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## Delayed graft function phenotypes and 12-month kidney transplant outcomes

Isaac E. Hall, MD, MS<sup>1</sup>, Peter P. Reese, MD, MSCE<sup>2,3,4</sup>, Mona D. Doshi, MD<sup>5</sup>, Francis L. Weng, MD, MSCE<sup>6</sup>, Bernd Schröppel, MD<sup>7</sup>, William S. Asch, MD, PhD<sup>8</sup>, Joseph Ficek, MA, MS<sup>9</sup>, Heather Thiessen-Philbrook, MMath<sup>9</sup>, and Chirag R. Parikh, MD, PhD<sup>9,10</sup>

<sup>1</sup>Department of Medicine, Division of Nephrology, Hypertension & Renal Transplantation, University of Utah School of Medicine, Salt Lake City, UT

<sup>2</sup>Renal-Electrolyte and Hypertension Division, University of Pennsylvania, Philadelphia, PA

<sup>3</sup>Leonard Davis Institute for Health Economics, University of Pennsylvania, Philadelphia, PA

<sup>4</sup>Department of Biostatistics and Epidemiology, University of Pennsylvania, Philadelphia, PA

<sup>5</sup>Wayne State University, Detroit, MI

<sup>6</sup>Saint Barnabas Medical Center, Livingston, NJ

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**Postpublication Corresponding Author:** Chirag R. Parikh, MD, PhD, Yale University School of Medicine, Section of Nephrology, Temple Medical Center, 60 Temple Street, 6th floor, Suite 6C, New Haven, CT 06510, Phone: 203-737-2676, Fax: 203-764-8373, Chirag.Parikh@Yale.edu.

### Authorship Page

- Isaac E. Hall, MD, MS  
Dr. Hall participated in the design and analyses for the study, interpreted the results and drafted the manuscript. This work was funded in part by a career development award that Dr. Hall received from the American Heart Association.
- Peter P. Reese, MD, MSCE  
Dr. Reese participated by contributing study subjects, interpreting results and helping with manuscript revisions.
- Mona D. Doshi, MD  
Dr. Doshi participated by contributing study subjects, interpreting results and helping with manuscript revisions.
- Francis L. Weng, MD, MSCE  
Dr. Weng participated by contributing study subjects, interpreting results and helping with manuscript revisions.
- Bernd Schröppel, MD  
Dr. Schröppel participated by contributing study subjects, interpreting results and helping with manuscript revisions.
- William S. Asch, MD, PhD  
Dr. Asch participated by interpreting results, providing important feedback and helping with manuscript revisions.
- Joseph Ficek, MA, MS  
Mr. Ficek participated by performing the statistical analyses and helping with manuscript revisions.
- Heather Thiessen-Philbrook, MMath  
Ms. Thiessen-Philbrook participated by providing important statistical feedback and helping with manuscript revisions.
- Chirag R. Parikh, MD, PhD  
Dr. Parikh conceived of the study, participated in its design, interpreted the results and helped write the manuscript.

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<sup>7</sup>Section of Nephrology, University Hospital, Ulm, Germany

<sup>8</sup>Section of Nephrology, Yale University School of Medicine, New Haven, CT

<sup>9</sup>Program of Applied Translational Research, Department of Medicine, Yale University School of Medicine, New Haven, CT

<sup>10</sup>Veterans Affairs Connecticut Healthcare System, New Haven, CT

## Abstract

**Background**—Ischemia-reperfusion injury (IRI) leading to delayed graft function, defined by the United Network for Organ Sharing as dialysis in the first week (UNOS-DGF), associates with poor kidney transplant outcomes. Controversies remain, however, about dialysis initiation thresholds and the utility for other criteria to denote less severe IRI, or slow graft function (SGF).

**Methods**—Multicenter, prospective study of deceased-donor kidney recipients to compare UNOS-DGF to a definition that combines impaired creatinine reduction in the first 48 hours or >1 dialysis session for predicting 12-month estimated glomerular filtration rate (eGFR). We also assessed 10 creatinine and urine output-based SGF definitions relative to 12-month eGFR.

**Results**—In 560 recipients, 215 (38%) had UNOS-DGF, 330 (59%) met the combined definition, 14 (3%) died and 23 (4%) had death-censored graft failure by 12 months. Both DGF definitions were associated with lower adjusted 12-month eGFR (95% CI)—by 7.3 (3.6–10.9) and 7.4 (3.8–11.0) ml/min/1.73m<sup>2</sup>, respectively. Adjusted relative risks for 12-month eGFR <30 ml/min/1.73m<sup>2</sup> were 1.9 (1.2–3.1) and 2.1 (1.1–3.7), with unadjusted areas under the curve of 0.618 and 0.627, respectively. For SGF definitions, postoperative day (POD) 7 creatinine had the strongest association with 12-month eGFR, and POD5 creatinine and creatinine reduction between POD1-2 demonstrated modest separations in 12-month eGFR.

**Conclusions**—While UNOS-DGF does not adequately predict 12-month function on its own, our findings do not support changing the definition. POD7 creatinine is correlated with 12-month eGFR, but large translational studies are needed to understand the biological link between IRI severity at transplant and longer-term outcomes.

## Introduction

Delayed graft function (DGF), defined by the Organ Procurement and Transplantation Network (OPTN) and the United Network for Organ Sharing (UNOS) as dialysis in the first week of kidney transplant, is an early complication that occurs in nearly a quarter of all deceased-donor kidneys.<sup>1</sup> Studies have linked DGF with increased costs, higher rates of acute and chronic rejection, and worse allograft and patient survival.<sup>2–4</sup> In the setting of these as well as recent clinical trial data,<sup>5,6</sup> the Food and Drug Administration (FDA) endorsed the concept of DGF as a clinically relevant registration endpoint for drug development trials in kidney transplantation.<sup>7</sup> Notwithstanding, the relationship between DGF and later outcomes is not absolute, and many recipients that require temporary dialysis within the first several days of transplant eventually achieve acceptable baseline allograft function. As a clear example of this disconnect, kidneys from donors with circulatory

determination of death (DCD) experience DGF at higher rates (over 40%) than standard-criteria kidneys (23%), but subsequent outcomes are comparable.<sup>1,8,9</sup>

Ischemia-reperfusion injury (IRI) resulting in acute kidney injury (AKI) of varying reversibility is the most common reason allografts fail to function immediately after implantation. In nontransplant settings, both severity and duration of AKI associate with mortality,<sup>10</sup> and AKI severity has been linked with chronic kidney disease progression.<sup>11,12</sup> While dialysis-defined DGF can be considered a severe form of AKI, the definition lacks granularity in terms of both severity and duration of allograft injury at transplantation. Furthermore, some degree of subjectivity is unavoidable with dialysis-defined DGF given that thresholds for dialysis decisions can differ between physicians and between centers in the early posttransplant period.<sup>13</sup>

Recognizing the subjective nature of some dialysis decisions, the FDA called for “better disease definitions in short-term appraisals” regarding DGF.<sup>7</sup> Even before this call to action, investigators used many different DGF definitions to describe the clinical experiences and outcomes at a number of centers,<sup>14</sup> and multiple investigators (including authors of the current work) have considered the concept of “slow graft function” (SGF) to describe varying serum creatinine (SCr) concentrations in peritransplant recipients that do not require dialysis.<sup>13,15–19</sup> Evaluating early posttransplant SCr reductions in the absence of dialysis avoids confusion because of intentional creatinine removal but still ignores variable center thresholds for early dialysis indications. A diagnostic algorithm for peritransplant graft function that incorporates all of these concepts relative to both severity and duration of allograft injury would be of tremendous benefit for kidney transplant trials.

