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Renal function following living, standard criteria deceased and expanded criteria deceased donor kidney transplantation: impact on graft failure and death

Mark A. Schnitzler,[1] Krista L. Lentine,[1] Adrian Gheorghian,[1] David Axelrod,[2] Digisha Trivedi[3] and Gilbert L'Italien[3,4]

1 Center for Outcomes Research, Saint Louis University, St. Louis, MO, USA
2 Dartmouth Hitchcock Medical Center, Hanover, NH, USA
3 Bristol-Myers Squibb, Health Services Division, Plainsboro, NJ, USA
4 Yale University, School of Medicine, New Haven, CT, USA

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Correspondence
Krista L. Lentine MD, MS, Saint Louis University Center for Outcomes Research, 3545 Lafayette Avenue, Salus Center, 4th Floor, SLUCOR St. Louis, MO 63104, USA.
Tel.: (314) 977-9477; fax: (314) 977-1101;
e-mail: lentinek@slu.edu

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Summary

We examined United States Renal Data System (USRDS) data for adult kidney transplant recipients in 1995–2003 (n = 87 575) to investigate associations of 12-month renal function with long-term clinical outcomes. Estimated glomerular filtration rate (eGFR) was computed by the Modification of Diet in Renal Disease (MDRD) equation. Associations of eGFR at the first transplant anniversary with graft and patient-survival in years 1–9 post-transplant were evaluated by multivariate nonlinear regression with spline forms, adjusted for recipient, donor, and transplant factors. Regardless of donor type, the likelihood of graft failure and death increased significantly with lower eGFR. The impact of poor eGFR was more pronounced for graft failure than death. Relative effects were similar across donor types, but were strongest among living-donor recipients. For example, compared with reference eGFR of 80 ml/min/1.73 m^2, 1-year eGFR of 20 ml/min/1.73 m^2 was associated with adjusted hazards ratios for subsequent death-censored graft failure of 9.2 in living, 8.9 in standard criteria deceased, and 5.9 in expanded criteria deceased-donor recipients. First-year renal function after kidney transplantation has strong, nonlinear associations with subsequent allograft and patient survival regardless of donor type. Post-transplant eGFR may be a useful end-point for discriminating benefits of care strategies that differentially affect renal function.

Introduction

Kidney transplant recipients face important challenges to long-term maintenance of allograft function including: reliance on a single, foreign kidney that may begin with limited functional capacity; insults from underlying causes of native end-stage renal disease (ESRD) such as diabetes and hypertension; immunologic damage in the form of acute and chronic rejection; and nephrotoxic effects of calcineurin inhibitors, which are a common component of contemporary maintenance immunosuppression but paradoxically cause chronic renal ischemia and fibrosis [1–5]. A majority of renal transplant recipients experience a gradual but steady decline in renal function after transplantation [6]. However, the rate of decline varies across individuals based on multiple factors including donor quality, recipient comorbidities, immunologic risk, and immunosuppressive regimen [7,8].

Graded associations of advancing stages of kidney dysfunction, as measured by estimated glomerular filtration rate (eGFR), with adverse outcomes including mortality have been observed in general, nontransplanted populations. In a study of more than one million adults in an integrated health care system, Go *et al.* reported nearly sixfold increases in the relative risk of death over an average of 2.8 years follow up [adjusted hazards ratio (aHR) 5.9, 95% CI 5.4–6.5] among persons with eGFR <15 ml/min/1.73 m^2 compared with ≥60 ml/min/1.73 m^2 [9]. A collaborative meta-analysis of general population cohorts comprising more than 100 000 participants recently found that the relative risk of mortality was fairly constant between eGFR 75 ml/min/1.73 m^2 and 105 ml/min/1.73 m^2 but increased at lower eGFRs [10]. Prior studies have described correlations of serum creatinine levels, serum creatinine changes and, more recently, eGFR with the risk of graft loss and death after kidney transplantation [1,11–14]. However, these relationships are not precisely quantified across a spectrum of function levels and donor types in large, contemporary samples.

Quantifying associations of early renal function with long-term graft and patient outcomes may provide important information for discriminating the impact of organ quality and treatment strategies that may differentially affect allograft function. Therefore, we examined national registry data for a large cohort of transplant recipients in the United States to characterize the relationship of kidney function at the first transplant anniversary, as measured by eGFR, with patient and allograft survival during years 1–9 after transplant. A unique methodological feature of this study was use of nonlinear spline regression to flexibly estimate risk relationships across incremental units of eGFR. Relationships were examined separately according to living donor (LD), standard criteria deceased (SCD) and expanded criteria deceased (ECD) donor source.

Materials and methods

Data, sample, and funding

Data for all recipients of single-organ kidney transplants in the US in 1995–2003 were drawn from the US Renal Data System (USRDS) database, as follow up in our study data was available through December 2004. The USRDS is a joint effort of the National Institute of Diabetes and Digestive and Kidney Disease (NIDDK) and the Centers for Medicare and Medicaid Services (CMS) that tracks many descriptive elements for all patients in the US ESRD program [15]. USRDS registries integrate information from the Organ Procurement and Transplantation Network (OPTN), CMS, and Medicare billing claims records. These elements are linked with a unique encrypted patient identifier, permitting investigators to combine patient-specific information from multiple tables without revealing patient identity. This study was conducted in accordance with the Health Insurance Portability and Accountability Act of 1996, and all standards regarding the security and privacy of an individual's health information were maintained. This work was supported in part by a grant from Bristol-Myers Squibb. The manuscript does not include discussion of any pharmaceutical product, other health care product, or off-label use of medications. The sponsor's support of the research does not cover publication nor is there any restriction of the authors' publication rights by the sponsor. The analyses, interpretation, medical writing and reporting of these data are the responsibility of the authors.

