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CLINICAL RESEARCH

Recalibration of the European Kidney Function Consortium eGFR Equation for the Indian Population

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Introduction: The new European Kidney Function Consortium (EKFC) eGFR equation uses rescaled serum creatinine (SCr) to an age- and sex-specific normal median value, making it applicable across the entire age spectrum. We evaluated the performance of the recalibrated $\text{EKFC}_{\text{crea}}$ equation using Indian-specific Q (for median SCr) and K (for normal glomerular filtration rate [GFR]) in a large Indian cohort and the ability to correctly classify chronic kidney disease (CKD).

Methods: Indian adults (healthy and patients with CKD) were recruited. Plasma iohexol clearance was used to assess measured GFR (mGFR). Indian-specific Q values were derived from healthy individuals, and K from those under the age of 40 years. We evaluated $\text{EKFC}_{\text{crea}}$, CKD- Epidemiology Collaboration $(\text{EPI})_{2021}$, and recalibrated the $\text{EKFC}_{\text{crea}}$ equations, incorporating the Indian Q (ISQ), Indian constant (ISK), and both (ISQ + ISK). We evaluated bias and accuracy (P_{30}) for all equations.

Results: A total of 1174 participants (615 healthy, 559 CKD), mean age 48 years, with equal sex distribution were recruited. The $\text{EKFC}_{\text{crea}}$ equation showed a mean bias of 9.9 (95% CI: 8.7– 11.1) ml/min per 1.73 m^2 with P_{30}; 58.1%. EKFC_{ISQ} reduced bias to 4.9 (95% CI: 3.7 6.0) ml/min per 1.73 m^2 and improved P_{30} to 64%. EKFC_{ISK} achieved a bias of −1.2 (95% CI: −0.1 to −2.2) ml/min per 1.73 m^2 and P_{30} of 69%. 30%, 48%, and 67% of CKD patients were categorized into lower categories using the EKFC_{ISQ}, EKFC_{ISK}, and $\text{EKFC}_{\text{ISQ+ISK}}$ equations, respectively, against the CKD-EPI $_{2021}$.

Conclusion: Recalibrating $\text{EKFC}_{\text{crea}}$ with Indian-specific Q and K reduced bias and improved accuracy, with EKFC_{ISK} emerging as the best model. Adopting this recalibrated equation in clinical practice and public health initiatives after validation in diverse cohorts could lead to more accurate CKD diagnosis and staging in India.

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Accurate estimation of GFR is critical for diagnosing and managing kidney disease. Given the difficulty of directly measuring GFR using exogenous markers,[1] GFR is commonly estimated from SCr.[2,3] The CKD-EPI, EKFC, and Lund-Malmö revised creatinine equations have been recommended by Kidney Disease: Improving Global Outcomes (KDIGO) guidelines as the

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preferred formulas for adults.[4] However, concerns have emerged that these creatinine-based equations may not be universally accurate, especially in ethnic groups with different non-GFR determinants of SCr, such as muscle mass, diet, and creatinine generation.[5,6] Investigations in Asian populations led to the development of population-specific adjustment factors for CKD-EPI.[7-10] These adjustments highlight that the same SCr can correspond to different true GFRs in different populations. In the predominantly vegetarian Indian population, lower muscle mass and dietary protein intake are associated with lower creatinine generation. Previous pilot studies have shown that creatinine-based equations overestimate GFR in Indian subjects.[11,12]

Recently, the EKFC developed a new creatinine-based estimated GFR (eGFR) equation intended to be applicable across the full age spectrum.[13] The EKFC approach "rescales" SCr to an age- and sex-specific normal median value, denoted by Q. The original EKFC equation was developed and validated in European cohorts and demonstrated improved accuracy and lower bias compared with previous equations. For instance, in the EKFC development study, the new equation achieved a bias of around -1 ml/min per 1.73 m^2 and P_{30} accuracy $> 75\%$, outperforming the CKD-EPI equation in European validation sets.[13] This methodology obviates the need for race-specific coefficients by directly adjusting for population differences in SCr distributions. A recent analysis in the US confirmed that using population-specific Q-values eliminated bias between Black and non-Black individuals, whereas a single "race-neutral" Q reduced the bias.[14]

The EKFC equation has not been evaluated in the Indian population, which is ethnically and biologically distinct from the European populations from which EKFC was derived. Given the overestimation by CKD-EPI in Indians, we hypothesized that recalibrating the EKFC equation with India-specific Q would improve its performance.

Although the Q value is central - the "107" in the $EKFC_{crea}$ equation corresponds to the median mGFR observed in living kidney donors in Europe below 40 years.[15] This value is very similar in Africa[16] and in the USA.[17] However, we recently showed that, in an Indian population of living kidney donors, the median mGFR is much lower (Yadav *et al.*,[12] this study). Therefore, in addition to the Indian Q-value, we also evaluated a specific Indian mGFR median value, that is, 90 instead of 107 (referred as K). The performance of the recalibrated equations was compared with that of the original $EKFC_{crea}$ and $CKD\text{-}EPI_{2021}$ equations, as well as their ability to correctly classify CKD.

METHODS

Study Population and Design

We analyzed data from 1174 Indian adults (aged > 18 years), comprising the following 2 subgroups: healthy individuals and patients with CKD. The healthy group consisted of 615 healthy kidney donors or randomly selected adult volunteers recruited from the general population in Chandigarh. We derived the calibration constants (Q and K) from this population. Healthy participants were defined as individuals with no history of hypertension, diabetes, chronic kidney disease, or cardiovascular disease, and meeting all of the following criteria at the time of assessment: blood pressure $< 140/90$ mm Hg without antihypertensive medications, fasting blood glucose < 126 mg/dl without diabetes medications, creatinine-based eGFR ($CKD\text{-}EPI_{2021}$) > 60 ml/min per 1.73 m^2, urinary albumin-creatinine ratio < 30 mg/g or protein-creatinine ratio < 150 mg/g. Living kidney donors underwent comprehensive medical evaluation per institutional protocols. Community volunteers underwent detailed history, examination, and laboratory screening to confirm absence of chronic conditions. A total of 559 participants with stable CKD of various causes, encompassing a wide range of GFR, were recruited from the outpatient clinics of the Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, and Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry. Individuals with organ transplants, those on dialysis, or those with conditions affecting creatinine generation (e.g., amputations, muscle-wasting diseases) were excluded.

The study was approved by the institutional ethics committees of the 2 centers, and written informed consent was taken from all participants. This analysis was conducted as a cross-sectional evaluation of eGFR equations against mGFR. Because our aim was to perform an internal validation of the EKFC equation recalibration, the full dataset was used both to derive calibration parameters and to assess equation performance; no separate external validation dataset was used.

