Analysis of chronic kidney disease staging with different estimated glomerular filtration rate equations in Chinese centenarians

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Abstract

Background: Accurate estimation of the glomerular filtration rate (GFR) and staging of chronic kidney disease (CKD) are important. Currently, there is no research on the differences in several estimated GFR equations for staging CKD in a large sample of centenarians. Thus, this study aimed to investigate the differences in CKD staging with the most commonly used equations and to analyze sources of discrepancy.

Methods: A total of 966 centenarians were enrolled in this study from June 2014 to December 2016 in Hainan province, China. The GFR with the Modification of Diet in Renal Disease (MDRD), Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) and Berlin Initiative Study 1 (BIS1) equations were estimated. Agreement between these equations was investigated with the κ statistic and Bland-Altman plots. Sources of discrepancy were investigated by partial correlation analysis.

Results: The κ values of the MDRD and CKD-EPI equations, MDRD and BIS1 equations, and CKD-EPI and BIS1 equations were 0.610, 0.253, and 0.381, respectively. Serum creatinine (Scr) explained 10.96%, 41.60% and 17.06% of the variability in these three comparisons, respectively. Serum uric acid (SUA) explained 3.65% and 5.43% of the variability in the first 2 comparisons, respectively. Gender was associated with significant differences in these 3 comparisons ($P < 0.001$).

Conclusions: The strengths of agreement between the MDRD and CKD-EPI equations were substantial, but those between the MDRD and BIS1 equations and the CKD-EPI and BIS1 equations were fair. The difference in CKD staging of the first 2 comparisons strongly depended on Scr, SUA and gender, and that of CKD-EPI and BIS1 equations strongly depended on Scr and gender. The incidence at various stages of CKD staging was quite different. Thus, a new equation that is more suitable for the elderly needs to be built in the future.

Keywords: Chinese centenarians; Estimated glomerular filtration rate; Modification of Diet in Renal Disease equation; Chronic Kidney Disease Epidemiology Collaboration equation; Berlin Initiative Study 1 equation

Introduction

The elderly population, including centenarians, has become the fastest-growing part of the population in the world, especially in China.[1] This growth has led to considerable social and economic burdens of diseases, such as chronic kidney disease (CKD), in this age group.[2] Therefore, prevention and treatment of CKD are particularly important and urgent in elderly patients. Glomerular filtration rate (GFR) is a sensitive index for evaluating renal function and is also an important basis for early diagnosis, staging, and treatment monitoring of CKD.[3] The gold standard of estimating GFR with 99mTc-diethylene triamine pentaaceticacid (99mTc-DTPA) isotope imaging is an invasive and tedious process.[4] To solve this problem, several serum creatinine (Scr)-based GFR estimation equations have been developed and tested over the past few years. The most reliable equations used to assess estimated GFR (eGFR) are the Modification of Diet in Renal Disease (MDRD), Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) and Berlin Initiative Study 1 (BIS1) equations.[5-7] However, none of these GFR prediction equations was initially developed in a large sample of

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elderly people. Thus, the accuracy of the application of these eGFR equations is questionable in the elderly, especially among centenarians.[8] Classifying a given patient into a different CKD stage implies that different measures would be needed to treat CKD.[9] Thus, it is of great clinical significance to accurately estimate GFR and CKD stage.[10]

Centenarians represent a unique population in experimental research because they develop all the signs and characteristics of the extreme ageing process.[11] However, there is currently no guideline that explicitly recommends which equation we should use when calculating GFR for the elderly. The agreements of these equations for eGFR have not yet been validated in centenarians, who have extreme longevity. The aim of the present study was to compare the MDRD, CKD-EPI, and BIS1 equations in Chinese centenarians and to assess the sources of discrepancies among these equations.

Methods

Ethical approval

The researchers obtained ethical approval for the study protocol from the Ethics Committee of the Hainan branch of the Chinese People's Liberation Army General Hospital (No. of serial: 301HNLL-2016-01). Participants received an extensive description of the study and signed an informed participation consent form that included permission to carry out analyses on biological specimens that were collected and stored. For those unable to fully consent because of cognitive or physical problems, surrogate consent was obtained from a close relative.

Data source

The data from the China Hainan Centenarian Cohort Study (CHCCS) were used, which was designed to investigate centenarians' physical and mental health status and their social conditions from June 2014 to December 2016 in Hainan province, China.

A total of 966 centenarians were enrolled in the present study. The details of the participant recruitment and study scheme are shown in Figure 1. CKD staging was performed according to the Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines: stage 1, eGFR$\geq$90; stage 2, 60$\leq$eGFR$<$90; stage 3, 30$\leq$eGFR$<$60; stage 4, 15$\leq$eGFR$<$30; and stage 5, eGFR$<$15 (unit: mL·min^{-1}·1.73 m^{-2}).

