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The new Asian modified CKD-EPI equation leads to more accurate GFR estimation in Chinese patients with CKD

Jinghua Wang[3] · Peng Xie[1] · Jian-min Huang[1] · Yan Qu[2] · Fang Zhang[1] · Ling-ge Wei[1] · Peng Fu[1] · Xiao-jie Huang[1]

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Abstract
Objective To verify whether the new Asian modified CKD-EPI equation improved the performance of original one in determining GFR in Chinese patients with CKD.
Method A well-designed paired cohort was set up. Measured GFR (mGFR) was the result of ^{99m}Tc-diethylene triamine pentaacetic acid (^{99m}Tc-DTPA) dual plasma sample clearance method. The estimated GFR (eGFR) was the result of the CKD-EPI equation (eGFR1) and the new Asian modified CKD-EPI equation (eGFR2). The comparisons were performed to evaluate the superiority of the eGFR2 in bias, accuracy, precision, concordance correlation coefficient and the slope of regression equation and measure agreement.
Results A total of 195 patients were enrolled and analyzed. The new Asian modified CKD-EPI equation improved the performance of the original one in bias and accuracy. However, nearly identical performance was observed in the respect of precision, concordance correlation coefficient, slope of eGFR against mGFR and 95 % limit of agreement. In the subgroup of GFR < 60 mL min^{-1}/1.73 m^2, the bias of eGFR1 was less than eGFR2 but they have comparable precision and accuracy. In the subgroup of GFR > 60 mL min^{-1}/1.73 m^2, eGFR2 performed better than eGFR1 in terms of bias and accuracy.
Conclusion The new Asian modified CKD-EPI equation can lead to more accurate GFR estimation in Chinese patients with CKD in general practice, especially in the higher GFR group.

Keywords Glomerular filtration rate · CKD-EPI equation · Chronic kidney disease

Introduction

Chronic kidney disease (CKD) has been a worldwide problem because of the high prevalence and severe financial burden [1–5]. Glomerular filtration rate (GFR) is an important index of kidney function in the diagnosis, staging, evaluation of therapeutic effect and prognosis prediction [6–9]. The most accurate method to determine GFR is inulin clearance rate, but it is not applied widely in clinical practice due to the time-consuming and cumbersome proceeding. Several available methods were developed to estimate GFR with the advantage of simplicity and low cost [10–17]. It is widely believed that the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation is the most accurate and recommended method based on serum creatinine [18–23]; however, the equation only considered Blacks and others. Creatinine generation differs among racial-ethnic groups, so the researchers developed a new CKD-EPI equation that includes a four-level

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✉ Peng Xie
woxinfly1982@126.com

Jinghua Wang
2178946586@qq.com

[1] Institute of Nuclear Medicine, The Third Hospital, Hebei Medical University, No. 139 Ziqiang Road, Qiaoxi District, Shijiazhuang 050051, Hebei, People's Republic of China

[2] Department of Research, The Third Hospital, Hebei Medical University, No. 139 Ziqiang Road, Qiaoxi District, Shijiazhuang 050051, Hebei, People's Republic of China

[3] Department of Nephrology, Bethune International Peace Hospital, No. 398 of Zhongshan Western Road, Shijiazhuang, Hebei Province, People's Republic of China

race variable (Black, Asian, Native American and Hispanic and others) [24]. We hypothesized that it requires more studies to verify whether the new equation improved the performance of original one in determining GFR in Chinese patients with CKD. Here, a well-designed paired cohort was set up in this study to assess the applicability of new Asian modified CKD-EPI equation comparing with the original one.

Subjects and methods

Ethics statement

The study protocol was approved by Hebei Medical University ethical committee. All the participants provided written informed consent for this research.

Patients

The diagnosis of CKD and the exclusion criteria was same with our study published in 2012 [25]. Data collected from each patient's included height, weight, age, sex, the volume of 24-h urine, serum urea nitrogen, the causes of CKD and CKD stages.

Measurement of GFR by dual plasma sample clearance method (mGFR)

The results of ^{99m}Tc-diethylene triamine pentaacetic acid (^{99m}Tc-DTPA) dual plasma sample clearance method were considered as the measured GFR in this study. The detailed operating procedures of ^{99m}Tc-DTPA dual plasma sample clearance method were described previously [25], which was estimated from a single exponential formula derived from the blood samples between 2 and 4 h after injection. The mGFR (mL min^{-1}) was normalized for a body surface area of 1.73 m^2 according to Haycock's equation [26].

