Cystatin C based equation to estimate GFR without the inclusion of race and sex

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Abstract

Background. How best to estimate kidney function from routine metabolic tests, such as serum creatinine (SCr), has been controversial. The creatinine-based European Kidney Function Consortium (EKFC-eGFR$_{Cr}$)-equation describes the relation between glomerular filtration rate (GFR) and rescaled SCr (SCr is divided by the median SCr among healthy persons such that variation in SCr-levels related to age, sex, or race differences are controlled for). In the present study the new EKFC-equation is applied to serum cystatin C (CysC), by replacing rescaled SCr with a rescaled CysC.

Methods. Individual patient data from Sweden (n=227,643) were used to estimate the rescaling factor for CysC in adults. Rescaled SCr was replaced by rescaled CysC in the EKFC-equation (EKFC-eGFR$_{Cys}$) which was then validated in White and Black cohorts from Europe (n=11,231), North America (n=1,093) and Africa (n=508), with measured GFR, SCr, CysC, age, and sex.

Results. The rescaling factor for CysC was estimated at 0.83 for adult men and women until age 50 years, and 0.83+0.005x(Age–50) thereafter. EKFC-eGFR$_{Cys}$ was unbiased, showed accuracy similar to EKFC-eGFR$_{Cr}$ in both White and Black people, and was more accurate than the KDIGO recommended equation CKD-EPI-eGFR$_{Cys}$. The arithmetic mean of EKFC-eGFR$_{Cr}$ and EKFC-eGFR$_{Cys}$ further improved the accuracy of estimating GFR over either biomarker equation alone.

Conclusion. In cohorts from Europe, North America, and Africa, an EKFC-eGFR$_{Cys}$-equation had the same mathematical form as the EKFC-eGFR$_{Cr}$, but with a different scaling factor for CysC that did not differ by race or sex, and improved the accuracy of GFR assessment over commonly used equations.

The glomerular filtration rate (GFR) is used to diagnose patients with chronic kidney disease (CKD) (defined as a GFR <60 ml/min/1.73m^2), and if CKD is present, to determine if it is severe enough (<20 ml/min/1.73m^2) to consider preparation for transplantation (being added to a deceased donor waitlist or pursuing living donor transplantation) or dialysis (e.g., placement of arteriovenous fistula to mature for eventual chronic hemodialysis). The GFR is also widely used to adjust the dose of numerous medications that are cleared primarily by the kidneys. Thus, an accurate and precise estimation of GFR (or eGFR) is considered of paramount importance in the evaluation and management of kidney health in patients.[1] With the current widespread and frequent use of the estimated GFR (eGFR), it is impractical to directly measure GFR using an expensive, labor-intensive, gold-standard method with an exogenous marker (e.g., iothalamate or iohexol). Instead, eGFR is commonly determined by equations based on simultaneous serum creatinine (SCr) or cystatin C (CysC) measurement. The recommended equations for estimating GFR in adults by the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines are the creatinine-based CKD-EPI-eGFR$_{Cr}$ and cystatin C-based CKD-EPI-eGFR$_{Cys}$ Chronic Kidney Disease Epidemiology Collaboration equations.[2,3] The CKD-EPI consortium recently developed a new CKD-EPI-eGFR$_{Cr}$-equation without the use of race in 2021, but still requires a sex variable to account for differences between men and women.[4]

The European Kidney Function Consortium has developed an alternative approach to estimating GFR from SCr (EKFC-eGFR$_{Cr}$-equation).[5] That approach adjusts - or rescales - SCr values such that the average healthy person regardless of age, sex, or race has a rescaled serum creatinine (SCr/Q) of '1'. Such an adjustment is accomplished through the determination of a rescaling "Q-value" factor based on the median SCr value in relatively healthy populations across the age spectrum (including both children and adults), sex, and race.[5] After dividing SCr by the derived rescaling factor, the patient's rescaled SCr-value represents the proportional increase in SCr (if >1) relative to the average value in healthy persons of the

same age, sex, and race. However, determining accurate rescaling factors for SCr across the diverse spectrum of human populations presents several challenges.[6]

