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# Delayed graft function requiring more than one-time dialysis treatment is associated with inferior clinical outcomes

Jayaram D, Kommareddi M, Sung RS, Luan FL. Delayed graft function requiring more than one-time dialysis treatment is associated with inferior clinical outcomes.

Abstract: Delayed graft function (DGF) is a common complication of deceased donor kidney transplantation with negative impact on clinical outcomes. In a single-center retrospective analysis, we compared patient and kidney survival, early renal function, and the incidence of acute rejection during the first year among all adult deceased donor kidney transplant patients without DGF, with DGF requiring one-time and/or more than one-time dialysis treatment between January 1, 2000, and December 31, 2008. Of 831 adult kidney transplant patients, 74 (8.9%) required one-time and 134 (16.1%) more than one-time dialysis treatment post-transplantation, respectively. While DGF patients with one-time dialysis treatment had comparable clinical outcomes to that of patients without DGF, patients with DGF requiring more than one-time dialysis treatment had a 45% increased risk for death (HR 1.45, 95% CI 1.02, 2.05, $p = 0.04$) after adjustment for the differences in demographic and baseline characteristics. Furthermore, DGF patients with more than one-time dialysis requirement displayed significantly lower renal function after recovery (OR 0.32, 95% CI 0.21, 0.49, $p < 0.001$, for eGFR $\geq$ 60 mL/min) and higher incidence of acute rejection during the first year (OR 1.66, 95% CI 1.11, 2.49, $p = 0.015$). Additional studies of therapeutic approaches to manage patients with prolonged DGF are needed.

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Delayed graft function (DGF) continues to be one of the common early complications following deceased donor kidney transplantation. The incidence of DGF varies widely from 5% to 50% in the literature reports, which is likely reflective of variation in the utilization of certain types of donor kidneys and in the definitions of DGF by centers (1–5). Many studies have demonstrated deleterious effects of DGF on clinical outcomes such as increased incidence of acute rejection, and inferior graft and/or patient survival (1, 4, 6). In addition, positive associations between DGF, the duration of DGF, acute rejection, and poor renal function have been suggested in several studies (1, 7–10).

While there have been as many as 10 different definitions recorded in the literature, the most commonly used definition of DGF is the requirement of any dialysis treatment within the first week after transplantation (1, 5, 11). Such definition remains problematic as the determination for the use of dialysis post-transplantation is not universally standardized and thus subject to the effects of center-specific and/or healthcare provider-specific differences in the clinical threshold for the use of dialysis (12). This could be particularly true when only one-time dialysis is required, often for the management of post-operative hyperkalemia or transient hypervolemia. It is possible, in this case, that ischemia and reperfusion injuries are less severe and the clinical implication different than if more than one-time dialysis is required. We undertook a single-center retrospective study to test the hypothesis that one-time requirement of dialysis treatment post-transplantation may not negatively affect clinical outcomes, whereas prolonged DGF with more than one-time dialysis requirement, a

surrogate marker of severity of ischemia and reperfusion injuries, is associated negatively with post-transplant outcomes such as increased risk of acute rejection, reduced graft and/or patient survival.

## Patients and methods

We identified all consecutive adult deceased donor kidney transplants performed at our institution from January 1, 2000, through December 31, 2008. The need and indication for dialysis treatment following the surgery, the numbers of dialysis treatment, baseline renal function (lowest and stable serum creatinine values during the first month for patients without DGF, and within one month after the discontinuation of dialysis in patients with DGF), the occurrence of acute rejection during the first year, the time of graft loss and patient death, and the cause of patient death were ascertained from the institutional electronic record. The demographic characteristics of study patient population were obtained by linking to the program-specific data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all donors, wait-listed candidates, and transplant recipients in the United States, submitted by the members of the Organ Procurement and Transplantation Network (OPTN), and has been described elsewhere (13). The Health Resources and Services Administration (HRSA), US Department of Health and Human Services, provides oversight to the activities of the OPTN and SRTR contractors. Patients who had primary non-function of kidney graft, defined as the lack of kidney graft function recovery and permanent need of dialysis since the first week of transplant surgery, or received a multi-organ transplant were excluded. DGF was defined as the need for at least one dialysis treatment within the first week (seven d) after kidney transplantation. Patients were separated into three cohorts: patients without DGF, patients with DGF requiring one-time dialysis, and patients with DGF requiring more than one-time dialysis treatment. The primary endpoints of the study were death-censored graft and patient survival at the end of study follow-up, August 31, 2011. The secondary endpoints were baseline renal function, after the recovery in patients who experienced DGF, expressed as estimated glomerular filtration rate (eGFR) using abbreviate Modification of Diet in Renal Disease (aMDRD) formula, and the incidence of AR within the first year post-transplant. Institutional review board approved the study.