Measurement of GFR

GFR was measured using iohexol plasma clearance, as described earlier.[12] Healthy donors underwent GFR measurement as part of donor evaluation, and CKD patients as part of research protocols. Briefly, iohexol (Omnipaque [300 mg iodine/ml]) was administered i.v. as a bolus, 5 ml or 3 ml, and flushed with 10 ml normal saline. Venous blood samples were collected from the contralateral arm at 60-, 120-, 180-, and 240-minutes postinjection. Plasma iohexol was extracted using 5 % perchloric method, and concentrations were measured by high-performance liquid chromatography using UltiMate 3000 (Thermo Fisher Scientific, MA). Plasma clearance was calculated from 3-point sampling (120, 180, and 240 minutes) using the method described by Jodal and Brøchner-Mortensen,[18] and mGFR was indexed to body surface area using the Du Bois and Du Bois formula.[19]

Laboratory Measurements

SCr was measured by the modified Jaffe's method traceable to isotope dilution mass spectrometry. All other tests were performed at the central biochemistry laboratory of PGIMER, Chandigarh, using a Cobas c702 auto-analyzer (Roche Diagnostics Limited, Risch-Rotkreuz, Switzerland).

Derivation of Indian-Specific Q and K Values

Following the EKFC methodology, we defined Q as the median SCr concentration in healthy adults, computed separately for males and females (to account for sex differences in creatinine because of muscle mass). Similarly, K was defined as the median mGFR in healthy adults under age 40 (pooled sexes, since GFR is normalized to body surface area). We chose 18 to 40 years to define healthy young adults based on EKFC's approach and to exclude age-related GFR decline. Out of the 615 healthy participants, 209 were under 40 years of age. No outliers were excluded. We hypothesized that Indians would have lower Q (reflecting lower median SCr) and possibly a different K.

We evaluated the following eGFR equations: $\text{EKFC}_{\text{crea}}$ (original creatinine), CKD-EPI_{2021}, recalibrated EKFC (ISQ, ISK, ISQ+ISK) –EKFC_{ISQ}, EKFC_{ISK}, $\text{EKFC}_{\text{ISQ+ISK}}$ (Supplementary Table S1). For all equations, eGFR was calculated in ml/min per 1.73 m^2.

Statistical Analysis

Data were analyzed using the SPSS for Macintosh, (version 26.0, IBM Corp., Armonk, NY) and SAS (version 9.4,SAS Institute, Cary, N C). Descriptive data are presented as mean ± SD, median (interquartile range [IQR]), 5th and 95th percentile, and range. Categorical data were reported as frequencies or proportions. We evaluated each equation's performance by calculating standard metrics of bias, precision, and accuracy, following recent recommendations. Bias was defined as the mean difference between eGFR and mGFR for each equation. We also examined median bias. The 95% distribution of bias (limits of agreement) was calculated as mean bias ± 1.96 × SD, representing the range that encompasses most differences between measured and estimated values. A bias within ± 5 ml/min per 1.73 m^2 is usually considered as acceptable. Precision was assessed as the 95% confidence interval (CI) and IQR (Q1–Q3). Accuracy was quantified by P_{30}; the percentage of eGFR values within 30% of mGFR, the root mean squared error of the differences, and the mean absolute error. A eGFR equation is generally considered acceptable if $P_{30} \geq$ 75% to 80%. For each metric, we compared the recalibrated EKFC equations against the original $\text{EKFC}_{\text{crea}}$ and CKD-EPI_{2021} equations. Differences in bias between equations were tested using paired *t* tests (for mean bias). Differences in P_{30} were evaluated using McNemar's test for paired accuracy outcomes. Bland-Altman plots were used to assess agreement between eGFR and mGFR. Median bias against age and mGFR was graphically presented using median quantile regression with 3rd degree polynomials. Similarly, P_{30} was graphically presented against age and mGFR using cubic splines with 3 free knots and third-degree polynomials.

As no separate external validation dataset was used, we performed 10-fold cross-validation to test the performance of the Indian-specific adjustment in the $\text{EKFC}_{\text{crea}}$ equations. The dataset was randomly divided into 10 approximately equal folds. In each iteration, 1-fold was held out, and the remaining 9 folds were appended to re-estimate Q (sex-specific median SCr) and K (median mGFR in healthy participants aged ≤ 40). These fold-specific constants were then used to compute EKFC_{ISQ}, EKFC_{ISK}, and $\text{EKFC}_{\text{ISQ+ISK}}$ for the held-out fold, and the results were combined across all folds.

We performed subgroup analyses to assess the consistency of equation performance. Subgroups were defined *a priori* by GFR category (mGFR ≥ 60 vs. <60 ml/min per 1.73 m^2), sex (male vs. female), and age (≤ 40, 41–65, and > 65 years). We examined whether any equation across showed noticeably divergent performance in any subgroups. Additionally, we reclassified eGFR category as per KDIGO classification using the original and recalibrated EKFC equations against CKD-EPI_{2021} equation.

We also did a sensitivity analysis of recalibrated equations for their performance in subjects with $r^2 > 0.975$ for iohexol slope ($n = 683$).

RESULTS

Cohort Characteristics and Derived Q and K Values

A total of 1174 participants were included, comprising 615 apparently healthy subjects and 559 with CKD. Table 1 summarizes their characteristics. The healthy subgroup had a mean age of 46 ± 12 years (median: 46; IQR: 37–55 years) and consisted of 34% males. The

Table 1. The demographic characteristics and clinical parameters of study population ($N = 1174$)

Characteristics	Total population ($N = 1174$)	Healthy ($n = 615$)	CKD ($n = 559$)
Age (yrs)	48 ± 12 48 (39–57)	46 ± 12 46 (37 –55)	50 ± 13 51 (40 –60)
Sex (Female/Male)	589/585 (50.1/49.9)	407/208 (66.1/33.9)	182/377 (32.6/67.4)
BMI (kg/m^2)	25.7 ± 4.8	26.2 ± 4.7	25.1 ± 4.7
Hemoglobin (g/dl)	12.2 ± 1.9	12.5 ± 1.8	11.8 ± 2.0
Serum creatinine (mg/dl)	1.5 ± 1.3	0.7 ± 0.2	2.4 ± 1.3
Serum urea (mg/dl)	41.1 ± 29.4	22.0 ± 10.4	62.1 ± 29.2
Serum albumin (g/dl)	4.4 ± 0.4	4.5 ± 0.4	4.3 ± 0.4
Serum Protein (g/dl)	7.3 ± 0.7	7.3 ± 0.8	7.3 ± 0.6
eGFR (CKD-EPI$_{2021}$)	74.2 ± 39.2	107.8 ± 14.7	37.2 ± 19.3
Protein intake (g/kg/d)	0.5 (0.4, 0.6)	0.5 (0.4, 0.7)	0.4 (0.3, 0.6)
Muscle mass (kg)	40.9 ± 9.0	39.2 ± 8.9	42.9 ± 8.6
Dietary habit			
Strict vegetarian	569 (48.5)	316 (51.4)	253 (45.3)
Eat eggs	81 (6.9)	44 (7.1)	37 (6.6)
Non-vegetarian	524 (44.6)	255 (41.5)	269 (48.1)
Frequency of non-vegetarian meals (per month)[a]	2 (1,4)	2 (2,4)	2 (1,4)

CKD-EPI$_{2021}$: creatinine-based Chronic Kidney Disease Epidemiology equation (version 2021, race free), eGFR; estimated glomerular filtration rate, BMI; body mass index.

