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Relationship between eGFR Decline and Hard Outcomes after Kidney Transplants

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ABSTRACT

Trials designed to assess the effect of interventions on death and graft failure in kidney transplant recipients are not feasible, because these are predominantly late events. Here, we examined the potential of percentage decline in eGFR as a surrogate for hard outcomes. We obtained deidentified data from the Australia and New Zealand Dialysis and Transplant Registry and studied 7949 transplants performed from 1995 to 2009, including 71,845 patient-years of follow-up, 1121 graft losses, and 1192 deaths. We used adjusted Cox proportional hazards models to determine risks of death or death–censored graft failure related to percentage change in eGFR between years 1 and 3 after transplant. Percentage change in eGFR was modeled as a restricted cubic spline. Rate of eGFR decline associated with exponentially increased risks of graft failure and death. Compared with stable eGFR, a ≥30% decline in eGFR, detected in 10% of patients, strongly associated with subsequent death (hazard ratio, 2.20; 95% confidence interval, 1.87 to 2.60) and death–censored graft failure (hazard ratio, 5.14; 95% confidence interval, 4.44 to 5.95). Decline in eGFR was superior to other surrogates, including acute rejection, doubling of serum creatinine level, and eGFR at year 1 or year 2. We conclude that 30% decline in eGFR between years 1 and 3 after kidney transplant is common and strongly associated with risks of subsequent death and death–censored graft failure, which mirrors findings in CKD. Percentage decline in eGFR should be considered for use as a surrogate outcome in kidney transplant trials.

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Kidney transplantation provides the optimal form of RRT for the majority of people with ESRD. Although 1-year patient and graft survival now exceeds 95% in major transplanting centers, long-term outcomes have failed to improve over time. Beyond the first post–transplant year, an annual attrition rate of 4%–5% has been reported in the United States, Australia, and other regions, which is caused in equal parts by graft failure and patient death with a functioning graft.[1,2]

The majority of clinical trials in kidney transplantation have focused primarily on outcomes during the first 1–3 years after transplantation, including the incidence of acute rejection and patient and graft survival. Because of the low rates of death or graft loss during the first 3 years after transplantation, current trials provide little insight into the effect of therapy on such outcomes over the longer term. Trials of therapies seeking to improve long-term outcomes require either very large numbers or extended follow-up duration. Although desperately needed, high cost and challenging logistics have resulted in a paucity of such trials.[3]

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The use of surrogate outcomes for mortality and late graft failure may enable investigators to design trials that are more affordable and feasible.[4] In this regard, kidney transplantation has much in common with CKD.[5] Trials in CKD have traditionally addressed primary outcomes of death, ESRD, or doubling of baseline serum creatinine. Using the large, multinational CKD Prognosis Consortium dataset, Coresh *et al.*[6] explored use of percentage reduction in eGFR as a surrogate for hard outcomes. Compared with traditional end points, the investigators reported that a ≥30% decline in eGFR over the typical trial durations of 1, 2, or 3 years was substantially more frequent but also, strongly predictive of ESRD and death on longer–term follow-up.[6] We, therefore, examined the relationship between eGFR decline and subsequent hard outcomes after kidney transplantation.

RESULTS

The analysis included 7949 grafts, with a median follow-up of 8.5 years and 71,845 patient-years in total. There were 1121 graft failures, 863 deaths with a functioning graft, and another 329 deaths after graft failure. Sixty-nine (0.87%) patients were lost to follow-up after a median of 9 years. The baseline characteristics of the patients are shown in Table 1.

Excluded patients (n=3994) were slightly older (mean [SD] =45.3 [12.9] versus 48.6 [13.2] years old; $P<0.001$), had a higher prevalence of comorbidities pretransplant (diabetes, 10% versus 17%; coronary disease, 12% versus 19%; both $P<0.001$), had higher donor age (median [interquartile range] =46 [33–55] versus 50 [39–59] years old; $P<0.001$), had a modestly greater degree of HLA mismatch (5–6 mismatch, 22% versus 30%), and had lower eGFR at both year 1 (mean [SD] =54.4 [18.0] versus 53.1 [20.9]; $P<0.01$) and year 3 when available (53.0 [19.5] versus 48.7 [24.4]; P=0.03), with no substantive differences in sex or race. Because the major reasons for exclusion were graft loss or death during the first 3 post-transplant years, it is expected that those excluded would exhibit a higher risk profile.