Demographic and baseline characteristics of the study population were compared using chi-square test and ANOVA, as appropriate. Kaplan–Meier survival analyses were performed for kidney graft (death-censored) and patient survival (overall and with graft function) among the three cohorts of patients. Multivariate Cox proportional hazards regression analyses were performed testing the association of DGF (three cohorts of patients: no DGF, DGF requiring one-time, and DGF requiring more than one-time dialysis treatment) with patient and/or kidney graft survival. Multivariate logistic regression analyses were used to assess the association of DGF requiring one-time and/or more than one-time dialysis treatment with baseline renal function (eGFR $\geq$ 60 vs. <60 mL/min) and the occurrence of acute rejection in the first year post-transplantation. The causes of death were compared among the three cohorts as well. The potential confounders that were examined in multivariate analyses included recipient, donor, and transplant-related factors such as age, gender, race, body mass index (BMI), diabetes as the cause of end-stage renal disease (ESRD), number of transplants, duration of pre-transplant dialysis, pre-existent cardiovascular morbidity, history of pre-transplant blood transfusion, panel reactive antibodies (PRA), types of donor kidneys such as standard criteria donor (SCD), expanded criteria donor (ECD), and donation after cardiac death (DCD) kidney, cold ischemia time (CIT), human leukocyte antigen (HLA) mismatches, donor/recipient cytomegalovirus serology pairs, and immunosuppression regimens for both induction and maintenance. Final models were adjusted for those confounders with $p < 0.10$ after backward selection.

All analyses were performed using SAS 9.2 (Cary, NC, USA), with statistical significance set at a two-sided $\alpha \leq 0.05$.

## Results

### Study population

A total of 831 deceased donor kidney transplant recipients were included in the study. The mean duration of follow-up was 5.1 yr (six d to 11.7 yr). Among them, 208 (25.0%) recipients had experienced DGF: 74 (8.9%) required one-time and 134 (16.1%) more than one-time dialysis, respectively. The number of dialysis treatment varies from as few as one to as high as 40 with a median of two and mean of 5, respectively. For DGF patients who had only one-time dialysis, hyperkalemia was the indication in all but five of them. Mean value of hyperkalemia was $6.6 \pm 0.6$ mM ranging between 5.7 and 8.0 mM. Table 1 displays the