Subjects who died or experienced graft failure prior to the first transplant anniversary were excluded. Subjects also were excluded if the data elements required for calculation of eGFR at 1-year post-transplant – the central variable of interest for this study – were not recorded in the database; these included the serum creatinine level and recipient age, gender, and race.

Predictor and outcome variable definitions

The main predictor variable of interest was renal function at the first post-transplant anniversary, as quantified by eGFR. eGFR was computed according to the abbreviated MDRD equation [16] as: eGFR (ml/min/1.73 m^2) = $186 \times (\text{Serum Creatinine mg/dl})^{-1.154} \times \text{Age}^{-0.203} \times (1.212$, if African-American) $\times (0.742$, if female). The abbreviated MDRD equation has superior performance for prediction of measured GFR among renal transplant patients when compared with the Nankivell and Cockcroft–Gault equations [17].

The primary outcomes of interest were patient death and graft failure assessed from 1–9 years post-transplant. Center reports of post-transplant death were augmented with Social Security Master Death File records within the USRDS. *Mortality* was defined as death from any cause. *Death-censored graft failure* was defined as the earliest reported date of return to maintenance dialysis or ''preemptive'' re-transplantation. *All-cause graft loss* was defined as the combination of mortality and death-censored graft failure. Patients were censored from survival analysis at the date of their last expected follow up.

Statistical analysis

Data management and analysis were performed with SAS for Windows software, version 9.2 (SAS Institute Inc., Cary, NC, USA). Multivariable Cox's regression was used to develop prediction models for all-cause graft loss, death-censored graft failure, and death after

transplant. In a preliminary investigation, level of kidney function was classified according to a modification of the eGFR-based schema of the Kidney Foundation, Kidney Disease Outcomes Quality Initiative (NKF/KDOQI) [18]. Patients with an eGFR of 60 ml/min/1.73 m^2 or more were combined as the reference group. KDOQI stage 3 (30–59 ml/min/1.73 m^2) was divided mid-way into stages 3A (45–59 ml/min/1.73 m^2) and 3B (30–44 ml/min/1.73 m^2). KDOQI stage 4 was defined as eGFR 15–29 ml/min/1.73 m^2. Patterns of nonlinear and accelerating increases in hazards of graft failure and death were observed. Therefore, a flexible nonlinear technique known as smoothed natural cubic splines was used to optimize fit of the survival functions. Spline fitting of curves was first described by Schoenberg in 1946 [19]. The smoothed natural splines employed here are cubic, or third power, polynomial expansions of an independent variable of interest in a regression equation [20], in this case eGFR. The reference function level for eGFR-related risk was set at eGFR 80 ml/min/1.73 m^2. Basis knots, which define the form of the polynomial expansion, where chosen to follow the K/DOQI ''Stages of Chronic Kidney Disease'' starting at 15 ml/min/1.73 m^2 with additional knots at intervals of 15 ml/min/1.73 m^2 through 150 ml/min/1.73 m^2. An additional knot at 22.5 ml/min/1.73 m^2 was found to significantly increase fit of graft survival models based on the likelihood function, and was included in all models. Equations for the spline functions in SAS are provided in Appendix 1. The predicted probability of 9-year all-cause graft survival among survivors to the first transplant anniversary according to 12-month eGFR and donor type was computed from the final Cox regression model.

The models in this study employed the structure and covariates developed by the UNOS Kidney Allocation Committee to predict survival after kidney transplantation [21]. All demographic and clinical characteristics known at the time of transplant were included in exact accordance with the UNOS models, with the exception of shared organ status, which was not present in the USRDS database available for public use. Recipient and donor race are omitted from the UNOS models but were included here (Appendix 2). Because the starting point for outcomes assessment in our study began at the first transplant anniversary, acute rejection during the first year was included as a baseline variable in all equations. No statistical variable selection was performed, such that the content of all regression models was determined prior to analysis. Unexpected patterns in the estimates were investigated with categorical breakdowns of the involved variables which are discussed; however, these are subanalyses, and the regression estimates reported do not deviate from the UNOS models. Continuous data were summarized as means and standard deviations, and categorical data were summarized as proportions.

Results

Demographic and clinical characteristics

There were 126 073 kidney transplants recorded in the USRDS database during the study period. Of these, 14 061 were excluded as a result of graft loss before the first post-transplant anniversary; 22 013 were excluded because of missing 12-month OPTN follow-up record; and 2424 were excluded as a result of missing one or more of the data elements required to calculate eGFR at one-year post-transplant. Thus, 87 575 patients were available for study. Median follow-up was 4.3 years after the first transplant anniversary.

The distribution of recipient, donor, and transplant characteristics varied considerably across donor types (Table 1). For example, recipients of LD allografts were younger, more commonly white race, and less frequently had diabetes or high levels of sensitization compared with deceased donor recipients. ECD recipients tended to be the oldest group and to have the highest frequency of diabetes. Overall, the majority of study participants received SCD organs ($n = 49\,551$); 32 681 received LD organs, and 5343 received ECD organs. Mean eGFR at 12-months post-transplant was similar among recipients of SCD (54.9 ml/min/1.73 m^2) and LD (57.9 ml/min/1.73 m^2) transplants, while mean eGFR at 12-months post-transplant was substantially lower in ECD recipients (37.8 ml/min/1.73 m^2). Overall, 5.6% of LD, 8.6% of SCD, and 23.8% of ECD transplants had a 1 year eGFR <30 ml/min/1.73 m^2.

