

Comparison of Estimating Equations for the Prediction of Glomerular Filtration Rate in Kidney Donors before and after Kidney Donation

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Abstract

The aim of this study is to investigate the usefulness of the GFR-estimating equations to predict renal function in kidney donors before and after transplantation. We compared the performance of 24-hour-urine-based creatinine clearance (24 hr urine-CrCl), the Cockcroft-Gault formula (eGFR_{CG}), the Modification of Diet in Renal Disease equation (eGFR_{MDRD}), and the Chronic Kidney Disease Epidemiology Collaboration equation (eGFR_{CKD-EPI}) with technetium-diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA) clearance (mGFR) in 207 potential kidney donors and 108 uninephric donors. Before donation, eGFR_{CKD-EPI} showed minimal bias and did not show a significant difference from mGFR ($P = 0.65$, respectively) while 24 hr urine-CrCl and eGFR_{MDRD} significantly underestimated mGFR ($P < 0.001$ for each). Precision and accuracy was highest in eGFR_{CKD-EPI} and this better performance was more dominant when renal function is higher than $90 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$. After kidney donation, eGFR_{MDRD} was superior to other equations in precision and accuracy in contrast to before donation. Within individual analysis, eGFR_{MDRD} showed better performance at post-donation compared to pre-donation, but eGFR_{CKD-EPI} and eGFR_{CG} showed inferior performance at post-donation. In conclusion, eGFR_{CKD-EPI} showed better performance compared to other equations before donation. In a uninephric donor, however, eGFR_{MDRD} is more appropriate for the estimation of renal function than eGFR_{CKD-EPI}.

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Introduction

Assessment of renal function is a critical component of donor evaluation in kidney transplantation and regular monitoring of it is recommended for the long-term safety of kidney donors. [1] In many centers, measurement of GFR using the ¹²⁵I-iothalamate GFR or technetium-99 m diethylenetriaminepentaacetic acid (^{99m}Tc DTPA) clearance is performed before kidney donation. [2,3] However, those studies are available only in a limited number of institutions. Moreover, they are not feasible for the post-donation monitoring of GFR in everyday clinical practice. Therefore, creatinine-based GFR estimations have been used as alternatives for the estimation of renal function before and after donation.

The 2 equations most commonly used are the Modification of Diet in Renal Disease (MDRD) Study equation and the Cockcroft-Gault (CG) formula. These formulas have some limitations for use in kidney donor workup, because they were developed based on data from patients with reduced renal function. [4,5,6] Recently, the Chronic Kidney Disease Epidemiology Collaboration developed a new equation (CKD-EPI). [7] Its aim was to eliminate the

weak point of the MDRD formula and the underestimation of GFR; the data set of the CKD-EPI formula included many participants with normal GFR in the development process. During the validation process in several populations, it has shown greater precision and reliability compared with those of the MDRD formula, especially for subjects with GFR of $>60 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$. [7,8,9].

The aim of this study was thus to investigate the performance of each GFR-estimating equations in the prediction of renal function in kidney donors. Second, we intended to determine the usefulness of those equations for the post-donation monitoring of renal function in uninephric donors.

Materials and Methods

Patients and Methods

A total of 207 healthy Korean adults who underwent the kidney donor workup at our center between March 2009 and September 2011 were included in this study. Laboratory evaluation included blood urea nitrogen, serum creatinine (Scr), and 24 hour urine-

based creatinine clearance (24-hour urine CrCl). Scr values were measured in a single laboratory using a “compensated” IDMS-traceable method (Hitachi Modular P-800; Roche Diagnostics, Germany). GFR was measured (mGFR) by ^{99m}Tc DTPA clearance with a single injection technique with a 4-point sampling approach at 10, 30, 180, and 240 minutes after injection, according to the method described by Russel et al. [10] After kidney donation, donors visited an outpatient clinic every 3 months, where blood chemistry examination including Scr was performed for 1 year after kidney transplantation (KT). ^{99m}Tc DTPA clearance was performed at around 6 months from KT, as part of the routine follow-up process. Out of 207 patient populations, 108 subjects completed studies after kidney donation, and they were included in the post-donation analysis.

Estimated glomerular filtration rate (eGFR) was calculated using the following equations.

- Creatinine clearance (CrCl) based on 24-hour urine chemistry:

$$\begin{aligned} &24\text{hr-CrCl}(\text{mL}/\text{min}) \\ &= \text{Ucr}/\text{Pcr} \times \text{urinevolume}(\text{mL}/24\text{hr})/1440(\text{min}/24\text{hr}) \end{aligned}$$

- Cockcroft-Gault method [5]:

$$\begin{aligned} &\text{eGFR}_{\text{CG}}(\text{mL}/\text{min}) \\ &= (140-\text{Age}) \times \text{Weight} \times 0.85(\text{if female})/72 \times \text{Scr} \end{aligned}$$

- MDRD formula [11]:

$$\begin{aligned} &\text{eGFR}_{\text{MDRD}}(\text{mL} \cdot \text{min}^{-1} \cdot 1.73\text{m}^{-2}) = 175 \times (\text{Scr})^{-1.154} \times (\text{Age})^{-0.203} \\ &\times 0.742(\text{if female}) \times 1.212(\text{if black}) \end{aligned}$$

- CKD-EPI equation [7]

$$\begin{aligned} &\text{eGFR}_{\text{CKD-EPI}}(\text{mL} \cdot \text{min}^{-1} \cdot 1.73\text{m}^{-2}) \\ &= 141 \times \min(\text{Scr}/k, 1)^a \times \max(\text{Scr}/k, 1)^{-1.209} \\ &\times 0.993^{\text{age}} \times 1.018(\text{if female}) \times 1.159(\text{if black}), \end{aligned}$$

where k is 0.7 for women and 0.9 for men, a is -0.329 for women and -0.411 for men, \min indicates the minimum of Scr/k or 1, and \max indicates the maximum or Scr/k or 1.

