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Delayed Graft Function Among Kidney Transplant Recipients Is Associated With an Increased Risk of Urinary Tract Infection and BK Viremia

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Background. Delayed graft function (DGF) among deceased donor kidney transplant recipients (DDKTRs) is a well-known risk factor for allograft rejection, decreased graft survival, and increased cost. Although DGF is associated with an increased risk of rejection, it is unclear whether it also increases the risk of infection. **Methods.** We reviewed all adult DDKTRs at our center between 2010 and 2018. The primary outcomes of interest were BK viremia, cytomegalovirus viremia, pneumonia, and urinary tract infection (UTI) within the first year of transplant. Additional analysis was made with censoring follow-up at the time of allograft rejection. **Results.** A total of 1512 DDKTRs were included, of whom 468 (31%) had DGF. As expected, several recipient, donor, and baseline immunological characteristics differed by DGF status. After adjustment, DGF was significantly associated with an increased risk of BK viremia (hazard ratio: 1.34; 95% confidence interval, 1.0-1.81; $P=0.049$) and UTI (hazard ratio: 1.70; 95% confidence interval, 1.31-2.19; $P<0.001$) but not cytomegalovirus viremia or pneumonia. Associations were similar in models censored at the time of rejection. **Conclusions.** DGF is associated with an increased risk of early infectious complications, mainly UTI and BK viremia. Close monitoring and appropriate management are warranted for better outcomes in this unique population.

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The overall incidence of delayed graft function (DGF) among kidney transplant recipients (KTRs) is on the rise because of the increasing use of marginal kidneys.[1] Based on the United States Renal Data System and Scientific Registry of Transplant Recipients data, the rate of DGF was 14.7% among deceased donors transplanted between 1985 and 1992. That has doubled to 29% between 2010 and 2018.[2-4] The incidence is >45% among donation after circulatory death (DCD) transplant recipients.[4]

Although there are multiple definitions of DGF, the most common definition, and that used by the United Network of Organ Sharing, is the need for dialysis within the first week after transplant.[5] DGF is associated with increased resource utilization, higher rates of rejection, and worse graft and patient survival.[6]

DGF is the clinical manifestation of ischemia–reperfusion injury.[7] Although the exact mechanism of the increased risk of rejection is not clear, it is believed that low perfusion in the donor leads to increased vascular tone, arteriolar vasoconstriction, and kidney injury. In the process of graft implantation and reperfusion, this damaged kidney augments the injury through multiple mechanisms, including complement activation, free radical accumulation, peroxynitrite-induced apoptosis, reactive oxygen species–mediated signaling, and cell stress–derived overexpression of proinflammatory biomolecules. These lead to the activation and recruitment of antigen-presenting cells, their migration to the secondary lymphoid tissue, and subsequent alloantigen presentation to T lymphocytes. In summary, the underlying injury of DGF gives rise to immunologic responses that link it to rejection.[8,9]

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Additionally, severe kidney injury is an inflammatory process leading to a rise in inflammatory markers.[10,11] Systemic inflammation may impair the normal immune system, leading to increased susceptibility to infections.[12] Additionally, the stress response to surgery includes dysregulation of both innate immunity and cell-mediated adaptive immunity.[13] This may also account for the increased incidence of upper respiratory tract infections, disruption in wound healing, and psychosocial stress when patients undergo surgery.[14] Although multiple studies have demonstrated an increased risk of rejection among recipients with DGF, limited studies address whether these recipients are also at increased risk for infections. Given the complex interaction between ischemia–reperfusion injury and dysregulation of the immune system, we hypothesized recipients with DGF will also be at increased risk of infection after kidney transplantation.

Infections are also common complications after kidney transplants, mainly within the first year of the transplant. The prevalence of BK viremia within 1 y after transplantation is approximately 20%.[15] Cytomegalovirus (CMV) infection after discontinuation of prophylaxis (usually 3–6 mo) is associated with late-onset CMV disease at around 18%.[16] Similarly, the prevalence of urinary tract infection (UTI) among KTRs varies widely from 23% to 75%, mainly occurring within the first 3 to 6 mo posttransplant.[17] Although high, the exact prevalence and cause of pneumonia posttransplant are unknown; however, most bacterial pneumonia occurs within 1 y after transplantation.[18] In this study, we looked for 4 common aforementioned posttransplant infections within the first year of kidney transplant and compared them with those who had DGF versus those who did not have DGF.

