ORIGINAL ARTICLE

Duration of delayed graft function and outcomes after kidney transplantation from controlled donation after circulatory death donors: a retrospective study

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SUMMARY

The impact of the duration of delayed graft function (DGF) on graft survival is poorly characterized in controlled donation after circulatory death (DCD) donor kidney transplantation. A retrospective analysis was performed on 225 DCD donor kidney transplants between 2011 and 2016. When patients with primary nonfunction were excluded ($n = 9$), 141 recipients (65%) had DGF, with median (IQR) duration of dialysis dependency of 6 (2–11.75) days. Longer duration of dialysis dependency was associated with lower estimated glomerular filtration rate at 1 year, and a higher rate of acute rejection. On Kaplan–Meier analysis, the presence of DGF was associated with lower graft survival (log-rank test $P = 0.034$), though duration of DGF was not ($P = 0.723$). However, multivariable Cox regression analysis found that only acute rejection was independently associated with lower graft survival [HR (95% CI) 4.302 (1.617–11.450); $P = 0.003$], whereas the presence of DGF and DGF duration were not. In controlled DCD kidney transplantation, DGF duration itself may not be independently associated with graft survival; rather, it may be that acute rejection associated with prolonged DGF is the poor prognostic factor.

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Key words
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Introduction

The emergence of donation after circulatory death (DCD) donors as a viable source of organs has been one of the defining themes of transplantation over the past decade. Kidneys from DCD donors have been extensively used for many years in the United Kingdom (UK), Belgium and the Netherlands, making up almost 50% of kidneys transplanted from deceased donors in these countries [1,2]. The number of kidneys transplanted from DCD donors is also increasing in the United States (US) and Australia [3,4].

Expansion in the use of kidneys from DCD donors, particularly from controlled DCD donors, has been driven partly by the growing demand for organs, and partly by successful reports of their use. Large risk-adjusted analyses examining kidneys transplanted from controlled DCD donors in the UK have shown

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equivalent medium-term graft survivals to those from donation after brain death (DBD) donors [1,5,6]. Interestingly, US data have not replicated these results, identifying a modest increase in graft failure in grafts from DCD versus DBD donors, even after risk adjustment [7]. These apparently conflicting findings may be explained by the longer cold ischaemic times (CITs) in the US data, as CIT is known to deleteriously affect kidneys from controlled DCD donors at lower time thresholds than those from DBD donors [5,6,8].

Although medium- and long-term outcomes are likely to be similar, early outcomes after controlled DCD donor kidney transplantation are very different than those from DBD donors. Delayed graft function (DGF), usually defined as the need for dialysis for any cause within the first 7 days post-transplant [9], occurs approximately twice as often after DCD donor than DBD donor kidney transplantation [1,10]. Importantly, although DGF is a well-described risk factor for graft loss in DBD donor kidney transplantation [11,12], particularly in recipients who also have acute rejection [13–15], this association is much less clear with controlled DCD donor kidney transplantation [4–6].

The apparent lack of association between the DGF and graft survival in controlled DCD donor kidney transplantation may be because of the subjectivity of using DGF as an outcome measure. The threshold for prescribing dialysis post-transplant is known to vary between clinicians and centres [16,17]. Recipients needing just one or two dialysis sessions post-transplant may not have required dialysis if peri-operative management had been different [11]. Therefore, dialysis dependency for longer durations post-transplant may be more indicative of prognostically significant graft dysfunction. It is therefore essential to consider not just the presence or absence of post-transplant dialysis, but also the *duration* of dialysis, as a possible risk factor for graft failure.

The association between dialysis duration post-transplant and graft survival has not been investigated in detail in controlled DCD donor kidney transplantation [18]. Therefore, we examined a large cohort of kidney transplants from controlled DCD donors, in order to detect a possible association between prolonged DGF and graft function and survival. Episodes of biopsy-proven acute rejection (BPAR) were recorded to determine if BPAR was associated with graft outcomes. Finally, analyses of death-censored graft survival were repeated including patients that were later diagnosed with PNF, in order to provide data for clinicians when DGF cannot be distinguished from PNF. To the best of our knowledge, this is the largest study of its type, to date.

Materials and methods

Study design and data collection

This was a retrospective analysis of adult patients who received a deceased donor kidney transplant in our unit between 1st January 2011 and 31st July 2016. Study follow-up ended on 31st January 2017. Recipients were included if they received a single kidney-only transplant from an adult controlled DCD donor (Maastricht categories III and IV) [19]. Patients transplanted pre-emptively, before requiring dialysis, were excluded from all analyses.

Data were obtained from a local database and the NHS Blood and Transplant national transplant registry. Donor risk indices were also collected [UK Kidney Donor Risk Index (UKKDRI) and Kidney Donor Risk Index (KDRI)] [20,21]. The UKKDRI is calculated using five variables: donor age; donor history of hypertension; donor weight; donor history of adrenaline use and number of days in hospital before donor death [20].

Clinical management

Kidneys were offered via nationally agreed offering schemes, as described elsewhere [22]. Donor and recipient selection criteria were the same as for kidneys from DBD donors. Accepted agonal phase times were in line with national guidance [23,24]. Hypothermic machine perfusion was not used [25].