Relative risks of all-cause graft loss

All-cause graft loss was strongly predicted by eGFR at 1-year post-transplant. Multivariate regression analyses describing the relative hazards of all-cause graft loss in relation to baseline factors among recipients of each donor type are presented in Table 2. Lower renal function, measured as eGFR, was a strong and statistically significant predictor of all-cause graft loss for each donor type ($P < 0.0001$). The spline terms are difficult to interpret numerically but are easily understood when displayed visually. Figure 1a displays the shape of the estimated aHR for all cause graft loss as it varies by eGFR for recipients of SCD organs compared with reference eGFR of 80 ml/min/1.73 m^2. Above 70 ml/min/1.73 m^2, the 95% confidence interval for the aHR bounds 1.00, indicating no significant difference in the relative risk of all-cause graft loss compared with eGFR of 80 ml/min/1.73 m^2. As eGFR drops below 70 ml/min/1.73 m^2, the hazard for all-

cause graft loss is significant and increases in an accelerating pattern. Our ability to identify the relationship between eGFR and all-cause graft loss diminishes below approximately 10 ml/min/1.73 m^2. This is caused by a small sample of subjects with reported graft viability at 12-months post-transplant at an eGFR less than 10 ml/min/1.73 m^2, as well as from edge effects of the spline fitting methods.

The relationship between eGFR and all-cause graft loss observed for SCD transplant recipients was similar among LD and ECD recipients. Figure 1b displays the aHR for all-cause graft loss with eGFR between 10 and 70 ml/min/1.73 m^2 for each donor type. A consistent pattern of rapidly increasing risk of graft loss at with reduced 12 month eGFR was observed across donor types.

The associations of other baseline covariates with the risk of all-cause graft loss were similar among SCD and ECD transplant recipients. However, more significant covariate effects were observed for SCD compared with ECD transplants, likely because of the nearly 10-fold larger sample of SCD recipients. Although fewer covariates showed significant associations with all-cause graft loss among LD recipients, most of the LD estimates followed the patterns observed for SCD transplants. However, there were differences in estimated preemptive transplant effects. It is important to note that the years of dialysis and preemptive transplant variables must be interpreted together and this interpretation can be complicated. The pattern of the estimates indicated that preemptive transplant is associated with reduced LD transplant graft loss. The pattern also suggests that a long duration dialysis is associated with lower risk of LD graft loss than a short duration of dialysis. However, LD transplantation after a long duration of dialysis is relatively rare and this interpretation was not found to be statistically significant in further investigation with a categorical breakdown of dialysis duration. Acute rejection was associated with significantly increased risk of all-cause graft loss among LD and SCD recipients and a consistent but nonsignificant pattern in ECD recipients. The size of the acute rejection effect was similar to impact of eGFR between 40 and 45 ml/min/1.73 m^2 and approximately one-tenth the impact of eGFR of 25 ml/min/1.73 m^2.

Relative risks of death-censored graft loss

Death-censored graft loss, defined as return to dialysis or preemptive re-transplant, was strongly predicted by eGFR at 12 months post-transplant. Multivariate analysis of death-censored graft loss for each donor type is presented in Table 3. The shape of the nonlinear relationship between eGFR and the aHR for death-censored graft loss (Fig. 1c) was similar to that for all-cause graft

Table 1. Characteristics of US kidney transplant recipients (1995–2003) by donor type.

	LD	SCD	ECD
Number of subjects	32 681	49 551	5343
Candidate/recipient variables			
eGFR at 1 Year Post-Transplant (ml/min/1.73 m^2; mean)	57.9	54.9	37.8
Recipient age (year; mean)	41.3	45.5	52.5
Male (%)	58.2	60.3	60.1
Pretransplant dialysis			
None (preemptive) (%)	52.2	6.0	4.8
Years of dialysis (mean)	3.9	4.7	4.2
Body mass index (kg/m^2; mean)	25.9	26.1	26.6
Missing (%)	25.0	26.3	27.1
Cause of ESRD			
Glomerulonephritis or diabetes (%)	45.0	42.5	42.7
Hypertension (%)	12.5	18.1	22.1
Polycystic kidney disease (%)	7.8	8.6	9.6
Other (%)	34.7	30.8	25.6
Diabetes (%)	23.2	26.5	45.8
Previous transplant (%)	8.8	31.4	27.6
Peak panel reactive antibody			
<10 (%)	80.5	70.3	73.3
10–79 (%)	13.1	20.3	19.3
80+ (%)	2.1	7.0	4.9
Missing (%)	4.3	2.4	2.5
HLA mismatches			
Zero A, B, and DR (%)	13.0	14.4	11
Zero DR (%)	26.7	23.8	23.2
Serum albumin at listing			
Serum albumin (g/dl; mean)	3.8	3.8	3.8
Missing (%)	68.3	82.5	84.8
Pre-emptive transplant (%)	52.2	6.0	4.8
Race			
White (%)	81	67.4	65.0
African-American (%)	13.9	26.5	27.8
Other (%)	5.1	6.1	7.2
Donor variables			
Age (year; mean)	39.3	31.2	62.1
Missing (%)	0.0	13.1	–
Hypertension (%)	–	12.2	58.4
Weight (kg)	88.2	72.3	79.1
Missing (%)	50.1	0.7	0.2
Race			
White (%)	82.3	86	92.7
African-American (%)	13.0	11.0	7.3
Other (%)	4.7	3.0	3.3
Cause of death			
Anoxia (%)	–	10.5	3.9
Cerebrovascular accident (%)	–	31.9	85.5
Head trauma (%)	–	54.0	8.9
CNS tumor (%)	–	1.1	0.6
Other (%)	–	2.4	1.3
First-year acute rejection			
Antibody treated (%)	4.2	4.2	4.5
Not antibody treated (%)	8.5	9.0	11.7

CNS, central nervous system; ECD, expanded criteria donor transplant; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HLA, human leukocyte antigen; LD, living donor transplant; SCD, standard criteria donor transplant.