Members of our research group previously proposed redefining DGF by combining the need for >1 dialysis session *or* a creatinine reduction ratio (CRR) <25% “within the first 48 h post-transplant.”<sup>14</sup> We therefore conducted the current multicenter study to primarily test the validity of this DGF definition and secondarily determine associations between frequently described definitions for SGF in the immediate posttransplant period with the following 12-month outcomes: estimated glomerular filtration rate (eGFR), death-censored graft failure, acute rejection and mortality. We hypothesized that 12-month eGFR would differ between recipients with versus without DGF by the UNOS definition, but that other DGF and SGF “phenotypes” would also associate with 12-month eGFR after multivariable adjustment for important donor, transplant and recipient characteristics.

## Materials and Methods

### Study Cohort

For this observational cohort study, we collected data from deceased kidney donors whose surrogates had consented to research at 5 organ procurement organizations (OPOs) between April 2010 and December 2013. We prospectively followed recipients of these donor kidneys at 5 transplant centers. The scientific review committees for participating OPOs and institutional review boards for the participating centers approved the protocol. We excluded recipients <16 years old and recipients of dual or en-bloc kidneys, kidneys from donors <5 years old, and multi-organ transplants other than simultaneous pancreas-kidneys. One

recipient of an allograft that immediately thrombosed and was removed 12 hours after transplantation was also excluded.

### Data Abstraction

This study also used data from the OPTN data system, which includes information on all donor, wait-listed candidates, and transplant recipients in the US, submitted by the members of the OPTN, as described elsewhere. The Health Resources and Services Administration (HRSA), US Department of Health and Human Services provides oversight to the activities of the OPTN contractor (currently UNOS). Donor variables were abstracted from OPO charts. We calculated the kidney donor risk index (KDRI) as described by Rao et al.<sup>20,21</sup> We converted the KDRI, as per convention,<sup>20</sup> to obtain the kidney donor profile index (KDPI) relative to all US deceased donors in 2010. Trained study coordinators reviewed all available medical records for recipient characteristics, treatments and outcomes. Daily SCr, urine output (UOP) and dialysis episodes were abstracted from initial transplant hospitalization records. After discharge, outpatient records were reviewed for subsequent dialysis needs and other data. The principal investigator at each site confirmed all posttransplant dialysis episodes and indications by reviewing medical records. Coordinators and analysts at the coordinating center (Yale School of Medicine) performed extensive data quality checks and validations.

### Exposure Variables

We categorized recipients as having DGF, SGF or “immediate graft function” (IGF) according to several literature-based definitions. We considered the following SCr criteria for defining SGF: SCr on postoperative day 5 (POD5Cr, cutoff >3 mg/dl),<sup>13</sup> SCr on POD7 (POD7Cr, cutoff <2.5 mg/dl),<sup>22,23</sup> CRR in the first 24 hours [CRR24h; ((POD0 SCr–POD1 SCr)/POD0 SCr), cutoff <25%],<sup>24</sup> CRR in the first 48 hours (CRR48h, cutoff <25%),<sup>14</sup> CRR between POD1-2 (CRR2, cutoff <30%),<sup>17</sup> CRR over 3 consecutive days within the first week (CRR3, cutoff <10%/day),<sup>25</sup> CRR between POD0-7 (CRR7, cutoff <70%),<sup>18</sup> and number of days to reach creatinine clearance >10 ml/min (CrCl10, cutoff >6 days, estimated by Cockcroft-Gault equation:  $[\text{Sex} * ((140 - \text{Age in years}) / (\text{SCr in mg/dl})) * (\text{kg}/72)]$ , where Sex=1 for male, 0.85 for female; ignoring SCr on days after dialysis posttransplant).<sup>15</sup> We calculated average hourly UOP from transplant to the morning of POD1 (UOP1) and from the morning of POD1 to 2 (UOP2). For both assessments, we used <42 mL/h to approximate <1000 mL/24h as the cutoff.<sup>26,27</sup> For each definition, recipients not dialyzed in the first week (ie, no UNOS-DGF) and not found to have SGF were categorized as having IGF.

For recipients dialyzed at least once in the first week (ie, those with UNOS-DGF), we defined dialysis duration as the number of days from transplant to the last dialysis session. We characterized dialysis timing and number based on whether recipients with only 1 session received it by POD1 (versus after POD1). Thus, we defined dialysis number as: –1=not dialyzed, 0=dialyzed once on POD1, 1=dialyzed once after POD1, 2=dialyzed twice, and 3=dialyzed 3 times. To analyze the previously proposed DGF definition, we categorized recipients with “DGF48h” if they had CRR48h <25% *or* underwent >1 dialysis session within the first week.

## Outcome Variables

We calculated eGFR from clinical SCr measurements at specified time-points via the Chronic Kidney Disease Epidemiology Collaboration equation.<sup>28</sup> No center routinely performed protocol biopsies during the study period. Acute rejection was defined according to the treating transplant physician (ie, biopsy-confirmed or clinically treated without biopsy). We defined death-censored graft failure as resumption (or initiation for preemptive transplants) of maintenance dialysis or retransplantation. Primary nonfunction was defined as continued dialysis beyond 90 days after transplant and was counted as death-censored graft failure. We imputed eGFR as 10 ml/min/1.73m<sup>2</sup> for recipients after death-censored graft failure. In the event of recipient death with a functioning allograft, we carried forward the last available SCr to calculate eGFR.

## Statistical Analysis

Descriptive statistics were reported as mean (SD—standard deviation or SE—standard error of the mean) or median [interquartile range] for continuous variables and as frequency (percentage) for categorical variables. We compared donor and recipient characteristics and 12-month outcomes (eGFR as the primary outcome along with the following secondary outcomes: acute rejection, death-censored graft failure and patient death) by UNOS-DGF status using Wilcoxon rank-sum tests and Pearson's chi-square tests. During analysis planning, we anticipated a minimal detectable difference in 12-month eGFR (at 80% power and alpha=0.05) of 5 ml/min/1.73m<sup>2</sup>. These estimates indicated our final analysis was capable of detecting a 5.4 ml/min/1.73m<sup>2</sup> difference between UNOS-DGF groups. We also calculated Pearson correlation coefficients between POD5Cr (log<sub>2</sub>-transformed), POD7Cr (log<sub>2</sub>-transformed), CRR24h, CRR48h, CRR2, CRR7, UOP1 (log<sub>2</sub>-transformed), UOP2 (log<sub>2</sub>-transformed), and 12-month eGFR. We then compared (via Wilcoxon rank-sum) 12-month eGFR by DGF48h status (capable of detecting a difference of 5.3 ml/min/1.73m<sup>2</sup> at 80% power and alpha=0.05). The various 3-level IGF-SGF-DGF criteria were evaluated by linear models utilizing planned contrasts for pair-wise comparisons for 12-month eGFR differences between groups (without statistical adjustment for multiple comparisons).

We fit multivariable regression models to estimate the relationship between each clinical scenario (UNOS-DGF, DGF48h and each IGF-SGF-DGF definition described above) and 12-month eGFR (continuous) and 12-month eGFR <30 ml/min/1.72m<sup>2</sup> (versus ≥30 ml/min/1.72m<sup>2</sup>, a dichotomous outcome). To account for the possible correlation of outcomes between recipients of kidneys from the same donor, we fit linear mixed regression models with a donor-specific random intercept for the continuous outcome and modified Poisson regression models to estimate relative risk for the dichotomous outcome. For multivariable adjustments, we added the following donor variables: age (years), black race, height (cm), weight (kg), hypertension, diabetes, stroke as cause of death, DCD status and terminal SCr (mg/dl); and we then added the following transplant/recipient variables: cold ischemia time (hours), number of human leukocyte antigen mismatches, age (years), black race, gender, previous kidney transplant, diabetes as the cause of end stage renal disease, body mass index (kg/m<sup>2</sup>), dialysis vintage (months) before transplant, and panel reactive antibody (percent).

