Delayed graft function and the risk of acute rejection in the modern era of kidney transplantation

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Delayed graft function (DGF) is commonly considered a risk factor for acute rejection, although this finding has not been uniformly observed across all studies. The link between DGF and acute rejection may have changed over time due to advances in immunosuppression and medical management. Here we conducted a cohort study of 645 patients over 12 years to evaluate the association of DGF and biopsy-proven acute rejection (BPAR) in a modern cohort of kidney transplant recipients. DGF was defined as the need for at least one dialysis session in the first week after kidney transplantation. The 1-, 3-, and 5-year cumulative probabilities of BPAR were 16.0, 21.8, and 22.6% in the DGF group, significantly different from the 10.1, 12.4, and 15.7% in the non-DGF group. In multivariable Cox proportional hazards model, the adjusted relative hazard for BPAR in DGF (vs. no DGF) was 1.55 (95% confidence interval (CI): 1.03, 2.32). This association was generally robust to different definitions of DGF. The relative hazard was also similarly elevated for T-cell- or antibody-mediated BPAR (1.52 (0.92, 2.51) and 1.54 (0.85, 2.77), respectively). Finally, the association was consistent across clinically relevant subgroups. Thus DGF remains an important risk factor for BPAR in a contemporary cohort of kidney transplant recipients. Interventions to reduce the risk of DGF and/or its aftereffects remain of paramount importance to improve kidney transplant outcomes.

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Kidney transplantation is the treatment of choice for patients with end-stage renal disease (ESRD). Despite its benefits, recipients may experience posttransplant complications that can negatively impact long-term allograft and patient outcomes. Delayed graft function (DGF) is a common complication experienced by kidney transplant recipients, particularly among those receiving deceased donor kidneys. It is most often defined as the need for dialysis within the first 7 days after kidney transplantation. The incidence of DGF ranges from 20% to 50% in deceased and from 4% to 10% in living donor kidney transplant recipients, with variations in incidence due to recipient, donor, and transplant factors, as well as the DGF definition used.

DGF has been associated with poor clinical outcomes, including death with graft function and graft failure.[1,2] DGF may also contribute to the development of chronic graft dysfunction, which may ultimately compromise graft longevity.[3] An increased tendency to chronic graft failure may be mediated by a history of acute rejection in patients with DGF. The ischemia–reperfusion injury leading to DGF may also increase the expression of human leukocyte antigen molecules on endothelial cell surfaces and thus increase the immunogenicity of the allograft.[3] Deciphering the links between DGF, acute rejection, and long-term outcomes may be of value in developing strategies to minimize chronic allograft dysfunction and graft failure.

Although some past studies have found no significant increase in the risk of acute rejection associated with DGF,[4,5] other reports have observed a direct relationship between the two entities.[2] However, most of these studies were conducted in cohorts from the 1990s, and a recent, more comprehensive assessment of this relationship is lacking. New immunosuppressive strategies aimed at decreasing the incidence of acute rejection have been developed and implemented in the past decade.[6] Wider use of expanded criteria donors (ECDs) and donation after circulatory death (DCD) has further increased the incidence of DGF, but the associated risk and outcome of acute rejection in patients receiving these kidneys are not clear. Furthermore, the validity of the traditional DGF definition has been questioned,[7] and thus alternate definitions have been considered.[8,9] The purpose of this study is to

evaluate and quantify the association of DGF and biopsy-proven acute rejection (BPAR) in the current era of deceased donor kidney transplantation at a large Canadian kidney transplant center and to determine whether the association is sensitive to the definition of DGF used.

RESULTS

After applying the *a priori* exclusion criteria, 645 deceased donor kidney transplant recipients were included in the final study cohort (Figure 1). A total of 233 (36.1%) experienced DGF. During 2744.6 patient-years of follow-up (median follow-up 3.5 years), there were 111 BPAR events. During 3164.1 patient-years of follow-up (median follow-up 4.5 years), there were 57 graft losses and 62 deaths with graft function resulting in 119 total graft failure events. The proportion of missing data across all the data elements used in this analysis ranged from 0% to 24% (Supplementary Appendix, SA-1 online).

