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ORIGINAL ARTICLE

Comparison of Pakistani CKD-EPI, new Asian-modified CKD-EPI and revised Lund–Malmö study equations in a South Asian CKD population: a study from a Pakistani CKD cohort

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Abstract

Background Newly proposed estimating glomerular filtration rate equations need to be studied, evaluated and compared for chronic kidney disease staging, diagnosis and medication dosing in South Asians. The objectives of the study were (1) to assess the performance of the CKD-EPI$_{PK}$, CKD-EPI$_{Asian\text{-}Modified,}$ and LM$_{Revised}$ equations in the Pakistani chronic kidney disease population, and (2) to investigate prospective implications on chronic kidney disease classification and end-stage kidney disease prevalence.

Methods We conducted a cross-sectional analysis on a chronic kidney disease cohort of 385 participants 18 years of age or above.

Results CKD-EPI$_{PK}$ showed the lowest bias (− 1.33 ml/min/1.73 m^2), highest precision [IQR, 2.33 (− 2.36, − 0.03)] and enhanced P30 accuracy (89.35%) compared to the CKD-EPI$_{Asian\text{-}Modified}$ and LM$_{Revised}$ equations. The mean difference (ml/min/1.73 m^2), 95% limit of agreement (ml/min/1.73 m^2) of the equations were; CKD-EPI$_{Asian\text{-}Modified}$: − 5.98, − 13.03, LM$_{Revised}$: − 4.06, − 8.13 and CKD-EPI$_{PK}$: − 1.18, − 6.14 ($P < 0.001$). CKD-EPI$_{Asian\text{-}Modified}$ and LM$_{Revised}$ showed upward re-classification of the GFR categories compared to the CKD-EPI$_{PK}$ equation except in the G5 category where the highest count (217, 56.36%) was noted for the CKD-EPI$_{PK}$ equation. End-stage kidney disease prevailed in all age groups according to all equations, and the prevalence was high in females in all equations.

Conclusion CKD-EPI$_{PK}$ showed the best performance, whereas both CKD-EPI$_{Asian\text{-}Modified}$ and LM$_{Revised}$ showed poor performance and did not offer a sufficient advantage in chronic kidney disease classification and end-stage kidney disease prevalence estimation over CKD-EPI$_{PK}$. Hence, CKD-EPI$_{PK}$ seems ideal for South Asians, thus appropriate measures should be taken for its implementation, at least in Pakistani laboratories.

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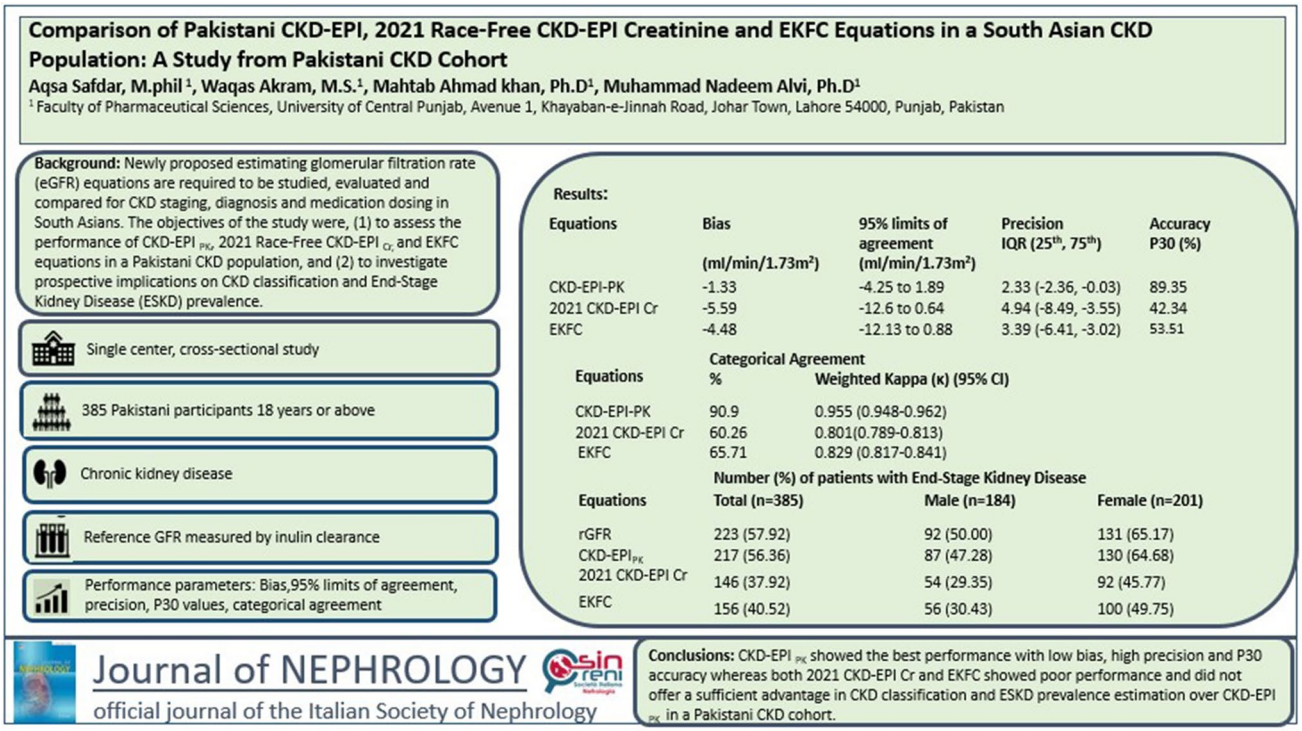
Graphical abstract



Keywords South Asians · Glomerular filtration rate · GFR equations · CKD-EPI$_{PK}$ · LM$_{Revised}$ · Asian-modified CKD-EPI

Introduction

Chronic kidney disease (CKD) is the 11th cause of death and is classified as the 18th source of disability-adjusted life years according to the 2019 Global Burden of Disease Study [1]. The worldwide prevalence of CKD is around 8.6% [1]. In South Asia, the prevalence of CKD ranges from 10.6% in Nepal to 23.3% in Pakistan [2]. According to a study, the overall prevalence of CKD among Pakistani adults was reported to be 21.2% [2]. According to other studies, the highest prevalence noted was 29.9% [3] and the lowest prevalence noted was 12.5% [4]. Glomerular filtration rate (GFR) is the most beneficial single index for evaluating kidney function and for diagnosing and staging CKD according to the Kidney Disease Improving Global Outcomes (KDIGO) guidelines [5]. Measuring GFR directly using radioisotope or inulin clearance is, however, not feasible in clinical practice, therefore, GFR based on estimating equations (eGFR) using endogenous filtration markers, such as serum levels of creatinine (SCr) and cystatin C (SCysC), is commonly employed [6].

