Delayed Graft Function and the Risk for Death with a Functioning Graft

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ABSTRACT

Delayed graft function (DGF) associates with an increased risk for graft failure, but its link with death with graft function (DWGF) is unknown. We used the US Renal Data System to assemble a cohort of all first, adult, deceased-donor kidney transplant recipients from January 1, 1998, through December 31, 2004. In total, 11,542 (23%) of 50,246 recipients required at least one dialysis session in the first week after transplantation. Compared with patients without DGF, patients with DGF were significantly more likely to die with a functioning graft (relative hazard 1.83 [95% confidence interval 1.73 to 1.93] and 1.53 [95% CI 1.45 to 1.63] for unadjusted and fully adjusted models, respectively). The risk for DWGF was slightly higher among women with DGF than among men. There was no significant heterogeneity among other subgroups, and the results were robust to sensitivity analyses. Acute rejection within the first year attenuated the DGF–DWGF association. Cardiovascular and infectious deaths were slightly more prevalent in the DGF group, but the relative hazards of cause-specific death were similar between DWGF and deaths during total follow-up. In summary, DGF associates with an increased risk for DWGF; the mechanisms underlying the negative impact of DGF require further study.

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Kidney transplantation has become the preferred modality for treatment of patients with ESRD. Kidney transplantation offers a survival advantage over dialysis treatment in essentially all patient subgroups[1,2]; however, the survival of kidney transplant recipients (KTR) is inferior to that of the general population.[3] Although early kidney dysfunction has a clear adverse effect on long-term allograft survival, there are fewer data on the relationship between early graft function and patient survival. In a retrospective study of 589 recipients of first deceased-donor allografts, mortality was significantly increased in patients with a primary nonfunction (*i.e.*, a graft that never functions) compared with those with less severe graft dysfunction (45 *versus* 20% at 6 yr)[4]; however, there was no significant difference in survival among patients with delayed graft function (DGF) *versus* immediate graft function.

Death can occur while the graft is functioning or after kidney allograft failure. Death with graft function (DWGF) has been reported to occur in 10 to 30% of patients.[5,6] In an analysis of the US Renal Data System (USRDS), Ojo *et al.*[7] studied 86,502 patients, 18,482 of whom died during a 10-yr period (7040 [38%] with graft function). Survival at 1, 5, and 10 yr was 97, 91, and 86%, respectively,

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Table 1. Study population characteristics by DGF status

Characteristic	DGF (n = 11,542)	No DGF (n = 38,704)
Recipient		
age (yr)		
18.0 to 34.9	1471 (12.7)	6003 (15.5)
35.0 to 49.9	3586 (31.1)	13,111 (33.9)
50.0 to 64.9	4927 (42.7)	14,928 (38.6)
≥65.0	1558 (13.5)	4662 (12.1)
gender		
male	7487 (64.9)	22,761 (58.8)
female	4055 (35.1)	15,943 (41.2)
race		
white	6505 (56.4)	25,420 (65.7)
black	4262 (36.9)	10,468 (27.1)
Asian	542 (4.7)	2147 (5.5)
other	233 (2.0)	669 (1.7)
cause of ESRD		
glomerulonephritis	2592 (22.5)	8872 (22.9)
diabetes	3785 (32.8)	11,657 (30.1)
hypertension	2697 (23.4)	7776 (20.1)
other	2044 (17.7)	8509 (22.0)
unknown/missing	424 (3.7)	1890 (4.9)
peak PRA (%)		
<10	7709 (66.8)	27,345 (70.7)
≥10	2708 (23.5)	7931 (20.5)
unknown/missing	1125 (9.7)	3428 (8.9)
time on dialysis (mo)		
none (preemptive)	140 (1.2)	2557 (6.6)
0 to 6	232 (2.0)	1916 (4.9)
6 to 12	564 (4.9)	3131 (8.1)
12 to 24	1889 (16.4)	7969 (20.6)
24 to 36	2167 (18.8)	7011 (18.1)
36 to 48	1983 (17.2)	5502 (14.2)
≥48	4567 (39.6)	10,618 (27.4)
Donor		
type		
SCD	7283 (63.1)	28,062 (72.5)
ECD	3590 (31.1)	9699 (25.1)
DCD	669 (5.8)	943 (2.4)
age (yr)		
0 to 9	336 (2.9)	1,888 (4.9)
10 to 39	3684 (31.9)	16,899 (43.7)
40 to 59	4590 (39.8)	11,712 (30.3)
≥60	1231 (10.7)	2629 (6.8)
unknown/missing	1701 (14.7)	5576 (14.4)
gender		
male	6754 (58.5)	22,933 (59.3)
female	4788 (41.5)	15,771 (40.7)
race		
white	9553 (82.8)	32,504 (84.0)
black	1288 (11.2)	4241 (11.0)
Asian	227 (2.0)	628 (1.6)
other	95 (0.8)	285 (0.7)
unknown/missing	379 (3.3)	1046 (2.7)
Study		
cause of death		
anoxia	1363 (11.8)	4,188 (10.8)
CVA/stroke	5649 (48.9)	14,224 (36.7)
head trauma	4189 (36.3)	19,077 (49.3)
CNS tumor	95 (0.8)	356 (0.9)
other	246 (2.1)	859 (2.2)
donor hypertension		
no	8171 (70.8)	31,864 (82.3)
yes	3371 (29.2)	6840 (17.7)
donor serum creatinine (mg/dl)		
<1.0	5107 (43.5)	20,704 (53.5)
1.0 to 1.4	4122 (35.7)	13,233 (34.2)
1.5 to 1.9	1428 (12.4)	3165 (8.2)
≥2.0	975 (8.5)	1602 (4.1)
cold ischemia time (h)		
0 to 12	1225 (10.6)	6976 (18.0)
12 to 24	5285 (45.8)	18,247 (47.1)
24 to 36	3145 (27.3)	7229 (18.7)
≥36	664 (5.7)	891 (2.3)
unknown/missing	1223 (10.6)	5361 (13.9)
HLA mismatches		
0	1172 (10.1)	5387 (13.9)
1	286 (2.5)	1080 (2.8)
2	830 (7.2)	2967 (7.7)
3	1948 (16.9)	6757 (17.5)
4	2761 (23.9)	8892 (23.0)
5	2795 (24.2)	8544 (22.1)
6	1495 (12.9)	4325 (11.2)
unknown/missing	255 (2.2)	752 (1.9)
induction therapy		
none	4160 (36.0)	16,139 (41.7)
depleting	3226 (28.0)	12,534 (32.4)
nondepleting	4156 (36.0)	10,031 (25.9)
transplantation era		
1998 to 2000	4691 (40.6)	15,981 (41.3)
2001 to 2002	3364 (29.1)	11,824 (30.5)
2003 to 2004	3487 (30.2)	10,899 (28.2)