MATERIALS AND METHODS

Study Population and Design

We studied all adult deceased donor kidney transplants (DDKTs) at the University of Wisconsin-Madison between 2010 and 2018. These dates were chosen to reflect more current approaches to immunosuppressive management and any infectious confounding associated with the COVID-19 pandemic. All data were collected prospectively. Recipients aged <18 y at the time of transplant and multiorgan recipients were excluded. We also excluded living donor KTRs, as DGF among living donor recipients is uncommon and has different mechanisms and risk factors compared with DDKT recipients (DDKTRs).[19] Recipients were divided into 2 groups based on the posttransplant need for dialysis: DGF group and no DGF group. Additional models considered rejection as a censoring event before infections within the first year of the transplant were induced. If recipients had rejections during the study period, they were included only before the rejection to assess the risk for infections. This additional model was intended to overcome the bias of rejection treatment leading to infections. This study was approved by the institutional review board of the University of Wisconsin Health Sciences (protocol number: 2014-1072). This study was in adherence to the Declaration of Helsinki. The clinical and research activities being reported were consistent with the Principles of the Declaration of Istanbul as outlined in "The Declaration of Istanbul on Organ Trafficking and Transplant Tourism." Due to the nature of the study, informed consent from study patients pertinent to this study was not obtained.

Variables and Definitions

DGF was defined as the need for dialysis within the first 7 d posttransplant.[20] All infections among the DGF group were after the diagnosis of DGF. BK infection was defined as BK polyomavirus (BKV) DNAemia (viremia) >1000 copies/mL from plasma via molecular diagnostic testing (polymerase chain reaction [PCR]) or a positive allograft biopsy for a simian virus 40 T antibody on staining for BKV-associated nephropathy. CMV infection was defined as viremia via molecular diagnostic testing (PCR) from plasma or biopsy-proven end-organ disease. UTI was defined by clinical symptoms and significantly positive urine culture. All UTIs were treated with appropriate antibiotics. Asymptomatic UTI was not included. Pneumonia was diagnosed on the basis of consistent radiological findings, along with clinical symptoms or significantly positive sputum culture. If recipients had >1 aforementioned infection complication, they were included in the analysis for risk of all infections.

Baseline patients' characteristics were collected and divided into donor-related, recipient-related, and immunological factors. Donor-related factors include age, gender, race, body mass index (BMI), cause of death, terminal serum creatinine, Kidney Donor Profile Index, DCD status, and cold ischemia time. Recipient-related factors include age, gender, race, BMI, cause of end-stage kidney disease, induction immunosuppression received, history of early steroid withdrawal, preemptive transplant, and CMV high-risk serostatus (D^+/R^-). Immunological factors included panel-reactive antibody, mean HLA mismatch, and history of previous transplant.

Immunosuppressive Protocols

Most KTRs at our center receive induction with either a depleting agent (antithymocyte globulin or alemtuzumab) or a nondepleting agent (basiliximab) followed by a triple immunosuppressant regimen predominantly consisting of tacrolimus, mycophenolic acid, and prednisone as described before.[21] Although not formally protocolized, DDKTRs at risk for DGF usually receive antithymocyte globulin for induction based on the transplant surgeon's discretion, given literature suggesting reduced rates of DGF with antithymocyte induction.[20,22]

Outcomes, Monitoring, and Prophylaxis Protocols

We investigated the incidence of 4 common posttransplant infections: BK infection, CMV infection, UTI, and pneumonia, within 1 y posttransplant. We limited outcomes up to 1 y posttransplant to better correlate the effect of DGF and early posttransplant infectious complications.

