Research Square

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The validation of the EKFC equation for Glomerular Filtration Rate estimation and comparison with the Asian Modified CKD-EPI equation in Chinese Chronic Kidney Disease patients in the external study

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Research Article

Keywords: The EKFC equation, The Asian Modified CKD-EPI equation, Chronic Kidney Disease (CKD), Glomerular filtration rate (GFR)

Posted Date: March 15th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1437549/v1

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Abstract

Objective To verify whether a Modified Full Age Spectrum Creatinine-Based Equation (EKFC equation) is more applicable than the Asian Modified CKD-EPI equation in the clinical practice, which was confirmed with higher accuracy in estimating Glomerular Filtration Rate (GFR) in our external Chronic Kidney Disease (CKD) populations.

Methods According to the EKFC equation and the Asian Modified CKD-EPI formula, we calculated estimated GFR_{EKFC} and $GFR_{CKD-EPI}$, separately. Clinical diagnostic performance of the two equations was assessed and compared by correlation coefficient, regression equation, Bland–Altman analysis, bias, precision, accuracy(P_{30}) and the incorrectly reclassified index under the premise of ^{99m}Tc-diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA) dual plasma sample clearance method as reference method for GFR measurement (mGFR).

Results Totally, 160 CKD patients were recruited in our external cohort. The GFR_{EKFC} was highly related with mGFR, with the correlation coefficient of 0.95 [95%CI, 0.93-0.96], (*P*<0.01) and regression equation of GFR_{EKFC}= mGFR*0.87+5.27. Compared with the Asian Modified CKD-EPI equation, the EKFC equation demonstrated a wider bias（-1.64 *vs* 0.84 ml/min/1.73 m^2, *P*<0.01）, nearly identical precision (12.69 *vs* 12.72 ml/min/1.73 m^2, *P*=0.42) and P_{30} (80.0% *vs* 74.4%, *P*=0.57). Furthermore, the 95% limit of agreement in Bland-Altman analysis of the two target equations were almost same (42.4 *vs* 44.4 ml/min/1.73 m^2). And, the incorrectly reclassified index among the different CKD stages between the two models was not statistically different.

In the mGFR≤60 ml/min/1.73 m^2 subgroup analysis, the precision of the EKFC equation was better than the Asian Modified CKD-EPI formula (9.78 *vs* 10.25 ml/min/1.73 m^2, *P*<0.01), and the bias and P_{30} were not statistically different. However, in the mGFR>60 ml/min/1.73 m^2 subgroup, the EKFC equation did not performed better than the Asian Modified CKD-EPI formula with a wider bias (-8.60 *vs* -0.42 ml/min/1.73 m^2, P<0.01), an inferior precision (16.39 *vs* 15.86 ml/min/1.73 m^2, P<0.01), and a statistically invalid P_{30} (95.7% *vs* 94.2%, *P*=1.00).

Conclusion The total performance of the EKFC equation is acceptable. However, compared with the Asian Modified CKD-EPI equation, the EKFC equation is not more accurate to estimate GFR in our external Chronic Kidney Disease populations.

Introduction

It is especially crucial for clinical laboratories to report an accurate glomerular filtration rate (GFR), which is a positive alternative for renal function assessment(1). Accurate renal function assessment plays an important role in early diagnosis, treatment adjustment, and prognostic management of Chronic Kidney Disease (CKD) patients. What is worth mentioning is that GFR is estimated by a variety of simple

creatinine-based equations in recent decades(2–4), as an alternative for inulin being the gold standard. We focus on how accurate the developed equations are in our external CKD populations.

Our previous study also assessed the clinical utility of various creatinine-based equations under the premise of ^{99m}Tc-diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA) dual plasma sample clearance method as reference method and demonstrated that Asian Modified CKD-EPI equation and FAS formula were clinically more acceptable for GFR estimation with lower bias, more precision and better $P_{30(5-8)}$. However, neither P_{30} is more than the benchmark standard of P30 ≥ 75%, which is considered being sufficient for good clinical decision-making according to the 2002 K/DOQI benchmark(9).