The measurement of serum creatinine

Serum creatinine (Sc) level was measured by the enzymatic method on an automatic biochemical analyzer (VITROS 5.1, Johnson Company, USA). And the results of Sc were recalibrated with isotope dilution mass spectrometry.

The estimated GFR determined by original CKD-EPI equation (eGFR1)

The CKD-EPI equation is as follows [11]:

Female with the concentration of serum creatinine $\leq$0.7 mg dL^{-1},

$$\text{eGFR1} = 144 \times (\text{Scr}/0.7)^{-0.329} \times (0.993)^{\text{age}};$$

Female with the concentration of serum creatinine >0.7 mg dL^{-1},

$$\text{eGFR1} = 144 \times (\text{Scr}/0.7)^{-1.209} \times (0.993)^{\text{age}};$$

Male with the concentration of serum creatinine $\leq$0.9 mg dL^{-1},

$$\text{eGFR1} = 141 \times (\text{Scr}/0.9)^{-0.411} \times (0.993)^{\text{age}};$$

Male with the concentration of serum creatinine >0.9 mg dL^{-1},

$$\text{eGFR1} = 141 \times (\text{Scr}/0.9)^{-1.209} \times (0.993)^{\text{age}}$$

The unit of Scr and age is mg dL^{-1} and year, respectively.

The estimated GFR determined by new Asian modified CKD-EPI equation (eGFR2)

The new Asian CKD-EPI equation is as follows [11]:

Female with the concentration of serum creatinine $\leq$0.7 mg dL^{-1},

$$\text{eGFR2} = 151 \times (\text{Scr}/0.7)^{-0.328} \times (0.993)^{\text{age}};$$

Female with the concentration of serum creatinine >0.7 mg dL^{-1},

$$\text{eGFR2} = 151 \times (\text{Scr}/0.7)^{-1.210} \times (0.993)^{\text{age}};$$

Male with the concentration of serum creatinine $\leq$0.9 mg dL^{-1},

$$\text{eGFR2} = 149 \times (\text{Scr}/0.9)^{-0.415} \times (0.993)^{\text{age}};$$

Male with the concentration of serum creatinine >0.9 mg dL^{-1},

$$\text{eGFR2} = 149 \times (\text{Scr}/0.9)^{-1.210} \times (0.993)^{\text{age}}$$

The unit of Scr and age is mg dL^{-1} and year, respectively.

Statistical analysis

The performance of eGFR1 and eGFR2 was assessed by the comparisons of bias, accuracy, precision, concordance correlation coefficient and the slope of regression equation, and a Bland–Altman analysis to measure agreement. The bias was defined as mGFR minus eGFR. The precision was inferred from the standard deviation of bias. The accuracy was calculated as the percentage of eGFR within 30 % deviation of mGFR. The concordance correlation coefficient and the slope of regression equation were calculated by means of Passing–Bablok regression and Lin correlation. Paired *T* test, *F* test and McNemar test were applied for comparing bias, precision and accuracy, respectively. All Statistical analyses were performed using SPSS (version 17.0, SPSS. Chicago IL, USA) and Medcalc (version 4.3, Medcalc software, Mariekerke, Belgium).

Results

During the study frame, a total of 195 CKD patients aged 21–83 years (mean age 55.46 ± 15.36 years, 52.30 % women) were enrolled and analyzed. The clinical characteristics of the patients are presented in Table 1. The causes of CKD were chronic glomerulonephritis 37.44 % (73/195), diabetic nephropathy 24.62 % (48/195), chronic pyelonephritis 14.36 % (28/195), hypertensive nephropathy 11.28 % (22/195), chronic interstitial nephritis 4.62 % (9/195), IGA nephropathy 3.08 % (6/195), polycystic kidney disease 3.08 % (6/195) and others 1.54 % (3/195). The prevalence of CKD stage 1, 2, 3, 4 and 5 was 20.51, 24.62, 23.08, 20.00 and 11.79 % according to mGFR, respectively. The mean (± SD) value of mGFR was 63.42 ± 38.25 mL min^{-1}/1.73 m^2, and the mean (± SD) eGFR by the original CKD-EPI equation was 59.97 ± 32.76 mL min^{-1}/1.73 m^2 and 63.21 ± 34.57 mL min^{-1}/1.73 m^2 by the new one. The difference between mGFR and eGFR1 or eGFR2 was not significant (all $P > 0.05$).