Baseline characteristics for the DGF and non-DGF groups are shown in Table 1. Recipients who developed DGF had greater body mass index, higher prevalence of diabetes as the cause of ESRD, and longer time on pretransplant dialysis. Recipients with DGF were also more likely to receive kidneys from donors who were older, male, and recovered after circulatory death. Other characteristics were similar between DGF and non-DGF groups. In particular, there were no significant differences in cold ischemic time, human leukocyte antigen mismatches, and transplant era. Notably, the distribution of calcineurin inhibitor levels over the first year posttransplant showed considerable overlap in DGF and non-DGF patients (Supplementary Appendix, SA-2 online).

The cumulative probabilities of developing BPAR in DGF and non-DGF groups are displayed in Figure 2. The cumulative probability was greater in DGF patients at all points over the follow-up period. The 1-, 3-, and 5-year probabilities of BPAR were 16.0% (95% confidence interval (CI): 11.8, 21.3), 21.8% (95% CI: 16.8, 27.9), and 22.6% (95% CI: 17.5, 28.9) in the DGF group and 10.1% (95% CI: 7.6, 13.5), 12.4% (95% CI: 9.5, 16.1), and 15.7% (95% CI: 12.2, 20.1) in the non-DGF group, respectively (log-rank $P=0.01$).

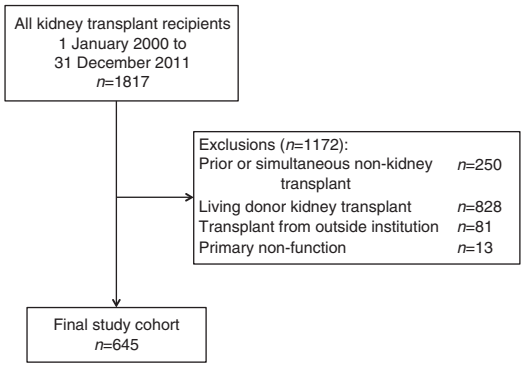

Figure 1 | Study flow diagram.

Table 2 shows the relative hazards for BPAR in DGF versus non-DGF patients estimated from multivariable Cox proportional hazards models. DGF was associated with an unadjusted hazard ratio of 1.66 (95% CI: 1.14, 2.42) for BPAR over the follow-up period. Sequential adjustments for an expanding set of covariates did not appreciably alter the univariable association. In the fully adjusted model (Model 4), the hazard ratio for BPAR was 1.55 (95% CI: 1.03, 2.32) in patients experiencing DGF vs. no DGF. Similar findings were seen when a backward stepwise procedure was used for covariate selection (Model 5). Moreover, the results were robust to whether graft failure or death with graft function was treated as censoring or competing events (Supplementary Appendix, SA-3 and SA-4 online).

The robustness of the DGF-BPAR association was evaluated as a function of the DGF definition used in the analysis (Table 3). The majority of the definitions evaluated showed a similarly elevated relative hazard for BPAR in patients who developed DGF in the postoperative setting. Interestingly, definitions that incorporated measures of kidney function in conjunction with the need for dialysis (definitions 5 and 6) generally showed a more attenuated association.

Figure 3 shows the Kaplan–Meier curves for the cumulative probability of developing acute antibody-mediated rejection (ABMR) and T-cell-mediated rejection (TCMR). DGF patients showed a higher cumulative probability of developing both types of BPAR over follow-up. However, the absolute risk of TCMR was greater than that of ABMR in both the DGF and non-DGF groups. The risk of developing ABMR increased most rapidly during the first month after transplant, whereas the risk of TCMR appeared to persist for a longer duration. In Cox proportional hazards models, the adjusted hazard ratios for acute TCMR and ABMR were 1.52 (95% CI: 0.92, 2.51; $P=0.10$) and 1.54 (95% CI: 0.85, 2.77; $P=0.15$), respectively. Similar results were observed for all DGF definitions examined (data not shown).

