

Variability of glomerular filtration rate estimation equations in elderly Chinese patients with chronic kidney disease

Xun Liu^{1,2,*}
Mu-hua Cheng^{3,*}
Cheng-gang Shi¹
Cheng Wang¹
Cai-lian Cheng¹
Jin-xia Chen¹
Hua Tang¹
Zhu-jiang Chen¹
Zeng-chun Ye¹
Tan-qi Lou¹

¹Division of Nephrology, Department of Internal Medicine, The Third Affiliated Hospital of Sun Yet-sun University, Guangzhou, China; ²College of Biology Engineering, South China University of Technology, Guangzhou, China; ³Department of Nuclear Medicine, The Third Affiliated Hospital of Sun Yet-sun University, Guangzhou, China

*These authors contributed equally to this paper

Background: Chronic kidney disease (CKD) is recognized worldwide as a public health problem, and its prevalence increases as the population ages. However, the applicability of formulas for estimating the glomerular filtration rate (GFR) based on serum creatinine (SC) levels in elderly Chinese patients with CKD is limited.

Materials and methods: Based on values obtained with the technetium-99m diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA) renal dynamic imaging method, 319 elderly Chinese patients with CKD were enrolled in this study. Serum creatinine was determined by the enzymatic method. The GFR was estimated using the Cockcroft–Gault (CG) equation, the Modification of Diet in Renal Disease (MDRD) equations, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, the Jelliffe-1973 equation, and the Hull equation.

Results: The median of difference ranged from -0.3 – 4.3 mL/min/1.73 m². The interquartile range (IQR) of differences ranged from 13.9 – 17.6 mL/min/1.73 m². Accuracy with a deviation less than 15% ranged from 27.6%–32.9%. Accuracy with a deviation less than 30% ranged from 53.6%–57.7%. Accuracy with a deviation less than 50% ranged from 74.9%–81.5%. None of the equations had accuracy up to the 70% level with a deviation less than 30% from the standard glomerular filtration rate (sGFR). Bland–Altman analysis demonstrated that the mean difference ranged from -3.0 – 2.4 mL/min/1.73 m². However, the agreement limits of all the equations, except the CG equation, exceeded the prior acceptable tolerances defined as 60 mL/min/1.73 m². When the overall performance and accuracy were compared in different stages of CKD, GFR estimated using the CG equation showed promising results.

Conclusions: Our study indicated that none of these equations were suitable for estimating GFR in the elderly Chinese population investigated. At present, based on overall performance, as well as performance in different CKD stages, the CG equation may be the most accurate for estimating GFR in elderly Chinese patients with CKD.

Keywords: elderly, equation, glomerular filtration rate, serum creatinine, Chinese

Introduction

Chronic kidney disease (CKD) is a worldwide problem that is in need of particular attention. The prevalence of CKD varies with age¹ and is markedly high in those of the population greater than 64 years old.^{2,3} In China, the population of those over 60 years old will increase by 16.55% every year; by 2040 this age group will account for 28% of the entire population, which means that China will be considered an ageing society.⁴ These findings highlight the clinical and public health importance of CKD. The glomerular filtration rate (GFR) is typically considered to be the best way to assess renal function in healthy or diseased states. Direct measurement of GFR by inulin

Correspondence: Tan-qi Lou
Division of Nephrology, Department of Internal Medicine, The Third Affiliated Hospital of Sun Yet-sun University, Guangzhou, 510630 China
Email lou.tq@163.com

clearance is often impractical. Radioisotopic methods using ethylenediaminetetraacetic acid (51Cr EDTA), 125 iodine iothalamate, and so on provide acceptable alternatives to inulin clearance.⁵ However, these methods are cumbersome, expensive, and are available to only a few hospitals. Many formulae using serum creatinine (SC) have been established to estimate GFR in adults. The National Kidney Foundation has recommended that the Cockcroft–Gault (CG) equation and the Modification of Diet in Renal Disease (MDRD) equations should be used to estimate GFR in adults.⁶ However, the SC-based equations were not initially developed for elderly people. Additionally, older individuals have decreased lean body mass and often suffer from chronic diseases associated with decreased muscle mass and SC levels,⁷ thus, when applied to elderly people, the effectiveness of such equations is doubtful.