Percentage change in eGFR between the end of years 1 and 3 post-transplant was significantly predictive of patient survival (Figure 1A). Greater reductions in eGFR decline were exponentially associated with increases in risk of death, whereas improvement in eGFR was not associated with death (Figure 1A). A decline in eGFR of ≥30% occurred in 10% of patients and was associated with a 2.2-fold increase in death compared with in those with stable eGFR (hazard ratio [HR], 2.20; 95% confidence interval [95% CI], 1.87 to 2.60).

Overall, graft loss and in particular, death–censored graft failure were also strongly and exponentially associated with percentage reduction in eGFR, whereas improvement in eGFR was not associated with graft loss (Figure 1, B and C, respectively). A decline in eGFR of ≥30% was associated with a 3.5-fold increase in graft failure (HR, 3.58; 95% CI, 3.16 to 4.05) and a fivefold increase in death–censored graft failure (HR, 5.14; 95% CI, 4.44 to 5.95).

Table 1. Baseline characteristics

Characteristic	Value
N	7949
Age at transplant, yr, mean (SD)	45.3 (12.9)
Recipient, men	4957 (62%)
Race	
White	6699 (84%)
Australian indigenous	186 (2%)
Asian	666 (8%)
Māori	172 (2%)
Pacific People	133 (2%)
Other	93 (1%)
Primary renal disease	
GN	4020 (51%)
Polycystic kidney disease	1076 (14%)
Reflux nephropathy	892 (11%)
Hypertension	313 (4%)
Diabetic nephropathy	562 (7%)
Other	1086 (14%)
Diabetes	808 (10%)
Coronary artery disease	935 (12%)
Peripheral vascular disease	469 (6%)
Cerebrovascular disease	299 (4%)
Chronic lung disease	389 (5%)
Living donor	3135 (39%)
Repeat transplant	946 (12%)
Donor age, yr, median (interquartile range)	46.0 (33.0–55.0)
HLA mismatches	
0–2	3262 (41%)
3–4	2908 (37%)
5–6	1779 (22%)
Peak panel–reactive antibody, median (interquartile range)	3.0% (0.0%–18.0%)
Transplant era	
1995–1997	1252 (16%)
1998–2000	1388 (17%)
2001–2003	1577 (20%)
2004–2006	1733 (22%)
2007–2009	1999 (25%)
eGFR at 1 yr, mean (SD)	54.4 (18.0)
eGFR at 3 yr, mean (SD)	53.0 (19.5)
Change in eGFR, year 3 versus 1, mean (SD)	0.5% (25.3%)

Separate sensitivity analyses restricted to first graft recipients using the Modification of Diet in Renal Disease 4 (MDRD-4) equation rather than the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation to estimate GFR[7,8] and examining change in eGFR between years 3 and 5 post-transplant yielded similar results. Stratification of the cohort by recipient age, presence or absence of diabetes, panel–reactive antibody percentage, donor source, year 1 eGFR, or cause of graft failure showed relatively consistent relationships between decline in eGFR and all–cause graft failure (Table 2).