Recipients received haemodialysis on the day of transplantation if their serum potassium was >5.5 mmol/l, or if there were signs of fluid overload, or if routine dialysis was due. Patients continued on peritoneal dialysis as usual, until transplantation. Recipients had a central venous line placed after induction of anaesthesia; an arterial line and/or oesophageal Doppler monitor were inserted according to the anaesthetist's preference. Recipients received 2000–4000 ml of crystalloids intra-operatively to maintain relative normotension, assuming standard blood loss of <250 ml. Postreperfusion kidney biopsies were taken to characterize and quantify baseline chronic donor changes (Karpinski score) [26], according to surgeon preference. Peritoneal dialysis catheters were routinely removed at the end of kidney transplantation [27]. Between January 2011 and January 2012, immunosuppression consisted of basiliximab induction, with oral cyclosporine, mycophenolate mofetil and prednisolone (all started on the day of transplant). From January 2012 onwards, oral tacrolimus replaced cyclosporine. Target trough cyclosporine or tacrolimus levels were not altered if DGF occurred.

Transplant International 2019; 32: 635–645

Postoperatively, recipients had urine and drain losses replaced 100% with intravenous Prismasol 2 mmol/l potassium solution (Gambro Lundia AB, Lund, Sweden), and boluses of crystalloid to maintain normotension, with a target body weight of 5% above preoperative dialysis 'dry weight'. The need for post-transplant haemodialysis was decided by daily consultant nephrologist review. Graft ultrasounds were performed within 24 h of the transplant. Patients with apparent DGF received graft ultrasounds ± biopsies every 7–10 days until graft function returned or the decision had been made to abandon the graft. There were no other differences in clinical management between those with or without DGF post-transplant.

Outcomes measures and study definitions

The following post-transplant outcome measures were collected: DGF; initial inpatient stay; estimated glomerular filtration rate (eGFR) using the four-variable Modification of Diet in Renal Disease equation; BPAR during the first year of transplant (Banff classification); death-censored graft survival (DCGS); and patient survival. 'Borderline' episodes of BPAR were included, in order to capture the possible clinical significance of this entity.

The duration from donor withdrawal of life-sustaining treatment (WLST) to asystole was termed the agonal phase time. Warm ischaemic time was defined as the duration between donor asystole and the start of *in situ* cold perfusion. Cold ischaemic time was the duration between the start of cold perfusion in the donor and the time of graft perfusion in the recipient. Anastomotic time was defined as the time between removal of the kidney from a bowl of ice to perfusion with recipient's blood. DGF was defined as the need for dialysis (for any cause) within the first week post-transplantation [9], whereas duration of DGF was defined as the number of days from the date of transplantation to the last dialysis session in those patients who subsequently became dialysis-independent. Primary nonfunction (PNF) was defined as failure of the transplanted kidney to ever function (i.e. freedom from dialysis) within the study follow-up period, regardless of cause. DCGS was defined as the time from transplantation to return to long-term dialysis or graft nephrectomy (whichever occurred first), censored for patient death.

Statistical analyses

Recipients were divided into groups based on the presence or absence of DGF. In those with DGF, further stratification was made on DGF duration (group I < 7 days; group II 7–14 days; group III >14 days). Patients with PNF were included in selected analyses. Patients whose grafts had failed before the time of eGFR measurement, or had not yet reached that point in their follow-up (or had died before the time point), were excluded from eGFR analyses at that time point.

Differences between groups were examined using Chi-squared or Fisher's exact test for categorical variables; the Mann–Whitney *U* test was used to compare nonparametric continuous variables whereas Student's *t*-test was used for parametric continuous variables. All continuous variables were tested for normality using the Kolmogorov–Smirnov test. Kaplan–Meier survival curves (with 95% confidence intervals) were used to demonstrate DCGS; a difference in survival between groups was examined using the log-rank test. Multivariable analyses were performed to assess the association between candidate variables and either DCGS or eGFR. Candidate variables were selected on the basis of previously demonstrated associations. The variance inflation factor was calculated for each covariate in the multivariable analyses; the covariate was removed if there was multicollinearity (defined as variance inflation factor ≥5) [28]. Cox regression was used to assess the association between candidate variables and DCGS, and results were expressed as hazard ratios (HR) with 95% confidence intervals (CI), with *P* values derived from likelihood ratio tests. Linear regression analysis and a univariate general linear model were used to assess the association with eGFR. A two-tailed *P* value of <0.05 was considered significant. All statistical analyses were performed using IBM SPSS version 24.0 (IBM, Armonk, NY, USA).

Results

Donor, recipient and operative characteristics and risk factors for DGF

During the study period, 245 single kidney-only transplants from adult controlled DCD donors were transplanted into adult recipients at our centre. Twenty recipients were transplanted pre-emptively, leaving 225 patients who were dependent on dialysis pretransplant. Of those, 9 (4%) had PNF. Causes of PNF were: renal vein thrombosis (3); rejection (2); renal artery thrombosis (2) and unknown (2). Median (IQR) follow-up was 37.6 (20.4–49.0) months.