Alternatively, CysC is a biomarker for estimating glomerular filtration rate that has less non-GFR variation related to age, sex and race than does SCr.[7] We propose the use of CysC in the same EKFC-equation used for SCr by simply replacing the rescaled SCr with a rescaled CysC. We posit that a rescaled CysC may be simpler and would require fewer rescaling factors across the spectrum of age, sex, and race compared to SCr. We also aim to demonstrate that further accuracy can be achieved by using the average of a SCr and a CysC based equation to estimate GFR.[8–12]

In the present study, we hypothesized that in the existing EKFC-$eGFR_{Cr}$ equation, rescaled SCr could be replaced with rescaled CysCand that rescaling of CysC can be accomplished without requiring race- or sex-specific rescaling factors.

Methods

This study was a cross-sectional analysis of patient data from multiple centers in Europe, USA and Africa where simultaneous assessments of standardized SCr, standardized CysC, measured GFR (mGFR), demographic (age, sex, race), and anthropomorphic characteristics (height and weight) were available. An overview of the source datasets are presented in Tables S1 and S2, Section 1, in the Supplementary Appendix.

The EKFC-equation, which was originally developed with SCr alone as the biomarker, was applied to both biomarkers (SCr and CysC) after dividing by the unique rescaling "Q" factors for each biomarker (see the Supplementary Appendix, Section 2, Figure S1)[5]. The general form of the EKFC-eGFR-equation is:

$$EKFC - eGFR = \frac{107.3}{[Biomarker/Q]^{\alpha}} \; x \; [0.990^{(Age-40)} \; if \; age > 40 \; years]$$

with α=0.322 when Biomarker/Q < 1 and α=1.132 when Biomarker/Q ≥ 1.

Derivation of Rescaling Factors for Serum Creatinine for the EKFC-eGFR$_{Cr}$-Equation

The rescaling "Q" factors for SCr were the median SCr-values from several healthy populations as previously described in White populations (Supplementary Appendix, Section 2.1)[5,11-12] and in Black African and Black European populations (Supplementary Appendix, Section 2.2).[13]

Derivation of Rescaling Factors for Serum Cystatin C for the EKFC-eGFR$_{Cys}$-equation

We first assessed whether there were differences in cystatin C levels between Black vs. White patients. Specifically, we matched Black Europeans (from a pool of n=697) 1:1 to White Europeans (from a pool of n=2,262) from one hospital of the Paris cohort on age ±3 years, sex, body mass index (BMI) ±2.5kg/m² and mGFR ±3mL/min/1.73m² (Supplementary Appendix, Section 3, Table S3). After establishing no significant differences in CysC between Black and White Europeans (see Supplementary Appendix, Section 3, Figure S2 and Table S4), we used a relatively healthy White patient sample to define the rescaling factors for CysC. Specifically, we used CysC measurements obtained in the period 2007–2020 from non-nephrology departments at Uppsala University Hospital, Sweden. The median values by age (determined with quantile regression using a linear spline with a knot at 50 years) in adults ≥18 years overall or by sex was determined for the CysC rescaling factor (See Supplementary Appendix, Section 4, Figures S3 and S4).

Validation Cohorts for EKFC-eGFR$_{Cys}$

We compared the performance of EKFC-eGFR$_{Cys}$, the mean of EKFC-eGFR$_{Cr}$ and EKFC-eGFR$_{Cys}$ (EKFC-eGFR$_{Cr+Cys}$), CKD-EPI-eGFR$_{Cys}$, and the composite CKD-EPI-eGFR$_{Cr+Cys}$ equations to mGFR in the EKFC multicenter cohort (n = 7,727),[5] and in datasets from France (Paris, Black participants (n=858) and White participants (n=2,646), Sub-Saharan Africa (Côte d'Ivoire Black participants (n=285) and Democratic Republic of Congo Black participants (n=223),[13-14] and North America (Rochester, Minnesota White participants (n=1,093)) (Tables 1 and 2). Since the EKFC equation coefficients were derived using the SCr and mGFR data from the European cohorts in the EKFC-dataset (n=7,727), except for the Kent and Lund

cohorts (see Table S1) these two cohorts were also used for external validation (Supplementary Appendix, Section 5, Table S5). All data were restricted to the first available measurement of CysC and mGFR. All participants were age ≥18 years. Data were anonymized and all procedures involving participants and data agreed with the ethical principles for medical research involving human participants established in the World Medical Association Declaration of Helsinki.

