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The Power of Renal Function Estimation Equations for Predicting Long-Term Kidney Graft Survival

A Retrospective Comparison of the Chronic Kidney Disease Epidemiology Collaboration and the Modification of Diet in Renal Disease Study Equations

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Abstract: Evaluation of renal function using an accurate estimation equation is important for predicting long-term graft survival. We designed this retrospective cohort study to evaluate the predictive power of renal function estimation by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) and the Modification of Diet in Renal Disease (MDRD) study equations for graft survival.

We reviewed data of 3290 adult kidney transplant recipients who underwent transplantation at a single center between April 1979 and September 2012. The reliability and agreement of chronic kidney disease (CKD) stages based on the estimated glomerular filtration rate (eGFR) as calculated by the CKD-EPI and MDRD equations were evaluated using Bland–Altman plots and Cohen weighted kappa analyses. The predictive power of CKD stages as classified by each equation for graft survival was investigated using Cox regression models. Additionally, Pearson and Spearman correlation coefficients were used to reveal the relationship between graft survival and eGFR equations.

Of 3290 kidney transplant recipients, 3040 were included in the analysis. The mean follow-up duration was 128.08 ± 83.54 months, and 29.8% of participants were reclassified to higher eGFR categories by the CKD-EPI equation compared to the category classification by the MDRD equation. eGFR calculated using the MDRD equation was underestimated compared to that calculated using the CKD-EPI equation, based on the Bland–Altman plot. In Cohen weighted kappa analysis, agreement across CKD stages classified using the 2 equations was reliable, but all CKD stages classified using the MDRD equation appeared to be in lower eGFR categories than those classified using the CKD-EPI equation. Pearson and Spearman correlation analyses indicated that the CKD stage as classified by the CKD-EPI equation, but not the MDRD equation, was significantly correlated with the risk of graft failure. In multivariable Cox regression analysis for graft failure after adjustment for CKD stage as determined using the MDRD equation, but not the CKD-EPI equation, stage reclassification was significantly associated with a lower graft failure risk.

Our data from this long-term follow-up study indicate that the CKD-EPI equation has a stronger predictive power for kidney graft survival than does the MDRD equation in transplantation settings.

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Abbreviations: AR = acute rejection, BMI = body mass index, CKD = chronic kidney disease, CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration, eGFR = estimated glomerular filtration rate, ESRD = end-stage renal disease, HLA = human leukocyte antigen, KT = kidney transplantation, MDRD = Modification of Diet in Renal Disease, mGFR = measured GFR.

INTRODUCTION

Chronic kidney disease (CKD) is a major health problem worldwide, and the number of patients with CKD is rapidly increasing.[1,2] The glomerular filtration rate (GFR) is widely used to diagnose and evaluate CKD. In particular, GFR < 60 mL/min/1.73 m^2, considered to indicate impaired kidney function, has been associated with an increased risk of progression to kidney failure and is a major risk factor for negative outcomes associated with CKD. Therefore, an accurate estimation of GFR is important for detecting CKD and assessing its severity, predicting kidney survival, and determining the appropriate management for CKD progression.[3–5]

Measured GFR (mGFR) is considered the gold standard marker of renal function in the general population, CKD patients, and patients who have undergone kidney transplantation (KT), but its use is limited in routine clinical settings. Estimated GFR (eGFR) provides an alternative for easily evaluating renal function because of the simplicity of sampling.[6–9] There are several equations for eGFR that have been applied to evaluate CKD[10–13] and these have been validated in CKD patients in many countries and under various conditions.[14–18] However, no single equation for GFR estimation is appropriate for all populations and GFR ranges.[19] Although equations for GFR calculation were developed using mGFR, which reflects the renal clearance of exogenous markers, systematic differences in these mGFR measurement methods could distort the validation of results when compared with results obtained by using the renal clearance of inulin as the gold standard.[20,21]

The first systematic review of a creatinine-based GFR estimation equation in solid-organ recipients was recently performed. The authors conducted a study of the diagnostic

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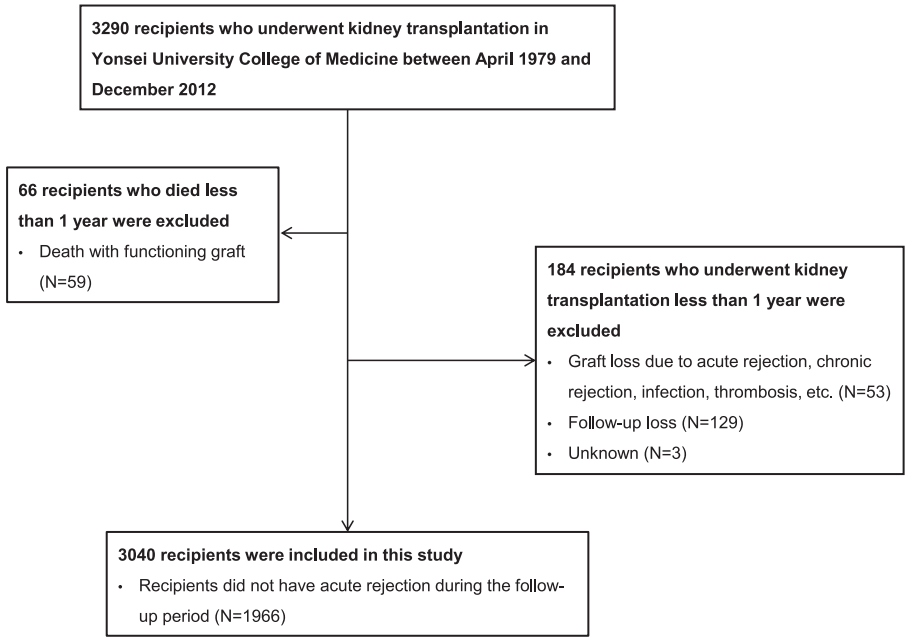