To choose the optimal decline in eGFR between years 1 and 3 for use as a surrogate outcome, we compared various thresholds in terms of risk prediction (Table 3). All cut points from ≥10% to ≥50% decline in eGFR were predictive of both graft

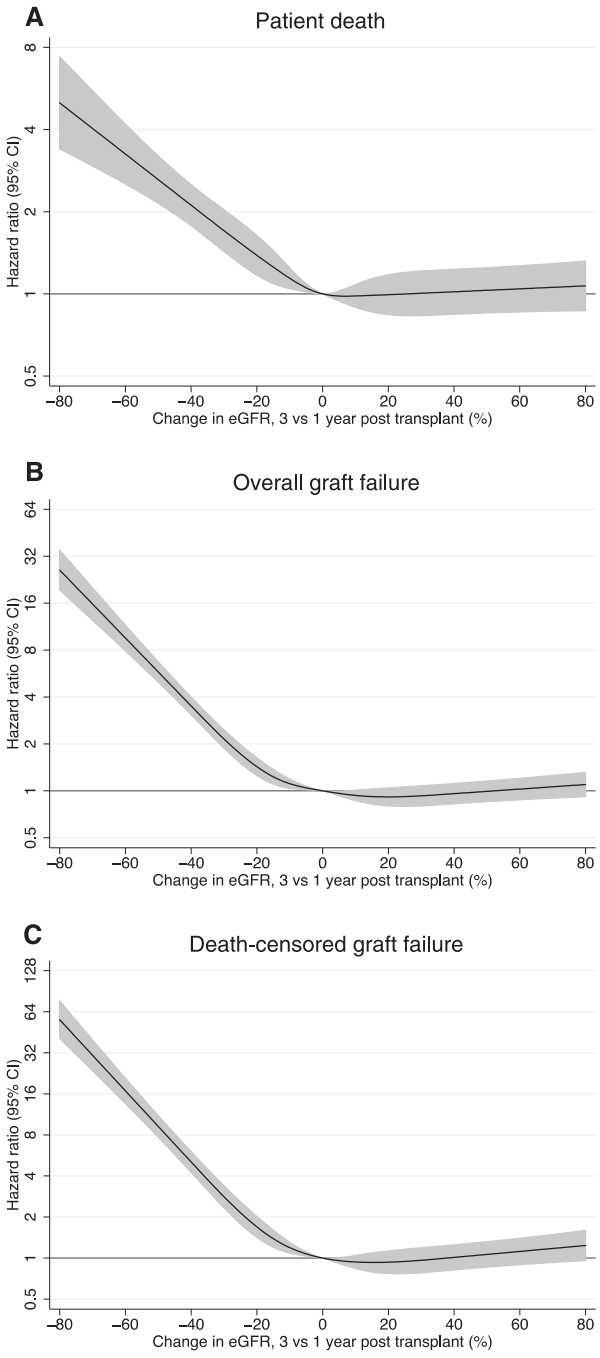

Figure 1. Relationship between decline in eGFR between years 1 and 3 post-transplant and hard outcomes. (A) Patient death, (B) overall graft failure, and (C) death-censored graft failure. The lines represent hazard ratios compared with no change in eGFR and the shaded regions are 95% CIs. Note the different scales on the y axes. All results are adjusted for the confounders reported in the text.

and patient survival. Predictably, the higher cut points were more strongly predictive but less common. Overall, no cut point was superior to others as assessed by *c* statistics. We favor a ≥30% decline as being both clinically plausible and exhibiting an acceptable tradeoff between prevalence and predictive power.

Table 2. HRs for the association between ≥30% decline in eGFR from years 1 to 3 and subsequent graft failure by subgroup