Measurement Methods for SCr, SCysC, and mGFR

All creatinine assays were calibrated against the isotope dilution mass spectrometry standard method, and all CysC assays were standardized against the international reference material (ERM-DA471/IFCC). Measured GFR was obtained using either plasma clearance (based on the decay of the plasma concentrations over time) or urinary clearance (based on urine excretion rate divided by plasma concentration) of exogenous filtration markers (iohexol, inulin, ^{99}Tc-DTPA, iothalamate or ^{51}Cr-EDTA), all methods that are commonly used to measure GFR.[15] All results of mGFR were indexed to 1.73m^2 body surface area with the DuBois equation.[16]

Statistical Analysis

The accuracy of EKFC-eGFR$_{Cys}$, EKFC-eGFR$_{Cr}$, and EKFC-eGFR$_{Cr+Cys}$ for estimating the mGFR was primarily compared to the KDIGO recommended CKD-EPI-eGFR$_{Cr}$ equation (2009 and the 2021 race-free versions)[2,4], CKD-EPI-eGFR$_{Cys}$ equation, and CKD-EPI-eGFR$_{Cr+Cys}$ equations.[3] The EKFC-eGFR$_{Cys}$ and EKFC-eGFR$_{Cr+Cys}$ equations were also compared with other full age range CysC-based or combined SCr- and CysC-based equations: Full Age Spectrum equation,[11,17] Caucasian Asian Paediatric Adult equation,[18] and the mean of the Lund-Malmö revised equation[19] and the CysC based Caucasian Asian Pediatric Adult equation.[20] Equations are presented in the Supplementary Appendix, Section 6, Table S6. Comparisons were overall and within age subgroups (18-40 y, 40-65 y and age ≥65 years) (see Supplementary Appendix, Section 7, Tables S7.1-S7.5).

Several commonly used statistics (See Box Insert) were used to assess the accuracy and precision of the difference in values between eGFR and mGFR. The bias between eGFR and mGFR across the age spectrum was graphically presented using median quantile regression. Likewise, the P30(%) by age was shown graphically using cubic splines. All analyses and calculations were performed using SAS 9.4 (SAS Institute Inc., Cary, NC).

Results

Evaluation for Racial Differences in Serum Creatinine and Cystatin C

In total, 577 European Black participants were matched on age, sex, BMI, and mGFR to 577 European White participants from the same hospital in Paris, 200 women (35%) and 377 men (65%) (Details in Supplementary Appendix, Section 3, Matched Cohort Analysis). Figure S2 shows that while SCr was higher at the same mGFR in Black compared to White persons, there was no significant difference in CysC at the same mGFR between the two groups.

Rescaling Factors (Q-values) for Serum Cystatin C

Given the lack of a race difference in serum cystatin C concentration at the same measured GFR, we used a large sample of White Europeans at Uppsala University Hospital, Sweden (95,469 women and 132,174 men) to calculate rescaling factors (Q-values) for CysC. Specifically, we plotted the median CysC for each 1-year interval against age and sex group (Supplementary Appendix, Section 4, Fig. S4). Between 18 and 50 years, the median CysC values were relatively constant with age, but higher in men than women. After about age 50 years, median CysC values increased with age and could be reasonably approximated with a linear spline regression with a knot at 50 years. That is, we fitted a two-piece linear spline with age cutoff at 50. This choice is made based on visual inspection and for convenient interpretation, but it may not be the cutoff that yields the optimal fitting adjustment curve. (see Supplementary Appendix, analysis in Section 4). Thus, a sex-specific rescaling factor for cystatin C was defined as 0.86mg/L in men and

0.79mg/L in women until age 50 years after which 0.005 x (Age–50) was also added for ages >50 years. Since sex differences in the median value of CysC were relatively small, a sex-independent rescaling factor for CysC was also defined using the overall median (0.83mg/L) until age 50 years after which 0.005 x (Age–50) was also added for ages >50 years.