As previously described,⁸ GFR estimation equations showed a great deal of bias in elderly Chinese CKD patients. In this study, we increased the sample size and again evaluated the accuracy of various GFR estimation equations in elderly Chinese patients with CKD, comparing them with radionuclide GFRs in a clinical setting.

Research design and methods

The present study was conducted among 319 elderly Chinese CKD patients (121 women; mean \pm SD age 70.0 ± 6.8 years; standard GFR (sGFR) measured by ^{99m}Tc-DTPA GFR was 39.4 ± 21.8 mL/min per 1.73 m²) from January 2005 through December 2009 at the Third Affiliated Hospital of Sun Yet-sun University, China. The patient exclusion criteria were as previously described.⁸ None of the subjects were undergoing dialysis during the study period. The CKD patients were assigned to one of five stages based on the National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative (K/DOQI) clinical practice guidelines.⁹ The causes and stages of CKD, as well as other details, are listed in Table 1. For convenience, stages 1 and 2, and stages 4 and 5 were combined. The study was approved by the institutional review board at the Third Affiliated Hospital of Sun Yet-sun University. All patients provided informed consent before participating in the study.

Glomerular filtration rate, measured by the ^{99m}Tc-DTPA renal dynamic imaging method and standardized by body surface area (BSA), was used as the sGFR.^{10–12} ^{99m}Tc-DTPA renal dynamic imaging (modified Gate's method) was measured by Millennium TMMPR SPECT using the General Electric Medical System. ^{99m}Tc-DTPA renal imaging showed good agreement with plasma clearance of 51Cr EDTA.¹³ The ^{99m}Tc-DTPA renal dynamic

Table 1 Patient characteristics

CKD cause	
Diabetic nephropathy	114 (35.7)
Hypertension	74 (23.2)
Chronic tubulointerstitial disease	53 (16.6)
Primary glomerular disease	36 (11.3)
Renovascular disease	22 (6.9)
Other causes or causes unknown	20 (6.3)
Age (year)	70.0 ± 6.8 (60–93)
Male/female (%)	62.1/37.9
Weight (kg)	61.4 ± 11.5 (30–98)
Height (cm)	162.0 ± 8.1 (142–184)
BSA (m ²)	1.65 ± 0.17 (1.15–2.18)
SC (umol/L)	245.0 ± 210.2 (32–1833)
DTPA-GFR (mL/min/1.73 m ²)	39.4 ± 21.8 (5.7–116.6)

Note: Results are expressed as mean \pm SD (range) or n (%).

Abbreviations: BSA, body surface area; SC, serum creatinine; DTPA-GFR, technetium-99m diethylenetriaminepentaacetic acid-glomerular filtration rate.

imaging method used was as previously described.⁸ After image acquisition, the patient's weight and height were entered into the eNTEGRA Workstation (General Electric Company, Waukesha, WI), on which all imaging data were recorded. The sGFR was automatically calculated, according to Gate's algorithm.

Estimations of renal function

$$\begin{aligned} &\text{Cockcroft-Gault (CG) equation, CrCl} \\ &= (140 - \text{age} [\text{years}] \times \text{weight} [\text{kg}] \\ &\quad \times [0.85 \text{ if patient is female}] / (72 \times \text{sc})^{14} \end{aligned} \quad (1)$$

$$\begin{aligned} &\text{Four-variable MDRD equation GFR} \\ &= 186 \times \text{sc} (\text{mg/dL})^{-1.154} \times \text{age} (\text{years})^{-0.203} \\ &\quad \times 0.742 (\text{if female}) \times (1.212 [\text{if patient is black}])^{15} \end{aligned} \quad (2)$$

