Calibrating Measured GFR in Evaluating Performance of Estimated GFR Equations: A Simulation

A CKD-EPI Technical Report

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INTRODUCTION

Current guidelines for clinical evaluation of glomerular filtration rate (GFR) recommend estimated GFR (eGFR) using serum creatinine (eGFRcr) as the initial test and eGFR using serum cystatin C with or without creatinine (eGFRcr-cys or eGFRcys, respectively), as appropriate, as a confirmatory test.[1] If greater accuracy is required, measured GFR (mGFR) using exogenous filtration markers is recommended. Clinical laboratories are advised to measure creatinine and cystatin C using assays traceable to international standard reference materials,[2-4] but no such standard exists for mGFR, which has implications for clinical practice, research and public health.

GFR cannot be measured directly in humans. The reference procedure for mGFR, the urinary clearance of inulin during a continuous infusion under standardized conditions, was described by Homer Smith more than 75 years ago,[5] but is rarely performed in clinical practice or research because inulin is not used widely and the urinary clearance method of Smith is impractical. Instead, alternative filtration markers and clearance methods are used in specialized centers worldwide with variable standardization and uncertain traceability to the reference procedure.[6,7] The use of different mGFR procedures in clinical practice leads to systematic variation across centers in results for confirmatory tests for GFR evaluation, with consequent variation in clinical decision making. The use of different mGFR procedures in clinical research as reference tests for development and evaluation of eGFR equations leads to systematic variation in eGFR equations and in their reported accuracy relative to the reference test. The use of different eGFR equations in population studies leads to variation in estimation of public health burden of acute and chronic kidney disease.[8-10] Current guidelines acknowledge regional variation in the accuracy of eGFR equations and recommend using "an equation that has been validated in the population of interest and which has been shown to be most accurate in comparison with mGFR," giving rise to the very likely possibility that the choice of eGFR equation across regions will be affected by the mGFR procedure used to develop and evaluate the eGFR equation.

Previously, in two large, independent study populations from North America and Europe using standardized assays for creatinine and cystatin C, we showed systemically lower eGFR when using the European Kidney Function Consortium (EKFC) and Kidney Recipients Specific (KRS) equations than Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations at higher eGFR.[11,12] In those analyses, we attributed variation in the relative performance of the equations to differences between the equation development populations in non-GFR determinants affecting serum concentrations of creatinine and cystatin C. Others have attributed these differences to differences in modeling

assumptions.[13] We did not consider the mGFR procedure used as the reference test for the development of equations as a source of differences in equation performance. In other publications, we have reviewed sources of error in GFR estimates (**Figure 1**).[7,14] In this technical report, we show the simulated effects of calibration for potential differences in mGFR procedures between the development and evaluation populations on accuracy of GFR estimating equations developed by various research groups.

METHODS

Study Population and Equations

We used the CKD-EPI 2021 validation dataset and the CKD-EPI 2024 solid organ transplantation dataset. Both populations comprise multiple studies (**Table 1**). In the 2021 validation dataset, we evaluated the following equations: for eGFRcr, the CKD-EPI 2021, CKD-EPI 2009 NB, EKFC 2021, and Lund-Malmo 2011 equations; for eGFRcys, the CKD-EPI 2012, CKD-EPI 2023, EKFC 2023, and CAPA 2014 equations; and for eGFRcr-cys, the CKD-EPI 2021 and CKD-EPI 2012 NB equations, and the average of the EKFC 2021 and 2023 equations, and the average of the Lund-Malmo 2011 and CAPA 2014 equations. In the transplant dataset, we evaluated the following eGFRcr equations: the CKD-EPI 2021, CKD-EPI 2009 NB, EKFC 2021 and KRS 2023 equations.

The CKD-EPI equations model eGFR with the use of least-squares linear regression to relate log transformed mGFR to log-transformed filtration markers, age and sex with separate slopes for higher as compared with lower levels of creatinine and cystatin C. CKD-EPI eGFRcr was developed with the same dataset as the 2009 CKD-EPI creatinine equation i.e. 8254 participants in 10 studies. CKD-EPI eGFRcr-cys was developed with the same dataset as CKD-EPI eGFRcys i.e. 5352 participants in 13 studies. Urinary clearance of iothalamate was the GFR measurement method used in all CKD-EPI development datasets.

EKFC equations were developed using assumptions about values for normal GFR and normal Scr or Scys (Q). Normal GFR was assumed to be 107.3 mL/min/1.73m^2. Q for Scr and Scys was assumed to vary according to sex and/or age. Using a development population of 11,251 non-Black participants from 7 studies, linear regression models of mGFR on Scr or Scys on the logarithmic scale were developed. The regressions were modeled as two-slope splines, with a less steep slope at low Scr or Scys levels. The EKFC equation was validated in a separate study population of 8378 participants in 6 studies. Plasma clearance of iohexol was the predominant GFR measurement method in EKFC development datasets.

Lund-Malmo Revised eGFRcr equation was developed using a single cohort of 436 presumed white Swedish participants and validated in another cohort of 414 presumed white Swedish participants. The equation was developed using linear regression, with natural logarithm of mGFR as the dependent variable and separate knots for plasma creatinine for males (180 µmol/L) and females (150 µmol/L) and with gender-specific coefficients for the association between plasma creatinine and mGFR below the plasma creatinine knots. GFR was measured by plasma clearance of iohexol in the study populations. CAPA eGFRcys equations was developed using 2295 randomly chosen Swedish adults, 413 Japanese adults, and 456 Swedish and Dutch children. The equation was internally validated in 1796 participants comprising of 1200 Swedish adults, 350 Japanese adults, and 246 Swedish and Dutch children. The CAPA equation was developed using linear regression model with measured GFR as the dependent variable and 1/Scys as the independent variable. Regression analyses were reweighted to give equal importance to the Swedish and Japanese adult populations. Plasma clearance of iohexol was the predominant GFR measurement used to develop the CAPA equation.

mGFR Calibration

Prior studies that directly compared urinary clearance of iothalamate versus plasma clearance of iohexol consistently report higher clearance with iothalamate compared to iohexol.[6,15,16] One of these studies, which performed concurrent measurement of iothalamate and iohexol in single urine and plasma samples to minimize both experimental and biological errors found that urinary clearance of iohexol was on average 15% less than that of iothalamate across a wide range of GFRs.[15] Another study on the accuracy of GFR measurement methods using urinary inulin clearance as reference noted an overall mean bias for urinary clearance of iohexol versus inulin of -11mL/min/1.73 m^2, with slightly positive mean bias for iothalamate versus inulin of +6 mL/min/1.73 m^2.[6]

For each study, we calibrated each participant mGFR according to the method used in development dataset for each equation and the method used in the study (**Table 1**). Based on prior study findings,[6,15,16] we hypothesized that the urinary/plasma clearance of iothalamate and EDTA may be 5-10% higher than plasma clearance of iohexol. Thus, for equations developed using plasma clearance of iohexol, we decreased each participant mGFR by 5% or 10% if the study mGFR method was urinary/plasma clearance of iothalamate or EDTA. Similarly, for equations developed using urinary clearance of iothalamate or EDTA, we increased each participant mGFR by 5% or 10% if the study mGFR method was plasma clearance of iohexol. We did not change the participant mGFR for equations developed using the same mGFR method as the study mGFR method.