Posttransplant quantitative serum BK PCR is monitored every 2 wk for the first 3 mo, monthly for months 3 to 12, and at the time of a kidney allograft biopsy. Additionally, BK PCR is monitored every 2 wk while treating allograft rejection. Recipients with detectable serum BK PCR are monitored every 2 wk until BK PCR is negative 3 consecutive times. Throughout the study period, monitoring and treatment protocols for BKV were stable. Real-time PCR chemistry based on the principles of fluorescence resonance energy transfer was used during the entire study period. The threshold for detection of BKV is 250 to 10 000 000 copies/mL with a minimum detection limit of 50 copies/mL, which did not change during the study period.

CMV prophylaxis protocols at our center were relatively stable throughout the study period. Valganciclovir at a renally

adjusted dose of 900 mg/d was used in the high-risk population donor-positive and recipient-negative (D^+/R^-), as well as seropositive patients (D^+, D^-/R^+) receiving lymphocyte depletion induction for 6 mo as described before.[23] Our center uses universal CMV prophylaxis with preventative antiviral therapy initiated within 72 h of transplant. Throughout the study period, the methodology for detecting and quantifying CMV viral load was unchanged. Our center used quantitative CMV nucleic acid amplification PCR testing throughout the study period. CMV viral load monitoring was not routinely done during prophylactic antiviral therapy, and during the study period, we did not practice protocolize surveillance monitoring after the completion of prophylaxis.

The prophylaxis for pneumocystis pneumonia was stable during the study period with patients receiving trimethoprim–sulfamethoxazole for 12 mo posttransplant with doses ranging from 160 to 800 mg 3 times per week to daily based on renal function. Monitoring for all UTIs and pneumonia was based on clinical signs and symptoms.

DGF and Regular Clinic Follow-up

Patients with DGF are followed up as outpatients in our dedicated DGF clinic as previously described. These patients are either discharged home (if local) or to a nearby hotel with a support person, with a scheduled clinic visit within 1 to 3 d of discharge. If dialysis is deemed necessary, an appointment is scheduled in the inpatient dialysis unit of the hospital that same day. If no improvement in graft function is noted within 7 to 14 d after transplantation, a kidney transplant biopsy is performed.[24,25]

We follow our KTRs at the University Hospital or various outreach regional clinics. After discharge from an initial kidney transplant admission or discharge from the DGF clinic, patients are typically seen at posttransplant times of 3 wk, 6 wk, 3 mo, 6 mo, 9 mo, 12 mo, 18 mo, 24 mo, and then annually. All patients have routine laboratory tests completed at our center before the clinic visit and this would overcome the bias of laboratory variabilities. All major health events, including earlier mentioned infectious complications, are managed by our transplant team. If deemed necessary for admission, we prefer patients to be admitted to the University Hospital, especially within the first year of transplant. Even if they are admitted to outside centers, all complications are documented in our master database. Therefore, it is unlikely that any of the outcomes of interest would have been missed.

Statistical Analyses

Baseline characteristics were compared using the chi-square test or *t* tests, as appropriate. Bivariable and multivariable logistic regression models and Cox proportional hazards regression models with a 95% confidence interval (CI) were used to assess associations of DGF with the risk of infection. All variables from baseline characteristics were included in multivariable analyses, which include donor factors, immunological factors, and recipient factors as listed in Table 1. Kaplan-Meier survival analysis for each infection was created comparing DGF versus no DGF. Additional models considered rejection as a censoring event. A P value of ≤0.05 was considered statistically significant. All analyses were conducted using Stata software (version SE 15; Stata-Corp LLC, College Station, TX).

RESULTS

A total of 1512 DDKTRs were included, of whom 468 (31%) had DGF (Table 1). Donors of those with DGF were older ($P<0.001$); were less likely to be non-White ($P=0.01$); had higher BMI ($P<0.001$), higher terminal serum creatinine ($P=0.004$), and higher Kidney Donor Profile Index ($P<0.001$); were more likely to be DCD donors ($P<0.001$); and had higher HLA mismatches ($P=0.02$) than donors of those without DGF. Recipients with DGF were less likely to be female ($P<0.001$); had higher BMI ($P<0.001$), their end-stage kidney disease from diabetes ($P=0.01$), received antithymocyte globulin for induction ($P<0.001$), and were less likely to be preemptive KTRs ($P<0.001$) than their counterparts without DGF.