$$\begin{aligned} &\text{Six-variable MDRD equation GFR} \\ &= 170 \times \text{sc} (\text{mg/dL})^{-0.999} \times \text{age} (\text{years})^{-0.176} \\ &\quad \times \text{screa} (\text{mg/dL})^{-0.170} \times \text{albumin} (\text{g/dL})^{+0.318} \\ &\quad \times 0.742 (\text{if female}) \\ &\quad \times (1.212 [\text{if patient is black}]) \end{aligned} \quad (3)$$

$$\begin{aligned} &\text{CKD-EPI equation GFR} = 141 \times (\text{Sc}/\kappa)^\alpha \\ &\quad \times (0.993)^{\text{Age}} \times (1.018 [\text{if patient is female}]) \\ &\quad \times (1.159 [\text{if patient is black}])^{17} \end{aligned}$$

- $\kappa = 0.7$ (female) or 0.9 (male);
- $\alpha = -0.329$ (female and $\text{sc} \leq 0.7$ mg/dL),
 $\alpha = -1.209$ (female and $\text{sc} > 0.7$ mg/dL);
- $\alpha = -0.411$ (male and $\text{sc} \leq 0.9$ mg/dL),
 $\alpha = -1.209$ (male and $\text{sc} > 0.9$ mg/dL)

$$\text{Jelliffe-1973 equation: CrCl} = (98 - 0.8 \times [\text{age (years)} - 20] \times [0.90 \text{ (if patient is female)}]) / \text{sc}^{18} \quad (5)$$

$$\text{Hull equation: CrCl} = ((145 - \text{age (years)}) / \text{sc} - 3 \times \text{weight} / 70 \times (0.85 \text{ [if patient is female]}))^{19} \quad (6)$$

The results of the CG equation, the Jelliffe-1973 equation, and the Hull equation were standardized for a BSA²⁰ of 1.73 m².

Other measurements

A single serum determination was performed on the same day prior to measurement of GFR using ^{99m}Tc-DTPA renal dynamic imaging. The SC levels, serum albumin, and urea were assayed on a Hitachi 7180 autoanalyzer (Hitachi, Tokyo, Japan) with reagents from Roche Diagnostics (Mannheim, Germany). Serum creatinine was determined by the enzymatic method. Sex, age, height, and weight were simultaneously recorded.

Statistical analysis

The sGFR and the estimated GFR (eGFR) were compared using Bland–Altman analysis. The precision was measured as the width between the 95% limits of agreement. A prior acceptable tolerance for the difference between eGFR and sGFR was defined as twice the limit for CKD stages, which is 60 mL/min/1.73 m².⁸ The accuracy of GFR estimates was determined as the percentage of results deviating less than 15%, 30%, and 50% from the sGFR. The sensitivity and specificity of all the equations in correctly classified CKD stage 3 (GFR < 60 mL/min/1.73 m²) were based upon the cut points established by the National Kidney Foundation⁹ and were calculated and compared according to the receiver operating characteristic (ROC) curve approach. In the preliminary analysis,⁸ the Jelliffe-1973 equation performed better than the other equations. Therefore, we chose eGFR measured by the Jelliffe-1973 equation as the reference against which

all comparisons between equations were made. Results were considered to be significant at $P < 0.05$. All statistical analyses were performed using SPSS software (version 11.0; IBM, Armonk, NY) and Medcalc for Windows (version 9.3.9.0; Medcalc Software, Mariekkerke, Belgium).

