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Cystatin C and Creatinine-based eGFR equation performance depends on patient characteristics

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Abstract

Background—The Kidney Disease Improving Global Outcomes (KDIGO) guideline recommends use of a cystatin C-based estimated glomerular filtration rate (eGFR) to confirm creatinine-based eGFR between 45–59 mL/min/1.73m^2. Prior studies have demonstrated that comorbidities such as solid-organ transplant strongly influence the relationship between measured GFR, creatinine and cystatin C. Our objective was to evaluate the performance of cystatin C based eGFR equations compared to creatinine-based eGFR and measured GFR across different clinical presentations.

Methods—The performance of the CKD-EPI 2009 creatinine-based estimated GFR equation ($eGFR_{Cr}$) and the newer CKD-EPI 2012 cystatin C-based equations ($eGFR_{Cys}$ and $eGFR_{Cr\text{-}Cys}$) were compared with measured GFR (iothalamate renal clearance) across defined patient populations. Patients (n = 1,652) were categorized as transplant recipients (n=568 kidney; n=319 other organ [non-kidney]), known chronic kidney disease (CKD) patients (n=618), or potential kidney donors (n=147).

Results—$eGFR_{Cr\text{-}Cys}$ showed the most consistent performance across different clinical populations. Among potential kidney donors without CKD (stage 2 or higher; eGFR >60mL/min/1.73m^2), $eGFR_{Cys}$ and $eGFR_{Cr\text{-}Cys}$ demonstrated significantly less bias than $eGFR_{Cr}$, however, all three equations substantially underestimated GFR when eGFR <60 mL/min/1.73m^2. Among transplant recipients with CKD stage 3B or lower (eGFR <45mL/min/1.73m^2), $eGFR_{Cys}$ was significantly more biased than $eGFR_{Cr}$. No clear differences among eGFR bias between equations were observed among known CKD patients regardless of eGFR range, or in any patient group with a GFR between 45–59 mL/min/1.73m^2.

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Disclosures

None.

Conclusions—The performance of eGFR equations depends on patient characteristics readily apparent upon presentation. Among the three CKD-EPI equations, $eGFR_{Cr\text{-}Cys}$ performed most consistently across the studied patient populations.

Keywords

Chronic kidney disease; glomerular filtration rate; estimated GFR; Cystatin C; Creatinine; iothalamate

Introduction

Estimation of glomerular filtration rate (eGFR) based on plasma creatinine has become standard practice to assess kidney function in routine clinical practice. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) recently developed two cystatin C-based eGFR equations to compliment the older creatinine-based equation. (1) The 2012 Kidney Disease Improving Global Outcomes (KDIGO) guideline (2) recommends use of a cystatin C-based eGFR to confirm an eGFR Cr 45–59 mL/min/1.73m^2. All three CKD-EPI equations were developed from a mix of patients that included a majority of chronic kidney disease (CKD) patients (~70%) together with a sizable minority of healthier populations such as kidney donors (~30%), while transplant recipients were excluded.(1) Ideally, a single equation could accurately estimate GFR in all clinical situations. However, prior studies have demonstrated that comorbidities such as solid-organ transplant strongly influence the relationship between measured GFR and either creatinine, cystatin C, or both.(3, 4)

In the present study, we sought to evaluate the performance of the two new cystatin C-based eGFR equations compared to creatinine alone-based eGFR and GFR measured by iothalamate clearance. Our previous studies demonstrated that creatinine-based eGFR equations perform differently based on patient presentation.(5) Thus, we grouped our results according to patient categories readily identified in clinical practice: normal kidney donors, patients with known CKD, and solid organ transplant recipients.

Study Population and Methods

Patient Population

All patient data was accessed in compliance with the Mayo Clinic Institutional Review Board. The current study describes 1,652 consecutive stable ambulatory outpatients with a clinically ordered iothalamate clearance study performed in the Mayo Clinic Renal Function Laboratory. Consecutive patients included 887 transplant recipients (568 kidney; 319 other organ [non-kidney]), 147 potential kidney donors (no known CKD prior to evaluation), and 618 CKD patients (known or suspected CKD and without transplant; Table 1). Patients who underwent renal function assessment for chemotherapy dosing, were paraplegic, quadriplegic, <18 years of age, or amputees were excluded, since these features are known to alter muscle mass (and hence creatinine generation); furthermore there were insufficient numbers to study them separately.