FIGURE 1. Algorithm used to define the study cohort.

testing accuracy of eGFR equations compared to that of mGFR equations and concluded that the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) and the Modification of Diet in Renal Disease (MDRD) study equations showed better performance than did alternative creatinine-based estimation equations. Thus, eGFR calculated using the CKD-EPI and MDRD study equations can be used for routine monitoring of kidney function in solid-organ transplant recipients.[22] Although a kidney function end-point would be ideal for evaluating definite outcomes related to KT or for developing clinical trials for patients undergoing KT, the use of such an endpoint is difficult in a clinical setting due to the large numbers of patients and the long-term follow-up period needed.[23]

A large meta-analysis demonstrated that the CKD-EPI equation was more accurate in categorizing the risk of mortality and progression to end-stage renal disease (ESRD) than was the MDRD study equation in a population with a broad range of demographic and clinical characteristics.[24] Moreover, for CKD patients with type 2 diabetes, the stages based on eGFR as calculated by the CKD-EPI equation were shown to be more reliable for risk stratification regarding CKD progression than were those calculated by the MDRD study equation, especially in earlier-stage CKD.[25]

Instead of comparing the accuracy of the CKD-EPI equation with that of other equations for predicting mGFR,[6,9] the present study was conducted to validate the eGFR as calculated by the CKD-EPI equation compared to the eGFR as calculated by the MDRD study equation for predicting long-term renal outcomes in a large number of KT patients in a single center.

METHODS

Study Population

This retrospective cohort study included all transplant recipients who underwent KT at the Severance Hospital Transplantation Center. We obtained the medical records of all adult patients undergoing KT between April 1979 and December 2012 who survived least 1 year for inclusion in this study. A total of 3290 transplant recipients were analyzed; 250 were excluded because of death, graft loss, or loss to follow-up within 1 year. We also performed a subgroup analysis for participants without an acute rejection (AR) episode (Figure 1).

This study was approved by the Institutional Review Board of Severance Hospital, Yonsei University College of Medicine, Seoul, Korea, and the need for informed consent was waived due to the retrospective nature of the study.

Immunosuppressive Protocol

Before 1984, participants were primarily treated with immunosuppressive agents such as azathioprine and prednisolone. After 1984, a double regimen with cyclosporine A and prednisolone, or a triple regimen with the addition of azathioprine or mycophenolic acid was used. Mycophenolic acid was introduced in 1997 and was used for appropriate recipients as part of the triple regimen with a calcineurin inhibitor. Since 1998, the calcineurin inhibitor tacrolimus has been used instead of cyclosporine A. Induction immunosuppression therapy (antithymocyte globulin, antilymphocyte globulin, and muromonab-CD3) was not used; however, induction therapy with an interleukin-2 receptor antibody (basiliximab) for high-risk recipients was initiated in 1999.

Steroid pulse therapy (methylprednisolone [500 mg/d × 4 for 5 days]) was considered the first-line therapy for AR. In the event of an inadequate response, an antilymphocyte antibody, such as OKT-3, or an antithymocyte antibody was used.

Clinical Variables

Clinical variables included donor and recipient age and sex, body mass index (BMI), dialysis duration before KT, human leukocyte antigen (HLA) mismatches, AR within 1 year of KT and during the follow-up period, diabetes mellitus, kidney

TABLE 1. Baseline Characteristics of Participants Overall and Those Without Acute Rejection

Variables	All Participants ($n = 3040$)	Participants Without AR ($n = 1966$)
Age, y	39.30 ± 10.85	39.82 ± 10.92
Sex (male, n (%))	1989 (65.43)	1267 (64.45)
Diabetes (yes, n (%))	816 (26.84)	497 (25.28)
BMI at KT, kg/m^2	21.72 ± 3.16	21.81 ± 3.16
Donor age, y	37.37 ± 11.63	37.22 ± 11.52
Dialysis duration prior KT, mo	23.64 ± 35.84	23.94 ± 36.24
HLA-mismatch (yes, n (%))	2678 (88.68)	1687 (86.29)
Number of HLA-mismatches per patient	2.41 ± 1.29	2.38 ± 1.35
Donor type (n (%))		
LRD	1584 (52.11)	1110 (56.46)
LURD	1206 (39.67)	671 (34.13)
Deceased	250 (8.22)	185 (9.41)
AR during 1st year (yes, n (%))	873 (30.90)	—
Number of AR per patient during 1st year	0.43 ± 0.65	—
MDRD eGFR (ml/min/1.73 m^2) at 1 year post-KT	59.64 ± 17.51	61.99 ± 15.98
CKD-EPI eGFR (ml/min/1.73 m^2) at 1 year post-KT	66.54 ± 19.85	69.24 ± 18.16
Graft survival, mo	128.08 ± 83.54	130.84 ± 87.16

