Kidneys from donation after circulatory death (DCD) donors are utilized variably worldwide, in part due to high rates of delayed graft function (DGF) and putative associations with adverse longer-term outcomes. We aimed to determine whether the presence of DGF and its duration were associated with poor longer-term outcomes after kidney transplantation from DCD donors. Using the UK transplant registry, we identified 4714 kidney-only transplants from controlled DCD donors to adult recipients between 2006 and 2016; 2832 recipients (60·1%) had immediate graft function and 1882 (39·9%) had DGF. Of the 1847 recipients with DGF duration recorded, 926 (50·1%) had DGF < 7 days, 576 (31·2%) had DGF 7–14 days, and 345 (18·7%) had DGF >14 days. After risk adjustment, the presence of DGF was not associated with inferior long-term graft or patient survivals. However, DGF duration of >14 days was associated with an increased risk of death-censored graft failure (hazard ratio 1·7, \( p = 0·001 \)) and recipient death (hazard ratio 1·8, \( p < 0·001 \)) compared to grafts with immediate function. This study suggests that shorter periods of DGF have no adverse influence on graft or patient survival after DCD donor kidney transplantation and that DGF >14 days is a novel early biomarker for significantly worse longer-term outcomes.

**KEYWORDS**
clinical research / practice, delayed graft function (DGF), donors and donation: donation after circulatory death (DCD), health services and outcomes research, kidney transplantation / nephrology, organ procurement and allocation, organ transplantation in general, patient survival
1 | INTRODUCTION

In the United Kingdom (UK), deceased donor kidney transplantation in adult recipients is increasing while the number of transplants from living donors has remained static. Deceased donors provide a valuable source of kidneys that are reducing the gap between organ supply and demand. The increasing implantation rate of patients on the UK kidney transplant waiting list has been attributed to multiple factors, including a strong donation after circulatory death (DCD) donor program.

In donation after brain death (DBD) donors, cessation of organ oxygenation and initiation of cold organ preservation occur almost simultaneously. In contrast, organ retrieval in DCD donors takes place in the absence of donor cardiac activity, leading to a period of organ warm ischemia. DCD is described as “controlled” when donor cardiac arrest occurs within close proximity to a prepared organ retrieval team. The additional ischemic injury sustained by circulatory death kidneys has led to concerns that DCD donors may be an inferior source of organs compared to DBD donors.

The perception that kidneys from controlled DCD donors may be suboptimal has been reinforced by the significant difference in early graft dysfunction rates after DCD versus DBD donor kidney transplantation. It is well-recognized that DCD donor kidney transplants often take days or weeks to start functioning. This period of delayed graft function (DGF) is a manifestation of acute kidney injury incurred before, during, or soon after transplantation. The rate of DGF in kidneys from DCD donors is approximately twice that of DBD donor kidneys. Patients with DGF also have longer hospital stay, increased risk of acute rejection, and are often subjected to invasive investigations such as transplant biopsies.

Furthermore, DGF is associated with double the risk of graft loss after living donor kidney transplantation, and a 40% greater risk of graft loss after DCD donor kidney transplantation. Perhaps surprisingly, the presence of DGF does not appear to significantly influence longer-term graft survival in DCD donor kidney transplants. Only one small study has suggested otherwise. However, it is also important to take into account DGF duration when considering the effects of DGF on longer-term graft outcomes, as this may better reflect the severity of the underlying acute kidney injury and the organ’s ability to recover. Prolonged DGF duration is known to increase the risk of graft loss in recipients of DBD donor kidney transplants. However, the influence of DGF duration on longer-term graft outcomes after DCD donor kidney transplantation has not been specifically examined in a large national analysis.

This risk-adjusted UK registry study assesses the influence of DGF presence and duration on longer-term graft and patient survival after kidney transplantation from controlled DCD donors. These issues are particularly relevant given the on-going disparities in the utilization of kidneys from DCD donors between countries, and the growing number of interventions that seek to improve patient outcomes by reducing rates of DGF.

2 | MATERIALS AND METHODS

2.1 | Study population

Kidneys from controlled DCD donors transplanted into adult recipients in the UK between January 2006 and December 2016 were identified through the National Transplant Registry held by National Health Service Blood and Transplant (NHSBT). All 23 adult kidney transplant centers in the UK submit mandatory data to the Registry. Study inclusion and exclusion criteria are shown in Supplemental Digital Content Table S1. Analyses were limited to recipients of first-time transplants to avoid bias associated with retransplantation, namely higher recipient age and greater comorbidity and increased HLA sensitization. Those with primary non-function were excluded from all analyses. Early patient deaths, and grafts with function but subsequent early graft loss were not excluded. Follow-up of the study cohort included all data submitted to NHSBT by October 1, 2018.

2.2 | Graft and patient outcomes and definitions

DGF was defined as the need for dialysis within 7 days of kidney transplantation, regardless of cause. The duration of DGF was defined as the number of days between transplantation and the last session of posttransplant dialysis. Recipients with DGF were grouped according to DGF duration (DGF < 7 days; DGF 7–14 days; DGF >14 days). Sensitivity analyses with other DGF duration thresholds were also undertaken.