Of the 216 patients that had a graft that functioned at some point post-transplant, 141 (65.3%) had DGF.

Donor, recipient and operative characteristics of all 216 patients are shown in Table 1. Median (IQR) donor age was 55 (49–65) years, and 64 donors (30%) had hypertension. Donor risk indices reflected the relatively high donor age and rate of co-morbidities, with median KDRI of 1.5. Median (IQR) recipient age was 54 (46–62) years, with a high proportion of black recipients (37%). Median CIT was fairly short (794 min). Table 1 also compares baseline characteristics of recipients with primary graft function versus those with DGF. Recipients with DGF were more likely to be black (47% vs. 18%; $P < 0.001$), on dialysis for a longer period pretransplant [1233 (731–2177) vs. 914 (464–1638) days; $P = 0.022$], and have more HLA mismatches. There were no statistically significant differences in donor or operative characteristics between those kidneys that had DGF post-transplant and those that did not.

Most patients (73/141; 51.8%) that had DGF recovered their graft function within 7 days of transplantation with a median (IQR) DGF duration of 6 (2–11.75) days. The longest DGF duration was 31 days. Patients with DGF were grouped according to DGF duration and baseline variables were compared (Table 2). There were no statistically significant differences in donor or operative variables between the three groups, though group II recipients (DGF duration 7–14 days, $n = 45$) had more HLA mismatches than those in the other two groups ($P = 0.004$). There was a trend towards longer duration of dialysis pretransplants in patients with prolonged DGF, but this was not statistically significant ($P = 0.07$).

Table 1. Donor, recipient and operative characteristics for all patients, and by presence of DGF post-transplant.*

	All patients† ($n = 216$)	No DGF ($n = 75$)	DGF ($n = 141$)	*P* value‡
Donor age, years	55 (49–65)	55 (48–65)	55 (49–65)	0.620
Donor gender M/F	128/88 (59/41)	38/37 (51/49)	90/51 (64/36)	0.081
Donor history of HT	64 (30)	22 (29)	42 (30)	1.000
Donor history of DM	12 (6)	6 (8)	6 (4)	0.350
Donor BMI, kg/m^2	25 (23–28)	24 (22–28)	26 (23–29)	0.090
Donor terminal creatinine, μmol/l	72 (53–98)	66 (52–95)	73 (53–104)	0.404
UKKDRI	1.3 (1.2–1.9)	1.3 (1.0–1.5)	1.3 (1.0–1.6)	0.357
KDRI	1.5 (1.2–1.9)	1.6 (1.2–1.9)	1.5 (1.2–2.0)	0.673
Agonal phase, min	17 (11–29)	19 (8–28)	18 (11–30)	0.887
Warm ischaemic time, min	12 (10–14)	11 (9–13)	12 (10–14)	0.077
Recipient age, years	54 (46–62)	53 (44–61)	56 (47–63)	0.284
Recipient gender M/F	153/63 (71/29)	50/25 (67/33)	103/38 (73/27)	0.348
Modality of dialysis HD/PD	172/44 (80/20)	50/25 (67/33)	122/19 (87/13)	0.001
Recipient black ethnicity	80 (37)	14 (18)	66 (47)	<0.001
Recipient BMI, kg/m^2	27 (24–30)	27 (23–29)	27 (24–30)	0.295
Recipient history of DM	54 (25)	13 (17)	41 (29)	0.070
Duration of pretransplant dialysis, days	1192 (639–1846)	914 (464–1638)	1233 (731–2177)	0.022
Highly sensitized recipient§	7 (4)	1 (2)	6 (5)	0.430
Previous kidney transplant	16 (7)	4 (5)	12 (9)	0.586
Number of HLA-DR mismatches	1 (0–1)	1 (0–1)	1 (0–1)	0.037
Total number of HLA-A, -B and -DR mismatches	3 (2–4)	3 (2–4)	3 (3–4)	0.021
Cold ischaemic time, min	794 (612–1004)	745 (589–962)	838 (663–1018)	0.052
Anastomotic time, min	39 (31–48)	40 (30–45)	39 (32–50)	0.443
Kidney Karpinski score	4 (3–5)	4 (2–5)	4 (3–5)	0.492

BMI, body mass index; DGF, delayed graft function; DM, diabetes mellitus; HD, haemodialysis; HLA, human leucocyte antigen; HT, hypertension; KDRI, Kidney Donor Risk Index; PD, peritoneal dialysis; UKKDRI, UK Kidney Donor Risk Index.

Data are presented as absolute number (%) or median (IQR).

*Missing data were <5%, except for terminal creatinine ($n = 21$; 10%), KDRI ($n = 27$; 13%), duration of pretransplant dialysis ($n = 48$, 22%), highly sensitized recipient ($n = 31$; 14%), anastomotic time ($n = 12$, 6%) and kidney Karpinski score ($n = 108$, 50%).

†Excluding those transplanted pre-emptively, or with PNF.

‡Comparing 'No DGF' and 'DGF' groups.

§Defined as calculated reaction frequency 85% or higher at the time of transplantation.