Table 2. Multivariate regression models for prediction of all-cause graft loss 1–9 years after transplant according to 1-year eGFR and other baseline factors.

	LD	SCD	ECD
	Adjusted hazards ratio	Adjusted hazards ratio	Adjusted hazards ratio
eGFR at 1 year post-transplant			
Joint significance of eGFR	See Fig. 1b¶	See Fig. 1b¶	See Fig. 1b¶
Candidate/recipient variables			
Recipient age (per year/10)	0.99	1.01	1.08†
Male	1.05	1.14§	1.21§
Pretransplant dialysis			
Preemptive transplant	0.59§	1.01	1.06
Per natural log of years of dialysis +1	0.70§	0.98	0.99
Body mass index (per kg/m^2)	1.01*	1.01§	1.02
>20	0.99*	0.99§	0.99*
Missing	1.12	1.07	1.20
Cause of ESRD			
Glomerulonephritis and diabetes	Reference	Reference	Reference
Hypertension	1.37	1.23§	1.21†
Polycystic kidney disease	0.59	0.67§	0.75†
Other	1.09	1.10‡	1.20†
Diabetes	0.91	0.84	1.34
Diabetes × Age (years/10)	1.10	1.13§	1.04
Previous transplant	1.62	1.18§	1.05
Peak panel reactive antibody (PRA)			
<10	Reference	Reference	Reference
10–79	1.13	1.07†	1.16†
80+	1.20	1.22§	1.35†
Missing	1.07	1.00	1.36
HLA mismatches			
Zero A, B, and DR	0.69§	0.90‡	0.89
Zero DR	0.93	0.95*	0.86*
Serum albumin at listing (per g/dl)	1.12	0.99	0.72
>3.5	0.94*	0.98	1.13
Missing	1.26	0.53	0.39
Race			
White	Reference	Reference	Reference
African-American	1.52*	1.58§	1.40§
Other	1.05	0.80§	1.02
Year of transplant	1.01	1.02†	1.02
Donor variables			
Age (per year)	1.03*	1.00	1.00
>18	0.98	1.00	–
Missing	2.54	1.08	–
Hypertension (cadaveric donor)	–	0.96	1.07
Cytomegalovirus positive	1.08*	1.07†	1.04
Per natural log of weight (kg)	0.83	0.94*	0.92
Weight missing	0.42	0.78	0.98
Race			
White	Reference	Reference	Reference
African-American	1.10	1.11‡	1.10
Other	1.05*	1.05	0.76
Cause of death			
Anoxia	–	Reference	Reference
Cerebrovascular accident	–	0.92	0.96
Head trauma	–	0.94	0.96
CNS tumor	–	0.96	0.95
Other	–	0.98	0.98
First-year acute rejection			
No rejection	Reference	Reference	Reference
Antibody treated	1.27§	1.34§	1.17
Not antibody treated	1.29§	1.26§	1.12

CNS, central nervous system; ECD, expanded criteria donor transplant; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HLA, human leukocyte antigen; LD, living donor transplant; SCD, standard criteria donor transplant.
P-values: **P* 0.02–0.04; †*P* 0.002–0.01; ‡*P* 0.0001–0.001; §*P* < 0.0001.
¶Spline terms as defined in Appendix 1.

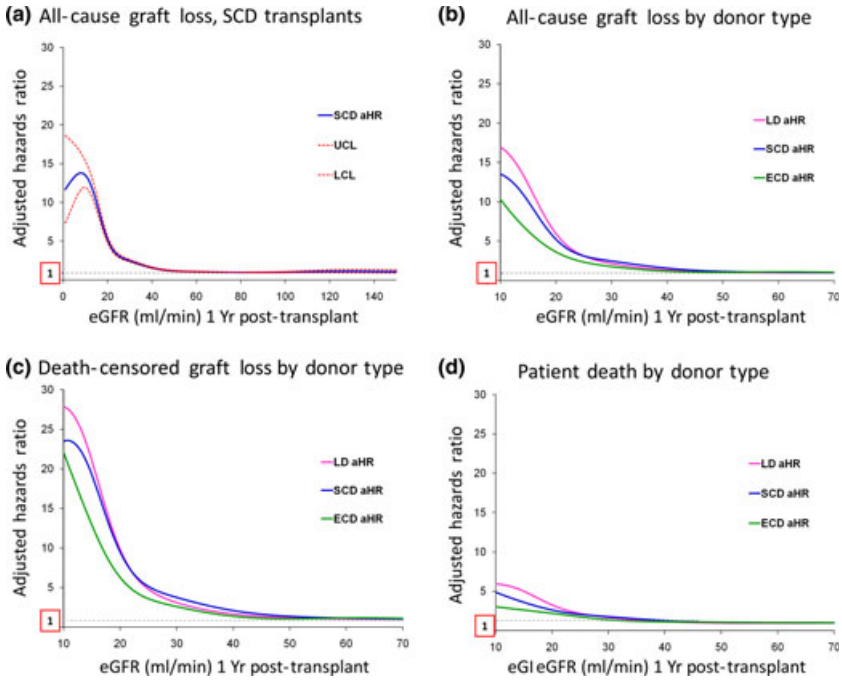

Figure 1 Relative hazard ratios for graft loss and death in years 1–9 after transplant according to 12-month eGFR by cubic spline regression. *aHR >1.0 indicates increased risk compared with the reference eGFR of 80 ml/min/1.73 m^2. Figure (a) includes 95% confidence limits for aHR for all-cause graft loss across renal function levels among SCD recipients. For clarity, confidence limits are excluded from plots stratified by donor type (b–d). Please see Table 5 for eGFR values corresponding to select levels of relative risk for each of the study outcomes.

loss (Fig. 1b), although the effect of low eGFR was somewhat magnified. As observed for all-cause graft loss, the patterns of risk for death-censored graft loss according to eGFR were similar among LD, SCD, and ECD recipients and highly significant in each case ($P < 0.0001$). No significant effects on death-censored graft loss risk were observed for eGFR greater than 65 ml/min/1.73 m^2 compared with 80 ml/min/1.73 m^2. Again, the ability to identify the relationship between eGFR and all-cause graft loss diminishes below approximately 10 ml/min/1.73 m^2.