The Lund–Malmö equations were revised by adding more complex terms such as lean body mass. The revised Lund–Malmö equations (LM$_{Revised}$) showed superior performance in a Swedish population [7–11]. A few studies have also assessed its performance in Asians [12, 13], but no study has been carried out specifically in South Asians. The new Asian-Modified CKD-EPI (CKD-EPI$_{Asian\text{-}Modified}$), a four-level race variable (Black, Asian, Native American and Hispanic, and White and other) was developed that significantly refined bias in Asians and in Chinese [14–18]; it has never been validated or compared in a South Asian population.

An influential and groundbreaking study from Karachi, Pakistan evaluated the performance of the present GFR estimation formulas, modified the present equations and developed a new equation for implementation in South Asians [19]. Modification factors of slope and intercept to the CKD-EPI formula led to a Pakistani CKD-EPI equation (CKD-EPI$_{PK}$) which significantly reduced bias and improved accuracy.

Previously, the CKD-EP I_{PK} equation was used to evaluate the prevalence, determinants and management of CKD in this region [4]. Moreover, it has recently been used to assess the variation in CKD in relation to demographics, comorbidities and outcomes [20] but there are only a few studies that compared this equation with other eGFR equations [21, 22]. Furthermore, there is no study that evaluated $LM_{Revised}$ and CKD-$EPI_{Asian\text{-}Modified}$ equations in comparison to CKD-EPI_{PK} in a South Asian population. In this report, we aim to assess the performance of the $LM_{Revised}$, CKD-$EPI_{Asian\text{-}Modified}$ and CKD-EPI_{PK} equations in the Pakistani CKD population and to investigate the prospective implications on CKD classification and End-Stage Kidney Disease (ESKD) prevalence across these eGFR equations in this population.

Methods

Participant's characteristics

We performed a cross-sectional analysis using estimating equations including the CKD-$EPI_{Asian\text{-}Modified}$, $LM_{Revised}$ equations and CKD-EPI_{PK} on a CKD cohort of 385 patients from December 2021 to February 2023. Patients sent by nephrologists for laboratory testing of kidney function who were diagnosed with CKD at Allama Iqbal Medical College, Jinnah Hospital, Lahore were included in this study. Chronic kidney disease was diagnosed according to the criteria of the KDOQI practice guidelines (GFR ≤ 60 ml/min/1.73 m^2 and albumin to creatinine ratio (ACR) > 30 mg/g for ≥ 3 months) [23]. The inclusion criteria were subjects aged > 18 years, with complete kidney function tests including BUN levels, ACR and serum creatinine values and with a confirmed diagnosis of CKD. Exclusion criteria were incomplete laboratory findings, diagnosis of kidney disease other than CKD, on-going dialysis, acute kidney failure or severe heart failure, severe malnutrition or edema, abdominal or pleural effusions, ketoacidosis, amputation or skeletal muscle atrophy. Patients taking cimetidine, angiotensin-converting enzyme inhibitors and/or angiotensin-receptor blockers and trimethoprim, or recently undergoing hemodialysis and glucocorticoid treatment were also excluded. Written informed consent was provided by each patient before participation. The study was approved by the Ethical Review Board of Allama Iqbal Medical College, Jinnah Hospital (ERB No. 167/23/12/2021/S2 ERB) in its 108th meeting dated 23/12/2021.

Measurement of reference GFR (rGFR)

Reference GFR (rGFR) was measured by employing the urinary clearance of inulin which was considered the gold standard. Inulin clearance was estimated from urine and serum concentrations and the flow rate of urine. A continuous infusion of 1% inulin was administered intravenously in all 385 patients for 2.5 h after 12 h of overnight fasting. Patients were hydrated orally with 65 ml of water after 30, 60, 90, and 120 min. During the infusion of inulin, serum samples were collected four times (0, 40, 70, and 100 min), whereas urine samples were collected three times (30–60, 60–90, and, 90–120 min) after completely voiding the bladder 30 min after inulin infusion was initiated. Samples of inulin were assayed according to the enzymatic method by utilizing a kit. Reference GFR was expressed in terms of body surface area as per 1.73 m^2 by multiplication of measured values $0.007184 \times W^{0.425} \times H^{0.725}$. The mean value of three measurements was expressed as the rGFR which served as a gold standard for comparison with eGFR equations.

Estimation of GFR

Estimation of GFR (ml/min/1.73 m^2) was carried out using the CKD-EPI_{PK}, $LM_{Revised}$ and CKD-$EPI_{Asian\ modified}$ equations. The list of included equations is shown in Table 1.

Table 1 Equations included in the study

No	Equations	
1	CKD-EPI_{PK}	$eGFR = 0.686 \times CKD - EPI^{1.059}$
2	$LM_{Revised}$	$eGFR = e^{X-0.0158\times Age+0.438\times \ln(Age)}$, where ln is the natural logarithm and $X = 2.50 + 0.0121 \times (150–SCr)$ for females with SCr < 150 mmol/L, $X = 2.50–0.926 \times \ln(SCr/150)$ for females with pCr ≥ 150 mmol/L, $X = 2.56 + 0.00968 \times (180–SCr)$ for males with SCr < 180 mmol/L, and $X = 2.56–0.926 \times \ln(SCr/180)$ for males with SCr ≥ 180 mmol/L
3	CKD-$EPI_{Asian\text{-}modified}$	$eGFR = 151 \times (Scr/0.7)^{-0.328} \times (0.993)^{age}$ for females SCr ≤ 0.7 mg/dL, $eGFR = 151 \times (Scr/0.9)^{-1.210} \times (0.993)^{age}$ for females SCr ≥ 0.7 mg/dL, $eGFR = 149 \times (Scr/0.9)^{-0.415} \times (0.993)^{Age}$ for males with SCr ≤ 0.9 mg/dL and $eGFR = 149 \times (Scr/0.9)^{-1.210} \times (0.993)^{age}$ for males with SCr ≥ 0.9 mg/dL

SCr serum creatinine; *CKD-EPI_{PK}* CKD-EPI equation with Pakistani modification factors; *$LM_{Revised}$* revised Lund–Malmö equation; *CKD-$EPI_{Asian\text{-}Modified}$* New Asian-modified CKD-EPI equation

Laboratory methods

Blood samples of each patient collected for inulin measurement were measured for serum creatinine by Jaffe reaction carried out on a Siemens analyzer, ADIVA 2120. Urine samples were collected for measurement of ACR by A1Care™ HbA1c and ACR analyzer (Precision; Albumin: ≤ 8% CV, Creatinine: 8% CV).