- Body-surface area (BSA) was calculated using the following formulae

$$\sqrt{\frac{\text{height}(\text{cm}) \times \text{weight}(\text{kg})}{3,600}}$$

The results of mGFR, 24 hr-CrCl, and eGFR_{CG} were corrected to standard BSA (1.73 m^2). This study was approved by the Institutional Review Board of Seoul St. Mary’s Hospital (KC12RISI0387).

Statistical Analysis

Data are presented as mean \pm SD or counts and percentages, depending on the data type. For continuous variables, mean values were compared using Oneway ANOVA and Dunnett’s test. The mean difference between equation-based GFR and the measured GFR was used to determine the bias. Pair-wise comparison of the mean difference was performed using the paired t -test. The precision of the estimates was determined as SD of the mean difference between mGFR and eGFR. [12] Accuracy-integrating precision and bias was calculated as the percentage of GFR estimates within 10% and 30% of the measured GFR as suggested. [13] McNemar’s test was used to evaluate the degree of accuracy. [14] Comparison of the correlation coefficients was performed using Z-statistics. Moreover, a graphical approach to assess accuracy was carried out according to the Bland-Altman method. [15] Statistical analyses were performed using SPSS software (version 15.0; SPSS Inc., Chicago, IL, USA) and MedCalc 11.2.1.0 (Medcalc, Mariakerke, Belgium). All tests were 2-tailed, and the results were considered significant when the P value was below 0.05.

Results

Baseline Characteristics of Patient Population

In the pre-donation analysis, the mean age of donors was 40.4 ± 11.3 years; 87 were male (42.0%). The mean height and weight were 164.0 ± 8.9 cm and 64.0 ± 11.9 kg, respectively. The mean body surface area (BSA) was $1.67 \pm 0.17 \text{ m}^2$; the mean body mass index (BMI) was $23.1 \pm 4.4 \text{ kg}/\text{m}^2$. The mean Scr was $0.78 \pm 0.16 \text{ mg}/\text{dL}$. In the post-donation analysis in 108 uninephric donors, the interval from KT to the measurement of GFR and Scr was 7.3 ± 3.9 months. Mean patient age was 39.0 ± 11.5 years; 51 patients were male (47.2%). Scr at the measurement of mGFR was $1.07 \pm 0.25 \text{ mg}/\text{dL}$.

Comparison of Each Equation’s Performance to Predict mGFR before Kidney Donation

Table 1 provides overall results for the bias, precision, and accuracy of all equations for the estimation of mGFR in this pre-donation cohort. eGFR_{CG} and eGFR_{CKD-EPI} showed minimal bias ($P = 0.99$ and $P = 0.92$ vs. mGFR, respectively), while 24 hr urine-CrCl and eGFR_{MDRD} significantly underestimated mGFR ($P < 0.001$ vs. mGFR in each case). eGFR_{CKD-EPI} showed highest precision (lowest SD of mean bias) among three equations. In addition, the accuracy of eGFR_{CKD-EPI} within 30% of mGFR was 91.8%, which is significantly higher than that of 24 hr urine-CrCl (71.5%) and eGFR_{MDRD} (84.1%) ($P < 0.001$ in each case) and it showed a higher tendency compared with eGFR_{CG} (86.0%) ($P = 0.06$).

Table 1. Comparison of the bias, precision and accuracy in the estimation of mGFR among each equation before kidney donation according to the mGFR level.

mGFR Group (mL/min/1.73 m ²)	eGFR	Value (mL/min/1.73 m ²) Mean ± SD	Mean difference to mGFR	Median difference to mGFR	SD of mean bias	Accuracy within	
						10% (%)	30% (%)
All (n = 207)	^{99m} Tc DTPA	110.3 ± 20.7	-	-	-	-	-
	24 hr urine-CrCl	97.4 ± 31.5*	-12.5 ^{#,†}	-13.2 (-89.3-119.4)	29.4 ^{‡,§}	25.1 [¶]	71.5 [¶]
	eGFR _{CG}	109.6 ± 27.9	-0.73 ^{**§}	-2.9 (-52.0-76.7)	22.9	33.3	86.0
	eGFR _{MDRD}	100.7 ± 20.4*	-9.6 ^{#,¶}	-9.0 (-69.1-50.8)	20.8	35.3	84.1 [¶]
	eGFR _{CKD-EPI}	108.7 ± 18.0	-1.6 ^{**§}	0.4 (-55.5-45.1)	19.1	40.6	91.8 ^{**#,§}
≥90 (n = 170)	^{99m} Tc DTPA	116.3 ± 17.7	-	-	-	-	-
	24 hr urine-CrCl	102.0 ± 32.1*	-14.3 ^{#,¶}	-16.6 (-89.3-119.4)	31.4 ^{‡,§}	24.9 [¶]	68.0 [¶]
	eGFR _{CG}	114.7 ± 27.5	-1.5 ^{**§}	-5.6 (-52.0-76.7)	24.4 [¶]	30.8 [¶]	84.6 [¶]
	eGFR _{MDRD}	103.7 ± 20.1*	-12.5 ^{#,¶}	-13.0 (-69.1-50.8)	21.0 ^{**}	33.7	82.2 [¶]
	eGFR _{CKD-EPI}	111.8 ± 17.3	-4.5 ^{**§}	-3.7 (-55.5-45.1)	19.1 ^{**}	42.0	94.7 ^{**#,§}
<90 (n = 37)	^{99m} Tc DTPA	83.1 ± 6.4	-	-	-	-	-
	24 hr urine-CrCl	78.7 ± 16.5	-4.5	-7.3 (-38.0-25.6)	15.7	27.0	89.2
	eGFR _{CG}	86.0 ± 15.1	2.9 [¶]	4.3 (-24.5-36.5)	13.9	45.9	81.1
	eGFR _{MDRD}	86.8 ± 15.1	3.6 [¶]	2.0 (-24.0-43.3)	13.9	43.2	94.6
	eGFR _{CKD-EPI}	94.7 ± 14.4*	11.6 ^{**#,§}	11.2 (-13.3-40.4)	12.6	35.1	81.1

