Graft Function Variability and Slope and Kidney Transplantation Outcomes

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Introduction: It is critical to identify kidney transplant recipients (KTRs) at higher risk for adverse outcomes, to focus on monitoring and interventions to improve outcomes. We examined the associations between graft function variability and long-term outcomes in KTRs in an observational study.

Methods: We identified 2919 KTRs in the Wisconsin Allograft Recipient Database (WisARD) who had a functioning allograft 2 years posttransplantation and at least 3 outpatient measurements of estimated glomerular filtration rate (eGFR) from 1 to 2 years posttransplantation. Graft function slope was calculated from a linear regression of eGFR, and variability was defined as the coefficient of variation around this regression line. Associations of eGFR variability and slope with death, graft failure, cardiovascular events, and acute rejection were estimated.

Results: Compared to the lowest quartile, the highest quartile of eGFR variability was associated with a higher risk of death (adjusted hazard ratio [HR] = 1.85; 95% CI = 1.23−2.76), but not with a higher risk of graft failure (subhazard ratio = 1.16; 95% CI = 0.85−1.58), independent of eGFR and slope of eGFR. Greater eGFR variability was associated with higher risk of cardiovascular- and infection-related death and cardiovascular events but not malignancy-related death or allograft rejection. Including variability of eGFR significantly improved prediction of mortality but not prediction of graft failure.

Conclusion: Variability of eGFR is independently associated with risk of death, especially cardiovascular disease−related death and cardiovascular events, but not graft failure. Variability of eGFR may help identify KTRs at higher risk for death and cardiovascular events.

K idney transplantation is the current optimal treatment for end-stage kidney disease (ESKD) in suitable candidates. With advances in surgical techniques and immunosuppression, short-term allograft and patient survival have improved markedly in recent decades.[1] However, long-term allograft survival has not changed significantly. The 10-year allograft failure for deceased donor transplant recipients was 52.8% in 2005 versus 59.2% in 1995.[2] One challenge is to identify recipients at higher risk at an early stage to allow more intensive monitoring and interventions to improve their long-term outcomes. As such, it remains critical to explore predictors of long-term outcomes posttransplantation.

Both short-term and long-term variability in kidney function are commonly observed in patients with native chronic kidney disease (CKD) and in kidney transplant recipients (KTRs).[3−5] Greater variability of estimated glomerular filtration rate (eGFR) has been linked to higher risk of mortality[4,6] and hospitalization[7] in patients with CKD, independent of eGFR level and slope of eGFR. These results suggest that kidney function variability is an independent risk factor for mortality and may allow us to further refine risk stratification for patients over time. Whether the association between kidney function variability and risk of death and/or graft failure holds true among KTRs is uncertain. Few studies have assessed the association between graft function variability and outcomes among KTRs.[5,8] These studies were not able to incorporate graft function slope appropriately and failed to differentiate the association of graft function variability with death from those with graft failure, which are competing risk events posttransplantation. These studies also did not assess whether variability provides additional prognostic information for transplantation outcomes.

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We aimed to examine the hypothesis that graft function variability, independent of concurrent graft function, slope of graft function, and other traditional risk factors, is associated with long-term outcomes in KTRs and whether these metrics provide additional prognostic information. In addition, we evaluated the associations between graft function variability and cause-specific death and graft loss to further elucidate the potential clinical significance of this indicator.

MATERIALS AND METHODS

Study Design

The Wisconsin Allograft Recipient Database (WisARD) was initiated to prospectively collect information on all solid organ transplantations performed at the University of Wisconsin. The current study includes all adult patients in WisARD who underwent a primary kidney transplantation between January 2000 and December 2014. Patients who were alive with a functioning graft at 2 years posttransplantation, had at least 3 outpatient serum creatinine measurements between 1 and 2 years posttransplantation, and at least 90 days between the first and last creatinine measurement during this window were included (see Figure S1 for patient selection). This time period was chosen to avoid transient changes in the first year following transplantation and to increase the likelihood that a linear slope would be able to capture eGFR change more accurately. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[9] Measurements of eGFR greater than 150 ml/min per 1.73 m^2 were excluded. The study was approved by the University of Wisconsin Health Sciences Institutional Review Board.

Primary Exposures

Concurrent eGFR level was defined as the last available eGFR level closest to 2 years posttransplantation. For each patient, we fit an ordinary least square (OLS) regression model to all outpatient eGFR measures between 1 and 2 years posttransplantation, and calculated eGFR slope and variability. A linear slope was extracted from these models. Variability was defined as the coefficient of variation (CV) of the regression line in the primary analyses. In the primary analyses, patients were grouped into CV quartiles. The CV was centered at the mean and scaled by its standard deviation when assessed as a continuous variable.

Outcomes

Primary outcomes of interest included total graft loss (i.e., death or graft failure), death, death-censored graft failure (DCGF), and death or graft failure as competing risk events. Secondary outcomes included cause-specific death (cardiovascular-, infection-, and malignancy-related death), cause-specific graft loss (due to acute rejection and chronic rejection), de novo ischemic heart disease (IHD) events [see Supplementary Methods for detailed diagnosis]), heart failure (HF), and de novo acute rejection. Cause of death and graft loss was defined accordingly to the Transplant Recipient Registration Form of United network for organ sharing (UNOS). All KTRs were followed from 2 years posttransplantation until death, graft failure, loss to follow-up, 10 years of follow-up, or 31 December 2016.

Statistical Analysis

Patient characteristics including demographic, transplantation-related, donor-related, laboratory data, variability of immunosuppression level at baseline period, infectious events, and malignancy were collected (see Supplementary Methods for data collection details). Data were presented as mean (SD), median (interquartile interval [IQI]), or frequency (percentage), as appropriate. Differences in continuous variable were tested using 1-way analysis of variance. Differences in categorical variables were tested using the Pearson χ^2 test.

Independent Association Between eGFR Variability and Outcomes of Interest

Associations between eGFR variability and outcomes were assessed by Cox proportional hazard models. The lowest quartile of CV was used as the reference group. Proportional hazard assumption was tested by checking the Schoenfeld partial residuals. Covariates were included in multivariable analyses if the P value for their association with CV quartiles was less than 0.1. Restricted cubic spline models were applied to explore nonlinear associations between eGFR variability as a continuous covariate and outcomes of interest.

Graft failure and death are competing events that might blur the association between eGFR variability and each of the outcomes. We carried out a competing risk analysis using the method of Fine and Gray[10] and assessed the subhazard of the risk of death and subhazard of graft failure.