Data are expressed as mean ± SD or frequency (percentage).
AR = acute rejection, BMI = body mass index, CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration, eGFR = estimated glomerular filtration rate, HLA = human leukocyte antigen, KT = kidney transplantation, LRD = living related donor, LURD = living unrelated donor, MDRD = Modification of Diet in Renal Disease.

function at 1 year after KT, and graft survival. AR was defined by the need for treatment, with or without biopsy confirmation. The total number of HLA mismatches was calculated as the sum of the mismatches in the A, B, and DR loci. Graft loss was defined as patient death, graft removal, or conversion to regular dialysis.

GFR Calculation

eGFR values were calculated using the four-variable MDRD study equation and the CKD-EPI equations.[12,26]

$$\text{MDRD eGFR} = 175 \times (\text{serum creatinine in mg/dL})^{-1.154} \times (\text{age})^{-0.203} (\times 0.742 \text{ if female}).$$

$$\text{CKD-EPI eGFR} = 141 \times (\text{minimum of standardized serum creatinine [mg/dL]}\}/\kappa \text{ or1})^{\alpha} \times (\text{maximum of standardized serum creatinine [mg/dL]}\}/\kappa \text{ or1})^{-1.209} \times 0.993^{\text{age}} (\times 1.018 \text{ if female}) (\times 1.159 \text{ if black})$$

where κ is 0.7 for women and 0.9 for men, and α is -0.329 for women and -0.411 for men.

For both equations, eGFR was calculated in mL/min/1.73 m^2, weight in kg, serum creatinine in mg/dL, and age in years. CKD was classified into 5 stages based on the eGFR category, according to the Kidney Disease: Improving Global Outcomes criteria: stage 1, eGFR $\geq$ 90 mL/min/1.73 m^2; stage 2, eGFR of 60 to 89 mL/min/1.73 m^2; stage 3, eGFR of 30 to 59 mL/min/1.73 m^2; stage 4, eGFR of 15 to 29 mL/min/1.73 m^2; and stage 5, eGFR $<$ 15 mL/min/1.73 m^2 or dialysis. Stage 3 CKD was further divided into 2 subgroups: stage 3a, eGFR 45 to 59 mL/min/1.73 m^2 and stage 3b, eGFR 30 to 44 mL/min/1.73 m^2.[27]

Statistical Analysis

The patients' baseline characteristics at transplantation and 1 year after transplantation are represented as the mean ± standard deviation or frequency (percentage). Bland–Altman plots were used to examine the agreement between eGFR values calculated by each equation. The frequency distribution of participants in each category of eGFR as determined by the 2 equations using clinical reference values ($\geq$90, 60–89, 45–59, 30–44, 15–29, and $\leq$15 mL/min/1.73 m^2) was confirmed using contingency tables, and the reliability of each category was analyzed based on Cohen weighted kappa. The association of ordinal CKD stages and the overall percentage of graft failure within each category were assessed based on Pearson and Spearman correlation coefficients. The Kaplan–Meier method was used to evaluate graft failure according to CKD stage and the estimated median graft failure time at each CKD stage. Cumulative event rates for the CKD stages were compared using the log-rank test. Univariate and multivariable Cox regression analyses were performed to investigate the effects of CKD stage on the prediction of graft failure. P values of $<$0.05 were considered statistically significant, and all analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC) and R package version 2.14.2.

RESULTS

A total of 3040 recipients were included in this study (Figure 1). The baseline characteristics for all participants and for those without acute rejection (AR) are shown in Table 1. The mean age in the 2 groups was 39.30 ± 10.85 and 39.82 ± 10.92 years, respectively. The mean follow-up duration was 128.08 ± 83.54 months overall and 130.84 ± 87.16 months for participants without AR. The mean eGFR values for all participants at 1 year after KT as calculated by the CKD-EPI and MDRD study equations were 66.54 ± 19.85 and 59.64 ± 17.51 mL/min/1.73 m^2, respectively. In participants without AR, the mean eGFR