mGFR, measured glomerular filtration rate, ^{99m}Tc DTPA, technetium-diethylenetriamine pentaacetic acid, 24 hr urine-CrCl, creatinine clearance; eGFR_{CG}, Cock-Croft Gault; eGFR_{MDRD}, Modification of Diet in Renal Disease; eGFR_{CKD-EPI}, chronic kidney disease-Epidemiology collaboration.

*P<0.05, vs. mGFR,

**P<0.05 vs. 24 hr urine-CrCl,

[#]P<0.05 vs. eGFR_{CG},

[§]P<0.05, vs. eGFR_{MDRD},

[¶]P<0.05 vs eGFR_{CKD-EPI}.

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Comparison of Each Equation’s Performance According to mGFR Level before Kidney Donation

We analyzed the performance of equations according to renal function (Table 1). In 170 subjects with normal renal function (mGFR ≥90 mL·min⁻¹·1.73 m⁻²), both 24 hr urine-CrCl and eGFR_{MDRD} significantly underestimated mGFR (P<0.001 vs. mGFR in each case), but eGFR_{CKD-EPI} showed little bias (P=0.92). eGFR_{CKD-EPI} showed higher precision and accuracy within 30% of mGFR (P<0.05 in each case) than the other 3 equations as well. In 37 subjects with decreased renal function (mGFR ≤90 mL·min⁻¹·1.73 m⁻²), eGFR_{CKD-EPI} significantly overestimated mGFR (P<0.001 vs. mGFR), and 24 hr-urine CrCl, eGFR_{CG} and eGFR_{MDRD} did not show significant bias to mGFR (P=0.094, P=0.211 and P=0.123 vs. mGFR, respectively). In precision and accuracy, no significant differences were detected in any comparisons between equations.

Comparison of Each Equation’s Performance to Predict mGFR after Kidney Donation

Table 2 provides overall results for the bias, precision, and accuracy of all three equations for the estimation of mGFR in this post-donation cohort. eGFR_{CKD-EPI} showed the least bias as compared with mGFR (P=1.0 vs. mGFR) as like in pre-donation analysis. In contrast, eGFR_{MDRD} (SD of mean bias: 17.2) showed significantly higher precision as compared to eGFR_{CG} (20.8) and eGFR_{CKD-EPI} (22.9) (P<0.001 in each case). The accuracy within 10% and 30% of mGFR was significantly higher for eGFR_{MDRD} as compared with eGFR_{CG} and eGFR_{CKD-EPI} as well (P<0.05 in each case) (Table 2).

Comparison of Each Equation’s Performance According to mGFR Level after Kidney Donation

We analyzed the performance of equations according to renal function in post-donation cohort (Table 2). In 23 subjects who showed normal renal function (mGFR ≥90 mL·min⁻¹·1.73 m⁻²), both eGFR_{MDRD} (P<0.001 vs. mGFR) and eGFR_{CKD-EPI} (P<0.05 vs. mGFR) significantly underestimated mGFR and bias was minimal in eGFR_{CG} (P=0.74 vs. mGFR). In precision, however, eGFR_{MDRD} (SD of mean bias: 17.2) showed superior value as compared to eGFR_{CKD-EPI} (SD of mean bias: 26.5) (P<0.05) and superior tendency compared to eGFR_{CG} (SD of mean bias : 21.9) (P=0.110). In 85 subjects who showed decreased renal function (mGFR <90 mL·min⁻¹·1.73 m⁻²), eGFR_{MDRD} demonstrated the least bias (P=0.95 vs. mGFR) and the highest precision (SD of mean bias: 12.6) among three equations but only eGFR_{CG} significantly overestimated mGFR (P<0.01 vs. mGFR). No significant differences in accuracy were detected in any pairs of comparisons in all equations in both groups with normal and decreased renal function (P>0.05, respectively).