Laboratory methods

As previously described,[8] Scr assays were either calibrated or measured on the Roche enzymatic method (Roche-Hitachi P-Module instrument with Roche Creatininase Plus assay, Hoffman-La Roche, Ltd., Basel, Switzerland), traceable to National Institute Standardized Technology (NIST) creatinine standard reference material 967.[17] Serum cystatin C assays were calibrated or measured using methods traceable to International Federation for Clinical Chemists (IFCC) Working Group for the Standardization of Serum Cystatin C and the Institute for Reference Materials and Measurements (IRMM) certified reference materials ERM-DA471/IFCC.[4]

Metrics for Equation Performance

For each equation, we compared the performance of eGFRcr, eGFRcys and eGFRcr-cys equations using bias, percent bias and P_{30}. Bias was estimated as the median difference between mGFR minus eGFR. Percent bias expresses bias as a percentage of the mGFR and was estimated as the median difference between mGFR minus eGFR, divided by mGFR, and multiplied by 100. P_{30} was defined as the percentage of individuals with estimated GFRs within 30% of mGFR. Plots and box plots were used to display the bias and percent bias and their distributions within the study populations.

RESULTS

Study Populations

The CKD-EPI 2021 validation dataset consists of 4050 adults in 11 studies. 38.4% of participants were female. Mean age and baseline mGFR was 57 years and 76.4 mL/min/m^2, respectively (**Table 2**). Plasma clearance of iohexol was the GFR measurement method used in 9 of the 11 studies (3492 participants, 86%); the other two studies used urinary clearance of EDTA (558 participants, 14%) (**Table 1**). The CKD-EPI 2024 solid organ transplantation dataset consists of 6580 adults in 19 studies. 44% of participants were female. Mean age and baseline mGFR was 51 years and 62 mL/min/1.73m^2, respectively (**Table 2**). Urinary clearance of iothalamate was the method used in 11 studies (4687 participants, 71%), plasma clearance of iohexol in 4 studies (645 participants, 10%), and plasma and/or urinary clearance of EDTA in 4 studies (1248 participants, 19%) (**Table 1**).

Performance of eGFRcr, eGFRcys and eGFRcr-cys in CKD-EPI Validation Dataset

As expected, mGFR calibration causes a uniform shift in the distribution of differences between mGFR and eGFR, but the effect varies among equations by different research groups (**Figures 2-4**). For eGFRcr equations, CKD-EPI 2021 bias and percent bias with no, 5%, and 10% calibration was −3.1, -0.1, and 2.7 mL/min/1.73 m^2, and −4.6, -0.2, and 3.9%, respectively. For CKD-EPI 2009 NB, bias and percent bias with

no, 5%, and 10% calibration was 0.4, 3.3, and 6.3 mL/min/1.73 m², and 0.6, 4.9, and 8.7%, respectively. For EKFC, bias and percent bias with no, 5%, and 10% calibration was 3.5, 3.2, and 2.8 mL/min/1.73 m², and 5.3, 4.8, and 4.3%, respectively. For Lund-Malmo, bias and percent bias with no, 5%, and 10% calibration was 7.0, 6.4, and 6.1 mL/min/1.73 m², and 10.1, 9.6, and 9.1%, respectively (**Table 3**).

For eGFRcys equations, CKD-EPI 2012 bias and percent bias with no, 5%, and 10% calibration was 0.6, 3.6, and 6.7 mL/min/1.73 m², and 0.9, 5.2, and 9.0%, respectively. For CKD-EPI 2023, bias and percent bias with no, 5%, and 10% calibration was 0.9, 3.6, and 6.8 mL/min/1.73 m², and 1.3, 5.4, and 9.1%, respectively. For EKFC, bias and percent bias with no, 5%, and 10% calibration was 1.2, 0.7, and 0.4 mL/min/1.73 m², and 1.6, 1.1, and 0.5%, respectively. For CAPA, bias and percent bias with no, 5%, and 10% calibration was 1.9, 1.5, and 1.3 mL/min/1.73 m², and 3.0, 2.3, and 1.9%, respectively (**Figures 2-4, Table 3**).

For eGFRcr-cys equations, CKD-EPI 2021 bias and percent bias with no, 5%, and 10% calibration was -2.5, 0.0, and 2.9 mL/min/1.73 m², and -4.2, 0.1, and 4.2%, respectively. For CKD-EPI 2012 NB, bias and percent bias with no, 5%, and 10% calibration was -0.1, 2.5, and 5.4 mL/min/1.73 m², and -0.2, 3.8, and 7.7%, respectively. For EKFC, bias and percent bias with no, 5%, and 10% calibration was 2.2, 1.7, and 1.3 mL/min/1.73 m², and 3.3, 2.6, and 2.0%, respectively. For Lund-Malmo-CAPA, bias and percent bias with no, 5%, and 10% calibration was 4.0, 3.6, and 3.2 mL/min/1.73 m², and 6.1, 5.7, and 4.8 %, respectively (**Figures 2-4, Table 3**).

Overall, without calibration and with either 5% and 10% mGFR calibration, P_{30} remained between 85% and 90% for all eGFRcr and eGFRcys equations and exceeded 90% for all eGFRcr-cys equations (**Table 3**).

Performance of eGFRcr in CKD-EPI Solid Organ Transplant Dataset

Again, mGFR calibration causes a uniform shift in the distribution differences between mGFR and eGFR, with variation among equations by different research groups (**Figures 5-7**). For CKD-EPI 2021, bias and percent bias with no, 5%, and 10% calibration was -1.6, -1.3, and -1.1 mL/min/1.73 m², and -3.0, -2.6, and -2.2%, respectively. For CKD-EPI 2009 NB, bias and percent bias with no, 5%, and 10% calibration was 1.0, 1.2, and 1.4 mL/min/1.73 m², and 2.0, 2.5, and 2.9%, respectively. For EKFC, bias and percent bias with no, 5%, and 10% calibration was 1.8, 1.4, and 0.8 mL/min/1.73 m², 3.6, 2.5, and 1.7%, respectively. For KRS, bias and percent bias with no, 5%, and 10% calibration was 1.6, 1.1, and 0.5mL/min/1.73 m², and 3.1, 2.2, and 1.1%, respectively. (**Figures 5-7, Table 4)**.

Overall, without calibration and with either 5% or 10% mGFR, P_{30} for all equations was similar at approximately 80% (**Table 4**).

DISCUSSION

Our study examines the hypothetical impact of plausible differences of 5% and 10% in calibration of measured GFR procedures between the equation development and evaluation populations on the performance of commonly used eGFRcr, eGFRcys, and eGFRcr-cys equations. We demonstrated consistent variation in bias in eGFRcr, eGFRcys, and eGFRcr-cys within equations developed by each research group, but differing magnitude of variation in eGFR across equations developed by different research groups. The magnitude of variation (up to 7 ml/min/1.73 m^2 or 10.2%) is large enough to have important implications on clinical practice, research and public health. Despite variation in bias, P_{30} remained relatively stable across non-calibrated and calibrated analyses; within the 85–90% range for eGFRcr and eGFRcys equations, and greater than 90% for eGFRcr-cys equations.