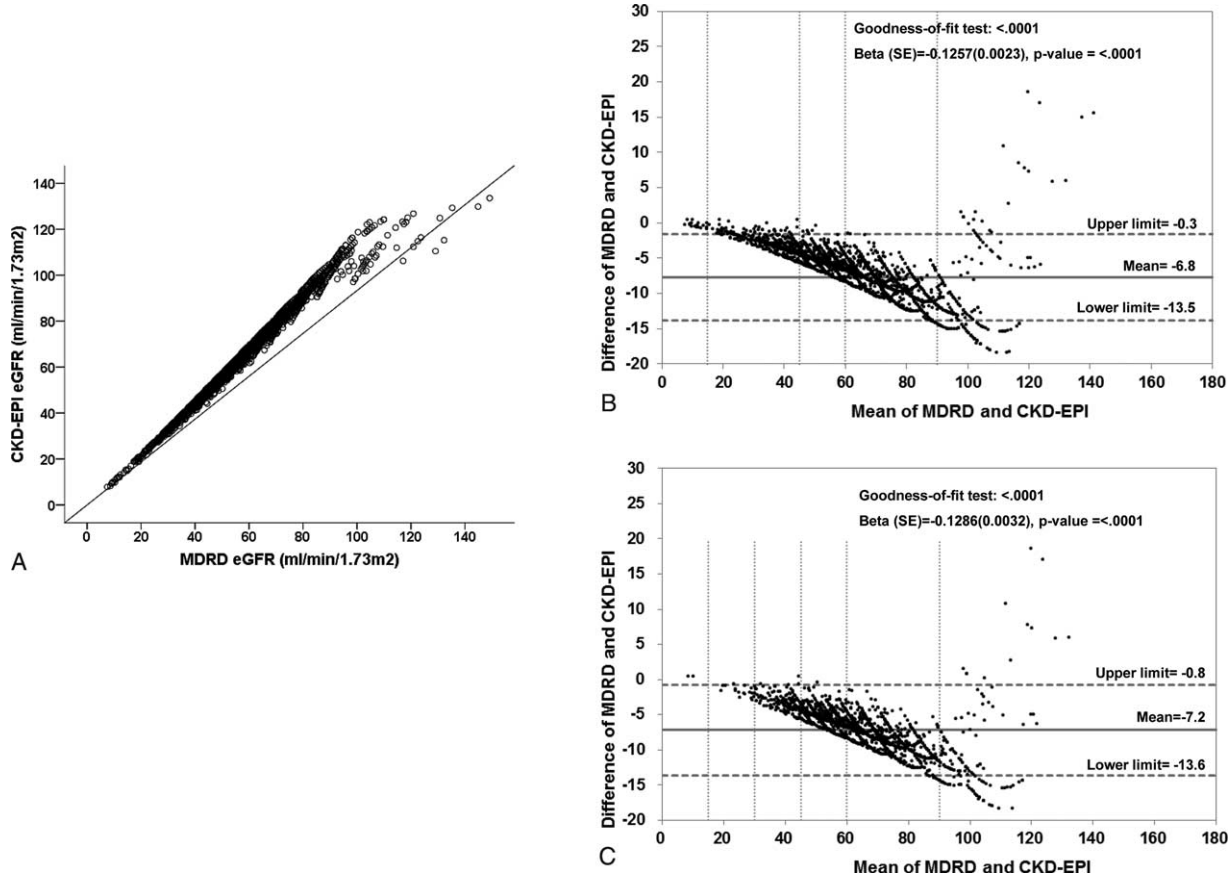


FIGURE 2. Comparison between eGFR values calculated by the CKD-EPI and MDRD equations. Scatter plots of eGFR values calculated by the CKD-EPI and MDRD equations (A). Bland–Altman plots of eGFR values calculated by the CKD-EPI and MDRD equations in all participants (B) and participants without AR (C). AR = acute rejection, CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration, eGFR = estimated glomerular filtration rate, MDRD = Modification of Diet in Renal Disease.

values calculated using the CKD-EPI and MDRD study equations at 1 year after KT were 69.24 ± 18.16 and 61.99 ± 15.98 mL/min/1.73 m^2, respectively. The mean number of ARs per patient during the first year after KT and the number of participants experiencing AR over the entire follow-up period was 0.43 ± 0.65 and 873, respectively (Table 1).

A scatter plot of eGFR values as calculated using the 2 equations indicated greater discrepancy between the 2 equations at higher eGFR values in all participants (Figure 2A). The Bland–Altman analysis performed to test the agreement between eGFR as calculated using the 2 equations revealed a mean difference between the 2 eGFR values of −6.8 overall, suggesting that the MDRD study equation underestimated eGFR compared to the CKD-EPI equation. Mean differences between the 2 eGFR values increased as eGFR values increased in all participants (beta (SE) = −0.1257 (0.0023), $P < 0.0001$) (Figure 2B). Similar results were observed in the Bland–Altman plot analysis of participants without an AR episode (beta (SE) = −0.1286 (0.0032), $P < 0.0001$) (Figure 2C).

Cohen weighted kappa statistics showed that the agreement of CKD stages based on eGFR as calculated by the 2 equations was reliable in the overall patient population and in participants without AR ($\kappa = 0.7053$ in the overall patient population, $P < 0.0001$; $\kappa = 0.6503$ in participants without AR, $P < 0.0001$). However, the CKD stages classified by the MDRD study equation were all in lower eGFR categories than were those classified by the CKD-EPI equation both in the overall patient population and in participants without AR (Figure 3). With the CKD stages assigned using the MDRD study equation as reference, CKD stages were reclassified in 29.8% of all participants on using the CKD-EPI equation. Most of the reclassifications were in participants classified as having stage 3a CKD according to the MDRD study equation both in the overall patient population and in participants without AR. Of the 1285 participants classified as having stage 2 CKD according to the MDRD study equation, 18.1% (n = 233) were reclassified as having stage 1 CKD based on the CKD-EPI equation, and 44.3% (n = 461) of the 1041 participants classified as having stage 3a CKD according to the MDRD study equation were reclassified as having stage 2 CKD based on the CKD-EPI equation. In participants classified as having stage 3b CKD according to the MDRD study equation, upward reclassification to stage 3a CKD based on the CKD-EPI was noted in 39.7% of participants ($n = 182/457$). Of the 1966 participants without AR, the CKD stage was reclassified in 30.6% of all participants on using the CKD-EPI equation; CKD was reclassified in 18.4% (n = 167) of stage 1 patients, 46.0% ($n = 325$) of stage 2 patients, 43.7% ($n = 100$) of stage 3a patients, and 45.8% ($n = 11$) of stage 3b patients (Figure 3).