An evaluation of potential subgroup effects is depicted as a forest plot in Figure 4. Notably, the point estimates showed that recipients who were older, diabetic, unsensitized, and received ECD kidneys at the time of transplantation tended to exhibit a more diminished association between DGF and BPAR. Interestingly, DCD kidney recipients showed a more accentuated hazard ratio than non-DCD kidney recipients. However, there was no statistically significant effect measure modification observed across any subgroups studied (P-value for interaction ≥ 0.13).

DISCUSSION

This study confirms that DGF continues to be an important risk factor for BPAR in the modern era of deceased donor kidney transplantation. The multivariable adjusted relative hazard for BPAR was significantly elevated at 1.64-fold in patients experiencing DGF (vs. no DGF), which is consistent with the findings of the meta-analysis by Yarlagadda *et al.*[2] The association was generally persistent across different

Table 1 | Baseline recipient, donor, and transplant characteristics by delayed graft function status after kidney transplantation

Variables	Number of patients	Non-DGF ($n=411$)	DGF ($n=234$)	*P*-value
Mean recipient age at transplant (years)	645	52.9 ± 12.8	53.4 ± 11.5	0.59
Recipient sex (%)				
Male	413 (254/159)	61.8	68	0.12
Female	232 (157/75)	38.2	32	
Recipient race (%)				
White	369 (237/132)	58.4	56.9	
Black	97 (56/41)	13.8	17.7	
East Asian	81 (47/34)	11.6	14.7	0.2
Indian subcontinent Asian	70 (53/17)	13.1	7.3	
Other	21 (13/8)	3.2	3.4	
Mean recipient body mass index (kg/m^2)	625 (403/222)	26.1 ± 4.9	27.9 ± 5.8	<0.001
Cause of ESRD (%)				
Diabetes	123 (68/55)	16.6	23.5	0.03
Non-diabetes	522 (343/179)	83.5	76.5	
Median PRA (%)				
0	275 (180/95)	44.3	40.6	0.36
>0	365 (226/139)	55.7	59.4	
Median time on dialysis before transplant (years)	644 (410/234)	5.0 (3.4, 7.0)	5.5 (3.7, 7.3)	0.03
Mean donor age at transplant (years)	632 (403/229)	46.9 ± 15.8	49.7 ± 15.2	0.03
Donor sex (%)				
Male	370 (219/151)	54.5	65.9	0.01
Female	261 (183/78)	45.5	34.1	
Mean donor body mass index (kg/m^2)	622 (396/226)	26.4 ± 5.9	27.5 ± 6.9	0.03
Cause of death (%)				
Cerebrovascular accident	375 (234/141)	58.8	63.51	
Anoxia	70 (46/24)	11.6	10.81	0.59
Trauma	126 (87/39)	21.9	17.57	
Other	49 (31/18)	7.79	8.11	
Mean terminal serum creatinine (umol/l)	578 (374/204)	65.5 (51, 84)	69.5 (58, 86.5)	0.01
Donor history of hypertension (%)				
Yes	192 (113/79)	31.2	40.1	0.04
No	367 (249/118)	68.8	59.9	
Expanded criteria donors (ECDs) (%)				
Yes	187 (113/74)	27.5	31.6	0.27
No	458 (298/160)	72.5	68.4	
Donation after cardiac death (DCD) (%)				
Yes	77 (39/38)	9.5	16.2	0.01
No	568 (372/196)	90.5	83.8	
Mean cold ischemia time (minutes)	489 (313/176)	821.2 ± 347.3	855.2 ± 389.8	0.32
CNI type (%)				
Tacrolimus	438 (279/159)	69.8	71.6	0.62
Cyclosporine	184 (121/63)	30.3	28.4	
Median HLA mismatched	552 (354/198)	5 (4, 5)	5 (4, 5)	0.07
Re-graft (%)				
Yes	84 (51/33)	12.4	14.1	0.54
No				
Transplant era (%)	561 (360/201)	87.6	85.9	
2000–2004	207 (129/78)	31.4	33.3	
2005–2008	232 (142/90)	34.6	38.5	0.3
2009–2011	206 (140/66)	34.1	28.2	