[a] Only in those consuming a nonvegetarian diet.

Data presented as mean ± SD, median (25th, 75th percentiles) or number (percentage).

Table 2. The mean mGFR and eGFR of the study population

$N = 1174$	Mean ± SD	Median (25th, 75th)	5th	95th
mGFR	60 ± 32	59 (32, 84)	16	113
CKD-EPI$_{2021}$	74 ± 39	84 (34, 111)	16	124
EKFC$_{crea}$	70 ± 36	77 (33, 104)	17	117
EKFC$_{ISQ}$	65 ± 36	69 (30, 97)	15	113
EKFC$_{ISK}$	59 ± 30	65 (28, 88)	14	99
EKFC$_{ISQ+ISK}$	55 ± 30	58 (25, 82)	12	95

CKD-EPI$_{2021,}$ creatinine-based chronic kidney disease epidemiology equation (version 2021, race free); Crea, Creatinine; EKFC, European kidney function consortium; ISQ, Indian-specific Q value; ISK, Indian-specific constant value (normal mGFR); ISQ + ISK, Indian-specific Q and constant value; mGFR, measured glomerular filtration rate.

CKD subgroup had a mean age of 50 ± 13 years (median: 51; IQR: 40–60 years), and 67% were male. Hypertension, diabetes, and cardiovascular disease were present in 466 (83%), 169 (30%), and 28 (5%) respectively, in patients having CKD, and 27 (5%) had a history of renal stone disease. By design, healthy donors had normal kidney function (mean mGFR: 83 ± 23, median: 82, IQR: 69–95 ml/min per 1.73 m^2), whereas patients with CKD had lower mGFR (mean: 34 ± 17, median: 31, IQR: 22–44 ml/min per 1.73 m^2).

We derived Indian-specific reference values from the healthy participants. The median SCr in males was 0.81 (IQR: 0.73–0.91) mg/dl, and in females was 0.63 mg/dl (IQR: 0.55–0.71), and these values were used as India-specific Q values. These values are lower than European Q-values (0.9 and 0.7 mg/dl in men and women, respectively). The median mGFR among healthy individuals younger than 40 years was 90 (IQR 80–103) ml/min per 1.73 m^2, lower than the 107 ml/min per 1.73 m^2 value that the EKFC equation assumes as the reference “normal” GFR. We adopted $K_{Ind} = 90$ ml/min per 1.73 m^2 for the recalibrated equation.

The mean mGFR of the study population was 60 ± 32 ml/min per 1.73 m^2. The mean eGFR values obtained using CKDEPI$_{2021}$ and EKFC$_{crea}$ equations were 74 ± 39 ml/min per 1.73 m^2 and 70 ± 36 ml/min per 1.73 m^2, respectively. With the Indian-specific Q (ISQ) adjustment, the mean eGFR values were 65 ± 36 ml/min per 1.73 m^2 for EKFC$_{ISQ}$. When the Indian-specific constant (ISK) value was used, the corresponding values were 59 ± 30 ml/min per 1.73 m^2 for EKFC$_{ISK}$. Using both Indian specific Q and K (ISQ+ISK), the mean eGFR values were 55 ± 30 ml/min per 1.73 m^2 for EKFC$_{ISQ+ISK}$ (Table 2). The mGFR and eGFRs of healthy and CKD participants are represented in Supplementary Table S2.

Overall Performance of Original Equations

Performance metrics for all equations in the full cohort ($n = 1174$) are presented in Table 3 and Figures 1 to 3. As expected, equations using SCr exhibited a substantial positive bias (eGFR-mGFR $>$ 0), indicating overestimation of GFR. The CKD-EPI$_{2021}$ had a bias of 14.4 ± 22.5 ml/min per 1.73 m^2 (95% CI: 13.1–15.7) and accuracy (P$_{30}$; 49.3% [95% CI: 46.5 –52.2]). The EKFC$_{crea}$ equation showed a reduced mean bias (9.9 ml/min per 1.73 m^2 [95% CI: 8.7–11.1], $P < 0.001$) and better P$_{30}$; (58.1% [95% CI: 55.3–60.9] , $P < 0.001$) as compared with CKD-EPI$_{2021}$.

Performance of Recalibrated EKFC Equations

Using Indian Q values while keeping K at 107 ml/min (EKFC$_{ISQ}$) corrected a large portion of the bias as compared with EKFC$_{crea}$. Bias significantly improved to 4.9 ml/min per 1.73 m^2 (95% CI: 3.7–6.0, $P < 0.001$), whereas P$_{30}$ rose to 63.9% (95% CI: 61.1–66.6 , $P < 0.001$). Replacing K with 90 ml/min EKFC$_{ISK}$) also reduced bias to -1.2 ml/min per 1.73 m^2 (95% CI: -2.2 to 0.1, $P < 0.001$), with P$_{30}$ of 68.9% (95% CI: 66.3–71.6, $P < 0.001$). Finally, applying both Indian-specific Q and K values to the EKFC equation yielded similar improvements in all performance metrics. The mean bias for EKFC$_{ISQ+ISK}$ was -5.4 ml/min per 1.73 m^2 (95% CI: -6.4 to 4.3; $P < 0.001$) and 64.2% of eGFR values fell within 30% of mGFR (P$_{30}$ 64.2% [95% CI: 61.5–67.0), $P < 0.001$]) (Table 3, Figures 1–3). A 10-fold cross-validation of the recalibrated equation indicates no deviation in performance from the internal validation dataset (Table 4, Supplementary Table S3).

Table 3. The performance of the different eGFR equations

eGFR equations	Bias		Precision		Accuracy			
	Mean ± SD (ml/min per 1.73 m^2)	Median (95% CI) (ml/min per 1.73 m^2)	95% CI (ml/min per 1.73 m^2)	IQR (Q1, Q3) (ml/min per 1.73 m^2)	95% distribution of bias (ml/min per 1.73 m^2)	MAE (95th CI) (ml/min per 1.73 m^2)	RSME (ml/min per 1.73 m^2)	P_{30} (95%CI) (%)
CKD-EPI_{2021}	14.4 ± 22.5	12.5 (10.8– 14.2)	13.1 –15.7	30.0 (−0.5 to 29.5)	−29.7 to 58.5	20.6 (19.7–21.6)	26.7	49.3 (46.5–52.2)
$EKFC_{crea}$	9.9 ± 20.9[a]	8.7 (7.1 –10.0)	8.7 –11.1	25.5 (−2.4 to 23.1)	−31.1 to 50.9	17.4 (16.6–18.3)	23.3	58.1 (55.3–60.9)[b]
$EKFC_{ISQ}$	4.9 ± 20.6[c]	3.6 (2.4 –4.5)	3.7 –6.0	23.4 (−6.4 to 17.0)	−35.4 to 45.2	15.6 (14.7–16.4)	21.1	63.9 (61.1–66.6)[d]
$EKFC_{ISK}$	−1.2 ± 18.8[c]	−1.4 (−2.3 to −0.4)	−2.2 to −0.1	19.5 (−10.1 to 9.4)	−38.1 to 35.8	13.6 (12.8–14.3)	18.9	68.9 (66.3–71.6)[d]
$EKFC_{ISQ+ISK}$	−5.4 ± 18.8[c]	−5.5 (−6.2 to −4.3)	−6.4 to 4.3	18.5 (-13.9 to 4.6)	−42.2 to 31.4	14.1 (13.4–15.0)	19.5	64.2 (61.5–67.0)[d]

CKD-EPI_{2021}, creatinine-based chronic kidney disease epidemiology equation (version 2021, race free), Crea: Creatinine; EKFC, European kidney function consortium; IQR, interquartile range; ISQ, Indian-specific Q value; ISK, Indian-specific constant value (normal mGFR); ISQ+ISK, Indian-specific Q and constant value; MAE, mean absolute error; P_{30}, Percentage of participants with eGFR within ± 30% of mGFR; RMSE, root mean square error.