Next, we performed Pearson and Spearman correlation analyses to investigate whether CKD stages based on the 2 equations were associated with graft failure in the overall

A

CKD stages based on eGFR by MDRD	CKD stages based on eGFR by CKD-EPI						
	Stage 1	Stage 2	Stage 3a	Stage 3b	Stage 4	Stage 5	Total
Stage 1	139	0	0	0	0	0	139
Stage 2	233 (18.1%)	1052	0	0	0	0	1285
Stage 3a	0	461 (44.3%)	580	0	0	0	1041
Stage 3b	0	0	182 (39.7%)	275	0	0	457
Stage 4	0	0	0	28 (28.0%)	72	0	100
Stage 5	0	0	0	0	2 (11.1%)	16	18
Total	372	1513	762	303	74	16	

Weighted Kappa (95% CI) = 0.7053 (0.6876-0.7230), p-value = <0.001

B

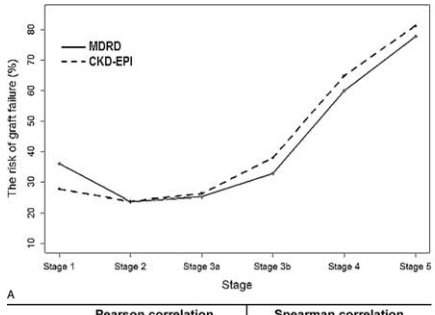
CKD stages based on eGFR by MDRD	CKD stages based on eGFR by CKD-EPI						
	Stage 1	Stage 2	Stage 3a	Stage 3b	Stage 4	Stage 5	Total
Stage 1	97	0	0	0	0	0	97
Stage 2	167 (18.4%)	741	0	0	0	0	908
Stage 3a	0	325 (46.0%)	381	0	0	0	706
Stage 3b	0	0	100 (43.7%)	129	0	0	229
Stage 4	0	0	0	11 (45.8%)	13	0	24
Stage 5	0	0	0	0	0	2	2
Total	264	1066	481	140	13	2	

Weighted Kappa (95% CI) = 0.6503 (0.6259-0.6748), p-value = <0.001

FIGURE 3. Status of reclassification of the CKD stage as determined by the CKD-EPI and MDRD equations in all participants (A) and in participants without acute rejection (AR) (B). Red type indicates movement to a higher eGFR category. Data are represented as the number (percentage) of participants in each CKD stage. CKD = chronic kidney disease, CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration, MDRD = Modification of Diet in Renal Disease.

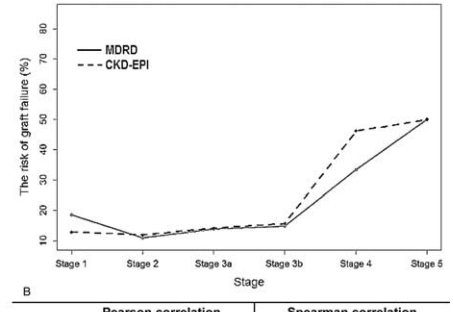
patient population or in those without AR. Pearson and Spearman correlation coefficients indicated that the CKD stages determined using the CKD-EPI equation were significantly correlated with the overall graft-failure percentage, while the CKD stage determined using the MDRD study equation was not significantly correlated in the overall patient population (Pearson coefficient: $r = 0.9019$, $P = 0.01$ vs $r = 0.8044$, $P = 0.05$; Spearman coefficient: $r = 0.8286$, $P = 0.04$ vs $r = 0.6571$, $P = 0.2$) (Figure 4A). Results for participants without AR were similar to those for the overall patient population (Pearson coefficient: $r = 0.8677$, $P = 0.02$, vs $r = 0.7949$, $P = 0.06$; Spearman coefficient: $r = 0.9427$, $P = 0.002$ vs $r = 0.6571$, $P = 0.2$) (Figure 4B).

Kaplan–Meier curves showed that the median graft-failure time was 254 months for CKD stage 1 as classified by the MDRD study equation; the median graft failure times for stages 2 and 3a as classified by the MDRD study equation were not reached during the follow-up period (Figure 5A). By contrast, the median graft failure time for stages 1 and 2 as classified by the CKD-EPI equation were not reached, and the median graft-failure time was shorter at higher stages (Figure 5B).



