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Performance of Cystatin C– and Creatinine-Based Estimated Glomerular Filtration Rate Equations Depends on Patient Characteristics

Jeffrey W. Meeusen,[1] Andrew D. Rule,[2,3] Nikolay Voskoboev,[1] Nikola A. Baumann,[1] and John C. Lieske[1,2*]

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 and 59 $mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$. 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 with creatinine-based eGFR and measured GFR across different clinical presentations.

METHODS: We compared 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 $eGFR_{Cr\text{-}Cys}$) with measured GFR (iothalamate renal clearance) across defined patient populations. Patients (n = 1652) were categorized as transplant recipients (n = 568 kidney; n = 319 other organ), 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 $>60\ mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$], $eGFR_{Cys}$ and $eGFR_{Cr\text{-}Cys}$ demonstrated significantly less bias than $eGFR_{Cr}$; however, all 3 equations substantially underestimated GFR when eGFR was $<60\ mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$. Among transplant recipients with CKD stage 3B or greater [eGFR $<45\ mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$], $eGFR_{Cys}$ was significantly more biased than $eGFR_{Cr}$. No clear differences in eGFR bias between equations were observed among known CKD patients regardless of eGFR range or in any patient group with a GFR between 45 and 59 $mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$.

CONCLUSIONS: The performance of eGFR equations depends on patient characteristics that are readily apparent on presentation. Among the 3 CKD-EPI equations, $eGFR_{Cr\text{-}Cys}$ performed most consistently across the studied patient populations.

The use of estimated glomerular filtration rate (eGFR)[4] on the basis of plasma creatinine has become standard practice to assess kidney function in routine clinical practice. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) recently developed 2 cystatin C–based eGFR equations to complement 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 $mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$. All 3 CKD-EPI equations were developed from a mix of patients that included a majority of chronic kidney disease (CKD) patients (approximately 70%) together with a sizable minority of healthier populations such as kidney donors (approximately 30%), whereas 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 creatinine, cystatin C, or both *(3, 4)*.

In the present study, we sought to evaluate the performance of the 2 new cystatin C–based eGFR equations compared with creatinine-based eGFR and GFR measured by iothalamate clearance (mGFR). Our previous studies demonstrated that creatinine-based eGFR equations perform differently depending on patient presentation *(5)*. Thus, we grouped our results according to patient categories readily identified in clinical practice:

[1] Department of Laboratory Medicine and Pathology, [2] Department of Internal Medicine, Division of Nephrology and Hypertension, and [3] Department of Health Sciences Research Division of Epidemiology, Mayo Clinic, Rochester, MN.
* Address correspondence to this author at: Division of Nephrology and Hypertension, Mayo Clinic, 200 First St SW, Rochester, MN 55905. Fax 507-266-7891; e-mail lieske.john@mayo.edu.

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[4] Nonstandard abbreviations: eGFR, estimated glomerular filtration rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; KDIGO, Kidney Disease Improving Global Outcomes; CKD, chronic kidney disease; mGFR, measured GFR.

Table 1. Patient demographic information and overall renal function data.[a]

Variable	Potential kidney donors	CKD patients	Kidney recipients	Other organ recipients
Demographics	147	618	568	319
Age, years	47 (13)	57 (15)	55 (14)	57 (13)
<40	43 (29)	63 (10)	87 (15)	33 (10)
>70	1 (1)	75 (12)	84 (15)	36 (11)
Female	85 (58)	253 (40)	245 (43)	139 (43)
African American	2 (1)	12 (2)	11 (2)	4 (1)
Height, cm	169 (8)	171 (12)	170 (10)	172 (10)
Weight, kg	80 (19)	84 (20)	85 (22)	82 (18)
Body mass index, kg/m^2	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)
mGFR, $mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$	101 (22)	66 (33)	55 (19)	58 (24)
eGFR, $mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$				
$eGFR_{Cr}$, $mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$	87 (17)	63 (30)	53 (18)	56 (22)
$eGFR_{Cys}$, $mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$	103 (20)	64 (31)	50 (19)	53 (24)
$eGFR_{Cr-Cys}$, $mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$	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

[a] Data are n, mean (SD), or n (%). To convert creatinine concentrations in mg/dL to mmol/L, multiply by 0.088.

healthy kidney donors, patients with known CKD, and solid organ transplant recipients.