Table 1 Characteristics of CKD patients

Characteristic ($n = 170$)	Value
Female/male	102/93
Age (years)	55.46 ± 15.36
Weight (kg)	61.36 ± 12.53
Height (cm)	166.28 ± 10.01
BSA (m^2)	1.73 ± 0.42
BMI	27.25 ± 4.83
Serum creatinine ($\mu mol\ L^{-1}$)	192.18 ± 182.74
Serum urea nitrogen ($mmol\ L^{-1}$)	10.88 ± 8.35
Volume of 24 h urine (mL)	2443.25 ± 882.31
Causes of CKD [*n* (%)]	
Chronic glomerulonephritis	73 (37.44)
Diabetic nephropathy	48(24.62)
Chronic pyelonephritis	28 (14.36)
Hypertensive nephropathy	22 (11.28)
Chronic interstitial nephritis	9 (4.62)
IGA nephropathy	6 (3.08)
Polycystic kidney disease	6 (3.08)
Others	3 (1.54)
CKD stages [*n* (%)]	
1	40 (20.51)
2	48 (24.62)
3	45 (23.08)
4	39 (20.00)
5	23 (11.79)

CKD chronic kidney disease, *BSA* body surface area, *BMI* body mass index

The comparison between eGFR1 and eGFR2 is presented in Table 2. In terms of both bias and accuracy, the new Asian CKD-EPI equation achieved more preferable results in estimating GFR (bias, 3.45 for eGFR1 vs. 0.21 mL min^{-1}/1.73 m^2 for eGFR2, $t = 22.84$, $P < 0.001$; 30 % accuracy, 74.36 % for eGFR1 vs. 78.46 %, $P = 0.021$). However, there was nearly identical performance of eGFR1 and eGFR2 in respect of precision, concordance correlation coefficient, slope of eGFR against mGFR and 95 % limit of agreement (Figs. 1, 2).

In the subgroup of GFR < 60 mL min^{-1}/1.73 m^2 ($n = 96$), the bias of eGFR1 was less than eGFR2 (−4.36 vs. −6.23 mL min^{-1}/1.73 m^2, $t = 14.559$, $P < 0.001$) but they have comparable identical precision and accuracy (all $P > 0.05$). In the subgroup of GFR > 60 mL min^{-1}/1.73 m^2 ($n = 99$), eGFR1 was more preferable in bias and accuracy (bias, 11.03 for eGFR1 vs. 6.47 mL min^{-1}/1.73 m^2 for eGFR2, $t = 28.017$, $P < 0.001$; 30 % accuracy, 81.82 % for eGFR1 vs. 89.90 %, $P = 0.008$).

Table 2 Comparison of the equations in determining glomerular filtration rate

Variables	eGFR1	eGFR2
Mean of difference (Bias)	3.45*	0.21
Precision	18.48#	18.33
30 % accuracy (%)	74.36*	78.46
Concordance correlation coefficient (95 % CI)	0.86 (0.82,0.89)	0.87 (0.84, 0.90)
Intercept of eGFR against mGFR (95 % CI)	−2.21 (−5.79, 0.80)	−2.13 (−5.88, 0.96)
Slope of eGFR against mGFR (95 % CI)	1.09 (1.01, 1.17)	1.03 (0.96, 1.10)
The 95 % limit of agreement [mL min^{-1} $(1.73\ m^2)^{-1}$]	72.5	71.8

eGFR1 estimated glomerular filtration rate by the original CKD-EPI equation, *eGFR2* estimated glomerular filtration rate by the new Asian modified CKD-EPI equation, *mGFR* glomerular filtration rate determined by ^{99m}Tc-DTPA dual plasma sample clearance method

* $P < 0.05$ (compared with the value of eGFR2)

\# $P > 0.05$ (compared with the value of eGFR2)

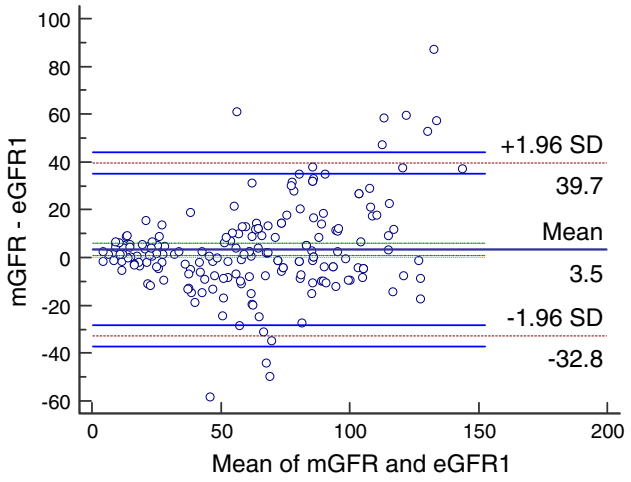

Fig. 1 Bland–Altman plots showing the disagreement between eGFR1 and mGFR. The *solid long line* indicates the mean of difference and the *dotted long line* represents the 95 % limits of agreement (2sd). *eGFR1* estimated glomerular filtration rate by the original CKD-EPI equation, *mGFR* glomerular filtration rate determined by ^{99m}Tc-DTPA dual plasma sample clearance method

