Access to Kidney Transplantation after a Failed First Kidney Transplant and Associations with Patient and Allograft Survival

An Analysis of National Data to Inform Allocation Policy

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Abstract

Background and objectives Patients who have failed a transplant are at increased risk of repeat transplant failure. We determined access to transplantation and transplant outcomes in patients with and without a history of transplant failure.

Design, setting, participants, & measurements In this observational study of national data, the proportion of waitlisted patients and deceased donor transplant recipients with transplant failure was determined before and after the new kidney allocation system. Among patients initiating maintenance dialysis between May 1995 and December 2014, the likelihood of deceased donor transplantation was determined in patients with (n=27,459) and without (n=1,426,677) a history of transplant failure. Among transplant recipients, allograft survival, the duration of additional kidney replacement therapy required within 10 years of transplantation, and the association of transplantation versus dialysis with mortality was determined in patients with and without a history of transplant failure.

Results The proportion of waitlist candidates (mean 14%) and transplant recipients (mean 12%) with transplant failure did not increase after the new kidney allocation system. Among patients initiating maintenance dialysis, transplant-failure patients had a higher likelihood of transplantation (hazard ratio [HR], 1.16; 95% confidence interval [95% CI], 1.12 to 1.20; $P<0.001$). Among transplant recipients, transplant-failure patients had a higher likelihood of death-censored transplant failure (HR, 1.44; 95% CI, 1.34 to 1.54; $P<0.001$) and a greater need for additional kidney replacement therapy required within 10 years after transplantation (mean, 9.0; 95% CI, 5.4 to 12.6 versus mean, 2.1; 95% CI, 1.5 to 2.7 months). The association of transplantation versus dialysis with mortality was clinically similar in waitlisted patients with (HR, 0.32; 95% CI, 0.29 to 0.35; $P<0.001$) and without transplant failure (HR, 0.40; 95% CI, 0.39 to 0.41; $P<0.001$).

Conclusions Transplant-failure patients initiating maintenance dialysis have a higher likelihood of transplantation than transplant-naïve patients. Despite inferior death-censored transplant survival, transplantation was associated with a similar reduction in the risk of death compared with treatment with dialysis in patients with and without a prior history of transplant failure.

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Introduction

The outcomes of patients with a history of transplant failure who return to dialysis are poor (1,2). Existing research has focused on improving the management of transplant-failure patients on dialysis (3−7). The role of repeat transplantation in the management of transplant-failure patients was informed by seminal studies demonstrating that these patients derive a survival benefit from repeat transplantation compared with treatment with dialysis (8,9). Current organ allocation policies have a noncohesive approach to patients with a previous transplant history (10). Changes to the United States kidney allocation system (KAS) in December 2014 increased the likelihood of transplantation in patients with high levels of antibodies against HLA and may have indirectly increased access for transplant-failure patients (10,11). This policy change has been challenged from both an equity and a utility perspective because second transplant outcomes are inferior to first transplant outcomes (12−14). However, the new KAS includes prior organ transplant history in the calculation of the expected post-transplant survival (EPTS). This may exclude repeat transplant candidates from receiving kidneys with the lowest risk of failure.

Given the insufficient supply of kidneys to meet the need for transplantation, the allocation of kidneys to high-risk patients, including transplant-failure patients,