Table 1. Demographic characteristics of study patient population

| | | With DGF | | |
|---|---|---|---|---|
| | No DGF n = 623 | One-time dialysis n = 74 | >One-time dialysis n = 134 | p |
| Recipient characteristics | | | | |
| Age, yr (SD) | 50.1 (13.1) | 52.2 (12.8) | 53.0 (12.2) | 0.03 |
| Gender, male (%) | 359 (57.7) | 47 (63.5) | 93 (69.4) | 0.03 |
| Race, African American (%) | 129 (20.7) | 30 (40.5) | 44 (32.8) | <0.01 |
| Body mass index, kg/m$^2$ (SD) | 28.1 (5.6) | 29.7 (5.8) | 30.5 (6.2) | <0.01 |
| Pre-transplant dialysis, yr (SD) | 3.3 (3.0) | 4.2 (2.4) | 4.7 (2.6) | <0.01 |
| Pre-emptive transplants, n (%) | 99 (15.9) | 4 (5.4) | 5 (3.7) | <0.01 |
| First transplant, n (%) | 515 (82.7) | 65 (87.8) | 116 (86.6) | 0.33 |
| Causes of ESRD | | | | |
| Diabetes, n (%) | 186 (29.9) | 22 (29.7) | 57 (42.5) | <0.001 |
| Hypertension, n (%) | 112 (18.0) | 29 (39.2) | 25 (18.7) | |
| Glomerulonephritis, n (%) | 151 (24.2) | 10 (13.5) | 26 (19.4) | |
| Polycystic kidneys, n (%) | 58 (9.3) | 6 (8.1) | 10 (7.5) | |
| Others, n (%) | 116 (18.6) | 7 (9.5) | 16 (11.9) | |
| Positive hepatitis C serology, n (%) | 38 (6.1) | 3 (4.1) | 9 (6.7) | 0.73 |
| Angina/coronary artery disease, n (%) | 66 (10.6) | 9 (12.2) | 26 (20.3) | <0.01 |
| Peripheral vascular disease, n (%) | 69 (11.1) | 6 (8.1) | 28 (20.9) | <0.01 |
| History of blood transfusion, n (%) | 377 (60.6) | 48 (64.9) | 81 (60.4) | 0.76 |
| PRA, mean (SD) | | | | |
| Peak | 20.3 (33.3) | 23.6 (35.1) | 20.3 (33.3) | 0.73 |
| Current | 14.7 (28.7) | 15.5 (29.2) | 14.1 (28.2) | 0.95 |
| Donor characteristics | | | | |
| Age, yr (SD) | 36.1 (15.5) | 39.5 (13.8) | 40.9 (15.6) | <0.01 |
| Gender, male (%) | 393 (63.1) | 45 (60.8) | 89 (66.4) | 0.68 |
| Race, African American (%) | 52 (8.4) | 8 (10.8) | 14 (10.4) | 0.62 |
| ECD, n (%) | 67 (10.8) | 9 (12.2) | 26 (19.4) | 0.02 |
| DCD, n (%) | 47 (7.5) | 10 (13.5) | 35 (26.1) | <0.01 |
| Smoking > 20 pack-years, n (%) | 222 (35.6) | 29 (39.2) | 55 (41.0) | 0.45 |
| History of hypertension, n (%) | 113 (18.1) | 12 (16.2) | 37 (27.6) | 0.03 |
| Transplant-related characteristics | | | | |
| Cold ischemia time, h | | | | |
| Mean (SD) | 15.7 (6.3) | 14.8 (6.4) | 16.4 (6.7) | 0.21 |
| Median (IQR) | 15.5 (11.4, 19.6) | 14.5 (10.5, 18.0) | 16.1 (12.8, 20.1) | 0.09 |
| HLA mismatch, n (SD) | 3.0 (2.1) | 3.5 (2.0) | 3.7 (1.8) | <0.01 |
| Induction regimen, n (%) | | | | |
| None | 464 (74.5) | 40 (54.1) | 69 (51.5) | <0.01 |
| rATG | 129 (20.7) | 26 (35.1) | 48 (35.8) | |
| aIL2R abs | 30 (4.8) | 8 (10.8) | 17 (12.7) | |
| Calcineurin inhibitor, n (%) | | | | |
| CsA | 588 (94.4) | 70 (94.6) | 126 (94.0) | 0.98 |
| Tac | 35 (5.6) | 4 (5.4) | 8 (6.0) | |
| Cytomegalovirus pairs, n (%) | | | | |
| | 144 (23.1) | 17 (23.0) | 20 (14.9) | 0.31 |
| donor+/recipient− | | | | |
| donor+/recipient+ | 215 (34.5) | 29 (39.2) | 50 (37.3) | |
| | 158 (25.4) | 18 (27.0) | 42 (31.3) | |
| donor−/recipient+ | | | | |
| | 106 (17.0) | 8 (10.8) | 22 (16.4) | |
| donor−/recipient− | | | | |