Associations of donor and recipient characteristics with the risk of death-censored graft loss were similar to those for all-cause graft loss with some notable exceptions. Recipient age was associated with significantly lower risk of death-censored graft loss regardless of donor type. Dialysis duration and preemptive transplant showed patterns for death-censored graft loss across the three donor types that were similar to the patterns observed for all-cause LD graft loss. As for all-cause graft loss, the suggestion of benefits from long duration dialysis was found to be insignificant when dialysis duration was broken into categories. Finally, the relative risk associated with African-American compared with white race doubled from approximately 10% for all-cause graft loss (aHR 1.1) to approximately 100% for death-censored graft loss (aHR 2.0) regardless of donor type. Acute rejection had significant associations with death censored LD and SCD graft loss that were comparable to the impact of eGFR between 45 and 50 ml/min/1.73 m^2.

Relative risks of patient death

Patient death was also significantly associated with eGFR at 12 months post-transplant. Multivariate analyses for prediction of death among recipients of each donor type are presented in Table 4. The shape of the nonlinear relationship between eGFR and the aHR for death (Fig. 1d) is similar but the effect size is diminished compared with the relationships of eGFR with graft loss risk (Fig. 1c). As observed for all-cause graft loss and death-censored graft loss, the patterns of the aHR for death at a given level of eGFR compared with 80 ml/min/1.73 m^2 were similar among LD, SCD, and ECD recipients and highly significant in each case ($P < 0.0001$). No significant effects on death hazard were observed for eGFR greater than 70 ml/min/1.73 m^2 compared with 80 ml/min.

The associations of other baseline covariates with mortality risk were generally similar to those for all-cause graft loss and death-censored graft loss with some notable exceptions. Older recipient age was a strong and significant predictor of death regardless of donor type. Dialysis

Table 3. Multivariate regression models for prediction of death-censored graft loss 1–9 years after transplant according to 1-year eGFR and other baseline factors.

	LD	SCD	ECD
	Adjusted hazards ratio	Adjusted hazards ratio	Adjusted hazards ratio
eGFR at 1 year post-transplant			
Joint significance of eGFR	See Fig. 1c¶	See Fig. 1c¶	See Fig. 1c¶
Candidate/recipient variables			
Recipient age (per year/10)	0.74§	0.74§	0.87§
Male	1.01	1.10‡	1.23†
Pretransplant dialysis			
Preemptive transplant	0.39§	0.76§	0.77*
Per natural log of years of dialysis + 1	0.54§	0.80§	0.80*
Body mass index (per kg/m^2)	1.00	1.01	1.01
>20	1.00	0.99‡	0.99
Missing	1.09	0.99	1.10
Cause of ESRD			
Glomerulonephritis and diabetes	Reference	Reference	Reference
Hypertension	1.47§	1.32§	1.18
Polycystic kidney disease	0.54§	0.69§	0.75*
Other	0.99	1.07*	1.17
Diabetes	1.30	0.86	1.07
Diabetes × Age (years/10)	0.94	1.07†	1.03
Previous transplant	2.05§	1.36§	1.11
Peak panel reactive antibody (PRA)			
<10	Reference	Reference	Reference
10–79	1.19†	1.10†	1.23†
80+	1.05	1.27§	1.48†
Missing	1.21*	1.01	1.19
HLA mismatches			
Zero A, B, and DR	0.69§	0.80§	0.81*
Zero DR	0.85†	0.91†	0.75‡
Serum albumin at listing (per g/dl)	1.19*	1.00	0.47
>3.5	0.91†	1.01	1.37*
Missing	1.40	0.94	0.15
Race			
White	Reference	Reference	Reference
African-American	2.05§	2.03§	1.80§
Other	1.04	0.96	1.34*
Year of transplant	1.03	1.03§	1.02
Donor variables			
Age (per year)	1.03†	1.00	1.00
>18	0.97†	1.00	–
Missing	0.001	1.12	–
Hypertension (cadaveric donor)	–	0.93	1.10
Cytomegalovirus positive	1.11*	1.06*	1.01
Per natural log of weight (kg)	0.67†	0.94	0.79*
Weight missing	0.16†	0.71	0.22
Race			
White	Reference	Reference	Reference
African-American	1.05	1.20§	1.2
Other	0.75	1.02	0.63*
Cause of death			
Anoxia	–	Reference	Reference
Cerebrovascular accident	–	0.74	1.01
Head trauma	–	0.78	1.14
CNS tumor	–	0.83	0.45
Other	–	0.85	1.47
First-year acute rejection			
No rejection	Reference	Reference	Reference
Antibody treated	1.34§	1.41§	1.12
Not antibody treated	1.34§	1.29§	1.07

CNS, central nervous system; ECD, expanded criteria donor transplant; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HLA, human leukocyte antigen; LD, living donor transplant; PRA, panel reactive antibody; SCD, standard criteria donor transplant.
P -values: **P* 0.02–0.04; †*P* 0.002–0.01; ‡*P* 0.0001–0.001; §*P* < 0.0001.
¶Spline terms as defined in Appendix 1.

Table 4. Multivariate regression models for prediction of patient death 1–9 years after transplant according to 1-year eGFR and other baseline factors.