Transplant International 2019; 32: 635–645

Postoperative outcomes and DGF

Recipients with DGF had longer initial inpatient stays than those without DGF [11 (9–15) vs. 8 (6–10) days; $P < 0.001$; Table 3], higher rates of BPAR within the first year post-transplant (24% vs. 13%; $P = 0.043$), and lower eGFRs at six-, 12- and 24-months post-transplant ($P = 0.001$, $P = 0.036$, $P = 0.043$ respectively; Table 3). Longer duration of DGF was associated with an increased initial hospital stay ($P < 0.001$), a higher rate of BPAR within the first year post-transplant ($P = 0.027$), and with lower eGFR at six and 12 months ($P = 0.007$ and $P = 0.009$ respectively; Table 4).

Linear regression analysis was used to identify variables associated with 12- and 24-month eGFR using the following candidate variables: UKKDRI; warm ischaemic time; anastomotic time; cold ischaemic time; DGF (yes/no); and BPAR (yes/no). Variables associated with DGF on univariate analysis (Table 1) were not included in this analysis, as DGF was already a candidate variable. Only UKKDRI and the presence of BPAR were statistically significantly associated with lower eGFR at 12 and 24 months (UKKDRI coefficient (95% CI): −25.731 (−35.609 to −15.853), $P < 0.001$ and −22.096 (−34.210 to −9.981), $P < 0.001$ respectively; BPAR coefficient (95% CI): −15.142 (−25.272 to −5.012), $P = 0.004$ and −12.702 (−24.421 to −0.983), $P = 0.034$ respectively; Table S1). A univariate general linear model was used to identify variables associated with 12- and 24-month eGFR in those recipients with DGF ($n = 141$). The same variables as above were included, though DGF duration replaced DGF (yes/no). Only UKKDRI was statistically significantly associated with lower eGFR at both 12 and 24 months [−23.140 (−35.438 to −10.841), $P < 0.001$ and −23.211 (−38.557 to −7.865), $P = 0.004$ respectively], whereas DGF duration >14 days was associated with lower 12-month eGFR only [−18.087 (−31.414 to −4.759), $P < 0.008$; Table S2].

Table 2. Donor, recipient and transplant-related characteristics stratified by duration of DGF post-transplant (group I < 7 days; group II 7–14 days; group III >14 days).

	Group I ($n = 73$)	Group II ($n = 45$)	Group III ($n = 23$)	P value
Donor age, years	54 (49–65)	56 (50–65)	56 (48–65)	0.916
Donor gender M/F	44/29 (60/40)	34/11 (76/24)	12/11 (52/48)	0.109
Donor history of HT	24 (33)	11 (24)	7 (30)	0.593
Donor history of DM	3 (4)	3 (7)	0 (0)	0.437
Donor BMI, kg/m^2	25 (23–28)	26 (23–30)	27 (23–33)	0.354
Donor terminal creatinine, μmol/l	74 (58–105)	76 (49–96)	53 (45–104)	0.283
UKKDRI	1.4 (0.9–1.6)	1.3 (1.0–1.6)	1.2 (1.0–1.9)	0.904
KDRI	1.7 (1.2–2.0)	1.4 (1.2–1.8)	1.3 (1.1–2.0)	0.337
Agonal phase, min	18 (13–30)	18 (11–34)	14 (11–23)	0.506
Warm ischaemic time, min	12 (10–13)	12 (10–13)	13 (9–15)	0.920
Recipient age, years	58 (47–63)	57 (48–63)	51 (43–61)	0.366
Recipient gender M/F	57/16 (78/22)	31/14 (69/31)	15/8 (65/35)	0.359
Modality of dialysis HD/PD	65/8 (89/11)	35/10 (78/22)	22/1 (97/3)	0.082
Recipient black ethnicity	36 (49)	16 (36)	14 (61)	0.117
Recipient BMI, kg/m^2	27 (24–30)	28 (24–30)	29 (24–31)	0.822
Recipient history of DM	26 (36)	10 (22)	5 (22)	0.208
Duration of pretransplant dialysis, days	1159 (604–1700)	1510 (821–2238)	1598 (738–2718)	0.070
Highly sensitized recipient*	4 (6)	1 (3)	1 (5)	0.724
Previous kidney transplant	5 (9)	5 (11)	2 (9)	0.722
Number of HLA-DR mismatches	1 (0–1)	1 (1–1)	1 (0–1)	0.183
Total HLA mismatches (0–6)	3 (2–4)	4 (3–4)	3 (3–4)	0.004
Cold ischaemic time, min	848 (672–1038)	780 (636–1003)	945 (685–1105)	0.417
Anastomotic time, min	38 (32–47)	40 (32–56)	38 (33–51)	0.437
Kidney Karpinski score	5 (3–5)	4 (3–5)	4 (2–4)	0.176

BMI, body mass index; DGF, delayed graft function; DM, diabetes mellitus; HD, haemodialysis; HLA, human leucocyte antigen; HT, hypertension; KDRI, Kidney Donor Risk Index; PD, peritoneal dialysis; UKKDRI, UK Kidney Donor Risk Index.

Data are presented as absolute number (%) or median (IQR).

*Defined as calculated reaction frequency 85% or higher at the time of transplantation.

Table 3. Clinical outcomes by presence of DGF post-transplant.