[a,b] $P < 0.01$compared with CKD-EPI_{2021}.

[c,d] $P < 0.01$compared with $EKFC_{crea}$.

Subgroup Analysis

Table 5 presents performance metrics stratified by key subgroups. In individuals with mGFR ≥ 60 ml/min per 1.73 m^2, the CKD-EPI_{2021} has bias of 18.1 ± 22.3 ml/min per 1.73 m^2 (95%CI: 16.3–19.9) and P_{30} 53.1% (95% CI: 49.0–57.1), The $EKFC_{crea}$ had better performance compared with CKD-EPI_{2021} as bias reduced to 11.1 ml/min per 1.73 m^2 (95%CI: 9.3–12.8, $P < 0.001$) and P_{30} rose to 66.1% (95% CI: 62.3–70.0, $P < 0.001$). The $EKFC_{ISQ}$ in this group showed lower bias 5.1 ml/min per 1.73 m^2, (95% CI: 3.3–6.9, $P < 0.001$) and higher P_{30} 74.7% (95% CI: 71.1–78.3, $P < 0.001$) as compared with $EKFC_{crea}$. The $EKFC_{ISK}$ further improved the bias to −4.6 ml/min per 1.73 m^2(95% CI: −6.2 to −3.0, $P < 0.001$) and P_{30} 84.6% (95% CI: 81.7–87.6 $P < 0.001$). $EKFC_{ISQ+ISK}$ showed a mean bias of −9.6 ml/min per 1.73 m^2 (95% CI: −11.3 to −8.0, $P < 0.001$) and P_{30} of 81.5% (95% CI: 78.3–84.7 , $P < 0.001$) better than $EKFC_{crea}$. In those with mGFR < 60, the bias of CKD-EPI_{2021} and $EKFC_{crea}$ was more modest (10.8 and 8.8 ml/min per 1.73 $m^{2,}$ respectively) with P_{30} of 45.8%(95% CI: 41.8–49.7) and 50.4 % (95% CI: 46.4–54.4). After recalibration, bias in this group was eliminated (4.7 ml/min per 1.73 m^2) and P_{30} improved to 53.6 %(95% CI: 49.6–57.6) for $EKFC_{ISQ}$. We also assessed male and female participants separately. Interestingly, the CKD-EPI_{2021} and $EKFC_{crea}$ bias was slightly larger in females (18.4 ml/min per 1.73 m^2 and 13.4 ml/min per 1.73 m^2) than males (10.3 ml/min per 1.73 m^2 and 6.4 ml/min per 1.73 m^2). After recalibration, the bias in both sexes was reduced (males 1.6 ml/min per 1.73 m^2, females 8.1 ml/min per 1.73 m^2) for $EKFC_{ISQ}$. Both sexes saw P_{30} rise from ∼ 62% to ∼ 65% in males and ∼ 54% to ∼ 63% in females (Supplementary Table S4). P_{30} improved further with $EKFC_{ISK}$ equation for both males −66.5% (95% CI: 62.7–70.3) % and females −71.3% (95% CI: 67.7–75.0). We divided the cohort by age (≤ 40, 41–65, and > 65 years; Supplementary Table S5). The original equations showed substantial bias in all age groups. After recalibration, all age groups had lower bias and improved P_{30} for $EKFC_{ISQ}$, $EKFC_{ISK}$, and $EKFC_{ISQ+ISK}$. P_{30} improved in all age groups to ∼ 62% to 71% (Supplementary Table S5).

Reclassification of eGFR Categories

As shown in Table 6, among the total 1174 participants, 347 (30%) with $CKDEPI_{cr}2021$ eGFR were reclassified by $EKFC_{ISQ}$ to lower eGFR categories. Similarly, 560 (48%) and 785 (67%) were reclassified to lower categories using $EKFC_{ISK}$ and $EKFC_{ISQ+ISK}$, respectively. Highest reclassification was observed in the eGFR category of 45 to 59 ml/min per 1.72 $m^{2,}$ where 67%, 80%, and 100% subjects were reclassified

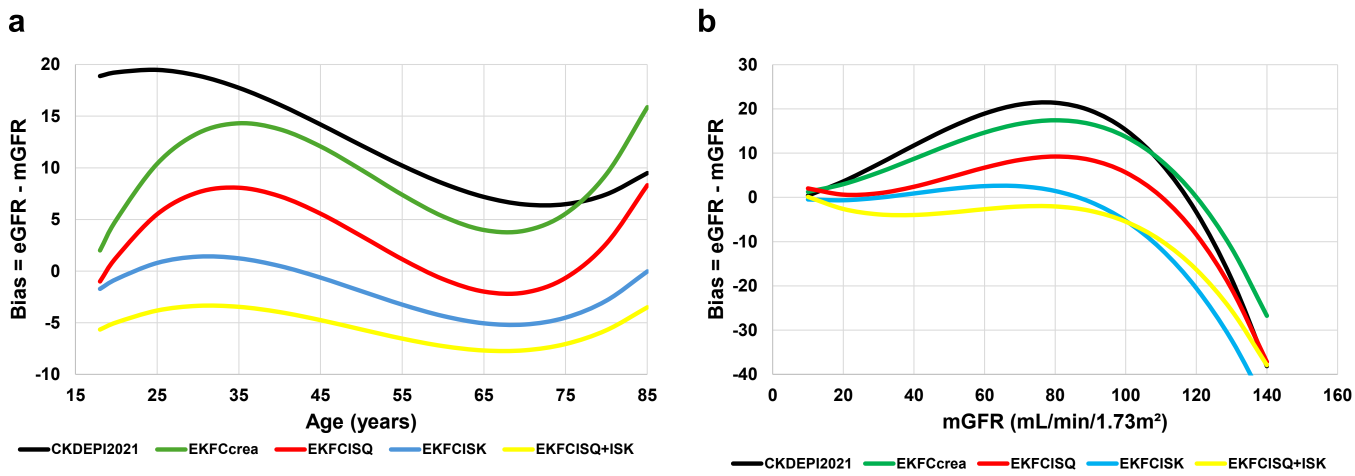

Figure 1. Bias of the CKD-EPI, EKFC and recalibrated equations against (a) age and (b) mGFR. mGFR, measured glomerular filtration rate; EKFC, European Kidney Function Consortium; EKFCISQ, European Kidney Function Consortium Indian Q; EKFCISK, European Kidney Function Consortium Indian constant; CKD-EPI, chronic kidney disease-epidemiology collaboration.CKD-EPI$_{2021}$: creatinine-based Chronic Kidney Disease Epidemiology equation (version 2021, race free), EKFC$_{crea}$: creatinine-based European Kidney Function Consortium equation, EKFC$_{ISQ}$: creatinine-based European Kidney Function Consortium equation recalibrated with Indian Specific normalized serum creatinine, EKFC$_{ISK}$: creatinine-based European Kidney Function Consortium equation recalibrated Indian normal GFR, EKFC$_{ISQ+ISK}$: creatinine-based European Kidney Function Consortium equation recalibrated Indian Specific normalized serum creatinine and Indian normal GFR. CKD-EPI, chronic kidney disease-epidemiology collaboration; EKFC, European Kidney Function Consortium; EKFCISQ, European Kidney Function Consortium Indian Q; EKFCISK, European Kidney Function Consortium Indian constant; mGFR, measured glomerular filtration rate.