Calibration of mGFR uniformly shifts the distribution of differences between mGFR and eGFR, thus affecting bias of eGFR using all filtration markers. As a result, consistent variation in bias in eGFRcr, eGFRcys and eGFRcr-cys is to be expected within equations developed by each research group. However, differences in variation in bias of eGFRs across research groups reflect differences in mGFR procedures used in the development population compared to the validation population. For example, in the CKD-EPI validation dataset, in which most studies used iohexol rather than iothalamate clearance (86% vs 14%), bias for eGFR varied more for CKD-EPI equations, which were developed using iothalamate clearance, than for EKFC and LMR equations, which were developed using primarily iohexol clearance. By contrast, in the CKD-EPI solid organ transplant dataset, in which more studies used iothalamate (71%) or EDTA (19%) than iohexol (10%) clearance, bias in eGFR varied more for EKFC and KRS equations than for CKD-EPI equations. Because calibration shifts outliers with positive vs. negative bias in the same direction, the variation on P30 is minimized, highlighting that commonly used accuracy metrics may not fully capture this source of clinically relevant systematic error.

These findings build on prior work demonstrating regional and population-specific differences in eGFR equation performance by showing that heterogeneity in reference mGFR methods also contributes to systematic variation across equations by different research groups (**Figure 1**). As discussed earlier, previous studies comparing plasma clearance of iohexol with urinary clearance of iothalamate or EDTA have reported differences of 5–10%,[6,15,16] justifying the calibration simulations applied in this analysis. By evaluating these reported differences using a structured analytic framework, our study provides

quantitative evidence that method-specific variation in mGFR measurement can translate into apparent differences in eGFR equation bias.

From a clinical perspective, our findings reinforce the importance of cautious interpretation of differences in bias when comparing eGFR equations, particularly when those equations were developed using different mGFR reference standards. Apparent superiority of one equation over another in a given dataset may, in some cases, reflect closer alignment of mGFR methods rather than true differences in equation performance. This is especially relevant when eGFR is used for confirmatory testing, for example, for drug dosing or transplant donor or recipient evaluation, where systematic over- or underestimation of GFR may influence decision-making.

For research and public health, the results underscore the need for greater transparency and, where possible, harmonization of mGFR procedures.[7,18] Lack of a universally accepted reference standard for mGFR complicates the comparison and synthesis of studies evaluating GFR. Our findings suggest that calibration adjustments, even when hypothetical, can materially change conclusions about bias and performance of equations, which may in turn affect estimates of chronic kidney disease prevalence and burden across populations.

This study has several limitations. First, the calibration scenarios applied were hypothetical and based on ranges reported in prior comparative studies of mGFR methods; actual differences between specific laboratories and protocols may vary. Second, our analyses were limited to datasets in North America and Europe. Bias in eGFRcr appears larger in Asia and Africa than in North America and Europe, in part due to non-GFR determinants of serum creatinine;[19,20] variation in bias due to mGFR differences in these regions may have larger effects than in observed in our simulations.

Future research should focus on direct comparisons of mGFR methods using standardized protocols and traceable reference materials to more clearly define methodological differences. Consideration of mGFR method harmonization in the development and validation of new eGFR equations could improve comparability across regions and populations. In addition, reporting standards for eGFR validation studies should explicitly document mGFR reference methods and consider sensitivity analyses to assess the impact of plausible calibration differences.

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TABLES AND FIGURES

Table 1. GFR Estimating Equation, mGFR Method, and Calibration Method

Studies in CKD-EPI 2021 validation and 2024 solid organ transplant datasets	mGFR measurement method of study	Calibration for CKD-EPI equations	Calibration for EKFC equations	Calibration for Lund Malmö and CAPA equations	Calibration for KRS equations
RASS*†	plasma clearance of iohexol	5 or 10% increase in mGFR	No change to mGFR	No change to mGFR	5 or 10% increase in mGFR
AGES*	plasma clearance of iohexol	5 or 10% increase in mGFR	No change to mGFR	No change to mGFR	5 or 10% increase in mGFR
STENO *†	plasma clearance of ^{51}CrEDTA	No change to mGFR	5 or 10 % decrease in mGFR	5 or 10 % decrease in mGFR	No change to mGFR
UMN DONOR*	plasma clearance of iohexol	5 or 10% increase in mGFR	No change to mGFR	No change to mGFR	5 or 10% increase in mGFR
Lund*†	plasma clearance of iohexol	5 or 10% increase in mGFR	No change to mGFR	No change to mGFR	5 or 10% increase in mGFR
Lund Donor*†	plasma clearance of iohexol	5 or 10% increase in mGFR	No change to mGFR	No change to mGFR	5 or 10% increase in mGFR
HIV*	plasma clearance of iohexol	5 or 10% increase in mGFR	No change to mGFR	No change to mGFR	5 or 10% increase in mGFR
MACS*	plasma clearance of iohexol	5 or 10% increase in mGFR	No change to mGFR	No change to mGFR	5 or 10% increase in mGFR
PERL*	plasma clearance of iohexol	5 or 10% increase in mGFR	No change to mGFR	No change to mGFR	5 or 10% increase in mGFR
MESA*	plasma clearance of iohexol	5 or 10% increase in mGFR	No change to mGFR	No change to mGFR	5 or 10% increase in mGFR
ALTOLD*	plasma clearance of iohexol	5 or 10% increase in mGFR	No change to mGFR	No change to mGFR	5 or 10% increase in mGFR
NephroTest*†	plasma and urinary clearance of ^{51}CrEDTA	No change to mGFR	5 or 10 % decrease in mGFR	5 or 10 % decrease in mGFR	No change to mGFR
Nephrotest Donor†	plasma and urinary clearance of ^{51}CrEDTA	No change to mGFR	5 or 10 % decrease in mGFR	5 or 10 % decrease in mGFR	No change to mGFR
Baylor†	urinary clearance of iothalamate	No change to mGFR	5 or 10 % decrease in mGFR	5 or 10 % decrease in mGFR	No change to mGFR
CCFP†	urinary clearance of iothalamate	No change to mGFR	5 or 10 % decrease in mGFR	5 or 10 % decrease in mGFR	No change to mGFR
CCFP Donor†	urinary clearance of iothalamate	No change to mGFR	5 or 10 % decrease in mGFR	5 or 10 % decrease in mGFR	No change to mGFR
CRIC†	urinary clearance of iothalamate	No change to mGFR	5 or 10 % decrease in mGFR	5 or 10 % decrease in mGFR	No change to mGFR
CRISP†	urinary clearance of iothalamate	No change to mGFR	5 or 10 % decrease in mGFR	5 or 10 % decrease in mGFR	No change to mGFR
DNA†	urinary clearance of iothalamate	No change to mGFR	5 or 10 % decrease in mGFR	5 or 10 % decrease in mGFR	No change to mGFR
DNA Donor†	urinary clearance of iothalamate	No change to mGFR	5 or 10 % decrease in mGFR	5 or 10 % decrease in mGFR	No change to mGFR
Groningen†	urinary clearance of iothalamate	No change to mGFR	5 or 10 % decrease in mGFR	5 or 10 % decrease in mGFR	No change to mGFR

Groningen Donor†	urinary clearance of iothalamate	No change to mGFR	5 or 10 % decrease in mGFR	5 or 10 % decrease in mGFR	No change to mGFR
Groningen Transplant†	urinary clearance of iothalamate	No change to mGFR	5 or 10 % decrease in mGFR	5 or 10 % decrease in mGFR	No change to mGFR
Interdiabetes†	plasma clearance of iohexol	5 or 10% increase in mGFR	No change to mGFR	No change to MGFR	5 or 10% increase in mGFR
Mayo Transplant†	urinary clearance of iothalamate	No change to mGFR	5 or 10 % decrease in mGFR	5 or 10 % decrease in mGFR	No change to mGFR
Froissart Transplant†	urinary clearance of ^{51}CrEDTA	No change to mGFR	5 or 10 % decrease in mGFR	5 or 10 % decrease in mGFR	No change to mGFR

*studies included in the CKD-EPI 2021 validation population.