Iothalamate Clearance, Serum Creatinine, Serum Cystatin C, and eGFR

GFR was measured by non-radiolabeled iothalamate clearance (mGFR). Patients were asked to fast and report for testing early in the day to minimize dietary and diurnal variations. Iothalamate was administered by subcutaneous injection following oral hydration to maintain a brisk urine flow, followed by timed collections of plasma and urine for iothalamate quantification by LC-MS/MS. (6) Iothalamate filtration rate was normalized to body surface area as estimated by the DuBois formula. (7)

Calculated GFR was corrected for body surface area and normalized to 1.73m^2. Serum creatinine was assessed using a standardized enzymatic assay on a Roche Cobas chemistry analyzer (c701 or c501; Roche Diagnostics; Indianapolis, USA) while cystatin C was measured using an immunoturbidometric assay (Gentian; Moss, Norway) that was traceable to an international reference material. GFR was estimated (eGFR) using the CKD-EPI (2009) creatinine equation ($eGFR_{Cr}$), the CKD-EPI (2012) cystatin C only equation ($eGFR_{Cys}$) and the CKD-EPI (2012) combined equation which incorporates both creatinine and cystatin C ($eGFR_{Cr\text{-}Cys}$). (1, 8)

Statistical analysis

Equation performance was compared between the three different equations and the four different patient populations. The CKD-EPI equations were developed using least-squares regression of log GFR.(1) Thus, the equations were originally derived to minimize bias between log mGFR and log eGFR across levels of log eGFR. Correspondingly, our validation analysis replicated this same methodology. Comparison graphs were plotted using linear regression with log eGFR as x-axis and log mGFR as y-axis. A more detailed defence of this approach to assessing bias with eGFR is included in the Appendix (Supplemental Methods). Bias was calculated on a logarithmic scale (4, 5, 9) and presented as a percentage. Equation bias was regressed using a smoother fit (lambda = 1,000,000) to graphically depict bias across eGFR for each patient population. Concordance (% agreement) between eGFR <60 ml/min/1.73 m^2 and mGFR <60 ml/min/1.73 m^2 was compared for each equation and each patient population. All statistical analysis was performed using JMP software (SAS Institute, Cary, NC).

Results

Overall eGFR performance

Patient demographics and renal function are described in Table 1. Potential kidney donors were significantly younger, more likely to be female, had lower serum creatinine and cystatin C concentrations, and had higher mGFR compared to all other categories (p <0.001 all cases). There were no significant differences in height, weight, body-mass index (BMI) or race between any patient categories, and no significant differences in serum creatinine, serum cystatin C, or mGFR values between CKD patients and transplant recipients.

Measured GFR was plotted as a function of eGFR for each equation and patient group (Figure 1). Correlation with mGFR was weakest among potential kidney donors and strongest among CKD patients (Table 1). Among CKD patients and transplant recipients,

correlation with mGFR was significantly stronger for $eGFR_{Cr\text{-}Cys}$, but not $eGFR_{Cys}$, when compared to $eGFR_{Cr}$ ($p<0.05$).

Overall, all three equations modestly underestimated mGFR among CKD patients and transplant recipients. The mean difference between eGFR and mGFR among potential kidney donors was significantly smaller for $eGFR_{Cys}$ and $eGFR_{Cr\text{-}Cys}$ compared to $eGFR_{Cr}$ ($p <0.0001$ both cases; Table 2). The mean bias between eGFR and mGFR was slightly but significantly larger for $eGFR_{Cys}$ and $eGFR_{Cr\text{-}Cys}$ compared to $eGFR_{Cr}$ among transplant recipients ($p <0.01$ all cases). Equation performance did not statistically differ by gender (Supplemental Table 1). Equation bias decreased with age among other (non-kidney) organ transplant recipients for $eGFR_{Cr}$ (p 0.02) and $eGFR_{Cr\text{-}Cys}$ (p 0.02) but not $eGFR_{Cys}$ (p 0.07; Supplemental Figure 1). No significant relationships with age were observed for any other equation or patient group.

