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ORIGINAL RESEARCH

Is the Chronic Kidney Disease Epidemiology Collaboration creatinine–cystatin C equation useful for glomerular filtration rate estimation in the elderly?

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This article was published in the following Dove Press journal:
Clinical Interventions in Aging
10 October 2013
Number of times this article has been viewed

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Background: We aimed to evaluate the performance of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine–cystatin C equation in a cohort of elderly Chinese participants.

Materials and methods: Glomerular filtration rate (GFR) was measured in 431 elderly Chinese participants by the technetium-99m diethylene-triamine-penta-acetic acid (^{99m}Tc-DTPA) renal dynamic imaging method, and was calibrated equally to the dual plasma sample ^{99m}Tc-DTPA-GFR. Performance of the CKD-EPI creatinine–cystatin C equation was compared with the Cockcroft–Gault equation, the re-expressed 4-variable Modification of Diet in Renal Disease (MDRD) equation, and the CKD-EPI creatinine equation.

Results: Although the bias of the CKD-EPI creatinine–cystatin C equation was greater than with the other equations (median difference, 5.7 mL/minute/1.73 m^2 versus a range from 0.4–2.5 mL/minute/1.73 m^2; $P<0.001$ for all), the precision was improved with the CKD-EPI creatinine–cystatin C equation (interquartile range for the difference, 19.5 mL/minute/1.73 m^2 versus a range from 23.0–23.6 mL/minute/1.73 m^2; $P<0.001$ for all comparisons), leading to slight improvement in accuracy (median absolute difference, 10.5 mL/minute/1.73 m^2 versus 12.2 and 11.4 mL/minute/1.73 m^2 for the Cockcroft–Gault equation and the re-expressed 4-variable MDRD equation, $P=0.04$ for both; 11.6 mL/minute/1.73 m^2 for the CKD-EPI creatinine equation, $P=0.11$), as the optimal scores of performance (6.0 versus a range from 1.0–2.0 for the other equations). Higher GFR category and diabetes were independent factors that negatively correlated with the accuracy of the CKD-EPI creatinine–cystatin C equation ($\beta = -0.184$ and -0.113, $P<0.001$ and $P=0.02$, respectively).

Conclusion: Compared with the creatinine-based equations, the CKD-EPI creatinine–cystatin C equation is more suitable for the elderly Chinese population. However, the cost-effectiveness of the CKD-EPI creatinine–cystatin C equation for clinical use should be considered.

Keywords: elderly, equation, glomerular filtration rate, serum creatinine, cystatin C

Introduction

Chronic kidney disease (CKD) is common in the elderly.[1] Glomerular filtration rate (GFR) is the best index of overall kidney function.[2] In two previous studies,[3,4] we found that creatinine-based GFR predicting equations were not suitable for elderly Chinese patients with CKD. In the present study, several improvements to study design were made. First, cystatin C was added as a new predicting variable, and was traceable to standard reference material for cystatin C measurement. Second, GFR was measured by the technetium-99m diethylene-triamine-penta-acetic acid (^{99m}Tc-DTPA) renal dynamic

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imaging method, and was calibrated equally to the dual plasma sample ^{99m}Tc-DTPA-GFR. Third, sample size was increased. We aimed to evaluate the performance of the new CKD Epidemiology Collaboration (CKD-EPI) creatinine–cystatin C equation[5] in a cohort of elderly Chinese participants, compared with the creatinine-based equations.

Materials and methods

Participants

Participants aged 60 years or older in the Third Affiliated Hospital of Sun Yat-sen University, People's Republic of China were enrolled between January 2010 and December 2012. Exclusion criteria included: 1) acute kidney function deterioration, edema, skeletal muscle atrophy, pleural effusion or ascites, malnutrition, amputation, heart failure, and ketoacidosis, or 2) on cimetidine or trimethoprim, or 3) being treated with dialysis at the time of the study. Study approval was obtained from the institutional review board at the Third Affiliated Hospital of Sun Yat-sen University. Informed consent of subjects was obtained prior to the beginning of the study.