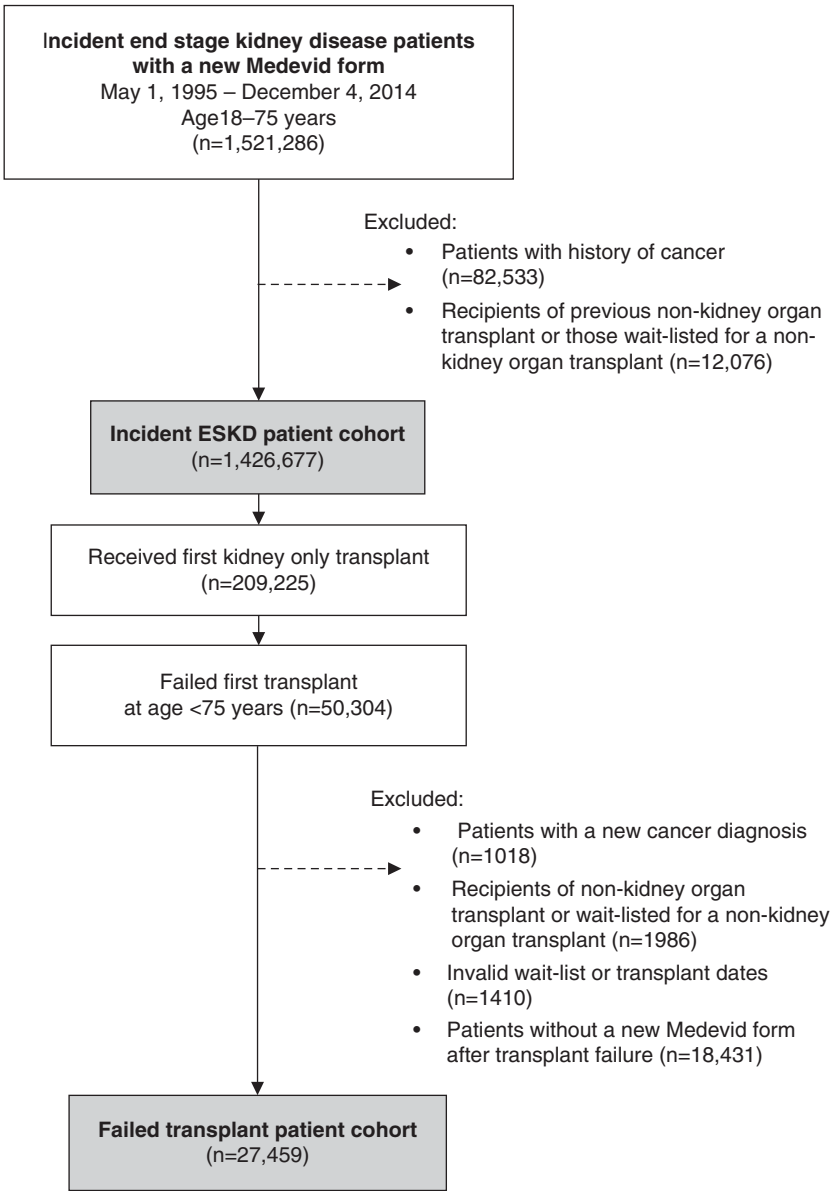

Figure 1. | **Assembly of incident ESKD and transplant-failure patient cohorts.** The incident ESKD patient cohort consists of 1,426,677 patients and the failed transplant patient cohort consists of 27,459 patients.

requires critical examination. To inform future allocation policy, we first determined secular changes in waitlisting and deceased donor transplantation among transplant-failure patients to determine any change with the new KAS, as well as the proportion of patients excluded from offers for kidneys with the lowest risk of failure because of inclusion of prior organ transplantation in the EPTS calculation. We then undertook a series of analyses directly comparing transplant access and transplant outcomes in transplant-failure patients and transplant-naïve patients with incident ESKD.

Materials and Methods

This study was approved by our hospital research ethics board and adheres to the Principles of the Declaration of Istanbul.

Data Source and Study Population

Secular changes in waitlisting and transplantation were on the basis of data reported by the Organ Procurement and Transplant Network and were accessed on December 31, 2018.

Data from the US Renal Data System were used to examine access and outcomes in transplant-failure patients and patients with incident ESKD (15). Patients aged 18–75 years who initiated maintenance treatment for ESKD between May 1995 and December 2014 were studied. The start date allowed inclusion of information in the updated version of the Centers for Medicare and Medicaid Services Form 2728 (Medevid Form). A current Medevid record was required for study inclusion. Patients were excluded if they had a history of cancer or had received or were waitlisted for a nonkidney transplant

(Supplemental Table 1). To ensure that transplant-failure patients and patients with incident ESKD had a similar total duration of ESKD, the transplant-failure group was limited to the subset of incident patients who received a transplant that subsequently failed during study follow-up. Because transplantation is rare in elderly patients, both groups were limited to patients aged <75 years (Figure 1).

Statistical Analyses

Time to deceased donor transplantation was determined from the date of first dialysis treatment or date of first transplant failure until the date of first or second transplant with follow-up censored at time of death, living donor transplantation, or end of follow-up (December 4, 2014). A Cox multivariable regression model was used to determine the relative risk of deceased donor transplantation after adjustment for group differences in the covariates shown in Supplemental Table 2. A category of "missing" was created and included in the models for covariates with missing data. Model assumptions were tested using log-negative-log plots of the within-group survivorship probabilities versus log-time and no violations were identified. Similar models were developed for the outcomes of waitlist activation and deceased donor transplantation after waitlisting (Supplemental Tables 3 and 4).

The likelihood of allograft loss from any cause including death (graft loss), death-censored graft loss (defined by a return to maintenance dialysis or preemptive repeat transplantation), and death with a functioning graft were determined with Cox proportional hazards models adjusted for covariates shown in Supplemental Table 5. Interaction terms were used to determine if the risk of transplant failure between patients with and without transplant failure varied by panel reactive antibody (PRA) and Kidney Donor Profile Index (KDPI).

To estimate the mean time that a further source of kidney replacement therapy (dialysis or repeat transplantation) would be required after allograft failure and before death (or the duration of unrecognized allograft function after patients die with a functioning allograft) over a 10-year period after transplantation, the difference in surface area between the 10-year patient survival and death-censored allograft survival curves was determined using numerical integration. These models included adjustment for patient demographics, body mass index, insurance type, comorbid conditions, transplant year, PRA, and KDPI.