Performance across levels of eGFR

All eGFR equations tended to underestimate mGFR for all patient categories, with some differences in magnitude depending on patient group and equation (Figure 2). Bias was significantly smaller for $eGFR_{Cys}$ and $eGFR_{Cr\text{-}Cys}$ compared to $eGFR_{Cr}$ among potential donors with eGFR >90mL/min/1.73m^2 ($p <0.001$ both cases). The bias was significantly lower for $eGFR_{Cr\text{-}Cys}$ ($p=0.002$), but not $eGFR_{Cys}$ ($p=0.087$) compared to $eGFR_{Cr}$ among potential donors with eGFR between 60–89 mL/min/1.73m^2 (Table 2). Among both kidney and other organ transplant recipients $eGFR_{Cys}$ was significantly more biased (negatively) than $eGFR_{Cr}$ for values between 30–59 mL/min/1.73m^2 ($p<0.01$; Table 2). Importantly, eGFR substantially underestimated mGFR for a mGFR between 45–59 mL/min/1.73m^2 in all patients using either creatinine or cystatin C based equations (Table 2).

Clinical performance of eGFR equations

Finally, the concordance between eGFR and mGFR for classifying patients according to CKD stage was compared for each equation and patient category. Classification was considered across all CKD stages (Stage 1 >90, Stage 2 60–90, Stage 3a 45–59, Stage 3b 30–44, Stage 4 15–29, and Stage 5 <15 mL/min/1.73m^2) or as a dichotomous function of greater or less than 60 mL/min/1.73m^2 (Table 3). Concordance between eGFR <60 and mGFR <60 mL/min/1.73m^2 was considered for each equation independently, and with confirming an $eGFR_{Cr}$ between 45 – 59 mL/min/1.73m^2 using $eGFR_{Cys}$ or $eGFR_{Cr\text{-}Cys}$).

Concordance with mGFR was significantly better for $eGFR_{Cr\text{-}Cys}$ compared to $eGFR_{Cr}$ among the potential donors, CKD patients, and non-kidney transplant recipients (Table 3). Among potential donors and non-kidney transplant recipients $eGFR_{Cys}$ also improved classification compared to $eGFR_{Cr}$ alone. In both cases the improved concordance was primarily due to reclassification of patients with eGFR <30 mL/min/1.73m^2 or >60 mL/min/1.73m^2 (Supplemental Table 2). Importantly, confirming an $eGFR_{Cr}$ value between 45–59 mL/min/1.73m^2 using $eGFR_{Cr\text{-}Cys}$ or $eGFR_{Cys}$ (according to KDIGO recommendations) only improved concordance with mGFR when classifying in relation to the 60 mL/min/1.73m^2 cutoff in the CKD and other organ (non-kidney) transplant recipient groups.

Discussion

These data support previous evidence that eGFR equation performance is strongly dependent on patient presentation. However, in the current cohort significant differences in equation performance were limited to patients with stage 3B or greater CKD (GFR <45mL/min/1.73m^2) and patients with good renal function (mGFR >60mL/min/1.73m^2). The cystatin C equations (eGFR$_{Cys}$ and eGFR$_{Cr\text{-}Cys}$) displayed significantly less bias than eGFR$_{Cr}$ among potential donors but significantly more bias (negative) than eGFR$_{Cr}$ among transplant recipients. Underestimation of mGFR by eGFR$_{Cr}$ in donors is consistent with the higher muscle mass in healthy donors than is present in CKD patient populations.(10) Underestimation of mGFR by eGFR$_{Cys}$ in transplant recipients is less clear but may be related to inflammation or immunosuppression effects on cystatin C.(11–13)

These findings support a strategy whereby the exact method used to assess GFR is chosen based on the type of patient being treated and the indication for testing. For example, there are certain circumstances where knowing the patient's actual GFR (*i.e.* mGFR) is more important than a prediction of patient outcomes. A common example is dosing of renally cleared drugs.(14) In this situation, accurate estimation of GFR will enhance drug safety (avoidance drug toxicity) and efficacy (adequate dose for treatment). In the current study, eGFR$_{Cr\text{-}Cys}$ was closest to mGFR across all patient groups and mGFR ranges, so might be the preferred default method for such purposes. Indeed, there is evidence that eGFR$_{Cr\text{-}Cys}$ provides superior clinical performance in vancomycin dosing.(15, 16)