Validation of the Cystatin C-Based EKFC-Equation and the Combined EKFC-Equation

Performance results for different eGFR-equations are presented for the five different populations in Tables 1 and 2. In general, the EKFC estimating equations (EKFC-eGFR$_{Cys}$, EKFC-eGFR$_{Cr}$, and EKFC-eGFR$_{Cr+Cys}$) performed better than the parallel CKD-EPI equations with similar or less bias, lower IQR of difference, higher P10%, and higher P30% relative to mGFR. This improvement in performance of EKFC equations over CKD-EPI equations remained in the independent Kent and Lund cohorts for EKFC-eGFR$_{Cys}$ and EKFC-eGFR$_{Cr}$, but not for EKFC-eGFR$_{Cr+Cys}$ (Table S5). In general, the statistical performance of the EKFC-eGFR$_{Cys}$ compared to EKFC-eGFR$_{Cr}$ with respect to estimation of mGFR was similar. There were no meaningful differences in EKFC-eGFR$_{Cys}$ and EKFC-eGFR$_{Cr+Cys}$ in estimation of GFR when sex-free rescaling factors were used rather than sex-specific rescaling factors for cystatin C (Tables S8.1 and S8.2). Comparison between equations (including Full Age Spectrum, Lund Malmö Revised, and Caucasian Asian Pediatric Adult equations) are made in the five populations in subgroups by age (Tables S7.1-S7.5), by mGFR-level <60 and ≥60 mL/min/1.73m², age and sex (Tables S9.1-S9.4), and BMI-category (Tables S10.1 to S10.4). Individual cohort specific performance of the EKFC equations is summarized in the Supplementary Appendix, Section 11, Table S11.

Graphs of bias and P30 for each EKFC and CKD-EPI equation vs. age are shown in Figure 1 using the pooled dataset of the EKFC cohort, the North American cohort, the Paris cohorts (both White and Black patients), and the Black African cohort. Graphical comparison (of bias and P30 vs. age) was also made with other equations and stratified by race and sex (Figures S5-S10). Bias across levels of mGFR are graphically presented in Figure S11. Scatterplots of EKFC-eGFR$_{Cys}$ and EKFC-eGFR$_{Cr+CysC}$ vs. mGFR show

more alignment with the line of identity +/-30% than was evident with CKD-EPI-eGFR$_{Cys}$ and CKD-EPI-eGFR$_{Cr+Cys}$ vs. mGFR (Figure S12-S14).

Discussion

Consistent with prior studies,[3,21-22] we found that our CysC-based equation (EKFC-eGFR$_{Cys}$) did not have better accuracy or precision for estimating mGFR than a SCr-based equation (EKFC-eGFR$_{Cr}$). Improvement in GFR estimation was observed only in the combined EKFC-eGFR$_{Cr+Cys}$ equation. These EKFC equations require appropriately rescaled SCr and CysC values that are generated by dividing by the median values (rescaling factors) in a healthy population. Unlike EKFC-eGFR$_{Cr}$, the EKFC-eGFR$_{Cys}$ equation can use age-based rescaling factors without race or sex. We also found that the average of EKFC-eGFR$_{Cr}$ and EKFC-eGFR$_{Cys}$ improved accuracy in GFR estimation. The use of CysC is still not in widespread use, possibly because of its cost as a test.[23] However, these data underscore an additional advantage for its adoption in that a cystatin C-based equation doesn't require sex or race variables for the determination of eGFR as is required with serum creatinine.

In our study, the EKFC-eGFR$_{Cys}$ and EKFC-eGFR$_{Cr+Cys}$ equations also showed better accuracy and precision for estimating GFR than the recommended CKD-EPI equations and other full age range CysC equations including Full Age Spectrum and Caucasian Asian Pediatric Adult equations. To demonstrate that CysC levels did not require race-adjustments to estimate GFR, we first demonstrated no significant difference in CysC levels between Black and White patients of the same age, sex, BMI, and mGFR. We then used a rescaling factor for CysC based on a White European cohort, but the resultant EKFC-eGFR$_{Cys}$ equation performed equally well in Black European, Congo, and Ivory Coast cohorts compared to White European and North American cohorts. A single rescaling factor for cystatin C that did not account for sex differences performed as well estimating GFR as having 2 separate sex-specific rescaling factors.