Laboratory methods

GFR was measured by the ^{99m}Tc-DTPA renal dynamic imaging method,[6,7] as described previously.[8] According to the method developed by Ma et al,[9] we determined the minimum sample size to be 36 (95% confidence interval and 80% power), using Open Epi Version 2 (http://www.openepi.com)[10] to compare means (in order to ensure that our measured GFR [mGFR] values were calibrated equally to the dual plasma sample ^{99m}Tc-DTPA-GFR). Calculation was based on the findings in a previous Chinese study.[11] We randomly selected 36 cases (GFR measured by the DTPA renal dynamic imaging method, range 15.6–106.3 mL/minute/1.73 m^2) and performed the dual plasma samples method ^{99m}Tc-DTPA clearance simultaneously with the renal dynamic imaging. After image acquisition, blood samples were taken 2 and 4 hours after injection from the opposite forearm. The plasma was separated, and radioactivity was counted in a multi-function well counter (ZD-6000 multi-function instrument; Zhida Technology Company, Xian, People's Republic of China).[12] The ^{99m}Tc-DTPA renal dynamic imaging GFR measured in our study can be calibrated to dual plasma samples ^{99m}Tc-DTPA clearance GFR using a linear regression equation:

Dual plasma sample ^{99m}Tc-DTPA-GFR (mL/minute/1.73 m^2)
$= -2.586 + 1.106 \times$ ^{99m}Tc-DTPA renal dynamic imaging-GFR (mL/minute/1.73 m^2)
($R^2 = 0.872$, $P < 0.001$)

Serum creatinine level was measured by the enzymatic method on a Hitachi 7180 AutoAnalyzer (Hitachi Ltd, Tokyo, Japan; reagents from Roche Diagnostics, Mannheim, Germany), and recalibrated to isotope dilution mass spectrometry. Serum cystatin C assays were traceable to the certified reference materials (ERM-DA471). Performance of the CKD-EPI creatinine–cystatin C equation was compared with the Cockcroft–Gault equation,[13] the re-expressed 4-variable Modification of Diet in Renal Disease (MDRD) equation,[14] and the CKD-EPI creatinine equation[15] (Table 1).

Statistical analyses

Bias was defined as the median of the difference between the mGFR and estimated GFR, and precision was measured

Table 1 GFR predicting equations

Basis of equation and sex	Serum creatinine	CYC	Equation for estimating GFR
Cockcroft–Gault equation[13]			
			(140 – Age) × Weight ÷ SC ÷ 72 × [0.85 if female] × 1.73 ÷ BSA
Re-expressed 4-variable MDRD equation[14]			
			$175 \times SC^{-1.154} \times Age^{-0.203}$ × [0.742 if female] × [1.212 if Black]
CKD-EPI creatinine equation[15]			
Female	≤0.7		$144 \times (SC \div 0.7)^{-0.329} \times 0.993^{Age}$ [× 1.159 if Black]
Female	>0.7		$144 \times (SC \div 0.7)^{-1.209} \times 0.993^{Age}$ [× 1.159 if Black]
Male	≤0.9		$141 \times (SC \div 0.9)^{-0.411} \times 0.993^{Age}$ [× 1.159 if Black]
Male	>0.9		$141 \times (SC \div 0.9)^{-1.209} \times 0.993^{Age}$ [× 1.159 if Black]
CKD-EPI creatinine–cystatin C equation[5]			
Female	≤0.7	≤0.8	$130 \times (SC \div 0.7)^{-0.248} \times (CYC \div 0.8)^{-0.375} \times (0.995)^{Age}$ × [1.08 if Black]
		>0.8	$130 \times (SC \div 0.7)^{-0.248} \times (CYC \div 0.8)^{-0.711} \times (0.995)^{Age}$ × [1.08 if Black]
Female	>0.7	≤0.8	$130 \times (SC \div 0.7)^{-0.601} \times (CYC \div 0.8)^{-0.375} \times (0.995)^{Age}$ × [1.08 if Black]
		>0.8	$130 \times (SC \div 0.7)^{-0.601} \times (CYC \div 0.8)^{-0.711} \times (0.995)^{Age}$ × [1.08 if Black]
Male	≤0.9	≤0.8	$135 \times (SC \div 0.9)^{-0.207} \times (CYC \div 0.8)^{-0.375} \times (0.995)^{Age}$ × [1.08 if Black]
		>0.8	$135 \times (SC \div 0.9)^{-0.207} \times (CYC \div 0.8)^{-0.711} \times (0.995)^{Age}$ × [1.08 if Black]
Male	>0.9	≤0.8	$135 \times (SC \div 0.9)^{-0.601} \times (CYC \div 0.8)^{-0.375} \times (0.995)^{Age}$ × [1.08 if Black]
		>0.8	$135 \times (SC \div 0.9)^{-0.601} \times (CYC \div 0.8)^{-0.711} \times (0.995)^{Age}$ × [1.08 if Black]

Abbreviations: BSA, body surface area; CYC, cystatin C; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; SC, serum creatinine.

by the interquartile range (IQR) for the difference. Accuracy was defined by both the median of the absolute difference and percentage of estimated GFR not deviating more than 30% from the mGFR. The Wilcoxon signed-rank test was used for difference, the bootstrap method[16] for IQR, and the McNemar test for 30% accuracy. Performances of the GFR estimating equations were assessed by three aspects, including bias, precision, and accuracy. An optimal score system[4] was developed. The equation that performed the best in each aspect in the entire cohort was scored as 1, and in each GFR subgroup as 0.5. The greater total scores, the better synthetic performance. All calculations and statistics were performed using SPSS software (version 11.0; IBM Corporation, Armonk, NY, USA) and Matlab software (version 2011b; The Mathworks, Boston, MA, USA).