We used a multivariable, nonproportional hazards analysis to determine the association of transplantation with mortality compared with treatment with dialysis, with transplantation treated as a time-dependent covariate to account for the fact that patients switched from dialysis to transplantation at different times. Survival was determined from the date of waitlisting with patients censored at time of removal from the waitlist, living donor transplantation, or the date of last follow-up (16–18). All analyses were intention to treat and patients were not censored at allograft failure. The model included adjustment for recipient age at wait-listing, sex, race, cause of ESKD, BMI, year of wait-listing, comorbid conditions, insurance type and employment status.

Table 1. Waitlisting and deceased donor transplantation of patients with previous history of transplant failure in the United States during 2000–2018

Year	Proportion of Waitlist Candidates with Previous Transplant Failure	Proportion of Deceased Donor Transplant Recipients with Previous Transplant Failure
2008	15	11
2009	15	12
2010	15	12
2011	14	11
2012	14	12
2013	14	11
2014	14	12
2015	14	13
2016	14	12
2017	12	11
2018	12	10

The time-varying survival curves in Figure 4 were produced by splitting each observation into time segments after transplantation. Separate hazard ratios (HRs) are produced for each time segment by comparing the survival of transplant recipients to patients with the same waiting time who remain waitlisted. The reference groups consist of either waitlisted patients with incident ESKD or waitlisted patients with transplant failure who have not yet received a deceased donor transplant. HR curves were created by interpolation between the HRs at the midpoint of each time interval. Similar models among subsets of waitlisted transplant-failure patients were used to determine the consistency of the association of transplantation compared with dialysis with mortality in select patient subgroups.

All analyses were conducted in R v3.4.4.

Results

The proportion of waitlist candidates and transplant recipients with transplant failure did not increase between 2008 and 2018 (Table 1). The increase in the proportion of transplant recipients with transplant failure immediately after KAS implementation (from 12% in 2014 to 13% in 2015) was not sustained. The proportion of transplant recipients with previous transplant failure was consistently lower than the proportion of such patients waitlisted for transplantation. The proportion of transplant-failure patients excluded from offers from kidneys with the lowest risk of failure was 58% with, and 39% without the variable for prior organ transplant included in the EPTS calculation.

Access to Transplantation

The assembly of the incident ESKD cohort (n=1,426,677), the subset of patients with incident ESKD who received a first transplant from any donor source (n=209,225) and the subset of patients that developed transplant failure (n=27,459) is shown in Figure 1, and the group characteristics are shown in Table 2. Transplant-failure patients were younger, more likely to be men, white, have

Table 2. Patient characteristics

Characteristic	Patients with Incident ESKD, *n*=1,426,677	Patients with Incident ESKD that Received a First Deceased or Living Donor Transplant, *n*=209,225	Patients with Failure of the First Transplant, *n*=27,459
Age, yr, median [IQR]	57 [49, 67]	47 [34, 60]	50 [40, 67]
Men	55%	61%	59%
Race			
White	62%	69%	65%
Black	32%	24%	30%
Other	7%	7%	5%
Cause of ESKD			
Diabetes	50%	33%	28%
Hypertension	24%	20%	20%
GN	11%	26%	31%
Polycystic disease	3%	9%	7%
Other	13%	12%	14%
Body mass index, kg/m^2			
<18.5	4%	4%	5%
18.5–24.9	31%	33%	36%
25.0–29.9	28%	30%	29%
≥30.0	37%	29%	30%
Medical insurance			
Medicare/Medicaid	54%	25%	50%
Private	26%	51%	39%
None	10%	10%	4%
Other	11%	14%	7%
Employment status			
Employed	14%	37%	24%
Unemployed	25%	21%	23%
Other	61%	42%	53%
Comorbid conditions			
Congestive heart failure	29%	10%	15%
Peripheral vascular disease	13%	4%	7%
Cerebrovascular disease	8%	3%	4%
Atherosclerotic heart disease	20%	8%	10%
Chronic obstructive pulmonary disease	7%	1%	3%
Inability to ambulate	5%	0%	3%
Alcohol dependence	2%	1%	0%
Drug dependence	2%	0%	1%
Current smoker	7%	4%	4%
Year of ESKD incidence/transplant failure			
1995–1999	19%	26%	4%
2000–2004	25%	31%	17%
2005–2009	27%	30%	34%
2010–2014	28%	14%	46%

Body mass index was missing for 4% of patients.

nondiabetes-related ESKD, nonobese, privately insured, employed, and have fewer comorbid conditions compared with patients with incident ESKD. Because transplant-failure patients are a subset of the incident ESKD cohort, more transplant-failure patients were identified in recent years. There were 18,431 transplant-failure patients excluded from the study because of the absence of an updated Medevid form at the time of transplant failure (Figure 1). Excluded patients were similar to the transplant-failure patients included in the study with the exception of a shorter duration of first transplant survival (Supplemental Table 1), which is expected because a new Medevid form is not required for patients who lose transplant function within 3 years of transplantation.