We used the Akaike information criterion (AIC) to compare between models to predict 12-month eGFR. The AIC is useful for comparing different types of models because it does not require the models to be nested (the smaller the AIC, the better fit that model provides relative to the others). Given the nested relationship between each of the IGF-SGF-DGF models and the UNOS-DGF model, we also compared each against UNOS-DGF for predicting 12-month eGFR with multivariable adjustment using likelihood-ratio tests. We generated penalized basis spline curves fit with 10 knots and automatically selected smoothing parameters to visualize the relationship between each continuous predictor and 12-month eGFR. We calculated the  $R^2$  value for each of these curves. For the dichotomous outcome, we performed receiver-operating characteristic curve analyses to determine the area under the curve (AUC) for each model.

Sensitivity analyses were performed after excluding graft failures or deaths (as opposed to imputing eGFR). With additional follow-up, we also analyzed 24-month eGFR as a secondary outcome. We performed additional linear regression analyses to test for possible interactions on 12-month eGFR for UNOS-DGF and DGF48h based on kidney quality (KDPI >85 and DCD status) and transplant center. We used SAS 9.3 statistical software for Windows (SAS Institute, Cary, NC) and applied a 2-sided significance level of 0.05 for all tests and confidence intervals.

## Results

### Cohort Description

A flow diagram for study exclusions is shown in Figure 1. Out of 560 transplants from 485 donors, 215 (38%) had UNOS-DGF. 330 (59%) recipients had DGF48h (192 with CRR48h <25% only, 33 with >1 dialysis session only, 105 with both CRR48h <25% and >1 dialysis session). By 12-month, 66 (12%) recipients experienced acute rejection, 23 (4%) had death-censored graft failure -[18 (78%) of which classified as primary non-function], 14 (3%) had died and 11 (2%) were lost to follow-up. Median 12-month eGFR was 54 [42–69] ml/min/1.73m<sup>2</sup>, and 65 (11%) recipients had 12-month eGFR <30 ml/min/1.73m<sup>2</sup>.

As shown in Table 1, only 2 out of 38 pre-emptive recipients experienced UNOS-DGF. Otherwise, those with UNOS-DGF tended to have longer dialysis vintage and were more often black race. Kidneys with UNOS-DGF tended to come from donors that were older, more frequently DCD, and had higher terminal SCr and KDPI values. For the 45 (21%) recipients with UNOS-DGF dialyzed only once by POD1, hyperkalemia was the most common indication (37 cases). For the 32 (15%) recipients with UNOS-DGF dialyzed once but after POD1, uremia was the most common indication (28 cases). Uremia was also the most common indication for recipients dialyzed more than once (>80% for uremia).

### Associations with 12-month Graft Function

As shown in Table 2, recipients with UNOS-DGF had significantly lower 12-month eGFR than those without UNOS-DGF with a difference (95% CI) of -11.9 (-15.6, -8.2) ml/min/1.73m<sup>2</sup>. Results were similar for DGF48h with a difference of -13.2 (-16.9, -9.5) ml/min/1.73m<sup>2</sup> compared to recipients without DGF48h. For eGFR <30 ml/min/1.73m<sup>2</sup> at 12

months, sensitivity and specificity were 58% and 64%, respectively for UNOS-DGF–81% and 44%, respectively for DGF48h. Adjusted relative risk (95% CI) for 12-month eGFR <30 ml/min/1.73m<sup>2</sup> with UNOS-DGF and DGF48h was 1.9 (1.2–3.1) and 2.1 (1.1–3.7), respectively. The AUC (95% CI) for predicting 12-month eGFR <30 ml/min/1.73m<sup>2</sup> was 0.62 (0.55–0.68) and 0.63 (0.57–0.68), respectively. The AUC with the clinical model alone was 0.78 (0.72–0.84), increasing slightly to 0.80 (0.74–0.86) with the addition of either UNOS-DGF or DGF48h (Supplemental Figure S1).

Continuous values for POD5Cr, POD7Cr, CRR24h, CRR48h, CRR2, CRR3, CRR7, UOP1 and UOP2 were significantly correlated with 12-month eGFR with Pearson coefficients of –0.37, –0.43, 0.25, 0.32, 0.28, –0.10, 0.38, 0.31 and 0.28 respectively (all p-values <0.0001). Using the typical literature-based cutoff and as shown in Table 3, mean 12-month eGFR ranged between 60–67 ml/min/1.73m<sup>2</sup> for IGF, compared with values between 50–58 ml/min/1.73m<sup>2</sup> for SGF. Mean (SD) 12-month eGFR with UNOS-DGF was 48 (22) ml/min/1.73m<sup>2</sup>. Table 4 shows adjusted mean (SE) 12-month eGFR by the different IGF-SGF-DGF cutoffs for each of these variables and UNOS-DGF. Only POD5Cr and CRR2 demonstrated significant separation in adjusted mean 12-month eGFR between IGF-SGF-DGF groups (i.e., each group was statistically different from the others via pair-wise comparisons). However, the AIC was smallest for POD7Cr, indicating the fully adjusted model that incorporates a SCr cutoff of 2.5 mg/dL on POD7 for recipients that do not require dialysis may be the best overall predictor of 12-month eGFR relative to all other models studied.

Table 5 provides additional unadjusted and adjusted linear regression results for 12-month eGFR utilizing continuous SCr and UOP-based variables (along with dialysis number and duration) rather than typical cutoffs. AIC results again point to POD7Cr as the strongest predictor. Figure 2 shows spline curves for 12-month eGFR versus POD7Cr and dialysis duration with resulting R<sup>2</sup> values (spline curves for the other continuous predictors included as Supplemental Figures S2–S4).

## Secondary Outcomes and Sensitivity Analyses

Table 2 shows acute rejection, death-censored graft failure and recipient death at 12 months separated by UNOS-DGF and DGF48h status. While neither definition was associated with acute rejection or death, both were associated with 12-month death-censored graft failure with unadjusted relative risks of 4.5 (1.8, 11.3) for UNOS-DGF and 3.3 (1.1, 9.5) for DGF48h. However, only UNOS-DGF remained independently associated with an adjusted relative risk for 12-month death-censored graft failure of 4.7 (1.6, 13.9). Rates of acute rejection, death-censored graft failure and death at 12 months varied slightly by the different SCr, UOP and dialysis-based criteria (Supplemental Table S1).

Between 12 and 24 months, an additional 11 recipients experienced acute rejections [total of 77 (14%) by 24 months], 8 developed death-censored graft failure [31 (6%) total], and 7 died [21 (4%) total]. Unadjusted and adjusted results for UNOS-DGF and DGF48h with regard to 24-month outcomes were slightly attenuated but otherwise similar to 12-month results (Supplemental Table S2). Table 3 provides mean (SD) 6-month and 24-month eGFR values in addition to mean 12-month eGFR separated by the different SCr and UOP-based

criteria. Figure 3 depicts mean 6, 12 and 24-month eGFR according to dialysis number and duration.

As shown in Table 2, sensitivity analyses did not substantially alter the primary 12-month results. However, excluding the 37 recipients with graft failure or death within 12 months attenuated the inverse association between UNOS-DGF and 12-month eGFR slightly more than between DGF48h and 12-month eGFR.

There was no apparent effect modification between UNOS-DGF or DGF48h and kidney quality (KDPI >85 or DCD status, all interaction p-values >0.05) with 12-month eGFR. There was also no discernible effect modification between transplant center and DGF48h on 12-month eGFR (p=0.59). The deleterious effect of UNOS-DGF on 12-month eGFR was potentially more severe (interaction p-values <0.05) at 2 of the participating centers with linear regression coefficients for UNOS-DGF ranging from -2.3 to -15.3 among all 5 centers.