	All patients (n = 216)	No DGF (n = 75)	DGF (n = 141)	P value*
Initial inpatient stay, days	10 (7–14)	8 (6–10)	11 (9–15)	<0.001
Biopsy-proven acute rejection	44 (20)	10 (13)	34 (24)	0.043
6-month eGFR, ml/min/1.73 m^2	44 (34–63)	54 (37–71)	42 (33–58)	0.001
12-month eGFR, ml/min/1.73 m^2	50 (35–65)	51 (40–77)	48 (34–62)	0.036
24-month eGFR, ml/min/1.73 m^2	51 (35–68)	54 (40–74)	50 (30–64)	0.043

DGF, delayed graft function; eGFR, estimated glomerular filtration rate.

Data are presented as absolute number (%) or median (IQR).

*Comparing 'No DGF' and 'DGF' groups.

Table 4. Clinical outcomes by duration of DGF post-transplant.

	Group I (n = 73)	Group II (n = 45)	Group III (n = 23)	P value
Initial inpatient stay, days	9 (7–13)	12 (10–17)	19 (13–26)	<0.001
Biopsy-proven acute rejection	12 (16)	12 (27)	10 (44)	0.027
6-month eGFR, ml/min/1.73 m^2	46 (36–64)	39 (31–59)	29 (20–47)	0.007
12-month eGFR, ml/min/1.73 m^2	51 (40–65)	44 (35–61)	32 (20–57)	0.009
24-month eGFR, ml/min/1.73 m^2	54 (35–74)	48 (32–63)	35 (28–62)	0.206

DGF, delayed graft function; eGFR, estimated glomerular filtration rate.

Group I < 7 days DGF, group II 7–14 days DGF, group III >14 days DGF. Data are presented as absolute number (%) or median (IQR).

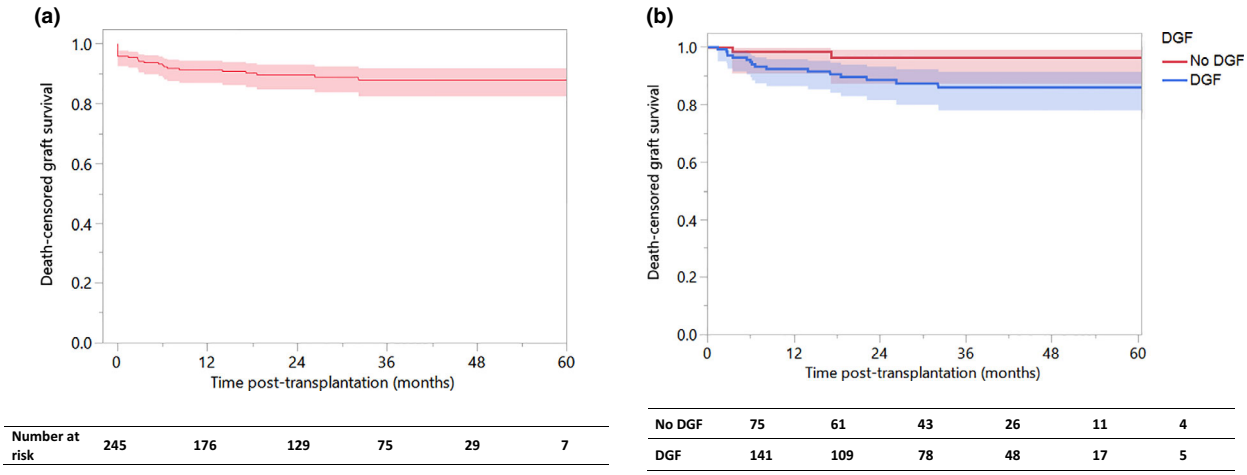
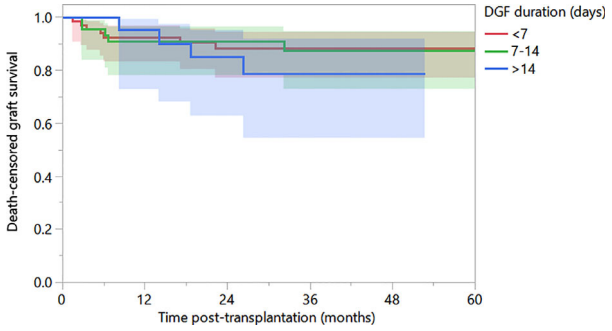


Figure 1 (a) Death-censored graft survival for all 245 recipients of controlled donation after circulatory death (DCD) donor kidney transplants, including those with primary nonfunction. The number at risk is given below. (b) Death-censored graft survival of recipients of controlled DCD donor kidney transplants, by presence of delayed graft function (DGF). Recipients with primary nonfunction were excluded. 'No DGF' (n = 75) versus 'DGF' (n = 141) P = 0.034. Numbers at risk are given below.