Comparison between Pre-donation and Post-donation Performance of Each Equation

For each individual equation, we compared the performance value between pre-donation and post-donation in 108 patients who took ^{99m}Tc-DTPA clearance (mGFR) before and after kidney donation (Table 3). In this analysis, eGFR_{MDRD} showed overall improved performance at post-donation. Precision significantly improved after donation (P<0.001) and the values of bias and

Table 2. Comparison of the bias, precision and accuracy in the estimation of mGFR among each equation after kidney donation according to the mGFR level.

mGFR group (mL/min/1.73 m ²)	eGFR	Value (mL/min/1.73m ²) Mean±SD	Mean difference to mGFR	Median difference to mGFR (Range)	SD of Mean bias	Accuracy within	
						10% (%)	30% (%)
All (n = 108)	^{99m} Tc DTPA	77.1±16.3	-	-	-	-	-
	eGFR _{CG}	83.4±20.0	6.3 ^{§,¶}	5.7 (-40.4-62.9)	20.8	25.0	72.2
	eGFR _{MDRD}	71.9±14.5	-5.2 [¶]	-5.1 (-43.9-30.0)	15.8 [¶]	39.8	83.3
≥90 (n = 23)	eGFR _{CKD-EPI}	76.9±21.2	-0.1 ^{¶,§}	1.9 (-60.3-45.0)	22.9 [§]	26.9	67.6
	^{99m} Tc DTPA	101.7±7.9	-	-	-	-	-
	eGFR _{CG}	97.3±20.0	-4.4	-5.9 (-40.4-31.2)	21.9	30.4	78.3
<90 (n = 85)	eGFR _{MDRD}	81.4±15.6*	-20.4	-16.2 (-43.9-5.6)	17.2	34.8	65.2
	eGFR _{CKD-EPI}	84.9±24.2*	-16.8	-17.9 (-60.3-26.6)	26.5	26.1	65.2
	^{99m} Tc DTPA	70.4±10.5	-	-	-	-	-
	eGFR _{CG}	79.7±18.4*	9.2 [§]	9.1 (-35.6-62.9)	19.6	23.5	70.6 [§]
	eGFR _{MDRD}	69.4±13.1	-1.03*	-2.9 (-30.6-30.0)	12.6 [¶]	41.2	88.2 ^{¶,¶}
	eGFR _{CKD-EPI}	74.8±19.9	4.4	5.6 (-40.8-45.0)	19.7 [§]	27.1	68.2 [§]

mGFR, measured glomerular filtration rate, ^{99m}Tc DTPA, technetium-diethylenetriamine pentaacetic acid, 24 hr urine-CrCl, creatinine clearance; eGFR_{CG}, Cock-Croft Gault; eGFR_{MDRD}, Modification of Diet in Renal Disease; eGFR_{CKD-EPI}, chronic kidney disease-Epidemiology collaboration.

*P<0.05, vs. mGFR,

¶P<0.05 vs. eGFR_{CG},

§P<0.05, vs. eGFR_{MDRD},

¶P<0.05 vs eGFR_{CKD-EPI}.

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accuracy were similar between pre- and post-donation. In contrast, eGFR_{CG} and eGFR_{CKD-EPI} showed overall inferior performance at post-donation compared to pre-donation. Bias from mGFR significantly increased in eGFR_{CG} (P<0.001) and precision significantly decreased in eGFR_{CKD-EPI} (P<0.05) and both equations showed inferior accuracy at post-donation as compared to pre-donation.

Bland and Altman Plots

The differences between each eGFR and mGFR were illustrated using a graphic technique developed by Bland and Altman. These figures display the span between +1.96 and -1.96 SD of the mean difference (limit of agreement), which represents 95% CI. Before kidney donation, a smaller limit of agreement was found for the eGFR_{CKD-EPI} (37.5) in comparison with the eGFR_{MDRD} (40.7), eGFR_{CG} (44.9), and 24 hr-CrCl (57.7)

(Figure 1A–D). However, eGFR_{MDRD} (31.0) showed a smaller limit of agreement than eGFR_{CG} (40.9) and eGFR_{CKD-EPI} (44.9) after kidney donation (Figure 2A–C).

Discussion

This study investigated the performance of formulas for estimating mGFR in both the pre-donation state (healthy adult) and the post-donation state (uninephric donors). In this study, as compared to other equations, eGFR_{CKD-EPI} showed superior performance in healthy donors, the pre-donation state. In contrast, its performance at predicting mGFR was worse than that of eGFR_{MDRD} in uninephric donors, and the inferiority was more significant in subjects with reduced renal function.

At the pre-donation state, 24 hr-urine CrCl and eGFR_{MDRD} significantly underestimated mGFR, but eGFR_{CKD-EPI} showed

Table 3. Comparison of the bias, precision and accuracy of each equation to estimate mGFR between before and after kidney donation.

		Mean difference to mGFR	Median	SD of mean bias	Accuracy within	
					10%(%)	30%(%)
eGFR _{CG}	Before	-0.73*	-2.9 (-52.0-76.7)	22.9	33.3*	86.0*
	After	6.3	5.7 (-40.4-62.9)	20.8	25.0	72.2
eGFR _{MDRD}	Before	-9.6	-9.0 (-69.1-50.8)	20.8 [¶]	35.3	84.1
	After	-5.2	-5.1 (-43.9-30.0)	15.8	39.8	83.3
eGFR _{CKD-EPI}	Before	-1.6	0.4 (-55.5-45.1)	19.1	40.6*	91.8*
	After	-0.1	1.9 (-60.3-45.0)	22.9	26.9	67.6

*P<0.05, vs. after donation, eGFR_{CG}, Cock-Croft Gault; eGFR_{MDRD}, Modification of Diet in Renal Disease; eGFR_{CKD-EPI}, chronic kidney disease-Epidemiology collaboration.