Within the first year of transplant, a total of 240 KTRs (16%) had BK infection, 145 (10%) had CMV infection, 313 (21%) had UTI, and 78 (5%) had pneumonia (Table 2). The median interval from transplant to BK was 91 (interquartile range [IQR], 60–166) d, to CMV was 163 (IQR, 91–235) d, to UTI was 42 (IQR, 19–114) d, and to pneumonia was 115 (IQR, 64–191) d. When censoring infection for the time of rejection, 237 had BK, 125 had CMV, 307 had UTI, and 75 had pneumonia (Table 3).

In unadjusted models, there was a tendency for increased risk of BKV (hazard ratio [HR]: 1.26; 95% CI, 0.95-1.62; $P=0.12$; Table 2; Figure 1). DGF was significantly associated with a higher risk of BKV after adjustment for baseline characteristics (aHR: 1.34; 95% CI, 1.0-1.81; $P=0.049$).

The risk for CMV was not significantly associated with DGF either in an unadjusted (HR: 1.17; 95% CI, 0.82-1.65; $P=0.39$) or adjusted model (adjusted HR [aHR]: 1.20; 95% CI, 0.82-1.76; $P=0.35$; Figure 2).

In unadjusted models, there was a tendency for increased risk of UTI (HR: 1.60; 95% CI, 1.28-2.02; $P<0.001$). DGF was significantly associated with a higher risk of UTI after adjustment for baseline characteristics (aHR: 1.70; 95% CI, 1.31-2.19; $P<0.001$; Figure 3).

The risk for pneumonia was not significantly associated with DGF either in an unadjusted (HR: 1.49; 95% CI, 0.94-2.36; $P=0.09$) or adjusted model (aHR: 1.34; 95% CI, 0.81-2.2; $P=0.25$; Figure 4).

The analysis censoring at the time of rejection included fewer infection events, with 3 fewer cases of BK, 19 fewer cases of CMV, 6 fewer cases of UTI, and 3 fewer cases of pneumonia. Similar estimates were observed in models censoring at the time of biopsy-proven rejection (Table 3).

DISCUSSION

DGF was significantly associated with an increased risk of UTI and BK viremia within 1 y posttransplant in this large cohort of DDKTRs. Although there was a trend for increased risk of CMV and pneumonia, these associations were not statistically significant.

There are no definitive interventions or management to reduce the rates of complications associated with DGF. Most of the current studies have been in the field of identifying risk factors and some of the noninfection complications associated with DGF, mainly focusing on rejection. In this study, we focused exclusively on the common infectious complications and observed increased risk for some of the common infections. A similar observation of DGF being associated with an

TABLE 1.

Baseline characteristics

		DGF (n = 468)	No DGF (n = 1044)	*P*
Donor factors	Mean age (y)	45.9 (13.9)	40.5 (16.3)	<0.001
	Female, n (%)	160 (34.2)	411 (39.4)	0.06
	Non-White, n (%)	29 (6.2)	107 (10.2)	0.01
	Mean BMI	30.1 (7.9)	28.5 (7.8)	<0.001
	Cause of death: cardiovascular, n (%)	136 (29.1)	288 (27.6)	0.56
	Terminal serum creatinine (mg/dL)	1.00 (0.60)	0.91 (0.46)	0.004
	Mean Kidney Donor Profile Index (%)	51.9 (21.7)	46.3 (20.7)	<0.001
	Donation after circulatory death, n (%)	241 (51.5)	240 (23.0)	<0.001
	Cold ischemia time (h)	15.7 (6.4)	15.9 (6.0)	0.48
Immunologic factors	cPRA >20%, n (%)	145 (31.0)	330 (31.6)	0.81
	Mean HLA mismatch (of 6)	4.1 (1.4)	3.9 (1.5)	0.02
	Previous transplant, n (%)	98 (20.9)	209 (20.0)	0.68
Recipients factors	Mean age (y)	53.5 (12.4)	52.6 (12.6)	0.22
	Female, n (%)	143 (30.6)	423 (40.6)	<0.001
	Non-White, n (%)	145 (31.0)	236 (31.2)	0.93
	Mean BMI	29.3 (4.9)	28.0 (5.3)	<0.001
	Causes of ESRD, n (%)			0.01
	Diabetes	148 (31.6)	250 (23.9)	
	Hypertension	81 (17.3)	170 (16.3)	
	Glomerulonephritis	101 (21.6)	276(26.6)	
	Polycystic kidney disease	45 (9.6)	130 (12.5)	
	Other	93 (19.9)	217 (20.8)	
	Induction immunosuppression, n (%)			<0.001
	Alemtuzumab	61 (13.0)	87 (8.3)	
	Antithymocyte globulin	228 (48.7)	427 (40.9)	
	Basiliximab	179 (38.3)	531 (50.9)	
	Preemptive transplant, n (%)	12 (2.5)	166 (15.9)	<0.001
	CMV high risk (D^+/R^-), n (%)	90 (19.2)	183 (17.5)	0.43