ECD, expanded criteria donor; DCD, donation after cardiac death; HLA: human leukocyte antigen; rATG: rabbit anti-thymocyte globulin; aIL2R abs: anti-IL2 receptor antibodies; CsA: cyclosporin A; Tac: tacrolimus.

demographic and baseline characteristics among patients who had no DGF, patients with DGF who required one-time, and those who required more than one-time dialysis treatment. Overall, the patients from three cohorts differed on many of demographic and baseline characteristics in a statistically significant way. Compared with patients with immediate graft function, DGF patients requiring one-time and more than one-time dialysis treatment were in general older, hea-

vier, more often males, more likely to be African American, had longer duration of dialysis pre-transplant, received less frequently pre-emptive transplant, had a higher degree of HLA mismatches, and were more frequently given induction with either rATG or anti-IL2R antibodies, as dictated often by center-specific induction protocols. On the other hand, only DGF patients requiring more than one-time dialysis treatment had a higher rate of comorbid medical conditions, such as diabetes mellitus, angina/coronary artery disease, and peripheral vascular disease, and received kidney more frequently from older donors, ECD and DCD, and donors with a history of hypertension.

### Effects of DGF on graft and patient survival

While the occurrence of DGF, with one-time and/or more than one-time dialysis requirement, did not affect kidney graft survival (death censored), it impacted negatively patient survival (Fig. 1a,b, log-rank $p = 0.279$ and $p < 0.001$, respectively). Applying Cox proportional regression analyses, DGF requiring more than one-time dialysis, but not one-time-only dialysis treatment, was associated with a statistically significant increase in risk for death with a HR of 1.71 with 95% CI 1.22, 2.42 in unadjusted univariate model and of 1.45 with 95% CI 1.02, 2.05 in fully adjusted multivariate model ($p = 0.002$ and $p = 0.04$, respectively;