doi:10.1371/journal.pone.0060720.t003

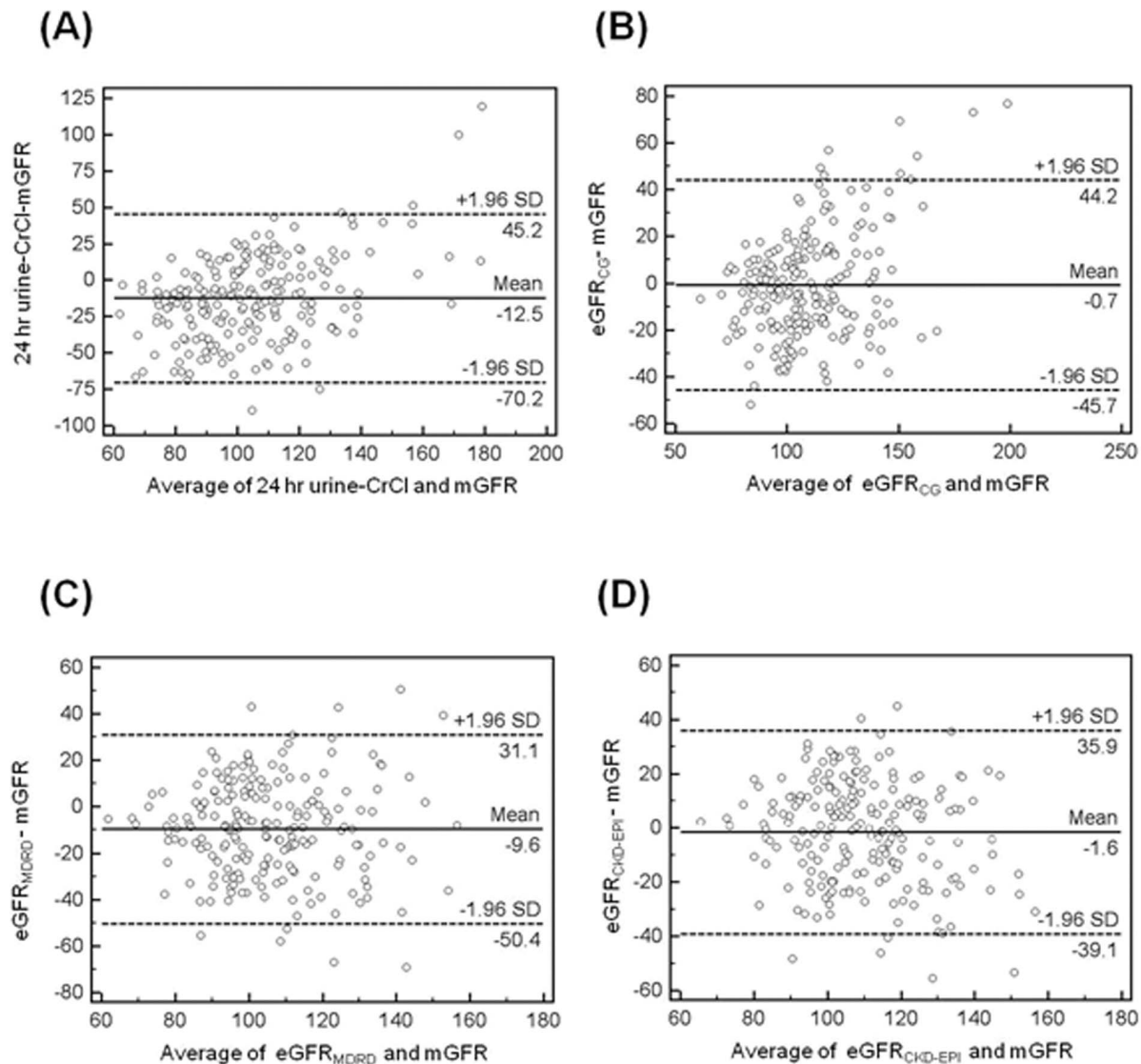


Figure 1. Bland-Altman plots at pre-donation showing the distribution of errors in estimation of measure GFR with eGFR when a given eGFR value is observed. (A) 24 hr urine-CrCl, (B) eGFR_{CG} (C) eGFR_{MDRD} (D) eGFR_{CKD-EPI} mGFR, measured glomerular filtration rate, 24 hr urine-CrCl, creatinine clearance; eGFR_{CG}, Cock-Croft Gault; eGFR_{MDRD}, Modification of Diet in Renal Disease; eGFR_{CKD-EPI}, chronic kidney disease-Epidemiology collaboration.

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only minimal bias. The SD of mean bias was lowest in eGFR_{CKD-EPI}, which suggests the highest precision of this equation. The percentage within 30% of mGFR was significantly higher in eGFR_{CKD-EPI} than in other equations, which suggests the superior accuracy of this equation compared to other equations. This result is fully consistent with the previous reports. [6,7,16,17].

The better performance of eGFR_{CKD-EPI} was more significant when we only included subjects with normal renal function. As reported previously, trends of mGFR underestimation were found in 24 hr-urine CrCl, eGFR_{MDRD}, and eGFR_{CG}, but only eGFR_{CKD-EPI} showed minimal bias in subjects with normal GFR in this study. [17,18] In precision and accuracy, eGFR_{CKD-EPI} was superior to the other 3 equations as well for that patient group. However, in subjects with reduced renal function, this better performance was not dominant. This discrepancy of performance according to renal function level may result from differences in the process of equation development. eGFR_{MDRD}

and eGFR_{CG} were developed based on CKD patients with reduced renal function, but eGFR_{CKD-EPI} was not specifically developed for that patient population. [4,7] Indeed, it was previously reported that performance was similar between eGFR_{CKD-EPI} and eGFR_{MDRD} in CKD patients. [19].