Calibration of serum creatinine assays

Calibration of the assay was carried out daily by two-point calibration with the help of calibrators provided by the manufacturer and traceable to isotope dilution mass spectrometry (IDMS) employing the National Institute of Standards and Technology (NIST) creatinine standard reference material (SRM 967). The system was standardized by routine internal quality control procedures and by involvement in external quality assurance surveys by the College of American Pathologists.

GFR categories

Chronic kidney disease was categorized as G3a: 45–59 ml/min/1.73 m^2, G3b: 30–44 ml/min/1.73 m^2, G4: 15–29 ml/min/1.73 m^2 and G5: < 15 ml/min/1.73 m^2 according to the KDIGO 2012 guideline [5, 23]. The prevalence of ESKD, defined as < 15 ml/min/1.73 m^2, was compared among the equations on the basis of the serum creatinine.

Statistical analysis

Data were analyzed using IBM-SPSS version 26.0. We assessed the performance of three equations with benchmarks of bias, precision, and accuracy as suggested by KDOQI guidelines along with a percentage of GFR category misclassification. Bias was expressed as median difference between rGFR and eGFR. A negative value of bias showed overestimation of rGFR by equations and vice versa. Precision was expressed as interquartile range (25th percentile; 75th percentile) of difference between rGFR and eGFR. P30 accuracy was defined as the percentage of participants within ± 30% of rGFR. Bland–Altman Plots were made to show the mean differences and limit of agreements between each equation. Scatter plots were made and regression equations were derived by linear regression method for each equation. Pearson's correlation coefficients (r) were calculated to describe the relationship between all equations and rGFR. Negligible correlations were attributed to r coefficients ≤ 0.30; low correlations were attributed to 0.30–0.49; moderate correlations were attributed to 0.50–0.69; high correlations were attributed to r coefficients 0.70–0.89; and very high correlations were attributed to r coefficients ≥ 0.90 [24]. Categorical agreement rates were estimated when rGFR and eGFR by each equation fell within similar GFR categories. Weighted kappa (κ) value was calculated to evaluate the degree of categorical agreement. The κ values were interpreted as follows: < 0.20, poor; 0.21–0.40, fair; 0.41–0.60, moderate; 0.61–0.80, good; and > 0.81, very good [25]. Counts with percentages were reported for the prevalence of ESKD. P-values < 0.001 were considered statistically significant. A lower significance level was chosen so that stronger evidence can be demonstrated before the null hypothesis is rejected.

Results

Baseline subject characteristics analysis

The baseline characteristics of the participants are shown in Table 2. Among 385 patients, 201 (52.2%) were females. Mean ± SD age (years) was 61.99 ± 16.66, weight (kg) was 80.14 ± 12.98, height (cm) was 168.19 ± 9.53, BMI (kg/m^2) was 28.56 ± 5.47, and body surface area (m^2) was 1.89 ± 0.16, respectively. Mean ± SD serum creatinine and rGFR were 3.72 ± 2.03 and 15.73 ± 10.59. Mean eGFR by CKD-EPI_{PK} was closest to rGFR while other equations yielded higher mean eGFR than the rGFR, and the degree of variation differed with the equations and age groups. The eGFR by CKD-EPI_{PK} was 16.91 ml/min/1.73 m^2, by CKD-$EPI_{Asian\text{-}Modified}$ it was 21.36 ml/min/1.73 m^2 and by $LM_{Revised}$ it was 19.79 ml/min/1.73 m^2.

Out of 385 participants, 0.52% had CKD Stage 3a, 12.20% had CKD Stage 3b, 29.35% showed CKD Stage 4 and 57.92% showed CKD Stage 5 according to rGFR.

There were 40.78% of patients with unknown cause of CKD, 21.56% of patients had diabetic nephropathy, 20.26% had hypertensive nephropathy, 8.31% had chronic glomerulonephritis, 5.45% had polycystic kidney disease and 3.64% had chronic interstitial nephritis (Table 2).

Serum creatinine levels, reference and estimated glomerular filtration rates were stratified by age groups and are shown in Table S1. A gradual reduction in the estimated GFR was noted in elderly patients by all the equations in this study.

Performance of GFR estimating equations in comparison to rGFR

CKD-$EPI_{Asian\text{-}Modified}$ and $LM_{Revised}$ showed the highest bias (median difference, − 5.32 ml/min/1.73 m^2; − 4.14 ml/min/1.73 m^2), respectively. Whereas, the CKD-EPI_{PK} equation showed the lowest bias (− 1.33 ml/min/1.73 m^2) in comparison to rGFR. CKD-EPI_{PK} also showed higher precision [IQR, 2.33 (− 2.36, − 0.03)], and P15 and P30 accuracy (70.39% and 89.35%) than the CKD-$EPI_{Asian\text{-}Modified}$

Table 2 Baseline characteristics of studied samples ($n = 385$)

Characteristic	*n* (%)
Gender	
Female	201 (52.2%)
Male	184 (47.79%)
	Mean ± SD
Age (years)	61.99 ± 16.66
Weight (kg)	80.14 ± 12.98
Height (cm^2)	168.19 ± 9.53
BMI[a] (kg/m^2)	28.56 ± 5.47
BSA[b] (m^2)	1.89 ± 0.16
BUN (mg/dL)	40.2 ± 13.76
ACR (mg/g)	188.14 ± 81.56
Serum creatinine (mg/dL)	3.72 ± 2.03
rGFR (ml/min/1.73 m^2)	15.73 ± 10.59
eGFR CKD-EPI_{PK} (ml/min/1.73 m^2)	16.91 ± 11.18
eGFR $LM_{Revised}$ (ml/min/1.73 m^2)	19.79 ± 11.04
eGFR CKD-$EPI_{Asian\text{-}Modified}$ (ml/min/1.73 m^2)	21.36 ± 13.43
CKD stages[c]	*n* (%)
Stage G3a	2 (0.52)
Stage G3b	47 (12.20)
Stage G4	113 (29.35)
Stage G5	223 (57.92)
Causes of CKD	*n* (%)
Unknown	157 (40.78%)
Diabetic nephropathy	83 (21.56%)
Hypertensive nephropathy	78 (20.26%)
Chronic glomerulonephritis	32 (8.31%)
Polycystic kidney disease	21 (5.45%)
Chronic interstitial nephritis	14 (3.64%)