Data are n (%). CNS, central nervous system; CVA, cerebrovascular accident; DCD, donation after cardiac death; ECD, expanded-criteria donor; SCD, standard-criteria donor.

among those with continued renal allograft function. Thirty-eight percent of all deaths were DWGF. This accounted for 42.5% of all graft losses. In the Cox regression analysis, DGF, along with other recipient, donor, and transplant factors, was independently and significantly associated with DWGF. Although the association between DWGF and factors such as recipient age and cause of ESRD were expected, the link between DGF and DWGF was somewhat unexpected. Of note, this analysis focused on patients who had ESRD and underwent transplantation between 1988 and 1997 in the United States. In light of the improving outcomes of kidney transplantation over time,[8] it would be important to reassess the relevance of DGF as a risk factor for DWGF in the more recent era.[7]

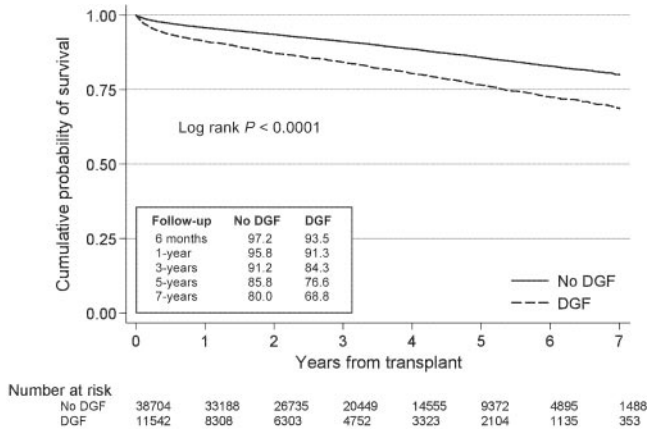

Figure 1. Kaplan-Meier curves, stratified by DGF status, for the cumulative probability of surviving with graft function during the follow-up period are shown.

Numerous studies have reported that DGF is strongly associated with graft failure; however, little work has been done to explore the link between DGF and DWGF. This is an important study end point, because DWGF accounts for half of all graft failures beyond the first year after kidney transplantation.[9] Thus, we pursued an analysis of the USRDS to determine the association between DGF and DWGF in patients who received deceased-donor kidney transplants in the modern era. In addition, we examined the potential causes of DWGF and evaluated patient subgroups that may be particularly vulnerable to the detrimental effects of DGF.

RESULTS

In total, 50,246 deceased-donor KTR from January 1, 1998, through December 31, 2004, were included in the study cohort. The median length of follow-up was 36.1 mo, which translated into 160,762 person-years at risk. A total of 11,542 (23%) patients had DGF (defined as the need for at least one dialysis session within the first week after kidney transplantation), and 7842 patients died during follow-up. These deaths represented 46.8% of all graft losses. Moreover, 5982 deaths occurred in patients with functioning grafts.