At post-donation state, we directly compared the performance between eGFR_{CKD-EPI} and eGFR_{MDRD}, and our results showed that eGFR_{CKD-EPI} was inferior to eGFR_{MDRD} in overall performance. eGFR_{CKD-EPI} showed less bias compared to eGFR_{MDRD}. But as shown in high SD of mean difference between mGFR and eGFR_{CKD-EPI}, which suggests low precision, the difference from mGFR was distributed widely in both the positive and negative directions. Negatively and positively biased values may offset each other during the calculation of mean value and may have resulted in the minimal bias of eGFR_{CKD-EPI}. In another performance such as precision and accuracy, eGFR_{CKD-EPI} showed inferior performance compared to eGFR_{MDRD}. In

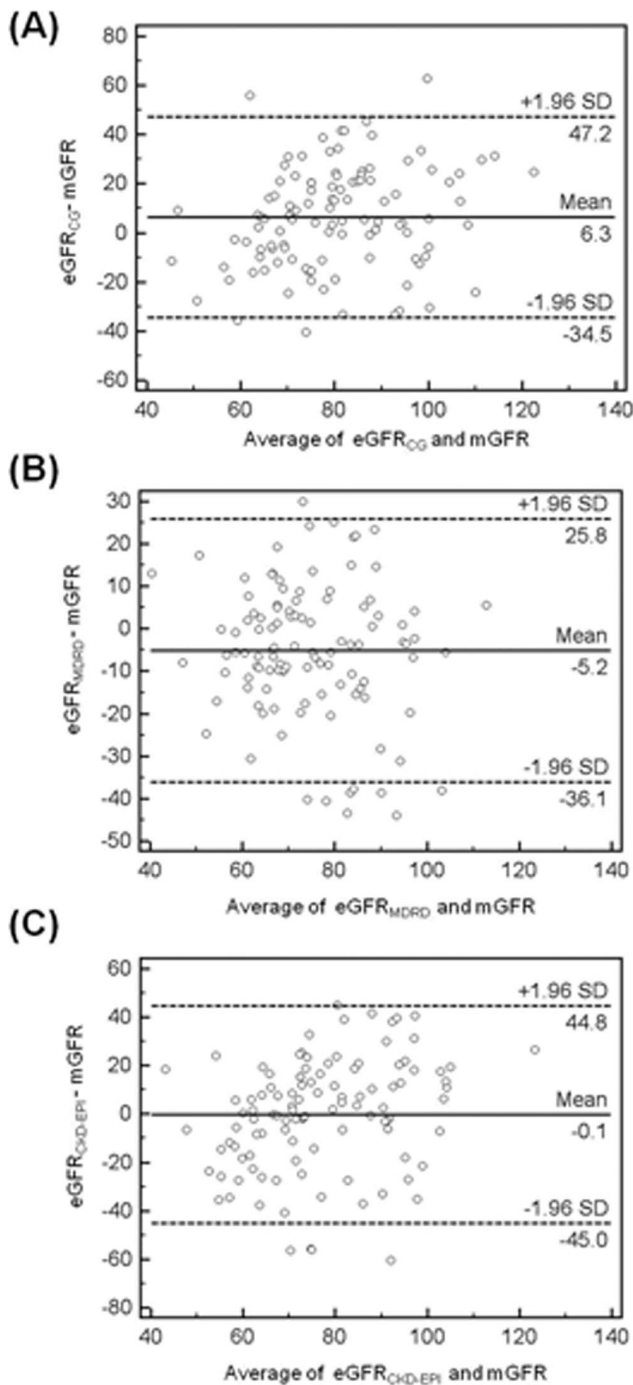


Figure 2. Bland-Altman plots at post-donation showing the distribution of errors in estimation of measure GFR with eGFR when a given eGFR value is observed. (A) eGFR_{CG} (B) eGFR_{MDRD} (C) eGFR_{CKD-EPI} mGFR, measured glomerular filtration rate, eGFR_{CG}, Cock-Croft Gault; eGFR_{MDRD}, Modification of Diet in Renal Disease; eGFR_{CKD-EPI}, chronic kidney disease-Epidemiology collaboration. doi:10.1371/journal.pone.0060720.g002

addition, eGFR_{MDRD} showed better or similar performance at post-donation compared to pre-donation, but eGFR_{CKD-EPI} showed inferior performance at post-donation compared to pre-donation within individual analysis.

The reason for the superior performance of eGFR_{MDRD} at post-donation state is unclear. One possible reason is that the

proportion of subjects with reduced renal function was greater in this group compared to the pre-donation group. Indeed, the performance of eGFR_{MDRD} is not inferior to eGFR_{CKD-EPI} in subjects with reduced renal function in pre-donation cohort. But it cannot explain the better performance of the eGFR_{MDRD} than eGFR_{CKD-EPI} in post-donation cohort with normal renal function. Hence, the more important reason may be the specific situation of uninephric kidney donors, which is different not only from healthy populations but also from patients with chronic kidney disease. In these subjects, removal of 1 kidney leads to a subsequent reduction in GFR without disease-associated changes in body composition. [17] Renal tissue reduction is accompanied by compensatory hyperfiltration by the remaining nephrons with increases in single-nephron GFR. [20,21] Therefore, the renal function only showed a modest decrease compared to its level before KT because of the remaining kidney's hyperfiltration. In this specific condition, the performance of estimating equations in those patients may show different pattern compared to healthy populations or chronic kidney disease state.

