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Appraisal of GFR Estimating Equations Following Kidney Donation

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Abstract

Background—It is not clear which serum creatinine-based glomerular filtration rate (GFR) estimating model performs best in kidney donors.

Study Design—Study of diagnostic accuracy.

Setting and Participants—From a population of 3,698 kidney donors, 255 donors underwent iothexol GFR measurement (mGFR).

Index Test (Intervention)—mGFR by the plasma disappearance of iothexol.

Reference Test or Outcome—eGFR was estimated using the Cockcroft-Gault equation, (eGFR_{CG}), the Mayo Clinic equation (eGFR_{MC}), and the MDRD Study equation (eGFR_{MDRD}).

Results—Mean mGFR was 71.8±11.8 mL/min/1.73m² and 85.5% had mGFR > 60 mL/min/1.73m². eGFR_{CG} underestimated mGFR by 3.96±13.3 mL/min/1.73m² and was within 30% of mGFR in 89.4% of the time. eGFR_{MC} overestimated mGFR by 8.44±11.9 mL/min/1.73m² and was within 30% of mGFR in 83.1% of cases. eGFR_{MDRD} underestimated mGFR by only 0.43±11.7 mL/min/1.73m² and the proportion within 30% of mGFR was the highest amongst the tested model; 94.1% of the time. The eGFR_{MC}, however, was most accurate in classifying donors according to having eGFR < 60 mL/min/1.73m².

Limitations—Lack of ethnic diversity and response bias.

Conclusions—The MDRD Study equation is least biased and since it is routinely reported by most laboratories, is the best readily available model for estimating GFR in kidney donors.

Index Words

Glomerular filtration rate; kidney donor; Cockcroft-Gault; Modification of Diet in Renal Disease

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INTRODUCTION

The benefits of living donor transplantation are well established and current evidence suggests that kidney donors enjoy a favorable renal course and their life expectancy is preserved.^{1–5} A particular area of interest is how to best measure renal function in those who have donated a kidney. Serum creatinine-based glomerular filtration rate (GFR) estimating models such as the Cockcroft-Gault creatinine clearance (CG CCr), the Modification of Diet in Renal Disease (MDRD) Study equation, and the Mayo Clinic equation are superior to serum creatinine in estimating renal function, and in response to the effort by the National Kidney Disease Education Program (NKDEP) to standardize serum creatinine values, the MDRD Study equation was recently re-expressed for use with the isotope-dilution mass spectrometry (IDMS) standardized serum creatinine assay.^{6–10}

We have previously reported on the performance of the CG CCr, 4-variable MDRD Study, and Mayo Clinic equations in a cohort of kidney donors who underwent iohexol GFR measurement and found that the MDRD Study equation was a reasonable substitute for, although clearly inferior to, formal GFR measurement.⁵ Herein, we report on the performance of serum creatinine-based GFR estimating equations in a larger number of donors and provide appraisal of the newly introduced MDRD Study equation that utilizes IDMS-traceable standardized serum creatinine, as well.

METHODS

As of December 2007, a total of 3,698 living donor nephrectomies had been performed at the University of Minnesota. In December 2003, we initiated a comprehensive, multi-step effort to contact all donors by consulting phone and internet directories and also asking their recipient. We generated donor lists of those known to be alive and stratified them by sex and years after donation (in 3-year intervals). Using this sample frame, a random start was used to generate random numbers using SAS Macro to select 5% to 10% of donors from each strata to undergo GFR measurements. Between 2003 and 2007, 255 donors underwent GFR measurement. If the selected donor refused participation, a new donor from the same sex and time from donation strata, following the same scheme, was contacted. All donors who underwent GFR measurements donated in the year 2000 or earlier. In total, 1785 donors were approached to undergo GFR measurement to find 255 who were agreeable. All studies were approved by the University of Minnesota Institutional Review Board.