to the 30 to 44 ml/min per 1.72 m^2 eGFR category using EKFC$_{ISQ}$, EKFC$_{ISK}$, and EKFC$_{ISQ+ISK}$, respectively. Similarly, 40%, 76%, and 86% of subjects in 30 to 44 ml/min per 1.72 m^2 eGFR category were reclassified to 15 to 29 ml/min per 1.72 m^2 eGFR category using EKFC$_{ISQ}$, EKFC$_{ISK}$, and EKFC$_{ISQ+ISK,}$ respectively. Overall, reclassification of eGFR led to lower eGFR categories for the EKFC$_{crea}$ equations, including the recalibrated equations, as compared with CKD-EPI$_{2021}$. We also analyzed the reclassification with reference to mGFR (Supplementary Table S6).

Sensitivity Analysis

As shown in Supplementary Table S7, the performance of all equations in the subjects with $R^2 > 0.975$ iohexol slope remained similar to that of the overall population.

DISCUSSION

This comprehensive study represents the first effort to validate and adjust the EKFC$_{crea}$ eGFR equation within an Indian adult demographic. Although the original EKFC equation showed lower bias than the CKD-EPI$_{2021}$ equation, it consistently overestimated the mGFR in the Indian population. This corresponds with earlier findings from Indian and other Asian cohorts,[8-12,20] presumably attributable to lower average muscle mass and unique dietary habits that affect SCr concentrations. Also, without recalibration, EKFC$_{crea}$ did not meet the accuracy benchmark in our cohort, despite its good performance in Europe.

The central innovation of our study lies in the successful use of Indian-specific variables to recalibrate the EKFC$_{crea}$ equation by using the median SCr (Q) and the median mGFR in healthy young individuals (K). This recalibration improved the accuracy of the equation, indicating the need for population-specific constants. The resulting Q values (males: 0.81, females: 0.63 mg/dl) were lower than those used in the original EKFC$_{crea}$ (0.90 and 0.70 mg/dl).[13]

The decision to use a lower K (90) in place of the EKFC reference (107) warrants explanation. In our data, 90 ml/min per 1.73 m^2 represents the empirically observed median mGFR in Indian living kidney donors and apparently healthy adults < 40 years, and thus functions as a population-specific calibration anchor rather than a redefinition of 'normal' kidney function. The lower K may reflect true physiological differences (smaller body size, lower protein intake, or lower nephron endowment) but could also be influenced by cohort characteristics and measurement protocols. A potential concern is that a lower reference K might reduce sensitivity to hyperfiltration or very early CKD in young adults; however, KDIGO definitions of CKD remain based on GFR < 60 ml/min per 1.73 m^2, rather than on the median GFR in healthy young individuals. Therefore, we view the K value of 90 ml/min per 1.73 m^2 as an internal calibration parameter within the EKFC framework for this Indian cohort, rather than a

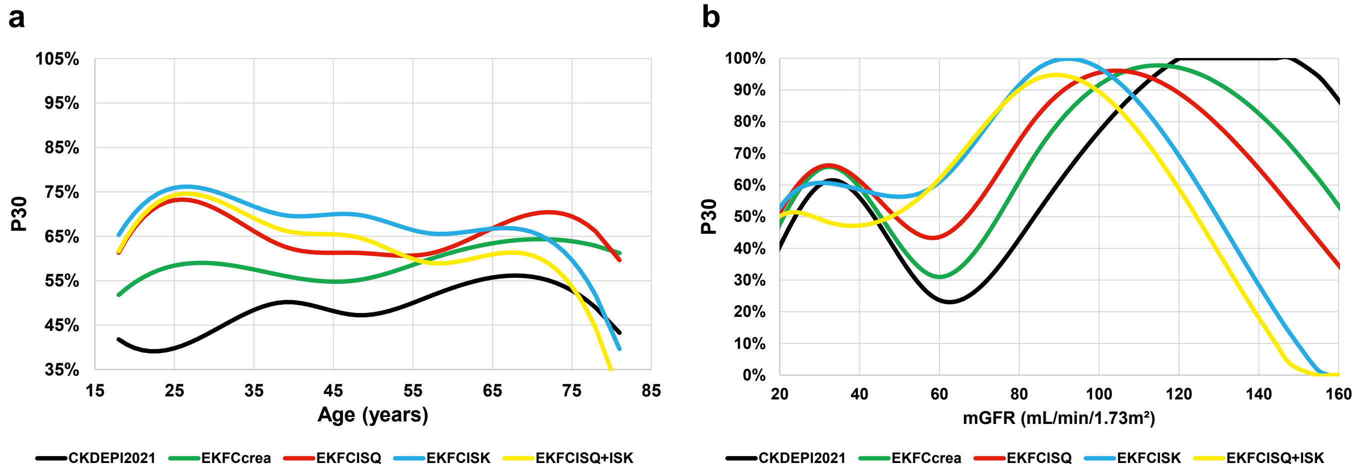

Figure 2. P_{30} of the CKD-EPI, EKFC and recalibrated equations against (a) age and (b) mGFR. CKD-EPI_{2021}: creatinine-based Chronic Kidney Disease Epidemiology equation (version 2021, race free), $EKFC_{crea}$: creatinine-based European Kidney Function Consortium equation, $EKFC_{ISQ}$: creatinine-based European Kidney Function Consortium equation recalibrated with Indian Specific normalized serum creatinine, $EKFC_{ISK}$: creatinine-based European Kidney Function Consortium equation recalibrated Indian normal GFR, $EKFC_{ISQ+ISK}$: creatinine-based European Kidney Function Consortium equation recalibrated Indian Specific normalized serum creatinine and Indian normal GFR. CKD-EPI, chronic kidney disease-epidemiology collaboration; EKFC, European Kidney Function Consortium; EKFCISQ, European Kidney Function Consortium Indian Q; EKFCISK, European Kidney Function Consortium Indian constant; mGFR, measured glomerular filtration rate.

proposal to revise normal GFR thresholds. Population-based and outcome-linked studies would be required before any such changes could be contemplated.