BMI body mass index; *BSA* body surface area; *BUN* blood urea nitrogen; *ACR* albumin to creatinine ratio; *rGFR* reference GFR; *eGFR* estimated glomerular filtration rate; *CKD-EPI*$_{PK}$ CKD-EPI equation with Pakistani modification factors; *LM*$_{Revised}$ revised Lund–Malmö equation; *CKD-EPI*$_{Asian\text{-}Modified}$ New Asian-modified CKD-EPI equation

[a]Defined by formula, BMI = $\frac{\text{weight(kg)}}{\text{height(m)}^2}$

[b]Defined by Du Bois formula, BSA = $0.007184 \times W^{0.425} \times H^{0.725}$

[c]Defined as the Chronic Kidney Disease Epidemiology Collaboration estimated glomerular filtration rate based on CKD-EPI_{PK} < 60 ml/min/1.73 m^2 or urine albumin to creatinine ratio ≥ 30 mg/g for ≥ 3 months

(11.69% and 40.78%) and $LM_{Revised}$ equations (24.94% and 54.55%) (Table 3).

Concordance between GFR estimating equations and rGFR

Mean differences and 95% limit of agreement

The mean differences between rGFR and eGFR by the three equations are illustrated by Bland–Altman plot. The mean difference of − 1.18 ml/min/1.73 m^2, 95% limit of agreement of − 6.14 ml/min/1.73 m^2 was shown between the CKD-EPI_{PK} equation and rGFR (Fig. 1). The mean difference of − 5.98 ml/min/1.73 m^2, 95% limit of agreement of − 13.03 ml/min/1.73 m^2 was shown between CKD-$EPI_{Asian\text{-}Modified}$ and rGFR (Fig. 2). The mean difference and 95% limit of agreement was − 4.06 ml/min/1.73 m^2 and − 8.13 ml/min/1.73 m^2 between the $LM_{Revised}$ equation and rGFR (Fig. 3). Bland–Altman plots also show that the data points for CKD-EPI_{PK} are evenly dispersed across the mean difference which is quite similar to the dispersion shown by $LM_{Revised}$.

The 95% limits of agreement for the CKD-$EPI_{Asian\text{-}Modified}$ and $LM_{Revised}$ equations are wider (− 13.03 ml/min/1.7 m^2, − 8.13 ml/min/1.73 m^2) as compared to the CKD-EPI_{PK} equation (− 6.14 ml/min/1.73 m^2). The higher negative values of the mean difference for both the CKD-$EPI_{Asian\text{-}Modified}$ and $LM_{Revised}$ equations (− 5.98 ml/min/1.73 m^2 and − 4.06 ml/min/1.73 m^2) illustrates the overestimation of rGFR by these equations in this CKD cohort compared to the CKD-EPI_{PK} equation.

Correlation and regression analysis

The r coefficients were 0.978 for CKD-$EPI_{Asian\text{-}Modified}$, 0.972 for $LM_{Revised}$ and 0.982 for CKD-EPI_{PK} compared to rGFR ($P < 0.001$). Hence, all equations showed statistically very high correlation with rGFR.

Figure S1 (supplementary data) represents the scatter plot and regression equation for the CKD-EPI_{PK} formula and rGFR (ml/min/1.73 m^2). In the regression equation $eGFR_{CKD-EPI-PK} = 0.46 + 1.05 * rGFR$, the intercept is below one and the slope is narrow.

Figure S2 represents the scatter plot and regression equation for the CKD-$EPI_{Asian\text{-}Modified}$ formula and rGFR (ml/min/1.73 m^2). In the regression equation $eGFR_{Asian-Modified} = 1.67 + 1.25 * rGFR$, the intercept is almost two but the slope is narrow.

Figure S3 represents the scatter plot and regression equation for the $LM_{Revised}$ equation and rGFR (ml/min/1.73 m^2). In the regression equation $eGFR_{LMRevised} = 3.64 + 1.03 * rGFR$, the intercept is almost four but the slope is narrow. According to Pearson's correlation and linear regression method, $LM_{Revised}$ and CKD-EPI_{PK} are closer to rGFR than CKD-$EPI_{Asian\ Modified}$ in this study population.

Categorical agreement rates

The rates of categorical agreement were 90.9%, 73.77% and 66.49% between rGFR and the CKD-EPI_{PK}, $LM_{Revised}$

Table 3 Performance of GFR estimating equations as compared to reference GFR by urinary inulin clearance

eGFR equation	Bias[a] (ml/min/1.73 m^2)	95% limits of agreement (ml/min/1.73 m^2)	Precision IQR (25th, 75th)	Accuracy P15 (%)[b]	Accuracy P30 (%)[c]
CKD-EPI-PK	−1.33	−4.25 to 1.89	2.33 (−2.36, −0.03)	70.39	89.35
$CKD\text{-}EPI_{Asian\text{-}Modified}$	−5.32	−12.14 to 0.89	4.6 (−7.85, −3.25)	11.69	40.78
$LM_{Revised}$	−4.14	−7.72 to −0.40	2.32 (−5.14, −2.83)	24.94	54.55

rGFR reference glomerular filtration rate; *eGFR* estimated glomerular filtration rate; *IQR* interquartile range; $CKD\text{-}EPI_{PK}$ CKD-EPI equation with Pakistani modification factors; $LM_{Revised}$ revised Lund–Malmö equation; $CKD\text{-}EPI_{Asian\text{-}Modified}$ new Asian-modified CKD-EPI equation