Table 1 shows the baseline characteristics of the study patients stratified by DGF status. The recipient factors that were more prevalent in the group with DGF (*versus* without DGF) were age ≥50 yr, male gender, black race, peak panel-reactive antibody (PRA) level ≥10%, and time on dialysis >36 mo. Among donor factors, expanded-criteria donors, donations after cardiac death, donor age ≥40 yr, stroke as the cause of death, history of hypertension, and a donor serum creatinine level of ≥1.5 mg/dl before organ recovery were more common among patients with DGF. Finally, among transplant factors, cold ischemia time of ≥24 h and the use of induction therapy were more frequently noted in the DGF group.

Figure 1 depicts the cumulative probability of patient survival with graft function (1 − probability of DWGF) by DGF status. The curves split early and continue to separate over time. The group with DGF had a 4.5 and 11.4% lower survival probability than the group without DGF at 1 and 7 yr of follow-up, respectively. The *P* value for the log rank test was <0.0001, indicating that the overall difference in the two survival functions was highly statistically significant.

Table 2 displays the results of Cox proportional hazard models evaluating the relation between DGF and DWGF, while adjusting for potential confounders, during the total follow-up period and conditional on 6- and 12-mo survival. We constructed sequential nested models, each incorporating a more extensive set of covariates. The unadjusted Cox model revealed that the hazard ratio (HR) for DWGF in patients with DGF (*versus* without DGF) was 1.83 (95% confidence interval [CI] 1.73 to 1.93). Adjusting for recipient (including baseline comorbidity), donor, and transplant factors attenuated the HR to 1.53 (95% CI 1.45 to 1.63). Fully adjusted Cox models for survival beyond 6 and 12 mo also showed increased HRs of 1.34 (95% CI 1.25 to 1.44) and 1.34 (95% CI 1.23 to 1.45), respectively.

Table 3 shows the independent predictors of DWGF on the basis of the fully adjusted Cox proportional hazards model. Along with DGF, older recipient age, diabetes or hypertension as the cause of ESRD, greater degree of sensitization, longer duration of dialysis before transplantation, and donor hypertension were associated with an increased risk for DWGF. Protective factors included female recipient gender, nonwhite recipient race, induction therapy, and the most recent era of transplantation (2003 through 2004).

Figure 2 reveals the distribution of causes of death by DGF

Table 2. Cox proportional hazards models for the impact of DGF on the risk for DWGF

Cox Models	Total Study Population (n = 50,246; HR [95% CI])	Survived to 6 Mo (n = 46,392; HR [95% CI])	Survived to 12 Mo (n = 41,496; HR [95% CI])
Model 1[a]	1.83 (1.73 to 1.93)	1.62 (1.51 to 1.73)	1.60 (1.49 to 1.73)
Model 2[b]	1.59 (1.51 to 1.68)	1.41 (1.31 to 1.51)	1.40 (1.29 to 1.51)
Model 3[c]	1.52 (1.44 to 1.61)	1.35 (1.26 to 1.45)	1.35 (1.25 to 1.45)
Model 4[d]	1.53 (1.44 to 1.62)	1.34 (1.25 to 1.44)	1.34 (1.24 to 1.45)
Model 5[e]	1.53 (1.45 to 1.63)	1.34 (1.25 to 1.44)	1.34 (1.23 to 1.45)

[a]DGF with no other adjustments.
[b]Model 1 with adjustment for recipient characteristics in Table 1.
[c]Model 2 with adjustment for donor characteristics in Table 1.
[d]Model 3 with adjustment for transplant characteristics in Table 1.
[e]Model 4 with adjustment for baseline comorbidity at initiation of dialysis (based on the Centers for Medicare and Medicaid Services ESRD 2728 form).