The contributions of each adjustment were shown via stepwise recalibration. $EKFC_{ISQ}$ (Indian Q only) cut the bias from 9.9 to 4.9 ml/min per 1.73 m^2 and raised P_{30} from 58.1% to 63.9%. Only changing K ($EKFC_{ISK}$) eliminated the mean bias and increased P_{30} to 68.9%, which was superior to all the other equations. Full recalibration ($EKFC_{ISQ+ISK}$) had a small positive bias and somewhat overcorrected but did better than the original models.

Subgroup analyses were revealing as well— those with mGFR $\geq$ 60 ml/min per 1.73 m^2 experienced the largest gains, with $EKFC_{ISK}$ and $EKFC_{ISQ+ISK}$ having P_{30} values of 84.6% and 81.5%, respectively, compared with the P_{30} from the original $EKFC_{crea}$ of 66.1% and CKD-EPI_{2021} of 53.1%. The better $EKFC_{ISK}$ performance in participants with mGFR $\geq$ 60 ml/min per 1.73 m^2 likely reflects greater stability of non-GFR

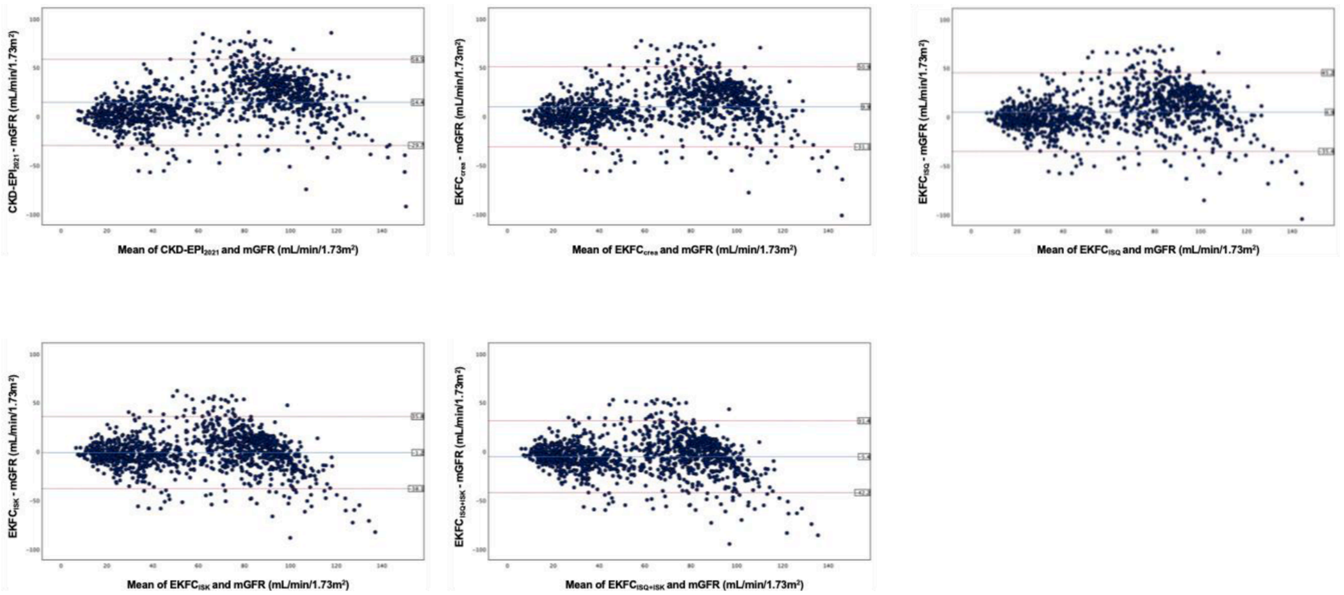

Figure 3. Bland-Altman plots for differences in agreement between eGFR and mGFR. Three lines represent the mean bias (center blue line) and 95% limits of agreement (upper- dotted and lower- dotted line in red). On the Y-axis, the difference between eGFR and mGFR, and on the X-axis, the mean of mGFR and eGFR has been plotted. eGFR, estimated glomerular filtration rate; mGFR, measured glomerular filtration rate; CKD-EPI, chronic kidney disease-epidemiology collaboration; EKFC, European Kidney Function Consortium.

Table 4. Performance metrics of recalibrated EKFC equations using 10-fold cross-validation in study participants

	Bias		Precision		Accuracy			
eGFR equations	Mean ± SD (ml/min per 1.73 m^2)	Median (95% CI) (ml/min per 1.73 m^2)	95% CI (ml/min per 1.73 m^2)	IQR (Q1, Q3) (ml/min per 1.73 m^2)	95% distribution of bias (ml/min per 1.73 m^2)	MAE (95th CI) (ml/min per 1.73 m^2)	RSME (ml/min per 1.73 m^2)	P_{30} (95%CI) (%)
$EKFC_{ISQ}$	4.6 ± 20.6	3.4 (2.1–4.4)	(3.3 –5.7)	23.3 (−6.8 to 16.5)	−35.7 to 44.9	15.45 (14.7–16.3)	21.1	64.2 (61.2–67.0)
$EKFC_{ISK}$	−1.1 ± 18.9	−1.32 (−2.2 to −0.3)	(−2.2 to −0.04)	19.4 (−10.0 to 9.4)	−38.1 to 35.9	13.6 (12.9–14.3)	18.9	68.8 (66.2–71.6)
$EKFC_{ISQ+ISK}$	−5.6 ± 18.8	−5.6 (−6.4 to −4.4)	(-6.7 to −4.6)	18.4 (−14.1 to 4.3)	−42.5 to 31.3	14.2 (13.5–14.9)	19.6	64.1 (61.5–66.8)

EKFC, European kidney function consortium; IQR, Interquartile range; ISQ, Indian-specific Q value; ISK, Indian-specific constant value (normal mGFR); ISQ+ISK, Indian-specific Q and constant value; MAE, mean absolute error; $P_{30,}$ Percentage of participants with eGFR within ±30% of mGFR; RMSE, root mean square error.

Table 5. The performance of the different eGFR equations between mGFR $\geq$ 60 ml/min per 1.73 m^2 and $<$ 60 ml/min per 1.73 m^2

