservation fluids, optimal storage conditions, and adequate intra- and post-operative fluid balance [12-14]. After reperfusion, the combination of vasoconstriction, activation and recruitment of innate and adaptive immune cells contribute to sustained epithelial cell damage and inflammatory response, manifesting clinically as DGF [15,16]. In a prospective longitudinal study of 318 kidney transplant recipients, kidneys that were complicated by DGF showed significantly higher degrees of tubulo-interstitial inflammation (i.e. higher Banff "t" and "i" scores) and higher Banff cumulative chronicity scores in protocol biopsy at 3 months compared to kidneys without DGF suggesting a potential role of inflammation in determining the longer-term graft outcomes in recipients with DGF [18]. With the greater utilization of DCD donors as a source of donor kidneys worldwide, it is therefore crucial to understand whether there is a differential association between DGF and graft survival in DCD compared to DBD kidney transplants.

The impact of DGF on overall graft function and graft loss is uncertain from the published literature. A recent systematic review of 33 randomized controlled trials, cohort and case control studies involving 151,194 kidney transplant recipients evaluating the impact of DGF and graft outcomes reported there was substantial heterogeneity in the current literature, limited by varying duration of follow-up period, definition of DGF and year of publication. In that study, the pooled relative risk (RR) for graft loss in recipients with DGF was 1.41 (95% CI 1.27–1.56, df=20, $p<0.01$, $I^2 = 52\%$) compared to those without DGF, with little difference in the point estimates if restricted to studies that had defined DGF as requiring dialysis (pooled RR 1.42, 95% CI 1.24–1.63, df=12, $p<0.01$, $I^2 = 61\%$) [5]. This meta-analysis included two DCD cohort studies, which showed that in contrast to DBD kidney transplants, there was no association between DGF and graft loss [19,20]. Similar findings of a lack of association between DGF and graft survival in DCD kidneys have been corroborated by other single centre retrospective cohort studies [6,7].

Our study findings suggested a higher incidence of overall graft loss and DCGL in DCD recipients who have experienced DGF, the causal relationship between DGF and overall graft loss and DCGL is not clear. There was no association between DGF and acute rejection suggesting that the greater risk of DCGL in recipients who had experienced DGF was not mediated by acute clinical rejection. In addition, there was no distinct pattern of graft loss in those with DGF, with graft loss attributed to acute rejection being reported for 8% of overall graft loss. There have been a few studies that have used paired kidneys for analysis, which minimizes donor and hidden selection biases and may offer a more accurate assessment of the association between the study factor and outcome of interest.

There are several limitations in our study. Even though a paired kidney approach was used, selection bias may still exist because there may be systematic differences in the management of

kidney transplant recipients between transplanting centres and clinicians. There may be unmeasured residual confounders such as the surgical approach/complications (e.g. duration of anastomotic time, complexities of recipient surgery) and intensity of immunosuppression (i.e. therapeutic drug levels), which are not collected by ANZDATA registry but may have modified the association between DGF and graft loss [21]. In view of the lack of detailed descriptor within the ANZDATA registry, misclassification bias of the outcomes could potentially occur but the bias is likely to be random and non-differential between the exposed and unexposed groups. The limited sample size and short follow-up period may lead to erroneous inference and therefore we are unable to generate reliable estimates with certainty. Despite these limitations, our study is the first paired kidney analysis that has evaluated the influence of DGF and graft and patient outcomes in DCD kidney transplants.

With the improved understanding of the complex mechanisms that cause DGF in DCD kidney transplants, therapeutic targets that modify these pathways could potentially reduce the development of DGF. Our study provides the point estimates that may be used to design a clinical trial using agents capable of reducing DGF and therefore reducing the risk of graft loss in DCD transplants.

Conclusion

DGF remains a vexing complication of DCD kidney transplants. In contrast to other studies, our paired kidney analysis has challenged the previously held belief that DGF has no deleterious effect on graft outcome by showing that 3-year death-censored graft survival for DCD recipients was 14% lower compared to those who did not experience DGF. Even though small numbers of DCD recipients were included in this study with short follow-up period, this is an important finding

given the increased utilization of DCD kidneys worldwide. Strategies aim to reduce the risk of DGF could potentially improve graft survival in DCD kidney transplants.

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Table 1. Baseline characteristics and clinical outcomes of paired donation after cardiac death kidney transplant recipients with and without delayed graft function (n = 74 pairs).