Graft and patient outcome measures included death-censored graft survival (DCGS), graft function, and patient survival. DCGS was defined as the time from transplantation to the date of graft failure (defined as the return to long-term dialysis or retransplantation, whichever occurred first), censored for patient death. Graft function was measured by the four-variable Modification of Diet in Renal Disease (MDRD) estimated glomerular filtration rate (eGFR). Patient survival was defined as the time from transplantation to patient death. Primary non-function was defined as failure of the transplanted kidney to ever function (i.e., freedom from dialysis) within 3 months of transplantation, regardless of cause. Acute rejection was defined as treatment for biopsy-proven rejection within 3 months of transplantation.

Donor risk was quantified by the non-normalized KDRI utilizing donor-only characteristics and the UKKDRIC. CIT was defined as the time between organ perfusion with cold preservation solution in the donor and reperfusion with recipient blood. Warm ischemia time was divided into donor asystole time (the time from donor circulatory arrest to perfusion with cold preservation fluid) and recipient anastomosis time (the time from kidney removal from ice to perfusion with recipient blood). Time between withdrawal of life-sustaining treatment to cold perfusion and data on donor hemodynamic instability following withdrawal of life-sustaining treatment were not adequately captured by the UK transplant registry with
high rates of missingness. Data on kidneys undergoing hypothermic machine perfusion (HMP) in the donor hospital were included, as were data from donors who had normothermic regional perfusion (NRP). Donor asystole times in NRP donors were not analyzed as these data are not adequately captured by the registry. HLA mismatch levels were using the 2006 UK National Kidney Allocation Scheme and were based on donor–recipient differences at HLA-A, HLA-B, and HLA-DR loci.

2.3 | Statistical analysis

All data were tested for normality using the Shapiro-Wilk test. Differences in donor, recipient, operative, or immunological characteristics between groups were examined using the Kruskal-Wallis test or the Chi-square test. Number and percentage of missing variable data were detailed in the appropriate tables and complete case analysis was employed. Kaplan-Meier survival estimates were used to demonstrate DCGS and patient survival, with patients censored at the end of the study or if lost to follow-up; univariate differences between groups were examined using the log-rank test.

Multivariable analyses of graft and patient survival and 1-year eGFR were performed in recipients with complete data for donor and recipient age, sex, and ethnicity, donor cause of death, recipient diabetes and hypertension, dialysis modality, donor–recipient HLA mismatch, recipient HLA sensitization, organ preservation method, cold ischemia time (CIT), and recipient anastomosis time. Acute rejection was not included in the multivariable analyses due to the potential to introduce bias. Severe rejection leading to graft failure during an apparent period of DGF without any subsequent freedom from dialysis would be coded as PNF by the transplant registry, and excluded from the analyses. Therefore, by definition, all episodes of rejection occurring during DGF in our study eventually resulted in graft function. A Cox proportional hazards model was used to assess the risk-adjusted association between DGF status and DCGS and patient survival. Linear regression was used to assess the risk-adjusted association between DGF status and eGFR at 1-, 3-, and 5-years posttransplant. Proportionality assumptions were checked for each variable in the Cox regression models. An interaction term between DGF and donor age, CIT, and recipient anastomosis time was applied to determine whether the effect of DGF on graft survival was modified by an interaction with these variables. Multivariable binary logistic regression enabled independent predictors of DGF >14 days to be determined. Binary logistic regression was favored over propensity score testing as the number of events per covariate was >7. Mediation analysis specifically designed to handle exposure-mediator interactions in survival data was used to determine whether acute rejection acts as a mediator between DGF duration and DCGS. Two-sided tests were conducted and $p < 0.05$ was considered statistically significant. Data were analyzed using IBM SPSS Statistics for Macintosh version 25 (IBM), and mediation analysis was performed using SAS 9.4 (SAS Institute).

3 | RESULTS

3.1 | Baseline data

During the study period, 4714 kidneys from controlled DCD donors were transplanted that met inclusion criteria (Supplemental Digital Content Figure S1, study flow diagram). Immediate graft function occurred in 2832 (60.1%) recipients with DGF in 1882 patients (39.9%). Median (interquartile range) patient follow-up was 4.0 (1.9–6.9) years. Donor, operative, immunological, and recipient variables for kidney transplants with and without DGF are shown in Table 1. The presence of DGF was associated with older, male, hypertensive, higher body mass index (BMI) donors, with a higher terminal creatinine. These risk factors are reflected in higher median kidney donor risk index (KDRI) and UK kidney donor risk index (UKKDRI) values in the DGF population. DGF was more likely if static cold storage only was used for organ preservation. Recipients with DGF were more likely to be older, male, higher BMI, from non-white ethnic backgrounds, on hemodialysis, and with higher human leukocyte antigen (HLA) mismatch levels. DGF was also associated with longer CIT and anastomosis times.