Time to Deceased Donor Kidney Transplantation

The adjusted cumulative incidence of deceased donor transplantation (Figure 2A) was low in both transplant-failure patients and patients with incident ESKD (15% and 14%, respectively, 10 years after the date of first dialysis treatment). Transplant-failure patients had a higher adjusted likelihood of transplantation (HR, 1.16; 95% confidence interval [95% CI], 1.12 to 1.20; $P<0.001$). This was because of a greater likelihood of activation to the waitlist among transplant-failure patients, and there was no difference in the time to transplantation after waitlisting between the groups (Figure 2, B and C). The adjusted likelihood of activation to the waitlist was higher in transplant-failure patients (HR, 1.49; 95% CI, 1.47 to 1.52; $P<0.001$), whereas the adjusted likelihood of transplantation after waitlisting was similar between groups (HR, 0.98; 95% CI, 0.94 to 1.01; $P=0.15$). The full Cox model outputs are shown in Supplemental Tables 2–4. Results were consistent in analyses including transplant-failure patients who lacked an updated Medevid form (data not shown).

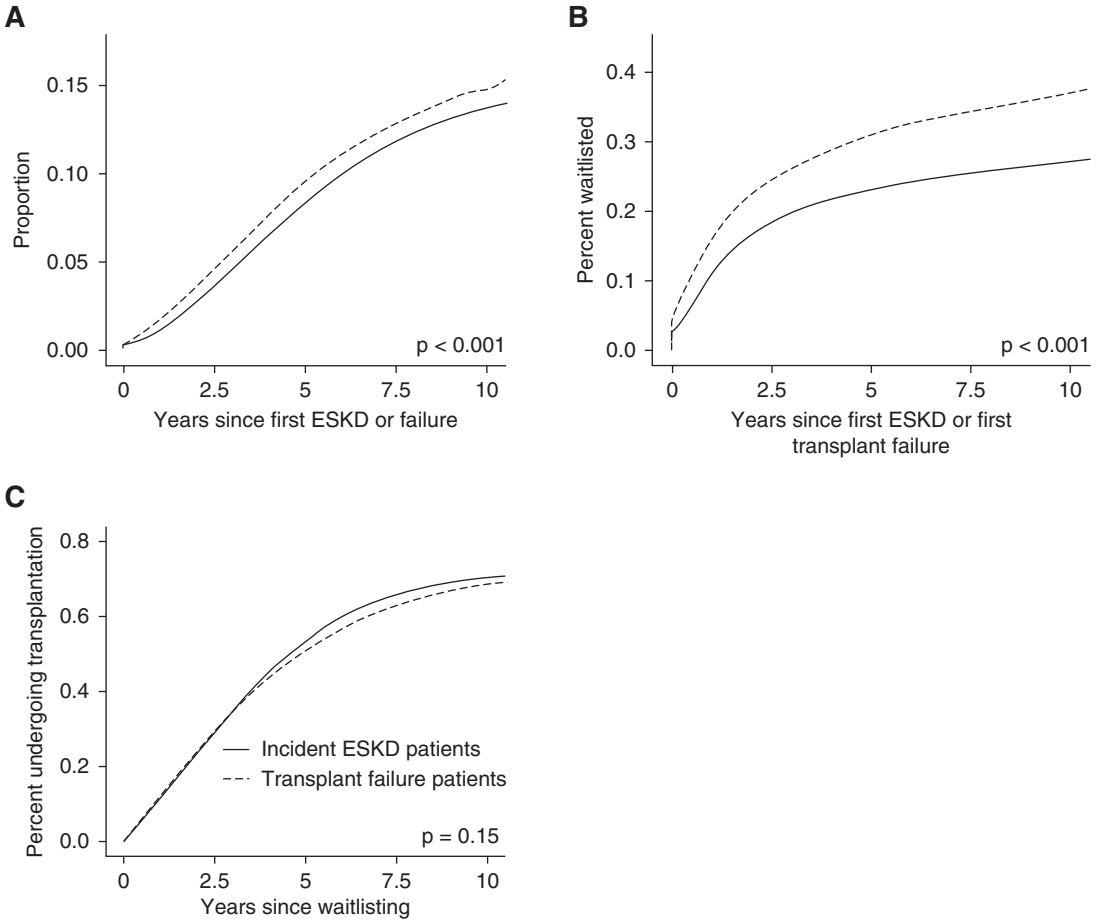

Figure 2. | **Access to transplantation in incident ESKD and Transplant Failure patients**. Estimated cumulative incidence of deceased donor transplantation (A) and activation to the waitlist (B) among 1,426,677 patients with incident ESKD (solid line) and 27,459 patients with a history of transplant failure (dotted line), truncated at 10 years. (C) Estimated cumulative incidence of deceased donor transplantation after waitlisting among 322,267 patients with incident ESKD (solid line) and 12,021 patients with a history of transplant failure (dashed line). The curves in A and B are representative of a cohort characterized by the mean of the variables used in multivariable Cox models, which included adjustment for age, sex, race, cause of ESKD, body mass index, year of first incidence of ESKD or first transplant failure, medical insurance, employment status, and the comorbid conditions. Curves in (C) are representative of a cohort characterized by the mean of the variables in a multivariable Cox model that included adjustment for age, sex, race, cause of ESKD, body mass index, year of first incidence of ESKD or first transplant failure, ABO blood group, and PRA.