Abbreviations: CNI, calcineurin inhibitor; DGF, delayed graft function; ESRD, end-stage renal disease; HLA, human leukocyte antigen; PRA, panel reactive antibody.

definitions of DGF. Moreover, DGF increased the risk of both TCMR and ABMR, although the absolute risk of the former was more prominent. Certain patient subgroups (i.e., older age, diabetics, unsensitized, and ECD) showed a slightly attenuated association, although our study was likely underpowered to assess for the presence of effect measure modification. The association of DGF and BPAR in this contemporary cohort persisted despite changes in the

maintenance immunosuppressive regimen over follow-up (i.e., program-wide adoption of tacrolimus as the first-line calcineurin inhibitor in 2007) and the universal administration of induction therapy.

It has long been established that DGF increases the risk of chronic allograft dysfunction and graft loss.[10] More recently, DGF has also been implicated in increasing the risk of death with graft function in both deceased and living donor kidney transplant recipients.[1,11] Notably, DGF has been shown to be a heterogeneous condition with varying etiologies (e.g., prolong cold ischemia time, DCD, etc.) that may impact on the prognosis of the kidney allograft.[12–14] The current study highlights the continued importance of DGF as a risk factor for acute rejection despite advances in induction/maintenance immunosuppressive therapies and medical management over the past several years.

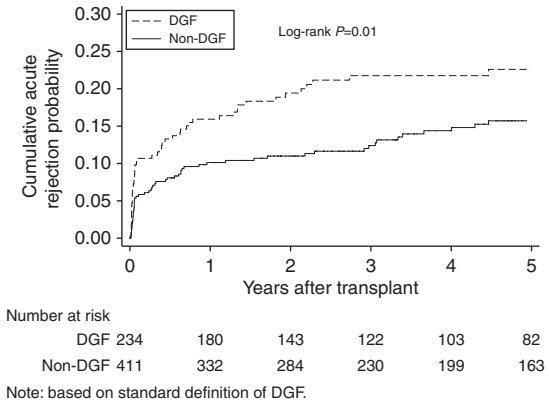

Figure 2 | Cumulative probability of biopsy-proven acute rejection according to delayed graft function (DGF) status after kidney transplantation.

Table 2 | Cox proportional hazards models for the risk of biopsy-proven acute rejection by delayed graft function (standard definition)

Cox proportional hazards model	Hazard ratio (95% CI)	*P*-value
Model 1	1.66 (1.14, 2.42)	0.01
Model 2	1.55 (1.05, 2.28)	0.03
Model 3	1.59 (1.07, 2.36)	0.02
Model 4	1.55 (1.03, 2.32)	0.04
Model 5	1.64 (1.11, 2.42)	0.01

Abbreviation: CI, confidence interval.

DGF is the clinical manifestation of ischemia–reperfusion injury resulting from insults incurred during the organ recovery, preservation, and re-implantation phases of the transplantation process.[3,15,16] Low perfusion states in the donor lead to increased vascular tone and arteriolar vasoconstriction. On the endothelial surface of blood vessels, heat-shock proteins and high mobility group protein B-1 activate Toll-like receptors and upregulate class 1 human leukocyte antigens. Acidic and reactive oxygen species cause phospholipolysis and injury to the cell membrane. In renal tubular epithelial cells, oxygen depletion and ATP degradation promote oxygen radical formation and limit metabolic rate. After graft implantation, reperfusion of the damaged kidney augments the injury through complement activation, accumulation of free radicals, peroxynitrite-induced apoptosis, reactive oxygen species–mediated signaling, and cell-stress-derived overexpression of pro-inflammatory biomolecules. This results in the recruitment and activation of antigen-presenting cells, which then migrate to secondary lymphoid tissues and present alloantigens to T-lymphocytes. The priming of T cells paves the way for the development of acute rejection.[17]