Study Population and Methods

PATIENT POPULATION

All patient data were accessed in compliance with the Mayo Clinic Institutional Review Board. The current study describes 1652 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), 147 potential kidney donors (no known CKD before evaluation), and 618 CKD patients (known or suspected CKD and without transplant) (Table 1). We excluded patients who underwent renal function assessment for chemotherapy dosing or who were paraplegic, quadriplegic, <18 years of age, or amputees, 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

We measured GFR by nonradiolabeled iothalamate clearance. 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 after 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 1.73 m^2. We assessed serum creatinine with a standardized enzymatic assay on a Roche Cobas chemistry analyzer (c701 or c501; Roche Diagnostics) and measured cystatin C with an immunoturbidometric assay (Gentian) that was traceable to an international reference material. GFR was estimated with the CKD-EPI (2009) creatinine equation ($eGFR_{Cr}$), the CKD-EPI (2012) cystatin C equation ($eGFR_{Cys}$), and the CKD-EPI (2012) combined equation, which incorporates both creatinine and cystatin C ($eGFR_{Cr-Cys}$) *(1, 8)*.

STATISTICAL ANALYSIS

We compared equation performance between the 3 different equations and the 4 different patient populations. The CKD-EPI equations were developed by use of 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 by use of linear regression with log eGFR as *x* axis and log mGFR as *y* axis. A more detailed defense of this approach to assessing bias with eGFR is included in Supplemental Methods file, which accompanies the online version of this article at http://www.clinchem.org/content/vol61/issue10. Bias was calculated on a logarithmic scale *(4, 5, 9)* and presented as a percentage. Equation bias was regressed by use of a smoother fit ($\lambda = 1\ 000\ 000$) to graphically depict bias across eGFR for each patient population. We compared concordance (percentage agreement) between eGFR <60 mL · min^{-1} · (1.73 m^2)$^{-1}$ and mGFR <60 mL · min^{-1} · (1.73 m^2)$^{-1}$ for each equation and each patient population. All statistical analysis was performed with JMP software (SAS Institute).

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 with all other categories ($P < 0.001$ all cases). There were no significant differences in height, weight, body mass index, 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 (Fig. 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 with $eGFR_{Cr}$ ($P < 0.05$).

Overall, all 3 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 with $eGFR_{Cr}$ ($P < 0.0001$ 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 with $eGFR_{Cr}$ among transplant recipients ($P < 0.01$ all cases). Equation performance did not differ statistically by sex (see online Supplemental Table 1). Equation bias decreased with age among nonkidney organ transplant recipients for $eGFR_{Cr}$ ($P = 0.02$) and $eGFR_{Cr\text{-}Cys}$ ($P = 0.02$) but not $eGFR_{Cys}$ ($P = 0.07$) (see online Supplemental Fig. 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 (Fig. 2). Bias was significantly smaller for $eGFR_{Cys}$ and $eGFR_{Cr\text{-}Cys}$ compared with $eGFR_{Cr}$ among potential donors, with eGFR >90 mL · min^{-1} · (1.73 m^2)$^{-1}$ ($P < 0.001$ both cases). The bias was significantly lower for $eGFR_{Cr\text{-}Cys}$ ($P = 0.002$), but not $eGFR_{Cys}$ ($P = 0.087$) compared with $eGFR_{Cr}$ among potential donors, with eGFR between 60 and 89 mL · min^{-1} · (1.73 m^2)$^{-1}$ (Table 2). Among kidney and other organ transplant recipients, $eGFR_{Cys}$ was significantly more biased (negatively) than $eGFR_{Cr}$ for values between 30 and 59 mL · min^{-1} · (1.73 m^2)$^{-1}$ ($P < 0.01$) (Table 2). Importantly, eGFR with either creatinine- or cystatin C–based equations substantially underestimated mGFR for mGFR between 45 and 59 mL · min^{-1} · (1.73 m^2)$^{-1}$ in all patients (Table 2).