[a]Bias is expressed as median difference between rGFR and eGFR

[b]P15% expressed as percentage of patients with eGFR within ± 15% of rGFR

[c]P30% expressed as percentage of patients with eGFR within ± 30% of rGFR

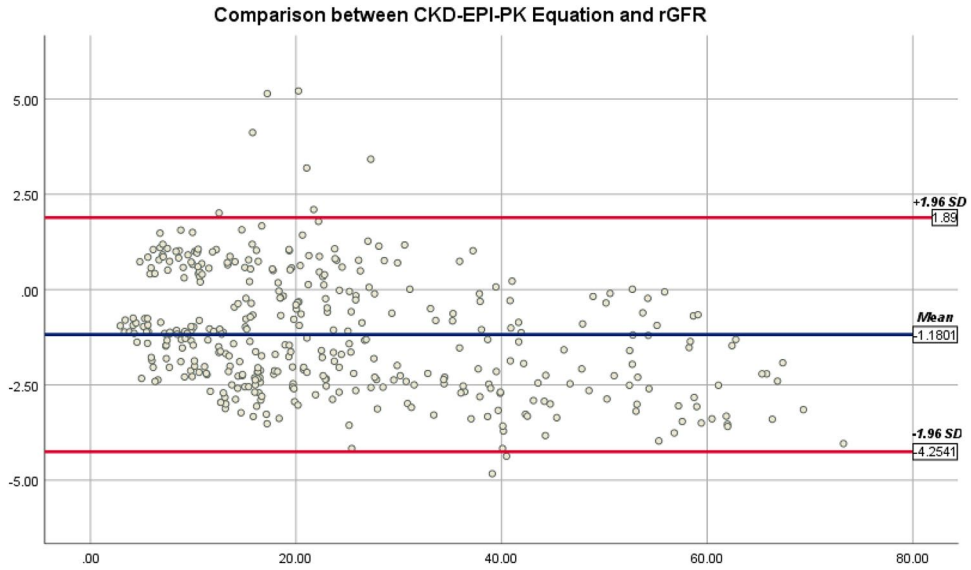


Fig. 1 Bland–Altman plot of $CKD\text{-}EPI_{PK}$ and rGFR (ml/min/1.73 m^2). The mean of $CKD\text{-}EPI_{PK}$ plus rGFR is located on the *x*-axis, and the value of rGFR minus $CKD\text{-}EPI_{PK}$ is located on the *y*-axis. Solid blue line represents mean difference between $CKD\text{-}EPI_{PK}$ and rGFR and dark red lines represent 95% limits of agreement of the mean difference between them

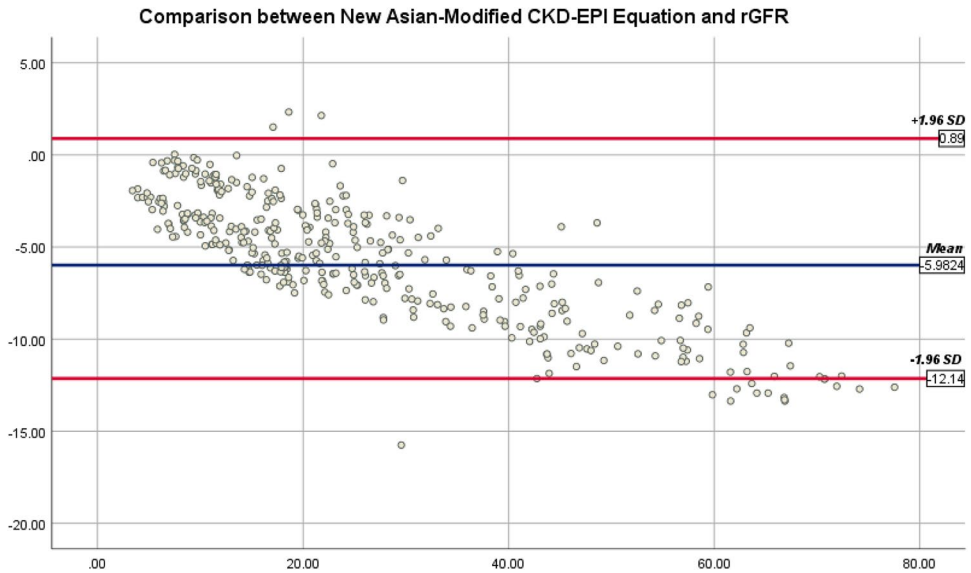


Fig. 2 Bland–Altman plot of $CKD\text{-}EPI_{Asian\text{-}Modified}$ and rGFR (ml/min/1.73 m^2). The mean of $CKD\text{-}EPI_{Asian\text{-}Modified}$ plus rGFR is located on the *x*-axis, and the value of rGFR minus $CKD\text{-}EPI_{Asian\text{-}Modified}$ is located on the *y*-axis. Solid blue line represents mean difference between $CKD\text{-}EPI_{Asian\text{-}Modified}$ and rGFR and dark red lines represent 95% limits of agreement of the mean difference between them

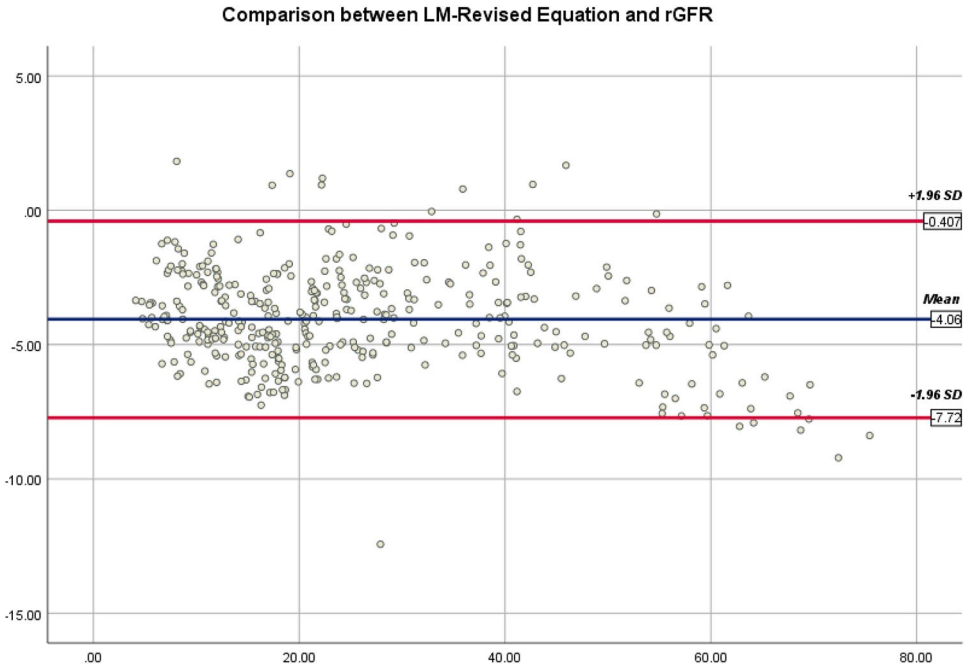


Fig. 3 Bland–Altman plot of $LM_{Revised}$ and rGFR (ml/min/1.73 m^2). The mean of $LM_{Revised}$ plus rGFR is located on the *x*-axis, and the value of rGFR minus $LM_{Revised}$ is located on the *y*-axis. Solid blue line represents mean difference between $LM_{Revised}$ and rGFR and dark red lines represent 95% limits of agreement of the mean difference between them