A

	Pearson correlation		Spearman correlation	
	r (95% CI)	P value	r (95% CI)	P value
MDRD	0.8044 (-0.1006-0.9739)	0.05	0.6571 (-0.3881-0.9521)	0.2
CKD-EPI	0.9019 (0.2550-0.9872)	**0.01**	0.8286 (-0.0309-0.9772)	**0.04**



B

	Pearson correlation		Spearman correlation	
	r (95% CI)	P value	r (95% CI)	P value
MDRD	0.7949 (-0.1258-0.9725)	0.06	0.6571 (-0.3881-0.9521)	0.2
CKD-EPI	0.8677 (0.1048-0.9826)	**0.02**	0.9427 (0.4909-0.9926)	**0.002**

FIGURE 4. Prediction of graft failure using Pearson and Spearman correlation analyses. Pearson and Spearman correlation analyses between the risk of graft failure and CKD stages determined by the MDRD and CKD-EPI equations in all participants (A) and in participants without acute rejection (AR) (B). CKD = chronic kidney disease, CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration, MDRD = Modification of Diet in Renal Disease.

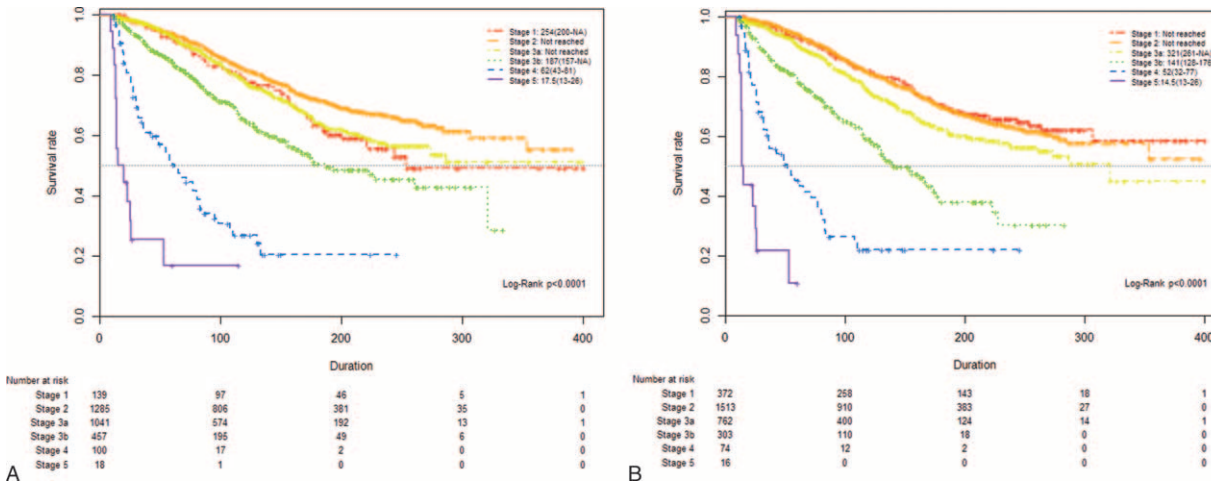


FIGURE 5. Kaplan–Meier curve for median time of graft survival according to CKD stages determined by each eGFR equation: MDRD (A) and CKD-EPI (B). Colored lines indicate CKD stages (red: stage 1, orange: stage 2, yellow: stage 3a, green: stage 3b, blue dotted: stage 4, purple: stage 5). CKD = chronic kidney disease, CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration, MDRD = Modification of Diet in Renal Disease.

In Univariate Cox regression analysis, male sex, AR, and a higher CKD stages as classified by either equation were significantly associated with a higher graft-failure risk, while stage reclassification was associated with a lower graft-failure risk (Table 2). Multivariable Cox regression analysis for graft failure was adjusted for age, sex, AR, stage reclassification, and CKD stage as classified by either equation. Stage reclassification was associated with a significantly decreased graft-failure risk after adjusting for age, sex, AR, and CKD stage as classified by the MDRD study equation. Interestingly, stage reclassification was not

TABLE 2. Univariate Cox Regression for Graft Failure

	All Participants ($n = 3040$)		Participants Without AR ($n = 1966$)	
Variables	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Age, y	0.996 (0.989–1.002)	0.19	0.984 (0.972–0.996)	0.01
Sex				
Female	1 (Ref)		1 (Ref)	
Male	1.310 (1.126–1.524)	<0.001	1.533 (1.154–2.037)	0.003
BMI at KT, kg/m^2	1.007 (0.967–1.048)	0.73	1.035 (0.974–1.100)	0.26
Dialysis duration, mo	1.000 (0.997–1.002)	0.81	0.998 (0.993–1.003)	0.38
AR				
No	1 (Ref)		—	—
Yes	3.409 (2.911–3.992)	<0.001	—	—
Stage reclassification				
No	1 (Ref)		1 (Ref)	
Yes	0.798 (0.685–0.930)	0.004	0.880 (0.673–1.150)	0.35
MDRD eGFR category				
Stage 1	1 (Ref)		1 (Ref)	
Stage 2	0.720 (0.534–0.971)	0.03	0.689 (0.417–1.139)	0.15
Stage 3a	0.916 (0.677–1.241)	0.57	1.135 (0.686–1.879)	0.62
Stage 3b	1.534 (1.112–2.115)	0.009	1.675 (0.942–2.975)	0.08
Stage 4	5.785 (3.956–8.459)	<0.001	12.089 (5.184–28.191)	<0.001
Stage 5	22.868 (12.535–41.720)	<0.001	146.928 (18.196–1186.378)	<0.001
CKD-EPI eGFR category				
Stage 1	1 (Ref)		1 (Ref)	
Stage 2	1.031 (0.828–1.284)	0.78	1.207 (0.826–1.763)	0.33
Stage 3a	1.361 (1.072–1.728)	0.01	1.813 (1.198–2.744)	0.005
Stage 3b	2.840 (2.170–3.717)	<0.001	3.623 (2.098–6.256)	<0.001
Stage 4	8.874 (6.267–12.565)	<0.001	28.650 (11.867–69.170)	<0.001
Stage 5	52.282 (28.795–94.925)	<0.001	221.576 (28.093–1747.605)	<0.001