†studies included in the CKD-EPI 2024 solid organ transplant population.

The CKD-EPI equations were developed in datasets that used urinary clearance of iothalamate as the mGFR measurement method. The EKFC, Lund Malmo and CAPA equations were developed in datasets that used plasma clearance of iohexol as the mGFR measurement method. The KRS equation was developed in datasets that use ^{51}Cr EDTA, ^{99}Tc DTPA and Inulin clearance. This table shows how we calibrated for differences between the mGFR assessment methods in the validation dataset when estimating mGFR.

Table 2. Characteristics of Study Populations

Demographic and clinical characteristics	CKD-EPI 2021 Validation	CKD-EPI 2024 Solid Organ Transplant
N of participants	4050	6580
Age, years	57.0 (17.4)	51.3 (14.3)
<40	715 (17.7)	1491 (22.7%)
40-65	1989 (49.1%)	3971 (60.4%)
>65	1346 (33.2%)	1118 (17.0%)
Sex		
Female	1557 (38.4%)	2898 (44.0%)
Male	2493 (61.6%)	3682 (56.0%)
Race		
Black	579 (14.3%)	427 (6.5%)
Non-Black	3471 (85.7%)	6153 (93.5%)
BMI, kg/m^2	26.9 (5.0)	27.5 (5.8)
Diabetes, %	1357 (34.8%)	1564 (24.9%)
mGFR, mL/min/1.73m^2	76.4 (29.6)	62.1 (31.2)
<30	254 (6.3%)	905 (13.8%)
30-<45	348 (8.6%)	1256 (19.1%)
45-<60	548 (13.5%)	1414 (21.5%)
60-<90	1601 (39.5%)	1745 (26.5%)
90-<120	986 (24.4%)	903 (13.7%)
≥120	313 (7.7%)	357 (5.4%)
Serum creatinine, mg/dL	1.16 (0.70)	1.47 (0.82)
Serum cystatin C, mg/L	1.18 (0.55)	

Table 3. Performance of eGFR Equations Compared to Measured GFR in the CKD-EPI 2021 Validation Dataset Accounting for Calibration in GFR Measurement Methods

Equation	Calibration	Bias (95% CI)	Percent Bias (95% CI)	P_{30} (95% CI)
eGFRcr				
CKD-EPI 2021	Non-calibrated	-3.1 (-3.5, -2.6)	-4.6 (-5.4, -3.9)	86.6 (85.5, 87.6)
	Calibrated by 5%	-0.1 (-0.5, 0.2)	-0.2 (-0.8, 0.4)	88.5 (87.5, 89.5)
	Calibrated by 10%	2.7 (2.2, 3.2)	3.9 (3.2, 4.5)	89.2 (88.3, 90.1)
CKD-EPI 2009 NB	Non-calibrated	0.4 (0.0, 0.8)	0.6 (0.0, 1.2)	89.0 (88.0, 90.0)
	Calibrated by 5%	3.3 (2.9, 3.7)	4.9 (4.3, 5.4)	89.7 (88.7, 90.6)
	Calibrated by 10%	6.3 (5.8, 6.9)	8.7 (8.1, 9.3)	87.8 (86.8, 88.8)
EKFC 2021	Non-calibrated	3.5 (3.1, 3.9)	5.3 (4.6, 6.0)	90.6 (89.7, 91.5)
	Calibrated by 5%	3.2 (2.8, 3.6)	4.8 (4.2, 5.5)	90.4 (89.5, 91.3)
	Calibrated by 10%	2.8 (2.4, 3.3)	4.3 (3.6, 4.8)	89.9 (88.9, 90.8)
Lund-Malmo 2014	Non-calibrated	7.0 (6.4, 7.4)	10.2 (9.5, 10.6)	88.3 (87.3, 89.2)
	Calibrated by 5%	6.4 (5.9, 7.0)	9.6 (9.1, 10.2)	88.7 (87.7, 89.7)
	Calibrated by 10%	6.1 (5.6, 6.5)	9.1 (8.5, 9.6)	88.5 (87.6, 89.6)
eGFRcys				
CKD-EPI 2012	Non-calibrated	0.6 (0.1, 1.1)	0.9 (0.1, 1.6)	88.2 (87.2, 89.2)
	Calibrated by 5%	3.6 (3.1, 4.2)	5.2 (4.5, 5.8)	87.6 (86.5, 88.5)
	Calibrated by 10%	6.7 (6.1, 7.2)	9.0 (8.3, 9.6)	85.9 (84.9, 87.0)
CKD-EPI 2023	Non-calibrated	0.9 (0.3, 1.3)	1.3 (0.5, 1.9)	86.3 (85.3, 87.4)
	Calibrated by 5%	3.6 (3.2, 4.1)	5.4 (4.7, 6.2)	86.4 (85.4, 87.5)
	Calibrated by 10%	6.8 (6.2, 7.3)	9.1 (8.5, 9.9)	85.2 (84.1, 86.3)
EKFC 2023	Non-calibrated	1.2 (0.6, 1.6)	1.6 (0.8, 2.3)	88.2 (87.2, 89.2)
	Calibrated by 5%	0.7 (0.2, 1.2)	1.1 (0.3, 1.7)	87.4 (86.4, 88.5)
	Calibrated by 10%	0.4 (-0.1, 0.8)	0.5 (-0.1, 1.1)	86.8 (85.8, 87.9)
CAPA 2012	Non-calibrated	1.9 (1.5, 2.4)	3.0 (2.3, 3.7)	86.7 (85.7, 87.8)
	Calibrated by 5%	1.5 (1.2, 2.0)	2.3 (1.8, 3.1)	86.3 (85.3, 87.4)
	Calibrated by 10%	1.3 (0.7, 1.7)	1.9 (1.2, 2.5)	85.7 (84.5, 86.8)
eGFRcr-cys				
CKD-EPI 2021	Non-calibrated	-2.5 (-2.9, -2.1)	-4.2 (-4.7, -3.4)	90.8 (89.9, 91.6)
	Calibrated by 5%	0.0 (-0.3, 0.4)	0.1 (-0.4, 0.6)	92.5 (91.7, 93.4)
	Calibrated by 10%	2.9 (2.5, 3.3)	4.2 (3.6, 4.7)	92.6 (91.8, 93.4)
CKD-EPI 2012 NB	Non-calibrated	-0.1 (-0.5, 0.2)	-0.2 (-0.9, 0.3)	92.2 (91.4, 93.0)
	Calibrated by 5%	2.5 (2.1, 2.9)	3.8 (3.3, 4.3)	92.9 (92.1, 93.7)
	Calibrated by 10%	5.4 (5.0, 5.8)	7.7 (7.2, 8.2)	91.8 (90.9, 92.6)
EKFC 2021/ EKFC 2023	Non-calibrated	2.2 (1.8, 2.6)	3.3 (2.6, 3.9)	93.1 (92.3, 93.9)
	Calibrated by 5%	1.7 (1.2, 2.2)	2.6 (2.0, 3.2)	92.4 (91.6, 93.2)
	Calibrated by 10%	1.3 (1.0, 1.8)	2.0 (1.4, 2.6)	91.4 (90.5, 92.3)
Lund-Malmo 2014/CAPA 2012	Non-calibrated	4.0 (3.6, 4.4)	6.1 (5.6, 6.7)	92.8 (91.9, 93.6)
	Calibrated by 5%	3.6 (3.3, 4.0)	5.7 (5.0, 6.2)	92.6 (91.8, 93.4)
	Calibrated by 10%	3.2 (2.9, 3.6)	4.8 (4.3, 5.6)	92.2 (91.3, 93.0)