Results

A total of 431 participants aged 60 years or older were enrolled. The mean age was 69.9 ± 6.8 years and the mean mGFR was 53.4 ± 26.9 mL/minute/1.73 m^2. Detailed characteristics are listed in Table 2.

Although the bias of the CKD-EPI creatinine–cystatin C equation was greater than with the other equations (median difference, 5.7 mL/minute/1.73 m^2 versus 0.4–2.5 mL/minute/1.73 m^2, $P<0.001$ for all comparisons), the precision was improved with the CKD-EPI creatinine–cystatin C equation (IQR for the difference, 19.5 mL/minute/1.73 m^2 versus 23.0–23.6 mL/minute/1.73 m^2, $P<0.001$ for all comparisons), leading to slight improvement in accuracy (median absolute difference, 10.5 mL/minute/1.73 m^2 versus 12.2 and 11.4 mL/minute/1.73 m^2 for the Cockcroft–Gault equation and the re-expressed 4-variable MDRD equation, $P=0.04$ for both; and 11.6 mL/minute/1.73 m^2 for the CKD-EPI creatinine equation, $P=0.11$); 30% accuracy, 59.9% versus 55.5%–57.5%, $P>0.05$ for all (Table 3). An optimal score system was developed to evaluate the performances between different equations (Table 4). The CKD-EPI creatinine–cystatin C equation achieved the optimal scores (6.0 versus a range from 1.0–2.0 for the other equations).

We used multiple regression analysis to determine the factors that affected the accuracy of the CKD-EPI creatinine–cystatin C equation, with 30% accuracy of the CKD-EPI creatinine–cystatin C equation as the dependent variable and GFR categories (category 1: 1; category 2; 2: category 3; 3: category 4; 4: category 5; 5), age (≤65 years: 1; >65 years: 2), sex (male: 1; female: 2), diabetes (non-diabetic: 1; diabetes: 2),

Table 2 Participants, characteristics*

Subjects (n)	431
Age (year)	69.9 ± 6.8
Male sex (n [%])	233 (54.1)
Diabetes (n [%])	263 (61.0)
Body mass index (kg/m^2)	24.2 ± 4.3
Body surface area (m^2)	1.66 ± 0.19
Serum creatinine (mg/dL)	2.0 ± 1.9
Serum cystatin C (mg/dL)	2.0 ± 1.2
Measured GFR (mL/minute/1.73 m^2)	53.4 ± 26.9
GFR categories	
<15 (mL/minute/1.73 m^2)	33 (7.7)
15–29 (mL/minute/1.73 m^2)	59 (13.7)
30–59 (mL/minute/1.73 m^2)	174 (40.4)
60–89 (mL/minute/1.73 m^2)	118 (27.4)
>90 (mL/minute/1.73 m^2)	47 (10.9)

Note: *Plus-minus values are means ± standard deviation.
Abbreviation: GFR, glomerular filtration rate.

Table 3 Performance between measured GFR and estimated GFR

Variable	Measured GFR (mL/minute/1.73 m^2)			
	Overall	<30	30–59	≥60
Bias – median difference (mL/minute/1.73 m^2)				
Cockcroft–Gault equation	2.5*	1.0*	3.3*	2.6*
Re-expressed 4-variable MDRD equation	0.4*	2.0*	1.1*	–4.2*
CKD-EPI creatinine equation	0.5*	2.7†	–0.4*	–0.7*
CKD-EPI creatinine–cystatin C equation	5.7	3.1	6.2	6.8
Precision – IQR for the difference (mL/minute/1.73 m^2)				
Cockcroft–Gault equation	23.6*	11.4*	22.9*	31.7*
Re-expressed 4-variable MDRD equation	23.6*	12.6*	23.7*	30.5*
CKD-EPI creatinine equation	23.0*	11.7*	25.7*	28.3*
CKD-EPI creatinine–cystatin C equation	19.5	8.8	22.4	24.6
Accuracy				
Median absolute difference (mL/minute/1.73 m^2)				
Cockcroft–Gault equation	12.2‡	5.7	13.2	16.8†
Re-expressed 4-variable MDRD equation	11.4‡	6.4‡	11.9	16.0
CKD-EPI creatinine equation	11.6	7.0†	12.7	14.0
CKD-EPI creatinine–cystatin C equation	10.5	6.0	12.7	12.2
30% accuracy (%)				
Cockcroft–Gault equation	57.5	37.0	52.3	74.5
Re-expressed 4-variable MDRD equation	57.5	37.0	55.7	74.5
CKD-EPI creatinine equation	55.5	35.9	48.9	74.5
CKD-EPI creatinine–cystatin C equation	59.9	40.2	51.7	79.4