Alternatively, eGFR has been used to establish risk of cardiovascular disease, hypertension and end-stage renal disease. Recent studies suggest that eGFR$_{Cys}$ is a better predictor of patient morbidity and mortality than eGFR$_{Cr}$.(17–20) Conversely, eGFR$_{Cr}$ is reported to more accurately detect the same risk factor and outcome associations seen with reduced mGFR compared to eGFR$_{Cys}$ or eGFR$_{Cr\text{-}Cys}$.(21–24). The reasons are likely due to the underlying risk related to production of the biomarker or other non-GFR-related biology of cystatin C.(25–27) Thus, different biomarker derived eGFR equations might be chosen depending on the outcome of interest and/or clinical need.

In our cohort, the net effect of confirming eGFR$_{Cr}$ between 45–59 mL/min/1.73m^2 with either eGFR$_{Cys}$ or eGFR$_{Cr\text{-}Cys}$ was minimal and depended upon patient presentation. Among patients with known CKD, confirmation significantly improved appropriate classification of patients as having a mGFR<60mL/min/1.73m^2. However, these patients were already diagnosed with CKD and the clinical value of the confirmatory testing is questionable. Only four potential donors had reduced mGFR <60 mL/min/1.73m^2, and at least two (50%) would still have been misclassified as having eGFR>60 mL/min/1.73m^2 regardless of the equation used.

Our study has certain limitations. The size of our cohort was less than that used to derive the CKD-EPI equations, and it contained very little racial/ethnic diversity. However, this cohort represents a relatively large group of patients with well-defined clinical diagnoses, standardized serum cystatin C and creatinine values, and mGFR using iothalamate clearance technique that was used to develop the CKD-EPI equations.

Moving forward, a conceptual shift may be helpful. Equations such as $eGFR_{Cr\text{-}Cys}$ that perform reasonably well among all patient groups could be used to estimate GFR for patient treatments that are critically dependent on mGFR (*e.g.* dosing of vancomycin). On the other hand, if knowledge regarding patient prognosis is important, (*e.g.* risk of CKD progression or death), alternative models of care could be developed that incorporate biomarkers (*e.g.* cystatin C) and clinical characteristics to estimate risk of end stage renal disease or other key outcomes such as mortality, rather than accurately estimating mGFR. Targeted use of cystatin C in this context would offset the increased cost of cystatin C compared to creatinine, a potential consideration when additional testing is ordered.(28, 29)

In conclusion, in the current study the combined $eGFR_{Cr\text{-}Cys}$ performs best across all patient types for predicting measured GFR. However, the performance of eGFR equations varies considerably across patient presentation and eGFR values. In particular, $eGFR_{Cr}$ is not advised in kidney donor evaluations and $eGFR_{Cys}$ or $eGFR_{Cr\text{-}Cys}$ is not advised in transplant recipients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

GFR	glomerular filtration rate
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
KDIGO	Kidney Disease Improving Global Outcomes
CKD	chronic kidney disease
$eGFR_{Cr}$	creatinine estimated GFR
$eGFR_{Cys}$	cystatin C estimated GFR
$eGFR_{Cr\text{-}Cys}$	creatinine and cystatin C combined estimated GFR