Hans Pottel *et al.* developed and validated a new Scr-based equation, namely the new European Kidney Function Consortium equation (EKFC equation) (4)that can be applied to the full spectrum of age and renal function, by combining the properties of the FAS(2) and CKD-EPI equations(10). The internal development and external validation data sets suggested that improved accuracy and precision compared with commonly used equations for estimating GFR from Scr levels. However, whether EKFC equation is more available than the Asian Modified EPI-CKD equation remains unknown, which was verified more accurate and convenient use in our external CKD patients. Current study performed clinical evaluation and validation of EKFC equation and compared with the Asian Modified CKD-EPI formula, to recommend a more suitable equation for clinical GFR assessment in our external CKD populations.

Methods

Ethics statement

The study protocol was approved by Hebei Medical University ethical committee (NO. 2017–027-1), and the written informed consent was obtained from each participant.

Study subjects

Chinese patients who met the diagnostic standard for CKD according to the National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (K/DOQI) clinical practice guidelines(11) were enrolled in the study cohort. Patients with acute kidney function deterioration, edema, cardiac insufficiency, pleural or abdomen effusion, disabled limb, and treated with cimetidine or trimethoprim or replacement therapy were excluded, as described in our published literature(12).

Staging criteria(9): According to the mGFR by the ^{99m}Tc-DTPA dual plasma sample clearance method, all patients were divided into 5 groups: Normal renal function group (GFR>90 ml /min/1.73m^2); Mildly decreased renal function group (GFR 60-90 ml /min/1.73m^2); Moderately decreased renal function group (GFR 30-59 ml/min/1.73 m^2); Severely decreased renal function group (GFR 15-29 ml /min/1.73 m^2); Renal failure group (GFR<15ml/min/1.73 m^2).

Grouping criteria：The patients were categorized into 2 subgroups based on the mGFR calculated by reference method: lower-GFR subgroup (mGFR ≤ 60ml/min/1.73m^2) and higher-GFR subgroup (mGFR > 60ml/min/1.73m^2).

Laboratory measurement

mGFR measurement by the ^{99m}Tc-DTPA dual plasma sample clearance method

At 2 and 4 hours after intravenous injection of ^{99m}Tc-DTPA, 3ml heparin anti-coagulated blood samples were collected from the elbow vein, and the plasma radioactivity was counted in multi-function well counter. Then, the clearance of ^{99m}Tc-DTPA (Cl') was calculated from a single exponential: $Cl' = [D*\ln(P_1/P_2)]/(t_2-t_1) *\exp[(t_1*\ln(P_2)-t_2*\ln(P_1))/ (t_2-t_1)]$. Then, Cl' was corrected to GFR by Brochner-Mortensen's formula (13), $GFR= 0.990778Cl' - 0.001218Cl'^2$, The GFR was also standardized for a BSA of 1.73 m^2, namely, mGFR=GFR*(1.73/BSA)，according to the Haycock formula(14) of BSA(m^2) = $0.024265 * Wt^{0.5378} * Ht^{0.3964}$, using the patients' height (cm) and weight (kg) chrematistics. Detailed procedures were described in previous work(12).

GFR measurement by the EKFC equation

The serum creatinine (Scr) was automatically measured by the enzymatic IDMS-traceable method using a biochemical analyzer (AU5821, Beckman company, USA).

The EKFC equation was shown in Table 1(4). Normalized serum creatinine (Scr/Q) was mathematically obtained, where Q was the median Scr from healthy populations to account for age and sex.

GFR measurement by the Asian Modified CKD-EPI equation ($GFR_{CKD-EPI}$)

The Asian Modified CKD-EPI equation was shown in Table2(15).

Statistical analysis

Continuous variables conforming to normal distribution were described as mean ± standard deviation (SD); otherwise, by median and interquartile (P_{25}–P_{75}). Categorical variables were described as frequency and percentage (%).