In all cohorts, the 2021 CKD-EPI-eGFR$_{Cr}$(AS)-equation showed higher bias and worse P10/P30 accuracy than the original 2009 CKD-EPI-eGFR$_{Cr}$(ASR)-equation or the SCr-based EKFC-eGFR-equation. When matching Black participants to White participants based on stringent criteria for age, sex, BMI and mGFR, we could demonstrate that there are clear differences in SCr between Black and White persons, and between men and women. Therefore, for the most accurate (unbiased) estimation of GFR based on SCr, population-demographic-specific adjustments at the SCr-level are required. The SCr-based EKFC-eGFR equation first rescales SCr to eliminate well-described race and sex differences in SCr levels.[22] This preserves SCr-based equation performance without directly adding race and sex to the GFR estimating equation. However, such population-specific adjustments are not required for CysC and the EKFC-eGFR$_{Cys}$-equation can be used without race and sex, like the Full Age Spectrum and Caucasian Asian Pediatric Adult equations, but with better performance properties as assessed from the data analyzed in this study.

Strengths of the current validation study include the large study population, including patients not only from Europe and USA but also from Africa, calibration of the SCr-assays in each study to standardized values (isotope dilution mass spectrometry equivalent), measurement of CysC against the certified reference material, and measurement methods for GFR that are used clinically and considered to have acceptable accuracy.[15] While there was variation in the methods for mGFR determination between cohorts, this has been a long-standing problem for the development of GFR estimating equations. There is not yet a standardized method for measuring GFR to ensure consistent data across numerous centers that often contribute to the development of GFR estimating equations. Additional limitations to this study include the lack of validation cohorts with White and Black Americans and Asians, or cohorts with children. Further studies in such populations may determine that there are settings where a race or sex specific rescaling factor is needed for cystatin C.

In conclusion, we found that a single mathematical equation (EKFC) for estimating GFR derived with serum creatinine could also be applied to cystatin C to accurately estimate GFR. The EKFC-eGFR$_{Cys}$ equation tested here showed equivalent performance to EKFC-eGFR$_{Cr}$ and somewhat improved accuracy over the 2021 CKD-EPI equations (refitted without the race coefficient), which have been the subject of recent reports.[24-29]

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

Funding

By grant 2019-00198 from the Swedish Research Council (Vetenskapsrådet).

Acknowledgments

We are grateful to all participating patients who gave consent and to study nurses, who contributed to the clinical studies that make part of this data collection.

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Key Concepts for Comparing eGFR to mGFR

The accuracy of estimated glomerular filtration rate (eGFR) compared to measured glomerular filtration rate (mGFR) can be assessed with several statistical metrics, along with the 95% Confidence Interval:

Median Bias: The individual differences (eGFR – mGFR) are rank ordered and the middle value (median) is reported. A value closer to 0 is less biased and more accurate.

IQR of difference: The Interquartile Range assesses the spread (imprecision) in the difference (eGFR – mGFR). The individual differences are rank ordered and the range of values between the 25th percentile and the 75th percentile is calculated. A smaller value reflects better precision of eGFR.

RMSE: root mean square error. The root of the mean of the squared differences (eGFR – mGFR). RMSE is expressed on the same scale as GFR (in mL/min/1.73m^2) and a smaller value reflects better accuracy and precision of eGFR.

P10: The frequency of differences where eGFR is within 10% of mGFR. A higher value reflects better precision and accuracy of eGFR.

P30: The frequency of differences where eGFR is within 30% of mGFR. A higher value reflects better precision and accuracy of eGFR. P30 > 75% has been considered "sufficient for good clinical decision making" by the Kidney Disease Outcomes Quality Initiative, although its goal is to reach a P30 greater than 90%.[30]

Figure Legend

Figure 1. Performance (bias and P30) against age of different eGFR-equations.