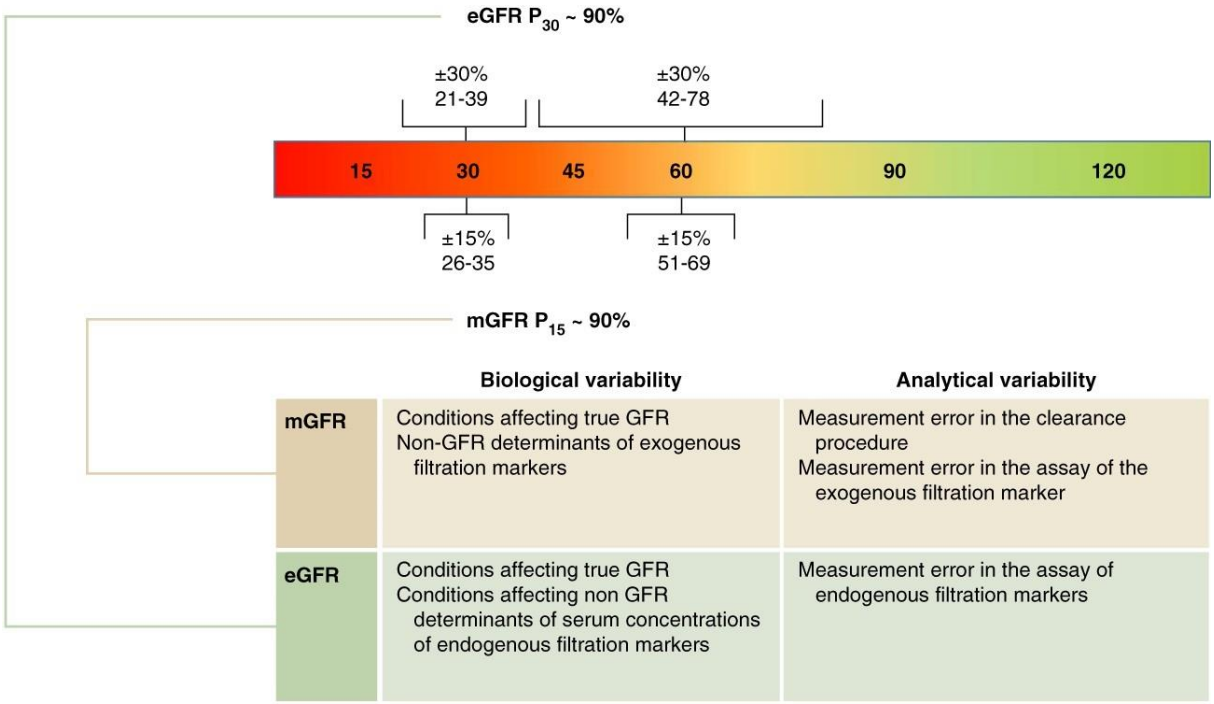
Non-calibrated means data is not calibrated for difference in GFR measurement method. Calibrated by 5%, data is calibrated for differences in GFR measurement method using a calibration factor of 5%. Calibrated by 10%, data is calibrated for differences in GFR measurement method using a calibration factor of 10%. Bias was estimated as the median difference between mGFR and eGFR. Percent bias was estimated as the median difference between mGFR and eGFR, divided by mGFR, and multiplied by 100. P_{30} was defined as the percentage of individuals with estimated GFRs within 30% of measured GFR. Units for Bias is mL/min/1.73m^2, and for Percent Bias and P_{30} are percent (%). A positive value for bias indicates eGFR underestimates mGFR, and a negative value indicates eGFR overestimates mGFR. Bias closer to zero is optimal. Abbreviations: NB, non-Black

Table 4. Performance of eGFR Equations Compared to Measured GFR in the CKD-EPI 2024 Solid Organ Transplant Dataset Accounting for Calibration in GFR Measurement Methods

Equation	Calibration	Bias (95% CI)	Percent Bias (95% CI)	P_{30} (95% CI)
eGFRcr				
CKD-EPI 2021	Non-calibrated	-1.6 (-2.0, -1.3)	-3.0 (-3.8, -2.4)	79.8 (78.9, 80.7)
	Calibrated by 5%	-1.3 (-1.7, -1.0)	-2.6 (-3.3, -2.0)	79.9 (78.9, 80.8)
	Calibrated by 10%	-1.1 (-1.5, -0.8)	-2.2 (-2.8, -1.5)	79.5 (78.5, 80.4)
CKD-EPI 2009 NB	Non-calibrated	1.0 (0.6, 1.3)	2.0 (1.2, 2.6)	81.8 (80.8, 82.7)
	Calibrated by 5%	1.2 (0.9, 1.5)	2.5 (1.8, 3.1)	81.5 (80.5, 82.4)
	Calibrated by 10%	1.4 (1.0, 1.7)	2.9 (2.1, 3.6)	80.9 (79.9, 81.9)
EKFC 2021	Non-calibrated	1.8 (1.4, 2.2)	3.6 (2.9, 4.2)	81.8 (80.8, 82.7)
	Calibrated by 5%	1.4 (1.0, 1.6)	2.5 (2.0, 3.2)	81.9 (80.9, 82.8)
	Calibrated by 10%	0.8 (0.4, 1.1)	1.7 (0.8, 2.2)	81.4 (80.4, 82.3)
KRS 2023	Non-calibrated	1.6 (1.1, 2.0)	3.1 (2.2, 3.8)	78.7 (77.7, 79.7)
	Calibrated by 5%	1.1 (0.7, 1.5)	2.2 (1.3, 2.9)	78.6 (77.6, 79.6)
	Calibrated by 10%	0.5 (0.2, 1.0)	1.1 (0.4, 1.8)	78.3 (77.3, 79.3)

Non-calibrated means data is not calibrated for difference in GFR measurement method. Calibrated by 5% data is calibrated for differences in GFR measurement method using a calibration factor of 5%. Calibrated by 10% data is calibrated for differences in GFR measurement method using a calibration factor of 10%. Bias was estimated as the median difference between mGFR and eGFR. Percent bias was estimated as the median difference between mGFR and eGFR, divided by mGFR, and multiplied by 100. P_{30} was defined as the percentage of individuals with estimated GFRs within 30% of measured GFR. Units for Bias is mL/min/1.73m^2, and for Percent Bias and P_{30} are percent (%).