GFR was measured using the plasma disappearance of iohexol.^{5,11–14} Via a small polyethylene catheter placed in an antecubital vein, we injected 5 mL of iohexol solution (647 mg of iohexol; 300 mg of iodine per mL). From the contralateral arm, via a second antecubital vein catheter, we then obtained serial samples at 120, 150, 180, 210, and 240 minutes (± 15 sec). Plasma was stored at -20°C for high performance liquid chromatography determination of iohexol concentration. To analyze the plasma profile, we used a 1-compartment model system with all data fitted by a nonlinear regression iterative program. We chose the plasma disappearance of iohexol method because it does not require timed urine collections which may result in incomplete bladder emptying and lead to significant variability in the GFR measurement, and in view of its excellent correlation with inulin clearance which is the gold standard of measuring GFR.¹⁴ Moreover, utilizing the single compartment model corrected with the Brochner-Mortenson formula simplifies GFR calculation and produces a correlation with inulin GFR that is virtually identical to the 2-compartment model.¹⁴ The coefficient of variation of the mGFR at our center is consistently $< 10\%$.

Serum creatinine was obtained on the morning of GFR measurement and after an 8–12 hour fast. Recognizing that large differences exist in serum creatinine assays across laboratories,

we previously sent 25 serum creatinine samples ranging from 0.6 to 2.3 mg/dL to the Cleveland Clinic Biochemistry Laboratory in 2006.^{5,15–17} This range was chosen since it would encompass the range observed in the overwhelming majority of donors, as we have shown in our previous studies.^{3,5,18–19} The aforementioned laboratory is where serum creatinine was assayed for the Modification of Diet in Renal Disease (MDRD) Study using the Beckmann Rate Jaffe'/CXR Synchron method, which is based on the kinetic alkaline picrate reaction.²⁰ We compared the Cleveland Clinic's results with ours from the University of Minnesota laboratories which use an identical method and instrument. The results from both institutions were virtually identical. The mean serum creatinine at our laboratory was 0.95 ± 0.41 mg/dL vs. 0.96 ± 0.40 mg/dL at the reference laboratory; mean difference was 0.0125 ± 0.03 mg/dL, the Pearson correlation coefficient between the measurements at the two institutions was 0.9965. Fitting a linear regression model with the University of Minnesota serum creatinine measurements as the outcome, revealed an intercept of -0.01376 and a slope of 1.00 (95% CI 0.967–1.042, SE 0.018). In May 2008 the creatinine assay at University of Minnesota laboratories changed from the Jaffe'/CXR Synchron method to the IDMS-traceable creatinine in compliance with the NKDEP recommendation to internationally standardize serum and urine creatinine measurements. The laboratory provided us with a formula for conversion of the Jaffe' creatinine to the IDMS-traceable creatinine (IDMS creatinine in mg/dL = $-0.111 + 0.964 \cdot$ Jaffe' creatinine in mg/dL) based on running creatinine assays by the two methods in a large number of samples. We used this formula to convert all creatinine values to IDMS-traceable values. To verify the accuracy of the conversion formula in our kidney donors, we randomly selected 50 serum samples from the pool of 255 donors and measured serum creatinine using the new IDMS traceable method. The average measured creatinine in these 50 samples was 0.95 ± 0.25 mg/dL as compared to 1.10 ± 0.26 mg/dL given by the older method and $r = 0.95$. Linear regression of the IDMS creatinine vs. the old method revealed an intercept of -0.03047 and a slope of 0.912 (95% CI 0.818–1.005, SE 0.046). The average creatinine predicted by the formula provided by the laboratory was 0.97 ± 0.25 mg/dL. Since values provided by the regression formula provided serum creatinine values that were identical to the directly measured one in the 50 samples, we used the values obtained from it for this analysis.

We estimated the re-expressed Cockcroft-Gault equation for estimation of GFR for use with standardized creatinine ($eGFR_{CG}$), the Mayo Clinic equation ($eGFR_{MC}$), and the MDRD Study equation ($eGFR_{MDRD}$). $eGFR_{CG}$ was calculated using the formula $(140 - \text{age}) \cdot \text{weight} / (72 \times \text{SCr}) \times (0.85 \text{ if female}) \left(\frac{1.73}{BSA}\right)^6$ multiplied by 0.8 to correct for the bias in the MDRD Study sample.²⁰ $eGFR_{MC}$ was calculated using the quadratic equation that estimates logarithmic GFR from serum creatinine, age and gender and after indirectly calibrating serum creatinine by applying the following regression relation: IDMS-traceable creatinine = $0.906 [-0.213 + (1.098 \cdot \text{Mayo Clinic creatinine})]$.^{8,21} In the original cohort the $eGFR_{MC}$ was developed in, those with serum creatinine ≤ 0.8 mg/dL were assigned a value of 0.8 mg/dL. In this analysis, an individual with any value ≤ 0.60 mg/dL ($0.8 \times$ correction factor) was assigned a value of 0.66 mg/dL. $eGFR_{MDRD}$ was calculated using the following formula: $175 \times \text{standardized SCr}^{-1.154} \times \text{age}^{-0.203} \times 1.210$ (if black) $\times 0.742$ (if female).⁹