Bias (left panel) and P30-accuracy (right panel) versus age for the SCr-based, CysC-based, and combined SCr+CysC EKFC and CKD-EPI (AS)-equations, in the pooled dataset (n=12,832) of White Europeans / North Americans and Black Europeans / Africans. The grey area indicates the region where bias is zero ± 5 (left panel) and the region where P30 > 75% (right panel). Bias versus age is based on median quantile regression using 4^{th} degree polynomials. P30 versus age is based on cubic splines with three free knots, using 3^{rd} degree polynomials.

Table 1. Performance of single biomarker (serum creatinine or cystatin C) based eGFR-equations

	Serum creatinine based equations				Cystatin C based equations	
White EKFC cohort n = 7,727	**CKD-EPI-eGFR$_{Cr}$ (ASR)**	**CKD-EPI-eGFR$_{Cr}$ (AS)**	**EKFC-eGFR$_{Cr}$**		**CKD-EPI-eGFR$_{Cys}$**	**EKFC-eGFR$_{Cys}$ (sex-free)**
Median bias [95%CI]	3.96 [3.67; 4.32]	7.40 [7.02; 7.76]	0.58 [0.32; 0.86]		0.28 [-0.02; 0.64]	0.00 [-0.37; 0.27]
IQR [Pct25; Pct75]	15.5 [-3.0; 12.5]	16.3 [0.0; 16.3]	14.5 [-6.5; 8.0]		19.1 [-7.9; 11.2]	14.4 [-7.9; 6.5]
RMSE [95%CI]	14.8 [14.4; 15.2]	16.3 [15.9; 16.6]	13.1 [12.8; 13.4]		15.8 [15.5; 16.1]	13.5 [12.9; 14.1]
P10 [95%CI]	40.3 [39.2; 41.4]	34.7 [33.6; 35.8]	43.3 [42.2; 44.4]		32.0 [31.0; 33.0]	41.7 [40.6; 42.8]
P30 [95%CI]	81.6 [80.8; 82.5]	75.7 [74.8; 76.7]	85.8 [85.0; 86.5]		80.8 [79.9; 81.7]	86.2 [85.4; 87.0]
White Paris cohort n = 2,646						
Median bias [95%CI]	0.30 [-0.21; 0.78]	3.22 [2.69; 3.86]	-1.24 [-1.75; -0.74]		- 2.85 [-3.35; -2.21]	-0.79 [-1.26; -0.31]
IQR [Pct25; Pct75]	15.2 [-6.8; 8.4]	15.9 [-4.1; 11.7]	14.6 [-8.3; 6.3]		16.4 [-10.3; 6.1]	15.3 [-8.5; 6.7]
RMSE [95%CI]	14.2 [13.6; 14.8]	14.8 [14.2; 15.4]	13.6 [13.0; 14.1]		14.5 [13.9; 15.1]	13.5 [12.9; 14.1]
P10 [95%CI]	39.5 [37.7; 41.4]	38.2 [36.4; 40.1]	40.9 [39.0; 42.7]		34.2 [32.4; 36.0]	38.2 [36.4; 40.1]