Subgroup	HR (95% CI)
Cause of graft failure	
Death with function	1.75 (1.42 to 2.16)
Acute rejection	4.48 (1.39 to 14.39)
Chronic allograft nephropathy	5.27 (4.46 to 6.22)
GN	5.04 (3.24 to 7.83)
Noncompliance	3.35 (1.86 to 6.03)
Other	5.08 (2.84 to 9.12)
Comorbid diabetes mellitus	
Yes	3.10 (2.22 to 4.33)
No	3.78 (3.30 to 4.31)
Donor source	
Deceased	3.39 (2.92 to 3.94)
Living	4.12 (3.31 to 5.13)
Prior transplant	
Yes	3.41 (2.48 to 4.70)
No	3.68 (3.22 to 4.20)
Cause of ESRD	
GN	4.22 (3.54 to 5.04)
Polycystic	3.53 (2.25 to 5.54)
Reflux	3.33 (2.26 to 4.89)
Hypertension	3.57 (1.83 to 6.98)
Diabetes	2.32 (1.58 to 3.40)
Other	4.14 (3.06 to 5.60)
Peak panel–reactive antibodies	
0%–49%	3.72 (3.25 to 4.27)
50%–79%	3.28 (2.09 to 5.15)
80%–100%	3.17 (2.12 to 4.74)
eGFR at year 1, ml/min per 1.73 m^2	
0–29	6.14 (4.25 to 8.89)
30–44	5.14 (4.03 to 6.56)
45–59	3.85 (3.04 to 4.86)
60–89	3.41 (2.68 to 4.33)
>90	5.12 (2.28 to 11.52)

A comparison of decline in eGFR between years 1 and 3 post-transplantation with various other potential surrogate markers of death and graft failure is shown in Table 4. Decline in eGFR of ≥30% between month 6 and year 2 post-transplantation was only modestly less predictive and less frequent. Doubling of serum creatinine between years 1 and 3 post-transplantation, the equivalent of a 57% decline in eGFR,[6] was more strongly predictive of both death and graft failure but less frequent than a ≥30% decline over the same period, occurring in only 1.9% of patients. Year 1 eGFR has been proposed[9] as a surrogate for trials; however, eGFR at years 1 or 2 post-transplantation was less strongly predictive than decline in eGFR. Acute rejection was common but only weakly predictive of death or graft failure.

We explored the effect of eGFR decline as a surrogate end point on power calculation for future clinical trials. If a treatment were to achieve an improvement of 5 ml/min per 1.73 m^2 in eGFR at year 3, on the basis of our data, 5% of treated subjects versus 10% of controls would experience a ≥30% decline in years 1–3 eGFR. To show this with 80% power, a trial enrolling 435 to each arm

Table 3. Relationships between percentage eGFR decline between years 1 and 3 post-transplant and outcome

eGFR Decline	Prevalence, %	Graft Failure		Patient Death	
		HR (95% CI)	*c* Statistic	HR (95% CI)	*c* Statistic
≥10%	33	2.09 (1.91 to 2.29)	0.68	1.52 (1.35 to 1.71)	0.75
≥20%	19	2.50 (2.26 to 2.77)	0.69	1.84 (1.62 to 2.10)	0.75
≥30%	10	3.58 (3.16 to 4.05)	0.70	2.20 (1.87 to 2.60)	0.75
≥40%	5	5.24 (4.43 to 6.20)	0.69	2.57 (2.04 to 3.22)	0.75
≥50%	3	7.90 (6.21 to 10.06)	0.67	2.96 (2.17 to 4.04)	0.75

would be required, rounded to 500 per arm to allow for dropouts. Such a difference in eGFR at 3 years has been achieved in recently reported trials comparing belatacept or everolimus with cyclosporin–based control groups.[10,11]

Use of inclusion criteria to enrich for patients at higher risk of eGFR decline, if possible, could reduce the numbers required for inclusion by ≤50%.

DISCUSSION

This registry analysis of a large cohort of kidney transplant recipients has shown that percentage decline in eGFR exhibits characteristics that would support its use as a surrogate marker for the important, hard, long–term outcomes of death and graft failure. Analogous to the situation in CKD, selecting a decline in eGFR over a 2-year trial period of ≥30% as a primary trial end point would, because of the higher frequency of this end point compared with ESRD or doubling of serum creatinine, facilitate the design of trials enrolling relatively smaller numbers of patients followed for 2 years. Such changes would reduce funding requirements and enhance feasibility, and they may thereby enable the conduct of trials now required to underpin improvements in long-term outcomes for kidney transplant recipients.[4]

A symposium conducted at the 2014 World Transplant Congress, "The Future of Transplantation Immunosuppression R&D: Problems and Solutions from Clinical, Biopharmaceutical and Regulatory Perspectives," concluded that use of surrogate outcomes should be considered to improve the feasibility of trials required to address the key unmet needs in clinical kidney transplantation (R. Morris, D. Kuypers, and P. O'Connell, personal communications).