Another possible reason is that the performance of equations for estimating GFR could be affected by the demographic and ethnic factors. Most estimating equations developed primarily based on western populations, hence they may show different performance when used in Asian because of the significant anthropometric difference. Of note, many studies about the performance of estimating equations conducted on Asian showed different outcomes compared to the result from Western populations. [22,23,24] For those reasons, it has been reported that modification is necessary in the use of eGFR_{CKD-EPI} on multiethnic Asian populations. [19,25] But clear conclusion about this issue in Korean may need further investigation.

It is interesting that eGFR_{CG} seems to be nearly unbiased in the potential kidney donors. Because the eGFR_{CG} was derived to estimate creatinine clearance, which is known to overestimate mGFR by 10% to 20% as a result of creatinine secretion, this may be interpreted as a fortuitous cancellation of errors. [14,26] eGFR_{CG} apparently underestimated creatinine clearance by 10% to 20%, thus producing a mean value close to the mean mGFR. In addition, some previous reports indicated that eGFR_{CG} is more appropriate than eGFR_{MDRD} in subjects without kidney disease. [23,27] Therefore, it is possible that eGFR_{CG} showed superior accuracy and less bias compared to eGFR_{MDRD} before kidney donation. After donation, however, when a significant portion of subjects showed reduced renal function, the overall performance of eGFR_{CG} was inferior to eGFR_{MDRD}, as expected.

Usually, CrCl using 24-hour urine collection is not recommended for the estimation of renal function because of the possibility of urine loss during collection, which can cause an inaccurate result. In addition, this method is so inconvenient for patients compared to other methods. [12] Indeed, 24 hour urine was adequately collected only in 31.9% of total donors according to normal range of creatinine excretion. [28] Hence the inaccuracy of 24-hour urine CrCl in the estimation of renal function, including the underestimation of mGFR, may not result from its own low performance but from the inadequate urine collection. Therefore, 24 hr-urine CrCl may not be appropriate for the estimation of GFR before or after donation considering the difficulty of adequate urine collection and patient's convenience.

This study does have some limitations. We could not use the inulin clearance, the gold standard method for measuring true GFR. However, ^{99m}Tc-DTPA clearance is relatively less biased and has been accepted as the accurate method for the measurement of GFR in previous reports. [10,29,30,31] Second, this is a retrospective single-center study, which only included

Korean adults. Therefore, the results of this study may not be definite in Western populations which have different anthropomorphic characteristics. To apply our results in those populations, further investigation may be required. Third, eGFR_{MDRD} showed tendency to overestimate the prevalence of CKD, as shown in a previous report, which means that this estimating equation must be used with some caution in the follow-up of uninephric donors. [32].

Nevertheless, this study differs from previous studies in that we used unified and standard methods to measure Scr. A weak point detected in many previous reports was that the Scr assay was either not standardized or not unified, hence the need for a calibration process, which could induce some bias in the results. [17,32] It is possible that the divergences in Scr determination and calibration may have accounted for the heterogeneity of the results in previous studies. [14,33,34] To overcome it, we only included subjects who were tested with isotope dilution mass spectrometry

(IDMS)-traceable creatinine, which helps to estimate GFR more accurately. [35].

In conclusion, in the potential kidney donor, eGFR_{CKD-EPI} showed better performance than other GFR estimating equations including eGFR_{MDRD} in the prediction of renal function. However, in the uninephric state after kidney donation, the overall performance of eGFR_{CKD-EPI} was inferior to eGFR_{MDRD}, which suggests that the eGFR_{MDRD} is more appropriate for the estimation of renal function during follow-up of uninephric kidney donors.

Author Contributions

Conceived and designed the experiments: BHC. Performed the experiments: JHY HJC J-IK ISM. Analyzed the data: CWP CWY Y-SK. Wrote the paper: BHC BSC.