The relationship between GFR_{EKFC}/$GFR_{CKD\text{-}EPI}$ and mGFR was assessed with the Spearman correlation analysis and linear regression method. The Bland–Altman method was applied to evaluate the degree of agreement between GFR_{EKFC} / $GFR_{CKD\text{-}EPI}$ and mGFR. The comparative performance indicators of GFR estimation for the EKFC equation and the Asian Modified CKD-EPI equation included bias, precision, accuracy and the incorrectly reclassified index. Bias and precision were defined as the median and the interquartile range (IQR) of the difference of GFR_{EKFC} /$GFR_{CKD\text{-}EPI}$ minus mGFR, respectively. The percentage of GFR within 30% deviation of mGFR (P_{30}) was employed as accuracy. And, respective 95% confidence intervals (95%CI) were calculated by means of bootstrap methods (2000 bootstraps)(16). We calculated the incorrectly reclassification index, which was the total percentage of incorrect patients reclassified into a different CKD stage by the EKFC equation and the Modified Asian CKD-EPI equation. Wilcoxon signed rank test was performed to compare the bias between the two models, whereas bootstrap method for precision comparison, and McNemar test for comparison of P_{30} and the incorrectly reclassification index. All statistical analysis was performed using IBM SPSS statistics 21.0 (IBM Corp., Armonk, NY, USA), MATLAB software (version 2020b, MathWorks) and MedCalc application (version 4.3, Medcalc software, Mariekerke, Belgium). *P* value was two sides and $P < 0.05$ was considered to be statistically significant.

Results

Characteristics of the study populations

We collected a total of 192 CKD patients with ^{99m}Tc-DTPA dual plasma sample clearance method for GFR estimation, whereas, 7 patients lacking of Scr data, 8 patients undergoing dialysis, 3 patients taking drugs effecting serum creatine value, 4 patients with edema and cardiac insufficiency, and 10 patients belonging to outliers after the outliner analysis. Totally, 160 patients were enrolled in our study cohort, 52 cases were chronic glomerulonephritis, 36 cases of diabetic nephropathy, 30 cases of chronic pyelonephritis, hypertensive nephropathy in 21 cases, and other causes or unknown causes in the remaining 21 cases. The basic characteristics of the patients was shown in **Table3.**

The clinical assessment of the EKFC equation

The GFR_{EKFC} was highly related with mGFR, with the correlation coefficient of 0.95 [95%CI, 0.93-0.96], $P<0.01$) and regression equation of GFR_{EKFC}=mGFR*0.87+5.27 (**Fig. 1**). The Bland–Altman plot showed the 95% limit of agreement for the EKFC equation was −23.2 to 19.2 ml/min/1.73 m^2 (**Fig. 2**).

Performance comparison of the EKFC equation and the Asian Modified CKD-EPI equation for GFR estimation

Compared with the Asian Modified CKD-EPI equation, the EKFC equation demonstrated a wider bias（-1.64 *vs* 0.84 ml/min/1.73 m^2, *P*<0.01）, nearly identical precision (12.69 *vs* 12.72 ml/min/1.73 m^2, *P*=0.42) and P_{30} (80.0% *vs* 74.4%, *P*=0.57). Furthermore, the 95% limit of agreement in Bland-Altman analysis of the two target equations were almost same (42.4 *vs* 44.4 ml/min/1.73 m^2) (**Fig. 3**).

And, the incorrectly reclassified index among the different CKD stages between the two models was not statistically different.

In the mGFR≤60 ml/min/1.73 m^2 subgroup analysis, the precision of the EKFC equation was better than the Asian Modified CKD-EPI formula (9.78 *vs* 10.25 ml/min/1.73 m^2, *P*<0.01), and the bias and P_{30} were not statistically different (1.48 *vs* -0.22 ml/min/1.73 m^2, *P*=0.18 and 59.3% vs 68.1%, *P*=0.87). However, in the mGFR>60 ml/min/1.73 m^2 subgroup, the EKFC equation did not performed better than the Asian Modified CKD-EPI formula with a wider bias (-8.60 vs -0.42 ml/min/1.73 m^2, *P*<0.01), an inferior precision (16.39 *vs* 15.86 ml/min/1.73 m^2, *P*<0.01), and a statistically invalid P_{30} (95.7% vs 94.2%, *P*=1.00). The performance comparison between the EKFC equation and the Asian Modified CKD-EPI equation was summarized in **Table 4** and **Table 5**.