Various measures of urinary protein excretion are predictive of long-term death and graft failure and have been considered as surrogate outcomes for trial purposes; however, lack of specificity[9] and test variability may limit the utility of single measures, such as spot urine protein-to-creatinine or albumin-to-creatinine ratios.[12,13]

Kidney function at 1 year post-transplant has previously been considered as a potential surrogate.[4,9,14] Hariharan *et al.*[14] studied 105,742 kidney recipients reported to United Network for Organ Sharing between 1988 and 1998 and described a strong, inverse relationship between 1-year serum creatinine and 5-year death–censored graft survival.[12] Using a cut point of 1.5 mg/dl, higher creatinine was most commonly associated with indicators of relative kidney mass at transplantation, such as men recipients, black recipients, women donors, older donors, and delayed graft function, whereas markers of alloimmune risk, such as incidence of acute rejection, HLA matching, and previous transplantation, seemed less strongly associated. On this basis, it can be argued that a single measure of graft function may be more reflective of endowment rather than ongoing immunologic processes.[4] Consistent with this hypothesis, the authors also examined "delta-creatinine" and found that change between month 6 and 1 year was superior to 1-year creatinine.[14] Limitations with this study include the lack of standardization of creatinine measurement, common use of cyclosporin and azathioprine rather than tacrolimus and mycophenolate, and higher rates of acute rejection in that era.[14] Kasiske *et al.*[9] examined the relationship between

Table 4. Associations between different eGFR–based surrogate outcomes and hard outcomes

Outcome	Prevalence, %	Graft Failure		Death–Censored Graft Failure		Patient Death	
		HR (95% CI)	*c* Statistic	HR (95% CI)	*c* Statistic	HR (95% CI)	*c* Statistic
≥30% decline eGFR 1–3 yr	9.9	3.58 (3.16 to 4.05)	0.70	5.14 (4.44 to 5.95)	0.75	2.20 (1.87 to 2.60)	0.75
≥30% decline eGFR 1–2 yr	6.1	3.51 (3.01 to 4.09)	0.68	4.69 (3.92 to 5.61)	0.72	2.33 (1.91 to 2.86)	0.75
≥30% decline eGFR 6 mo to 2 yr	8.7	2.94 (2.59 to 3.35)	0.68	4.16 (3.59 to 4.83)	0.73	1.99 (1.68 to 2.36)	0.75
eGFR at 1 yr <45 ml/min per 1.73 m^2	32.3	1.85 (1.69 to 2.02)	0.67	2.60 (2.31 to 2.93)	0.73	1.39 (1.24 to 1.56)	0.74
eGFR at 2 yr <45 ml/min per 1.73 m^2	33.7	2.21 (2.01 to 2.42)	0.68	3.16 (2.78 to 3.58)	0.74	1.68 (1.49 to 1.89)	0.75
Rejection first 6 mo	24.4	1.34 (1.21 to 1.47)	0.66	1.37 (1.21 to 1.55)	0.69	1.27 (1.12 to 1.44)	0.75
Double creatinine 1–3 yr	1.9	9.87 (7.27 to 13.42)	0.66	15.20 (11.18 to 20.67)	0.70	2.81 (1.84 to 4.29)	0.75
ΔeGFR 1–3 yr <−15 ml/min per 1.73 m^2	12.0	2.48 (2.20 to 2.81)	0.68	3.28 (2.84 to 3.80)	0.72	1.77 (1.50 to 2.09)	0.75

All models are adjusted for age at transplant, sex, race, primary disease, diabetes, coronary artery disease, peripheral vascular disease, cerebrovascular disease, chronic lung disease, donor type, prior transplant, donor age, HLA mismatch, peak panel–reactive antibodies, and era.