3.2 | Presence of DGF and longer-term outcomes

On univariate analyses, the presence of DGF was associated with poorer graft and patient outcomes. Patients with DGF had lower median eGFR at 1-, 3-, and 5-years posttransplant ($p < 0.001$ throughout; Supplemental Digital Content Table S2). Multivariable linear regression indicated that at 1-year, DGF was an independent predictor of inferior eGFR ($4 \text{ ml/min/1.73 m}^2$ lower) relative to organs with immediate function ($p < 0.001$; data not shown). There was also a higher incidence of acute rejection within 3 months of transplantation in recipients with DGF compared to those with immediate graft function ($p < 0.001$; Supplemental Digital Content Table S3). Unadjusted survival analysis indicated that the presence of DGF was associated with inferior DCGS ($p = 0.006$; Supplemental Digital Content Figure S2) and patient survival ($p = 0.005$; Supplemental Digital Content Figure S3).

After adjustment for donor and recipient age, sex, and ethnicity, donor cause of death, recipient diabetes and hypertension, dialysis modality, donor–recipient HLA mismatch, recipient HLA sensitization, organ preservation method, CIT, and recipient anastomosis time, Cox regression analysis indicated that there was no difference in death-censored graft loss in kidneys with DGF compared to kidneys that had immediate graft function (adjusted hazard ratio [aHR] 1.1 [95% confidence interval (CI) 0.9–1.4], $p = 0.19$, Supplemental Digital Content Table S4). Interaction tests demonstrated that the presence of DGF did not appear to modify the effect of donor age, CIT, and recipient anastomosis time on DCGS (Supplemental Digital Content Table S5). Increasing donor or recipient age and hemodialysis prior to transplantation were independently associated with poorer graft survival. Univariate sensitivity analyses showed no differences in DCGS when stratified by donor asystolic time quartile or whether data were missing (data not shown). Of note, CIT was...
| Variable                          | Immediate function (n = 2832) | Delayed graft function (n = 1882) | p value |
|----------------------------------|-------------------------------|-----------------------------------|----------|
| Donor age (years)                |                               |                                   |          |
| <40                              | 708 (25-0%)                   | 326 (17-3%)                      | <·001    |
| 40–49                            | 532 (18-8%)                   | 364 (19-3%)                      |          |
| 50–59                            | 745 (26-3%)                   | 520 (27-6%)                      |          |
| 60–69                            | 651 (23-0%)                   | 496 (26-4%)                      |          |
| >70                              | 196 (6-9%)                    | 176 (9-4%)                       |          |
| Donor sex                        |                               |                                   | <·001    |
| Male                             | 1636 (57-8%)                  | 1199 (63-7%)                     |          |
| Female                           | 1196 (42-2%)                  | 683 (36-3%)                      |          |
| Cause of death                   |                               |                                   | <·001    |
| Stroke                           | 2169 (76-6%)                  | 1414 (75-1%)                     |          |
| Trauma                           | 279 (9-9)                     | 148 (7-9)                        |          |
| Other                            | 384 (13-6)                    | 320 (17-0)                       |          |
| Donor ethnicity                  |                               |                                   | .26      |
| White                            | 2741 (96-8)                   | 1813 (96-3)                      |          |
| Black                            | 12 (0-4)                      | 13 (0-7)                         |          |
| Asian                            | 40 (1-4)                      | 36 (1-9)                         |          |
| Other                            | 38 (1-3)                      | 20 (1-1)                         |          |
| Donor diabetes mellitus          | 164 (6-1)                     | 129 (7-2)                        | .13      |
| Donor hypertension               | 645 (24)                      | 522 (29-5)                       | <·001    |
| Donor body mass index (kg/m²)    | 26 (23-29)                    | 27 (24-30)                       | <·001    |
| Kidney Donor Risk Index (KDR)    | 1·45 (1-13–1-86)              | 1·55 (1·22–1·92)                 | <·001    |
| Terminal creatinine (micromol/L) | 67 (53–88)                    | 70 (55–96)                       | <·001    |
| Preservation method              |                               |                                   | <·001    |
| Static cold storage alone        | 2140 (79-1)                   | 1503 (85-0)                      |          |
| Hypothermic machine perfusion    | 538 (19-9)                    | 261 (14-8)                       |          |
| Normothermic regional perfusion  | 26 (1-0)                      | 5 (0-3)                          |          |
| Recipient age (years)            |                               |                                   | <·001    |
| <40                              | 424 (15-0%)                   | 233 (12-4%)                      | <·001    |
| 40–49                            | 571 (20-2%)                   | 336 (17-9%)                      | .01      |
| 50–59                            | 782 (27-6%)                   | 561 (29-8%)                      |          |
| 60–69                            | 817 (28-8%)                   | 583 (31-0%)                      |          |
| >70                              | 238 (8-4%)                    | 169 (9-0%)                       |          |
| Recipient sex                    |                               |                                   | <·001    |
| Male                             | 1830 (64-7)                   | 1317 (70-0)                      |          |
| Female                           | 999 (25-3)                    | 564 (30-0)                       |          |
| Recipient ethnicity              |                               |                                   | <·001    |
| White                            | 2223 (78-8)                   | 1381 (73-8)                      |          |
| Black                            | 160 (5-7)                     | 174 (9-3)                        |          |
| Asian                            | 365 (12-9)                    | 267 (14-3)                       |          |
| Other                            | 72 (2-6)                      | 50 (2-7)                         |          |

(Continues)
independently associated with inferior graft survival (CIT >12 hours aHR 1.2 [95% CI 1.02–1.51], p = .03) when DGF was removed from the model. After risk adjustment, patient survival was no different between the DGF and immediate graft function groups (aHR 1.1 [95% CI 0.9–1.3], p = .36, Supplemental Digital Content Table S6).