BMI, body mass index; CMV, cytomegalovirus; cPRA, calculated panel-reactive antibody; D/R, donor and recipient; DGF, delayed graft function; ESRD, end-stage renal disease.

TABLE 2.

Risk for infections

		Unadjusted			Adjusted[a]		
Complications		**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
BK (n = 240)	No DGF	Ref	Ref	Ref	Ref	Ref	Ref
	DGF	1.26	0.95-1.62	0.12	1.34	1.00-1.81	0.049
CMV (n = 145)	No DGF	Ref	Ref	Ref	Ref	Ref	Ref
	DGF	1.17	0.82-1.65	0.39	1.20	0.82-1.76	0.35
UTI (n = 313)	No DGF	Ref	Ref	Ref	Ref	Ref	Ref
	DGF	1.60	1.28-2.02	<0.001	1.70	1.31-2.19	<0.001
Pneumonia (n = 78)	No DGF	Ref	Ref	Ref	Ref	Ref	Ref
	DGF	1.49	0.94-2.36	0.09	1.34	0.81-2.21	0.25

[a]Adjusted for all baseline characteristics.
CI, confidence interval; CMV, cytomegalovirus; DGF, delayed graft function; HR, hazard ratio; UTI, urinary tract infection.

increased risk of infections was reported by Guimarães-Souza et al.[26] In their study, the authors categorized KTRs into 3 groups: immediate graft function (>30% decrease in serum creatinine on the second day of transplant), slow graft function (<30% decrease in serum creatinine on the second day of transplant), and DGF as need for dialysis within the first week of transplant. They reported slow graft function and DGF to have a higher rate of viral infections within 2 y of transplant at 46% for each compared with 31% among immediate graft function ($P = 0.05$).[26] The authors hypothesized that this observation could be related to some degree of immunosuppression secondary to uremic toxins, as patients with kidney disease are more susceptible to infections.[27] Similar to our study, a few studies report a 1.5 to 4 times higher risk of UTI among recipients with DGF.[28-30] The authors hypothesized that increased risk of UTI among patients with DGF could be related to low urine output and poor immune system.

In contrast to our study, a few studies showed no association between DGF and BK viremia.[31,32] Budhiraja et al[33] found that among 1714 DDKTs, of whom 59.4% had DGF, the rate of BK viremia within the first year of the transplant was not significantly different between those with and without DGF ($P = 0.24$); 116 (16.7%) in no DGF, 106 (14.2%) in DGF lasted ≤14 d, 31 (14.3%) in DGF lasted 15 to 28 d, and 4 (7.7%) in DGF lasted >28 d. A few studies assessed the associations of prolonged cold ischemia time and DCD kidneys,

TABLE 3.