Results

Overall performance of the equations

The medians of difference of the four-variable MDRD equation and the six-variable MDRD equation were less than those of the other equations. The interquartile range (IQR) of difference for the CG equation and the Hull equation were smaller. The accuracies with a deviation less than 15% from the sGFR of the Hull equation and the CG equation were higher. The CG equation and the Jelliffe-1973 equation provided better results than the others in accuracies with deviations less than 30% and 50% from the sGFR. However, none of the equations had accuracies that reached 70% while differing less than 30% from the sGFR. Chronic kidney disease stage misclassifications by the four-variable MDRD equation and the Jelliffe-1973 equation were less than that of the other equations. All of the equations had CKD stage misclassification higher than 42% (Table 2). We used Bland–Altman plot (see Figure 1) analysis to calculate the mean of the difference between eGFR and sGFR and the precision of eGFR. Using this approach, the CKD-EPI equation and the Jelliffe-1973 equation demonstrated less means of the difference than the other equations. The precisions of the GFR estimated by the CG equation and the CKD-EPI equation were better than the other equations. However, the agreement limits of the equations, except for the CG equation, exceeded the prior acceptable tolerances, defined as 60 mL/min/1.73 m². The ROC curve analysis showed that the maximum diagnostic accuracy of all the equations for the diagnosis of moderate renal failure (GFR < 60 mL/min/1.73 m²) was not statistically significant ($P > 0.05$ compared with the Jelliffe-1973 GFR). Detailed performances are listed in Tables 2 and 3, and Figure 2.

Table 2 Overall performances of eGFR and sGFR

	Precision	Difference			Accuracy within			CKD stage misclassification
		Mean	Median	IQR	15%	30%	50%	
Cockcroft–Gault equation	58.5	−3.0	−4.3	13.9	31.3	57.7	81.5	43.9
Six-variable MDRD equation	69.2	1.0	−1.2	16.0	29.5	53.6	76.5	44.2
Four-variable MDRD equation	73.4	2.4	−0.3	17.6	27.9	54.5	74.9	42.9
CKD-EPI equation	62.4	−0.6	−1.9	16.7	27.6	54.9	75.5	44.2
Jelliffe-1973 equation	76.4	0.8	−1.8	15.1	30.1	57.1	81.2	43.6
Hull equation	64.2	−1.9	−3.9	14.6	32.9	55.2	79.3	43.9

Abbreviation: IQR, interquartile range.