Discussion

It was clearly stated that the diagnostic basis and staging criteria of CKD were mainly dependent on patient's GFR in the Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines in 2002. In the current clinical practice, a variety of formulas were constructed for an estimation for GFR. Hans Pottel *et al.* developed and validated a EKFC equation which is a modified full age spectrum, Scr-based GFR estimation equation in 2021. How accurate is the EKFC equation in externally validated populations was the subject of our research.

In the current study, we assessed the clinical utility of the EKFC equation and demonstrated it was acceptable in the clinical practice. The GFR_{EKFC} was highly related with mGFR, and regression coefficient was near to zero and slope was close to one. Furthermore, the Bland–Altman plot showed the 95% limit of agreement for the EKFC equation was satisfactory in our externally validated populations. As a full age spectrum equation, the new EKFC equation provides continuity across the entire age range, and facilitates the GFR reporting in the clinical laboratory by the simple calculating. However, compared with the Asian Modified CKD-EPI equation, the EKFC equation demonstrated a wider bias (-1.64 *vs* 0.84 ml/min/1.73 m^2), in spite of nearly identical precision and P_{30} in the total external population. Although, the incorrectly reclassified index among the different CKD stages between the two models was not statistically different. The performance of the EKFC equation was disappointing in the mGFR > 60 ml/min/1.73 m^2 subgroup, with wider bias (-8.60 *vs* -0.42 ml/min/1.73 m^2), an inferior precision (16.39 vs 15.86 ml/min/1.73 m^2), compared with the Asian Modified CKD-EPI formula in our external validated CKD patients.

The reason why the performance of the EKFC equation was worse in our external validation populations may focus on the following points. Firstly: The EKFC equation was developed basing on a cross-sectional analysis of pooled data, in which many algorithms were developed by different reference methods, for example ^{99m}Tc-DTPA renal dynamic imaging. Actually, a large number of studies have shown that ^{99m}Tc-DTPA renal dynamic imaging for GFR is not ideal and should not be used as a reference standard(17), where may introduce errors in the process of development and assessment of EKFC equation. In our validation cohort, we used the ^{99m}Tc-DTPA dual plasma clearance method as the reference standard, which was accepted as the standard GFR method at the 21st International Annual Meeting of the Society of Nuclear Medicine Europe. The different gold standards utilization may cause the different validating results in our external validation. Secondly, the median mGFR values were different between the EKFC equation internal and external validation group and our external validation populations. In the establishment and verification cohorts of EKFC equation, the median value of mGFR was more than 70 ml/min/1.73 m^2, belonging to the subgroup of mGFR > 60 ml/min/1.73 m^2. Whereas, the median value of mGFR in our study was less than 50 ml/min/1.73 m^2, belonging to the subgroup of mGFR ≤ 60 ml/min/1.73 m^2. In the verification conclusion, we found the estimating P_{30} accuracy was higher in the subgroup mGFR > 60 ml/min/1.73 m^2 than that in the subgroup mGFR ≤ 60 ml/min/1.73 m^2. Thirdly, the EKFC equation was developed and validated in white populations, our study population belong to Asian ethnicity, where the median Scr concentration was different among the various ethnicities, led to the Q value different where Q represented the median creatine value of healthy persons and distinct GFR according to EKFC equation. This was the one after another significant cause for different validating results. Maybe, we should calculate the Q value according to the Asian median Scr concentration, and got a different GFR by EKFC equation.

Our study has some limitations. Firstly, our validating population's sample size was not enough. Secondly, our study included Asian adult CKD patients, therefore, we cloud not conclude the accuracy of the EKFC equation in children's populations. More external validating studies were also needed to perform to verify the clinical practice of EKFC equation.