### 3.3 | Duration of DGF and longer-term outcomes

Recipients with DGF were further stratified by DGF duration, and associations with longer-term outcomes were analyzed. Of the 1882 patients with DGF posttransplant, 35 patients had missing DGF duration data and were excluded from all further analyses. Of the remaining 1847 recipients, 926 (50.1%) had DGF duration <7 days, 576 (31.2%) had DGF of 7–14 days, and 345 (18.7%) had DGF duration >14 days (Supplemental Digital Content Figure S4). Differences in baseline characteristics when DGF was stratified by duration are shown in Supplemental Digital Content Table S7. DGF of >14 days was associated with older donors and recipients, kidneys with increased KDRI and UKKDRI, and organs with longer CITs.

Prolonged DGF of duration >14 days was associated with inferior eGFR compared to shorter duration DGF at 1-, 3-, and 5-years posttransplant (p < .001, p < .001, and p = .04, respectively; Supplemental Digital Content Table S2). On multivariable linear
regression, longer DGF duration was an independent predictor of poorer graft function 1-year posttransplant, with a 7 ml/min/1.73 m² reduction in eGFR in organs with >14 days DGF relative to organs with immediate function (p < .001; data not shown). Prolonged DGF >14 days was associated with a 2.5 times higher rate of acute rejection within 3 months of transplantation compared to those with DGF lasting <7 days (Supplemental Digital Content Table S3).

There was no significant difference in DCGS between patients with immediate graft function and DGF <7 days (p = .85), or DGF 7–14 days (p = .61, Figure 1). However, there appeared to be a marked threshold effect when DGF duration exceeded 14 days, with a significantly inferior DCGS compared to all other groups (p < .001). Using immediate graft function as a reference group, there was no increased adjusted risk of death-censored graft loss in recipients with DGF duration < 7 days (aHR 0.9 [95% CI 0.7–1.2], p = .46), or DGF duration 7–14 days (aHR 1.0 [95% CI 0.8–1.3], p = .91) on multivariable analysis (Figure 2). The threshold effect observed in the univariate survival analysis was also seen in the multivariable analysis. DGF exceeding 14 days was independently associated with almost double the risk of graft loss compared to immediate graft function (aHR 1.7 [95% CI 1.3–2.3], p = < .001). Other covariates associated with death-censored graft loss in DCD donor kidney transplantation are shown in Supplemental Digital Content Table S8. Other thresholds for categorizing DGF duration were also explored (Supplemental Digital Content Table S9). Risk-adjusted mediation analysis showed that acute rejection accounted for 26.1% of the effect between DGF duration and DCGS.

DGF duration of >14 days was associated with inferior patient survival compared to the other groups (p < .001; Figure 3). There was no difference in patient survival between recipients with immediate graft function and DGF duration of less than or equal to 14 days. After adjusting for donor, operative, immunological, and recipient risk factors, there was no added risk of patient death in recipients with immediate graft function compared to DGF duration < 7 days (aHR 0.9, 95% CI 0.8–1.2, p = .61) or DGF duration 7–14 days (aHR 0.9, 95% CI 0.7–1.2, p = .60). The 14-day DGF threshold was observed again, with almost double the risk of patient death relative to those with immediate graft function (aHR 1.8, 95% CI 1.3–2.3, p = < .001; Figure 4). Other covariates associated with patient death after kidney transplantation from controlled DCD donors are shown in Supplemental Digital Content Table S10.

Older donor age, donor male sex, pretransplant hemodialysis, and longer organ cold ischemia and recipient anastomosis times were independent predictors of prolonged DGF >14 days (Table 2). HMP was associated with reduced risk of prolonged DGF when compared to static cold storage alone.

4 | DISCUSSION

This large risk-adjusted registry analysis has shown that a period of DGF lasting less than 2 weeks was not associated with adverse graft

---

**FIGURE 1** Death-censored graft survival in recipients of kidneys from controlled DCD donors, by the duration of DGF. Recipients with more than 2 weeks of delayed transplant function had significantly worse graft survival (p < .001)

**FIGURE 2** Forest plot showing the adjusted hazard ratio and 95% confidence intervals of the association between DGF duration and death-censored graft loss in donation after circulatory death donor kidney transplantation. Adjusted for donor age, sex, ethnicity and cause of death, recipient age, sex, ethnicity, dialysis modality, diabetes, hypertension, HLA mismatch level, HLA sensitization, cold ischemia time, recipient anastomosis time, and organ preservation method.
or patient survivals following controlled DCD donor kidney transplantation. However, a novel threshold effect was demonstrated. DGF lasting more than 14 days was associated with almost double the risk of graft failure and patient death. This temporal threshold was confirmed on a sensitivity analysis, and it identifies a previously undefined group of transplant recipients who are at significantly increased risk of serious adverse longer-term outcomes. This is the largest study to date in this field, providing a fuller and more nuanced understanding of the impact of DGF after kidney transplantation from this increasingly important organ source.