Notes: *$P<0.001$ compared with the CKD-EPI creatinine–cystatin C equation GFR; †$P<0.01$ compared with the CKD-EPI creatinine–cystatin C equation GFR; ‡$P<0.05$ compared with the CKD-EPI creatinine–cystatin C equation GFR.
Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; GFR, glomerular filtration rate; IQR, interquartile range; MDRD, Modification of Diet in Renal Disease.

Table 4 Optimal scores* by equation

Equation	Total scores
Cockcroft–Gault equation	1.0
Re-expressed 4-variable MDRD equation	2.0
CKD-EPI creatinine equation	1.0
CKD-EPI creatinine–cystatin C equation	6.0

Note: *The equation which performed the best overall scored 1, and in each GFR subgroup scored 0.5.
Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease.

body mass index (<20 kg/m^2: 1; ≥ 20 kg/m^2 and <25 kg/m^2: 2; ≥ 25 kg/m^2 and ≤ 30 kg/m^2: 3; >30 kg/m^2: 4) as the independent variables for regression analysis. We found that both higher GFR category and diabetes were independent factors that negatively correlated with 30% accuracy of the CKD-EPI creatinine–cystatin C equation ($\beta = -0.184$ and -0.113, $P<0.001$ and $P=0.02$, respectively).

Discussion

Recently, measurement of serum cystatin C has been advocated as a simple, reliable, and accurate marker of GFR.[17] Cystatin C is a low molecular weight protein that is freely filtered across the glomerular barrier and almost completely reabsorbed and catabolized by tubular cells.[17] A cystatin-C-based equation has many advantages over a creatinine-based one in the assessment of renal function in the elderly, since the creatinine-based one can be affected by a reduced muscle mass and other confounding factors such as age, race, sex, diabetes, and day-to-day variables. However, there is still no explicit evidence for superiority in this population in clinical practice.[18,19] Furthermore, a cystatin-C-based estimation of GFR also showed only limited improvement in contrast to a creatinine-based formula.[18] In 2012, a new CKD-EPI creatinine–cystatin C equation was developed based on both serum cystatin C and creatinine. The combined equation performed better than equations based on either marker alone.[5] However, the CKD-EPI creatinine–cystatin C equation has not been validated in the elderly. The current study was designed to evaluate its performance in GFR estimation for the elderly Chinese population.

In this study, we found that although the bias of the CKD-EPI creatinine–cystatin C equation was greater than the other creatinine-based equations, the precision was improved with the CKD-EPI creatinine–cystatin C equation, leading to slight improvement in accuracy and the optimal scores of performance as well. Both higher GFR category and diabetes were independent factors negatively correlated with the 30% accuracy of the CKD-EPI creatinine–cystatin C equation. These results confirmed that the combination of novel filtration markers, such as cystatin C and serum creatinine, into the GFR estimating formula may be a key to improving accuracy.

There were some limitations to this study. First, subjects represented a specific elderly cohort in the People's Republic of China; further validations in other age or racial populations are needed. Second, the difference in the measurement of GFR introduced systemic bias.[20] Third, GFR estimating equation may be influenced by the difference of mGFR distribution and the cause of disease in the development population.[21]

In summary, comparing the creatinine-based equations, the CKD-EPI creatinine–cystatin C equation is more suitable for the elderly Chinese population. However, the cost-effectiveness of the CKD-EPI creatinine–cystatin C equation for clinical use should be considered.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (grant number 81370866 and number 81070612), the China Postdoctoral Science Foundation (grant number 201104335), the Guangdong Science and Technology Plan (grant number 2011B031800084), the Fundamental Research Funds for the Central Universities (grant number 11ykpy38), and the National Project of Scientific and Technical Supporting Programs Funded by the Ministry of Science and Technology of China (grant number 2011BAI10B00). This work was also supported in part by the National Natural Science Foundation of China (grant numbers 91029742, 81170647, and 81370837 to Hui Huang).

Disclosure

The authors report no conflicts of interest in this work.

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