P30 [95%CI]	84.5 [83.1; 85.8]	82.5 [81.1; 84.0]	86.5 [85.2; 87.7]		82.7 [81.3; 84.2]	87.6 [86.3; 88.9]
White North American cohort n = 1,093						
Median bias [95%CI]	2.83 [1.65; 3.64]	7.11 [6.15; 7.97]	-2.69 [-3.68; -1.79]		12.1 [11.1; 13.3]	4.26 [3.33; 5.08]
IQR [Pct25; Pct75]	18.8 [-6.6; 12.2]	18.7 [-2.2; 16.5]	18.5 [-11.9; 6.6]		21.5 [1.5; 23.0]	18.3 [-5.3; 13.0]
RMSE [95%CI]	16.2 [15.0; 17.4]	17.5 [16.4; 18.6]	16.2 [14.9; 17.4]		21.3 [20.3; 22.2]	16.8 [15.7; 17.9]
P10 [95%CI]	41.9 [39.0; 44.8]	39.4 [36.5; 42.3]	41.4 [38.5; 44.4]		29.4 [26.7; 32.1]	41.5 [38.6; 44.5]
P30 [95%CI]	86.0 [83.9; 88.1]	81.0 [78.6; 83.3]	89.3 [87.5; 91.1]		72.9 [70.3; 75.6]	83.9 [81.7; 86.1]
Black Paris cohort n = 858						
Median bias [95%CI]	0.24 [-0.64; 0.81]	-5.09 [-5.68; -4.14]	-2.58 [-3.49; -1.71]		-0.62 [-1.71; 0.28]	1.40 [0.38; 2.23]
IQR [Pct25; Pct75]	19.3 [-12.7; 4.1]	16.8 [-12.7; 4.1]	14.9 [-9.9; 5.1]		17.9 [-8.1; 9.8]	14.3 [-5.6; 8.8]
RMSE [95%CI]	16.0 [14.7; 17.2]	14.9 [13.5; 16.1]	13.9 [12.4; 15.2]		15.4 [14.0; 16.6]	13.5 [12.1; 14.7]
P10 [95%CI]	35.4 [32.2; 38.6]	33.0 [29.8; 36.1]	37.5 [34.3; 40.8]		36.2 [33.0; 39.5]	41.0 [37.7; 44.3]
P30 [95%CI]	79.8 [77.1; 82.5]	82.3 [79.7; 84.8]	85.5 [83.2; 87.9]		81.5 [78.9; 84.1]	87.4 [85.2; 89.6]
Black African cohort n = 508						
Median bias [95%CI]	12.2 [10.7; 15.0]	2.48 [0.72; 4.15]	-1.45 [-2.82; 0.62]		2.82 [1.43; 4.48]	1.74 [0.28; 3.25]
IQR [Pct25; Pct75]	30.0 [-3.2; 26.8]	23.3 [-9.0; 14.3]	20.4 [-10.6; 9.9]		23.7 [-7.7; 16.0]	19.5 [-7.4; 12.1]
RMSE [95%CI]	24.5 [22.7; 26.1]	18.1 [16.6; 19.4]	16.4 [15.0; 17.8]		18.5 [17.1; 19.8]	16.0 [14.7; 17.2]
P10 [95%CI]	19.5 [16.0; 22.9]	34.4 [30.3; 38.6]	38.0 [33.8; 42.2]		33.1 [29.0; 37.2]	40.6 [36.3; 44.8]
P30 [95%CI]	63.6 [59.4; 67.8]	74.4 [70.6; 78.2]	78.9 [75.4; 82.5]		77.4 [73.7; 81.0]	83.5 [80.2; 86.7]