The influence of DGF duration on long-term graft outcomes appears to have a credible clinicopathological rationale. Deceased donor kidneys undergo a series of insults during the process of donor death, organ retrieval, transport, and implantation. Injuries include pro-inflammatory cytokine release, hypoperfusion and hypoxia, ischemia-reperfusion injury (IRI), and damage via alloimmune pathways. DCD donor kidneys seem to tolerate a degree of acute injury before longer-term graft survival becomes compromised, possibly through upregulation of resilience-enhancing molecular mechanisms, as shown recently. The duration of DGF likely reflects the magnitude of the acute kidney injury and the propensity of the organ to recover from it.

This study suggests that DGF duration is a more clinically relevant short-term outcome measure in DCD donor kidney transplantation than simply the presence or absence of DGF. Furthermore, short-duration DGF may not truly reflect significant acute kidney injury, as the decision to continue dialysis for 1 or 2 days postoperatively is likely to be influenced by many factors, including local fluid and hyperkalemia management policies and clinician-to-clinician variability.

DGF can manifest as a result of multiple pathological processes, including IRI and acute rejection. However, these two processes are not independent of each other. IRI can increase organ immunogenicity through the activation of antigen presenting cells and promotion of alloantibody production, thus increasing the likelihood of acute rejection. Therefore, the possible interaction between DGF and acute rejection was considered in this study. Separating the independent and interdependent effects of DGF and acute rejection is challenging with a retrospective observational study. However, the mediation analysis suggests that acute rejection acts as a partial mediator between DGF duration and subsequent graft loss, in agreement with the findings of Lim et al.

Given that DGF duration of more than 14 days was found to be strongly associated with worse graft and patient outcomes after DCD donor kidney transplantation, we identified the clinical variables independently predictive of prolonged periods of dialysis dependency. The use of donors aged ≥70 years was strongly associated with prolonged DGF, with almost triple the risk of graft loss and 1.6 times the risk of patient death compared to donors aged <50 years. However, these risks should be weighed against the risks

![Figure 3](image-url1)

**FIGURE 3** Patient survival in recipients of kidneys from controlled DCD donors, by the duration of delayed graft function (DGF). DGF of more than 2 weeks was associated with significant worse patient survival (p < .001).

![Figure 4](image-url2)

**FIGURE 4** Forest plot showing the adjusted hazard ratio with 95% confidence interval of the association between DGF duration and patient death in donation after circulatory death donor kidney transplantation. Adjusted for donor age, sex, ethnicity and cause of death, recipient age, sex, ethnicity, dialysis modality, diabetes, hypertension, HLA mismatch level, HLA sensitization, cold ischemia time, warm anastomosis time, and organ preservation method.
TABLE 2 Multivariable binary logistic regression analysis showing factors independently predictive of prolonged delayed graft function (>14 days)

| Variable                        | Odds ratio | 95% confidence interval | p value |
|---------------------------------|------------|--------------------------|---------|
| Donor age (years)               |            |                          |         |
| <50                             | Reference  | —                        | —       |
| 50–59                           | 1.4        | 1.0 to 1.9               | .04     |
| 60–69                           | 1.5        | 1.1 to 2.1               | .007    |
| ≥70                             | 2.5        | 1.7 to 3.6               | <.001   |
| Donor male sex                  | 1.5        | 1.2 to 1.9               | .002    |
| Recipient dialysis modality     |            |                          |         |
| Peritoneal dialysis             | Reference  | —                        | —       |
| Hemodialysis                    | 1.4        | 1.0 to 1.8               | .02     |
| Cold ischemia time (hours)      |            |                          |         |
| <12                             | Reference  | —                        | —       |
| ≥12 and < 18                    | 1.6        | 1.2 to 2.2               | .002    |
| ≥18 and < 24                    | 2.0        | 1.4 to 2.9               | <.001   |
| ≥24                             | 2.9        | 1.7 to 5.0               | <.001   |
| Organ preservation method       |            |                          |         |
| Static cold storage alone       | Reference  | —                        | —       |
| Hypothermic machine perfusion   | 0.7        | 0.5 to 0.9               | .02     |
| Normothermic regional perfusion | 0.4        | 0.01 to 3.4              | .43     |
| Recipient anastomosis time (mins)|          |                          |         |
| ≤40                             | Reference  | —                        | —       |
| >40                             | 1.3        | 1.1 to 1.7               | .01     |