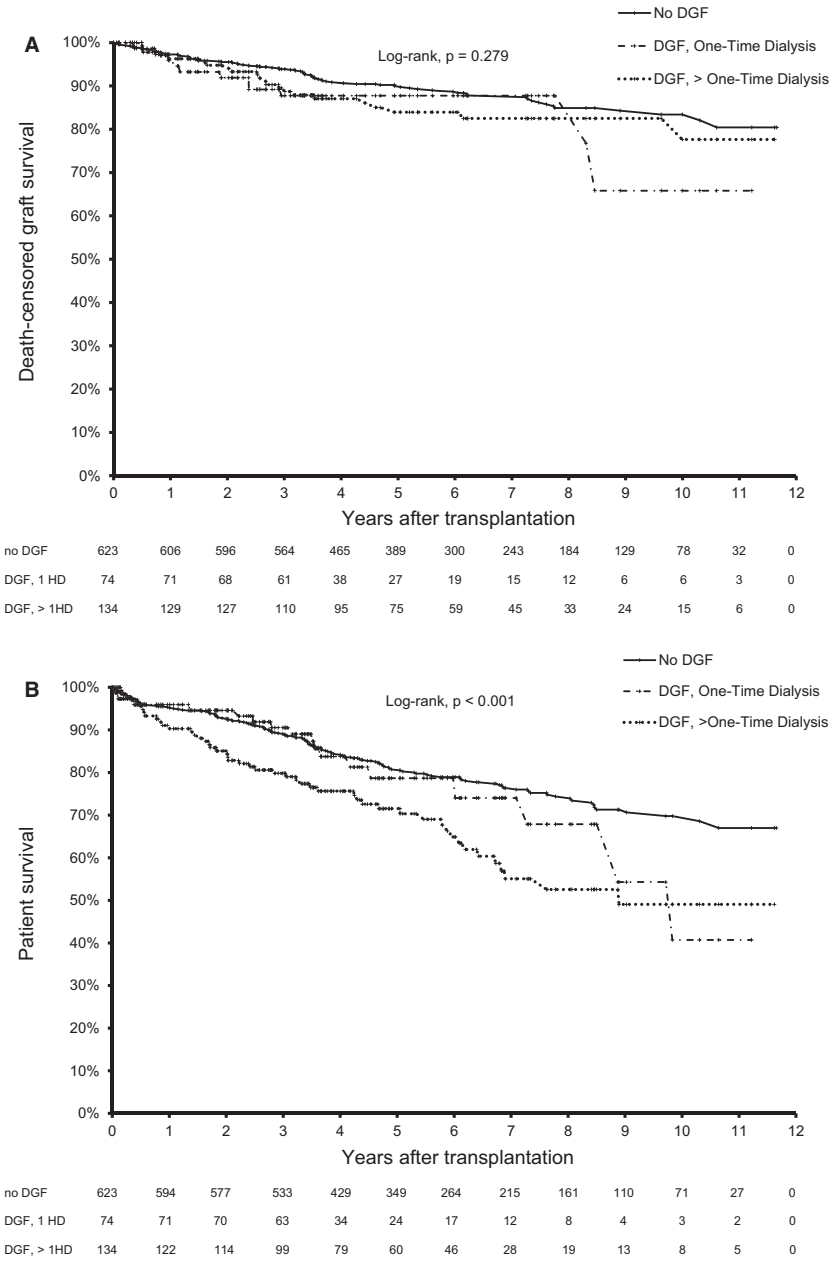


*Fig. 1.* Kaplan–Meier survival analyses among three cohorts of patients for (A) death-censored kidney graft survival and (B) patient survival.

Table 2. Association of DGF with mortality risk

| | No DGF | DGF, one-time dialysis | | | DGF, >one-time dialysis | | |
|---|---|---|---|---|---|---|---|
| | | HR | 95% CI | p | HR | 95% CI | p |
| Model 1[a] | Ref. | 1.29 | 0.78, 2.14 | 0.33 | 1.71 | 1.22, 2.42 | 0.002 |
| Model 2[b] | | 1.15 | 0.69, 1.91 | 0.60 | 1.45 | 1.02, 2.05 | 0.04 |

[a]Baseline model: univariate analysis.
[b]Final model: multivariate analysis.

Table 2). When only death with functioning graft was considered, similar results were obtained, although with a reduced statistical power owing to the smaller number of deaths with graft function (HR = 1.44, 95% CI 0.98, 2.12, p = 0.06).

Other factors associated with increased mortality risk included patient age (HR 1.08, 95% CI 1.05, 1.10, $p < 0.001$), history of diabetes (HR 1.57, 95% 1.18, 2.10, p = 0.002), and longer duration of pre-transplant dialysis (HR 1.10, 95% CI 1.05, 1.15, $p < 0.001$). The differential use of immunosuppression, neither induction agents nor calcineurin inhibitors, the types of donor, and other comorbid conditions prior to transplantation, such as angina/CAD and PVD, were not associated with increased mortality risk (data not shown).

The most common causes of death were infection (30.8%), CVD (28.2%), and malignancy (9.2%) with approximately 31.8% dying of unknown causes. However, there was no difference in causes of death among the three cohorts (data not shown).

### Effects of DGF on baseline graft function and the incidence of acute rejection in the first year

To explore the potential mechanisms of observed mortality risk associated with DGF requiring more than one-time dialysis treatment, we considered two subsequent clinical events, baseline renal graft function and occurrence of acute rejection during the first year, which were likely affected by the presence and/or severity of DGF and which in turn could affect the patient and/or kidney graft survival (4, 6, 14).

DGF patients with more than one-time dialysis treatment had significantly lower baseline renal function, expressed as eGFR by aMDRD formula (61.5 ± 21.6 vs. 73.7 ± 24.1 mL/min in patients without DGF and 70.3 ± 19.3 mL/min in patients with DGF who required only one-time dialysis treatment, respectively, $p < 0.001$), and were less likely to achieve an eGFR equal or >60 mL/min following the recovery from DGF (45.5% vs. 72.6% in patient without DGF and 64.9% in patients with DGF requiring only one-time dialysis, respectively, $p < 0.001$; Fig. 2). Multivariate logistic regression analysis confirmed that only DGF requiring more than one-time dialysis was associated with a 68% lower likelihood of achieving an eGFR equal or >60 mL/min (OR 0.32, 95% 0.21, 0.49, $p < 0.001$). Other factors associated with lower renal function included older donor age, female donor, non-AA race, non-diabetes status, and higher BMI.