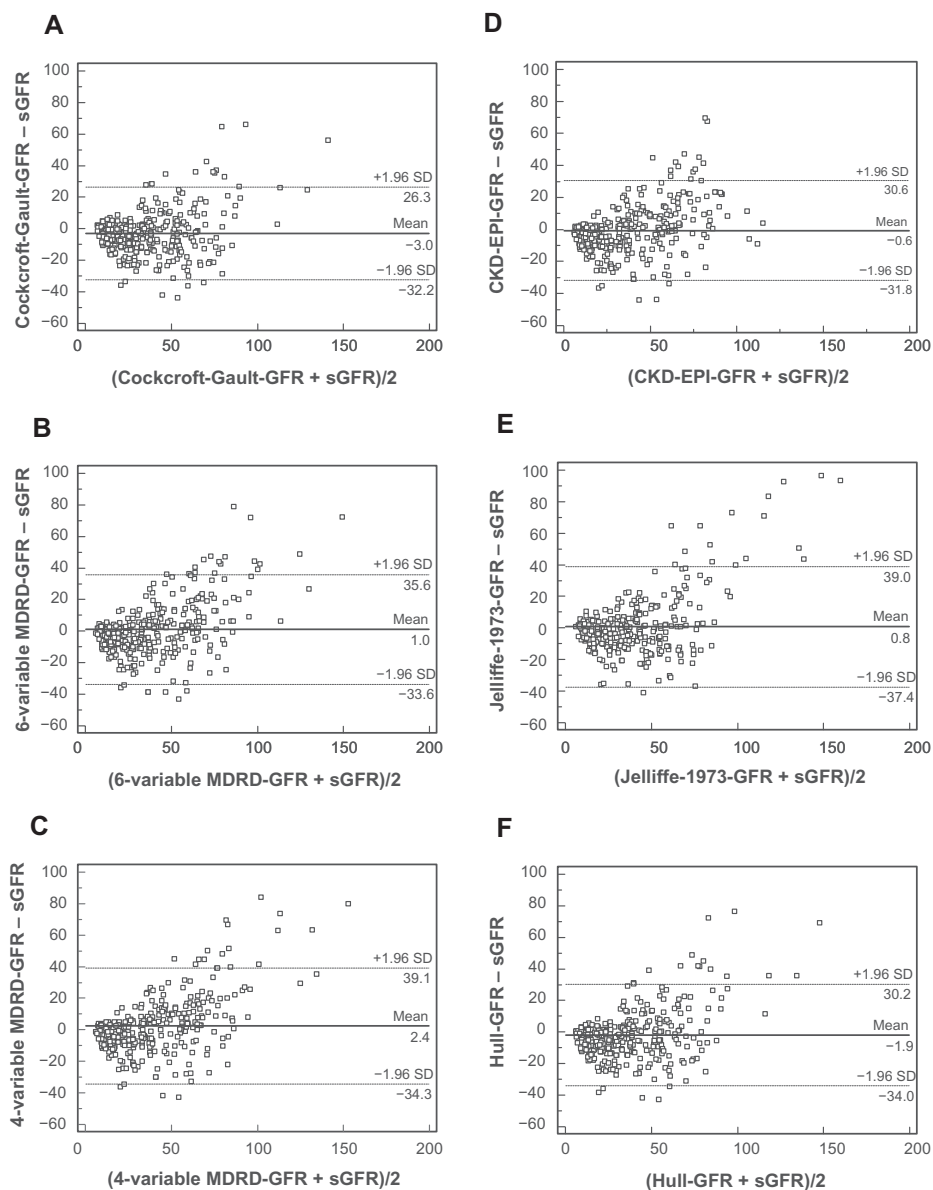


Figure 1 Bland–Altman plot of eGFR and sGFR (mL/min/1.73 m²). Solid line represents the mean of difference between methods; dashed lines represent 95% limits of agreement of the mean of difference between methods. (A–F) Represent for the GFR results estimated using Cockcroft–Gault equation, six-variable MDRD equation, four-variable MDRD equation, CKD-EPI equation, Jelliffe-1973 equation, and Hull equation, respectively.

Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; sGFR, standard glomerular filtration rate; MDRD, Modification of Diet in Renal Disease.

Performance of various stages of CKD

In CKD stages 1 and 2, the median of the difference of the Jelliffe-1973 equation was smaller. The IQR of difference for the CKD-EPI equation was smaller. The CKD-EPI equation provided better results than the others in accuracies with deviations less than 15%, 30%, and 50% from the sGFR. In CKD stage 3, the median of the difference of the six-variable MDRD equation was smaller. The IQR of difference for the CG equation was smaller. Accuracy with a deviation less than 15% from the sGFR of the Hull equation was higher. The CG equation provided better results than the others in accuracies with deviations less

than 30% and 50% from the sGFR. In CKD stages 4 and 5, the median of the difference for the Jelliffe-1973 equation was smaller. The IQRs of difference for the CG equation and the Jelliffe-1973 equation were smaller. The Jelliffe-1973 equation revealed higher accuracies with deviation less than 15%, 30%, and 50% from the sGFR (Table 4).

Discussion

A report from the Dialysis and Transplantation Registration Group of the Chinese Society of Nephrology revealed that in 1999, the population undergoing maintenance dialysis

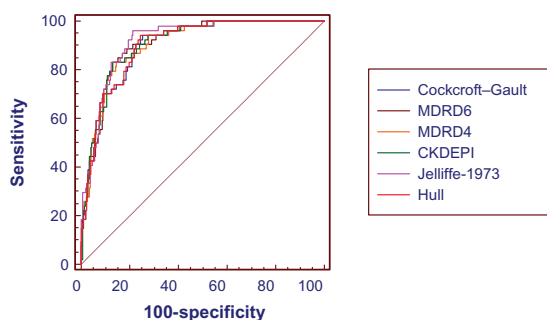
Table 3 AUCs, sensitivity, and specificity of eGFR for the diagnosis of moderate renal failure (GFR < 60 mL/min/1.73 m²)

	AUC	Sensitivity	Specificity
Cockcroft–Gault equation	0.903 ± 0.019	0.593	0.917
Six-variable MDRD equation	0.909 ± 0.018	0.815	0.868
Four-variable MDRD equation	0.906 ± 0.019	0.796	0.872
CKD-EPI equation	0.908 ± 0.019	0.778	0.883
Jelliffe-1973 equation	0.919 ± 0.017	0.630	0.925
Hull equation	0.904 ± 0.019	0.667	0.917

Note: $P < 0.05$ comparing with Jelliffe-1973-GFR.