Transplant Outcomes

During the mean follow-up of 6.5±4.6 years in first and 5.0±3.8 years in second deceased donor transplant recipients, the time to graft loss was shorter in second compared with first transplant recipients. This was because of a higher incidence of death-censored graft loss (Supplemental Figure 1). Compared with first transplant recipients, the adjusted risks (HRs) of graft loss with and without censoring for death, and death with a functioning graft among second transplant recipients, were 1.44 (95% CI, 1.34 to 1.54; $P<0.001$), 1.26 (95% CI, 1.19 to 1.34; $P<0.001$), and 0.90 (95% CI, 0.80 to 1.01; $P=0.07$), respectively. The Cox model outputs for the outcome of graft loss are shown in Supplemental Table 5. Tests for interaction of second transplant status with PRA and KDPI were not significant in any of the models.

Figure 3, A and B shows the difference in adjusted patient survival and death-censored allograft survival among first transplant recipients (n=127,670) and second transplant recipients (n=3848) during the first 10 years after transplantation. The difference between these curves is equivalent to the expected duration of other forms of kidney replacement therapy (*i.e.*, dialysis or further transplantation) required. In both groups, patient survival was higher than death-censored allograft survival, but the difference between the curves was greater in second transplant recipients (mean difference, 9.0; 95% CI, 5.4 to 12.6 months versus mean difference, 2.1; 95% CI, 1.5 to 2.7 months). Table 3 shows the mean difference between adjusted patient and death-censored survival curves in subgroups of first and second transplant recipients over 10 years after transplantation. Among nondiabetic patients aged <60 years, the duration of additional kidney replacement therapy required was greater in second compared with first transplant recipients. Among first transplant recipients aged 40–60 years with diabetes-related ESKD, the difference between the curves was −7.9 months, indicating that a mean of 7.9 months

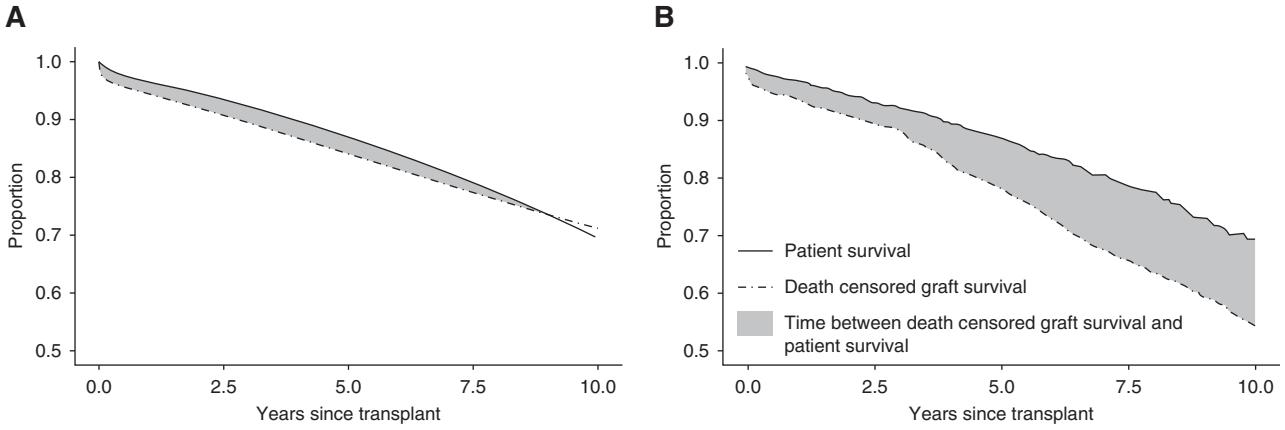

Figure 3. | The difference in adjusted patient survival and death-censored allograft failure among (A) first (*n*=127,670) and (B) second deceased donor transplant recipients (*n*=3848). Curves were developed from Cox models adjusted for age, sex, race, cause of ESKD, body mass index, type of medical insurance, year of transplant, congestive heart failure, peripheral vascular disease, cerebrovascular disease, atherosclerotic heart disease, chronic obstructive pulmonary disease, alcohol or drug dependencies, tobacco use, the inability to ambulate, PRA, and KDPI.

of allograft function was lost within 10 years of transplantation because of patient death with allograft function. In contrast, second transplant recipients in this subgroup required an additional 7.0 months of kidney replacement therapy because of an excess of death-censored allograft failure. Among first and second transplant patients aged >60 years with or without diabetes-related ESKD, the mean difference between the adjusted patient and death-censored allograft survival curves was negative, indicating patients in these subgroups died with varying durations of unrecognized allograft function (Table 3).