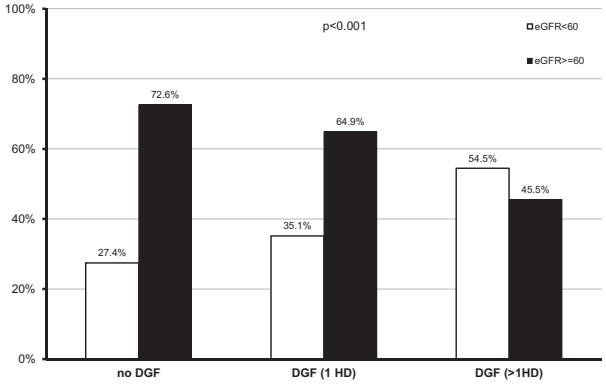


*Fig. 2.* Baseline renal function among three cohorts of patients.

Similarly, patients with DGF requiring more than one-time dialysis treatment had experienced more biopsy-proven acute rejection during the first year (38.1% vs. 26.2% in patients without DGF and 25.7% in patients with DGF requiring one-time dialysis, respectively, p = 0.019). Again, only DGF requiring more than one-time dialysis was significantly associated with increased risk for the occurrence of AR (OR 1.66, 95% CI 1.11, 2.49, p = 0.015). Additional risks associated with AR included repeat transplant, AA race, and higher HLA mismatches.

## Discussion

In this single-center retrospective study, we showed for the first time that patients with DGF who required only one-time dialysis treatment had similar clinical outcomes compared with patients who did not have DGF, whereas patients with DGF who required more than one-time dialysis treatments were at increased risk for poor clinical outcomes including lower baseline renal function, a higher acute rejection rate within the first post-transplant year, and ultimately reduced patient survival during subsequent follow-up.

Various definition of DGF existed in the literature, although the most commonly used one is the need for dialysis within the first week post-transplantation (5). Such definition remains problematic, mostly for the center-specific and/or individual healthcare provider-specific differences in the threshold of using dialysis post-transplantation, particularly if only one-time dialysis treatment was needed for the management of post-operative hyperkalemia and/or transient hypervolemia (12). While the negative consequences of DGF on clinical transplant outcomes have been documented by many studies through the years, the impact of one-time use of dialysis treatment after transplantation has not been reported. Furthermore, the reasons for one-time use of dialysis have rarely been explored. Although limited by its single-center and retrospective nature, our study adds on to a growing body of literature showing negative effects of DGF on patient survival and, most importantly, suggests different clinical implication of DGF requiring one-time dialysis from DGF requiring more than one-time dialysis. It is conceivable that kidneys of DGF patients who required only one-time dialysis had suffered less severe ischemia and reperfusion injuries compared with kidneys from patients with DGF who required more than one-time dialysis treatments. Such difference in the severity of ischemia and reperfusion injuries could have determined the duration of dialysis requirement and possibly lead to different long-term clinical outcomes as demonstrated by the present study.