	LD	SCD	ECD
	Adjusted hazards ratio	Adjusted hazards ratio	Adjusted hazards ratio
eGFR at 1 year post-transplant			
Joint significance of eGFR	See Fig. 1d¶	See Fig. 1d¶	See Fig. 1d¶
Candidate/recipient variables			
Recipient age (per year/10)	1.56§	1.61§	1.58§
Male	1.08	1.16§	1.13
Pretransplant dialysis			
Pre-emptive transplant	0.96	1.35§	1.39†
Per natural log of years of dialysis + 1	1.03	1.23§	1.23*
Body mass index (per kg/m^2)	1.01*	1.02§	1.03*
>20	0.99*	0.98§	0.98†
Missing	1.08	1.14*	1.24
Cause of ESRD			
Glomerulonephritis and diabetes	Reference	Reference	Reference
Hypertension	1.30§	1.19§	1.27†
Polycystic kidney disease	0.67‡	0.69§	0.88
Other	1.26§	1.11†	1.28†
Diabetes	4.64§	4.54§	6.74§
Diabetes × Age (years/10)	0.86§	0.87§	0.82‡
Previous transplant	1.30†	1.07	0.96
Peak panel reactive antibody			
<10	Reference	Reference	Reference
10–79	1.04	1.08†	1.06
80+	1.40†	1.24§	1.47†
Missing	0.94	1.02	1.40*
HLA mismatches			
Zero A, B, and DR	0.73§	0.97	0.99
Zero DR	1.03	0.95	1.00
Serum albumin at listing (per g/dl)	0.92	0.91	0.89
>3.5	1.00	0.97	1.02
Missing	0.77	0.60	0.60
Race			
White	Reference	Reference	Reference
African-American	1.12	1.17§	1.05
Other	0.98	0.72§	0.71*
Year of transplant	0.97	1.00	1.02
Donor variables			
Age (per year)	1.02	1.00	1.00
>18	0.98	1.00	–
Missing	5.67	1.09	–
Hypertension (cadaveric donor)	–	0.98	1.07
Cytomegalovirus positive	1.01	1.07†	1.10
Per natural log of weight (kg)	0.98	0.93*	1.03
Weight missing	0.95	0.91	1.63
Race			
White	Reference	Reference	Reference
African-American	1.12	0.99	0.95
Other	0.98	1.15	0.86
Cause of death			
Anoxia	–	Reference	Reference
Cerebrovascular accident	–	0.93	1.04
Head trauma	–	0.96	1.01
CNS tumor	–	0.94	0.85
Other	–	0.91	1.04
First-year acute rejection			
No rejection	Reference	Reference	Reference
Antibody treated	1.18*	1.13*	1.07
Not antibody treated	1.01	1.12†	1.23*

CNS, central nervous system; ECD, expanded criteria donor transplant; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HLA, human leukocyte antigen; LD, living donor transplant; SCD, standard criteria donor transplant.
P-values: **P* 0.02–0.04; †*P* 0.002–0.01; ‡*P* 0.0001–0.001; §*P* < 0.0001.
¶Spline terms as defined in Appendix 1.

duration and preemptive transplant were not significantly associated with death among LD recipients and suggested that short dialysis durations (less than 2 years) are related to less death risk than either preemptive or long dialysis durations among SCD and ECD recipients. Further investigation with a categorical breakdown of dialysis duration showed that this was significant for ECD ($P = 0.002$) and marginally significant for SCD ($P = 0.05$), and may be because of characteristics of patients receiving transplants after short dialysis durations, particularly younger age. For both SCD and ECD, the categorical investigation confirmed that significantly higher death rates are associated with long dialysis durations. Acute rejection effects were comparable to the impact of an eGFR of 40 ml/min/1.73 m^2 for LD, 45 ml/min/1.73 m^2 for SCD and 33 ml/min/1.73 m^2 for ECD.

Table 5 provides eGFR levels corresponding to select relative risk levels for each of the study outcomes, across donor types.

Predicted probability of 9-year all-cause graft survival

Variation in the predicted probability of 9-year all-cause graft survival among survivors to the first transplant anniversary according to 12-month eGFR and donor type is shown in Table 6. Among those with 12-month eGFR >60 ml/min/1.73 m^2, the predicted 9-year all-cause graft survival in LD, SCD, and ECD recipients was 63.4%, 57.7%, and 46.3, respectively. In those with 12-month eGFR of 40 ml/min/1.73 m^2, the predicted 9-year all-cause graft survival in LD, SCD, and ECD recipients was 53.3%, 42.0%, and 39.3, respectively. Predicted all-cause graft survival was less than 10% in all recipients with 12-month eGFR of 20 ml/min/1.73 m^2, regardless of donor type.

Table 6. Predicted probability of 9-year graft survival among survivors to the first transplant anniversary, according to 12-month eGFR and donor type.

12-month eGFR (ml/min/1.73 m^2)	LD survival (%)	SCD survival (%)	ECD survival (%)
>60	63.4	57.7	46.3
50	60.3	52.6	46.4
40	53.3	42.0	39.3
30	36.2	26.0	25.5
20	7.2	6.4	7.6

ECD, expanded criteria donor transplant; eGFR, estimated glomerular filtration rate; LD, living donor transplant; SCD, standard criteria donor transplant.

Discussion

A more detailed understanding of the relationships of renal function with patient and graft survival after kidney transplant may improve prediction of long-term clinical outcomes and thereby provide a useful surrogate measure for assessing of the impact of graft quality and early clinical interventions. We examined national registry data for a large cohort of US transplant recipients to quantify associations of eGFR at the first transplant anniversary with patient and allograft survival in years 1–9 after transplant. Flexible functions known as cubic splines [20] were employed to allow the shape of the risk relationships to vary nonlinearly across levels of eGFR. We found that eGFR measured at 1-year after kidney transplant is strongly associated with subsequent graft loss and patient death. The relative risk of all-cause graft loss rose as eGFR declined less than 70 ml/min/1.73 m^2 among SCD recipients, and was 5-fold higher in those with 1-year eGFR of 20 ml/min/1.73 m^2 compared with 80 ml/min/1.73 m^2.