References

1. United Network for Organ Sharing. US Transplantation Data. Available: http://www.unos.org/donation/index.php?topic=living_donation Accessed 2012 Nov 1.
2. Issa N, Meyer KH, Arrigain S, Choure G, Fatica RA, et al. (2008) Evaluation of creatinine-based estimates of glomerular filtration rate in a large cohort of living kidney donors. *Transplantation* 86: 223–230.
3. Kang KY, Lee YJ, Park SC, Yang CW, Kim YS, et al. (2007) A comparative study of methods of estimating kidney length in kidney transplantation donors. *Nephrol Dial Transplant* 22: 2322–2327.
4. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, et al. (1999) A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 130: 461–470.
5. Cockcroft DW, Gault MH (1976) Prediction of creatinine clearance from serum creatinine. *Nephron* 16: 31–41.
6. Stevens LA, Coresh J, Feldman HI, Greene T, Lash JP, et al. (2007) Evaluation of the modification of diet in renal disease study equation in a large diverse population. *J Am Soc Nephrol* 18: 2749–2757.
7. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, et al. (2009) A new equation to estimate glomerular filtration rate. *Ann Intern Med* 150: 604–612.
8. White CA, Akbari A, Doucette S, Fergusson D, Knoll GA (2010) Estimating glomerular filtration rate in kidney transplantation: is the new chronic kidney disease epidemiology collaboration equation any better? *Clin Chem* 56: 474–477.
9. Carter JL, Stevens PE, Irving JE, Lamb EJ (2011) Estimating glomerular filtration rate: comparison of the CKD-EPI and MDRD equations in a large UK cohort with particular emphasis on the effect of age. *QJM* 104: 839–847.
10. Russell CD, Bischoff PG, Rowell KL, Kontzen F, Lloyd LK, et al. (1983) Quality control of Tc-99m DTPA for measurement of glomerular filtration: concise communication. *J Nucl Med* 24: 722–727.
11. Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, et al. (2006) Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med* 145: 247–254.
12. Walsler M (1998) Assessing renal function from creatinine measurements in adults with chronic renal failure. *Am J Kidney Dis* 32: 23–31.
13. (2002) K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 39: S1–266.
14. Poggio ED, Wang X, Greene T, Van Lente F, Hall PM (2005) Performance of the modification of diet in renal disease and Cockcroft-Gault equations in the estimation of GFR in health and in chronic kidney disease. *J Am Soc Nephrol* 16: 459–466.
15. Chen L, Leatham E, Chester M, Huang J, Kaski JC (1995) Aggressive pattern of angina after successful coronary angioplasty: the role of clinical and angiographic factors. *Eur Heart J* 16: 1085–1091.
16. Teruel Briones JL, Gomis Couto A, Sabater J, Fernandez Lucas M, Rodriguez Mendiola N, et al. (2011) Validation of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation in advanced chronic renal failure. *Nefrologia* 31: 677–682.
17. Tent H, Rook M, Stevens LA, van Son WJ, van Pelt IJ, et al. (2010) Renal function equations before and after living kidney donation: a within-individual comparison of performance at different levels of renal function. *Clin J Am Soc Nephrol* 5: 1960–1968.
18. Michels WM, Grootendorst DC, Verduijn M, Elliott EG, Dekker FW, et al. (2010) Performance of the Cockcroft-Gault, MDRD, and new CKD-EPI formulas in relation to GFR, age, and body size. *Clin J Am Soc Nephrol* 5: 1003–1009.
19. Teo BW, Xu H, Wang D, Li J, Sinha AK, et al. (2011) GFR estimating equations in a multiethnic Asian population. *Am J Kidney Dis* 58: 56–63.
20. Hostetter TH, Olson JL, Rennke HG, Venkatachalam MA, Brenner BM (1981) Hyperfiltration in remnant nephrons: a potentially adverse response to renal ablation. *Am J Physiol* 241: F85–93.
21. Brenner BM (1985) Nephron adaptation to renal injury or ablation. *Am J Physiol* 249: F324–337.
22. Kang YS, Han KH, Han SY, Kim HK, Cha DR (2005) Characteristics of population with normal serum creatinine impaired renal function and: the validation of a MDRD formula in a healthy general population. *Clin Nephrol* 63: 258–266.
23. Mahajan S, Mukhiya GK, Singh R, Tiwari SC, Kalra V, et al. (2005) Assessing glomerular filtration rate in healthy Indian adults: a comparison of various prediction equations. *J Nephrol* 18: 257–261.
24. Jafar TH, Schmid CH, Levey AS (2005) Serum creatinine as marker of kidney function in South Asians: a study of reduced GFR in adults in Pakistan. *J Am Soc Nephrol* 16: 1413–1419.
25. Horio M, Imai E, Yasuda Y, Watanabe T, Matsuo S (2010) Modification of the CKD epidemiology collaboration (CKD-EPI) equation for Japanese: accuracy and use for population estimates. *Am J Kidney Dis* 56: 32–38.
26. Shemesh O, Golbetz H, Kriss JP, Myers BD (1985) Limitations of creatinine as a filtration marker in glomerulopathic patients. *Kidney Int* 28: 830–838.
27. Al-Khader AA, Tamim H, Sulaiman MH, Jondeby MS, Taher S, et al. (2008) What is the most appropriate formula to use in estimating glomerular filtration rate in adult Arabs without kidney disease? *Ren Fail* 30: 205–208.
28. Kampmann J, Siersbaek-Nielsen K, Kristensen M, Hansen JM (1974) Rapid evaluation of creatinine clearance. *Acta Med Scand* 196: 517–520.
29. Zhao WY, Zeng L, Zhu YH, Wang LM, Zhou MS, et al. (2009) A comparison of prediction equations for estimating glomerular filtration rate in Chinese potential living kidney donors. *Clin Transplant* 23: 469–475.
30. Srinivas S, Annigeri RA, Mani MK, Rao BS, Kowdle PC, et al. (2008) Estimation of glomerular filtration rate in South Asian healthy adult kidney donors. *Nephrology (Carlton)* 13: 440–446.
31. Poge U, Gerhardt T, Stoffel-Wagner B, Sauerbruch T, Woitas RP (2011) Validation of the CKD-EPI formula in patients after renal transplantation. *Nephrol Dial Transplant* 26: 4104–4108.
32. Tan JC, Ho B, Busque S, Blouch K, Derby G, et al. (2010) Imprecision of creatinine-based GFR estimates in uninephric kidney donors. *Clin J Am Soc Nephrol* 5: 497–502.
33. White CA, Huang D, Akbari A, Garland J, Knoll GA (2008) Performance of creatinine-based estimates of GFR in kidney transplant recipients: a systematic review. *Am J Kidney Dis* 51: 1005–1015.
34. Hsu CY, Chertow GM, Curhan GC (2002) Methodological issues in studying the epidemiology of mild to moderate chronic renal insufficiency. *Kidney Int* 61: 1567–1576.
35. Levey AS, Coresh J, Greene T, Marsh J, Stevens LA, et al. (2007) Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardized serum creatinine values. *Clin Chem* 53: 766–772.