Most of the original studies that established the link between DGF and acute rejection were conducted on patient cohorts assembled in the 1990s.[18–28] Many of these studies did not use multivariable modeling or the focus was on the outcomes of patients with both DGF and acute rejection. Moreover, the relevance of these studies in the contemporary era is questionable, as there has been significant uptake of anti-lymphocyte induction therapy in many transplant centers, and the spectrum of deceased donor kidney quality has broadened over the past decade.[29] The increasing use of older, more marginal kidneys may heighten the risk of acute rejection in the setting of DGF because of their potential for greater immunogenicity.[30] More recent studies have examined non-invasive approaches for diagnosing acute rejection in patients with DGF,[31] risk factors for acute rejection among patients with DGF,[32] and the effect modifying the role of DCD on the DGF–acute rejection association.[13] All of these studies had small sample sizes (<100), and they did not assess the relation between DGF and acute rejection as their primary study question.

Table 3 | Cox proportional hazards models for the risk of biopsy-proven acute rejection by different definitions of delayed graft function

Definition number	Definition of delayed graft function (DGF)	No DGF	DGF	Hazard ratio (95% CI)	*P*-value
1	Need for at least two dialysis sessions in the first week after transplant	505	140	1.59 (1.02, 2.47)	0.04
2	Need for at least one session of dialysis within 24 h of transplant	457	188	1.54 (1.00, 2.37)	0.05
3	Need for at least one session of dialysis within 48 h of transplant	424	221	1.54 (1.01, 2.33)	0.04
4	Need for at least one session of dialysis within 72 h of transplant	416	229	1.47 (0.98, 2.21)	0.06
5	Definition 2 or urine output <1 liter and $<25\%$ drop in SCr 24 h after transplant	436	209	1.39 (0.92, 2.11)	0.12
6	Definition 4 or SCr decrease $<10\%$ per day for 3 consecutive days from transplant	416	229	1.47 (0.98, 2.21)	0.06

Abbreviations: CI, confidence interval; SCr, serum creatinine.

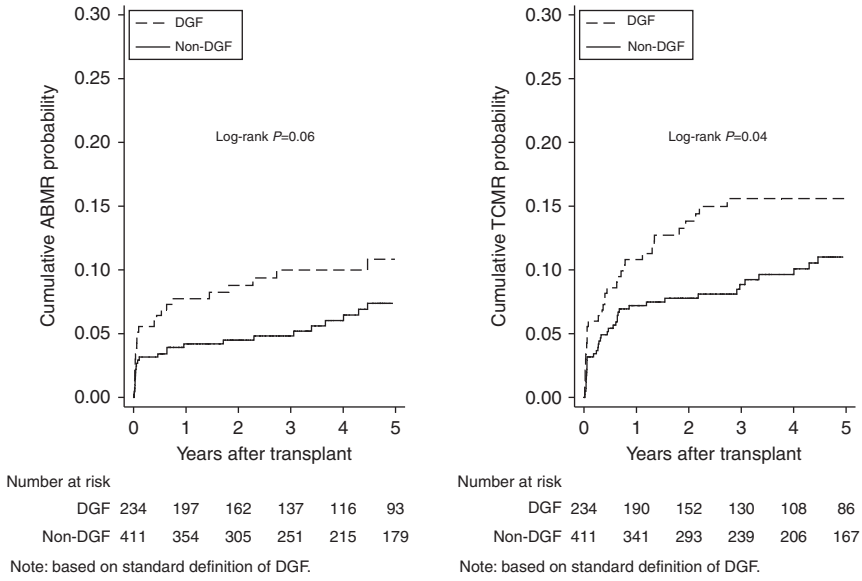

Figure 3 | Cumulative probability of acute antibody-mediated rejection (left) and acute T-cell-mediated rejection (right) according to delayed graft function (DGF) status after kidney transplantation.