Association of Deceased Donor Transplantation with Mortality Compared with Treatment with Dialysis

Figure 4 shows the adjusted time-varying relative risk of death in 127,670 first transplant recipients (dotted curve) and 3848 second (solid curve) transplant recipients. The reference groups (relative risk of 1.0) included 322,267 patients with incident ESKD and 12,021 transplant-failure patients who had been activated to the waitlist. The relative risk of death in first transplant recipients was compared with patients with incident ESKD who had equal lengths of time since placement on the waitlist but had not yet received a first transplant, whereas the relative risk of death

Table 3. Differences between patient and death-censored allograft survival curves during a 10-year period after kidney transplantation (in months, with 95% confidence intervals)

Age	No. of Patients	First Transplant Recipients[a]	Second Transplant Recipients[a]	Difference between Second and First Transplant Recipients[b]
All patients	131,518	2.1 [1.5 to 2.7]	9.0 [5.4 to 12.6]	6.8 [3.6 to 9.9]
18–40 yr, no diabetes	27,672	16.8 [15.7 to 18.0]	24.7 [19.9 to 29.4]	7.9 [4.2 to 11.4]
18–40 yr, diabetes	11,375	2.4 [0.6 to 4.2]	4.4 [−14.0 to 22.5]	2.4 [−0.7 to 18.3]
40–60 yr, no diabetes	41,671	2.3 [1.3 to 3.3]	7.4 [1.7 to 13.0]	5.0 [0.3 to 9.7]
40–60 yr, diabetes	27,791	−7.9 [−9.3 to −6.6]	7.0 [−6.8 to 20.4]	6.9 [−0.4 to 20.2]
>60 yr, no diabetes	14,125	−12.8 [−14.8 to −10.8]	−9.7 [−23.4 to 4.2]	0.0 [−0.1 to 4.0]
>60 yr, diabetes	8884	−20.8 [−23.6 to −17.9]	−10.0 [−38.2 to 16.6]	0.3 [0.0 to 16.5]

[a]The difference between patient survival and death-censored allograft survival curves are shown over 10 years after the date of first or second transplantation. In subgroups with positive values, the difference is equivalent to the duration of additional kidney replacement therapy (dialysis or transplantation) required. Negative values are seen when the average patient survival is less than average death-censored graft survival and are equivalent to the duration of allograft function lost because of the outcome of death with a functioning allograft. The values are calculated by subtracting the integral of the death-censored allograft survival curve from the integral of the patient survival curve over 10 years. This describes the area that is highlighted in gray on Figure 3.

[b]The difference between the duration of additional kidney replacement therapy (dialysis or transplantation) expected to be required by second transplant recipients compared with first transplant recipients is given in the last column. This is the difference in curves only when the average patient survival is longer than average graft survival. If the average patient survival is shorter than the graft survival then no additional kidney replacement therapy would be required and a value of 0 is adopted for these timepoints in the calculation. All analyses are adjusted for age, sex, race, cause of ESKD, body mass index, medical insurance, congestive heart failure, peripheral vascular disease, cerebrovascular disease, atherosclerotic heart disease, chronic obstructive pulmonary disease, alcohol or drug dependencies, tobacco use, the inability to ambulate, transplant year, panel reactive antibody, and Kidney Donor Profile Index.

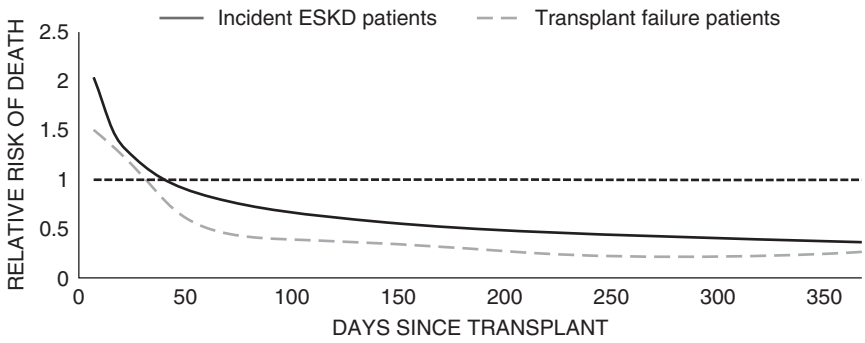

Figure 4. | The adjusted relative risk of death in first deceased donor transplant recipients (*n*=127,670; solid curve) and second deceased donor transplant recipients (*n*=3848, dashed curve) compared with patients waitlisted for transplantation (dotted line with relative risk =1.0). The reference group for the first transplant recipient includes 322,267 patients waitlisted for a first transplant, and the reference group for second transplant patients includes the 12,021 patients waitlisted for a second transplant. Transplant recipients in each group were compared with waitlisted patients from the same group who had been on dialysis for equal lengths of time but who had not yet received a first or second deceased donor kidney transplant. The multivariable model included adjustment for recipient age at waitlisting, sex, race, cause of ESKD, body mass index, year of waitlisting, comorbid conditions, insurance type, and employment status. The long-term adjusted risk of death was lower in both first and second transplant recipients, but the relative risk reduction associated with transplantation was greater among second transplant recipients.