AR = acute rejection, BMI = body mass index, CI = confidence interval, CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration, HR = hazard ratio, KT = kidney transplantation, MDRD = Modification of Diet in Renal Disease.

TABLE 3. Multivariable Cox Regression for Graft Failure in the Participants

	All Participants (n = 3040)				Participants Without AR (n = 1966)			
	MDRD eGFR Category		CKD-EPI eGFR Category		MDRD eGFR Category		CKD-EPI eGFR Category	
Variables	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Age, y	0.987 (0.979–0.994)	<0.001	0.987 (0.979–0.994)	<0.001	0.980 (0.968–0.993)	0.002	0.980 (0.968–0.993)	0.002
Sex								
Female	1 (Ref)		1 (Ref)		1 (Ref)		1 (Ref)	
Male	1.423 (1.194–1.697)	<0.001	1.430 (1.199–1.705)	<0.001	1.519 (1.142–2.020)	0.004	1.547 (1.162–2.059)	0.003
AR								
No	1 (Ref)		1 (Ref)					
Yes	2.676 (2.263–3.165)	<0.001	2.666 (2.254–3.153)	<0.001				
Stage Reclassification								
No	1 (Ref)		1 (Ref)		1 (Ref)		1 (Ref)	
Yes	0.678 (0.565–0.814)	<0.001	0.990 (0.820–1.197)	0.92	0.661 (0.496–0.881)	0.005	1.081 (0.812–1.440)	0.59
eGFR Category								
Stage 1	1 (Ref)		1 (Ref)		1 (Ref)		1 (Ref)	
Stage 2	0.796 (0.532–1.192)	0.27	1.100 (0.823–1.470)	0.52	0.755 (0.456–1.252)	0.2763	1.281 (0.863–1.900)	0.22
Stage 3a	1.179 (0.782–1.777)	0.43	1.441 (1.057–1.963)	0.02	1.443 (0.857–2.428)	0.1674	1.977 (1.282–3.049)	0.002
Stage 3b	1.667 (1.083–2.566)	0.02	2.634 (1.854–3.742)	<0.001	2.228 (1.227–4.045)	0.0085	4.283 (2.405–7.629)	<0.001
Stage 4	5.025 (3.106–8.128)	<0.001	6.854 (4.470–10.509)	<0.001	15.733 (6.657–37.184)	<0.0001	34.424 (13.897–85.275)	<0.001
Stage 5	24.110 (11.833–49.126)	<0.001	45.607 (22.930–90.708)	<0.001	219.758 (26.425–1827.576)	<0.0001	345.031 (42.161–2823.595)	<0.001

AR = acute rejection, CI = confidence interval, CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration, eGFR = estimated glomerular filtration rate, HR = hazard ratio, MDRD = Mo-Modification of Diet in Renal Disease.

associated with decreased graft survival after adjustment for age, sex, AR, and CKD stage as classified by the CKD-EPI equation as opposed to CKD stage as classified by the MDRD study equation. Similar results were observed in participants without AR (Table 3).

DISCUSSION

Our data of 3040 KT recipients over a 10-year follow-up period showed that eGFR was reclassified to a higher eGFR category based on the CKD-EPI equation as compared to the MDRD study equation classification in almost one-third of participants. This retrospective cohort study also demonstrated that stage reclassification was associated with a significantly lower risk of graft failure.

Several methods for GFR measurement have been used since the use of urinary inulin clearance for GFR measurement was developed, but these direct measurements are only available in major medical centers. Therefore, GFR estimation using endogenous filtration markers rather than mGFR is commonly employed to evaluate CKD.[28] However, Shaffi et al[22] reported a wide range of bias and accuracy across studies, with both the overestimation and underestimation of mGFR using creatinine-based estimation equations because of differences in race, the reference standard used for GFR measurement, and creatinine assay calibration. A recent study reported that the CKD-EPI creatinine equation was not a better predictor of GFR than the MDRD study equation in a large cohort of transplant patients in whom GFR was evaluated by either urinary inulin clearance or plasma ^{51}Cr-EDTA clearance.[6] Instead of comparing the performance of these 2 equations to approximate the mGFR, the present study validated creatinine-based GFR estimation equations using long-term clinical outcomes in KT patients in a single center. In this study, eGFR determined by the CKD-EPI equation at 1 year post-KT had good predictive power for graft survival in a large cohort of KT patients over a 10-year follow-up period. In clinical practice, a simple tool to assess renal function may be more important for predicting graft survival and the risk of mortality in KT patients than mGFR, which is difficult to determine repeatedly in KT patients.