	Bias		Precision		Accuracy			
eGFR equations	Mean ± SD (ml/min per 1.73 m^2)	Median (95% CI) (ml/min per 1.73 m^2)	95% CI (ml/min per 1.73 m^2)	IQR (Q1, Q3)	95% distribution of bias (ml/min per 1.73 m^2)	MAE (95% CI) (ml/min per 1.73 m^2)	RSME (ml/min per 1.73 m^2)	P_{30} (95%CI) (%)
mGFR $\geq$ 60 ml/min per 1.73 m^2 ($n = 573$)								
CKD-EPI_{2021}	18.1 ± 22.3	22.2 (20.3–23.6)	16.3–19.9	25.8 (7.6–33.4)	−25.7 to 61.8	24.8 (23.7–26.0)	28.7	53.1 (49.0–57.1)
$EKFC_{crea}$	11.1 ± 21.7[a]	14.7 (12.9–16.4)	9.3–12.8	25.5 (0.4–25.9)	−31.4 to 53.6	20.1 (19.0–21.2)	24.7	66.1 (62.3–70.0)[b]
$EKFC_{ISQ}$	5.1 ± 22.1[c]	8.6 (6.0–10.1)	3.3–6.9	26.5 (−6.3 to 20.2)	−38.1 to 48.3	17.9 (16.8–19.0)	22.6	74.7 (71.1–78.3)[d]
$EKFC_{ISK}$	−4.6 ± 20.2[c]	−1.4 (−3.2 to 0.4)	−6.2 to −3.0	24.0 (−14.5 to 9.5)	−44.3 to 35.0	15.0 (13.9–16.3)	20.7	84.6 (81.7–87.6)[d]
$EKFC_{ISQ+ISK}$	−9.6 ± 20.4[c]	−6.7 (−8.6 to −4.7)	−11.3 to −8.0	23.8 (−19.5 to 4.3)	−49.7 to 30.4	16.3 (15.1–17.7)	22.6	81.5 (78.3–84.7)[d]
mGFR $<$ 60 ml/min per 1.73 m^2 ($n = 601$)								
CKD-EPI_{2021}	10.8 ± 22.1	5.4 (4.4–7.2)	9.1–12.7	21.1 (-3.5 to 17.6)	−32.5 to 54.2	16.6 (15.1–18.1)	24.6	45.8 (41.8–49.7)
$EKFC_{crea}$	8.8 ± 20.1[a]	4.3 (3.2–5.5)	7.3–10.6	19.9 (−3.6 to 16.3)	−30.6 to 48.2	14.8 (13.5–16.2)	21.9	50.4 (46.4–54.4)
$EKFC_{ISQ}$	4.7 ± 19.1[c]	0.01 (−1.1 to 1.9)	3.2–6.3	17.7 (−6.6 to 11.1)	−32.7 to 42.1	13.3 (12.2–14.5)	19.6	53.6 (49.6–57.6)
$EKFC_{ISK}$	2.1 ± 16.8[c]	−1.4 (−2.6 to −0.03)	0.7–3.6	17.3 (−8.1 to 9.2)	−30.8 to 35.1	12.2 (11.3– 13.2)	16.9	53.9 (49.9–57.9)
$EKFC_{ISQ+ISK}$	−1.4 ± 16.0[c]	−4.2 (−5.7 to −3.3)	−2.6 to 0.1	15.5 (−10.8 to 4.7)	−32.8 to 30.1	12.1 (11.2–13.0)	16.1	47.8 (43.8–51.7)

Crea, Creatinine; EKFC, European kidney function consortium; MAE, mean absolute error; P_{30}, Percentage of participants with eGFR within ±30% of mGFR; IQR, Interquartile range; ISQ, Indian-specific Q value; ISK, Indian-specific constant value (normal mGFR); ISQ+ISK, Indian-specific Q and constant value; RMSE, root mean square error; mGFR, measured glomerular filtration rate.

[a,b] $P < 0.01$compared with CKD-EPI_{2021}.

[c,d] $P < 0.01$compared with $EKFC_{crea}$.

Table 6. Reclassification of eGFR subgroups among total population with reference to CKD-EPI$_{2021}$

		EKFC$_{ISQ}$					
eGFR equation	**eGFR (ml/min per 1.73 m^2)**	**≥ 90 (n = 409)**	**89–60 (n = 218)**	**59–45 (n = 86)**	**44–30 (n = 164)**	**29–15 (n = 232)**	**< 15 (n = 65)**
CKD-EPI$_{2021}$	≥ 90 (n = 553)	409 (74)	144 (26)				
	89–60 (n = 121)		74 (61)	47 (39)			
	59–45 (n = 119)			39 (32.8)	80 (67.2)		
	44–30 (n = 141)				84 (59.6)	57 (40.4)	
	29–15 (n = 194)					175 (90.2)	19 (9.8)
	< 15 (n = 46)						46 (100)

		EKFC$_{ISK}$					
eGFR equation	**eGFR (ml/min per 1.73 m^2)**	**≥ 90 (n = 253)**	**89–60 (n = 356)**	**59–45 (n = 89)**	**44–30 (n = 160)**	**29–15 (n = 246)**	**< 15 (n = 70)**
CKD-EPI$_{2021}$	≥ 90 (n = 553)	253 (45.8)	300 (54.2)				
	89–60 (n = 121)		56 (46.3)	65 (53.7)			
	59–45 (n = 119)			24 (20.2)	95 (79.8)		
	44–30 (n = 141)				65 (46)	76 (54)	
	29–15 (n = 194)					170 (87.6)	24 (12.4)
	< 15 (n = 46)						46 (100)

		EKFC$_{ISQ+ISK}$					
eGFR equation	**eGFR (ml/min per 1.73 m^2)**	**≥ 90 (n = 165)**	**89--60 (n = 406)**	**59–45 (n = 84)**	**44–30 (n = 158)**	**29–15 (n = 258)**	**< 15 (n = 103)**
CKD-EPI$_{2021}$	≥ 90 (n = 553)	165 (29.8)	385 (69.6)	3 (0.6)			
	89–60 (n = 121)		21 (17.4)	81 (66.9)	19 (15.7)		
	59–45 (n = 119)				119 (100)		
	44–30 (n = 141)				20 (14.2)	121 (85.8)	
	29–15 (n = 194)					137 (70.6)	57 (29.4)
	< 15 (n = 46)						46 (100)

		EKFC$_{crea}$					
eGFR equation	**eGFR (ml/min per 1.73 m^2)**	**≥ 90 (n = 480)**	**89–60 (n = 176)**	**59–45 (n = 120)**	**44–30 (n = 150)**	**29–15 (n = 206)**	**< 15 (n = 42)**
CKD-EPI$_{2021}$	≥ 90 (n = 553)	480 (86.8)	73 (13.2)				
	89–60 (n = 121)		103 (85.1)	18 (14.9)			
	59–45 (n = 119)			102 (85.7)	17 (14.3)		
	44–30 (n = 141)				127 (90)	14 (10)	
	29–15 (n = 194)				6 (3.1)	187 (96.4)	1 (0.5)
	< 15 (n = 46)					5 (10.9)	41 (89.1)

CKD-EPI$_{2021,}$ creatinine-based Chronic Kidney Disease Epidemiology equation (version 2021, race free); Crea, Creatinine; EKFC, European Kidney Function Consortium; ISQ, Indian-specific Q value; ISK, Indian-specific constant value; ISQ+ISKK, Indian-specific Q and constant value; eGFR, estimated glomerular filtration rate.
Data presented as number (percentage).

creatinine determinants at higher GFR levels and increased impact of individual variation in muscle mass, dietary factors, and tubular creatinine handling at lower GFR. The modest accuracy in advanced CKD underscores the need for cystatin C-based or combined equations in this population. Sex-specific recalibration substantially reduced gender disparities in equation performance. The original EKFC$_{crea}$ showed a larger bias in women than men (difference of 7.0 ml/min per 1.73 m^2). After Indian Q recalibration, this gap narrowed to 6.5 ml/min per 1.73 m^2 and was further reduced to 2.4 ml/min per 1.73 m^2 with EFKC$_{ISK}$, an improvement of 66% over the original equation. Although small absolute differences persist, the systematic directional overestimation that affects women more than men has largely been eliminated. These patterns are similar to what was found in China and Pakistan, where local calibration raised P$_{30}$ from 58%–74% to 80%–89%.[8,10] In cohorts from West Africa and Europe, EKFC$_{crea}$ showed optimal performance when using population-specific constants.[21] These statistics corroborate the global transition, endorsed by KDIGO 2024[4],towards more precise, population-tailored equations that eliminate the need for race modifiers by replacing with directly measured, biologically grounded parameters.