## Discussion

Using prospective, multicenter cohort data for deceased-donor kidney transplant recipients in the modern era, we have shown that UNOS-defined DGF is associated with a reduced eGFR at 12 months by approximately 7 ml/min/1.73m<sup>2</sup> after adjusting for multiple donor, transplant and recipient factors. We found a previously proposed but not validated DGF definition (based on the combination of impaired creatinine reduction in the first 48 hours or >1 dialysis session in the first week)<sup>14</sup> resulted in 12-month allograft outcomes that were generally similar to UNOS-DGF. We also found several SCr and UOP-based criteria reported in the literature to describe SGF in the absence of dialysis are associated with 12-month eGFR. Two criteria (POD5Cr and CRR2) demonstrated significant separation in adjusted 12-month eGFR between all 3 IGF-SGF-DGF groups; however, POD7Cr demonstrated the strongest overall association with 12-month eGFR.

There continues to be much interest in appraising peri-transplant function. Mallon et al recently reported comparable predictive power, in terms of 12-month eGFR and long-term graft survival, for 10 DGF definitions at a single center in the UK.<sup>29</sup> The authors concluded by recommending universal adoption of the UNOS-DGF definition given the arguable lack of superiority for any other definition evaluated, its descriptive simplicity, and its applicability regarding both length of stay and retrospective analyses. We would offer (what we believe also reflects FDA recommendations) that the primary motivation to improve peri-transplant functional assessment should be the development of a reliable early surrogate outcome for use in clinical trials, with less emphasis on retrospective studies.

Future trials to reduce in-hospital dialysis after transplant could be worthwhile in moderating costs. However, with meaningful improvements in long-term allograft function and longevity as the primary goal, we could expect even greater and more durable savings in terms of the economics of chronic kidney disease care, need for retransplantation, and recipient work productivity. As an example of the potential impact of using another definition, data from the current study show that 59% of recipients without UNOS-DGF



would be correctly reclassified as high risk (14% with UNOS-DGF correctly reclassified as low risk) for poor 12-month allograft function (eGFR <30 ml/min/1.73m<sup>2</sup>) if the early outcome were instead defined by DGF48h. This alternate definition is clearly not perfect, however, and could even be deleterious to future trial design given tradeoffs between improved sensitivity and worse specificity for 12-month eGFR <30 ml/min/1.73m<sup>2</sup> compared with the UNOS-DGF definition. In terms of other dialysis-based definitions, we noted a significant step-wise decrease in 12-month eGFR according to dialysis number, but we were somewhat surprised by numerically (though not significantly) better eGFRs for dialysis durations between 8–14 days compared with durations between 1–7 days. Most importantly, these analyses highlight the limitations of current DGF definitions based on SCr, UOP and/or dialysis.

The current study also demonstrates an important consideration about allograft functional assessments both peri-transplant and during follow-up—ie, our continued reliance on SCr itself. SCr does not accurately reflect GFR in the nonsteady state, which is the rule peri-transplant and a common occurrence during follow-up. Numerous conditions other than GFR also affect SCr, including muscle mass and medications. In addition, because dialysis removes creatinine, pre-transplant dialysis timing can greatly affect CRRs, which we observed while investigating apparent outliers in this cohort. This issue leads some to ignore SCr on post-dialysis days (eg, CrCl10 in the current study based on work by Giral-Classe et al.).<sup>15</sup> Furthermore, because SCr is used to estimate GFR, the fact that POD7Cr had the strongest association with 12-month eGFR is not too surprising and is consistent with the SCr data (particularly POD7 and 10) reported by Mallon et al.<sup>29</sup> In terms of allograft survival, a recently proposed tool to predict 5-year survival on POD7 incorporated discharge eGFR with dialysis-defined DGF along with multiple other variables.<sup>30</sup>

We would anticipate that later SCr and/or eGFR values would associate with subsequent allograft function and survival even better than POD7Cr. Kaplan et al showed each 1 mg/dl increase in SCr during the first year of follow-up was associated with over 2-fold risk for allograft failure,<sup>31</sup> but they argued that the change in SCr had poor predictive value with an AUC for allograft failure of only 0.627. While Smail and colleagues noted worse death-censored allograft survival in recipients of expanded-criteria kidneys with SGF (which they defined as CRR <20% in the first 24 hours) but no allograft survival difference based on dialysis-defined DGF, they found a >30% decline in eGFR from month 1 to 12 after transplant was associated with worse allograft survival (hazard ratio of 2.2, p=0.02).<sup>32</sup> Most recently, Clayton et al also found that a 30% decline in eGFR (though from year 1 to 3 after transplant) was associated with over 5-fold risk of subsequent death-censored graft failure.<sup>33</sup> As these prior reports infer, rather than relying on predictors that only become available years later, additional prospective studies are needed to discover effective, mechanistic peritransplant predictors of long-term allograft survival. We believe more studies are needed to determine whether measuring the degree of ischemic injury at transplant with biomarkers like neutrophil gelatinase-associated lipocalin or interleukin-18,<sup>19,27</sup> or assessing the allograft's early response to injury with biomarkers like YKL-40,<sup>34</sup> better capture the biology of peri-transplant renal IRI and recovery as it relates to long-term allograft function and longevity.

Study strengths include careful, standardized and prospective data collection for a relatively large number of recipients at multiple transplant centers with very few losses to follow-up. There are some limitations to consider, however. Despite multivariable adjustment, residual confounding is possible given the observational design. Also, we did not adjust for multiple comparisons in order to identify potential relationships requiring additional study. To evaluate the effects of DGF related to severe allograft IRI at transplant on 12-month outcomes, living-donor kidney transplants were not included. Though 12-month (and subsequently 24-month) follow-up data are now complete, longer-term outcome information is not yet available for the entire cohort.

In conclusion, experimental evidence as well as clinical data from native kidney settings suggest the severity and duration of renal IRI affects subsequent function following recovery. DGF is the corollary to this concept in kidney transplantation. With unquestioning acceptance of DGF as dialysis in the first week, however, we run the risk of forgetting that DGF is a (dichotomous) clinical term to describe poor allograft recovery after IRI (which likely varies across a spectrum). Early dialysis may be indicated for reasons unrelated to severe allograft injury (eg, hyperkalemia with surgical fasting), which may not adversely affect long-term allograft function. We noted SCr on POD7 had the strongest association with 12-month eGFR while 2 other SCr-based criteria demonstrated clear separation in 12-month eGFR with regard to SGF in the absence of dialysis. However, our data indicate that none of the current definitions for DGF or SGF are ideal, stand-alone surrogate outcomes in transplantation, though some are probably sufficient in certain situations (eg, as practical endpoints for low-cost pragmatic trials to optimize peri-transplant care). Nonetheless, the question remains whether pathophysiologic biomarkers of kidney injury and recovery could improve early prognostic determinations at the individual-patient level and prove useful for therapeutic trials. The transplant community should not grow complacent with a DGF definition that is simply “good enough” for more retrospective analyses.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Dr. Parikh had full access to all of the study data and takes responsibility for its integrity and the accuracy of all analyses. Dr. Parikh also affirms that everyone who made substantial contributions to this work has been properly listed.

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(OPTN). The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy of or interpretation by the OPTN or the US Government.