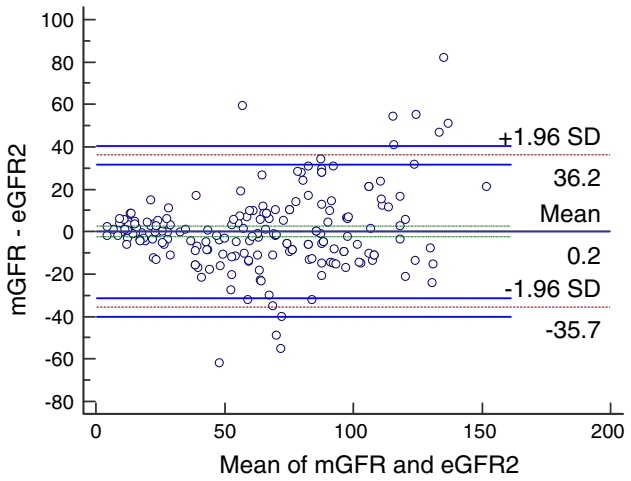

Fig. 2 Bland–Altman plots showing the disagreement between eGFR2 and mGFR. The *solid long line* indicates the mean of difference and the *dotted long line* represents the 95 % limits of agreement (2sd). *eGFR2* estimated glomerular filtration rate by the new Asian modified CKD-EPI equation, *mGFR* glomerular filtration rate determined by ^{99m}Tc-DTPA dual plasma sample clearance method

Discussion

It is widely believed that the CDK-EPI equation is a satisfactory and simple method to determine the GFR [18–23]. Unfortunately, only a two-level racial variable (Black vs. White and other) was utilized when the CDK-EPI equation was developed in 2009 [13]. It is proposed that the creatinine generation varies with racial, ethnic and geographic group due to muscle and diet, which is neglected by the CDK-EPI equation developers [27, 28]. The Asians (including Chinese) have less muscle mass, and lower dietary can lead to less creatinine generation. So Stevens et al. captured pooled data from ten studies ($N = 8254$) and developed a new four-level race variable (Black, Asian, Native American and Hispanic, and White and others) CKD-EPI equation with urinary clearance of iothalamate as the reference method. Nevertheless, only 100 Asian samples with or without kidney diseases were included. It is necessary to evaluate whether the new Asian modified CDK-EPI equation is definitely more accurate than the original one in calculating GFR in Chinese patients with CKD.

^{99m}Tc-DTPA dual plasma sample clearance method was employed as the reference method to measure GFR which guaranteed the dependability of the results in this study. Totally, 195 Chinese patients with CKD were enrolled in our study, and the results of comparison between the new Asian modified CDK-EPI equation and the original one showed that the latter one achieved less bias and greater accuracy. However, the two equations resembled each other in precision, concordance correlation coefficient, slope of eGFR against mGFR and 95 % limit of agreement. All the performance above revealed new Asian modified CDK-EPI equation was more accurate than the original one. These results were consistent with the previous findings derived from validation data set [24]. Specifically, the advantage of the new Asian modified CDK-EPI was mainly reflected in the higher GFR group.

It can be noted that there are several limitations. First, the sample size in this study was relatively small, so it is difficult to make detailed analysis according to different stages. Moreover, the included samples were all CKD patients, so more research is needed to extend the application range of new Asian modified CDK-EPI equation.

In conclusion, we confirmed that the new Asian modified CKD-EPI equation improves the performance of GFR estimation, and it should be the foremost choice in determining GFR in Chinese patients with CKD, especially in the higher GFR group.

Author contributions YQ Provided and used the software.PX and JMH conceived and designed the experiments. PX, JMH, ZF, LGW, PF and LPP performed the experiments. PX and JMH analyzed the data. PX, JMH and YQ contributed reagents/materials/analysis tools. PX and JMH Wrote the paper.

Compliance with ethical standards

Conflict of interest The authors have declared that no competing interests exist.

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