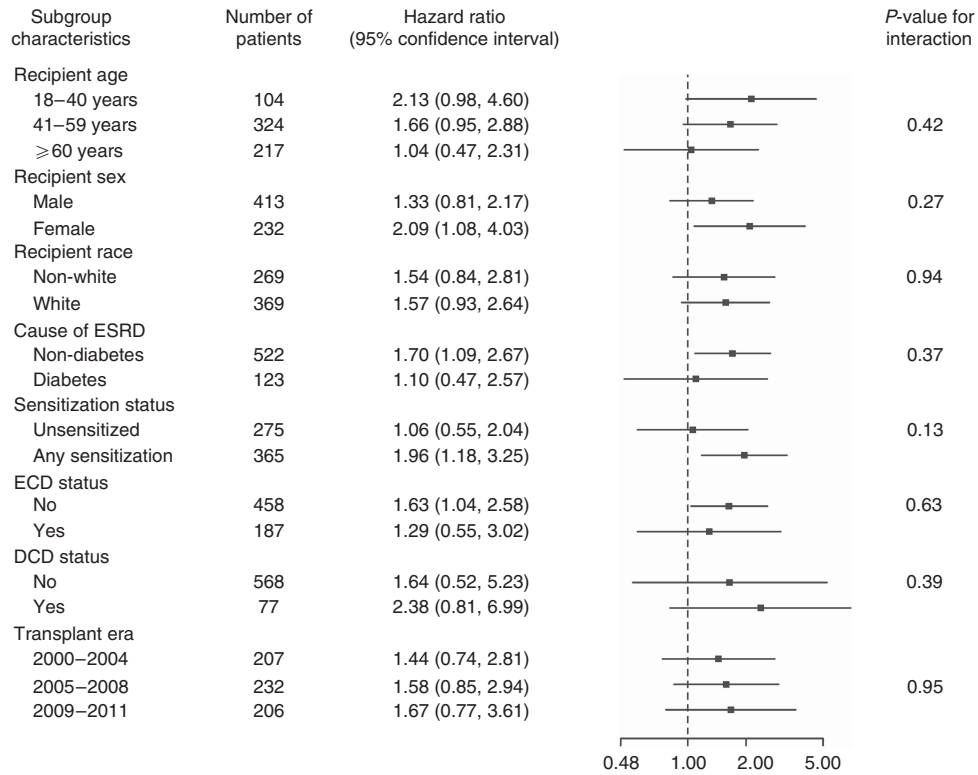

Figure 4 | Subgroup analyses for the association of delayed graft function and biopsy-proven acute rejection. DCD, donation after circulatory death; ECD, expanded criteria donor; ESRD, end-stage renal disease.

The definition of DGF has been shown to impact on the results of studies examining DGF as a risk factor or an end point.[7,8] To determine whether the association of DGF and BPAR was sensitive to the DGF definition used, we conducted additional analyses that accounted for different definitions of DGF. We chose definitions that were most commonly used in the published literature.[8] These analyses confirm that the point estimates remain elevated regardless of the definition

used. However, the definitions that simultaneously incorporated measures of kidney function and the need for dialysis (definitions 5 and 6) generally showed a more attenuated association when compared with the definitions using the need for dialysis alone. As noted in a recent systematic review,[8] the use of treatment-based diagnostic criteria for DGF (i.e., the need for dialysis in a specific time frame) is an important limitation and reinforces the need to develop a more pathophysiologically relevant definition of DGF.[33]