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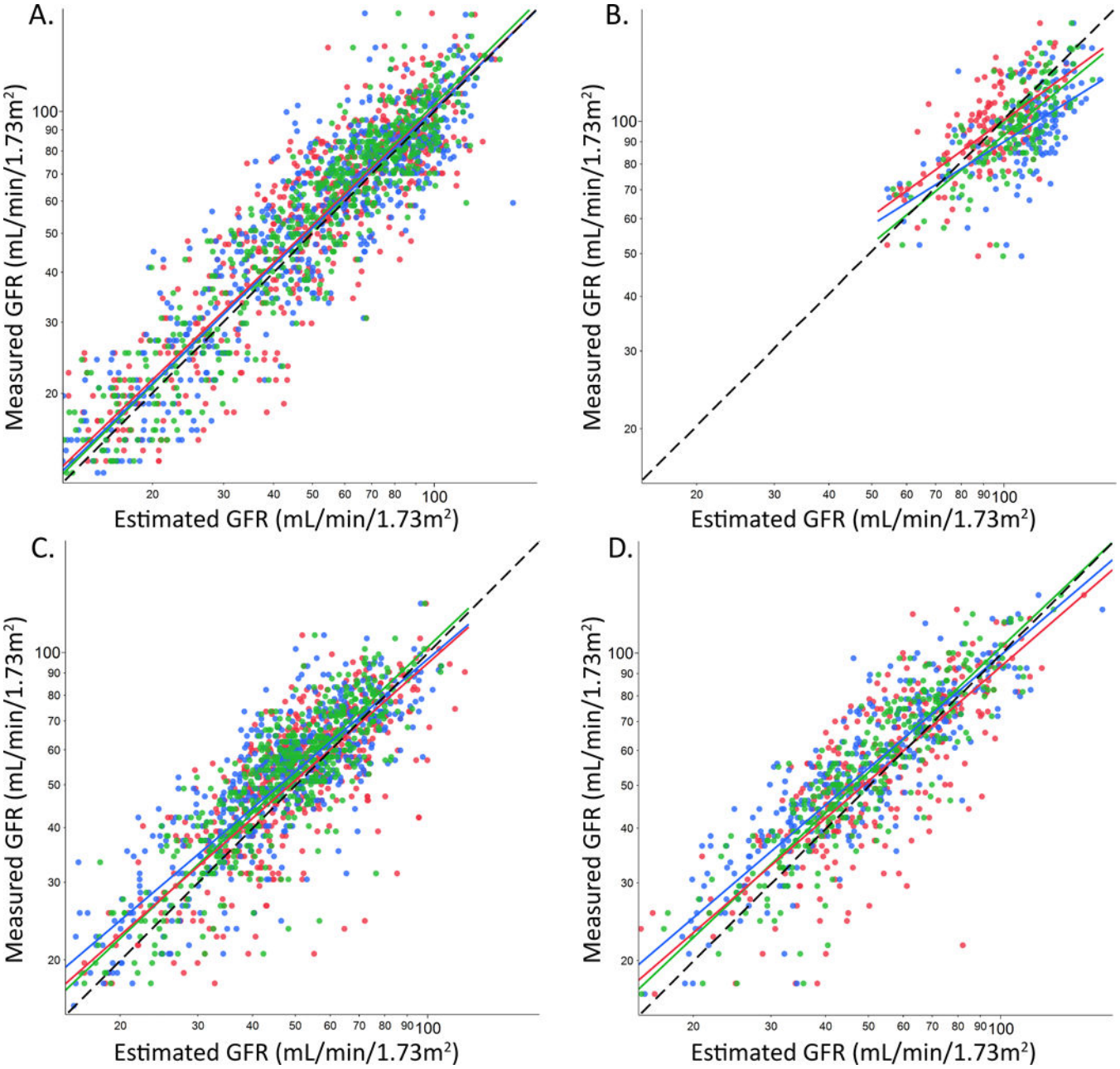

Figure 1. Comparison of measured and estimated GFR according to equation and patient category

Log $eGFR_{Cr}$ (red), $eGFR_{Cys}$ (blue) and $eGFR_{Cr\text{-}Cys}$ (green) values are plotted on the x-axis and log mGFR on the y-axis for (**A**) CKD patients, (**B**) potential donors, (**C**) kidney transplant recipients, and (D) other organ (non-kidney) transplant recipients. The black dashed line represents the line of identity that an unbiased equation would follow.