Prediction Performance

We assessed additional prognostic information provided by eGFR, eGFR linear slope, and CV of eGFR for outcomes prediction. We used Cox regression to assess the univariate associations between outcomes of interest and patient characteristics. Patient characteristics that were significantly associated with the outcomes of interest were then included in multivariable analyses. We constructed a base model and a saturated model for prediction comparison. The base model included patient age, sex, race, cause of ESKD, and live donor transplantation. The saturated model further included

other factors included in the aforementioned multivariable model. Discrimination was assessed by the Harrell concordance index.[11] Calibration was assessed by a visual examination of the calibration plots.

We used continuous net reclassification improvement (NRI) for censored survival data for model performance comparison.[12,13] The continuous NRI can be interpreted as the sum of the net proportion of events assigned a higher risk and net proportion of non-events assigned to a lower risk. We assessed internal validity by using a bootstrap procedure to generate 1000 datasets from resampling the original dataset and calculated the optimism-corrected 95% confidence interval.

Approximately 20% of participants were missing smoking information and 3.5% were missing serum albumin information. We used multiple imputation to generate 20 datasets by means of a conditional specification approach.

Several sensitivity analyses were conducted to examine the robustness of our results. First, we calculated eGFR slope and variability using log-transformed eGFR measurements. Second, we repeated the analyses within strata of acute rejection, diabetes, peripheral arterial disease (PAD), eGFR at 2 years posttransplantation (<60 vs. ≥60 ml/min per 1.73 m^2), and cardiovascular di sease (CVD). Third, as eGFR variability might be an indicator of exposure to extrinsic events that compromise graft function and may lead to hospitalization, we limited our analyses to KTRs without hospitalization during the baseline period. Fourth, we further adjusted for body mass index (BMI) at transplantation, induction immunosuppression, delayed graft function, smoking, and race of donor, even though they did not meet the inclusion criterion of $P < 0.1$. Fifth, we limited the analyses to transplantations between 2010 and 2014 to explore potential era effect. Sixth, we excluded outcomes that occurred within 2.5 years posttransplantation to exclude reverse causality (i.e., patients at higher risk for outcomes may result in greater variability). Seven, we repeated the above analyses using mean absolute residuals and root mean square error from eGFR regression models as alternative indicators of variability. Eighth, we repeated the primary analyses using CV of creatinine as the main exposure. All analyses were performed using R (www.R-project.org/).[14]

RESULTS

Characteristics of Study Participants

Among 3771 KTRs who underwent kidney transplantation between 2000 and 2014, a total of 2919 (77.4%) KTRs were included in the study. These recipients had a total of 40,498 serum creatinine measurements during the baseline period. On average, each patient had 14 eGFR measurements (median = 12, IQI = 9-15). Compared to enrolled participants, patients who were excluded from analysis were generally in worse condition: they were more likely to have longer pretransplantation dialysis, greater human leukocyte antigen (HLA) mismatch, acute rejection, delayed graft function, CVD, and diabetes mellitus (DM) (Table S1).

Patients with greater variability were more likely to be female, to have ESKD due to DM, and to have longer pretransplantation dialysis duration (Table 1). Patients with greater variability also were more likely to be diagnosed with CVD, DM, and PAD. In addition, they were more likely to have greater immunosuppression variability, lower serum albumin level at 2 years posttransplantation, higher incidence of hospitalization, and a kidney from a male donor. Patients with higher variability were more likely to have negative eGFR slope, to have a higher eGFR at 2 years, and to have more eGFR measurements between 1 and 2 years posttransplantation. No associations between infectious events or malignancy and eGFR variability were observed.

Total Graft Loss

With a total of 15,504 person-years of follow-up and a median follow-up of 5.1 (IQI = 2.5−8.4) years, approximately 9.9% of KTRs were lost to follow-up, predominately because of transferring to other providers. There were 873 (29.9%) total graft losses. Patients in the highest quartile of eGFR variability had significantly higher risk of total graft loss (hazard ratio [HR] = 1.50, 95% confidence interval [CI] = 1.25−1.80 in unadjusted analyses; HR = 1.33, 95% CI = 1.08−1.62 in adjusted analysis) (Table 2, Figure 1a). No significant association was observed for patients in quartile 2 or 3 compared to quartile 1. Higher eGFR level and more positive eGFR slope also were significantly associated with lower risk of total graft loss.

All-Cause Death

There were 506 deaths (17.3%) among study participants. Patients with the highest quartile of variability had a higher risk of death compared to the lowest quartile group (HR = 1.85, 95% CI = 1.23−2.76 in adjusted analysis) (Table 2, Figure 1b). No significant association was observed for patients in quartile 2 or 3 compared to quartile 1. Higher eGFR level was associated with significantly lower risk of mortality. However, eGFR slope was not associated with risk of mortality (Figure S2).