Abbreviations: AUC, area under the receiver operating characteristic curve; eGFR, estimated glomerular filtration rate.

numbered 41,755.²¹ Liu and his colleagues found that, in China, about 14.82% of the 13,383 hospitalized patients investigated were diagnosed as having CKD.²² They also found that the prevalence of CKD increases dramatically in older people. Therefore, in the elderly population, the evaluation of renal function is critically important in clinical practice, since it has a great impact on diagnosis and medical treatment requiring adjustment in drug dosages in the elderly. The changes in renal function that accompany aging present a decrease in GFR – more than 1 mL/min/1.73 m²/year in those over the age of 40 years.²³ However, this change can vary. Gault and Cockcroft²⁴ found that the variability of creatinine clearance also increased with increasing age. This was accordant with a recent report from the Baltimore Longitudinal Study of Aging, which demonstrated that variability, such as decrease, increase, or no change, in creatinine clearance emerged in 254 healthy individuals followed up for as long as 23 years.²³ This variability causes additional difficulties in the estimation of GFR. The American Diabetes Association

**Figure 2** Receiver operating characteristic curves of eGFR for the diagnosis of moderate renal failure (GFR < 60 mL/min/1.73 m²).

Notes: Cockcroft–Gault, MDRD6, MDRD4, CKDEPI, Jelliffe-1973, and Hull represent the results of GFR estimated by Cockcroft–Gault equation, six-variable MDRD equation, four-variable MDRD equation, CKD-EPI equation, Jelliffe-1973 equation, and Hull equation, respectively.

Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; sGFR, standard glomerular filtration rate; MDRD, Modification of Diet in Renal Disease.

Table 4 Performances of eGFR and sGFR in the different stages of CKD

	Difference		Accuracy within		
	Median	IQR	15%	30%	50%
Stage 1–2					
Cockcroft–Gault equation	–10.8	29.1	35.2	70.4	92.6
Six-variable MDRD equation	5.9	29.5	42.6	66.7	87.0
Four-variable MDRD equation	6.6	33.0	38.9	61.1	83.3
CKD-EPI equation	2.2	23.9	50.0	74.1	94.4
Jelliffe-1973 equation	0.0	44.3	24.1	64.8	79.6
Hull equation	–6.2	30.4	33.3	68.5	90.7
Stage 3					
Cockcroft–Gault equation	–3.8	16.9	37.8	62.9	83.9
Six-variable MDRD equation	–0.4	22.7	30.1	56.6	78.3
Four-variable MDRD equation	3.8	22.3	29.4	60.1	76.9
CKD-EPI equation	1.3	21.1	28.7	58.7	76.2
Jelliffe-1973 equation	–2.2	20.2	34.3	58.7	86.7
Hull equation	–3.3	18.2	38.5	61.5	81.8
Stage 4–5					
Cockcroft–Gault equation	–2.8	9.7	22.1	45.9	73.8
Six-variable MDRD equation	–2.4	11.0	23.0	44.3	69.7
Four-variable MDRD equation	–2.6	10.9	21.3	45.1	68.9
CKD-EPI equation	–4.2	11.2	16.4	41.8	66.4
Jelliffe-1973 equation	–1.8	9.7	27.9	51.6	75.4
Hull equation	–4.1	10.2	26.2	41.8	71.3

Abbreviations: IQR, interquartile range; eGFR, estimated glomerular filtration rate; sGFR, standard glomerular filtration rate.

recommended estimation of GFR using prediction equations based on SC determinations.²⁵ However, this has still not been validated in elderly populations.