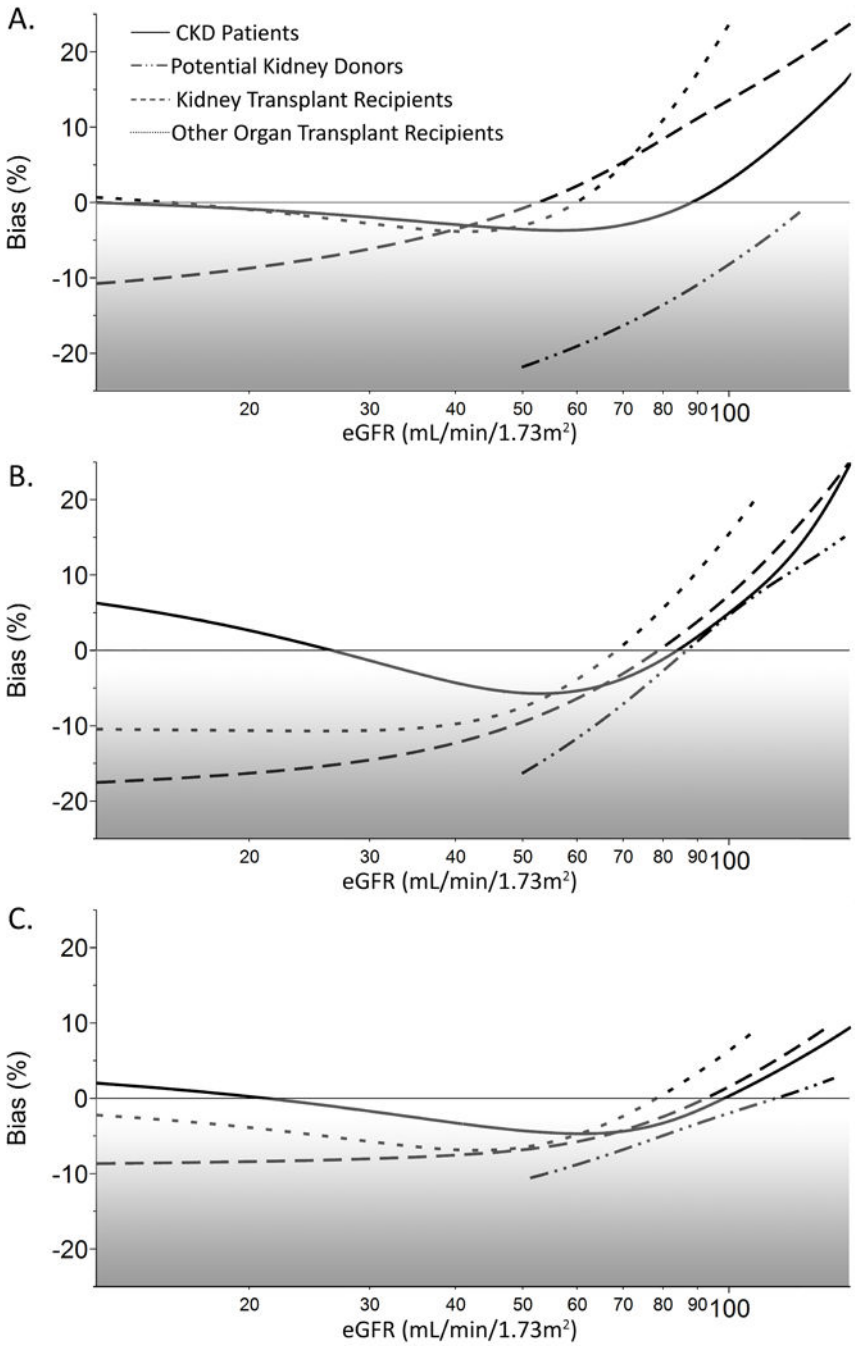

Figure 2. Equation bias as a function of eGFR

Bias (exp[log eGFR − log mGFR] − 1) plotted as a function of (**A**) $eGFR_{Cr}$, (**B**) $eGFR_{Cys}$, and (**C**) $eGFR_{Cr\text{-}Cys}$ for CKD patients (solid), potential kidney donors (dash-dot), kidney transplant recipients (dotted), and other-organ transplant recipients (dashed).

Table 1

Patient demographic information and overall renal function data.