Table 3. Independent predictors of DWGF

Study Characteristic	HR	95% CI	*P*
DGF			
no	1.00	–	–
yes	1.53	1.44 to 1.62	<0.0001
Recipient age (yr)			
18 to 34	1.00	–	–
35 to 49	1.69	1.49 to 1.92	<0.0001
50 to 64	3.37	2.99 to 3.80	<0.0001
≥65	5.66	4.98 to 6.42	<0.0001
Recipient gender			
male	1.00	–	–
female	0.92	0.87 to 0.97	0.002
Recipient race			
white	1.00	–	–
black	0.92	0.86 to 0.98	0.010
Asian	0.69	0.61 to 0.79	<0.0001
other	0.81	0.67 to 0.99	0.042
Cause of ESRD			
glomerulonephritis	1.00	–	–
diabetes	2.04	1.88 to 2.20	<0.0001
hypertension	1.43	1.30 to 1.55	<0.0001
other	1.12	1.02 to 1.22	0.019
unknown/missing	1.34	1.15 to 1.55	<0.0001
Peak PRA (%)			
<10	1.00	–	–
≥10	1.11	1.04 to 1.18	0.002
unknown/missing	0.90	0.79 to 1.03	0.114
Time on dialysis (mo)			
none (preemptive)	1.00	–	–
0 to 6	1.10	0.90 to 1.35	0.349
6 to 12	1.20	1.01 to 1.42	0.044
12 to 24	1.35	1.15 to 1.57	<0.0001
24 to 36	1.50	1.28 to 1.75	<0.0001
36 to 48	1.53	1.30 to 1.79	<0.0001
≥48	1.86	1.60 to 2.17	<0.0001
DCD			
no	1.00	–	–
yes	0.97	0.82 to 1.14	0.695
Donor age (yr)			
0 to 10	1.00	–	–
10 to 40	0.86	0.75 to 0.98	0.029
40 to 60	1.01	0.88 to 1.17	0.855
≥60	1.14	0.97 to 1.34	0.098
unknown/missing	0.96	0.83 to 1.11	0.586
Donor gender			
male	1.00	–	–
female	1.03	0.97 to 1.08	0.379
Donor race			
white	1.00	–	–
black	1.06	0.97 to 1.15	0.176
Asian	0.93	0.76 to 1.15	0.529
other	1.05	0.78 to 1.41	0.754
unknown/missing	0.98	0.83 to 1.15	0.827
Cause of death			
anoxia	1.00	–	–
CVA/stroke	1.04	0.95 to 1.14	0.432
head trauma	0.95	0.87 to 1.04	0.306
CNS tumor	0.82	0.61 to 1.10	0.182
other	0.97	0.80 to 1.17	0.741
Donor hypertension			
no	1.00	–	–
yes	1.14	1.07 to 1.21	<0.0001
Donor serum creatinine (mg/dl)			
<0.1	1.00	–	–
1.0 to 1.4	0.98	0.92 to 1.04	0.531
1.5 to 1.9	0.99	0.90 to 1.08	0.786
≥2.0	0.98	0.88 to 1.11	0.793
Cold ischemia time (h)			
0 to 12	1.00	–	–
12 to 24	1.01	0.94 to 1.10	0.694
24 to 36	1.05	0.96 to 1.14	0.294
≥36	1.07	0.92 to 1.24	0.370
unknown/missing	1.16	1.05 to 1.28	0.003
HLA mismatches			
0	1.00	–	–
1	1.15	0.98 to 1.34	0.077
2	0.91	0.81 to 1.03	0.139
3	1.02	0.93 to 1.12	0.680
4	1.02	0.93 to 1.12	0.600
5	1.03	0.94 to 1.13	0.534
6	1.15	1.03 to 1.28	0.011
unknown/missing	1.19	1.01 to 1.42	0.044
Induction therapy			
none	1.00	–	–
depleting	0.90	0.84 to 0.96	0.002
nondepleting	0.90	0.85 to 0.95	0.001
Transplantation era			
1998 to 2000	1.00	–	–
2001 to 2002	0.95	0.89 to 1.01	0.123
2003 to 2004	0.83	0.76 to 0.91	<0.0001

status for total mortality, DWGF, and death after graft loss (DAGL). The predominant causes of death in the groups with and without DGF were cardiovascular and infectious diseases, but patients with DGF exhibited a slightly higher prevalence of both causes. Interestingly, the proportion of mortality events as a result of cardiovascular disease/stroke was markedly higher in patients who died after graft loss *versus* patients who died with graft function in both groups with and without DGF. Of note, the proportion of missing data was different in patients who sustained DWGF *versus* DAGL, with the former having two-fold greater missingness than the latter.

Table 4 displays Cox models for cause-specific DWGF, DAGL, and death during the entire follow-up (*i.e.*, before or after graft failure). The HR for DWGF was increased for all causes, especially cardiovascular and infectious events; however, these cause-specific HRs for DWGF were similar for deaths occurring in patients with graft function *versus* deaths occurring during the entire follow-up period. In contrast, DGF did not significantly increase the hazard for DAGL across the various causes of mortality studied.