Table 1. Patient characteristics

	eGFR coefficient of variation quartile				
Characteristic	<7.2% (n = 729)	7.2%−9.4% (n = 730)	9.4%−12.1% (n = 729)	≥12.1% (n = 731)	P value
Recipient characteristics					
Patient age at transplantation, yr	49.7(13.4)	49.5 (14.3)	50.1 (13.8)	50.3 (14.5)	0.69
Sex, male (%)	500 (68.6)	470 (64.4)	400 (54.9)	323 (44.2)	<0.001
Race (%)					0.83
Black	53 (7.3)	55 (7.5)	47 (6.4)	53 (7.3)	
Other	52 (7.1)	56 (7.7)	66 (9.1)	63 (8.6)	
White	624 (85.6)	619 (84.8)	616 (84.5)	615 (84.1)	
BMI at transplantation, kg/m^2	27.5 (5.4)	27.6(5.3)	27.2 (5.2)	27.2 (5.6)	0.43
Cause of ESKD					<0.001
DN	137 (18.8)	149 (20.4)	175 (24.0)	257 (35.2)	
GN	190 (26.1)	193 (26.4)	197 (27.0)	155 (21.2)	
HTN	72 (9.9)	84 (11.5)	63 (8.6)	57 (7.8)	
Others	212 (29.1)	199 (27.3)	186 (25.5)	193 (26.4)	
PKD	118 (16.2)	105 (14.4)	108 (14.8)	69 (9.4)	
Dialysis before transplantation, n (%)	488 (66.9)	521 (71.4)	506 (69.4)	573 (78.4)	<0.001
Dialysis duration, mo, median (IQI)	10 (0, 28)	10 (0, 28)	11 (0,29)	14 (2, 32)	<0.001
Year of transplantation	2007 (2004, 2011)	2007 (2003,2011)	2007 (2003, 2010)	2006 (2003,2010)	0.011
Prior transplantation	128 (17.6)	119 (16.3)	143 (19.6)	171 (23.4)	0.004
HLA_miscat (%)					0.28
1 or 2	206 (28.3)	176 (24.1)	199 (27.3)	196 (26.8)	
3 or 4	287 (39.4)	303 (41.5)	312 (42.8)	284 (38.9)	
5 or 6	236 (32.4)	251 (34.4)	218 (29.9)	251 (34.3)	
PRA	4.7 (14.7)	5.3 (15.3)	6.5 (17.6)	6.2 (17.4)	0.08
Induction IS (%)					0.71
Campath	134 (18.4)	149 (20.4)	145 (19.9)	147 (20.1)	
Others	44 (6.0)	38 (5.2)	33 (4.5)	33 (4.5)	
Simulect	431 (59.1)	423 (57.9)	424 (58.2)	409 (56.0)	
Thymo	120 (16.5)	120 (16.4)	127 (17.4)	142 (19.4)	
Maintenance IS (%)					0.035
CSA	177 (24.3)	202 (27.7)	197 (27.0)	217 (29.7)	
Others	72 (9.9)	57 (7.8)	42 (5.8)	51 (7.0)	
Tacrolimus	480 (65.8)	471 (64.5)	490 (67.2)	463 (63.3)	
Acute rejection	127 (17.4)	132 (18.1)	139 (19.1)	159 (21.8)	0.07
Delayed graft function	93 (12.8)	103 (14.1)	99 (13.6)	109 (14.9)	0.68
Smoking					0.23
Current	50 (6.9)	42 (5.8)	46 (6.3)	37 (5.1)	
Never	374 (51.3)	395 (54.1)	372 (51.0)	375 (51.3)	
Past	229 (31.4)	218 (29.9)	231 (31.7)	213 (29.1)	
Missing	76 (10.4)	75 (10.2)	80 (17.3)	106 (14.5)	
Cardiovascular disease	198 (27.2)	203 (27.8)	230 (31.6)	247 (33.8)	0.016
Diabetes	162 (22.2)	170 (23.3)	196 (26.9)	282 (38.6)	<0.001
Peripheral arterial disease	39 (5.3)	46 (6.3)	50 (6.9)	77 (10.5)	0.001
CMV infection	81 (11.1)	77 (10.5)	94 (12.9)	97 (13.3)	0.30
BK infection	96 (13.2)	88 (12.1)	88 (12.1)	76 (10.4)	0.44
Malignancy	78 (10.7)	84 (11.5)	77 (10.6)	81 (11.1)	0.94
Incidence of hospitalization between 1 and 2 years, per person-year	0.29	0.31	0.38	0.85	<0.001
Serum albumin, g/dl	3.97 (0.44)	3.97 (0.41)	3.95 (0.45)	3.85 (0.49)	<0.001
Percentage in lowest quartile of maintenance IS	151 (20.7)	145 (19.9)	175 (24.0)	182 (24.9)	0.09
CV of IS, median (IQI)	23.7 (16.5, 37.1)	25.7 (17.7, 38.8)	25.9 (18.5, 37.8)	32.8 (22.9, 48.2)	<0.001
Donor characteristics					
Live donor	334 (45.8)	337 (46.2)	303 (41.6)	297 (40.6)	0.064
Age of donor, yr	43.6 (14.9)	42.4 (13.7)	41.4 (14.4)	41.3 (14.7)	0.008
Donor sex, male	369 (50.6)	360 (49.3)	418 (57.3)	404 (55.3)	0.005
Donor race					0.78
Black	13 (1.8)	16 (2.2)	17 (2.3)	19 (2.6)	
Other	33 (4.5)	27 (3.7)	35 (4.8)	38 (5.2)	
White	683 (93.7)	687 (94.1)	677 (92.9)	674 (92.2)	

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Table 1. (Continued)

Characteristic	eGFR coefficient of variation quartile				P value
	<7.2% (n = 729)	7.2%−9.4% (n = 730)	9.4%−12.1% (n = 729)	≥12.1% (n = 731)	
eGFR measure characteristics					
Last observed eGFR at 2 yr	60.7(21.7)	61.9 (17.9)	62.9 (17.9)	63.0 (19.6)	0.075
Slope of eGFR, ml/min per 1.73 m² per yr	0.67 (9.62)	1.08 (11.80)	0.33 (12.21)	−0.70 (17.24)	0.058
RMSE	3.14 (1.39)	5.09 (1.46)	6.70 (1.80)	9.76 (3.30)	<0.001
Mean absolute residuals	2.26 (1.05)	3.74 (1.09)	4.96 (1.42)	7.21 (2.53)	<0.001
Number of eGFR measurement	10.1 (4.4)	13.0 (6.4)	14.2 (6.8)	17.6 (13.3)	<0.001
Interval between first and last eGFR measurement, days	301.9 (58.7)	319.6 (41.1)	324.8 (37.8)	321.3 (39.6)	<0.001

BMI, body mass index; BK, ; CMV, cytomegalovirus; CSA, cyclosporine; CV, coefficient of variation; DN, diabetic nephropathy; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; GN, glomerulonephritis; HLA_miscat, ; HTN, hypertension nephropathy; IQI, interquartile interval; IS, immunosuppression; PKD, polycystic kidney disease; PRA, panel reactive antibody; RMSE, root mean square error.

Death-Censored Graft Failure

There were 367 DCGFs among study participants. No significant association was observed between eGFR variability and the risk of DCGF (highest quartile: HR = 1.10, 95% CI = 0.83−1.45 in unadjusted analysis; HR = 1.17, 95% CI = 0.85−1.61 in adjusted analysis) (Table 2). In contrast, higher eGFR level and more positive eGFR slope were both associated with significantly lower risk of DCGF (adjusted HR = 0.76, 95% CI = 0.70−0.83 per 10 ml/min per 1.73 m² for eGFR level; HR = 0.92, 95% CI = 0.86−0.99 per ml/min per 1.73 m² per year for eGFR slope).

Death or Graft Failure in Competing Risk Analysis

In competing risk analysis, patients in the highest quartile of variability exhibited a significantly higher risk of death (subhazard ratio [subHR] = 1.50, 95% CI = 1.10−2.04 in adjusted analysis) (Table 3), but not higher risk of graft failure (subHR = 1.16, 95% CI = 0.85−1.58). Similar results were observed in cumulative incidence estimates of death and graft failure (Figure 2). Conversely, higher eGFR level and more positive eGFR slope were associated with lower risk of graft failure but not risk of death.