	No DGF (n=74)	DGF (n=74)	P-value
Demographics (recipient)			
Age (years, mean±SD)	50.3±12.8	49.6±14.5	0.77
Male (n, %)	43 (58.1)	47 (63.5)	0.50
Race (n, %)			0.60
Caucasian	54 (73.0)	54 (73.0)	
Asian	15 (20.3)	12 (16.2)	
Indigenous	5 (6.7)	8 (10.8)	
Diabetes (n, %)	13 (17.6)	19 (25.7)	0.23
BMI (kg/m^2, mean±SD)	24.9±5.0	27.7±6.1	0.003
Coronary artery disease (n, %)	6 (8.1)	8 (10.8)	0.57
Smoking (n, %)			0.90
None	37 (50.0)	39 (53.4)	
Former	28 (37.8)	25 (34.2)	
Current	9 (12.2)	9 (12.3)	
Cause of ESKD (n, %)			0.43
Glomerulonephritis	27 (36.5)	29 (39.2)	
Diabetes	10 (13.5)	16 (21.6)	
Cystic	12 (16.2)	7 (9.5)	
Vascular	6 (8.1)	8 (10.8)	
Others	19 (25.7)	14 (18.9)	
Waiting time (years, mean±SD)	3.9±2.9	3.7±2.2	0.76
Immunology/Transplant			
HLA-ABDR mismatches (total, mean±SD)	3.6±1.5	3.7±1.6	0.88
Peak PRA (%, mean±SD)	9.4±17.4	10.7±19.7	0.67
Ischaemic time (hours, mean±SD)	12.8±4.4	12.3±4.7	0.46

Induction (n, %)	61 (82.4)	68 (91.9)	0.08
Initial prednisolone (n, %)	72 (97.3)	74 (100.0)	0.15
Initial CNI (n, %)			0.57
None	3 (4.1)	1 (1.4)	
Cyclosporin	14 (18.9)	16 (21.6)	
Tacrolimus	57 (77.0)	57 (77.0)	
Initial anti-metabolite (n, %)			0.32
None	2 (2.7)	0 (0.0)	
Azathioprine	3 (4.1)	2 (2.7)	
MMF	69 (93.2)	72 (97.3)	
Transplant state/country			1.00
New South Wales	21 (28.4)	21 (28.4)	
Queensland	15 (20.3)	14 (18.9)	
South Australia	8 (10.8)	8 (10.8)	
Victoria	25 (33.8)	26 (35.2)	
Western Australia	4 (5.4)	4 (5.4)	
New Zealand	1 (1.3)	1 (1.3)	
Outcomes			
Rejection first 6 months (n, %)	14 (18.9)	12 (16.2)	0.67
eGFR (mL/min/1.73m^2, mean$\pm$SD)			
1-year eGFR (n=109 – 52/57)	52.4$\pm$30.5	46.6$\pm$32.8	0.34
3-years eGFR (n=54 – 24/30)	51.5$\pm$18.9	38.1$\pm$29.5	0.06
Graft loss (n, %)			
1 year	3 (4.1)	7 (9.5)	0.19
3 years	3 (4.1)	10 (13.5)	0.04
Causes of graft loss at 3 years (n)			
Death with functioning graft	3	2	0.01
Acute rejection	0	1	0.004
CAN/IFTA	0	2	

De novo/recurrent GN	0	2	
Infection	0	1	
Others	0	2	
DCGL (n, %)			
1 year	0 (0.0)	6 (8.1)	0.012
3 years	0 (0.0)	8 (10.8)	0.004
Death (n, %)			
1 year	3 (4.1)	3 (4.1)	1.00
3 years	3 (4.1)	4 (5.4)	0.70
Death with functioning graft (n, %)			
1 year	3 (4.1)	1 (1.4)	0.31
3 years	3 (4.1)	2 (2.7)	1.00

Data expressed as number (proportion) or as mean ± standard deviation (SD). ESKD – end-stage kidney disease, HLA – human leukocyte antigen, PRA – panel reactive antibody, CNI – calcineurin-inhibitor, MMF – mycophenolate, DCGL – death censored graft loss, eGFR – estimated glomerular filtration rate, CAN/IFTA – chronic allograft nephropathy/interstitial fibrosis and tubular atrophy, GN – glomerulonephritis.

Figure Legends

Figure 1. Forest plots of the adjusted hazard ratios (HR) with 95% confidence intervals (95%CI) of acute rejection in the first 6 months, overall graft loss at 1 and 3 years post-transplant, all-cause mortality and death with functioning graft at 3 years post-transplant stratified by delayed graft function (DGF) status, adjusted for recipient age, panel reactive antibody, body mass index and waiting time.

Figure 2. Adjusted Kaplan Meier curves for overall graft survival (A) and death censored graft survival (B) according to delayed graft function (DGF) status, adjusted for recipient age, panel reactive antibody, body mass index and waiting time.