We assessed the performance of $eGFR$ from the three equations against $mGFR$ in several ways:

1. Bias: the average prediction error = $\Sigma (eGFR - mGFR)/n$, where n is the number of GFR studies performed (i.e. 255). Relative bias, % deviation from $mGFR$, was also calculated.
2. Precision: the value of R^2 from the linear regression of $mGFR$ on $eGFR$, interquartile range of differences and root mean squared error (RMSE), and
3. Relative accuracy: the percent of estimates falling within 10, 30 and 50% of $mGFR$.

The equations were compared statistically on each of these measures. The comparisons were made using a paired t-test for bias, a paired test of proportions for relative accuracy,²² and the Hotelling-Williams test for precision, R^2 .²³ All of these tests take into account that all equations were calculated for the same set of subjects. The equations were then compared using an average rank derived from these three criteria. Each equation was ranked from 1 to 3 based on its performance in terms of bias, precision, and relative accuracy.

Residual plots were performed for all equations. This sort of analysis plots the (eGFR – mGFR) on the y – axis against mGFR on the x – axis. Graphically, this depicts the mean difference between the two methods bracketed by the observed ± 2 standard deviations of the difference between the two methods which permits detection of a trend in bias.

We also compared these 3 models on their ability to accurately identify donors with mGFR < 60 mL/min/1.73m² and assessed their performance in donors with hypertension, diabetes or albuminuria.

Results are expressed as mean $\pm$ standard deviation unless indicated otherwise. Statistical significance was assessed with a Bonferroni – adjusted threshold of 0.05/6 since 6 pairs of formulas were compared. Analyses and graphs were completed using statistical software SAS 9.1 (Cary, NC, SAS Institute) and R version 2.5.0.

RESULTS

Since 1963, 3698 patients donated a kidney at the University of Minnesota. Utilizing the Social Security Death Master File, we found that 3,404 are alive, 268 have died, and 26 of the donors were foreign nationals with missing Social Security numbers in whom vital status could not be ascertained. At the beginning of our efforts to contact all donors in December 2003, 2,199 returned health status updates and laboratory results. Of these 2,199 individuals, 255 were randomly selected for GFR measurement; roughly 1 out of 7 donors invited to undergo GFR measurement agreed (Figure 1). The 255 donors who underwent mGFR were similar to the donor population without formal GFR measurement (n = 3443) in current age and sex distribution. However, the donors with mGFR were older at donation (41.1 ± 11.0 years vs. 38.4 ± 11.7 years, $p < 0.001$) and also had a shorter time from donation (12.2 ± 9.2 years vs. 16.3 ± 11.0 years, $p < 0.001$). Roughly 62% of donors with mGFR were women, 98.8% were white, 24.7% reported a diagnosis and treatment for hypertension and 8% reported a diagnosis and treatment for diabetes with oral hypoglycemic agents and/or insulin (Table 1).