Abbreviations

CKD: Chronic Kidney Disease

GFR: Glomerular Filtration Rate

CKD-EPI: Chronic Kidney Disease-Epidemiology Collaboration

EKFC：Modified Full Age Spectrum Creatinine-Based Equation

^{99m}Tc-DTPA: ^{99m}Tc-diethylenetriaminepentaacetic Acid

Scr: Serum creatinine

IQR: Interquartile Range

FAS：Full Age Spectrum Creatinine-Based Equation

Declarations

Ethics approval and consent to participate

All procedures performed in study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study protocol was approved by Hebei Medical University ethical committee (NO. 2017-027-1). The written informed consent was obtained from each participant.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the correspondence author on reasonable request.

Consent for publication

Not applicable.

Competing interests

The authors have declared that no competing interests exist.

Funding

This project was partially funded by Natural Science Foundation of Hebei Province (H2020206422).

Acknowledgements

None

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Contributions:

Li Zhao and Huan-li Li analyzed the data and wrote the main manuscript.

Hui-jing Liu and Jin-Ma collected basic characteristics, the serum specimen of study subjects and performed the experimental operation.

Jian-min Huang and Ling-ge Wei performed the ^{99m}Tc-diethylenetriaminepentaacetic acid (99mTc-DTPA) dual plasma sample experiment.

Peng Xie designed experiments and revised the manuscript.

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Tables

Table 1

The EKFC equation

Age	Scr/Q	Equation for GFR estimation(Age, years)
2-40y	<1	$107.3*(Scr/Q)^{-0.322}$
	≥1	$107.3*(Scr/Q)^{-1.132}$
>40y	<1	$107.3*(Scr/Q)^{-0.322}*0.990^{(Age-40)}$
	≥1	$107.3*(Scr/Q)^{-1.132}*0.990^{(Age-40)}$

Table 2

The Asian Modified CKD-EPI equation(15)

Gender	Scr(mg/dl)	Equation for GFR estimation (Age, years)
Female	≤0.7	$151*(Scr/0.7)^{-0.328}*(0.993)^{age}$
	0.7	$151*(Scr/0.7)^{-1.210}*(0.993)^{age}$
Male	≤0.9	$149*(Scr/0.7)^{-0.412}*(0.993)^{age}$
	0.9	$149*(Scr/0.7)^{-1.210}*(0.993)^{age}$

Table 3

Basic characteristics of study populations

Variables	Overall Patients(n=160)	≤60 ml/min/1.73m^2 subgroup (n=91)	>60ml/min/1.73m^2 subgroup (n=69)
Males, n (%)	75(46.9%)	45(49.5%)	30(43.5%)
Age, years, X (SD)	56.14(15.23)	59.98(14.21)	51.07(15.14)
Height(cm), X (SD)	165.48(7.96)	165.19(7.87)	165.86(8.13)
Weight(kg), X (SD)	69.00(13.75)	68.81(13.78)	69.25(13.81)
Serum creatinine (mg/dL), M(P25-p75)	1.27(0.91-2.32)	1.99(1.40-3.74)	0.88(0.78-1.03)
mGFR (ml/min/1.73m^2), M(P25-p75)	47.88(25.37-81.27)	26.91(16.95-42.41)	86.39(72.28-100.28)
GFR_{EKFC} (ml/min/1.73m^2), M(P25-p75)	54.03(24.49-78.39)	28.58(15.28-51.30)	82.41(65.34-94.00)
$GFR_{CKD-EPI}$ (ml/min/1.73m^2), M(P25-p75)	56.64 (24.81-85.80)	41.78(32.06-55.19)	88.13(70.96-103.67)