Table 5 shows the relation between DGF and DWGF across prespecified patient subgroups. There was a greater tendency for female recipients with DGF to experience an increased risk

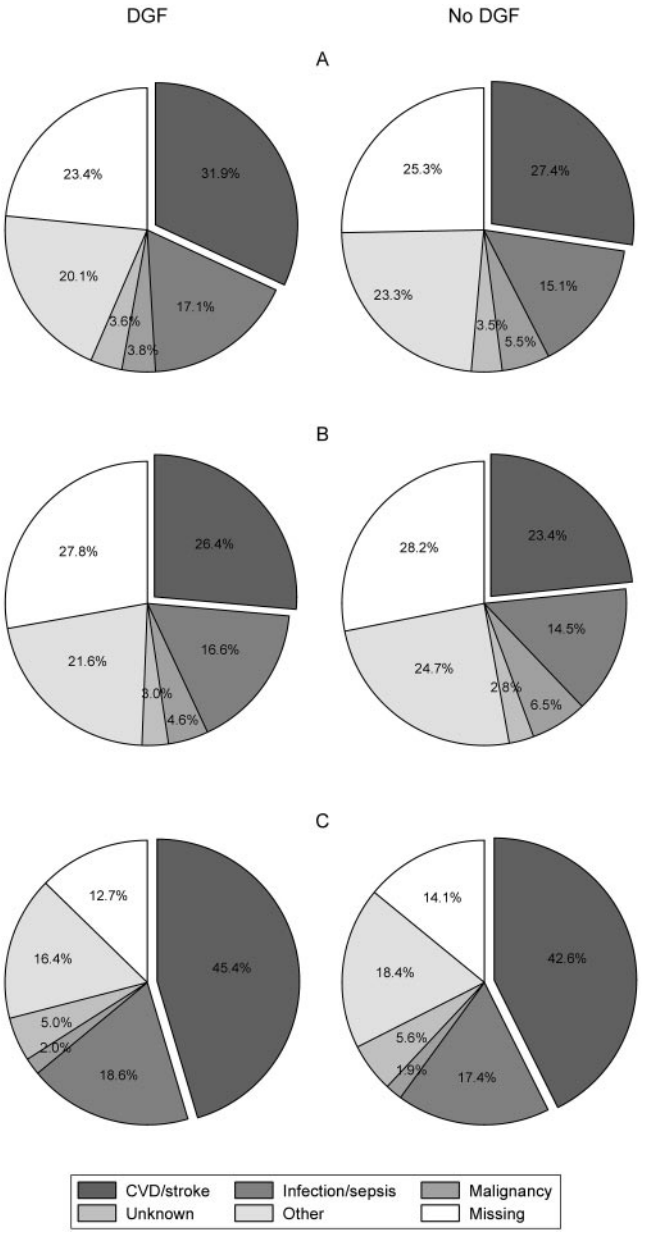

Figure 2. (A through C) Distribution of causes for all deaths (A), DWGF (B), and DAGL (C), stratified by DGF status, is shown.

for DWGF than in female recipients without DGF; however, minimal heterogeneity was observed across all other subgroups. Notably, adjustment for the occurrence of acute rejection within 6 and 12 mo of the transplantation did not appreciably change the DGF-DWGF HR in models that conditioned on allograft survival to these time points (data not shown); however, the relation between DGF and DWGF was attenuated among KTR with *versus* without an acute rejection episode in the first 6 mo (relative hazards 1.12 [95% CI 0.93 to 1.35] *versus* 1.39 [95% CI 1.27 to 1.51], respectively; $P = 0.039$ for interaction) and 12 mo (relative hazards 1.18 [95% CI 0.98 to 1.42] *versus* 1.39 [95% CI 1.26 to 1.54], respectively; $P = 0.125$ for interaction) after transplantation. The acute rejection variable displayed a significant amount of missing data (29.5 and 41.6% at 6 and 12 mo, respectively); therefore, these results were not included in Table 5.

We performed sensitivity analyses to ascertain the robustness of the main findings. First, adjustment for clustering by transplant center did not change the primary results. Second, accounting for baseline immunosuppression had little impact on the overall results. Third, using an alternative definition of DGF (<25% decline in serum creatinine during the first 24 h after transplantation) led to an attenuation of the association in the fully adjusted model (HR 1.53 [95% CI 1.45 to 1.63] *versus* HR 1.32 [95% CI 1.24 to 1.40] for the original and alternative definitions, respectively); however, the DGF-DWGF HR remained significantly elevated. Fourth, when we examined a "low-risk" subcohort (recipient age <50 yr, causes of ESRD other than diabetes or hypertension, low-level PRA, time on dialysis <24 mo), the HR for the DGF–DWGF relation remained significantly elevated (HR 1.90; 95% CI 1.20 to 3.00).

Finally, the HRs for DGF and DWGF were comparable in strata of achieved Modification of Diet in Renal Disease (MDRD) estimated GFR (eGFR) at 6 and 12 mo after transplantation (Table 6). The most prominent impact of DGF on DWGF occurred in patients with eGFR from 45 to 89 ml/min. The HR for patients missing eGFR values at each time point mirrored those of patients with eGFR 45 to 89 ml/min. The DGF rates among patients missing *versus* not missing eGFR data were 20.3 *versus* 23.8% at 6 mo and 20.1 *versus* 18.1% at 12 mo, respectively. Baseline characteristics of KTR with and without missing eGFR data were broadly similar except for a higher prevalence in the former of recipients who were younger than 50 yr, ESRD from diabetes, and transplants before 2003.