Demographics	Potential Kidney Donors	CKD Patients	Kidney Recipients	Other Organ Recipients
Patients, n	147	618	568	319
Age, mean±SD	47 ±13	57 ±15	55 ±14	57 ±13
Age <40 year, n (%)	43 (29)	63 (10)	87 (15)	33 (10)
Age >70 years, n (%)	1 (1)	75 (12)	84 (15)	36 (11)
Female, n (%)	85 (58)	253 (40)	245 (43)	139 (43)
African American, n (%)	2 (1)	12 (2)	11 (2)	4 (1)
Height (cm), mean±SD	169 ±8	171 ±12	170±10	172±10
Weight (kg), mean±SD	80 ±19	84 ±20	85±22	82±18
BMI (kg/m^2), mean±SD	28 ±4.7	29 ±5.7	29±6.7	28±4.8
Renal function				
Serum creatinine (mg/dL)*	0.9±0.2	1.5±1.0	1.5±0.6	1.3±0.5
Serum cystatin C (mg/L)*	0.80±0.17	1.44±0.74	1.59±0.54	1.52±0.47
Measured GFR ($mL/min/1.73m^2$)*	101±22	66±33	55±19	58±24
eGFR ($mL/min/1.73m^2$)*				
$eGFR_{Cr}$	87±17	63±30	53±18	56±22
$eGFR_{Cys}$	103±20	64±31	50±19	53±24
$eGFR_{Cr-Cys}$	96±17	63±30	50±17	54±22
Correlation with mGFR				
$eGFR_{Cr}$	0.6485	0.8629	0.7459	0.7943
$eGFR_{Cys}$	0.6101	0.8653	0.7940	0.8583
$eGFR_{Cr-Cys}$	0.7136	0.9047	0.8374	0.8913

* mean±SD

Table 2

Percent bias in different populations across clinically relevant eGFR ranges. Means with 95% confidence intervals that include zero are not significantly different from iothalamate corrected mGFR.

eGFR	Potential Donors	CKD Patients	Kidney Recipients	Other Organ Recipients
Overall				
eGFRCr	−11.6 (−14, −8.9)	−0.8 (−3.0, 1.3)	0.5 (−2.2, 3.2)	1.3 (−2.2, 4.9)
eGFRCys	4.8 (1.4, 8.1)	0.1 (−1.9, 2.2)	−5.4 (−7.8, −3.0)	−7.7 (−10, −5.4)
eGFRCr-Cys	−2.7 (−5.4, 0)	−1.9 (−3.6, −0.2)	−4.8 (−7.0, −2.6)	−5.6 (−7.8, −3.5)
≥90 mL/min/1.73m^2				
eGFRCr	−5.8 (−9.7, −1.9)	5.0 (1.5, 8.6)	29 (11.6, 46.4)	13.5 (5.5, 22)
eGFRCys	8.5 (4.9, 12.1)	8.2 (4.7, 11.8)	14.5 (4.8, 24.2)	7.4 (0.8, 14)
eGFRCr-Cys	−1.4 (−4.5, 1.8)	3.1 (−0.1, 6.3)	6.7 (−3.4, 16.7)	5.5 (−0.6, 12)
60–89 mL/min/1.73m^2				
eGFRCr	−15 (−18.9, −11.2)	−4.0 (−7.4, −0.7)	7.1 (2.1, 12.2)	6.4 (−2.0, 15)
eGFRCys	−7.9 (−15.2, −0.6)	−2.4 (−5.7, 0.9)	3.6 (0.3, 7)	−2.6 (−6.8, 1.5)
eGFRCr-Cys	−4.3 (−9.7, 1.1)	−5.0 (−7.5, −2.4)	−0.7 (−3.9, 2.6)	−4.7 (−8.6, −0.8)
45–59 mL/min/1.73m^2				
eGFRCr	−20.5 (−27.3, −13.7)	−3.5 (−9.3, 2.3)	−6.3 (−9.7, −2.9)	−0.5 (−6.5, 5.6)
eGFRCys	−17.2 (−29.5, −4.8)	−7.3 (−12.3, −2.4)	−9.7 (−12.7, −6.8)	−7.2 (−12, −2.4)
eGFRCr-Cys	−18.5 (−28.7, −8.3)	−4.2 (−8.6, 0.1)	−7.9 (−10.8, −4.9)	−7.5 (−11, −3.7)
30–44 mL/min/1.73m^2				
eGFRCr	–	−2.5 (−9.0, 4.1)	−2.9 (−7.9, 2.0)	−4.5 (−10, 1.5)
eGFRCys	–	−5.5 (−11, 0.0)	−11.3 (−16, −6.8)	−14.2 (−19, −9.7)
eGFRCr-Cys	–	−3.7 (−8.7, 1.3)	−7.8 (−12, −3.7)	−6.9 (−11, −2.5)
<30 mL/min/1.73m^2				
eGFRCr	–	0.3 (−6.2, 6.8)	5.2 (−10, 21)	−5.1 (−16, 6.0)
eGFRCys	–	4.4 (−1.9, 11)	−6.1 (−17, 5.1)	−15.5 (−21, −10)
eGFRCr-Cys	–	0.7 (−4.6, 6)	−0.1 (−12, 12)	−7.5 (−15, −0.1)