CKD stage as defined by MDRD eGFR at 1-year post-transplant and graft failure at 10 years among 13,671 patients transplanted between 1990 and 2007 and captured within the Patient Outcomes in Renal Transplant Study. Significantly increased hazards for graft loss were observed for those with CKD stage 3b (eGFR=30–45 ml/min per 1.73 m^2), with successive increases in hazards for stages 4 and 5. Similar limitations to those in the work by Hariharan *et al.*[14] apply to this data, and ΔGFR was not examined. In our dataset, eGFR<45 ml/min per 1.73 m^2 was present in 32.3% of the cohort at year 1, although it was less strongly associated with both graft and patient survival than ≥30% decline in eGFR between 1 and 3 years (Table 4).

Measures of alloimmune processes are another potential surrogate and have the advantage of measuring the target of immunosuppressive therapy. However, practical tests of alloimmunity are limited and have not been adequately predictive of long-term outcomes. Development of donor-specific antibodies is an infrequent event, and the relationship between donor–specific antibody development and graft and patient survival requires clarification.[15] Biopsy–proven acute rejection (BPAR) is clear demonstration of destructive alloimmunity; however, BPAR has become relatively infrequent, and the relationship between BPAR and graft and patient survival has been attenuated in recent eras. In our cohort, at 24.4% incidence, BPAR was more commonly observed than in current trials in kidney transplantation; however, it was less strongly associated with either patient or graft survival than was a ≥30% decline in eGFR between 1 and 3 years (Table 4).

Multiple potential causes of graft loss after kidney transplantation exist, including rejection, calcineurin inhibitor toxicity, hypertension, progression of donor-derived lesions, and recurrence of primary disease, and decline in eGFR as a surrogate provides limited insight into which of these is at play. Because a causal understanding is important, particularly in trials of immunosuppressive drugs, the use of dual or composite primary end points may provide greater insight. Use of composite primary end points has been common in clinical trials in transplantation, typically combining infrequent hard outcomes of death and graft loss with a more frequent surrogate, such as acute rejection. Combining the incidence of acute rejection with eGFR decline, death, or graft loss has significant appeal because of its frequency (incidence of 30% eGFR decline and/or acute rejection was 31.7% of our cohort), association with hard outcomes, and documentation of pathology.

The magnitude and timing of eGFR decline as an outcome measure may require tailoring to the specific trial requirements. We selected a 30% decline in eGFR between years 1 and 3, because it provided the best balance between frequency, clinical significance, and strength of association with hard outcomes. This timeframe would be best suited to switch trials,[11] and given the subtly different characteristics of different magnitudes of eGFR decline within the range of ≥20% to ≥40% (Table 3), we would encourage exploration of different cut points in designing such trials. Regarding *de novo* trials, ≥30% decline in eGFR between 6 months and 2 years post-transplant has great appeal, because this was only modestly less frequent and predictive of hard outcomes compared with ≥30% eGFR decline between years 1 and 3 (Table 4) but offers a far more pragmatic timeframe for *de novo* studies.

A surrogate end point is only useful in a trial context if the effect of intervention on the surrogate is subsequently mirrored by similar effects on hard outcomes. Recently, support for the use of either doubling of serum creatinine (the equivalent of a 57% decline in eGFR) or proteinuria as a surrogate for ESRD has been provided in this regard by calculation of a treatment effect ratio in a meta-analysis of 27 trials including 97,458 participants with CKD stages 1–4, a minority of whom were transplant recipients. The analysis found that treatment effects on both measures were consistent with the effects on ESRD and concluded that doubling of serum creatinine is generally a good surrogate for ESRD.[16] Demonstration of this in a purely transplant context may be difficult; however, registry–based long–term follow-up of trial participants may offer a means of confirming such a relationship in this context.[17,18]