Risk for infections censored to the time of rejection

		Unadjusted			Adjusted[a]		
Complications		**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
BK (n = 237)	No DGF	Ref	Ref	Ref	Ref	Ref	Ref
	DGF	1.23	0.94-1.61	0.14	1.33	0.99-1.80	0.06
CMV (n = 126)	No DGF	Ref	Ref	Ref	Ref	Ref	Ref
	DGF	1.02	0.69-1.50	0.92	1.05	0.69-1.60	0.83
UTI (n = 307)	No DGF	Ref	Ref	Ref	Ref	Ref	Ref
	DGF	1.61	1.28-2.03	<0.001	1.72	1.33-2.23	<0.001
Pneumonia (n = 75)	No DGF	Ref	Ref	Ref	Ref	Ref	Ref
	DGF	1.43	0.90-2.30	0.13	1.26	0.75-2.11	0.38

[a]Adjusted for all baseline characteristics.

CI, confidence interval; CMV, cytomegalovirus; DGF, delayed graft function; HR, hazard ratio; UTI, urinary tract infection.

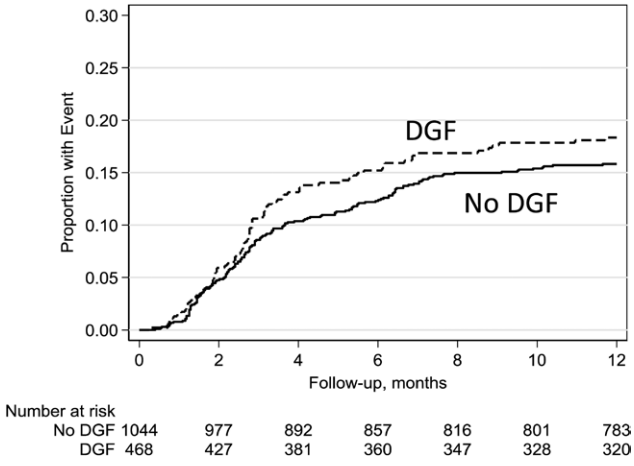

FIGURE 1. Kaplan-Meier analysis curve comparing the proportion of BK polyomavirus infection between 2 groups. DGF, delayed graft function.

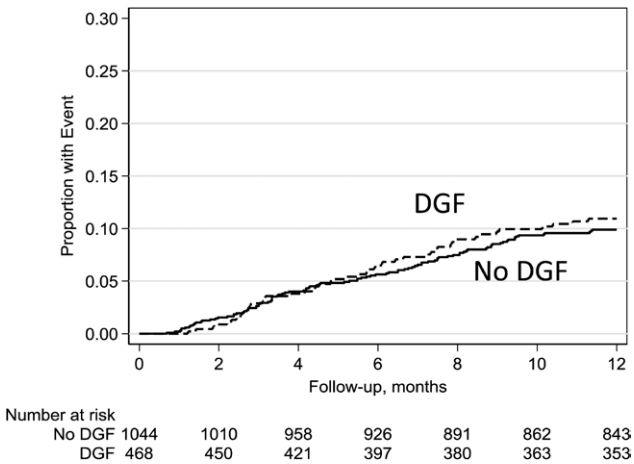

FIGURE 2. Kaplan-Meier analysis curve comparing the proportion of cytomegalovirus infection between 2 groups. DGF, delayed graft function.

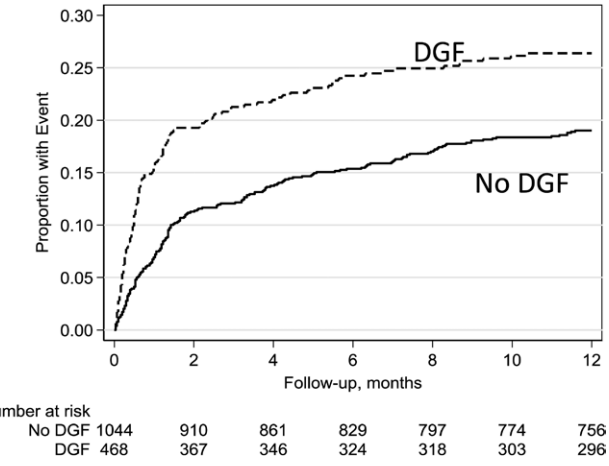

FIGURE 3. Kaplan-Meier analysis curve comparing the proportion of urinary tract infection between 2 groups. DGF, delayed graft function.