DISCUSSION

Our analysis reveals that deceased-donor KTR who experience DGF continue to show an increased risk for DWGF as compared with KTR who do not experience DGF. This association persisted after adjustment for recipient, donor, and transplant factors. The association was maintained in subgroups surviving up to 6 and 12 mo after transplantation. This finding suggests that DGF has a prolonged effect on the risk for DWGF. The major causes of death for both groups with and without DGF were cardiovascular disease/stroke, infection/sepsis, and malignancy. KTR who died with graft function were no more likely to die of a particular cause than KTR who died at any time point after transplantation. The main results were robust to various sensitivity analyses. Interestingly, DGF did not have an impact on the risk for DAGL. This supports the notion that transplant-related exposures are more important in influencing the probability of transplant-related outcomes than events after graft loss.

Interestingly, female KTR seemed to be somewhat more susceptible to the negative effects of DGF on DWGF, despite

Table 4. Impact of DGF on the risk for cause-specific DWGF, DAGL, and death during total follow-up

Cause of Death	DWGF		DAGL		Death during Total Follow-up	
	No. of Deaths	HR (95% CI)	No. of Deaths	HR (95% CI)	No. of Deaths	HR (95% CI)
CVD/stroke	1455	1.70 (1.51 to 1.90)	814	1.02 (0.87 to 1.19)	2269	1.75 (1.60to 1.91)
Infection/sepsis	908	1.76 (1.52 to 2.03)	333	0.87 (0.68 to 1.11)	1241	1.70 (1.51to 1.92)
Malignancy	351	1.31 (1.01 to 1.69)	36	1.36 (0.64 to 2.89)	387	1.27 (1.00to 1.62)
Other	1419	1.33 (1.18 to 1.51)	327	0.78 (0.61 to 1.00)	1746	1.32 (1.19to 1.47)
Unknown	171	1.64 (1.17 to 2.30)	99	0.92 (0.59 to 1.45)	270	1.64 (1.26to 2.13)
Missing	1678	1.47 (1.32 to 1.64)	251	0.84 (0.63 to 1.12)	1929	1.39 (1.25to 1.53)
Total	5982	1.53 (1.44 to 1.62)	1860	0.92 (0.83 to 1.02)	7842	1.52 (1.45to 1.60)

Death during total follow-up includes all deaths from a given cause occurring before or after graft failure. CVD, cardiovascular disease.

Table 5. Prespecified subgroup analyses

Study Characteristic	Patients (*n* [%])	HR (95% CI)	*P* for HR	*P* for Interaction
Recipient age (yr)				
18 to 34	7474 (14.9)	1.89 (1.47 to 2.42)	<0.0001	
35 to 49	16,697 (33.2)	1.52 (1.34 to 1.71)	<0.0001	0.1012
50 to 64	19,855 (39.5)	1.58 (1.46 to 1.71)	<0.0001	
≥65	6220 (12.4)	1.39 (1.23 to 1.55)	<0.0001	
Recipient gender				
male	30,248 (60.2)	1.47 (1.37 to 1.57)	<0.0001	0.0464
female	19,998 (39.8)	1.65 (1.50 to 1.81)	<0.0001	
Recipient race				
white	31,925 (63.5)	1.58 (1.47 to 1.70)	<0.0001	
black	14,730 (29.3)	1.45 (1.31 to 1.60)	<0.0001	0.5171
Asian	2689 (5.3)	1.43 (1.08 to 1.91)	0.013	
other	902 (1.8)	1.55 (1.03 to 2.33)	0.037	
Cause of ESRD				
diabetes	15,442 (30.7)	1.57 (1.46 to 1.70)	<0.0001	0.2594
not diabetes	34,804 (69.3)	1.48 (1.36 to 1.61)	<0.0001	
Peak PRA (%)				
<10	35,054 (69.8)	1.52 (1.42 to 1.63)	<0.0001	
≥10	10,639 (21.2)	1.57 (1.40 to 1.76)	<0.0001	0.7319
unknown/missing	4553 (9.1)	1.41 (1.09 to 1.82)	0.009	
Donor type				
SCD	35,345 (70.3)	1.56 (1.45 to 1.68)	<0.0001	
ECD	13,289 (26.5)	1.48 (1.35 to 1.63)	<0.0001	0.5671
DCD	1612 (3.2)	1.39 (1.01 to 1.90)	0.043	
Induction therapy				
depleting	14,187 (28.2)	1.53 (1.38 to 1.71)	<0.0001	
nondepleting	15,760 (31.4)	1.63 (1.47 to 1.81)	<0.0001	0.2364
none	20,299 (40.4)	1.46 (1.34 to 1.59)	<0.0001	
Transplantation era				
1998 to 2000	20,672 (41.1)	1.48 (1.37 to 1.59)	<0.0001	
2001 to 2002	15,188 (30.2)	1.64 (1.48 to 1.82)	<0.0001	0.2629
2003 to 2004	14,386 (28.6)	1.53 (1.32 to 1.76)	<0.0001	