For the 245 study patients, graft survival was acceptable, with >80% DCGS at 5 years post-transplant (Fig. 1a). When pre-emptively transplanted patients and those with PNF were excluded, univariate analysis showed that recipients with DGF had worse DCGS than those without DGF (P = 0.034; Fig. 1b). Duration of DGF was not associated with worse DCGS (P = 0.723; Fig. 2). However, by definition, DGF can only be

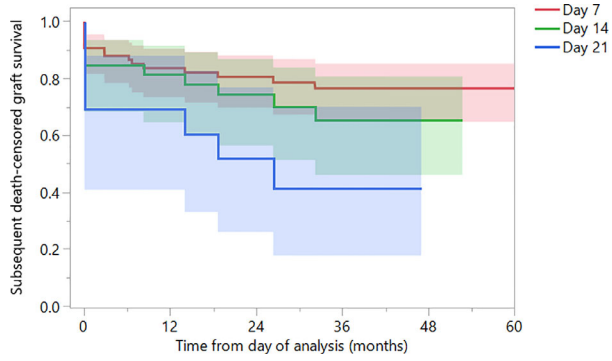
Transplant International 2019; 32: 635–645



<7 days	73	53	33	18	8	3
7–14	45	38	32	21	7	3
>14	23	20	15	11	4	1

Figure 2 Death-censored graft survival of recipients of controlled donation after circulatory death (DCD) kidney transplants with delayed graft function (DGF), by duration of DGF. Recipients with primary nonfunction were excluded. Group I (DGF <7 days, $n = 73$), group II (DGF 7–14 days, $n = 45$), group III (DGF >14 days, $n = 23$); $P = 0.723$. Numbers at risk are given below.

diagnosed retrospectively (i.e. after graft function returns). In order to enable an assessment of graft survival in patients where DGF cannot be distinguished from PNF, DCGS analyses were repeated including patients that were later diagnosed with PNF, conditional on the day of observation. Figure 3 demonstrates that patients with nonfunctioning grafts *in situ* on days 7 or 14 had 2-year DCGS of approximately 80%. However, patients with nonfunctioning perfused grafts *in situ* whose grafts had still not functioned by day 21 had 2-year DCGS of approximately 50% ($P = 0.043$).



Day 7	75	57	46	31	10	3
Day 14	33	25	19	13	4	1
Day 21	13	9	7	5	1	1

Figure 3 Subsequent death-censored graft survival of recipients of controlled donation after circulatory death kidney transplants with perfused, nonfunctioning grafts *in situ* at day 7 ($n = 75$), day 14 ($n = 33$) and day 21 ($n = 13$) post-transplant. Log-rank $P = 0.043$. Numbers at risk are given below.

Biopsy-proven acute rejection within the first year post-transplant was associated with reduced DCGS ($P = 0.002$; Fig. 4a). However, stratification by BPAR and DGF indicated that DCGS was excellent in those patients with either DGF or BPAR, but was significantly poorer if both were present (Fig. 4b; $P < 0.001$). Of the 34 patients with both DGF and BPAR within 1 year of transplantation, 17 (50%) had an episode of BPAR diagnosed during DGF. There was no difference in DCGS between those patients with BPAR during DGF versus those with DGF that had their first episode of BPAR after recovering graft function ($P = 0.587$; data not shown). Excluding the eight patients who had borderline acute rejection as their first episode of BPAR did not significantly change the DCGS of those with DGF and BPAR, or the outcome of the analysis on the effect of the timing of BPAR relative to DGF (data not shown).

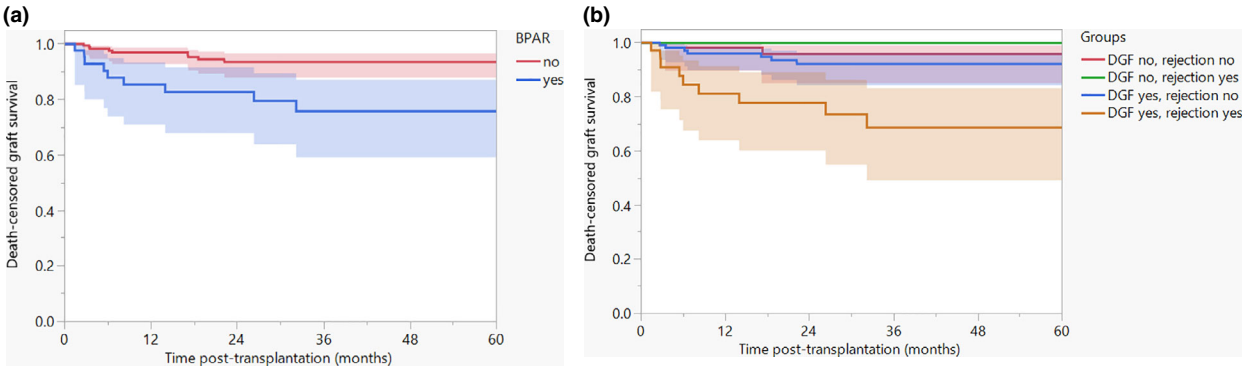
Cox regression analysis was performed to identify variables associated with DCGS in the 216 patients that had a graft that functioned at some point post-transplant, using the same candidate variables as above. Of these, only the presence of BPAR was statistically significantly associated with lower DCGS [HR (95% CI) 4.302 (1.617–11.450); $P = 0.003$] (Table S3). The presence of DGF was not significant ($P = 0.102$). The only variable associated with DCGS in recipients with DGF ($n = 141$) was the presence of BPAR [HR (95% CI) 6.456 (2.021–20.620); $P = 0.002$]. DGF duration failed to reach significance (Table S4).