The strengths of our study are the detailed data elements available for analysis from our Comprehensive Renal Transplant Research Information System (CoReTRIS) database, the evaluation of various DGF definitions, our comprehensive multivariable modeling strategy, and the continued relevance of the study question to the clinical practice of kidney transplantation. Despite these strengths, there are some limitations that deserve mention. First, we did not have repeated measures of donor-specific antibodies to determine whether the development of these antibodies is increased in patients with DGF. However, the relative impact of DGF on TCMR and ABMR appeared to be comparable in our study population. Second, we did not have stored samples to assess the relevance of specific serum or urinary biomarkers of acute kidney injury to the likelihood of subsequent alloimmune insults to the allograft. Third, although this is one of the largest single-center studies on the topic, the precision of some our estimates may not have been to sufficient to show smaller associations. Finally, the potential for residual confounding is a perennial problem in observational studies. However, we made every attempt to adjust for all relevant measured confounders using multivariable modeling to increase the validity of the inferences made from our data.

In summary, our study highlights the continued importance of DGF as a risk factor for acute rejection in kidney transplantation. Our results emphasize the importance of optimizing immunosuppression in patients with DGF, particularly in those who are otherwise low immunologic risk. In addition, more intensive surveillance of these patients, both with respect to immunosuppressive drug level monitoring and graft structure/function, may mitigate the incidence and implications of acute rejection events. The role of novel biomarkers to predict the risk of acute rejection in patients experiencing DGF and the impact of newer interventions (such as complement inhibitors) to reduce the incidence of DGF (and its potential sequelae such as acute rejection) require further study.

MATERIALS AND METHODS

Study design and participants

This is an observational cohort study of all eligible adult (≥18 years) kidney transplant recipients at the Toronto General Hospital, University Health Network, Toronto, Canada transplanted from 1 January 2000 to 31 December 2011. Exclusion criteria included living donor kidney transplants, kidney transplants performed at outside institutions, receipt of a simultaneous or a prior non-kidney transplant, and primary non-function of the kidney allograft. Patient follow-up was initiated at the time of transplant and continued until the earliest of BPAR, graft loss, death, loss to follow-up, or the conclusion of the observation period. The minimum follow-up time was 6 months.

Data sources

All data for this study were retrieved from our in-center research database, the CoReTRIS. CoReTRIS contains an extensive set of recipient, donor, transplant, laboratory, pathology, treatment, and follow-up data on all patients receiving kidney transplants at the Toronto General Hospital since 1 January 2000. These data have been abstracted from patient charts (electronic and paper), entered into the database, and audited for completeness and accuracy.[34]

Immunosuppression

All recipients universally received either depleting or non-depleting induction therapy. Maintenance immunosuppression included a calcineurin inhibitor, mycophenolate mofetil, and prednisone. Prior to 2007, the first-line calcineurin inhibitor was cyclosporine microemulsion with C2 level monitoring. Subsequently, tacrolimus with trough level monitoring became the first-line calcineurin inhibitor. BPAR was treated with intravenous corticosteroids, rabbit anti-thymocyte globulin, intravenous immunoglobulin, plasmapheresis, and/or rituximab. The specific therapies were chosen based on the type and severity of BPAR.

Patient follow-up

Upon discharge from their transplant admission, patients are followed at the Toronto General Hospital Kidney Transplant Clinic weekly for 1 month, biweekly for 2 months, monthly from months 4–6, bimonthly from months 7–12, every 3–4 months from 13 to 24 months, and then every 6–12 months beyond 24 months. Routine blood work is performed three times per week for 2 weeks after discharge, then twice per week for 2 weeks, weekly for 4 weeks, biweekly from months 3–6, monthly from months 7–12, and then every 2–3 months beyond 12 months.