that female recipient gender was associated with a decreased risk for DWGF in the total population. This suggests the possibility that a gender-specific response to the DGF milieu leads to a differential risk for DWGF. The subgroup of patients developing acute rejection by 6 and 12 mo after transplantation were less susceptible to the detrimental impact of DGF on DWGF (*versus* those without acute rejection). Because KTR with acute rejection episodes were more likely to experience death-censored allograft failure (data not shown), the latter was a competing event and thus decreased the likelihood of observing DWGF in these patients. Last, the DGF–DWGF association was most prominent in patients with MDRD eGFR from 45 to 89 ml/min at 6 and 12 mo after transplantation. This was likely due to the larger patient numbers and a greater opportunity to die with function in this group (*versus* eGFR <30 ml/min). The HR for patients missing eGFR measurements at each time point mirrored those of patients with eGFR 45 to 89 ml/min.

Table 6. Impact of DGF on the risk for DWGF by MDRD eGFR category at 6 and 12 mo after transplantation

MDRD eGFR Category (ml/min)	Survived to 6 Mo (n = 46,392)		Survived to 12 Mo (n = 41,496)	
	No. of Patients	HR (95% CI)[a]	No. of Patients	HR (95% CI)[b]
≥90	2473	1.19 (0.85 to 1.65)	2167	1.28 (0.87 to 1.89)
60 to 89	14,016	1.35 (1.15 to 1.58)	12,205	1.26 (1.05 to 1.51)
45 to 59	13,622	1.38 (1.20 to 1.59)	11,651	1.37 (1.18 to 1.60)
30 to 44	10,335	1.19 (1.05 to 1.36)	9135	1.34 (1.17 to 1.55)
15 to 29	3343	1.14 (0.95 to 1.38)	3280	1.06 (0.86 to 1.29)
<15	362	0.98 (0.50 to 1.92)	352	1.34 (0.64 to 2.83)
Missing	2241	1.36 (1.10 to 1.68)	2706	1.41 (1.12 to 1.78)

[a] $P = 0.5165$ for interaction.
[b] $P = 0.5007$ for interaction.

In general, patient mortality has received less attention than graft failure in studies that have examined the long-term impact of DGF on KTR. A systematic review and meta-analysis by Yarlagadda *et al.*[10] combined the results of eight studies that included patient survival as an outcome of interest and found no significant increase in the risk for mortality for patients with DGF. A recent report by Patel *et al.*[11] (published after the period covered by the meta-analysis) revealed that DGF was associated with an increased risk for 12-mo mortality but no difference in death-censored graft failure among high-risk KTR who underwent induction therapy with anti-thymocyte globulin; however, none of the aforementioned studies explicitly evaluated DWGF as an outcome of interest.

Ojo *et al.*[7] investigated risk factors for DWGF in a cohort of US KTR during the period of January 1, 1988, through June 30, 1997. The study highlighted the importance of DWGF as a cause of graft loss. The independent association of DGF with the risk for DWGF was uncovered but not further explored. Our study examined this relation not only in the total study population but also across various predefined patient subgroups and in the context of sensitivity analyses. It reveals that DWGF continues to be a major cause of graft loss in the more recent era of transplantation. In contrast to the study by Ojo *et al.*, living-donor KTR were not included in this analysis. The relation between DGF and DWGF among living-donor KTR was found to be even more pronounced than deceased-donor KTR in our study cohort. In light of this finding, living-donor transplants will be examined separately.

An early event such as DGF and a long-term outcome such as DWGF may seem difficult to link pathophysiologically; however, data in the acute kidney injury (AKI) literature suggest a causal relation between AKI-associated ischemia-reperfusion injury and extrarenal sequelae.[12–15] These adverse effects may partially contribute to the poor long-term survival observed in patients who have AKI and eventually recover renal function.[16,17] Similar to AKI, DGF in KTR is associated with the modulation of leukocyte/endothelial function, upregulation of cytokines/adhesion molecules, and increase in markers of oxidative stress.[18] The combination of ischemia-reperfusion injury, donor procurement injury, and immunosuppressive therapy in the setting of uremia all may participate in creating an unfavorable recipient milieu that has implications for long-term survival.