in second transplant recipients was compared with transplant-failure patients who had equal lengths of time since waitlisting but had not yet received a second transplant. Transplant recipients had a higher risk of death immediately after transplantation compared with patients who remained waitlisted, and this risk was higher among first transplant recipients. The risk of death remained elevated for 22 and 36 days after transplantation among first and second transplant recipients, respectively. Among second transplant recipients, transplantation was associated with a 68% lower adjusted risk of death (HR, 0.32; 95% CI, 0.29 to 0.35; $P<0.001$) compared with treatment with dialysis. In comparison, among first transplant recipients, transplantation was associated with a 60% lower adjusted risk of death (HR, 0.40; 95% CI, 0.39 to 0.41; $P<0.001$). The large risk reduction for mortality in second transplant recipients is explained by a higher adjusted risk of death on dialysis during waitlisting in transplant-failure patients compared with patients with incident ESKD (HR, 1.07; 95% CI, 1.03 to 1.13; $P=0.002$). Second transplantation was associated with a large reduction in the risk of death compared with treatment with dialysis in all subgroups examined (Table 4).

Discussion

The study provides contemporary evidence to inform consideration of changes to organ allocation policies for transplant-failure patients. In our opinion, the findings support continued equal treatment of first and second transplant candidates. We found no sustained increase in waitlisting or transplantation of transplant-failure patients after the new KAS in 2014. Although these data are descriptive and should continue to be monitored, it is notable that the proportion of transplant recipients with prior transplant failure was consistently lower than their representation on the waitlist. Transplantation was associated with a clinically similar reduction in the risk of death compared with treatment with dialysis in patients with and without a prior history of transplant failure and we were unable to identify a subgroup of transplant-failure patients who did not derive a large survival benefit from a second transplant. However, we acknowledge that the study findings also support alternative conclusions. Specifically, the finding that second transplant outcomes remain inferior to first transplant outcomes in the current era and that, on average, second transplant recipients will require an additional form of kidney replacement therapy (either dialysis or another transplant) in the first 10 years after transplantation for approximately 7 months longer than first transplant recipients (Table 3), may lead some readers to conclude that repeat transplantation is a suboptimal use of scarcely available deceased donor organs. Notwithstanding these alternative interpretations, the study unequivocally highlights the need for focused strategies to improve the outcomes of transplant-failure patients both on dialysis and after a second transplant.

We hypothesized a systematic bias in referral and waitlisting of transplant-failure patients for repeat transplantation. Surprisingly, we found that transplant-failure patients had a higher likelihood of transplantation than patients with incident ESKD, because of a higher likelihood of waitlisting. This finding may be explained by the fact that transplant-failure patients have first-hand experience of the benefits of transplantation and are familiar with negotiating the process of accessing transplantation. Although several studies have highlighted disparities in access to transplantation among various patient groups (19−22), to our knowledge no study has directly compared access to first and second transplantation. Although the likelihood of transplantation was higher in transplant-failure patients, <15% of patients in either group received a transplant, making it difficult to justify a policy change that would further limit access in second transplant candidates.

The study showed repeat transplant outcomes remain inferior to those achieved in first transplant recipients in the current era, confirming findings from earlier studies (12,13).

Table 4. Associations of second kidney transplant (compared with transplant waitlisting) with mortality among patients who experienced failure of a first kidney transplant

Patient Subgroup	No. of Patients Waitlisted	Received Transplant	Died without Second Transplant	Died after Second Transplant	Hazard Ratio [95% Confidence Interval) for Death in Transplant Recipients	*P* Value for Hazard Ratio
All patients waitlisted for second transplant	12,021	3848	1858	582	0.36 [0.32 to 0.40]	<0.001
Age at time of waitlisting, yr						
18–40	3725	1430	294	107	0.29 [0.22 to 0.38]	<0.001
41–60	6182	1852	1021	328	0.35 [0.31 to 0.41]	<0.001
>60	2114	566	543	147	0.40 [0.32 to 0.49]	<0.001
Diabetes-related ESKD	1725	442	557	146	0.34 [0.27 to 0.42]	<0.001
Nondiabetes-related ESKD	10,296	3406	1301	436	0.37 [0.32 to 0.42]	<0.001
Panel reactive antibody						
0%	2672	872	463	171	0.32 [0.26 to 0.40]	<0.001
1%–30%	1391	616	207	132	0.37 [0.28 to 0.49]	<0.001
31%–80%	2160	761	344	96	0.27 [0.20 to 0.35]	<0.001
>80%	5796	1597	844	183	0.38 [0.32 to 0.46]	<0.001
Kidney Donor Profile Index[a,b]						
0%–20%	1600	1012	NA	144	0.32 [0.27 to 0.39]	<0.001
21%–84%	4386	2555	NA	366	0.35 [0.31 to 0.40]	<0.001
85%–100%	281	234	NA	55	0.44 [0.33 to 0.59]	<0.001
Duration of first transplant survival						
<3 yr	2360	1157	317	278	0.45 [0.37 to 0.55]	<0.001
3–5 yr	3020	919	593	141	0.33 [0.27 to 0.41]	<0.001
>5 yr	6641	1772	948	163	0.33 [0.27 to 0.39]	<0.001

All analyses are adjusted for differences in recipient age, sex, race, cause of ESKD, body mass index, year of waitlisting, insurance type, employment status, congestive heart failure, peripheral vascular disease, cerebrovascular disease, atherosclerotic heart disease, chronic obstructive pulmonary disease, alcohol or drug dependencies, tobacco use, and the inability to ambulate. The reference population in each of these subgroup models is made up of the subgroup's waitlisted patients that have not yet received (or do not ever receive) a transplant.