CLINICAL PERFORMANCE OF eGFR EQUATIONS

Finally, we compared the concordance between eGFR and mGFR for classifying patients according to CKD stage for each equation and patient category. Classification vis-à-vis GFR 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} · (1.73 m^2)$^{-1}$] or as a dichotomous function of > or <60 mL · min^{-1} · (1.73 m^2)$^{-1}$ (Table 3). Concordance between eGFR <60 and mGFR <60 mL · min^{-1} · (1.73 m^2)$^{-1}$ was considered for each equation independently and after confirming an $eGFR_{Cr}$ between 45 and 59 mL · min^{-1} · (1.73 m^2)$^{-1}$ with $eGFR_{Cys}$ or $eGFR_{Cr\text{-}Cys}$.

Concordance with mGFR was significantly better for $eGFR_{Cr\text{-}Cys}$ compared with $eGFR_{Cr}$ among the potential donors, CKD patients, and nonkidney transplant recipients (Table 3). Among potential donors and nonkidney transplant recipients, $eGFR_{Cys}$ also improved classification compared with $eGFR_{Cr}$ alone. In both cases, the improved concordance was primarily due to reclassification of patients with eGFR <30 or >60 mL · min^{-1} · (1.73 m^2)$^{-1}$ (see online Supplemental Table 2). Importantly, confirming an $eGFR_{Cr}$ value between 45 and 59 mL · min^{-1} · (1.73 m^2)$^{-1}$ with $eGFR_{Cr\text{-}Cys}$ or $eGFR_{Cys}$ (according to KDIGO recommendations) improved concordance with mGFR only when classifying in relation to the 60 mL · min^{-1} ·