Table 4 Categorical agreement and discordant KDIGO GFR categories between rGFR and estimating equations

	GFR categories[a]	CKD classification based on rGFR					Categorical agreement	
		G3a	G3b	G4	G5	Total	%	Weighted Kappa (κ) (95% CI)
CKD-EPI-PK	G3a	**2**	5	0	0	7	90.9	0.955 (0.948–0.962)
	G3b	0	**42**	9	0	51		
	G4	0	0	**97**	13	110		
	G5	0	0	8	**209**	217		
$LM_{Revised}$	G3a	**2**	12	0	0	14	73.77	0.869 (0.858–0.88)
	G3b	0	**34**	16	0	50		
	G4	0	1	**96**	70	167		
	G5	0	0	2	**152**	154		
$CKD\text{-}EPI_{Asian\text{-}Modified}$	G3a	**2**	29	0	0	31	61.29	0.812 (0.799–0.825)
	G3b	0	**18**	47	1	66		
	G4	0	0	**66**	71	137		
	G5	0	0	1	**150**	151		
Total		**2**	47	114	222	385		

Bold numbers show the individuals with categorical agreement to rGFR

rGFR Reference GFR; $CKD\text{-}EPI_{PK}$ CKD-EPI equation with Pakistani Modification Factors; $LM_{Revised}$ revised Lund–Malmö equation; $CKD\text{-}EPI_{Asian\text{-}Modified}$ New Asian-Modified CKD-EPI equation

[a]Defined according to the KDIGO guidelines

and $CKD\text{-}EPI_{Asian\text{-}Modified}$ equations, respectively (Table 4). Upward reclassification was observed from G4 to G3b and from G3b to G3a by both $LM_{Revised}$ and $CKD\text{-}EPI_{Asian\text{-}Modified}$ equations compared to rGFR but not for G5 stage where a downward reclassification was observed. Categorical agreement and discordant KDIGO GFR categories between rGFR and all equations are shown in Table 4. Weighted

kappa values were 'good' for CKD-EPI$_{Asian\text{-}Modified}$ and 'very good' for CKD-EPI$_{PK}$ and LM$_{Revised}$ equations.

Prevalence of end-stage stage kidney disease

The prevalence of ESKD (≤ 15 ml/min/1.73 m^2) stratified by gender and age group are shown in Table S2. Overall, ESKD prevalence is the highest according to the CKD-EPI$_{PK}$ equations (56.3%), whereas the prevalence according to CKD-EPI$_{PK}$ was closer to that shown by rGFR. Of note, high percentages of ESKD were observed in patients in their 80's according to both the CKD-EPI$_{PK}$, (80–89, 64.44%; 90–99, 75.00%) and LM$_{Revised}$ (80–89, 62.22%; 90–99, 75.00%) equations. Although ESKD prevailed in all age groups according to all equations, the prevalence was higher in females in all equations.

Discussion

The KDIGO guidelines recommend using CKD-EPI equations unless a substitute equation has been proven to be more reliable in a given population [5]. CKD-EPI equations are recommended in Australia, Europe and North America; different eGFR equations, after sufficient evaluation, are applicable in other regions [5, 6, 14]. This is the first external validation study that has evaluated the CKD-EPI$_{PK}$, CKD-EPI$_{Asian\text{-}Modified}$ and LM$_{Revised}$ equations in comparison to rGFR by urinary inulin clearance in this region. We compared these equations according to the KDIGO guidelines in a Pakistani CKD cohort and assessed their performance, prospective implications on CKD classification and ESKD prevalence.

CKD-EPI$_{PK}$, the CKD-EPI formula with Pakistani modification factors, showed the best performance in our CKD study population. It has a lower bias [median difference: − 1.33 ml/min/1.73 m^2], higher precision [IQR 25th, 75th: 4.94 (− 8.49, − 3.55)], and elevated P30 accuracy [89.35%]. This finding is in line with the development study of this equation [19]. Although the sample population of that study did not have sufficient participants with decreased GFR, and had limited assessment of performance in individuals with different levels of advanced CKD, our study showed ideal performance of this equation in advanced CKD. The categorical agreement with reference GFR was also high (90.9%). Furthermore, CKD-EPI$_{PK}$ was also associated with a high percentage of ESKD which is similar to previous studies [4, 20].

The second closest equation to rGFR identified in this study after CKD-EPI$_{PK}$was LM$_{Revised}$ (mean difference − 4.14 ml/min/1.73 m^2; 95% limit of agreement − 8.12 ml/min/1.73 m^2) (Fig. 3). Although in our study, LM$_{Revised}$ showed lower bias and higher precision (Table 3) and correlated well with rGFR (Figure S3), accuracy is still poor (Table 3) and there are discrepancies in the assignment of GFR categories and ESKD prevalence (Table 4). Therefore, LM$_{Revised}$ is not suitable in the Pakistani population. This lack of suitability can be explained by the fact that CKD-EPI$_{PK}$ was derived from the linear regression models of natural logarithms of mean GFR (mGFR) versus eGFR calculated by the original CKD-EPI equation in the Pakistani population. The slopes and intercept were back transformed to exponential form and utilized as correction factors with two terms (eGFR $= 0.686 \times \text{CKD} - \text{EPI}^{1.059}$) to modify the equation [19], whereas LM$_{Revised}$ was modified by adding the factor of lean body mass derived from Swedish Caucasians [7]. However, the percentage of categorical agreement was comparatively higher for LM$_{Revised}$ (73.77%) than CKD-EPI$_{Asian\text{-}Modified}$ (61.29%) (Table 4) in our study, and both equations showed very high correlation with rGFR (*P* value < 0.001).

More interestingly, the overestimation by eGFR$_{Asian-ModifiedCKD-EPI}$ was greater than by eGFR$_{LMRevised}$ compared to eGFR$_{CKD-EPI-PK}$ as shown by the differences among the regression lines and the identity lines on their scatter plots (supplementary data; Figure S1, S2, S3). Although eGFR$_{Asian-ModifiedCKD-EPI}$ has previously been proven to be more appropriate for East Asians [15–18, 26], according to our results it overestimates GFR in South Asians.