[a]For the Kidney Donor Profile Index, transplant recipients are compared with all waitlist patients as waitlisted patients cannot be assigned a Kidney Donor Profile Index value.

[b]Kidney Donor Profile Index could not be determined for 47 transplant patients.

The inferior outcomes of second transplant recipients were due to allograft failure rather than patient death, suggesting the need for better strategies to prevent and treat immunologic causes of graft loss in these patients. Repeat transplant recipients may be excluded from clinical trials and dedicated studies in these patients are relatively infrequent. Recent work has focused on the role of induction immunosuppression in second transplant recipients (23), the association of first transplant characteristics with second transplant survival (24), and the importance of avoiding repeat HLA mismatches (25). Of note, tests for an interaction between second transplant status and PRA or KDPI were not significant, indicating that the risk of allograft loss associated with second transplantation was not modified in patients with high PRA or recipients of high-scoring KDPI kidneys.

We found a longer requirement for additional kidney replacement therapy over a 10-year period after transplantation among second transplant recipients. Quantifying the difference in patient survival and death-censored allograft survival provides a novel metric of the utility of transplantation in different patient groups and may be used to inform allocation policy (26,27). For example, transplantation may not be justified in some high-risk second transplant candidates in whom the duration allograft function is too short to provide a reasonable duration of freedom from dialysis or repeat transplantation over a fixed time horizon. In subgroup analyses, the requirement for additional kidney replacement treatment was consistently longer in second transplant recipients. This approach may be useful in reconsidering our expectations for second transplant outcomes; for example, it may be unrealistic to expect that some patient groups (*i.e.*, patients aged <40 years without diabetes) will not require a third transplant in their lifetime.

Despite inferior transplant outcomes, transplantation was associated with a clinically similar reduction in the risk of death compared with treatment with dialysis in patient with and without a prior history of transplant failure, and this was consistent in all subgroups examined.

Previous studies have documented a lower risk of death with repeat transplantation (9,8), but to our knowledge, no study has directly determined the association of a first and second transplant with mortality in a single model. The large reduction in the risk of mortality associated with second transplantation was related to a high risk of waitlist death among transplant-failure patients, an observation that reinforces the need for strategies to improve the dialysis survival of these patients (1,2). The use of transplantation in higher-risk patient groups (*i.e.*, patients with diabetes, long dialysis exposure, high immune risk, and recipients of high-risk donors) (16,28–30) has primarily been justified by the relative survival benefit derived from transplantation compared with treatment with dialysis. By providing additional outcome measures (*i.e.*, absolute allograft survival, and the duration of additional kidney replacement therapy needed within 10 years after transplantation) this study advances a broader approach to evaluating the use of transplantation in high-risk patients.

Readers should consider the inherent limitations of observational studies on the basis of administrative data when interpreting the results of this study. The study is primarily focused on transplant-failure patients whose first transplants functioned for >3 years. Our analysis of access to transplantation included all patients with incident ESKD and was designed to inform the existence of a bias against transplant-failure patients with regard to referral and waitlisting for repeat transplantation. We considered alternate analyses including matching transplant-failure patients and patients with incident ESKD. The matched analysis yielded similar findings with regard to transplant outcomes and the survival benefit of transplantation, but showed a lower likelihood of transplantation in transplant-failure patients. Because not all patients with incident ESKD are eligible for transplantation, a matched design may help exclude ineligible patients. However, given that most patients with ESKD could benefit from transplantation if more organs were available (30−32), the drift in clinical practice to more restrictive waitlisting practices (33), and inequities in access to the waitlist (34), we chose to include all patients with incident ESKD as the comparator group for this analysis. We believe this approach, together with robust multivariable adjustment for comorbid factors and ensuring the groups had a similar total duration of ESKD, ensures the external validity of our findings compared with a matched cohort design.

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Disclosures

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Supplemental Material

This article contains the following supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.01530219/-/DCSupplemental.

Supplemental Table 1. Transplant-failure patients included and excluded from the study.

Supplemental Table 2. Factors associated deceased donor transplantation from date of first dialysis or transplant failure.

Supplemental Table 3. Factors associated with activation to the waitlist.

Supplemental Table 4. Factors associated with deceased donor transplantation after waitlisting.

Supplemental Table 5. Factors associated with allograft loss from any cause.

Supplemental Figure 1. Time to transplant failure.

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