Serum creatinine at the time of GFR measurement was 1.1 ± 0.2 mg/dL, and eGFR_{MDRD} was 84.0 ± 13.6 mL/min/1.73m² at donation and 71.4 ± 14.8 mL/min/1.73m² at the time of this study. mGFR in these 255 donors was 71.8 ± 11.8 mL/min/1.73m² as compared to 67.9 ± 16.3 mL/min/1.73m² for eGFR_{CG}, 80.3 ± 15.5 mL/min/1.73m² for eGFR_{MC} and, as mentioned above, 71.4 ± 14.8 mL/min/1.73m² for eGFR_{MDRD}. Reassuringly, 85.5% of donors had a mGFR > 60 mL/min/1.73m², 14.5% had a mGFR between 30–60 mL/min/1.73m², and no donor had a mGFR of <30 mL/min/1.73m². Moreover, 87.3% of donors were normoalbuminuric at the time of GFR measurement, as assessed by first void urinary albumin-creatinine ratio, 11.5% were microalbuminuric, and only 1.2% were macroalbuminuric. None of the donors had both a mGFR < 45 mL/min/1.73m² and albuminuria. The distribution of donors by the presence of hypertension, diabetes and albuminuria according to mGFR levels is shown in Table 2; 83 donors had at least one of these three conditions, 3 had both diabetes and hypertension, 11 had both hypertension and albuminuria, 1 donor had diabetes and albuminuria but none had all three conditions. None of the diabetic or albuminuric donors had an mGFR less than 45 mL/min/1.73m² and only 2 hypertensive donors fell within this range. The majority (66/83) of hypertensive, diabetic and albuminuric donors had mGFR > 60 mL/min/1.73m². mGFR was

inversely related to age; there was a $0.49 \text{ mL/min/1.73m}^2/\text{year}$ decline in mGFR [95% CI, $(-0.62) - (-0.34)$]. In men the decline was 0.34 [95% CI $(-0.55) - (-0.14)$] and in women, -0.60 [95% CI $(-0.78) - (-0.43)$] (Figure 2).

eGFR_{CG} underestimated mGFR by $3.96 \pm 13.3 \text{ mL/min/1.73 m}^2$ and had a relative bias of $-5.18 \pm 17.9\%$ (Figure 3a, b). The precision, or R^2 estimate, was 0.35 . eGFR_{CG} fell within 10%, 30%, and 50% of mGFR in 37.3%, 89.4%, and 98.8% of the cases, respectively (Table 3).

eGFR_{MC} overestimated mGFR by $12.43 \pm 17.5 \text{ mL/min/1.73 m}^2$ (Figure 4a) and the residual plot revealed a wide $\pm 2\text{SD}$ interval (Figure 4b). Precision was 0.42 . The relative accuracy of eGFR_{MC} was similar to eGFR_{CG} as 36.9%, 83.1% and 97.7% fell within 10%, 30% and 50%, respectively (Table 3).

eGFR_{MDRD} was the least biased. In fact, it had a bias of only $-0.43 \pm 11.7 \text{ mL/min/1.73m}^2$ and the relative bias was $-0.10 \pm 16.2\%$ (Figure 5a). The residual plot demonstrates a much narrower variability around the difference between mGFR and eGFR_{MDRD}, Figure 5b. eGFR_{MDRD} was similar in its precision to the other two models; $R^2 = 0.41$. eGFR_{MDRD} was within 10%, 30%, and 50% of mGFR in 45.5%, 94.1%, and 99.2% of cases, respectively (Table 2). In all, its relative accuracy and precision were most comparable to that of eGFR_{CG}.

We next assessed the performance of these 3 models in donors who developed diabetes, hypertension or albuminuria after donation. As mentioned previously, there were 83 such donors. The results were almost identical to those observed in the entire cohort (Table 4).

Finally, we compared the percentage of donors who had an eGFR $< 60 \text{ mL/min/1.73m}^2$ by the different models. 14.5% had a mGFR $< 60 \text{ mL/min/1.73m}^2$, 33.3% by eGFR_{CG}, 10.2% by eGFR_{MC} and 24.3% by eGFR_{MDRD} (Figure 6). All estimation equations yielded results which were significantly different from mGFR with the exception of eGFR_{MC}. Very comparable results were observed in the 83 donors with hypertension, diabetes or albuminuria; i.e. eGFR_{MC} was least likely to misclassify this high risk group as having eGFR $< 60 \text{ mL/min/1.73m}^2$.