The above-mentioned associations remained consistent in models including CV as a continuous variable, with higher risk of total graft loss and death mainly among KTRs with high variability (Figure 2b and 3b). No significant association between CV and risk of DCGF was found (Figure S3).

Secondary Outcomes: Cause-Specific Death, Graft Loss Due to Acute and Chronic Rejection, De Novo Cardiovascular Events, and De Novo Acute Rejection

Considering that KTRs in the lower 3 CV quartiles had similar risk of death and graft loss in the primary results, we grouped the lower 3 quartiles as the reference group.

There were 91 CVD-related deaths, 106 infection-related deaths, and 86 malignancy-related deaths among study participants. Greater variability was associated with higher risk of CVD-related death (adjusted HR = 2.32, 95% CI = 1.50−3.61 of quartile 4 compared with the lower 3 quartiles) (Table 4). Greater variability also was associated with higher risk of infection-related death (adjusted HR = 1.65, 95% CI = 1.10−2.49 of quartile 4 vs. quartiles 1−3). However, no association between variability and malignancy-related death was found (adjusted HR = 1.35, 95% CI = 0.83−2.19).

There were 37 graft losses due to acute rejection and 204 graft losses due to chronic rejection. No significant association between variability and graft loss due to acute rejection or chronic rejection was found (adjusted HR = 1.12, 95% CI = 0.53−2.36 for graft loss due to acute rejection; adjusted HR = 0.94, 95% CI = 0.68−1.30 for graft loss due to chronic rejection).

Among 1776 patients with no diagnosis of IHD at 2 years posttransplantation, 171 IHD events were diagnosed. Greater variability was associated with higher risk of IHD (adjusted HR = 1.62, 95% CI = 1.15−2.28). Similarly, greater variability was associated with higher risk of heart failure (adjusted HR = 1.76, 95% CI = 1.23−2.53). Among 2362 patients with no diagnosis of acute rejection at 2 years posttransplantation, 282 acute rejection events were diagnosed. No association between variability and acute rejection was observed (adjusted HR = 1.05, 95% CI = 0.73−1.47).

Prediction Improvement of eGFR Level, Slope, and Variability
Bivariable and Multivariable Analyses

We first investigated the prognostic factors that were associated with risk of mortality and risk of DCGF in bivariable analyses (Tables S2 and S3). In multivariable analyses, the following independent predictors of long-term risk of mortality were identified: age at transplantation, sex, prior transplantation, acute rejection, cardiovascular disease, previous hospitalization,

Table 2. Quartiles of eGFR CV and the risk of total graft loss and death

	Total graft loss, n (%)	Unadjusted	Adjusted[a]
CV Q1 (<7.2%) (n = 729)	197 (27.0)	1.0 (Ref)	1.0 (Ref)
CV Q2 (7.2%–9.4%) (n = 730)	197 (27.0)	0.95 (0.78–1.16)	1.00 (0.81–1.23)
CV Q3 (9.4–12.1%) (n =729)	183 (25.1)	0.87 (0.71–1.06)	0.91 (0.73–1.13)
CV Q4 (≥12.1%) (n = 732)	296 (40.4)	1.50 (1.25–1.80)[b]	1.33 (1.08–1.62)[c]
eGFR, per 10 ml/min per 1.73 m^2		0.91 (0.89–0.93)[b]	0.94 (0.92–0.96)[c]
Slope of eGFR, per 5 ml/min per 1.73 m^2 per yr		0.96 (0.94–0.97)[b]	0.98 (0.96–0.99)[a]
	Death, n (%)	**Unadjusted**	**Adjusted**
CV Q1 (<7.2%)	103 (14.1)	1.0 (Ref)	1.0 (Ref)
CV Q2 (7.2%–9.4%)	109 (14.9)	1.01 (0.77–1.32)	0.98 (0.74–1.30)
CV Q3 (9.4–12.1%)	101 (13.9)	0.92 (0.70–1.21)	0.88 (0.66–1.18)
CV Q4 (≥12.1%)	193 (26.4)	1.87 (1.47–2.38)[c]	1.47 (1.13–1.92)[c]
eGFR, per 10 ml/min per 1.73 m^2		0.82 (0.78–0.87)[b]	0.89 (0.88–0.99)[a]
Slope of eGFR, per 5 ml/min per 1.73 m^2 per yr		0.95 (0.90–1.02)	0.95 (0.95–1.05)
	DCGF, n (%)	**Unadjusted**	**Adjusted**
CV Q1 (<7.2%)	94 (12.9)	1.0 (Ref)	1.0 (Ref)
CV Q2 (7.2%–9.4%)	88 (12.1)	0.89 (0.67–1.19)	1.02 (0.75–1.39)
CV Q3 (9.4–12.1%)	82 (11.2)	0.81 (0.61–1.10)	0.92 (0.67–1.27)
CV Q4 (≥12.1%)	103 (14.1)	1.10 (0.83–1.45)	1.17 (0.85–1.61)
eGFR, per 10 ml/min per 1.73 m^2		0.78 (0.73–0.84)[b]	0.76 (0.70–0.83)[c]
Slope of eGFR, per 5 ml/min per 1.73 m^2 per yr		0.83 (0.78–0.89)[b]	0.92 (0.86–0.99)[a]

Model adjusted for patient age at transplantation, sex, race, cause of ESKD, CVD, PAD, hospitalization between 1 and 2 years posttransplantation, pretransplantation dialysis, and pretransplantation dialysis duration, prior transplantation, PRA, year of transplantation, maintenance immunosuppressant level and variability, acute rejection, and albumin level, live donor, age and sex of donor, last observed eGFR, annual slope of eGFR, and number of eGFR measurement between 1 and 2 years.
CV, coefficient of variation; CVD, cardiovascular disease; DCGF, death-censored graft failure; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; PAD, peripheral arterial disease; Q, quartile; Ref, reference.
[a]$P < 0.05$.
[b]$P < 0.001$.
[c]$P < 0.01$.

albumin level, CV of eGFR ($P < 0.05$ for all). For risk of DCGF, the following factors were identified: patient age, race, previous hospitalization, transplantation year, acute rejection, delayed graft function, albumin level, last eGFR, eGFR slope, and CV of immunosuppression.