## Abbreviations

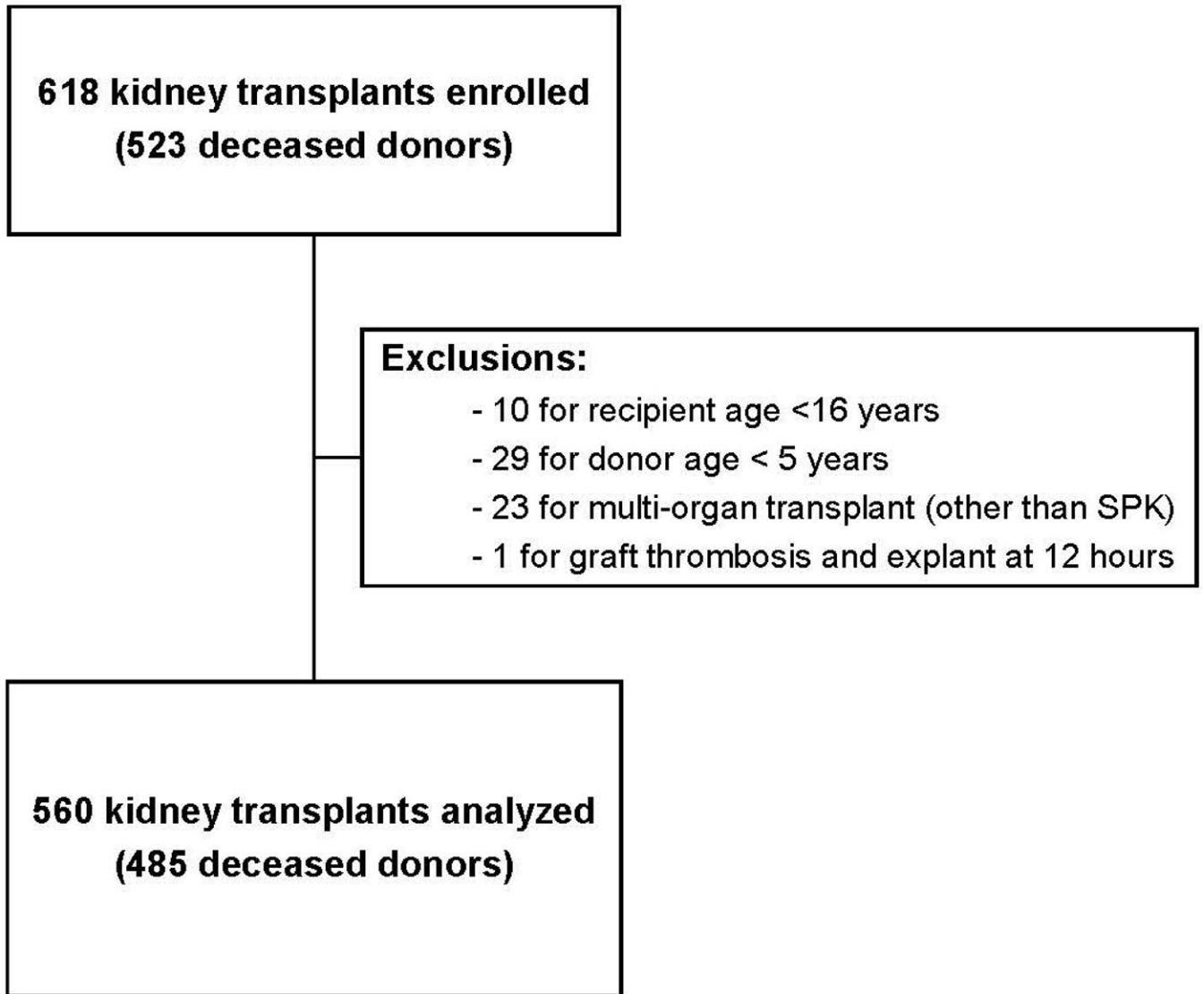
<b>AKI</b>	acute kidney injury
<b>CRR</b>	creatinine reduction ratio
<b>DCD</b>	donation after circulatory determination of death
<b>DGF</b>	delayed graft function
<b>eGFR</b>	estimated glomerular filtration rate
<b>FDA</b>	Food and Drug Administration
<b>IGF</b>	immediate graft function
<b>IRI</b>	ischemia-reperfusion injury
<b>KDPI</b>	kidney donor profile index
<b>KDRI</b>	kidney donor risk index
<b>OPTN</b>	Organ Procurement and Transplantation Network
<b>POD</b>	postoperative day
<b>SCr</b>	serum creatinine
<b>SGF</b>	slow graft function
<b>UNOS</b>	United Network for Organ Sharing
<b>UOP</b>	urine output