Figure 1. Sources of Error in Measured and Estimated GFR



	Biological variability	Analytical variability
mGFR	Conditions affecting true GFR Non-GFR determinants of exogenous filtration markers	Measurement error in the clearance procedure Measurement error in the assay of the exogenous filtration marker
eGFR	Conditions affecting true GFR Conditions affecting non GFR determinants of serum concentrations of endogenous filtration markers	Measurement error in the assay of endogenous filtration markers

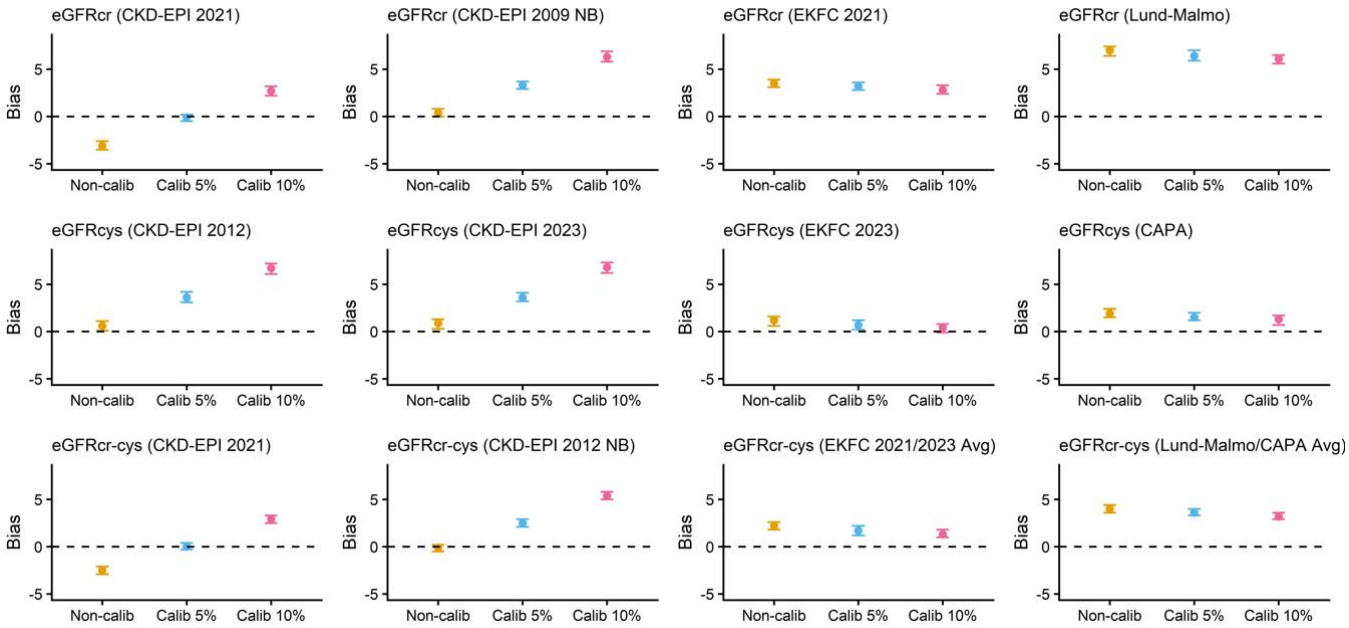
True GFR, non-GFR determinants of filtration markers, mGFR procedures and eGFR equations are associated with biological and analytical variability, which leads to differences in mGFR and eGFR from "true GFR." True GFR is the parameter of interest and could be defined as the average value of reference mGFR over several days. Biologic variability in true GFR is due to surfeit or deficit of extracellular fluid, pregnancy, hyperglycemia, use of antihypertensive agents, dietary protein intake, exercise, time of day, and acute and chronic kidney disease. Filtration markers are affected by non-GFR determinants, in addition to true GFR, including generation, tubular handling, and extraurinary elimination, which may vary across populations and disease states. mGFR is associated with biological variability in true GFR and analytical variation due to the effect of non-GFR determinants of the exogenous filtration markers and measurement error in the clearance procedures or assays. eGFR is associated with biological variability in the plasma concentration of the endogenous filtration marker from variability in true GFR and conditions affecting the non-GFR determinants of the marker. For each filtration marker, eGFR is associated with analytical variation in methods for equation development and assays. Biological conditions and analytical factors can vary over time, leading to time-to-time variability in both mGFR and eGFR. If measurement error is minimized, time-to-time variability reflects biological variability.

P30 for eGFR refers to the percent of eGFRs that are within 30% of mGFR.5, If accuracy within 30% is acceptable (P30 >75-80%) or optimal (P30 >90%), eGFR may be sufficient, provided that there are not large deviations in non-GFR determinants of endogenous filtration markers. If greater accuracy is needed, mGFR is advised. The accuracy for mGFR is based on time-to-time variability. P15 for mGFR refers to the percent of one mGFR that was within 15% of the second.6 At a GFR of 60 ml/min per 1.73 m^2, 30% accuracy for eGFR corresponds to 42 to 78 ml/min per 1.73 m^2 and 15% accuracy for mGFR corresponds to 51 to 69 ml/min per 1.73 m^2. At a GFR of 30 ml/min per 1.73 m^2, 30% accuracy for eGFR corresponds to 21 to 39 ml/min per 1.73 m2 and 15% accuracy for mGFR corresponds to 26 to 35 ml/min per 1.73 m^2.

From: Reprinted from Levey, A. S., Ramesh, S, Inker, L. A. Glomerular Filtration Markers: Current and Emerging Insights. CJASN ():10.2215/CJN.0000001090, April 17, 2026.

Figure 2. Plots of Bias and Percent Bias By Calibration Method in CKD-EPI 2021 Validation Dataset