Prediction of Mortality
Including CV of eGFR significantly improved mortality risk prediction in both the base model and the saturated model. Including CV in the base model resulted in continuous NRI of 0.216 (95% CI = 0.041−0.321) for 1-year risk prediction (C index 0.774, 95% CI = 0.728−0.811) (Table 5). However, adding eGFR level or eGFR slope to models did not significantly improve mortality prediction. Including eGFR, slope of eGFR, and CV resulted in NRI of 0.263 (0.114−0.343) for 1-year risk prediction (C index 0.786, 95% CI = 0.742−0.822). The CV alone and combined with eGFR and slope provided less information in the saturated model compared to that in the base model, but still significantly improved prediction for 1- and 3-year mortality. The calibration plot showed good agreement between the predicted and observed mortality

(Figure S4). Similarly, the CV of eGFR provided additional information on risk of total graft loss, especially in short-term follow-up (Table S4).

Prediction of DCGF
The CV of eGFR was not independently predictive of DCGF. Including CV in the base model resulted in NRI of 0.055 (−0.193 to 0.201) for 1-year DCGF risk prediction (Table 6). In contrast, the eGFR level provided substantial prognostic information on risk of DCGF (NRI 0.252 (0.098−0.365) for 1-year risk of DCGF, and NRI 0.213 (0.153−0.307) for 10-year risk of DCGF prediction). Including eGFR slope in models also significantly improved DCGF risk prediction in both the base model and the saturated model. The calibration plot showed good agreement between the predicted and observed risk of graft failure (Figure S5).

Results of Sensitivity Analyses
Results were similar in analyses using a log-linear regression model for eGFR. Patients in the highest quartile of log-eGFR variability were at higher risk for death but not graft failure (subHR = 1.7, 95% CI =
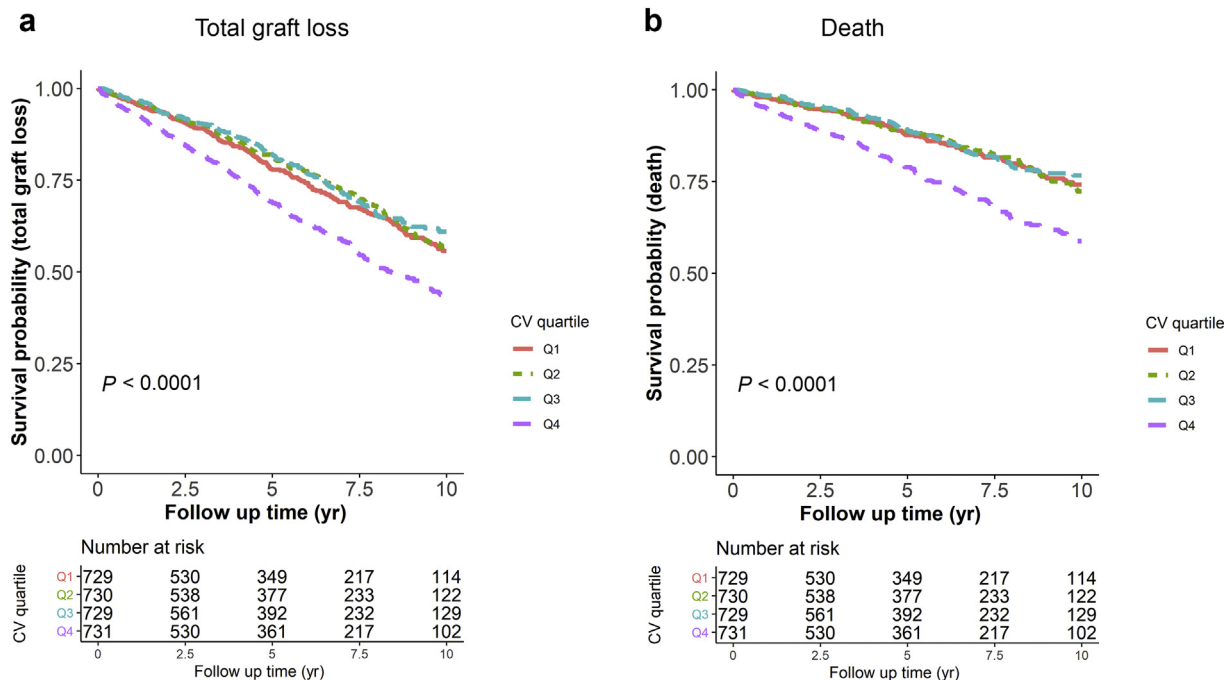
Figure 1. Kaplan–Meier curves of survival probability of (a) total graft loss and (b) death across estimated glomerular filtration rate (eGFR) coefficient of variation quartiles. Here follow-up time started after baseline period (i.e., 2 years posttransplantation). CV, coefficient of variation; Q, quartile.

1.3–2.2 for death; subHR = 1.2, 95% CI = 0.9–1.6 for graft failure) (Table S5).

There was limited evidence of any interaction between eGFR variability and acute rejection, diabetes, PAD, eGFR category at 2 years, or history of CVD (*P* for interaction >0.1 for all). However, slightly stronger associations between CV and risk of death were observed in KTRs who were doing relatively well (i.e., no acute rejection, no diabetes, no PAD, or better graft function) (Table S6). Among 2193 KTRs (75.1%) who had no hospitalization between 1 and 2 years posttransplantation, results remained consistent (Table S7).

The results remained similar in analyses limited to transplantations between 2010 and 2014 (Table S8), excluding outcomes that occurred within 2.5 years posttransplantation (Table S9), and using CV of creatinine as the main exposure (Table S10). The associations between mean absolute residuals and RMSE and outcomes of interest were consistent with the main results (Table S11 and Table S12). The results were consistent in analyses further adjusted for BMI at transplantation, induction immunosuppressant, delayed graft function, smoking, and race of donor (data now shown).