There were no differences in patient survival between those recipients that had DGF and those that did not ($P = 0.159$; Fig. S1).

Discussion

This large single-centre retrospective analysis examined the impact of duration of DGF on outcomes after kidney transplantation from controlled DCD donors. Prolonged DGF duration (defined as dialysis dependency) was associated with longer inpatient stays, reduced early graft function and higher rates of BPAR. Increasing length of DGF duration was not associated with worse DCGS when analysed 'retrospectively', that is with PNFs excluded. However, when analysed 'prospectively', that is when those kidneys that were eventually found to have PNF were included, prolonged dialysis dependency post-transplant was strongly associated with poor graft survival. To the best of our knowledge, this is the largest study of its type, to date.

Large studies have examined post-transplant dialysis duration and graft outcomes in deceased donor kidney



BPAR						
No	172	135	93	54	23	5
Yes	43	34	27	19	6	4

DGF no, rejection no	65	52	34	19	10	2
DGF no, rejection yes	9	9	9	7	3	3
DGF yes, rejection no	107	84	60	36	14	4
DGF yes, rejection yes	34	26	19	13	4	2

Figure 4 (a) Death-censored graft survival of recipients of controlled donation after circulatory death (DCD) kidney transplants, by presence of biopsy-proven acute rejection (BPAR) within the first year post-transplant. Recipients with primary nonfunction were excluded. No BPAR (n = 172), BPAR (n = 44); P = 0.002. Numbers at risk are given below. (b) Death-censored graft survival of recipients of controlled DCD kidney transplants, by presence of BPAR within the first year post-transplant, and delayed graft function (DGF). Recipients with primary nonfunction were excluded. DGF no, rejection no (n = 65); DGF no, rejection yes (n = 10); DGF yes, rejection no (n = 107); DGF yes, rejection yes (n = 34); P < 0.001. Numbers at risk are given below.

transplantation, but have not examined DCD donor kidneys specifically [29–31]. To our knowledge, the only study that has done so prior to ours was that of Renkens *et al.* [18], who analysed transplants from 39 uncontrolled and 66 controlled DCD donors. Renkens *et al.* also found that increasing duration of DGF was associated with lower post-transplant eGFRs but had no effect on graft survival if PNFs were excluded. Of note, average CITs in their study were more than 24 h, and approximately 40% of their recipients had DGF for more than 2 weeks. The number of patients with PNF was not reported. Given that the median CITs and PNF rates in our study were in line with UK averages [5,6], that only approximately 10% of our patients had DGF for >14 days, and that we examined transplants from controlled DCD donors only, our study is relevant to contemporaneous practice. The analysis of graft survival in recipients with prolonged dialysis dependency where PNF/DGF were not yet diagnosed enables clinicians to provide more accurate prognoses to similar patients.

In our study, univariable analysis showed that the presence of DGF was associated with lower DCGS. However, multivariable analyses found that DGF was not independently associated with worse graft survival. This is in keeping with previous studies of kidney transplants from DCD donors [1,5,10,32]. Our analyses also demonstrated that the *duration* of DGF did not appear to be associated with graft failure in DCD donors. This contrasts with findings In DBD donor kidney transplantation, where dialysis dependency for more than 15 days post-transplant was strongly associated with 1-year DCGS [33]. Other studies of DBD donor kidneys used alternative definitions of DGF [34] or showed that dialysis duration did not alter graft survival [29]. The strongest evidence that dialysis duration affects graft survival in DBD kidney transplantation comes from a recent analysis of over 7000 recipients of deceased donor kidneys in Australia and New Zealand [30]. Lim *et al.* showed that for every 5-day increase in DGF duration (defined as dialysis dependency), the adjusted HR (95%) for graft loss was 1.11 (1.02–1.20; P = 0.011). Approximately 80% of kidneys came from DBD donors in Lim's study, and a subgroup analysis on DCD donor transplants was not performed. Marek *et al.* [31] found an independent association between duration of dialysis dependency post-transplant and 1-year eGFR, but did not examine graft survival. Thirty-five of 83 recipients with DGF post-transplant had received kidneys from DCD donors, and a separate analysis was not performed.

Of note, our analysis showed that only BPAR within the first year post-transplant was associated with DCGS on multivariable analysis. In addition, BPAR was associated with lower 12- and 24-month eGFR on linear regression analysis (along with increased UKKDRI). The timing of BPAR relative to DGF appeared not to impact on DCGS. The number of patients in these groups was

Transplant International 2019; 32: 635–645

small, however. The interaction between DGF duration and BPAR is likely to be complex, as acute rejection during DGF may prolong dialysis dependency, and because DGF makes it more difficult to detect early acute rejection.

Nevertheless, our study suggests that BPAR is an independent negative prognostic factor for DCGS after controlled DCD donor kidney transplantation, whereas the presence and duration of DGF are not. Again, findings in DBD donor kidney transplantation are different; Lim's mediation analysis estimated that the proportion of the effect of DGF duration on graft loss because of acute rejection was less than 10% [30].