Based on data from patients with CKD, several limitations of the MDRD study equation have been reported, including a lack of precision and an underestimation of GFR, especially in patients with early-stage CKD.[25,29] In a recent meta-analysis of data from 1.1 million adults, eGFR was reclassified to a higher category in approximately one-fourth of participants on using the CKD-EPI equation compared to the stage determined using the MDRD study equation. Interestingly, participants in whom eGFR was reclassified upward had a lower risk of mortality and ESRD than those in whom eGFR was not reclassified, after adjusting for age, sex, race/ethnicity, and other potential confounders.[24] Our study also demonstrated that participants in whom eGFR was reclassified upward based on the CKD-EPI equation had a lower graft-failure risk after adjusting for age, sex, AR status, and CKD stage. Notably, all KT patients in whom eGFR was reclassified showed a move to a higher eGFR category based on the CKD-EPI equation compared with the MDRD study equation classification. Additionally, a Bland–Altman plot analysis of our results showed that eGFR was significantly underestimated by the MDRD study equation at all CKD stages compared to the CKD-EPI equation classification.

In a previous report regarding CKD progression in CKD patients with type 2 diabetes, the CKD-EPI equation facilitated more accurate stratifications in earlier-stage CKD than did the MDRD study equation.[25] Our Kaplan–Meier analysis indicated that CKD stage stratification by the CKD-EPI equation was more accurate in predicting graft failure than was stratification by the MDRD study equation and revealed poorer graft survival in stage 1 CKD patients than in stage 2 and 3a CKD patients. Multivariable Cox regression analysis also showed that CKD stages as classified by the CKD-EPI equation were more accurately associated with increased hazard ratios (HRs) for graft failure than were those classified by the MDRD study equation.

Several studies have shown that a higher eGFR was paradoxically associated with increased mortality with respect to muscle wasting secondary to poor health.[24,30] A recent meta-analysis reported that this risk was not evident in the unadjusted analysis but was evident after age adjustment, suggesting that the CKD-EPI equation could not fully overcome this limitation inherent to creatinine-based eGFR equations.[24] Moreover, GFR prediction equations using serum creatinine have been reported to overestimate mGFR in KT patients on and off steroid regimens.[31] Kasiske et al reported that relatively lower serum creatinine levels in some patients were due to decreased muscle mass and that the comorbidity giving rise to decreased muscle mass may have been associated with a higher risk of graft failure. The small number of KT patients with stage 1 CKD at 12 months after transplantation had a higher rate of graft failure due to increased mortality.[32] By contrast, in the present study, higher CKD stages as classified by the CKD-EPI equation were significantly associated with greater HRs for graft failure (HR: 1.1 for stage 2 and 1.441 for stage 3a based on the CKD-EPI equation), whereas stage 2 CKD as classified by the MDRD study equation had lower HRs for graft failure (HR for graft failure: 0.796 for stage 2; 1.179 for stage 3a based on the MDRD study equation) in both Univariate and multivariable Cox analyses, after adjusting for age, sex, AR, and stage reclassification. Taken together, these results suggest that CKD stages determined by the CKD-EPI equation might more accurately predict graft survival in patients with KT than might those determined using the MDRD equation, especially in the earlier stages. Moreover, the multivariable Cox analysis suggested that stage reclassification was associated with a lower risk of graft failure after adjustment for CKD stages as classified by the MDRD study equation, while any significant association with a decreased risk of graft failure was lost after adjustment for CKD stages classified by the CKD-EPI equation.

In addition to its retrospective nature, there are several limitations to this study. First, we did not evaluate the accuracy of the 2 equations for estimating GFR in KT patients by comparing the eGFR values with mGFR values using inulin or isotopes. Second, although the CKD-EPI equation has stronger clinical implications than does the MDRD study equation for the earlier stages of CKD, it still involves the inherent limitations of the use of serum creatinine, which is dependent on muscle mass, creatinine generation, and tubular secretion. A large overestimation was observed in our transplant recipients at eGFR levels $\geq$90 mL/min/1.73 m^2 and this can be considered an artifact. This overestimation was attributable to low serum creatinine levels caused by muscle wasting with comorbid conditions in transplant recipients. Finally, this study comprised only Korean KT patients, preventing our results from being generalized to other ethnic populations.

In summary, we found that eGFR was underestimated by the MDRD equation compared to eGFR determined by the CKD-EPI equation in KT patients. Both Univariate and

multivariable Cox regression analyses indicated that higher CKD stages as determined by the CKD-EPI equation were significantly associated with a greater risk of graft failure, whereas a stage 2 classification based on the MDRD study equation was associated with a lower risk of graft failure. Stage reclassification was associated with a significantly decreased risk of graft failure, after adjusting for age, sex, AR, and CKD stage as classified by the MDRD equation but not the CKD-EPI equation in multivariable Cox regression analysis. Our results suggest that eGFR calculated by the CKD-EPI equation has a stronger predictive power for long-term kidney graft survival in transplantation settings than does that determined by the MDRD study equation.

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