of remaining on the waiting list and the likelihood of receiving a kidney from a much younger donor. This emphasizes the importance of longevity matching and careful patient counseling. Organ CIT was strongly associated with longer periods of DGF, with a marked dose-dependent effect. Previous studies have demonstrated the differential effect of prolonged organ CIT on DCD versus DBD donor kidneys, and it is important that this modifiable risk factor is minimized in order to achieve improved graft outcomes post-transplant. It is notable that graft survivals after DCD donor kidney transplantation in the United States are inferior to those from DBD donors, even after risk adjustment, and this may be due to longer average organ CITs when compared to those in the UK. DCD donor kidney allocation and offering schemes should reflect the need for shorter CITs. Our data also suggest that HMP may reduce the risk of prolonged DGF, although we note that HMP had no statistically significant effect on DCGS or patient survival. This adds to the evidence-base surrounding the use of HMP in controlled DCD donor kidney transplantation.

A number of clinical trials have examined whether pharmacological or novel organ preservation methods can reduce the incidence of DGF after deceased donor kidney transplantation. Many of these interventions target DCD donor kidneys, as DGF is more common in this donor type and thus necessitates fewer recipients to be recruited for the study to be adequately powered. Our finding that DGF duration of more than 14 days is independently associated with reduced long-term graft and patient survivals may have significant implications for prospective interventional studies in this field, as DGF duration (rather than its presence) could better be used as an early surrogate biomarker of longer-term outcomes.

We acknowledge the limitations of this study. Many of these are inherent to the design of a retrospective registry analysis, namely the possibility of reporting bias and missing data, and the inability to ascribe causality. Unfortunately, the UK Transplant Registry did not adequately capture pertinent data on time between withdrawal of life-sustaining treatment and cold perfusion or donor hemodynamic stability following withdrawal, with a high rate of missingness. We note that a recent report suggested that prolonged time between withdrawal and cold perfusion may influence graft survival. Machine perfusion parameters and preimplantation kidney biopsy data were also not available, which may have provided important perspectives into the pathogenesis, development, and predictability of DGF. However, the impact of donor kidney biopsy on UK organ utilization rates is currently being examined. Data on immunosuppression held by the UK Transplant Registry lacked sufficient detail for the purposes of this study, including induction immunosuppression agents, target tacrolimus, and cyclosporin A levels or whether transplant units withheld tacrolimus in recipients with DGF. Overall, rates of missing data were low (apart from donor asystole times) and therefore a complete case analysis was undertaken. Our findings may not be generalizable to other patient groups. Creatinine-based definitions of DGF were not able to be examined as the UK Transplant Registry does not record these data. For this reason, recipients who were predialysis at the time of transplantation were excluded. Very few kidney transplants from uncontrolled DCD donors have been performed in the UK, and therefore recipients of this donor type were also excluded. When considering acute rejection rates, it is acknowledged that patients with DGF are more likely to get a transplant biopsy relative to those with immediate graft function, thus introducing the potential for bias. Finally, recipients with primary non-function were not included in this study due to the fundamental definition of DGF and therefore the graft and patient survival outcomes must be interpreted accordingly. Shamal et al have addressed these complexities previously.

Controlled DCD donors are an increasingly important source of deceased donor kidneys, though the use of these organs is less frequent in the United States than the UK and many other European countries. We believe that the higher rate of DGF in DCD versus DBD donor kidneys should not deter transplant programs from utilizing these organs, as our study indicates that approximately 80% of recipients with DGF had comparable graft and recipient survival
to those with immediate graft function. DGF after DCD donor kidney transplantation therefore represents a transient period of hypofunction with no significant adverse long-term implications in the majority of recipients. This should be reassuring for both clinicians and patients. When DGF duration exceeds 14 days, graft and patient outcomes worsen, suggesting that this patient group requires additional monitoring and support.

Overall, these findings confirm that controlled DCD donors are a valuable source of deceased donor kidneys. However, clinicians and transplant policy makers should seek to minimize modifiable risk factors such as organ CIT. Novel machine perfusion and pharmacological therapies aimed at reducing DGF and promoting organ recovery should target controlled DCD donor kidneys at risk of prolonged DGF beyond 14 days.

ACKNOWLEDGMENTS
We are grateful to Professor Tyler J. VanderWeele, Harvard University, for his kind assistance with the mediation analysis in this work.

DISCLOSURE
The authors of this manuscript have conflicts of interest to disclose as described by the American Journal of Transplantation. Benedict L. Phillips’ salary was funded by a grant from Kidney Research UK. The salaries of Maria Ibrahim and George H. B. Greenhall were funded by fellowships from National Health Service Blood and Transplant.