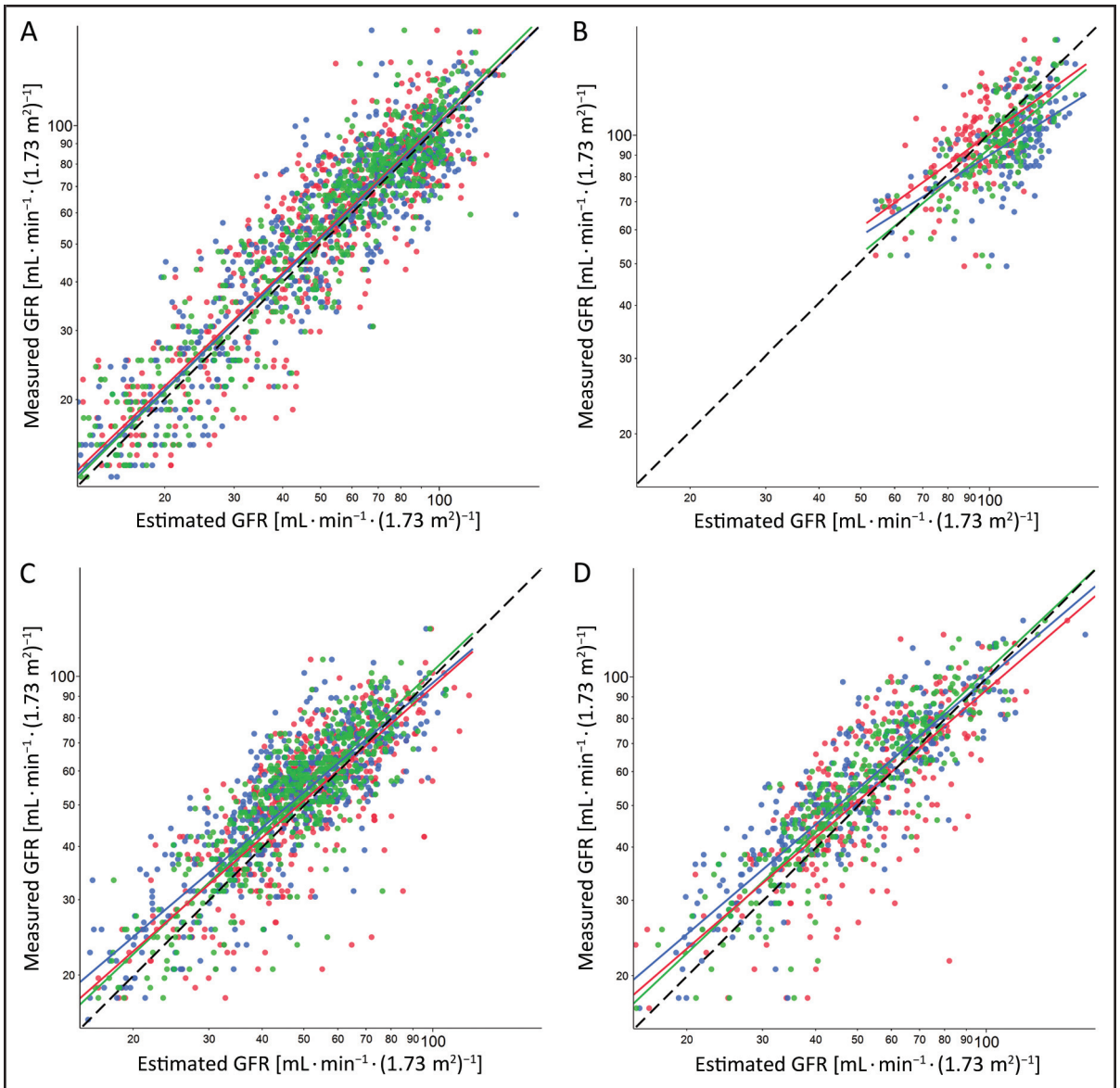

Fig. 1. Comparison of mGFR and eGFR according to equation and patient category.

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 CKD patients (A), potential donors (B), kidney transplant recipients (C), and recipients of other organ transplants (D). The black dashed line represents the line of identity that an unbiased equation would follow.

$(1.73\ m^2)^{-1}$ cutoff in the CKD and nonkidney 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 <45 $mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$] and patients with good renal function [mGFR >60 $mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$]. 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 in CKD pa-

Table 2. Percent bias in different populations across clinically relevant eGFR ranges.[a]

eGFR	Potential donors	CKD patients	Kidney recipients	Other organ recipients
Overall				
eGFRCr	−11.6 (−14 to −8.9)	−0.8 (−3.0 to 1.3)	0.5 (−2.2 to 3.2)	1.3 (−2.2 to 4.9)
eGFRCys	4.8 (1.4 to 8.1)	0.1 (−1.9 to 2.2)	−5.4 (−7.8 to −3.0)	−7.7 (−10 to −5.4)
eGFRCr-Cys	−2.7 (−5.4 to 0)	−1.9 (−3.6 to −0.2)	−4.8 (−7.0 to −2.6)	−5.6 (−7.8 to −3.5)
>90 mL · min^{-1} · (1.73 m^2)$^{-1}$				
eGFRCr	−5.8 (−9.7 to −1.9)	5.0 (1.5 to 8.6)	29 (11.6 to 46.4)	13.5 (5.5 to 22)