Owing to chronic organ shortage as well as clinical evidence suggesting survival benefit, the use of kidneys from ECD and/or DCD has increased in the recent years (15–18). As a consequence, the incidence of DGF among deceased donor kidney transplant patients remains high (19). Understanding the impact of DGF on short- and long-term outcomes will help us to focus our efforts on improving preservation of deceased donor kidney organs, such as using hypothermic machine perfusion (20), and on improving management of kidney transplant patients experiencing DGF, particularly, of prolonged duration. Previous studies have variably demonstrated the negative impact of DGF on late clinical outcome. Using national transplant registry data, Ojo et al. (1) showed that DGF was associated with a reduced graft survival. Pérez Fontán et al. (21) published data reporting increased mortality as well as increased rates of AR in patients who had long-lasting DGF. In a meta-analysis, Yarlagadda et al. (6) have shown that DGF was associated with 38% and 41% higher relative risk for acute rejection and kidney graft loss, respectively. More recently, Tapiawala et al. (4), using USRDS data, showed that the presence of DGF was associated with increased risk for death with graft function independent of AR and/or renal function achieved following the recovery from DGF, although the inclusion of AR in their analysis attenuated the mortality risk associated with DGF to certain degree. As DGF with more than one-time dialysis requirement was strongly associated with higher risk of having reduced early renal function and higher incidence of AR within the first year post-transplant, we could speculate that high mortality risk in patients with DGF requiring more than one-time dialysis treatment could be at least partly mediated through events such as poor renal function early after transplantation as well as higher rate of AR. Finally, our present findings support the argument, made by Akkina et al. (12), for the need of a different definition of DGF as currently practiced in the transplant community. To this end, the knowledge of specific reasons for the need of dialysis, the number of dialysis treatment, and/or the duration of dialysis requirement early post-transplantation could help to improve the risk stratification and thus the care of patients experiencing DGF, and should be considered in the nationwide data collection of transplant patient information, so the findings of our single-center study can be confirmed. It could be argued that only patients who required more than one-time dialysis treatment early after transplantation (within the first week) should be classified as truly having DGF. Ultimately, the future studies, possibly using biomarker technology, to understand the pathogenic mechanisms of early kidney allograft dysfunction may enable us to replace the use of dialysis requirement as the definition for DGF and to better direct transplant patient-care.

Our study has several limitations. First, being a retrospective and single-center observational study of small size, our findings can only suggest an association but not causality between DGF requiring more than one-time dialysis treatment and inferior clinical outcomes, and may not necessarily be generalizable because of some inherent center characteristics, such as peri-operative care, the choice of immunosuppression regimens. Second, many patient baseline and demographic characteristics were significantly different among the cohorts, particularly between patients without DGF and those with DGF requiring more than one-time dialysis treatment. The use of appropriate statistical approaches does not eliminate the possibility of residual confounding and bias, especially for factors or variables that were not collected, and

thus unaccounted for. Third, the decision of providing patients dialysis treatment shortly after surgery was not uniformly determined rather based on individual physician's judgment, an inherent problem with the current definition of DGF (12). This is of particular problem when only one-time dialysis treatment was required for hyperkalemia as shown by our own data. Indeed, a wide range of hyperkalemia (from as low as 5.7 to as high as 8.0 mM) was recorded as the indication for the need of dialysis. As a consequence, some patients may have had prolonged poor initial renal function yet were not given dialysis treatment, while others received dialysis treatment simply because of some modest hyperkalemia and were thus classified as having had DGF. The results of our study, in one way or another, should not be used to guide the decision making of healthcare providers whether a given patient should receive or not dialysis treatment and for how long following kidney transplantation. On the other hand, the main objectives of our study were to emphasize the deleterious effects of longer DGF duration, thus likely more severe ischemic injuries, on the clinical outcomes post-transplantation. It has been previously shown that even slow graft function was associated with poor clinical outcome (8). Thus, including patients with slow graft function among all patients without DGF could only have reduced the magnitude of our findings on the deleterious effects of DGF. Finally, the difference in the incidence of AR could be simply the results of overdiagnosis as patients experiencing prolonged DGF were more likely to undergo a biopsy, as demanded by center-specific protocols.

In conclusion, more than one-time requirement of dialysis treatment for kidney transplant patients experiencing DGF is associated with poor short- and long-term clinical outcomes. The improvement in kidney organ preservation techniques and novel therapeutic approaches to shorten the duration of DGF and additional interventional studies to improve the management of patients with prolonged DGF are needed.

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## Authors' contributions

D.J. was involved in data collection and manuscript preparation; M.K. was involved in statistical analyses, manuscript editing, and revision of the manuscript; R.S.S. was involved in study design and manuscript editing; F.L.L. was involved in data collection, study design and manuscript preparation, editing and revision of the manuscript.

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