Table 5. eGFR values corresponding to select levels of relative risk for each of the study outcomes, by donor type*.

		eGFR level (ml/min/1.73 m^2) corresponding to indicated relative risk level, by donor type		
Outcome	Relative risk level	LD	SCD	ECD
All-cause graft loss	aHR significantly increased versus reference	47	76	37
All-cause graft loss	aHR 2.0	38	41	34
All-cause graft loss	aHR 5.0	31	34	27
Death-censored loss	aHR significantly increased versus reference	51	75	39
Death-censored loss	aHR 2.0	42	47	38
Death-censored loss	aHR 5.0	36	40	34
Patient death	aHR significantly increased versus reference	40	49	29
Patient death	aHR 2.0	33	35	38
Patient death	aHR 5.0	26	25	22

aHR, adjusted hazards ratio; ECD, expanded criteria donor transplant; eGFR, estimated glomerular filtration rate; LD, living donor transplant; SCD, standard criteria donor transplant.

*aHR were estimated using a reference eGFR of 80 ml/min/1.73 m^2 in all models. Please see Fig. 1 for graphical displays of the estimated aHR for each of the study outcomes across eGFR values.

Importantly, magnitude of risk for graft loss and patient death increases as eGFR declines in a nonlinear fashion, a novel finding revealed by the spline methodology. Associations were present among recipients of LD, SCD, and ECD allografts. The overall similarity of the eGFR effects across donor types illustrates the importance of renal function preservation after kidney transplantation for all recipients regardless of the source of the donated organ.

Prior studies have described associations of post-transplant renal function at 12 months with subsequent clinical outcomes. Based on registry data for US transplant recipients in 1988–1998, Hariharan *et al.* reported a 63% increase in the relative risk of long-term graft loss (HR 1.63, 95% CI 1.61–1.65) for each 1.0 mg/dl increment in serum creatinine measured at the first transplant anniversary [1]. More recently, with the development and validation of eGFR from the MDRD equation as a superior measure of renal function in populations including transplant recipients [17], low eGFR has been linked with inferior clinical outcomes including post-transplant survival. Large administrative database studies and prospective cohort meta-analysis have confirmed the predictive value of eGFR for general population mortality [9,10]. Among transplant recipients, a small study of 447 DD recipients at one center found that 10-year graft and patient survival were 87% and 96%, respectively, in patients with 12-month eGFR ≥90 ml/min/1.73 m^2 vs. 23% and 62% in those with eGFR <30 ml/min/1.73 m^2 [13]. We recently found that compared with transplant recipients with 12-month eGFR ≥60 ml/min/1.73 m^2, the adjusted relative risk of death-censored graft failure in years 1–3 was 31% greater with eGFR 45–59 and 622% greater with eGFR 15–30 ml/min/1.73 m^2 [14]. The current study is notable for employing a nonlinear regression approach that explored the shape of risk relationships across a clinically relevant spectrum of eGFR values, comparison of eGFR-outcome associations across donor types, and use of large sample that allowed inclusion of the standard adjustment covariates of the UNOS Kidney Committee. These methods provide a more complete understanding of the long-term consequences of early allograft dysfunction.

Acute rejection has been incorporated within composite end-points in immunosuppression trials among kidney transplant recipients [22]. Consideration of renal function as a clinical trial end-point is relatively new [23]. In the current study, we found that eGFR at 1-year post-transplant may have an impact on subsequent graft survival that is more than an order of magnitude larger than the impact of first-year acute rejection. Renal function at 1-year post-transplant may have an impact on subsequent survival that is more than an order of magnitude larger than the impact of acute rejection. Therefore, eGFR may prove to be a useful clinical trial end-point, offering an advance in trial design that may allow more efficient discrimination of the benefits of alternative therapeutic regimens independent of donor source.

This study is limited by the retrospective design. It is possible that future changes in clinical practice may modify the outcomes implications of renal function at the first transplant anniversary [7]. An additional limitation is the use of eGFR as a surrogate for measured renal function (e.g., by methods such as iothalamate clearance), which has likely introduced statistical noise in the estimates. The typical consequence of statistical noise is a reduction in estimated effect sizes. Therefore, it is possible that the relationship between true GFR and survival in renal transplantation is larger than reported here. Although the use of measured GFR might provide more accurate estimates of the relationship of renal function with clinical outcomes, measured GFR is not commonly obtained in the care of kidney transplant patients and is difficult and expensive to acquire for a large samples. eGFR has advantages of widespread availability and the thus facilitates the comparison of results across broad samples.

In conclusion, we examined US national registry data to quantify the relationships of eGFR at 1 year post-transplant with the risks of long-term all-cause graft loss, death-censored graft failure, and mortality among kidney transplant recipients. Strong nonlinear associations were observed in each case, with significantly increased risk as eGFR fell below approximately 70 ml/min/1.73 m^2. Risk markedly accelerated among patients with 1-year eGFR levels below approximately 30 ml/min/1.73 m^2, which occur in approximately 5.6% of LD recipients, 8.6% of SCD recipients and 23.8% of ECD recipients. These relationships hold when independently estimated across donor types. Prospective validations of the predictive value of first-year renal function for long-term clinical outcomes are warranted. Strategies that slow the decline in transplant renal function have the potential to generate substantial benefits in patient and graft survival. Future trials should also address the benefits of clinical strategies designed to stabilize or improve renal function among patients with low eGFR.