AUTHOR CONTRIBUTIONS
BLP contributed to study initiation, study design, data management, statistical analysis, and writing of the manuscript. MI and GHBG contributed to data management, statistical analysis, and writing of the manuscript. LM contributed to data management and the writing of the manuscript, and AD contributed to study initiation, study design, and the writing of the manuscript. CC is the senior author and contributed to the study initiation, study design, and writing of the manuscript.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID
Benedict L. Phillips https://orcid.org/0000-0001-6608-7100
Maria Ibrahim https://orcid.org/0000-0003-2980-4478
George H. B. Greenhall https://orcid.org/0000-0002-4816-1474
Anthony Darling https://orcid.org/0000-0003-3102-2600
Chris J. Callaghan https://orcid.org/0000-0003-3334-4152

REFERENCES
1. Annual report on Kidney transplantation 2018-2019. NHS Blood and Transplant. https://nhsbtdata.blob.core.windows.net/umbraco-assets-corp/17289/kidney-annual-report-2018-19-november19.pdf. Published November 2019. Accessed July 22, 2020.
2. Thuong M, Ruiz A, Evrard P, et al. New classification of donation after circulatory death donors definitions and terminology. Transplant Int: official journal of the European Society for Organ Transplantation. 2016;29(7):749-759.
3. Siedlecki A, Irish W, Brennan DC. Delayed graft function in the kidney transplant. Am J Transplant: official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2011;11(11):2279-2296.
4. Summers DM, Watson CJE, Pettigrew GJ, et al. Kidney donation after circulatory death (DCD): state of the art. Kidney Int. 2015;88(2):241-249.
5. Locke JE, Segev DL, Warren DS, Dominici F, Simpkins CE, Montgomery RA. Outcomes of kidneys from donors after cardiac death: implications for allocation and preservation. Am J Transplant: official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2007;7(7):1797-1807.
6. Serrano OKMD, Vock DMP, Chinnakotla SMD, et al. The relationships between cold ischemia time, kidney transplant length of stay, and transplant-related costs. Transplantation. 2019;103(2):401-411.
7. Qureshi F, Rabb H, Kasiske BL. Silent acute rejection during prolonged delayed graft function reduces kidney allograft survival. Transplantation. 2002;74(10):1400-1404.
8. Shoskes DA, Parfrey NA, Halloran PF. Increased major histocompatibility complex antigen expression in unilateral ischemic acute tubular necrosis in the mouse. Transplantation. 1990;49(1):201-207.
9. Williams WW, Taheri D, Tolkoft-Rubin N, Colvin RB. Clinical role of the renal transplant biopsy. Nat Rev Nephrol. 2012;8(2):110-121.
10. Redfield RR, Scalea JR, Zens Tj, et al. Predictors and outcomes of delayed graft function after living-donor kidney transplantation. Transplant Int: official journal of the European Society for Organ Transplantation. 2016;29(1):81-87.
11. Yarlagadda SG, Coca SG, Formica RN Jr, Poggio ED, Parikh CR. Association between delayed graft function and allograft and patient survival: a systematic review and meta-analysis. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2009;24(3):1039-1047.
12. Summers DM, Johnson RJ, Allen J, et al. Analysis of factors that affect outcome after transplantation of kidneys donated after cardiac death in the UK: a cohort study. Lancet (London, England). 2010;376(9749):1303-1311.
13. de Kok MJ, McGuinness D, Shiels PG, et al. The neglectable impact of delayed graft function on long-term graft survival in kidneys donated after circulatory death associates with superior organ resilience. Ann Surg. 2019;270(5):877-883.
14. Singh RP, Farney AC, Rogers J, et al. Kidney transplantation from donation after cardiac death donors: lack of impact of delayed graft function on post-transplant outcomes. Clin Transplant. 2011;25(2):255-264.
15. Shamali A, Kassimatis T, Phillips BL, Burton H, Kessaris N, Callaghan C. Duration of delayed graft function and outcomes after kidney transplantation from controlled donation after circulatory death donors: a retrospective study. Transplant Int: official journal of the European Society for Organ Transplantation. 2019.
16. Schaapherder A, Wijermars LGM, de Vries DK, et al. Equivalent long-term transplantation outcomes for kidneys donated after brain death and cardiac death: conclusions from a nationwide evaluation. EClinicalMedicine. 2018;4-5:25-31.
17. Lim WH, McDonald SP, Russ GR, et al. Association between delayed graft function and graft loss in donation after cardiac death kidney transplants-a paired kidney registry analysis. Transplantation. 2017;101(6):1139-1143.
18. Lim WHP, Johnson DWP, Teixeira-Pinto AP, Wong GP. Association between duration of delayed graft function, acute rejection, and allograft outcome after deceased donor kidney transplantation. Transplantation. 2019;103(2):412-419.
19. Renkens JJ, Rouflart MM, Christiaans MH, van den Berg-Loonen EM, van Hooft JP, van Heurn LW. Outcome of nonheart-beating
donor kidneys with prolonged delayed graft function after transplantation. Am J Transplant: official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2005;5(11):2704-2709.

20. Ibrahim M, Vecz G, Mehew J, et al. An international comparison of deceased donor kidney utilization: What can the United States and the United Kingdom learn from each other? Am J Transplant: official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2019.

21. Moers C, Smits JM, Maathuis M-H, et al. Machine perfusion or cold storage in deceased-donor kidney transplantation. N Engl J Med. 2009;360(1):7-19.