The GFR category distribution for this study population differed according to the formula employed, especially for the new Asian-Modified CKD-EPI formula. The highest percentage of the study population (56.36%) was in the G5 category (< 15 ml/min/1.73m^2) according to the CKD-EPI$_{PK}$ equation, whereas it was in G4 (15-29 ml/min/1.73m^2) according to the LM$_{Revised}$ equation (43.38%) (Table S1). CKD-EPI$_{PK}$ classified more than 50% of the patients in stage G5 than any of the other equations. This highlights the importance of considering ethnicity factors for different ethnic groups in CKD-EPI$_{Asian\text{-}Modified}$ and LM$_{Revised}$ to correctly classify individuals in GFR categories. Furthermore, the Pakistani population is at high risk of ESKD, and implementation of any of these two equations would lead to under-diagnosis and under-treatment of high risk individuals whereas it would result in an over-diagnosis of other CKD stages (G3a, G3b, G4).

The mean rGFR was 15.73 ml/min/1.73 m^2 with a standard deviation of 10.59 ml/min/1.73 m^2 which was comparatively lower than that estimated by the CKD-EPI$_{Asian\text{-}Modified}$ and LM$_{Revised}$ equations in this study (Table 2). Thus, upward reclassification is common in this study. Moreover, CKD-EPI$_{PK}$, the equation corrected with a

Pakistani correction factor, also showed the best performance; thus, this shows that the GFR may be on the lower side for the South Asian population as compared to the Western or other Asian populations of different race/ethnicity. This also highlights the need to re-adjust the GFR categories for individuals in this region and re-define the cut-off value of 60 ml/min/1.73 m^2 so as to classify them in the correct CKD category. This finding is identical to one of a previous study [4].

In the current study, the prevalence of ESKD was differently reported depending on the GFR estimating equation employed (Table S2). End-stage kidney disease prevailed in all age groups in all equations but regardless of the equation that was employed, the prevalence was higher in women than in men. Moreover, high prevalence percentages of ESKD ($\leq$ 15 ml/min/1.73 m^2) were observed in patients in their 80's according to CKD-EPI_{PK} and $LM_{Revised}$. These trends are similar to those observed in other studies [12, 27–30]. KDIGO risk groupings, gender ratios and CKD prevalence also varied widely in Southeast Asian countries depending on the equation employed [31].

According to a prevalence study carried out in Karachi, Pakistan, it was noted that clinically significant decreased kidney function is common in Pakistani adults, and that the overall prevalence of decreased kidney function was 12.5% [4]. Another recent study noted that South Asian subjects with decreased kidney function were younger and had more advanced stages than the White population. The risk of ESKD was high and CKD-EPI_{PK} was linked with the risk of ESKD in the South Asian population [20]. These findings are similar to those of the present study where prevalence of ESKD is observed in the entire sample regardless of age range, and the CKD-EPI_{PK} equation showed the highest percentage (56.36%) of ESKD prevalence in the present population than any other equation.

Here, it is important to note that CKD-EPI_{PK} was associated with a consistent increase in the percentage of patients with kidney impairment (Table 4). This predicts not only the high prevalence of CKD and associated mortality in this region but it also indicates the elevated risk of developing cardiovascular disease, diabetes mellitus, ESKD events, anemia, gout, secondary hyperparathyroidism, and bone disease. The socio-economic status of the region, poor healthcare infrastructure, underdiagnosis of impaired kidney function, and lack of sufficient dialysis facilities for ESKD patients all lead to compromised patient care, poor quality of life and elevated mortality rates, consequently resulting in an added economic burden to the healthcare system. Specified interventional strategies, including the implementation of the CKD-EPI_{PK} equation, at least in Pakistani laboratories, to encourage earlier identification of CKD and timely referral to secondary care for effective management are necessary to reduce CKD risk, slow its progression and impede the associated consequences such as higher ESKD incidence, cardiovascular events and associated mortality rates.

This study has numerous strengths. First, we employed urinary inulin clearance as a gold standard for measuring true GFR. Second, this is the first external validation study of the CKD-EPI_{PK}, CKD-$EPI_{Asian\text{-}Modified}$ and $LM_{Revised}$ equations in a Pakistani CKD cohort against reference GFR by urinary inulin clearance. Third, our sample population was derived from the nephrology center of a renowned government hospital with an excellent turnover of kidney patients from all over Pakistan, hence our results can be generalized, at least for this region. Lastly, our estimation of prospective ESKD prevalence based on both albuminuria and eGFR also amplifies the strength of our study [5, 32].

Our study has some limitations. First, the findings of this study are limited to the Pakistani population and have to be confirmed in other South Asian populations, however, it presents a novelty in validating new equations which have not been validated previously in this population. Second, considering that the equations included in this study also have limitations, there is still room for improvement by further optimization and modification of the equations to achieve more accurate eGFR [19, 33, 34]. Third, SCr levels were computed using recommended techniques with sufficient quality control and standardization. However, SCr levels can be affected by biological and analytical changes. Such uncertainties in measurement cannot be eliminated completely in the present study [35]. Lastly, the Jaffe method used for SCr measurement is subject to bias due to susceptibility to interference compared to enzymatic methods [36, 37] and may have increased CKD misclassification. However, the potential for misclassification is lower as CKD staging was based on not only consecutively lower eGFR values but also on albuminuria for $\geq$ 3 months.

In conclusion, CKD-EPI_{PK} showed the best performance with low bias, high precision and P30 accuracy, whereas both CKD-$EPI_{Asian\text{-}Modified}$ and $LM_{Revised}$ showed poor performance and did not offer sufficient advantage in CKD classification and ESKD prevalence estimation over CKD-EPI_{PK}.

CKD-$EPI_{Asian\text{-}Modified}$ and $LM_{Revised}$ need to be modified with ethnicity coefficients for better performance in the Pakistani CKD population, whereas CKD-EPI_{PK} seems ideal for South Asian individuals and appropriate measures should be taken for its implementation, at least in Pakistani laboratories.

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Author contributions WA conceived and supervised the study. AS conducted data collection and data analysis. AS wrote and edited the manuscript. WA, MAK and MNA reviewed and approved the paper.

Declarations

Conflict of interest All the authors declare no competing interests. The authors had full responsibility for data collection, data interpretation, and writing of the report.

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Ethical approval This study was approved by the Ethical Review Board of Allama Iqbal Medical College, Jinnah Hospital (ERB No. 167/23/12/2021/S2 ERB) in its 108th meeting dated: 23/12/2021.

Informed consent Informed consent to participate in the study was obtained from all participants.

Data availability All data generated or analyzed during this study are included in the published article and its supplementary information files.