Authorship

MAS: participated in study design, data acquisition, data analysis, and writing of the paper. KLL, AG, and DA: participated in interpretation and writing of the paper. DT and GL: participated in study design, interpretation, and writing of the paper. KLL and MAS: wrote the first draft of the manuscript. All authors agreed to publish the paper.

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Appendix 1

Cubic spline functions used to represent eGFR in the Cox regression models (SAS syntax). Splines are polynomial expansions of an independent variable of interest in a regression equation

$$\begin{aligned}\text{Spline\_1} = {} & ((\text{gfr\_y1} - 1) * *3) * (\text{gfr\_y1}{>}1) - ((\text{gfr\_y1} - 120) * *3) * (\text{gfr\_y1}{>}120) * (150 - 1)/(150 - 120) \\ & + ((\text{gfr\_y1} - 150) * *3) * (\text{gfr\_y1}{>}150) * (120 - 1)/(150 - 120)\end{aligned}$$

$$\begin{aligned}\text{Spline\_2} = {} & ((\text{gfr\_y1} - 15) * *3) * (\text{gfr\_y1}{>}15) - ((\text{gfr\_y1} - 120) * *3) * (\text{gfr\_y1}{>}120) * (150 - 15)/(150 - 120) \\ & + ((\text{gfr\_y1} - 150) * *3) * (\text{gfr\_y1}{>}150) * (120 - 15)/(150 - 120)\end{aligned}$$

$$\begin{aligned}\text{Spline\_3} = {} & ((\text{gfr\_y1} - 22.5) * *3) * (\text{gfr\_y1}{>}22.5) - ((\text{gfr\_y1} - 120) * *3) * (\text{gfr\_y1}{>}120) * (150 - 22.5)/(150 - 120) \\ & + ((\text{gfr\_y1} - 150) * *3) * (\text{gfr\_y1}{>}150) * 120 - 22.5)/(150 - 120)\end{aligned}$$

$$\begin{aligned}\text{Spline\_4} = {} & ((\text{gfr\_y1} - 30) * *3) * (\text{gfr\_y1}{>}30) - ((\text{gfr\_y1} - 120) * *3) * (\text{gfr\_y1}{>}120) * (150 - 30)/(150 - 120) \\ & + ((\text{gfr\_y1} - 150) * *3) * (\text{gfr\_y1}{>}150) * (120 - 30)/(150 - 120)\end{aligned}$$

$$\begin{aligned}\text{Spline\_5} = {} & ((\text{gfr\_y1} - 45) * *3) * (\text{gfr\_y1}{>}45) - ((\text{gfr\_y1} - 120) * *3) * (\text{gfr\_y1}{>}120) * (150 - 45)/(150 - 120) \\ & + ((\text{gfr\_y1} - 150) * *3) * (\text{gfr\_y1}{>}150) * (120 - 45)/(150 - 120)\end{aligned}$$

$$\begin{aligned}\text{Spline\_6} = {} & ((\text{gfr\_y1} - 60) * *3) * (\text{gfr\_y1}{>}60) - ((\text{gfr\_y1} - 120) * *3) * (\text{gfr\_y1}{>}120) * (150 - 60)/(150 - 120) \\ & + ((\text{gfr\_y1} - 150) * *3) * (\text{gfr\_y1}{>}150) * (120 - 60)/(150 - 120)\end{aligned}$$

$$\begin{aligned}\text{Spline\_7} = {} & ((\text{gfr\_y1} - 90) * *3) * (\text{gfr\_y1}{>}90) - ((\text{gfr\_y1} - 120) * *3) * (\text{gfr\_y1}{>}120) * (150 - 90)/(150 - 120) \\ & + ((\text{gfr\_y1} - 150) * *3) * (\text{gfr\_y1}{>}150) * (120 - 90)/(150 - 120)\end{aligned}$$

Appendix 2

Covariates included in the regression models of graft loss and death after kidney transplant.

UNOS Kidney Committee Model (21)

1. Recipient age in years/10
2. Recipient male gender
3. Recipient dialysis history
   a. Preemptive transplant (recipient not undergoing dialysis before transplant)
   b. Years since dialysis start: natural log of (1+ years since start of dialysis)
4. Recipient Body mass index
   a. Per kg/m^2
   b. >20 kg/m^2 (indicator)
   c. Missing
5. Cause of recipient ESRD
   a. Reference: glomerulonephritis and diabetes
   b. Polycystic kidney disease
   c. Hypertension
   d. Other/missing
6. Recipient diabetes
   a. Any indication of diabetes
   b. Diabetes indicator*recipient age at diabetes diagnosis in years/10
7. Previous transplant
8. Peak panel reactive antibody (latest if peak not recorded)
   a. Reference <10
   b. 10–79
   c. 80+
   d. Missing
9. HLA mismatches
   a. Zero A, B, and DR
   b. Zero DR
10. Recipient serum albumin at listing
    a. Per g/dl
    b. >3.5 g/dl (indicator)
    c. Missing
11. Calander year of transplant (Reference 1998)
12. Donor age
    a. Per year
    b. >18 years (indicator)
    c. Missing
13. Donor hypertension
14. Donor cytomegalovirus positive
15. Donor weight
    a. Natural log (kg)
    b. Missing
16. Donor cause of death
    a. Anoxia
    b. Cerebrovascular accident
    c. Head trauma
    d. Central nervous system tumor
    e. Other

Additional variables beyond the UNOS Kidney Committee models
1. Recipient race
   Reference: White
   African-American
   Other
2. Donor race
   Reference: White
   African-American
   Other
3. Acute rejection in first year post-transplant
4. eGFR at 1 year post-transplant

ESRD, end-stage renal disease.