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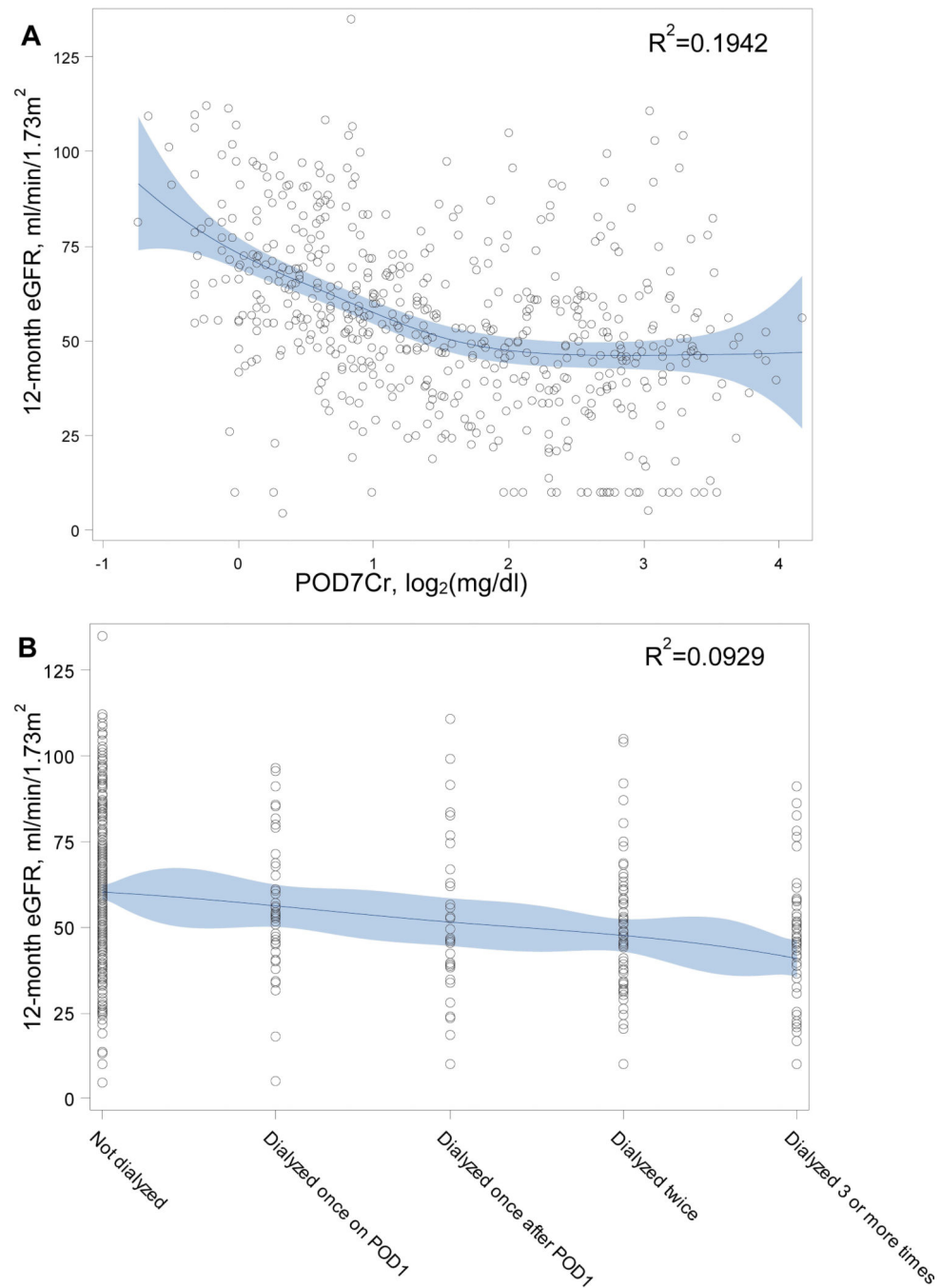
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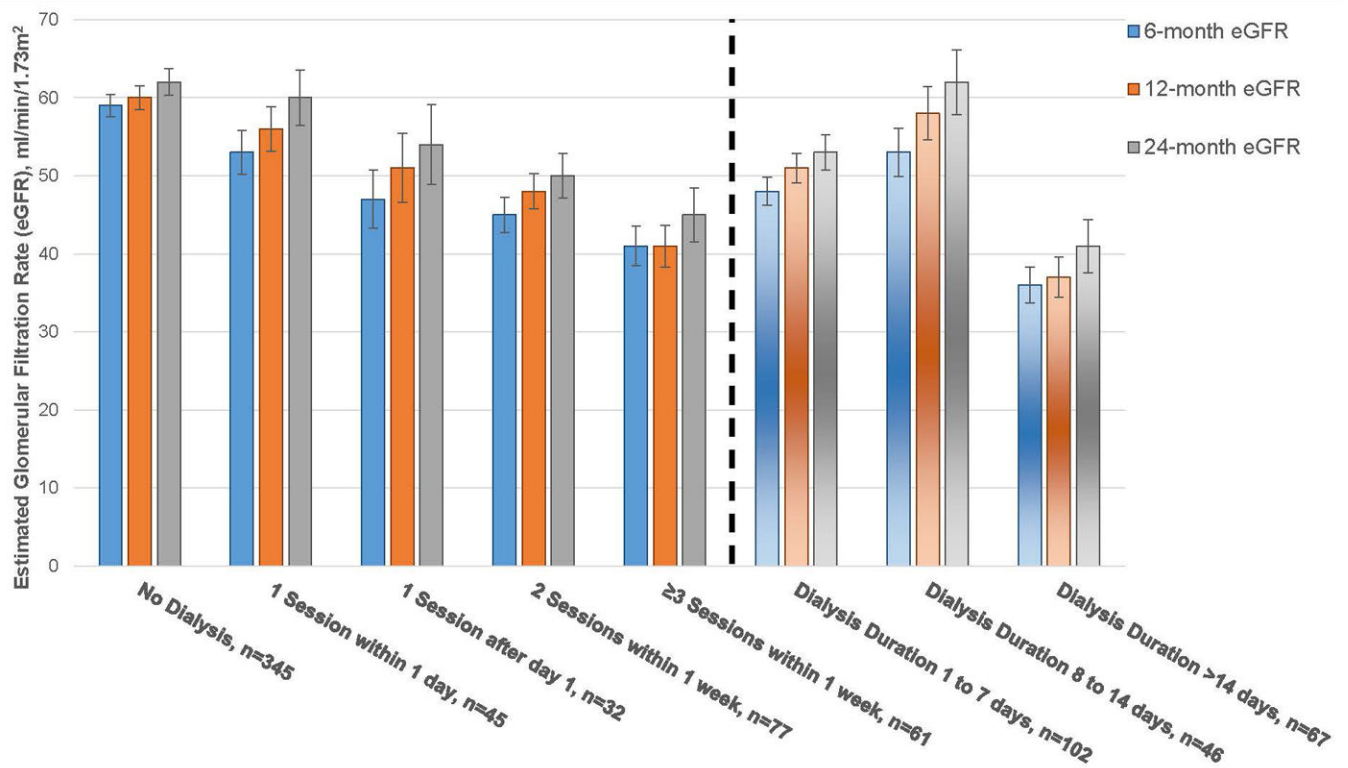
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**Figure 1.**  
Study flow diagram. SPK, simultaneous pancreas-kidney transplant.



**Figure 2.** Basis spline curves. **A.** 12-month estimated glomerular filtration rate (eGFR) vs. postoperative day 7 serum creatinine concentration (POD7Cr, log<sub>2</sub>-transformed). **B.** 12-month eGFR vs. number of dialysis sessions in the first week. Solid line represents the penalized basis spline curve fit with 10 knots and automatically selected smoothing parameter. Shaded area represents the 95% confidence limits.



**Figure 3.**

Mean 6, 12 and 24-month estimated glomerular filtration rate (eGFR) by dialysis number and duration. Standard error bars are shown above and below each mean value. A total of 215 recipients were dialyzed at least once in the first week of dialysis. A dotted vertical line separates the different dialysis-based criteria for the cohort.



Table 1

a. Recipient Characteristics					
Characteristic	ALL (N=560)	No UNOS-DGF (N=345)	UNOS-DGF (N=215)	P-value*	
Age, years	55 [46, 63]	54 [45, 63]	55 [46, 64]	0.287	
Sex, male	353 (63%)	207 (60%)	146 (68%)	0.059	
Black race	262 (47%)	138 (40%)	124 (58%)	<0.001	
Body mass index, kg/m <sup>2</sup>	27 [24, 31.1]	27 [24, 30]	29 [25, 33]	<0.001	
Cause of ESRD	Diabetes	88 (26%)	55 (26%)		0.338
	Hypertension	143 (26%)	84 (24%)	59 (27%)	
	Glomerulonephritis	77 (14%)	52 (15%)	25 (12%)	
	CAKUT	42 (8%)	21 (6%)	21 (10%)	
	Failed transplant	85 (15%)	58 (17%)	27 (13%)	
Dialysis type before transplant	Other	70 (13%)	42 (12%)	28 (13%)	
	Hemodialysis	446 (80%)	248 (73%)	198 (92%)	
	Peritoneal	72 (13%)	57 (17%)	15 (7%)	<0.001
Pre-emptive	38 (7%)	36 (11%)	2 (1%)		
Dialysis vintage, months	49 [19.5, 71]	40.5 [10, 65.5]	59 [36, 76.5]	<0.001	
Hepatitis C seropositive	38 (7%)	25 (7%)	13 (6%)	0.451	
PRA, %	0%	367 (66%)	224 (65%)	143 (67%)	
	1–20%	37 (7%)	20 (6%)	17 (8%)	
	21–80%	75 (13%)	44 (13%)	31 (14%)	0.278
	>80%	81 (14%)	57 (17%)	24 (11%)	

b. Allograft (Donor) Characteristics					
Characteristic	ALL (N=560)	No UNOS-DGF (N=345)	UNOS-DGF (N=215)	P-value*	
Age, years	43 [27, 53]	38 [25, 51]	47 [31, 56]	<0.001	
Sex, male	347 (62%)	217 (63%)	130 (60%)	0.564	
Black race	96 (17%)	62 (18%)	34 (16%)	0.510	
Kidney Donor Risk Index	1.22 [0.97, 1.52]	1.11 [0.92, 1.47]	1.36 [1.12, 1.62]	<0.001	

b. Allograft (Donor) Characteristics				
Characteristic	ALL (N=560)	No UNOS-DGF (N=345)	UNOS-DGF (N=215)	P-value*
Kidney Donor Profile Index, %	49 [26, 70]	40 [21, 67]	60 [40, 76]	<0.001
Cause of death	Head trauma	113 (33%)	43 (20%)	0.003
	Anoxia	113 (33%)	75 (35%)	
	Stroke	116 (34%)	92 (43%)	
	Other	2 (1%)	5 (2%)	
History of diabetes	58 (10%)	31 (9%)	27 (13%)	0.177
History of hypertension	166 (30%)	88 (26%)	78 (36%)	0.007
Hepatitis C seropositive	16 (3%)	11 (3%)	5 (2%)	0.551
DCD	100 (18%)	46 (13%)	54 (25%)	<0.001
Terminal SCr, mg/dl	1 [0.7, 1.4]	0.9 [0.7, 1.2]	1.1 [0.7, 1.6]	0.001
Cold ischemia time, hours	16.2 [12.5, 22]	16 [12, 21.5]	17 [13, 23.4]	.064
Number of HLA mismatches	0	20 (4%)	5 (2%)	0.844
	1	11 (2%)	4 (2%)	
	2	13 (2%)	5 (2%)	
	3	75 (13%)	48 (14%)	
	4	140 (25%)	89 (26%)	
	5	186 (33%)	109 (32%)	
6	111 (20%)	67 (20%)	44 (21%)	