Table 4

Performance comparison of the EKFC and the Asian Modified CKD-EPI equations

Indicators	Overall (ml/min/1.73m^2)	mGFR≤60ml/min/1.73m^2	mGFR>60ml/min/1.73m^2
Bias—median difference (95% CI)			
The Asian Modified CKD-EPI equation	0.84 [-0.63-3.60]	1.48[-0.55-4.10]	-0.42[-3.50-5.44]
The EKFC equation	-1.64 [-3.17– -0.25], *P**<0.01	-0.22[-1.35-1.59], *P*=0.18	-8.60[-11.1-3.40], *P** <0.01
Precision- IQR of the difference (95% CI)			
The Asian Modified CKD-EPI equation	12.72 [9.88-14.67]	10.25[6.83-14.59]	15.86[13.14-20.59]
The EKFC equation	12.69 [10.38-16.61], *P*=0.42	9.78[6.87-12.12], *P**<0.01	16.39[12.59-19.38], *P** <0.01
Accuracy—P_{30}(95% CI)			
The Asian Modified CKD-EPI equation	74.4% [61.6-89.0%]	59.3% [44.6-77.4%]	94.2% [72.7-120.1%]
The EKFC equation	80.0% [66.7–95.1%], *P*=0.57	68.1% [52.2-87.3%], *P*=0.87	95.7% [74.0-121.7%], *P*=1.00

Table 5

The results of incorrectly reclassified index between the two models

CKD stages	patients	The EKFC equation	The Asian Modified CKD-EPI equation	
ml /min/1.73m^2	n	Incorrectly Reclassified, n (%)	Incorrectly Reclassified, n (%)	*P*-value
<15	17	5(29.4%)	4(23.5%)	0.74
15-29	32	11(34.4%)	12(37.5%)	0.83
30-59	42	11(26.2%)	15(35.7%)	0.44
60-90	41	11(26.8%)	14(34.1%)	0.56
>90	28	5(17.9%)	5(17.9%)	1.00