DISCUSSION

In a large cohort of kidney transplant recipients, variability of eGFR between 1 and 2 years posttransplantation was associated with higher risk of death but not graft failure. The association was

independent of both traditional baseline characteristics and other markers of graft function, including eGFR and slope of eGFR. Greater eGFR variability was associated with higher risk of cardiovascular- and infection-related death and cardiovascular events but

Table 3. Association between eGFR variability and death/graft failure-competing risk analysis

	Unadjusted	Adjusted[a]
SubHR for death		
CV Q1 (<7.2%)	1.0 (Ref)	1.0 (Ref)
CV Q2 (7.2%–9.4%)	1.06 (0.83–1.35)	1.01 (0.78–1.31)
CV Q3 (9.4–12.1%)	0.97 (0.75–1.24)	0.90 (0.69–1.18)
CV Q4 (≥12.1%)	1.78 (1.42–2.22)[b]	1.49 (1.16–1.91)[b]
eGFR, per 10 ml/min per 1.73 m²	0.94 (0.92–0.96)	0.99 (0.97–1.03)
Slope of eGFR, per 5 ml/min per 1.73 m² per yr	0.99 (0.97–1.02)	1.00 (0.98–1.02)
SubHR for graft failure		
CV Q1 (<7.2%)	1.0 (Ref)	1.0 (Ref)
CV Q2 (7.2%–9.4%)	0.93 (0.70–1.23)	1.02 (0.76–1.37)
CV Q3 (9.4–12.1%)	0.89 (0.67–1.18)	1.04 (0.76–1.42)
CV Q4 (≥12.1%)	1.03 (0.78–1.34)	1.16 (0.85–1.58)
eGFR, per 10 ml/min per 1.73 m²	0.92 (0.90–0.95)[c]	0.89 (0.86–0.93)[c]
Slope of eGFR, per 5 ml/min per 1.73 m² per yr	0.93 (0.90–0.95)[c]	0.98 (0.96–0.99)[d]

CV, coefficient of variation; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; PAD, peripheral arterial disease; Q, quartile; Ref, reference; SubHR, subhazard ratio.
[a]Model adjusted for patient age at transplantation, sex, race, cause of ESKD, CVD, PAD, hospitalization between 1 and 2 years posttransplantation, pretransplantation dialysis, and pretransplantation dialysis duration, prior transplantation, panel reactive antibody, year of transplantation, maintenance immunosuppressant level and variability, acute rejection, and albumin level, live donor, age and sex of donor, last observed eGFR, and number of eGFR measurements between 1 and 2 years.
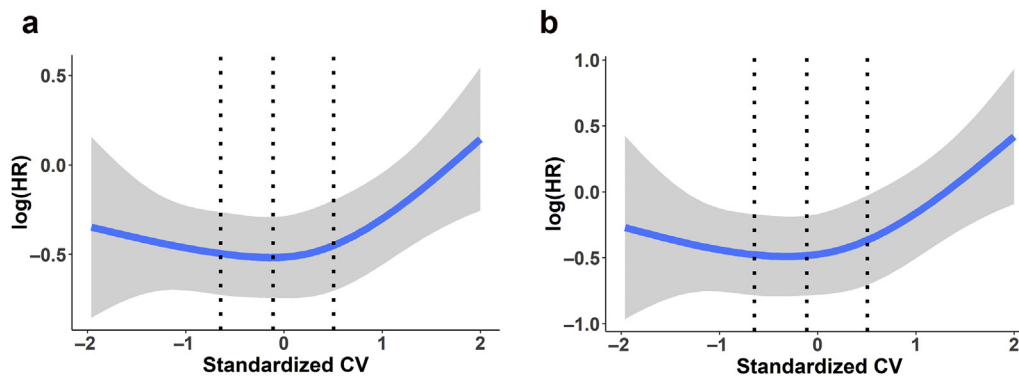[b]*P* < 0.05.
[c]*P* < 0.001.
[d]*P* < 0.01.

Figure 2. Adjusted association between standardized coefficient of variation (CV) and (a) risk of total graft loss and (b) risk of death.

not malignancy-related death or acute rejection. Including eGFR variability in models improved prediction of mortality. Conversely, eGFR level and eGFR slope were significantly associated with and improved prediction of graft failure. Our results suggest that dynamic changes in eGFR during 1 and 2 years post-transplantation may help to identify patients at higher risk for cardiovascular death or cardiovascular events, and may provide important prognostic information for long-term outcomes.

Our results on graft function variability associated with higher risk of death, independent of eGFR, eGFR slope, and other risk factors, are consistent with previous work in the native CKD population.[4,6,15] Specifically, greater graft function variability was associated with higher risk of CVD- and infection-related death. In addition, greater variability was associated with greater risk of CVD events. These results suggest that variability may be an indicator of vascular condition or subclinical vascular disease. It is possible that the association between variability and infection-related death also is related to vascular condition, as patients with worse vascular condition are more fragile and at higher risk for death from a given infectious episode. Consistently across studies[4,6,7] as well as in our own data, greater eGFR variability was observed in patients with diabetes, CVD, and PAD. These results further supported variability of graft function as a marker of vascular disease. In contrast, we did not find any associations between graft function variability and risk of graft failure or acute rejection. This is consistent with a previous study in CKD patients in which variability of eGFR was not associated with ESKD progression.[15] Extrinsic events, such as hospitalization, acute rejection, and poor adherence to immunosuppressant, may compromise graft function and result in greater graft function variability. However, after accounting for these factors, graft function variability was not associated with higher risk of graft failure or acute rejection. Altogether, our results support that graft function variability is less a marker of graft health *per se,* but is more likely an

indicator of vascular disease. In our work, the associations were limited mainly to those in the highest quartile of graft function variability, as also observed in previous studies.[4,6] These findings suggest a threshold effect, such that the associations with CVD events or death may be apparent only when the underlying vascular condition is worse than a certain threshold. As such, assessment of eGFR variability may provide valuable information in KTRs, especially for cardiovascular-related death and cardiovascular events.

We observed strong associations between eGFR level and slope and risk of graft failure. This also is consistent with previous studies in transplant recipients.[16-18] Clayton *et al*. showed that a 30% decline in eGFR between 1 and 3 years post-transplantation is strongly associated with risk of death-censored graft failure.[18] However, in contrary to previous work,[18,19] we did not find significant associations between eGFR level and slope and mortality in multivariable analyses. There are several possible explanations for the null associations. First, similar to variability of eGFR, decline in eGFR is probably a surrogate marker of patient characteristics
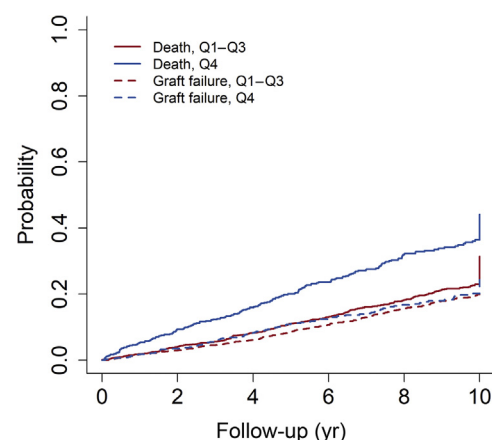

Figure 3. Cumulative incidence estimates for death and graft failure, respectively, across estimated glomerular filtration rate (eGFR) coefficient of variation (CV) quartiles (lower 3 quartiles vs. highest quartile). Q, quartile.