eGFRCys	8.5 (4.9 to 12.1)	8.2 (4.7 to 11.8)	14.5 (4.8 to 24.2)	7.4 (0.8 to 14)
eGFRCr-Cys	−1.4 (−4.5 to 1.8)	3.1 (−0.1 to 6.3)	6.7 (−3.4 to 16.7)	5.5 (−0.6 to 12)
60–89 mL · min^{-1} · (1.73 m^2)$^{-1}$				
eGFRCr	−15 (−18.9 to −11.2)	−4.0 (−7.4 to −0.7)	7.1 (2.1 to 12.2)	6.4 (−2.0 to 15)
eGFRCys	−7.9 (−15.2 to −0.6)	−2.4 (−5.7 to 0.9)	3.6 (0.3 to 7)	−2.6 (−6.8 to 1.5)
eGFRCr-Cys	−4.3 (−9.7 to 1.1)	−5.0 (−7.5 to −2.4)	−0.7 (−3.9 to 2.6)	−4.7 (−8.6 to −0.8)
45–59 mL · min^{-1} · (1.73 m^2)$^{-1}$				
eGFRCr	−20.5 (−27.3 to −13.7)	−3.5 (−9.3 to 2.3)	−6.3 (−9.7 to −2.9)	−0.5 (−6.5 to 5.6)
eGFRCys	−17.2 (−29.5 to −4.8)	−7.3 (−12.3 to −2.4)	−9.7 (−12.7 to −6.8)	−7.2 (−12 to −2.4)
eGFRCr-Cys	−18.5 (−28.7 to −8.3)	−4.2 (−8.6 to 0.1)	−7.9 (−10.8 to −4.9)	−7.5 (−11 to −3.7)
30–44 mL · min^{-1} · (1.73 m^2)$^{-1}$				
eGFRCr		−2.5 (−9.0 to 4.1)	−2.9 (−7.9 to 2.0)	−4.5 (−10 to 1.5)
eGFRCys		−5.5 (−11 to 0.0)	−11.3 (−16 to −6.8)	−14.2 (−19 to −9.7)
eGFRCr-Cys		−3.7 (−8.7 to 1.3)	−7.8 (−12 to −3.7)	−6.9 (−11 to −2.5)
<30 mL · min^{-1} · (1.73 m^2)$^{-1}$				
eGFRCr		0.3 (−6.2 to 6.8)	5.2 (−10 to 21)	−5.1 (−16 to 6.0)
eGFRCys		4.4 (−1.9 to 11)	−6.1 (−17 to 5.1)	−15.5 (−21 to −10)
eGFRCr-Cys		0.7 (−4.6 to 6)	−0.1 (−12 to 12)	−7.5 (−15 to −0.1)