DISCUSSION

These results confirm and extend our previous observation that the majority of donors had a mGFR $> 60 \text{ mL/min/1.73m}^2$, were normoalbuminuric and the rate of mGFR decay with age is not accelerated. The MDRD Study equation was least biased and was reasonably precise. The eGFR_{CG} underestimated mGFR but this bias was comparable to that observed with eGFR_{MC}. In regard to its precision and relative accuracy, it was very comparable to that of the MDRD study equation. When assessed on their ability to accurately classify kidney donors by eGFR $< 60 \text{ mL/min/1.73m}^2$ the eGFR_{MC} was most reliable. In all, the MDRD Study equation was least biased and had the highest likelihood of being within 30% of mGFR, the 3 models have comparable precision and eGFR_{MC} was least likely to result in misclassification of donors according to the conventional $60 \text{ mL/min/1.73m}^2$ GFR cutpoint. Similar results were obtained in donors who developed post-donation hypertension, diabetes, or albuminuria.

Serum creatinine-based GFR estimation models were developed in specific subgroups in populations which are different than this study population. Nevertheless, they seem to perform well in patients who have undergone uninephrectomy for donation. The CG CCr formula was developed in a population of 249 patients with renal disease; furthermore, it predicts creatinine clearance which overestimates GFR due to creatinine secretion.⁶ In our previous assessment of this model, we found it to be a reasonable estimate of mGFR as it overestimated mGFR by only $3.35 \pm 13.6 \text{ mL/min/1.73m}^2$.⁵ It is clear that correcting the CG CCr for the bias in the MDRD study sample to produce eGFR_{CG} does not alter its precision but reverses the direction

of its bias. The MDRD Study equation was developed in patients with CKD.⁷ In contrast, the group from Mayo Clinic used a population of 580 healthy individuals combined with 320 patients with chronic kidney disease to develop their quadratic equation.⁸ The current results demonstrate improvement over our previous results when it comes to $eGFR_{MC}$. This may stem directly from the indirect calibration of serum creatinine. Most recently, the MDRD Study equation has been re-expressed for use with the standardized IDMS-traceable creatinine in an effort to standardize results between various laboratories.⁹ This represents a major improvement as this new equation reduced the underestimation of $mGFR$ by over 6 mL/min/1.73m² when compared to the older version of the MDRD study equation. Unfortunately it did not enhance its precision.⁵ Overall, it seems possible that GFR prediction formulas behave differently in patients with chronic kidney disease when compared to healthy people and perhaps also individuals who have previously donated a kidney.

These data also show that the majority of former kidney donors have a $GFR > 60$ mL/min/1.73m². Importantly, the donors at highest risk for reduced GFR (hypertensive, diabetic and albuminuric donors) also enjoyed preserved GFR since only 2 out of 83 such donors had a GFR less than 45 mL/min/1.73m², 15 donors between 45–60 mL/min/1.73m² and the rest were above 60 mL/min/1.73m². Longer follow-up is, of course, needed in these high risk donors. These studies also confirm the inverse relationship between GFR and age as donors lost 0.5 mL/min/year; a rate that is comparable to what has been described in people with full complement of nephrons.²⁴ We hope that our planned future studies that entail serial measurement of GFR in donors will better quantify the rate of GFR decay as the cross-sectional nature of this data is not an ideal way of assessing longitudinal changes in GFR .

While, to our knowledge, this is the largest series to report on $mGFR$ in donors, it is still small in size and from a single center. In addition, the population is 98.8% white. Although we selected donors randomly for formal GFR measurement, there were significant differences in this population when compared to the donor population as a whole: the donors with measured GFR were older and had a shorter period of elapsed time since donation. Moreover, this data suffers not only from response bias but also survival bias.

The three studied models have reasonable performance in those who donated a kidney in the past but in the absence of formal GFR measurement, the MDRD Study equation provides the least biased estimate of GFR , provides improvement over previous equations and should be the preferred model of estimating GFR . Accurately estimating renal function in studies of subjects who have undergone nephrectomy would improve our ability to counsel future donors regarding their level of post-donation kidney function.

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Figure 1.
Participant flow.

Figure 2. Age vs. measured GFR depicted as a regression line and 95% C.I.; 2a: Entire cohort, 2b: Men, 2c: Women.

Figure 3.
eGFR_{CG} vs. mGFR; 3a: Scatterplot, 3b: Residual plot.

Figure 4.
eGFR_{MC} vs. mGFR; 4a: Scatterplot, 4b: Residual plot.

Figure 5.
eGFR_{MDRD} vs. mGFR; 5a: Scatterplot, 5b: Residual plot.