Table 4. Association between eGFR variability and cause-specific death, graft loss due to acute and chronic rejection, *de novo* cardiovascular events, and acute rejection

	No. of events, n (%)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)[a]
Death			
CVD-related death			
CV quartile [Q1−Q3], n = 2188	51 (2.3)	1.0 (Ref)	1.0 (Ref)
CV quartile [Q4], n = 731	40 (5.5)	2.43 (1.60–3.67)	2.32 (1.50–3.61)
Infection-related death			
CV_quartile [Q1−Q3], n = 2188	62 (2.8)	1.0 (Ref)	1.0 (Ref)
CV_quartile [Q4], n = 731	44 (6.0)	2.19 (1.49–3.23)	1.65 (1.10–2.49)
Malignancy-related death			
CV_quartile [Q1−Q3], n = 2188	60 (2.7)	1.0 (Ref)	1.0 (Ref)
CV_quartile [Q4], n = 731	26 (3.6)	1.35 (0.85–2.13)	1.35 (0.83–2.19)
Graft loss			
Acute rejection-related			
CV_quartile [Q1−Q3], n = 2188	26 (1.2)	1.0 (Ref)	1.0 (Ref)
CV_quartile [Q4], n = 731	11 (1.5)	1.28 (0.63–2.60)	1.12 (0.53–2.36)
Chronic rejection related			
CV_quartile [Q1−Q3], n = 2188	148 (6.8)	1.0 (Ref)	1.0 (Ref)
CV_quartile [Q4], n = 731	56 (7.7)	1.19 (0.87–1.61)	0.94 (0.68–1.30)
Ischemic heart disease[b]			
CV_quartile [Q1−Q3], n = 1378	117 (8.5)	1.0 (Ref)	1.0 (Ref)
CV_quartile [Q4], n = 398	54 (13.6)	1.61 (1.16–2.22)	1.62 (1.15–2.28)
Heart failure[b]			
CV_quartile [Q1−Q3], n = 1882	88 (4.7)	1.0 (Ref)	1.0 (Ref)
CV_quartile [Q4], n = 612	52 (8.5)	1.87 (1.33–2.63)	1.76 (1.23–2.53)
Acute rejection[b]			
CV_quartile [Q1−Q3], n = 1790	200 (9.1)	1.0 (Ref)	1.0 (Ref)
CV_quartile [Q4], n = 572	82 (11.2)	1.05 (0.75–1.47)	1.05 (0.73–1.47)

CV, coefficient of variation; Q, quartile.
[a]Adjusted for age at transplantation, sex, prior transplantation, acute rejection, cardiovascular disease, previous hospitalization, and albumin level.
[b]Analyses limited to patients without prior diagnosis of ischemic heart disease, heart failure, or acute rejection, respectively.

and posttransplantation events, including acute rejection, immunosuppressant toxicity, donor-derived lesions, and so forth. Covariates in our multivariable analyses may be the causal factors between eGFR and mortality and thus explained away the association. Second, we assumed a linear slope between 1 and 2 years posttransplantation instead of allowing a potentially nonlinear pattern. This may miss the true

association, and part of the residual association was then captured by variability and risk of mortality.

It is relatively easy to implement an algorithm to capture eGFR level and to calculate eGFR slope and variability in clinical practice with widely available electronic health records. Variability of eGFR is likely an indicator of vascular condition and can be applied to identify patients at higher risk for death and

Table 5. Continuous net reclassification index in mortality risk prediction after including CV

Mortality risk	1 yr[a]	3 yr[a]	5 yr[a]	10 yr[a]
Base model				
+ CV	0.216 (0.041, 0.321)[b]	0.161 (0.058, 0.238)[c]	0.109 (0.002, 0.173)[c]	0.08 (−0.021, 0.131)
+ last_EGFR	0.066 (−0.062, 0.160)	0.111 (−0.07, 0.180)	0.088 (0.002, 0.135)[c]	0.096 (−0.004, 0.174)
+ slope_yr	0.003 (−0.176, 0.127)	0.007 (−0.135, 0.101)	0.014 (−0.081, 0.082)	0.029 (−0.085, 0.087)
+ CV, eGFR, and slope	0.263 (0.114, 0.343)[b]	0.227 (0.083, 0.300)[b]	0.161 (0.066, 0.221)[c]	0.096 (0.019, 0.183)[c]
Saturated model				
+ CV	0.097 (−0.016, 0.156)	0.072 (0.001, 0.132)[c]	0.037 (−0.067, 0.111)	0.114 (−0.068, 0.228)
+ last_EGFR	0.095 (−0.07, 0.173)	0.096 (−0.093, 0.173)	0.126 (−0.065, 0.171)	0.054 (−0.127, 0.168)
+ slope_yr	−0.019 (−0.13, 0.097)	−0.018 (−0.074, 0.066)	0.008 (−0.066, 0.073)	0.034 (−0.105, 0.092)
+ CV, eGFR, and slope	0.117 (0.001, 0.213)[c]	0.077 (0.003, 0.147)[c]	0.042 (−0.02, 0.156)	0.164 (0.005, 0.251)[c]

Base model included age, sex, race, cause of end-stage kidney disease (ESKD), and live donor. Saturated model included patient age at transplantation, sex, race, cause of ESKD, cardiovascular disease, peripheral arterial disease, hospitalization between 1 and 2 years posttransplantation, pretransplantation dialysis, and pretransplantation dialysis duration, prior transplantation, panel reactive antibody, year of transplantation, maintenance immunosuppressant level and variability, acute rejection, and albumin level, live donor, age and sex of donor, last observed eGFR, annual slope of eGFR, and number of eGFR measurements between 1 and 2 years.
CV, coefficient of variation; eGFR, estimated glomerular filtration rate.
[a]Here follow-up time started after baseline period (i.e., 2 years posttransplantation).
[b]P < 0.01.
[c]P < 0.05.