Values are median [interquartile range] or n (%). DGF, delayed graft function; ESRD, end-stage renal disease; CAKUT, congenital anomalies of the kidney and urinary tract; PRA, panel reactive antibody.

\* Wilcoxon rank sum test for continuous variables and Pearson's chi-square test for categorical variables.

Values are median [interquartile range] or n (%). DGF, delayed graft function; DCD, donation after circulatory determination of death. HLA, human leukocyte antigen.

Table 2

Comparison of UNOS-DGF and DGF48h as predictors of 12-month eGFR

12-month Outcome	UNOS-DGF				DGF48h			
	No n=345	Yes n=215	Unadjusted Association (95% CI) *	Adjusted Association (95% CI) **	No n=230	Yes n=330	Unadjusted Association (95% CI) *	Adjusted Association (95% CI) **
eGFR, ml/min/1.73m <sup>2</sup>	60±22	48±22	-11.9 (-15.6, -8.2)	-7.3 (-10.9, -3.6)	64±22	50±21	-13.2 (-16.9, -9.5)	-7.4 (-11.0, -3.8)
eGFR <30 ml/min/1.73m <sup>2</sup>	27 (8)	38 (18)	2.3 (1.4, 3.6)	1.9 (1.2, 3.1)	12 (5)	53 (16)	3.1 (1.7, 5.6)	2.1 (1.1, 3.7)
Acute Rejection	41 (12)	25 (12)	1.0 (0.6, 1.6)	1.0 (0.6, 1.7)	23 (10)	43 (13)	1.3 (0.8, 2.1)	1.4 (0.9, 2.4)
Death-Censored Graft Failure	6 (2)	17 (8)	4.5 (1.8, 11.3)	4.7 (1.6, 13.9)	4 (2)	19 (6)	3.3 (1.1, 9.5)	2.2 (0.7, 6.3)
Recipient Death	7 (2)	7 (3)	1.6 (0.6, 4.5)	1.4 (0.4, 5.7)	3 (1)	11 (3)	2.5 (0.7, 9.0)	2.1 (0.5, 8.0)
<b>Sensitivity Analyses</b> (after removing 37 recipients with graft failure or death)								
12-month Outcome	UNOS-DGF				DGF48h			
	No n=332	Yes n=191	Unadjusted Association (95% CI) *	Adjusted Association (95% CI) **	No n=223	Yes n=300	Unadjusted Association (95% CI) *	Adjusted Association (95% CI) **
eGFR, ml/min/1.73m <sup>2</sup>	60±21	52±19	-8.2 (-11.7, -4.7)	-3.7 (-7.1, -0.3)	65±20	52±19	-12.2 (-15.6, -8.7)	-7.1 (-10.5, -3.8)
eGFR <30 ml/min/1.73m <sup>2</sup>	21 (6)	18 (9)	1.5 (0.8, 2.7)	1.2 (0.7, 2.2)	7 (3)	32 (11)	3.4 (1.5, 7.6)	2.5 (1.1, 5.4)
Acute Rejection	38 (11)	22 (12)	1.0 (0.6, 1.7)	1.0 (0.6, 1.7)	21 (9)	39 (13)	1.4 (0.8, 2.3)	1.5 (0.9, 2.6)

United Network for Organ Sharing-defined delayed graft function (UNOS-DGF) is any dialysis in the first posttransplant week. DGF48h is delayed graft function defined as a serum creatinine reduction of <25% in the first 48 h or >1 dialysis session in the first posttransplant week. Values are mean ± standard deviation, n (%), or measure of association (95% confidence interval) as indicated.

\* Unadjusted associations with continuous eGFR tested via mixed effects linear regression and with dichotomous eGFR <30 ml/min/1.73m<sup>2</sup> via modified Poisson regression

\*\* Same regressions as above adjusted for the following *donor variables*: age, circulatory death (rather than brain death), black race, hypertension, diabetes, height, weight, stroke as cause of death, and terminal serum creatinine; and the following *transplant/recipient variables*: cold ischemia time, age, black race, gender, previous kidney transplant, diabetes as the cause of end stage renal disease, number of human leukocyte antigen mismatches, body mass index, duration (vintage) of dialysis before transplant, and percent panel reactive antibody.

Mean 6, 12 and 24-month eGFR by literature-based definitions of IGF and SGF in recipients that did not require posttransplant dialysis

**Table 3**

	Mean 6-month eGFR		Mean 12-month eGFR		Mean 24-month eGFR	
	IGF	SGF	IGF	SGF	IGF	SGF
Serum creatinine						
	Postoperative day 5	64 (20)	51 (20)	66 (25)	66 (25)	60 (24)
	Postoperative day 7	63 (20)	48 (20)	66 (24)	67 (24)	56 (25)
Creatinine reduction ratio	Over 1 <sup>st</sup> 24 h	68 (19)	55 (20)	70 (26)	59 (24)	61 (24)
	Over 1 <sup>st</sup> 48 h	63 (20)	52 (21)	65 (25)	59 (24)	60 (24)
	Postoperative day 1 to 2	65 (20)	54 (21)	67 (26)	59 (24)	60 (24)
	Over 3 consecutive days in 1 <sup>st</sup> week	61 (21)	52 (19)	63 (25)	59 (25)	60 (24)
	Postoperative day 0 to 7	64 (20)	53 (20)	66 (25)	58 (24)	60 (24)
Days to reach creatinine clearance >10 ml/min						
Urine output						
	Postoperative day 1	60 (21)	45 (17)	63 (25)	52 (22)	55 (22)
	Postoperative day 1 to 2	59 (20)	55 (26)	63 (25)	57 (24)	62 (23)

Values are mean (standard deviation) estimated glomerular filtration rate (eGFR, calculated from serum creatinine via the Chronic Kidney Disease Epidemiology Collaboration equation) in mL/min/1.73m<sup>2</sup>, that result from categorizing all 345 recipients that did not require dialysis in the first 7 days after transplant as having either immediate graft function (IGF) or slow graft function (SGF) according to each literature-based cutoff as described below. Mean (standard deviation) eGFR at 6, 12 and 24 months for all 345 recipients was 59 (21), 60 (22) and 62 (25) mL/min/1.73m<sup>2</sup>, respectively. Postoperative day 5 serum creatinine (POD5Cr): IGF <3 mg/dL, n=197; SGF 3 mg/dL, n=148, postoperative day 7 serum creatinine (POD7Cr): IGF <2.5 mg/dL, n=240; SGF 2.5 mg/dL, n=10, creatinine reduction ratio over the first 24 h (CRR24h): IGF 0.25, n=93; SGF <0.25, n=252, creatinine reduction ratio over the first 48 h (CRR48h): IGF 0.25, n=204; SGF <0.25, n=141, creatinine reduction ratio from postoperative day 1 to 2 (CRR2): IGF 0.3, n=141; SGF <0.3, n=204, creatinine reduction ratio over 3 consecutive days in the first week (CRR3): IGF 0.1, n=83; creatinine reduction ratio from postoperative day 0 to 7 (CRR7): IGF 0.7, n=184; SGF <0.7, n=161, days to reach a creatinine clearance by Cockcroft-Gault equation 10 ml/min (CfCl10): IGF 6 days, n=331; SGF >6 days, n=14, average hourly urine output from transplant to the morning of postoperative day 1 (UOP1): IGF 42 ml/h, n=307; SGF <42 ml/h, n=30, average hourly urine output from the morning of postoperative day 1 to 2 (UOP2): IGF 42 ml/h, n=302; SGF <42 ml/h, n=42).