The findings of this study seem robust given the large dataset examined and the consistency of results across sensitivity analyses examining patient mix, transplant number, different eGFR equations, and timing post-transplant. Indeed, the striking similarity to the results obtained from similar analyses in CKD cohorts[6] provides additional weight to the findings after kidney transplantation. However, extending these findings across populations of differing racial mix and comorbidity profiles and across recipients of different immunosuppressive regimens (steroid-free maintenance and use of lymphocyte–depleting induction therapy were both uncommon in this cohort) should be undertaken to ensure generalizability. Furthermore, a decline in kidney function post-transplant may be caused by alloimmune events, such as acute or chronic rejection, but also, other processes, including recurrent disease, drug toxicity, and hypertension. Another limitation in our study is the absence of data on proteinuria, donor-specific antibody, and graft histology, which precluded direct comparison of these potential surrogates with decline in eGFR. As discussed, a composite end point of decline in GFR and a measure of alloimmunity, such as BPAR, may represent a logical direction for immunosuppressive drug trial design.

We conclude that, as was the case in CKD,[6] a ≥30% decline in eGFR over 2 years was strongly associated with both death and graft loss among kidney transplant recipients, supporting consideration of this as a new surrogate end point for trials in kidney transplantation.

CONCISE METHODS

We analyzed deidentified data from the Australia and New Zealand Dialysis and Transplant Registry. The registry collects data on all patients receiving RRT in Australia and New Zealand. We included kidney transplant recipients in Australia and New Zealand over 1995–2009 (n=13,199) with follow-up until December 31, 2012. We

excluded recipients of multiorgan transplants (n=553) and patients aged <18 years old at the time of transplant (n=703). We further excluded those whose grafts functioned for <3 years (n=3810), those missing data for eGFR at 1 and/or 3 years (n=121), and those missing data for confounders (n=63), yielding a final cohort of 7949.

We used Cox proportional hazards models to examine the relationship between percentage change in eGFR calculated using the CKD-EPI equation[8] between the end of years 1 and 3 post-transplant and subsequent patient, graft, and death–censored graft survival. Patient survival was censored at retransplantation. Percentage change in eGFR was modeled as a restricted cubic spline. All models were adjusted for recipient age, sex, race, primary disease, comorbidities (diabetes, coronary artery disease, peripheral vascular disease, cerebrovascular disease, and chronic lung disease), graft number (primary versus subsequent), donor type (living versus deceased), donor age, HLA mismatch, peak panel–reactive antibody, and transplant era (five eras of 3 years each). We used cluster robust variance estimators to account for patients with more than one graft during the study period. Model fit was assessed using scaled Schoenfeld residuals, Martingale residuals, Cox–Snell residuals, and Harrell c concordance statistics.

In a sensitivity analysis, we examined seven other potential eGFR–based surrogates: percentage change in eGFR from 6 months to 2 years post-transplant and from 1–2 years post-transplant, eGFR at 1 year of <45 ml/min per 1.73 m^2, eGFR at 2 years of <45 ml/min per 1.73 m^2, rejection within the first 6 months post-transplant, doubling of serum creatinine between 1 and 3 years post-transplant, and the absolute change in eGFR between 1 and 3 years post-transplant of <−15 ml/min per 1.73 m^2. Each of these surrogates was examined using Cox models adjusted for the same confounders as the primary analysis. We compared the different predictors using prevalence, HRs, and Harrell c statistics.

Analyses were conducted in Stata/IC 14 (StataCorp., College Station, TX).

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The data reported here were supplied by the ANZDATA Registry. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the ANZDATA Registry.

DISCLOSURES

W.H.L. has participated in industry–sponsored clinical trials and symposia and received educational grants, travel support, or honoraria from companies producing immunosuppressant drugs, including Novartis (Basel, Switzerland), Alexion, Genzyme (Sanofi US, Bridgewater, NJ), and Pfizer. S.J.C. has participated in industry–sponsored clinical trials and symposia and received travel support or honoraria from companies producing immunosuppressant drugs, including Novartis, Astellas, Alexion, Roche (Basel, Switzerland), and Pfizer. The other authors of this manuscript have no conflicts of interest to disclose.

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