Some limitations of our study deserve note. First, the definition of DGF was based on the need for dialysis within the first week after transplantation. This is the standard epidemiologic definition used in renal registries; however, milder degrees of graft dysfunction or "slow" graft function have been shown to have prognostic significance.[19,20] As a result, we were unable to ascertain a dose-response relation between varying degrees of early graft dysfunction and the risk for DWGF. Second, data on causes of death were incomplete in the USRDS, and thus a robust analysis of cause-specific mortality could not be performed. Moreover, some degree of misclassification in causes of death was likely, and it is plausible that these errors were independent of DGF status. As a result, this would lead to nondifferential outcome misclassification and a tendency to underestimate the true measure of association.[21] Finally, residual confounding is always a concern in observational studies, and our study is no exception. In particular, the absence of updated comorbidity data prevented us from properly accounting for comorbid disease burden at the time of transplantation. As a surrogate, we used comorbidity at the start of dialysis in a sensitivity analysis and found no impact on the overall results. To address this issue further, we examined the DGF–DWGF relation in a "low-risk" subcohort of KTR and found an association that was comparable to the total study population. These analyses provide some reassurance that the study results were not driven by differences in comorbid disease burden.

In summary, DGF is an important independent risk factor for DWGF among US KTR. This excess risk is established early and persists over long-term follow-up. Further research is needed to uncover the mechanisms that underlie this phenomenon and to confirm the potential role of recipient gender in modifying the relation between DGF and DWGF. These insights will be important for the development of effective interventions that may improve the survival of patients with DGF after kidney transplantation.

CONCISE METHODS

This was a retrospective cohort study using data from the USRDS. All adult (age ≥18 yr) patients who had ESRD and received deceased-

donor kidney transplants in the United States from January 1, 1998, through December 31, 2004 (with follow-up until June 30, 2005), were eligible for study inclusion. Exclusion criteria were (*1*) patients who were younger than 18 yr, (*2*) multiorgan transplant recipients (including kidney-pancreas), (*3*) re-grafts, and (*4*) recipients of living-donor kidney transplants. Recipients whose allografts never functioned (*i.e.*, primary nonfunction) were also excluded.

The primary exposure of interest was the development of DGF after transplantation. DGF was defined as the need for at least one dialysis session within the first week after kidney transplantation. The indicator variable "fwdial" in the USRDS Standard Analysis File was used to determine a patient's DGF status. The main outcome of interest was DWGF, defined as graft failure as a result of patient death. This was ascertained in the USRDS by identifying individuals whose date of death and date of graft failure were identical. Graft failures not due to patient death were censored at the time of the failure event.

The following potential confounders were examined in multivariable statistical models: (*1*) Recipient factors (age, gender, race, cause of ESRD, peak PRA level, and time on dialysis); (*2*) donor factors (age, gender, race, cause of death, donor hypertension, terminal serum creatinine, and donation after cardiac death); and (*3*) transplant factors (cold ischemia time, number of HLA mismatches, use of induction therapy, and transplant year). The impact of baseline comorbid conditions at dialysis initiation (from the Centers for Medicare and Medicaid Services ESRD 2728 form) was also assessed in adjusted analyses. Patients with missing data on recipient/donor gender, recipient race, donor type, cause of death, terminal serum creatinine, donor hypertension, or DGF status were excluded from the analysis ($n = 903$ [1.8%] of the initial cohort).

The relation between DGF and DWGF was examined in prespecified subgroups to assess for effect measure modification. The robustness of the main results was evaluated in the following sensitivity analyses: (*1*) Adjustment for clustering by transplant center; (*2*) evaluation of the association within categories of achieved MDRD eGFR at 6 mo after transplantation; (*3*) inclusion of baseline immunosuppressive therapy in multivariable models; (*4*) use of an alternative definition of DGF (<25% decline in serum creatinine during the first 24 h after transplantation); and (*5*) assessment of the impact of DGF on DWGF in a low-risk subcohort of patients (recipient age <50 yr, causes of ESRD other than diabetes or hypertension, low-level PRA, and time on dialysis <24 mo).

Frequencies within categories of each study variable were calculated, and their distributions were compared across DGF groups. Time to DWGF, stratified by DGF status, was graphically assessed using the Kaplan-Meier product limit method, and differences across survival curves were evaluated using the log-rank test. The risk for DWGF in patients with *versus* without DGF was modeled in Cox proportional hazards models, adjusting for the influence of potential confounders. Schoenfeld residuals and plots of the log-negative log of the within-group survivorship functions *versus* log-time showed that the proportional hazards assumption was not violated.

Heterogeneity in the relation between DGF and DWGF across prespecified subgroups was examined using interaction terms in the Cox model. A similar strategy was used to assess the impact of acute rejection by 6 and 12 mo after transplantation on the relation between DGF and DWGF in models conditioning on allograft survival to 6 and 12 mo, respectively. Adjustment for transplant center clustering was achieved using the robust variance estimator of Lin and Wei.[22] All statistical analyses were performed using Stata/MP 10.1 (Stata Corp, College Station, TX). A two-sided $P < 0.05$ was considered statistically significant. The research ethics board of the Toronto General Hospital, University Health Network, approved the study.

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DISCLOSURES

None.

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