Exposure assessment and classification

The exposure of interest was DGF, defined as the need for ≥1 dialysis session within the first week after kidney transplantation (i.e., the standard definition of DGF). Six alternate definitions of DGF were also applied to test the robustness of the DGF–BPAR association. These definitions were as follows: (i) the need for at least two sessions of dialysis in the first week after transplant; (ii) the need for at least one session of dialysis within 24 h of transplant; (iii) the need for at least one session of dialysis within 48 h of transplant; (iv) the need for at least one session of dialysis within 72 h of transplant; (v) definition 2 or urine output <1 liter and <25% drop in serum creatinine (vs. baseline) within 24 h of transplant; and (vi) definition 4 or serum creatinine decrease <10% per day for 3 consecutive days from the time of transplant.[8]

Outcome assessment and classification

The primary outcome was BPAR, based on for-cause biopsies, reviewed by a renal pathologist, and classified using the Banff criteria.[35] Patients were censored if they were transferred to another institution, lost to follow-up, experienced graft failure, or died. BPAR was further classified as either TCMR or ABMR. Acute rejection was suspected in patients with an unexplained fixed rise in serum creatinine of at least 15% vs. baseline. Sub-therapeutic immuno-

suppressive drug levels and/or the development of donor-specific antibodies were considered supportive information in conjunction with a reduction in kidney function. C4d staining was routinely available at the Toronto General Hospital starting in 2004. Preemptive donor-specific antibody monitoring was initiated on incident kidney transplant recipients in 2013 (i.e., after the cohort entry period).

Potential confounders

The following potential confounders were examined in multivariable models: (i) recipient factors (age, sex, race, cause of ESRD, body mass index, peak panel reactive antibody level, time on dialysis); (ii) donor factors (age, sex, race, body mass index, preterminal serum creatinine, cause of death, and DCD status); and (iii) transplant factors (cold ischemia time, type of calcineurin inhibitor, number of human leukocyte antigen mismatches, re-graft status, and transplant era).

Subgroup analyses

Clinically relevant subgroups were identified *a priori* and analyzed for the presence of effect measure modification. These subgroups were based on recipient age (18–40 vs. 41–60 vs. >60 years), sex, race (white vs. non-white), cause of ESRD (diabetes vs. non-diabetes), sensitization status, ECD status, and transplant era (2000–2004 vs. 2005–2007 vs. 2008–2011).

Statistical analyses

The distributions of baseline characteristics across DGF categories were evaluated using parametric and nonparametric tests as appropriate. The cumulative probabilities of time-to-BPAR were graphically assessed using the Kaplan–Meier product limit method, and differences across survival distributions were examined using the log-rank test. The risk for BPAR was evaluated in a Cox proportional hazards model, adjusting for potential confounders. Models were sequentially fit with an expanding set of covariates. These covariates were chosen based on clinical judgment and prior literature. A backward stepwise selection procedure was also applied to covariate selection to determine the robustness of the DGF-BPAR hazard ratio to the model fitting procedure (see Supplementary Appendix, SA-5 online, for more details). Plots of the Schöenfeld residuals and the log(cumulative hazard) functions were constructed to assess the proportional hazards assumption. No important departures were detected. We used the method of multiple imputation to impute missing covariate data (see Supplementary Appendix, SA-5 online, for more details).[36]

The Research Ethics Board at the Toronto General Hospital approved this study. All statistical analyses were performed using Stata/MP 12.1 (StataCorp, College Station, TX). A two-sided $P<0.05$ was considered statistically significant.

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

SA-1. Table of missing data for the variables used in the analysis.
SA-2. Tacrolimus and cyclosporine levels over the first year posttransplant stratified by delayed graft function status (standard definition).
SA-3. Cumulative incidence function for biopsy-proven acute rejection as a function of delayed graft function status with graft failure or death with graft function as competing events.
SA-4. Cox proportional subdistribution hazards models for the risk of biopsy-proven acute rejection by delayed graft function status (standard definition) with graft failure or death with graft function as competing events.
SA-5. Stepwise variable selection and dealing with missing data.
Supplementary material is linked to the online version of the paper at http://www.nature.com/ki

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