A. Bias plots



B. Percent bias plots

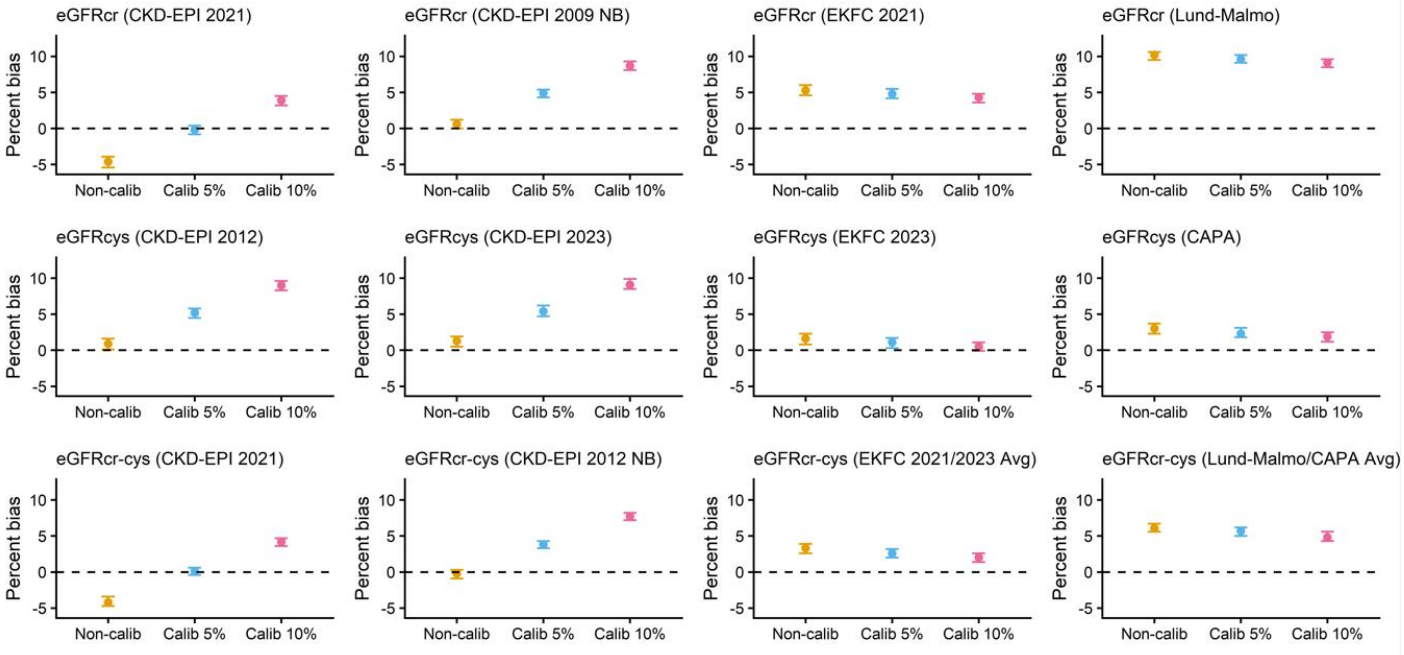


Figure 3. Box Plots of Distribution of Bias By Calibration Method in CKD-EPI 2021 Validation Dataset

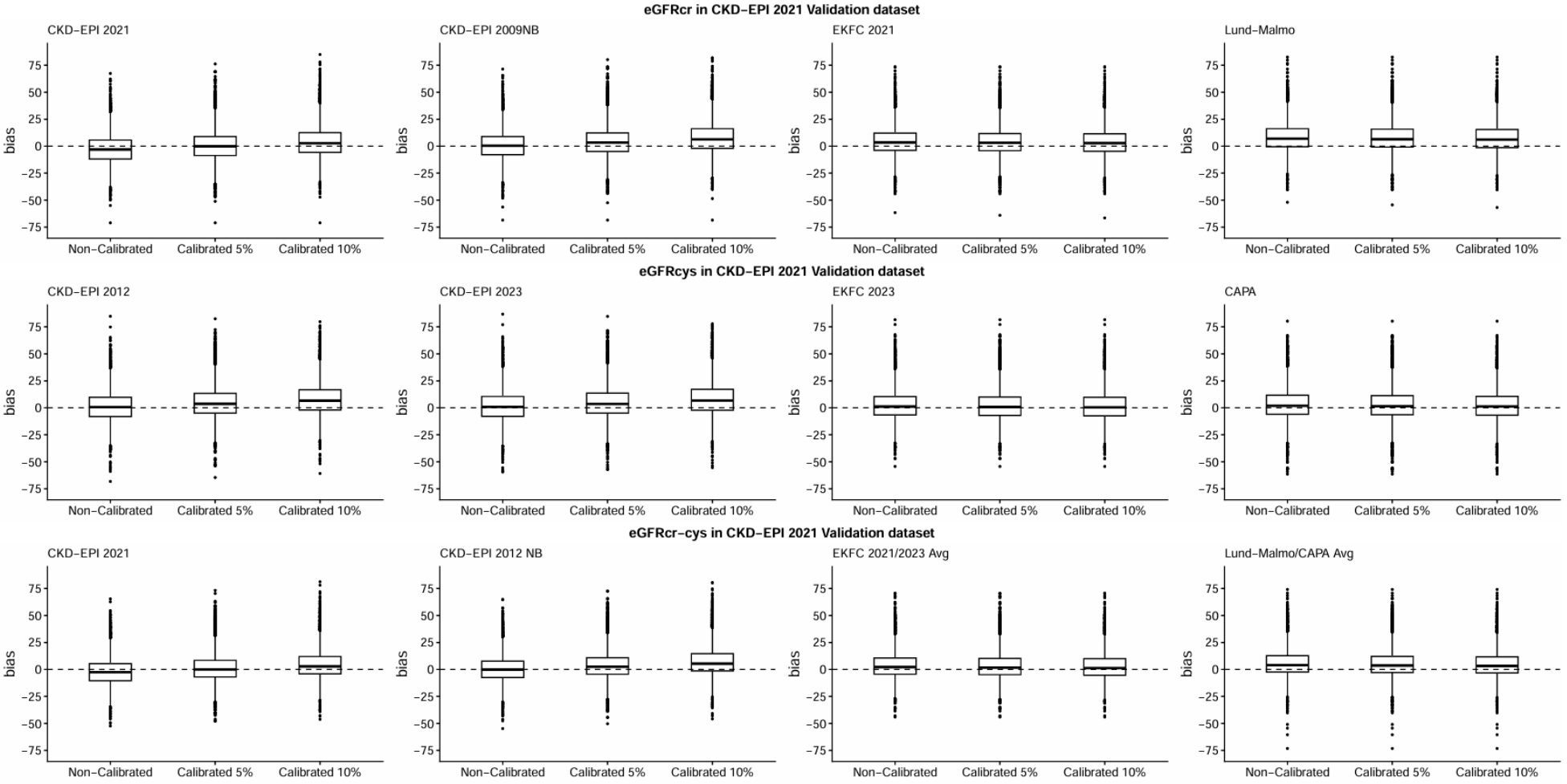


Figure 4. Box Plots of Distribution of Percent Bias By Calibration Method in CKD-EPI 2021 Validation Dataset