Table 3

Concordance of estimated GFR with measured GFR when classifying patients between all CKD stages or dichotomously as <60 mL/min/1.73m^2.

	All CKD Stages		<60 mL/min/1.73m^2	
	Concordance, % (95CI)	**p–value***	**Concordance, % (95CI)**	**p–value***
Potential Donors				
$eGFR_{Cr}$	55.0 (47.0, 62.9)	–	92.1 (87.8, 96.4)	–
$eGFR_{Cys}$	71.5 (64.3, 78.7)	**0.002**	93.4 (89.5, 97.4)	0.63
$eGFR_{Cr-Cys}$	76.2 (69.4, 83.0)	**<0.001**	94.1 (90.3, 97.9)	0.45
$eGFR_{Cr}/eGFR_{Cys}$†	56.3 (48.4, 64.2)	0.81	94.7 (91.2, 98.3)	0.30
$eGFR_{Cr}/eGFR_{Cr-Cys}$†	57.6 (49.7, 65.5)	0.64	94.7 (91.2, 98.3)	0.30
CKD Patients				
$eGFR_{Cr}$	54.2 (50.3, 58.1)	–	87.3 (84.7, 89.9)	–
$eGFR_{Cys}$	58.7 (54.8, 62.6)	0.11	88.1 (85.6, 90.7)	0.66
$eGFR_{Cr-Cys}$	62.9 (59.1, 66.7)	**0.002**	89.7 (87.3, 92.1)	0.18
$eGFR_{Cr}/eGFR_{Cys}$†	57.9 (54.0, 61.8)	0.19	91.3 (89.1, 93.5)	**0.02**
$eGFR_{Cr}/eGFR_{Cr-Cys}$†	58.4 (54.5, 62.2)	0.14	90.5 (88.2, 92.8)	0.07
Kidney Transplant Recipients				
$eGFR_{Cr}$	52.4 (48.4, 56.5)	–	76.9 (73.5, 80.4)	–
$eGFR_{Cys}$	55.1 (51.0, 59.1)	0.37	77.6 (74.2, 81.0)	0.78
$eGFR_{Cr-Cys}$	58.0 (54.0, 62.1)	0.06	79.2 (75.9, 82.5)	0.35
$eGFR_{Cr}/eGFR_{Cys}$†	52.1 (48.0, 56.2)	0.12	78.5 (75.1, 81.9)	0.52
$eGFR_{Cr}/eGFR_{Cr-Cys}$†	53.8 (49.8, 57.9)	0.6	78.5 (75.1, 81.9)	0.52
Other Organ Transplant Recipients				
$eGFR_{Cr}$	46.9 (41.4, 52.3)	–	80.1 (75.8, 84.5)	–
$eGFR_{Cys}$	55.3 (49.8, 60.7)	**0.03**	86.4 (82.6, 90.1)	**0.03**
$eGFR_{Cr-Cys}$	56.8 (51.4, 62.2)	**0.01**	86.4 (82.6, 90.1)	**0.03**
$eGFR_{Cr}/eGFR_{Cys}$†	50.0 (44.5, 55.5)	0.43	86.7 (82.9, 90.4)	**0.02**
$eGFR_{Cr}/eGFR_{Cr-Cys}$†	51.6 (46.1, 57.0)	0.23	84.8 (80.9, 88.7)	0.11

*P-value for comparison to $eGFR_{Cr}$.

†Patient's with $eGFR_{Cr}$ between 45–59 mL/min/1.73m^2 re-classified by $eGFR_{Cys}$ or $eGFR_{Cr-Cys}$ in comparison to $eGFR_{Cr}$