Given that the graft survival implications of DGF appear quite different in DCD donor versus DBD donor kidney transplants, it is likely that the underlying mechanisms of early graft dysfunction are also dissimilar. DGF in a DCD donor kidney may be because of warm ischaemia, whereas DGF in a DBD donor kidney may be primarily driven by the pro-inflammatory response at the time of the donor's brain death [11,35]. As Lim's study was predominantly in DBD donor kidney transplants, this may explain the disparate findings with regards to the relative importance of acute rejection in the two analyses. Although Nagaraja *et al.* [35] could not identify a link between BPAR in the first year post-transplant and DCGS in DCD kidney transplants, only 80 recipients were analysed, and just seven had BPAR. Because biopsies were performed every 7–10 days in our patients with DGF, it is possible that clinically irrelevant episodes of borderline rejection might have been identified during DGF, biasing the analysis. However, excluding patients with borderline rejection did not alter the poor outcomes of those with both DGF and BPAR.

Our unit policy was not to alter target trough tacrolimus levels during DGF. The prognostic significance of BPAR identified in our study would support avoiding reduced immunosuppression in patients with DGF who are given nondepleting induction agents. However, the optimal immunosuppressive strategy has not yet been defined in controlled DCD kidney transplantation, in part because kidneys from DCD donors have been excluded from almost 25% of relevant trials [36]. Interestingly, a retrospective analysis of 45 DCD donor kidney transplants from the UK showed that recipients given anti-thymocyte globulin induction therapy had a lower rate of BPAR and post-transplant dialysis duration that those given daclizumab [37]. There were no differences in graft survivals between the two induction groups, however. Alemtuzumab (depleting) induction therapy in DCD donor kidney transplantation has also been reported in nonrandomized trials, with varying outcomes [38,39]. The 3C Study has convincingly shown that alemtuzumab-based induction therapy reduces BPAR within the first 6 months of transplantation when compared to basiliximab-based induction [40]. Although transplants from controlled DCD donors were included in the trial, longer term graft outcomes in this sub-group have not yet been published.

We acknowledge the weaknesses of our study. First, median follow-up was just over 3 years and DCGS was good, meaning that there were relatively few graft failure events to analyse. This reduced our ability to detect possible subtle associations between putative risk factors and graft outcomes. Second, we used dialysis dependency as the definition of DGF duration. It is possible that a different indicator of the duration of early graft dysfunction, such as time to attain a creatinine clearance threshold [34], might have yielded different results. However, we note that Mallon *et al.* [9] could not distinguish between prognostic values of various DGF definitions when the presence of DGF, rather than DGF duration, was investigated. Third, this study had relatively few patients with DGF duration of more than 14 days ($n = 23$), and may be underpowered to detect clinically significant differences. However, it is the largest study of its type to date. Fourth, these results reflect our unit practices (e.g. intra-operative fluid management, donor and recipient selection, frequency of graft imaging and biopsies, management of rejection, discharge policies) and may not be applicable to all units. Finally, this study did not include data on donor physiological parameters after withdrawal of life-sustaining treatment, as these are not routinely collected by UK donor co-ordinators. It is conceivable that these parameters might have been associated with DGF duration and/or DCGS [41], and could have been confounding variables for the BPAR analysis. Interestingly, warm ischaemic time was not associated with graft outcomes in our study. Anastomosis time did not have a significant impact on duration of DGF or longer term graft outcomes, though this association has been demonstrated in a recent large study [42].

Kidney transplant recipients with a nonfunctioning graft for more than a day or so postoperatively face an anxious wait to know whether their graft will eventually function or not. We therefore felt that it was important to perform an analysis where patients with PNF were included, conditional on the day of observation. This showed that patients with progressively longer durations of dialysis dependency postoperatively (where PNF had not yet been diagnosed) had step-wise deteriorations in

graft survivals. This analysis is relevant for advising patients on expected graft outcomes if their transplant has not yet functioned; the remainder of this study is pertinent to patients who become dialysis-independent after a period of DGF.

Controlled DCD donors are an important source of kidneys for transplantation. In the UK, despite the use of organs from older donors and those with higher risk indices, acceptable outcomes can be achieved. In our study of recipients of controlled DCD donor kidneys, the duration of DGF was not an independent risk factor for worse graft survival, but BPAR was. The reduction of BPAR in DCD donor kidney transplantation may lead to improved graft outcomes.

Authorship

AS, BLP, NK and HB collected the data for the manuscript. TK, AS and BLP also analysed the data. CC involved in design of the study. All authors involved in writing of the manuscript.

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Conflict of interest

The authors have no conflicts of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Linear regression of graft function estimated glomerular filtration rate at 12 and 24 months (n = 216).

Table S2. Univariate general linear model of graft function estimated glomerular filtration rate at 12 and 24 months, in recipients with delayed graft function (n = 141).

Table S3. Univariate and multivariable Cox regression analysis of death-censored graft survival (n = 216).

Table S4. Univariate and multivariable Cox regression analysis of death-censored graft survival, in recipients with delayed graft function (n = 141).

Figure S1. Patient survival and delayed graft function, 216 patients.

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