Figure 6. Percentage of donors with GFR < 60 mL/min/1.73m². Different letters represent statistically significant differences (McNemar's test); Grey bars: All donors, Black bars: Donors with hypertension, diabetes, or albuminuria.

Table 1**Characteristics of Study Population**

Number of donors	255
Age at donation (years)	41.1 ± 11.0
Age at GFR measurement (years)	53.2±10.0
Time from donation (years)	12.2 ± 9.2
Women	61.6%
White	98.8%
BMI at GFR measurement (kg/m ²)	27.9 ± 4.7
Hypertension *	24.7%
Diabetes *	3.1%
Serum creatinine at donation (mg/dL)	0.91±0.16
Serum creatinine at GFR measurement (mg/dL)	1.1 ± 0.2
IDMS-traceable creatinine at GFR measurement (mg/dL)	0.95±0.25
GFR (ml/min/1.73 m ²)	
Iohexol GFR	71.8 ± 11.8
eGFR _{CG}	67.9 ± 16.3
eGFR _{MC}	80.3 ± 15.5
eGFR _{MDRD}	71.4 ± 14.8

* Self-reported by study participants

BMI: body mass index, IDMS: isotope-dilution mass spectrometry, GFR: glomerular filtration rate, MDRD: Modification of Diet in Renal Disease, CG: Cockcroft-Gault, MC: Mayo Clinic

Note: Conversion factors for units: serum creatinine in mg/dL to mmol/L, x88.4; GFR in mL/min/1.73 m² to mL/s/1.73 m², x0.01667.

Table 2

Distribution of donors according to mGFR by the presence of hypertension, albuminuria and diabetes

	mGFR (mL/min/1.73m ²)		
	30–45 (n = 2)	46–60 (n = 41)	> 60 (n = 212)
Hypertension (n = 63)	2	11	50
Albuminuria (n = 32)	0	3	29
Diabetes (n = 8)	0	1	7

Table 3
Overall performance of eGFR_{CG}, eGFR_{MC} and eGFR_{MDRD} in kidney donors

	eGFR < 60 mL/ min/ 1.73m ²	Bias (mL/min)	IQR ^{**}	Relative Bias (%)	R ²	RMSE ⁺	Within 10% of mGFR	Within 30% of mGFR	Within 50% of mGFR
eGFR _{CG} (Rank)	33.3%	-3.96±13.3 (2.5)	17.5	-5.18±17.9 (2)	0.35 (2)	13.9	37.3 (2)	89.4 (1.5)	98.8 (2)
eGFR _{MC} (Rank)	10.2%	8.44±11.9 (2.5)	16.5	12.43±17.5 (3)	0.42 (2)	14.6	36.9 (2)	83.1 (3)	97.7 (2)
eGFR _{MDRD} (Rank)	24.3%	-0.43± 11.7 (1)	15.4	-0.10±16.2 (1)	0.41 (2)	11.6	45.5 (2)	94.1 (1.5)	99.2 (2)

N=255

Rank of Performance based on paired tests: 1 = Best. Ties are assigned the average of the values they would have received if there were no ties. CG: Cockcroft Gault, MC: Mayo Clinic

^{**} IQR: Interquartile range of differences,

⁺ RMSE: Root mean squared error of differences.

Table 4
Overall performance of eGFR (CG), eGFR_{MC} and eGFR_{MDRD} in kidney donors with albuminuria, hypertension, or diabetes

	eGFR < 60 mL/min/ 1.73m ²	Bias (mL/min)	IQR *	Relative Bias (%)	R ²	RMSE ⁺	Within 10% of mGFR	Within 30% of mGFR	Within 50% of mGFR
eGFR _{CG}	39.8	-3.41±15.7	17.4	-4.62±20.6	0.33	15.9	34.9	84.3	97.6
eGFR _{MC}	14.5	7.82±12.7	17.8	11.25±18.0	0.45	14.9	36.1	81.9	100.0
eGFR _{MDRD}	22.9	1.11±13.1	16.7	1.91±17.8	0.39	13.0	41.0	89.2	100.0

n=83
CG: Cockcroft Gault, MC: Mayo Clinic
* IQR: Interquartile range of differences,
+ RMSE: Root mean squared error.