[a] Data are bias (95% CI). Means with 95% CIs that include zero are not significantly different from iothalamate-corrected mGFR.

tient 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 on the basis of the type of patient being treated and the indication for testing. For example, there are certain circumstances in which 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, and therefore, 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 with $eGFR_{Cys}$ or $eGFR_{Cr\text{-}Cys}$ *(11, 21–23)*. The reasons is likely the underlying risk related to production of the biomarker or other non–GFR-related biology of cystatin C *(24–26)*. 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 and 59 mL · min^{-1} · (1.73 m^2)$^{-1}$ with either $eGFR_{Cys}$ or $eGFR_{Cr\text{-}Cys}$ was minimal and depended on patient presentation. Among patients with known CKD, confirmation significantly improved appropriate classification of patients as having mGFR <60 mL · min^{-1} · (1.73 m^2)$^{-1}$. However, these patients were already diagnosed with CKD, and the clinical value of the confirmatory testing is questionable. Only 4 potential donors had reduced mGFR <60 mL · min^{-1} · (1.73 m^2)$^{-1}$, and at

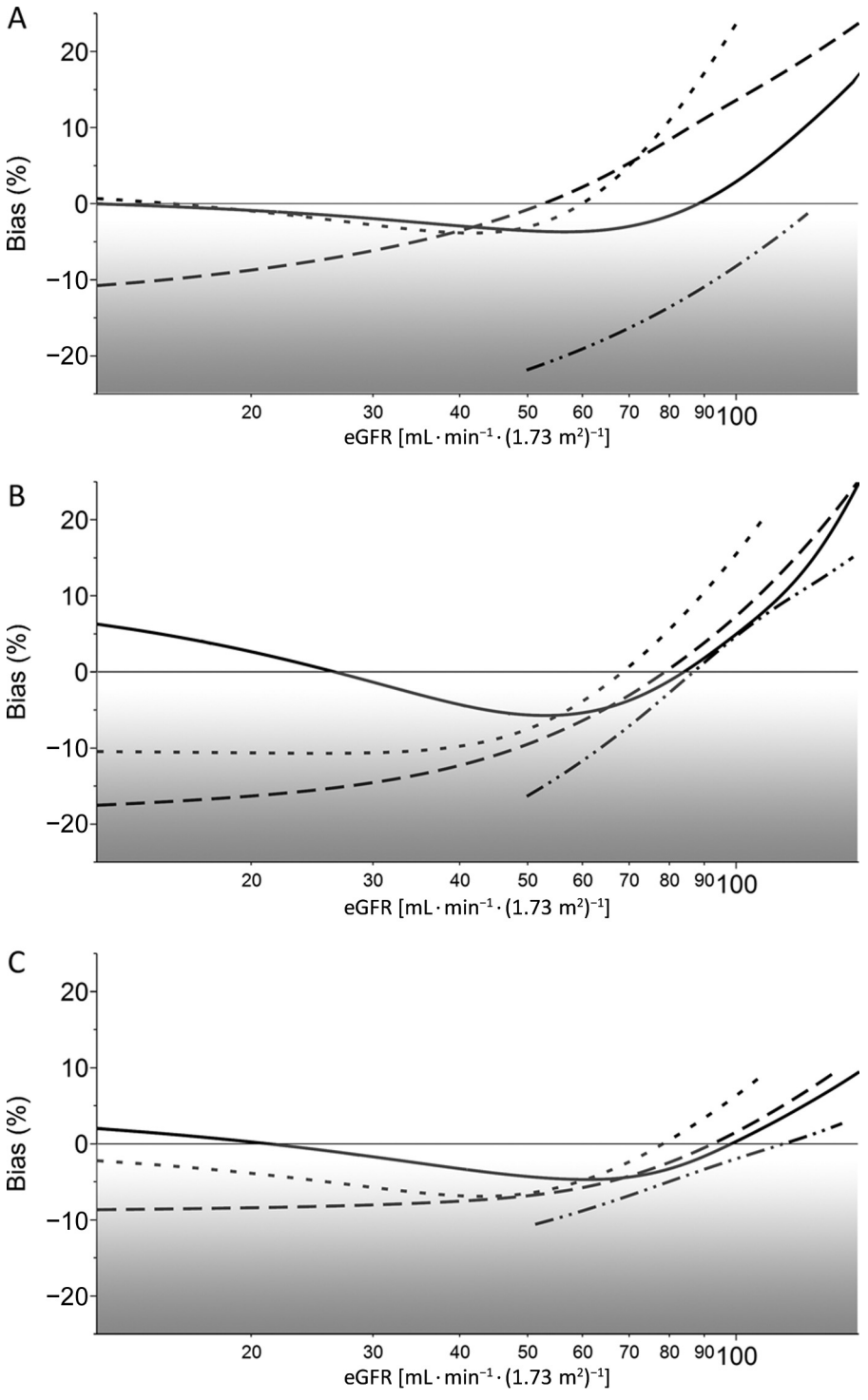

Fig. 2. Equation bias as a function of eGFR.

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

Table 3. Concordance of eGFR with mGFR when classifying patients between all CKD stages or dichotomously as <60 mL · min^{-1} · (1.73 m^2)$^{-1}$.

	All CKD stages		<60 mL · min^{-1} · (1.73 m^2)$^{-1}$	
Patient	Concordance (95% CI)	*P* [b]	Concordance (95% CI)	*P* [b]
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
$eGFR_{Cr\text{-}Cys}$	76.2 (69.4–83.0)	**<0.001**	94.1 (90.3–97.9)	0.45
$eGFR_{Cr}/eGFR_{Cys}$ [c]	56.3 (48.4–64.2)	0.81	94.7 (91.2–98.3)	0.30
$eGFR_{Cr}/eGFR_{Cr\text{-}Cys}$ [c]	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
$eGFR_{Cr\text{-}Cys}$	62.9 (59.1–66.7)	**0.002**	89.7 (87.3–92.1)	0.18
$eGFR_{Cr}/eGFR_{Cys}$ [c]	57.9 (54.0–61.8)	0.19	91.3 (89.1–93.5)	**0.02**
$eGFR_{Cr}/eGFR_{Cr\text{-}Cys}$ [c]	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
$eGFR_{Cr\text{-}Cys}$	58.0 (54.0–62.1)	0.06	79.2 (75.9–82.5)	0.35
$eGFR_{Cr}/eGFR_{Cys}$ [c]	52.1 (48.0–56.2)	0.12	78.5 (75.1–81.9)	0.52
$eGFR_{Cr}/eGFR_{Cr\text{-}Cys}$ [c]	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**
$eGFR_{Cr\text{-}Cys}$	56.8 (51.4–62.2)	**0.01**	86.4 (82.6–90.1)	**0.03**
$eGFR_{Cr}/eGFR_{Cys}$ [c]	50.0 (44.5–55.5)	0.43	86.7 (82.9–90.4)	**0.02**
$eGFR_{Cr}/eGFR_{Cr\text{-}Cys}$ [c]	51.6 (46.1–57.0)	0.23	84.8 (80.9–88.7)	0.11

[a] Bold values indicate statistical significance.
[b] *P* for comparison to $eGFR_{Cr}$.
[c] Patients with $eGFR_{Cr}$ between 45 and 59 mL · min^{-1} · (1.73 m^2)$^{-1}$ reclassified by $eGFR_{Cys}$ or $eGFR_{Cr\text{-}Cys}$ in comparison with $eGFR_{Cr}$.

least 2 (50%) would still have been misclassified as having eGFR >60 mL · min^{-1} · (1.73 m^2)$^{-1}$ 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 had 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 determined by the 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 with creatinine, a potential consideration when additional testing is ordered *(27, 28)*.

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.

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