Table 6. Continuous net reclassification index in risk of death censored graft loss risk prediction after including CV

Mortality risk	1 yr[a]	3 yr[a]	5 yr[a]	10 yr[a]
Base model				
+ CV	0.055 (–0.193, 0.201)	0.005 (–0.210, 0.203)	0.003 (–0.190, 0.232)	0.002 (–0.225, 0.240)
+ last_EGFR	0.252 (0.098, 0.365)[b]	0.238 (0.171, 0.327)[b]	0.251 (0.167, 0.343)[c]	0.213 (0.153, 0.307)[c]
+ slope_yr	0.091 (–0.062, 0.210)	0.124 (0.039, 0.225)[c]	0.157 (0.077, 0.228)[c]	0.158 (0.052, 0.210)[c]
+ CV, eGFR, and slope	0.278 (0.129, 0.387)[b]	0.278 (0.164, 0.347)[b]	0.257 (0.195, 0.326)[c]	0.215 (0.119, 0.305)[c]
Saturated model				
+ CV	–0.016 (–0.148, 0.170)	–0.029 (–0.081, 0.118)	–0.013 (–0.056, 0.068)	–0.009 (–0.062, 0.082)
+ last_EGFR	0.196 (0.024, 0.359)[b]	0.263 (0.140, 0.338)[c]	0.233 (0.157, 0.308)[b]	0.173 (0.090, 0.271)[b]
+ slope_yr	0.057 (–0.040, 0.243)	0.126 (0.016, 0.224)[b]	0.144 (0.056, 0.225)[c]	0.119 (0.005, 0.200)[d]
+ CV, eGFR, and slope	0.179 (0.058, 0.351)[c]	0.280 (0.150, 0.359)[b]	0.256 (0.161, 0.327)[b]	0.186 (0.089, 0.258)[c]

Saturated model included patient age at transplantation, sex, race, cause of end-stage kidney disease, cardiovascular disease, peripheral arterial disease, hospitalization between 1 and 2 years posttransplantation, pretransplantation dialysis, and pretransplantation dialysis duration, prior transplantation, panel reactive antibody, year of transplantation, maintenance immunosuppressant level and variability, acute rejection, and albumin level, live donor, age and sex of donor, last observed eGFR, annual slope of eGFR, and number of eGFR measurements between 1 and 2 years.

CV, coefficient of variation; eGFR, estimated glomerular filtration rate.

[a]Here follow-up time started after baseline period (i.e., 2 years posttransplantation).

[b]$P < 0.001$.

[c]$P < 0.01$.

[d]$P < 0.05$.

cardiovascular events. Our results showed that variability of eGFR improved mortality risk prediction, whereas eGFR level and slope improved graft failure prediction. Incorporating these metrics may help to identify patients at higher risk for adverse outcomes. External studies incorporating eGFR variability among kidney transplantation recipients are needed to validate these findings and to assess the potential impact.

Our study has several strengths. First, WisARD provides detailed patient information, allowing us to account for a large number of potential confounders. Second, using competing risk analyses, we were able to disentangle the association between eGFR variability and death versus graft failure. Third, we used model-based metrics for variability, which are able to incorporate eGFR slope over time. Our results are robust, given the good agreement in results using alternative variability indicators as well as a different modeling strategy for the eGFR trajectory. Fourth, checking cause-specific death and graft failure further illustrated potential underlying mechanism associated with eGFR variability.

Our study also has limitations. We excluded patients who did not have a functioning graft at 2 years posttransplantation and who did not have an adequate number of outpatient eGFR measurements between 1 and 2 years. Participants included in the analyses were healthier and may have had lower eGFR variability. More advanced modeling strategies that are able to incorporate complicated patterns of eGFR trajectory early posttransplantation and survival outcomes, such as joint modeling, are needed to explore their etiologic associations. Second, our results may be affected by ascertainment bias, as patients with more eGFR measurements had greater variability and higher risk of adverse outcomes. We adjusted for number of glomerular filtration rate (GFR) measurements in analyses, but potential bias may

still remain. Third, our findings are limited by the potential for measurement error in graft function introduced by using serum creatinine and eGFR rather than directly measured GFR.[20] Fourth, we did not have data on some important covariates such as proteinuria and dosage change of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers. Fifth, we assumed a linear slope of eGFR in the baseline period. It is possible that eGFR may have a nonlinear change pattern over time. However, we limited the baseline period to 1 and 2 years posttransplantation, and we expect a less complicated eGFR change than earlier posttransplantation. Sixth, we applied only internal validation by bootstrap. External validation studies are needed to further demonstrate applicability of our results.

In summary, in a large transplantation cohort, greater variability in eGFR between 1 and 2 years posttransplantation was strongly associated with an increased risk of death that is independent of traditional prognostic factors, eGFR level, and eGFR slope, but not increased risk of graft failure. Specifically, greater variability of eGFR was associated with higher risk of cardiovascular- and infection-related death and cardiovascular events. Our work demonstrates that using these eGFR metrics may help to identify patients at higher risk for adverse transplantation outcomes.

DISCLOSURE

AUTHOR CONTRIBUTIONS

BL and BCA designed the study; BL and BCA analyzed the data; BL, DAM, AD, and BCA interpreted the data; BL

drafted the paper; BL, DAM, AD, and BCA participated in critical revision of the paper. All authors approved the final version of the manuscript.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)
Supplementary Methods
Table S1. Characteristics of excluded and enrolled patients
Table S2. Bivariable association between patient characteristic and risk of death within 10 years.
Table S3. Bivariable association between patient characteristic and risk of DCGF within 10 years.
Table S4. Continuous net reclassification index in risk of total graft loss risk prediction after including CV
Table S5. Variability of loglinear eGFR and the risk of outcomes
Table S6. Association between eGFR variability and competing risk analyses by patient characteristics
Table S7. Associations between eGFR variability and the risk of outcomes among KTRs not hospitalized between 1 and 2 years posttransplantation
Table S8. Associations between coefficient of variation of eGFR and outcomes of interest among transplantation between 2010 and 2014
Table S9. Association between variability of eGFR and outcomes of interest limiting events happened at least 2.5 years posttransplantation
Table S10. Association between mean absolute residuals of eGFR and outcomes of interest
Table S11. Associations between root mean square error (RMSE) of eGFR and outcomes of interest
Table S12. Association between coefficient of variation of creatinine and outcomes of interest
Figure S1. Flow chart of study population
Figure S2. Associations between patient characteristics and the risk of death.
Figure S3. Associations between standardized CV and the risk of death censored graft failure.
Figure S4. Calibration plots at 3 (A), 5 (B), and 10 (C) years of risk of mortality using model that included age, sex, race, cause of ESKD, live donor, eGFR, eGFR slope and eGFR CV.
Figure S5. Calibration plots at 3 (A), 5 (B), and 10 (C) years of risk of graft failure using model that included age, sex, race, cause of ESKD, live donor, eGFR, eGFR slope and eGFR CV.
STROBE Statement (PDF)

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