Participants under the age of 40 years had greater accuracy (P$_{30}$: 69%–74%) than those above 40 years (P$_{30}$: 60%–68%). This age gradient has been observed in previous studies and may indicate a more stable creatinine metabolism in younger individuals.[22] A Chinese study found that EKFC worked best for younger adults and those with a higher GFR.[23] European studies showed similar age-related performance gradients.[21]

Internal 10-fold cross-validation confirmed that improvements in performance metrics (bias, accuracy, and precision) remained stable across folds, indicating that the recalibration was not driven by overfitting to the derivation sample. This supports the robustness of the Indian-specific Q and K values derived from the healthy subgroup.

Reclassification analysis shows that the new equations move a substantial proportion of participants into lower eGFR categories than with the CKD-EPI$_{2021}$ equation. Although this may be more accurate, we lack outcome data to confirm that these reclassifications translate into higher risk. Moreover, widespread adoption of equations that lower eGFR estimates will increase apparent CKD prevalence, with implications for resource allocation, healthcare costs, patient anxiety, and access to treatments. Finally, some individuals reclassified to more advanced CKD may not have a worse prognosis, particularly if their lower eGFR reflects population-level physiological differences rather than kidney damage. Prospective studies linking recalibrated eGFR values to clinical outcomes are essential before policy changes.

The EKFC equation's superior adaptability likely stems from its mathematical structure. The model accounts for population physiology by scaling SCr to the median creatinine level in healthy individuals (Q) and using a fixed K (the median GFR in healthy young adults). In contrast, CKD-EPI models use predefined coefficients that may not reflect how creatinine levels change. Recalibrating K to 90 from 107, as set by EFKC$_{crea}$ based on European data[24], substantially corrected the baseline GFR discrepancy, removing systematic bias and improving performance. This finding confirms that accounting for lower creatinine generation in Indians is key to accurate GFR estimation.

Even while performance got better, accuracy remained below 75% to 80%, especially for those with mGFR <60 ml/min per 1.73 m^2 (P$_{30}$ 53.9%). This remaining inaccuracy is probably because of individual variation in creatinine generation, differences in muscle mass, dietary protein intake, physical activity, medication effects, and disease-specific effects (metabolic acidosis, altered protein metabolism, tubular creatinine secretion inhibition, and sarcopenia), and noise in both mGFR and creatinine tests. Studies show that even when equations are unbiased, individual-level error can be large, with 95% limits of agreement spanning 40 to 50 ml/min per 1.73 m^2.[25]

Strengths of this study include the relatively large sample size, inclusion of both healthy individuals and pateints with CKD across a wide GFR range, and use of mGFR by iohexol plasma clearance. We derived population-specific calibration constants from healthy participants and validated performance across the full cohort with cross-validation and subgroup analyses. This study has several limitations. As an internal validation study, Q and K were derived and tested in the same cohort, which may result in overfitting and inflated performance metrics. India specific Q and K obtained here were derived in 1 region (North India), rather than being nationally representative. External validations across regions and different demographic strata are still needed before the equation is promoted for national implementation or inclusion in guidelines. CKD will be defined using the same threshold of 60 ml/minute per 1.73 m^2. However, an adjustment for the Indian population is necessary. Even the best-performing recalibrated equation remained below the accepted P$_{30}$ targets, particularly among participants with mGFR $<$ 60 ml/min per 1.73 m^2. Healthy volunteers were partly defined using CKD-EPI$_{2021}$ eGFR $>$ 60 ml/min per 1.73 m^2; given that CKD-EPI$_{2021}$ itself overestimates GFR in Indians, this selection criterion may have allowed individuals with true GFR below 60 to enter the "healthy" group and influence Q and K values downward. Although we believe this effect is small, it represents a potential source of bias. Our subsequent mGFR measurements confirmed that the healthy cohort had a median mGFR of 82 ml/min per 1.73 m^2 (IQR: 69–95), supporting the validity of this group for deriving reference values. We did not assess cystatin C–based equations. Creating EKFC equations for India that use cystatin C or a combination of cystatin C and creatinine may improve accuracy, especially amongst people with unusual muscle mass. Cost, however, remains a challenge. Studies are also needed to determine whether recalibrated equations more accurately predict CKD development and clinical outcomes, as observed in European contexts.

In conclusion, the recalibrated EKFC equations, particularly EKFC$_{ISK}$, show improved performance in the studied population, particularly at higher GFR. However, several steps are required before wider clinical implementation, as follows: external validation in independent, diverse Indian cohorts; longitudinal studies to evaluate the impact on CKD progression, mortality, and cardiovascular events; and a cost-effectiveness analysis of implementation. If successfully validated, the equation should be incorporated into Indian nephrology practice guidelines and laboratory reporting systems to improve the accuracy of CKD diagnosis and staging.

DISCLOSURE

VJ has received grant funding from GSK, Baxter Healthcare, and Biocon and honoraria from Bayer, AstraZeneca, Boeringer Ingelheim, NephroPlus and Zydus Cadilla, under the policy of all honoraria being paid to the George Institute for Global Health. PD is consultant for Nephrolyx. All other authors declared no competing interests.

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DATA AVAILABILITY STATEMENT

All the data supporting the study are included in this manuscript and its supplementary files. Any additional data related to study can be made available upon reasonable request to the corresponding author subject to institute ethics committee approval.

AUTHOR CONTRIBUTIONS

Study design was done by AKY, VJ, and PD. Study participants enrollment and data curation was done by VK, HSK, PA, RK, AP, SP, and JST. The experimental analysis was conducted by JK and AKY, biochemistry analysis by AP and statistical analysis by AKY, JK, PD, and HP. Supervision of the study procedures was the work of NS and VK. The original manuscript was drafted by AKY, JK, PD, and VJ. All authors reviewed and approved the final version.

SUPPLEMENTARY MATERIAL

Supplementary file (PDF)

Table S1. CKD-EPI$_{2021,}$ EKFC$_{crea}$ and Indian specific recalibrated EKFC equation.

Table S2. The mean mGFR and eGFR values between the healthy and CKD populations.

Table S3. 10-fold cross-validation of recalibrated EKFC equations representing the performance metrics in each fold.

Table S4. The performance of the different eGFR equations between males and females.

Table S5. The performance of the different eGFR equations according to age groups.

Table S6. Reclassification of eGFR subgroups among total population with reference to mGFR.

Table S7. The performance of the different eGFR equations among subjects with $r^2 > 0.975$ for plasma iohexol clearance slope.

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