Median bias [95%CI] (mL/min/1.73m²), imprecision (interquartile range, IQR), root mean square error (rmse) [95%CI], P10(%) [95%CI] and P30(%) [95%CI] accuracy for different creatinine and cystatin C based equations in the EKFC-validation dataset, and the White Paris, White North American, Black Paris and Black African cohorts. CKD-EPI-eGFR$_{Cr}$ (ASR), CKD-EPI-eGFR$_{Cr}$ (AS) and CKD-EPI-eGFR$_{Cys}$ serve as a benchmark (as the KDIGO recommended equations). (ASR=age, sex and race factors, AS = age and sex but no race factor), Pct=percentiles;

Table 2. Performance of combined serum creatinine and cystatin C based eGFR equations

White EKFC cohort n = 7,727	**CKD-EPI-eGFR$_{Cr+Cys}$ (ASR)**	**CKD-EPI-eGFR$_{Cr+Cys}$ (AS)**	**EKFC-eGFR$_{Cr+Cys}$ (sex-free)**
Median bias [95%CI]	2.50 [2.17; 2.76]	5.04 [4.69; 5.36]	0.37 [0.14; 0.66]
IQR [Pct25; Pct75]	14.8 [-3.6; 11.2]	16.7 [-1.8; 14.9]	12.0 [-5.9; 6.1]
RMSE [95%CI]	13.1 [12.8; 13.4]	14.7 [14.4; 15.0]	11.3 [11.0; 11.6]
P10 [95%CI]	41.5 [40.4; 42.6]	37.2 [36.2; 38.3]	48.9 [47.8; 50.0]
P30 [95%CI]	88.3 [87.6; 89.0]	84.2 [83.4; 85.0]	90.4 [89.8; 91.1]
White Paris cohort n = 2,646			
Median bias [95%CI]	-1.35 [-1.82; -0.97]	0.64 [0.16; 1.15]	-0.65 [-1.06; -0.23]
IQR [Pct25; Pct75]	13.4 [-7.5; 5.8]	14.1 [-5.8; 8.3]	12.4 [-6.8; 5.6]
RMSE [95%CI]	12.1 [11.6; 12.7]	12.6 [12.0; 13.1]	11.8 [11.2; 12.4]
P10 [95%CI]	43.9 [42.0; 45.8]	42.3 [40.4; 44.1]	45.8 [43.9; 47.7]
P30 [95%CI]	89.7 [88.5; 90.8]	89.2 [88.0; 90.4]	92.1 [91.1; 93.1]
White North American cohort n = 1,093			
Median bias [95%CI]	9.23 [8.45; 10.1]	13.9 [13.1; 14.9]	0.97 [0.01; 2.12]
IQR [Pct25; Pct75]	18.4 [0.5; 18.8]	18.1 [5.1; 23.3]	17.4 [-8.2; 9.2]
RMSE [95%CI]	18.1 [17.1; 19.1]	21.0 [20.1; 22.0]	15.5 [14.3; 16.7]
P10 [95%CI]	37.1 [34.3; 40.0]	28.1 [25.4; 30.8]	45.7 [42.7; 48.6]
P30 [95%CI]	79.5 [77.1; 81.9]	72.1 [69.4; 74.8]	88.7 [86.9; 90.6]
Black Paris cohort n = 858			
Median bias [95%CI]	-0.37 [-1.06; 0.57]	-2.08 [-2.71; -1.32]	-0.65 [-1.23; 0.11]
IQR [Pct25; Pct75]	15.2 [-6.4; 8.8]	14.0 [-7.9; 6.1]	12.4 [-6.2; 6.2]
RMSE [95%CI]	13.3 [11.9; 14.6]	12.6 [11.2; 13.9]	11.6 [10.0; 13.0]
P10 [95%CI]	38.7 [35.4; 42.0]	38.9 [35.7; 42.2]	48.3 [44.9; 51.6]
P30 [95%CI]	87.9 [85.7; 90.1]	89.0 [87.0; 91.1]	92.0 [90.1; 93.8]
Black African cohort n = 508			
Median bias [95%CI]	8.55 [6.87; 10.3]	4.08 [2.37; 5.78]	0.42 [-1.03; 1.51]
IQR [Pct25; Pct75]	24.7 [-4.5; 20.1]	22.0 [-7.4; 14.7]	17.1 [-7.2; 10.0]
RMSE [95%CI]	19.7 [18.2; 21.1]	17.2 [15.8; 18.5]	14.7 [13.3; 16.0]
P10 [95%CI]	28.7 [24.8; 32.7]	34.3 [30.1; 38.4]	43.5 [39.2; 47.8]
P30 [95%CI]	75.0 [71.2; 78.8]	77.6 [73.9; 81.2]	84.3 [81.1; 87.4]

Median bias [95%CI] (mL/min/1.73m²), imprecision (interquartile range, IQR), root mean square error (rmse) [95%CI], P10(%) [95%CI] and P30(%) [95%CI] accuracy for the combined creatinine and cystatin C based equations in the EKFC-validation dataset, and the White Paris, White North American, Black Paris and Black African cohorts. CKD-EPI-eGFR$_{Cr+Cys}$ (ASR), CKD-EPI-eGFR$_{Cr+Cys}$ (AS) serve as a benchmark (as the KDIGO recommended equations). (ASR = age, sex and race factors, AS = age and sex but no race factor); Pct = Percentiles; EKFC-eGFR$_{Cr+CysC}$ is the arithmetic mean of EKFC-eGFR$_{Cr}$ and EKFC-eGFR$_{Cys}$