Table 4

12-month adjusted eGFR by phenotypes for IGF-SGF-DGF.

IGF-SGF Definition	Adjusted 12-month eGFR			AIC <sup>***</sup>	P-value <sup>***</sup>	
	IGF	SGF	DGF			
Serum creatinine	Postoperative day 5	56 (3) <sup>*</sup>	50 (3) <sup>*</sup>	45 (2)	4786.5	0.004
	Postoperative day 7	56 (3) <sup>*</sup>	47 (3)	45 (2)	4780.3	<.001
Creatinine reduction ratio	Over 1 <sup>st</sup> 24 h	55 (3)	52 (2)	45 (2) <sup>*</sup>	4793.1	0.169
	Over 1 <sup>st</sup> 48 h	54 (3)	51 (3)	45 (2) <sup>*</sup>	4792.8	0.144
	Postoperative day 1 to 2	56 (3) <sup>*</sup>	51 (2) <sup>*</sup>	46 (2) <sup>*</sup>	4790.6	0.036
	Over 3 consecutive days in 1 <sup>st</sup> week	54 (3)	50 (3)	46 (2)	4791.6	0.066
Days to reach creatinine clearance >10 ml/min	Postoperative day 0 to 7	55 (3)	51 (3)	45 (2) <sup>*</sup>	4791.6	0.068
Urine output	Postoperative day 1	53 (2)	52 (5)	45 (2)	4794.9	0.899
	Postoperative day 1 to 2	53 (2)	48 (4)	45 (2)	4792.8	0.144
		53 (2)	53 (4)	45 (2) <sup>*</sup>	4795.0	0.916

Predicted mean (standard error) 12-month estimated glomerular filtration rate (eGFR) in ml/min/1.73m<sup>2</sup> via linear regression models adjusted for the following *donor variables*: age, circulatory death (rather than brain death), black race, hypertension, diabetes, height, weight, stroke as cause of death, and terminal serum creatinine; and the following *transplant/recipient variables*: cold ischemia time, age, black race, gender, previous kidney transplant, diabetes as the cause of end stage renal disease, number of human leukocyte antigen mismatches, body mass index, duration (vintage) of dialysis before transplant, and percent panel reactive antibody.

Immediate graft function (**IGF**) and slow graft function (**SGF**) were defined according to the literature-based cutoffs described below. Delayed graft function (**DGF**) was defined as any dialysis in the first week after transplant according to the United Network for Organ Sharing definition. Postoperative day 5 serum creatinine (**POD5Cr**): IGF <3 mg/dL, n=197; SGF 3 mg/dL, n=148, postoperative day 7 serum creatinine (**POD7Cr**): IGF <2.5 mg/dL, n=240; SGF 2.5 mg/dL, n=10, creatinine reduction ratio over the first 24 h (**CRR24h**): IGF 0.25, n=93; SGF <0.25, n=252, creatinine reduction ratio over the first 48 h (**CRR48h**): IGF 0.25, n=204; SGF <0.25, n=141, creatinine reduction ratio from postoperative day 1 to 2 (**CRR2**): IGF 0.3, n=141; SGF <0.3, n=204, creatinine reduction ratio over 3 consecutive days in the first week (**CRR3**): IGF 0.1, n=262; SGF <0.1, n=83, creatinine reduction ratio from postoperative day 0 to 7 (**CRR7**): IGF 0.7, n=184; SGF <0.7, n=161, days to reach a creatinine clearance by Cockcroft-Gault equation 10 ml/min (**CtCr10**): IGF 6 days, n=331; SGF >6 days, n=14, average hourly urine output from transplant to the morning of postoperative day 1 (**UOPI**): IGF 42 ml/h, n=307; SGF <42 ml/h, n=30, average hourly urine output from the morning of postoperative day 1 to 2 (**UOP2**): IGF 42 ml/h, n=302; SGF <42 ml/h, n=42).

\* Single asterisk indicates which (if any) IGF-SGF-DGF group is significantly different from the other 2 groups in terms of 12-month eGFR via pair-wise comparisons for that particular row.

\*\* AIC, Akaike information criterion (smaller values indicate better estimated statistical quality of the adjusted model).

\*\*\* Likelihood ratio test for each adjusted IGF-SGF-DGF model against the adjusted null model of UNOS-DGF versus Non-DGF.

**Table 5**

Linear regression for 12-month eGFR using continuous predictors

Effect		Unadjusted	Adjusted*	AIC
Dialysis number **		-4.5 (-5.7, -3.3)	-2.9 (-4.1, -1.7)	4699.3
Dialysis duration (days)		-0.02 (-0.07, 0.02)	0.00 (-0.03, 0.04)	4719.5
Serum creatinine	Postoperative day 5 (log <sub>2</sub> mg/dl)	-7.9 (-9.5, -6.2)	-5.9 (-7.7, -4.1)	4680.8
	Postoperative day 7 (log <sub>2</sub> mg/dl)	-8.7 (-10.3, -7.0)	-6.5 (-8.2, -4.8)	4666.9
Creatinine reduction ratio	Over 1 <sup>st</sup> 24 h	17.5 (10.1, 25.0)	4.8 (-2.2, 11.9)	4719.7
	Over 1 <sup>st</sup> 48 h	18.4 (13.1, 23.7)	9.5 (4.4, 14.6)	4708.7
	Postoperative day 1 to 2	22.8 (15.6, 29.9)	14.3 (7.7, 20.8)	4703.5
	Postoperative day 0 to 7	20.5 (15.8, 25.3)	12.8 (8.2, 17.5)	4692.7
Days to reach creatinine clearance >10 ml/min		-0.7 (-1.0, -0.3)	-0.5 (-0.8, -0.2)	4710.2
Urine Output	Postoperative day 1 (log <sub>2</sub> ml/h)	3.2 (2.4, 4.1)	2.0 (1.1, 2.9)	4700.6
	Postoperative day 1 to 2 (log <sub>2</sub> ml/h)	3.2 (2.2, 4.2)	1.9 (0.9, 2.9)	4707.0

The unadjusted and adjusted values are linear regression coefficients (95% confidence intervals). AIC, Akaike information criterion (smaller values indicate better estimated statistical quality when comparing all of the adjusted models).

\* Adjusted for the following *donor variables*: age, circulatory death (rather than brain death), black race, hypertension, diabetes, height, weight, stroke as cause of death, and terminal serum creatinine; and the following *transplant/recipient variables*: cold ischemia time, age, black race, gender, previous kidney transplant, diabetes as the cause of end stage renal disease, number of human leukocyte antigen mismatches, body mass index, duration (vintage) of dialysis before transplant, and percent panel reactive antibody.

\*\* Continuous variable coded as follows: -1 = Not dialyzed, 0 = Dialyzed once on POD1, 1 = Dialyzed once after POD1, 2 = Dialyzed twice, 3 = Dialyzed 3 or more times.