Figures

Figure 1

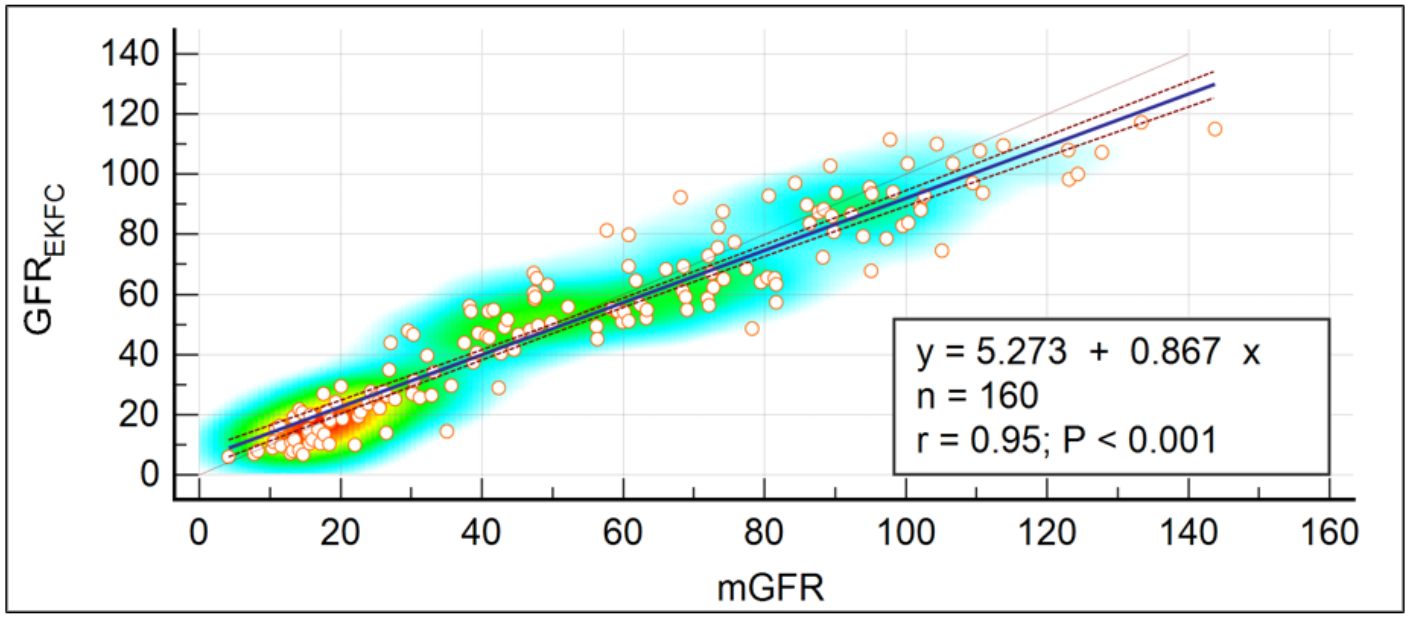

Figure 1

Scatter plots and regression equation of GFR_{EKFC} and mGFR (ml/min/1.73m^2). The mGFR was located on the X axis, and the GFR_{EKFC} was located on Y axis. The solid blue line represented the regression line between GFR_{EKFC} against mGFR, dashed red lines represented 95% confidence intervals for the regression line. The solid red line represented the identity line of y=x.