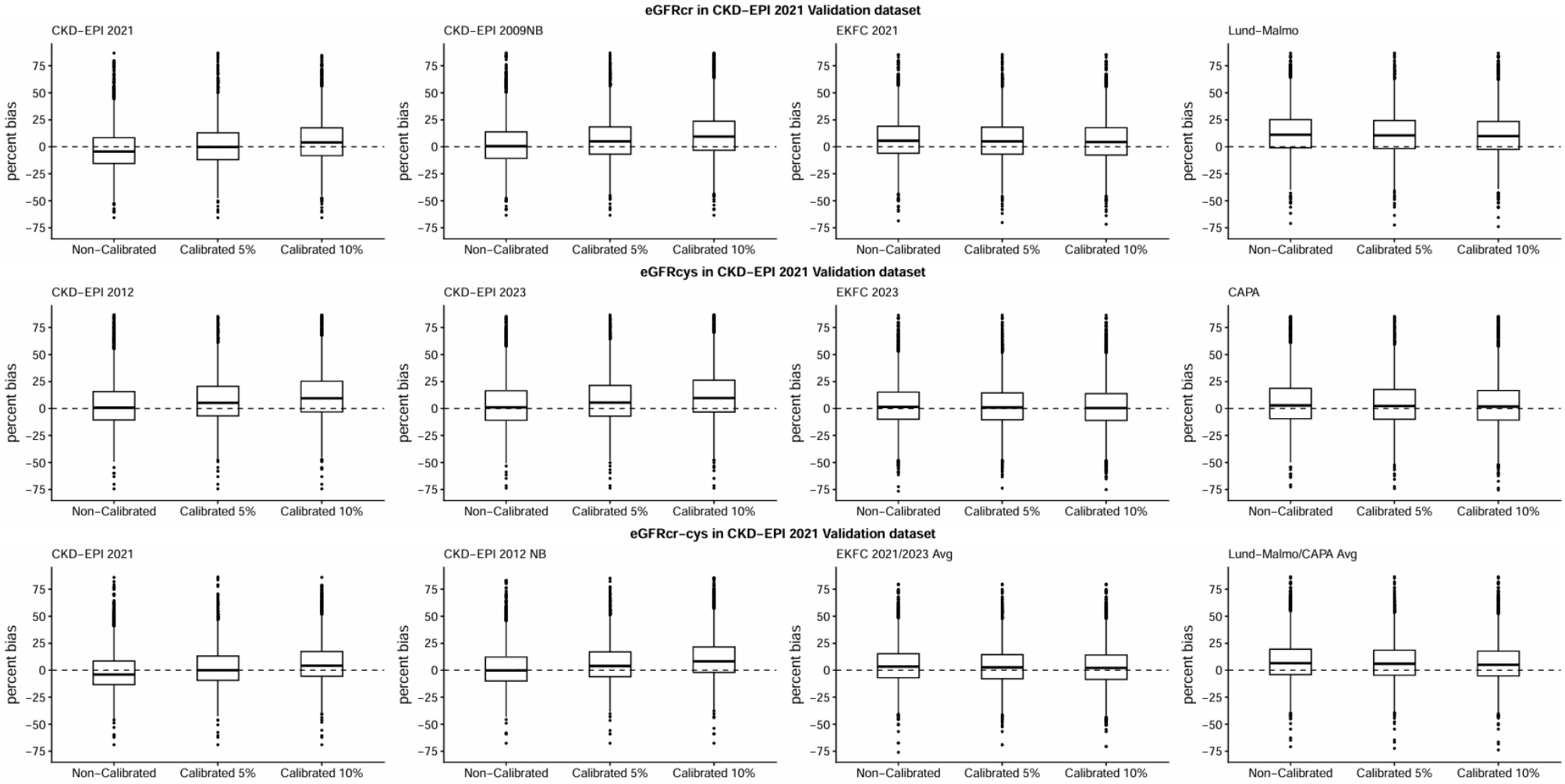
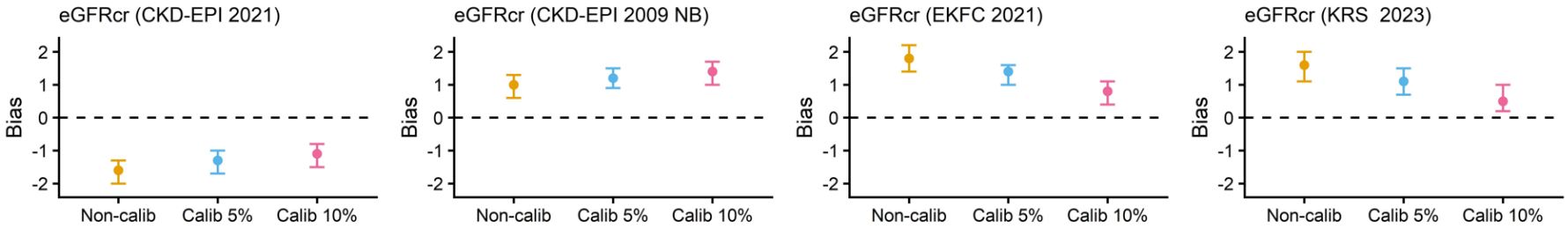


Figure 5. Plots of Bias and Percent Bias By Calibration Method In CKD-EPI 2024 Solid Organ Transplant Dataset

A. Bias plots



B. Percent bias plots

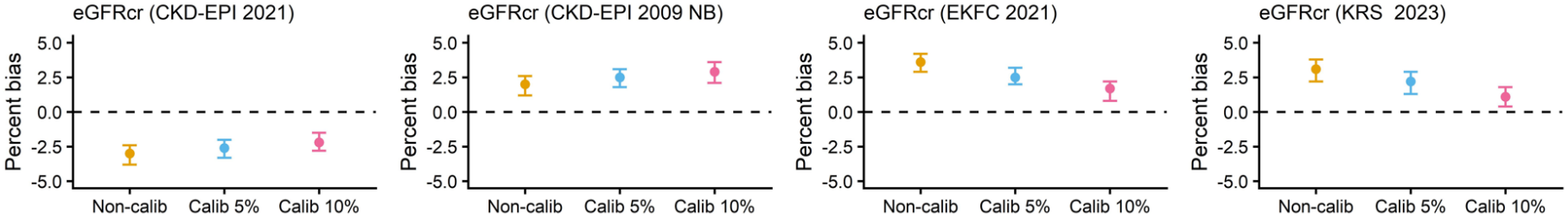


Figure 6. Box Plots of Distribution of Bias By Calibration Method in CKD-EPI 2024 Solid Organ Transplant Dataset

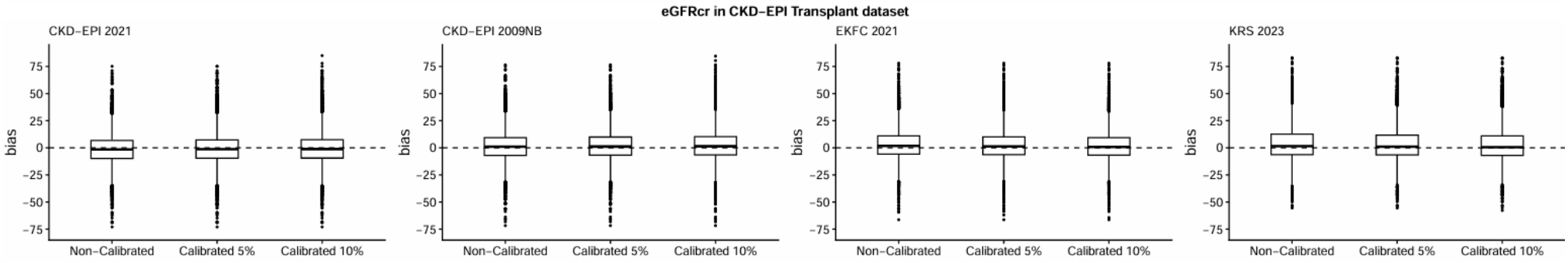


Figure 7. Box Plots of Distribution of Percent Bias By Calibration Method in CKD-EPI 2024 Solid Organ Transplant Dataset