22. Hosgood SA, Saeb-Parsy K, Wilson C, Callaghan C, Collett D, Nicholson ML. Protocol of a randomised controlled, open-label trial of ex vivo normothermic perfusion versus static cold storage in donation after circulatory death renal transplantation. BMJ open. 2017;7(1):e012237.

23. Sureshkkumar KK, Hussain SM, Ko TY, Thai NL, Marcus R. Effect of high-dose erythropoietin on graft function after kidney transplantation: a randomized, double-blind clinical trial. Clin J Am Soc Nephrol. 2012;7(9):1498-1506.

24. Orban JC, Quintard H, Cassuto E, Jambou P, Samat-Long C, Ichai C. Effect of N-acetylcysteine pretreatment of deceased organ donors on renal allograft function: a randomized controlled trial. Transplantation. 2015;99(4):746-753.

25. Mallon DH, Summers DM, Bradley JA, Pettigrew GJ. Defining delayed graft function after renal transplantation: simplest is best. Transplantation. 2013;96(10):885-889.

26. Levey AS, Coresh J, Greene T, et al. The Modification of Diet in Renal Disease study equation for estimating glomerular filtration rate with standardized serum creatinine values. Clin Chem. 2007;53(4):766-772.

27. Rao PS, Schaubel DE, Guidinger MK, et al. A comprehensive risk quantification score for deceased donor kidneys: the kidney donor risk index. Transplantation. 2009;88(2):231-236.

28. Watson CJ, Johnson RJ, Birch R, Collett D, Bradley JA. A simplified donor risk index for predicting outcome after deceased donor kidney transplantation. Transplantation. 2012;93(3):314-318.

29. Oniscu GC, Randle LV, Muiesan P, et al. In situ normothermic regional perfusion for controlled donation after circulatory death—the United Kingdom experience. Am J Transplant: official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2014;14(12):2846-2854.

30. Johnson RJ, Fuggle SV, Mumford L, Bradley JA, Forsythe JL, Rudge CJ. A New UK 2006 national kidney allocation scheme for deceased heart-beating donor kidneys. Transplantation. 2010;89(4):387-394.

31. Cepeda MS, Boston R, Farrar JT, Strom BL. Comparison of logistic regression versus propensity score when the number of events is low and there are multiple confounders. Am J Epidemiol. 2003;158(3):280-287.

32. Valeri L, Vanderweeke TJ. Mediation analysis allowing for exposure-mediator interactions and causal interpretation: theoretical assumptions and implementation with SAS and SPSS macros. Psychol Methods. 2013;18(2):137-150.

33. Eltzschig HK, Eckle T. Ischemia and reperfusion—from mechanism to translation. Nat Med. 2011;17(11):1391-1401.

34. Akkina SK, Connaire JJ, Israni AK, Snyder JJ, Matas AJ, Kasiske BL. Similar outcomes with different rates of delayed graft function may reflect center practice, not center performance. Am J Transplant: official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2009;9(6):1460-1466.

35. Nace G, Evankovich J, Eid R, Tsung A. Dendritic cells and damage-associated molecular patterns: endogenous danger signals linking innate and adaptive immunity. J Innate Immun. 2012;4(1):6-15.

36. Liu L, Fang C, Fu W, et al. Endothelial cell-derived IL-18 released during ischemia reperfusion injury selectively expands T peripheral helper cells to promote alloantibody production. Circulation. 2019.

37. Tingle SJ, Figueiredo RS, Moir JAG, et al. Hypothermic machine perfusion is superior to static cold storage in deceased donor kidney transplantation: a meta-analysis. Clin Transplant. 2020;34(4):e13814.

38. Kostakis ID, Kassimatis T, Flach C, Karydis N, Kessaris N, Loukopoulos I. Hypoperfusion warm ischaemia time in renal transplants from donors after circulatory death. Nephrology, Dialysis, Transplantation: official publication of the European Dialysis and Transplant Association - European Renal Association. 2020;35(9):1628-1634.

39. Gill J, Rose C, Lesage J, Joffres Y, Gill J, O’Connor K. Use and outcomes of kidneys from donation after circulatory death donors in the United States. J Am Soc Nephrol: JASN. 2017;28(12):3647-3657.

40. Ayorinde JOO, Summers DM, Pankhurst L, et al. Preimplantation Trial of Histopathology In renal Allografts (PITHIA): a stepped-wedge cluster randomised controlled trial protocol. BMJ open. 2019;9(1):e026166.

41. Lomero M, Gardiner D, Coll E, et al. Donation after circulatory death today: an updated overview of the European landscape. Transplant Int: official journal of the European Society for Organ Transplantation. 2020;33(1):76-88.

SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Phillips BL, Ibrahim M, Greenhall GH, Mumford L, Dorling A, Callaghan CJ. Effect of delayed graft function on longer-term outcomes after kidney transplantation from donation after circulatory death donors in the United Kingdom: A national cohort study. Am J Transplant. 2021;00:1-10. https://doi.org/10.1111/ajt.16574