Application of SC-based GFR prediction equations to elderly patients with CKD is limited. Bevc et al²⁶ found that both the MDRD equations and the CKD-EPI equation lacked precision, and the accuracy within 30% of estimated ⁵¹Cr EDTA clearance values differs according to the stage of CKD. Burkhardt et al²⁷ demonstrated that the accuracies and precisions of the CG equation and the MDRD equations were low, and that there was an underestimation of actual GFR. A cross-sectional study in a French hospital with mostly Caucasian patients²⁸ also found that the CG equation seemed to be the most accurate and appropriate formula. The present study revealed that none of the equations had acceptable accuracy to exactly predict GFR in an elderly population. A new equation is still needed to provide a more accurate estimation of GFR in elderly patients.

Age and body mass are important sources of bias in the prediction. All the equations in our study are based on the SC value. The generation of creatinine is determined primarily by muscle mass and dietary intake. Muscle mass is considered a constant part of total body weight. However, elderly people often have decreased lean body mass and suffer from many chronic diseases associated with

decreased muscle mass and SC levels.⁷ Additionally, elderly patients are often malnourished and Compan et al found that patients classified as malnourished account for 25% of the hospitalized elderly.²⁹ Older and malnourished patients are particularly at risk of having decreased GFR even with normal SC levels.^{30,31} All of these factors could influence the accuracy of application of the equations. Recent research finds that applying the CG equation corrected by BSA may be more precise than the MDRD equations in patients with malnutrition or inflammation. In the present study, the CG equation had higher accuracy than the other equations; however, it still did not provide acceptable accuracy.

In these prediction equations, the subjects enrolled did not adequately represent subjects older than 70 years of age. The MDRD equation had not been initially validated in older people, and the mean age was 50.6 ± 12.7 years.¹⁶ The CG equation was originally established with 249 patients aged 18 to 92 years. Among the patients, only 59 (23%) were over the age of 70 years and women accounted for only 4% of the patients,¹⁴ yet when a study was applied in an elderly population to calculate creatinine clearance, most of the subjects were female. A correction factor of 0.85 was proposed for females, according to data from earlier studies, but in Cockcroft and Gault's own study, data on females were extremely limited, so this figure must be considered pure speculation.³² Special attention must be given to the application of equations extended to populations not represented in the original study.

The large percentage of diabetic patients in the present study is also a source of bias. Related investigations found that many of the diabetic patients had a supernormal GFR before the onset of overt clinical diabetic nephropathy and progressive renal insufficiency.^{33,34} A surrogate marker based on SC cannot effectively detect emerging hyperfiltration in the early phase of diabetic nephropathies.²⁷ In our study, diabetic patients make up 35.7% of the patients, so the remarkable underestimation of actual GFR by formula estimators is, in part, on account of an undetectable hyperfiltration in patients with diabetes; this is consistent with previous results.^{35,36} Considering the number of elderly patients with diabetes, it is understandable that our results underestimated the actual GFRs.

The methods used to measure SC were different in each study. In the original MDRD study, SC was measured by the CX3 Beckman method.^{15,16} In the CKD-EPI equation,¹⁷ SC was determined by the enzymatic method. The other equations in our study were published long ago, and the methods used for SC measurement have not been available until now.³⁶ In our study, SC was measured using the enzymatic method, different from

that in the MDRD study. Several studies have proven that calibration of SC assays can influence the accuracy of MDRD.^{37,38} Variability among clinical laboratories in the calibration of SC assays results in bias in the estimation of GFR.

In conclusion, our data indicated that when SC was measured by the enzymatic method, none of the equations considered were suitable for use in the elderly Chinese population invested in our study. Further improved formulae are needed to assess GFR in elderly Chinese CKD patients. At present, based on both overall performance and performance in different CKD stages, the CG equation may be the most accurate for use in elderly Chinese patients with CKD.

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Authors' contributions

Contributions of each author: XL, CGS, ZJC, and TQL, planning of the project; XL, HT, and ZCY, performed the experimental work; XL, MHC, CW, JXC, and CLC, intellectual analysis of the data; XL, writing of the paper.

Disclosure

The authors report no conflicts of interest in this work.

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