Figure 2

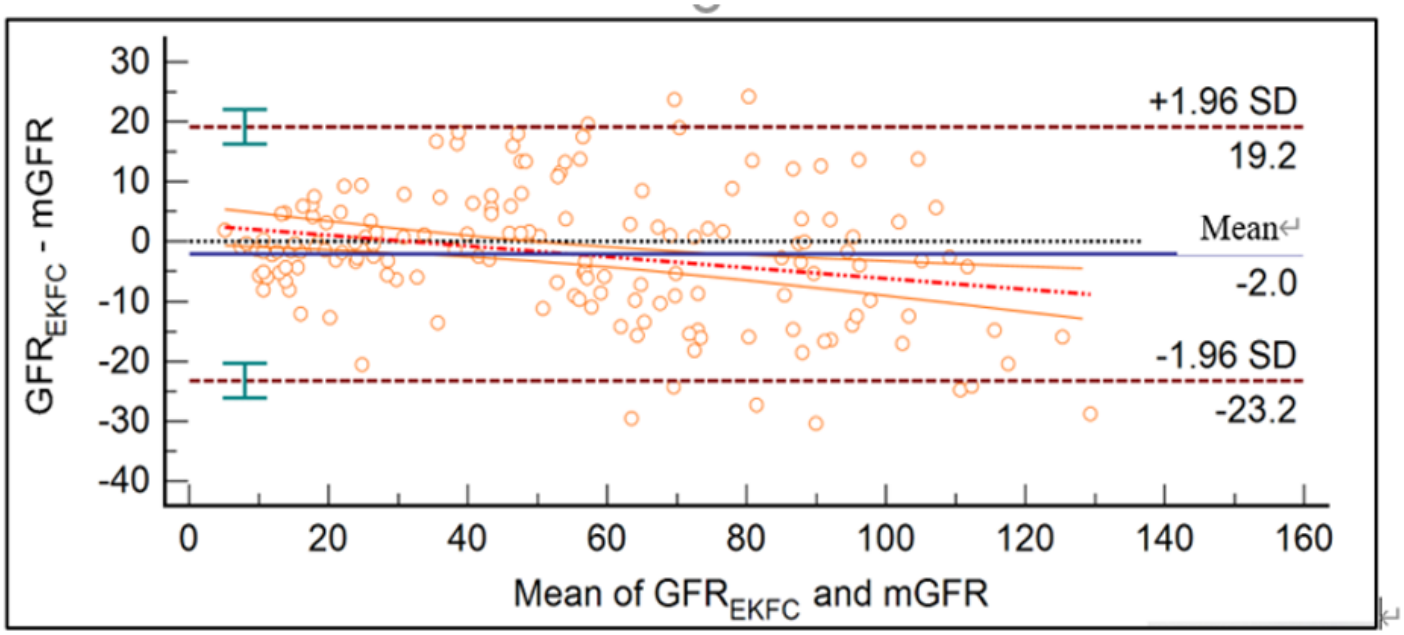

Figure 2

Bland–Altman plot of GFR_{EKFC} and mGFR (ml/min/1.73 m^2). The mean of mGFR plus GFR_{EKFC} was located on the X axis, and the value of mGFR minus GFR_{EKFC} was located on the Y axis. Solid blue line represented the mean of difference between methods, dashed dark red lines represented 95% limits of agreement of the mean of difference between methods, dotted red line represented the regression line of the difference between methods against mGFR, solid orange lines represented 95% confidence intervals for the regression line.

Figure 3

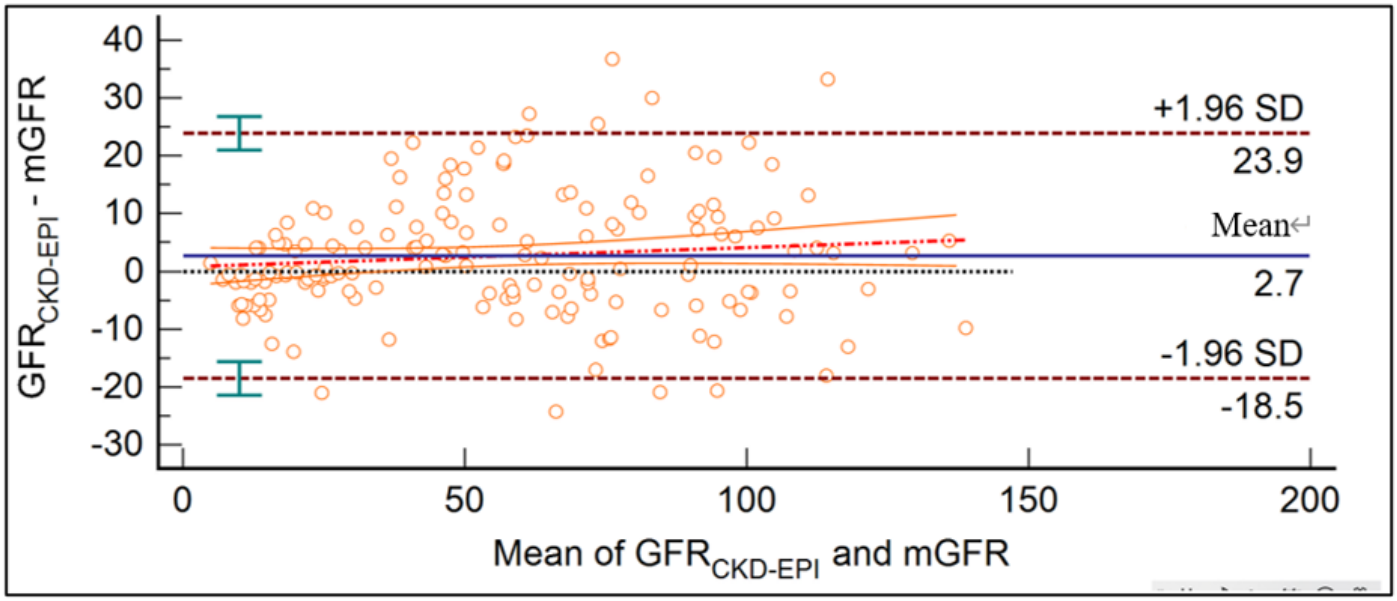

Figure 3

Bland–Altman plot of $GFR_{CKD\text{-}EPI}$ and mGFR (ml/min/1.73 m^2). The mean of mGFR plus $GFR_{CKD\text{-}EPI}$ was located on the X axis, and the value of mGFR minus $GFR_{CKD\text{-}EPI}$ was located on the Y axis. Solid blue line represented the mean of difference between methods, dashed dark red lines represented 95% limits of agreement of the mean of difference between methods, dotted red line represented the regression line of the difference between methods against mGFR, solid orange lines represented 95% confidence intervals for the regression line.