References

1. Vos T et al (2020) Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet 396(10258):1204–1222
2. Hasan M et al (2018) Prevalence of chronic kidney disease in South Asia: a systematic review. BMC Nephrol 19(1):1–12
3. Jafar TH, Schmid CH, Levey AS (2005) Serum creatinine as marker of kidney function in South Asians: a study of reduced GFR in adults in Pakistan. J Am Soc Nephrol 16(5):1413–1419
4. Jessani S, Bux R, Jafar TH (2014) Prevalence, determinants, and management of chronic kidney disease in Karachi, Pakistan—a community based cross-sectional study. BMC Nephrol 15(1):1–9
5. Andrassy KM (2013) Comments on 'KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease.' Kidney Int 84(3):622–623
6. Levey AS et al (2020) Measured and estimated glomerular filtration rate: current status and future directions. Nat Rev Nephrol 16(1):51–64
7. Björk J et al (2011) Revised equations for estimating glomerular filtration rate based on the Lund–Malmö Study cohort. Scand J Clin Lab Invest 71(3):232–239
8. Nyman U et al (2014) The revised Lund–Malmö GFR estimating equation outperforms MDRD and CKD-EPI across GFR, age and BMI intervals in a large Swedish population. Clin Chem Lab Med (CCLM) 52(6):815–824
9. Björk J et al (2020) A novel method for creatinine adjustment makes the revised Lund–Malmö GFR estimating equation applicable in children. Scand J Clin Lab Invest 80(6):456–463
10. Björk J et al (2012) Validation of the Lund–Malmö, chronic kidney disease epidemiology (CKD-EPI) and modification of diet in renal disease (MDRD) equations to estimate glomerular filtration rate in a large Swedish clinical population. Scand J Urol Nephrol 46(3):212–222
11. Björk J et al (2015) Performance of GFR estimating equations stratified by measured or estimated GFR: implications for interpretation. Am J Kidney Dis 66(6):1107–1108
12. Ji M et al (2016) Comparing results of five glomerular filtration rate-estimating equations in the Korean general population: MDRD Study, revised Lund–Malmö, and three CKD-EPI equations. Ann Lab Med 36(6):521
13. Jeong T-D et al (2017) Accuracy assessment of five equations used for estimating the glomerular filtration rate in Korean adults. Ann Lab Med 37(5):371–380
14. Stevens LA et al (2011) Evaluation of the chronic kidney disease epidemiology collaboration equation for estimating the glomerular filtration rate in multiple ethnicities. Kidney Int 79(5):555–562
15. Wang J et al (2016) The new Asian modified CKD-EPI equation leads to more accurate GFR estimation in Chinese patients with CKD. Int Urol Nephrol 48(12):2077–2081
16. Ji H et al (2017) eGFRs from Asian-modified CKD-EPI and Chinese-modified CKD-EPI equations were associated better with hypertensive target organ damage in the community-dwelling elderly Chinese: the Northern Shanghai Study. Clin Interv Aging 12:1297
17. Gao J-Q et al (2021) Comparative performance of FAS equation and Asian modified CKD-EPI in the determination of GFR in Chinese patients with CKD with the 99mTc-DTPA plasma clearance as the reference method. Nefrologia 41(1):27–33
18. Zhao L et al (2021) The ensemble learning model is not better than the Asian modified CKD-EPI equation for glomerular filtration rate estimation in Chinese CKD patients in the external validation study. BMC Nephrol 22(1):1–8
19. Jessani S et al (2014) Estimation of GFR in South Asians: a study from the general population in Pakistan. Am J Kidney Dis 63(1):49–58
20. Major RW et al (2022) Comorbidities and outcomes in South Asian individuals with chronic kidney disease: an observational primary care cohort. Nephrol Dial Transplant 37(1):108–114
21. Wang Y et al (2022) Performance of serum β2-microglobulin– and β-trace protein–based panel markers and 2021 creatinine-and cystatin-based GFR estimating equations in Pakistan. Kidney Med 4(4):100444
22. Ahmed S, Jafri L, Khan AH (2017) Evaluation of'CKD-EPI Pakistan'equation for estimated glomerular filtration rate (eGFR): a comparison of eGFR prediction equations in Pakistani population. J Coll Phys Surg Pak 27(7):414
23. Kidney Disease Improving Global Outcomes (2012) KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Available from https://kdigo.org/wp-content/uploads/2017/02/KDIGO_2012_CKD_GL.pdf. Accessed 18 Mar 2023
24. Mukaka MM (2012) A guide to appropriate use of correlation coefficient in medical research. Malawi Med J 24(3):69–71
25. McHugh ML (2012) Interrater reliability: the kappa statistic. Biochem Med 22(3):276–282
26. Liu X et al (2014) A new modified CKD-EPI equation for Chinese patients with type 2 diabetes. PLoS One 9(10):e109743
27. Trocchi P et al (2017) Impact of the estimation equation for GFR on population-based prevalence estimates of kidney dysfunction. BMC Nephrol 18(1):1–10
28. Kim H et al (2022) European Kidney Function Consortium Equation vs. Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) refit equations for estimating glomerular filtration rate: comparison with CKD-EPI equations in the Korean population. J Clin Med 11(15):4323
29. Anothaisintawee T et al (2009) Prevalence of chronic kidney disease: a systematic review and meta-analysis. Clin Nephrol 71(3):244
30. Glassock RJ, Warnock DG, Delanaye P (2017) The global burden of chronic kidney disease: estimates, variability and pitfalls. Nat Rev Nephrol 13(2):104–114

31. Kitiyakara C et al (2012) The impact of different GFR estimating equations on the prevalence of CKD and risk groups in a Southeast Asian cohort using the new KDIGO guidelines. BMC Nephrol 13(1):1–9
32. Duggal V et al (2021) National estimates of CKD prevalence and potential impact of estimating glomerular filtration rate without race. J Am Soc Nephrol 32(6):1454–1463
33. Pottel H et al (2021) Development and validation of a modified full age spectrum creatinine-based equation to estimate glomerular filtration rate: a cross-sectional analysis of pooled data. Ann Intern Med 174(2):183–191
34. Inker LA et al (2021) New creatinine-and cystatin C–based equations to estimate GFR without race. N Engl J Med 385(19):1737–1749
35. Jonker N et al (2020) Critical appraisal and meta-analysis of biological variation estimates for kidney related analytes. Clin Chem Lab Med (CCLM) 60(4):469–478
36. Schmidt RL et al (2015) A risk assessment of the Jaffe vs enzymatic method for creatinine measurement in an outpatient population. PLoS ONE 10(11):e0143205
37. Küme T et al (2018) Evaluation and comparison of Abbott Jaffe and enzymatic creatinine methods: could the old method meet the new requirements? J Clin Lab Anal 32(1):e22168