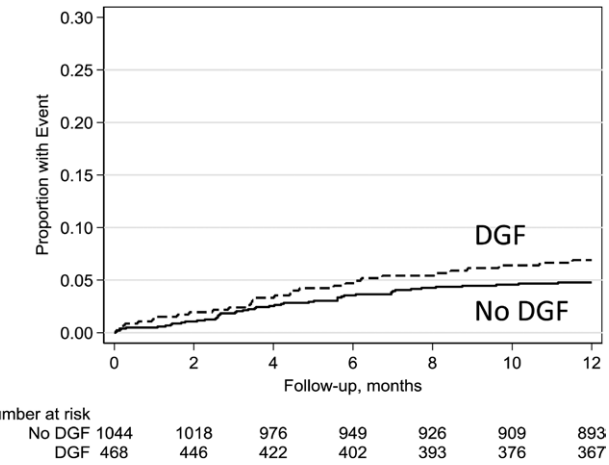

FIGURE 4. Kaplan-Meier analysis curve comparing the proportion of pneumonia between 2 groups. DGF, delayed graft function.

which are also important risk factors for DGF, and found an increased risk of BK replication likely because of ischemia–reperfusion injury.[34,35]

There are mixed reports assessing the association between DGF and CMV. In contrast to our study, in 1 multicenter study among KTRs transplanted before 1998, the authors noted an increased risk of CMV among recipients with DGF; however, there was no mention of CMV prophylaxis or CMV serostatus among donors and recipients (D/R).[36] Another study also suggested an association between DGF and increased risk of CMV.[37] Even in the current era of CMV prophylaxis, Kleinherenbrink et al[38] reported an increased risk of CMV among patients with DGF, along with an increased risk of CMV disease despite valganciclovir prophylaxis, possibly

suggesting a suboptimal effect of prophylaxis among recipients with DGF. The lack of association in our study may be explained by our aggressive approach to CMV prophylaxis using 900 mg/d dose in all patients at risk, likely because of our high rates of CMV high-risk recipients (D^+/R^-) compared with centers in less rural and geographically dispersed areas.[39] Similar to our study, Freedman et al[40] found no statistically significant association between CMV and DGF when looking specifically at the CMV high-risk population.[40] Finally, in contrast to our study, assessing risk for DGF and pneumonia, a few studies reported an increased risk of pneumonia among recipients with DGF.[41-43]

This study has the expected limitations of a single-center observational study, reflecting our specific population and clinical approach. Our findings reflect our specific practice, which should be factored into the interpretation. However, this substantial data set with more granular data than are generally available in registries provides a useful basis for estimating risks and outcomes. Another potential advantage of our single-center data is that they reflect a more homogeneous clinical approach to patient selection, surgical technique, and medical management, in contrast to registry data involving multiple centers. Also, we are limited only to 4 common infectious complications up to 1 y posttransplant. However, this approach may reduce noise that could cloud our results by focusing on a more targeted analysis. Additionally, the DGF population represents a medically complex patient substrate with more hospital exposure, which may increase the risk of certain infections. However, this may be negated by the close monitoring these patients receive in the outpatient setting, resulting in early detection, improved education, and other preventative measures. A further argument against this factor acting as a confounder is the lack of increased risk of pneumonia seen in our study, which along with UTI is the most common hospital-associated infection after bloodstream infections. Furthermore, care was taken to control for important aspects of the population associated with increased infectious risk, including rejection, through statistical modeling and subgroup analysis. To the best of our knowledge, this is the first study assessing various common infections posttransplant comparing DGF and no DGF. In summary, DGF is associated with an increased risk for UTI and BK, 2 common posttransplant infections. In DGF, most of the rejection occurs within the first month of transplant, and the risk of rejection decreases further out from the time of transplant.[44] After DGF recovery, immunosuppression tailoring and maintaining lower immunosuppressive maintenance could be considered weighing risks and benefits. Also, focusing particularly on BK PCR monitoring and managing appropriately and identifying and treating UTIs early may prevent deleterious outcomes.

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