Experimental procedures

Community-based surveys were conducted to collect demographic information (gender, age, and ethnicity). Questionnaires were administered and blood samples were obtained from each participant. Health-related variables, such as standing height, weight, systolic blood pressure (SBP), and diastolic blood pressure (DBP), waist circumference, and hip circumference, were measured as described by He *et al*.[2] Blood samples were obtained after the patients had fasted for 12 h and rested for at least 15 min and were stored separately in refrigerated containers until they were analyzed on the same day. Blood biochemical and blood routine examinations were conducted using enzymatic assays (Roche Products Ltd., Basel, Switzerland) on a fully automatic biochemical autoanalyzer (Cobas 8000; Roche Products Ltd., Basel, Switzerland).

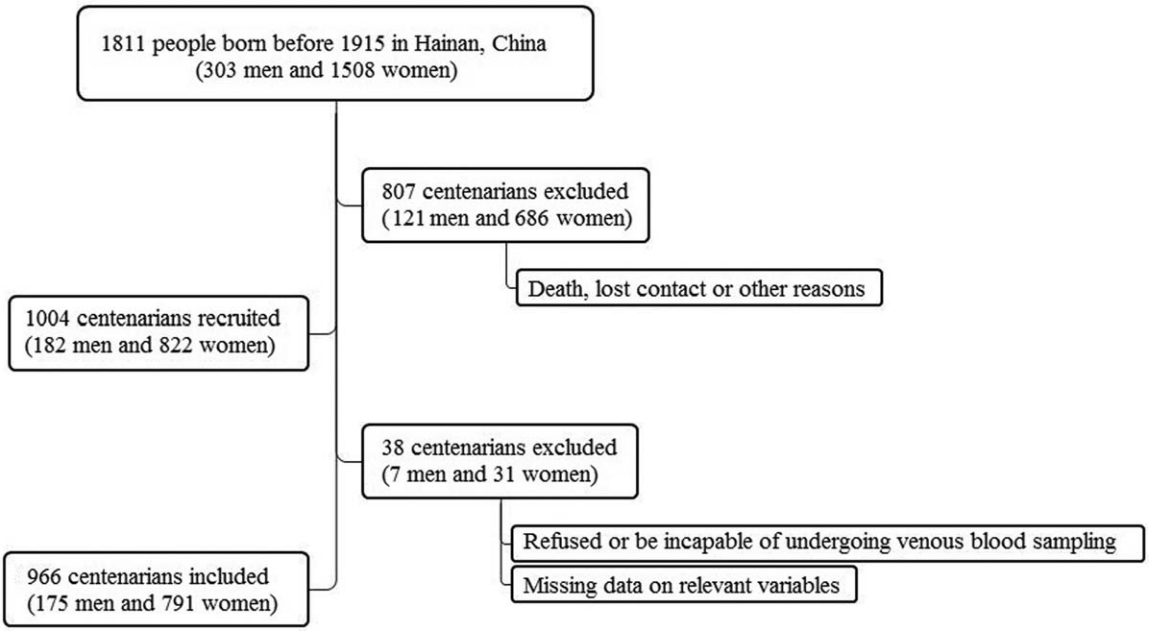

Figure 1: Flow diagram of participant recruitment in this study.

Statistical analysis

Normally distributed data were expressed as the means ± standard deviation (SD) and compared with unpaired Student's *t*-test. Non-normal variables were expressed as medians (Q1, Q3) and compared with Mann-Whitney *U* test. The agreement between the MDRD, CKD-EPI and BIS1 equations was assessed with Bland-Altman plots using 95% limits of agreement that were calculated as the mean difference ±1.96 SD. To assess factors that might have influenced any discordance between GFR estimates, Spearman correlation, and partial correlation analyses were used to evaluate the relationships of the variables and the difference values (Δ) of these 3 equations. Given that the categories were ordered, agreement was quantified by the linear-weighted κ statistic to quantify the agreement among three different equations. Statistical analysis was performed using SPSS software version 19.0 (SPSS Inc., Chicago, IL, USA), GraphPad Prism software vision 6 (GraphPad Software Inc., San Diego, CA, USA) and Medcalc for Windows version 9.3.9.0 (Medcalc software Inc., Mariakerke, Belgium). *P* values less than 0.05 were considered statistically significant.

Results

Overview of the whole study population

Demographic and clinical features of the participants included in the analysis are reported in Table 1. Hypertension was the most frequent disease (23.50%), followed by cardiovascular disease (4.04%). Overall, the general health status of the studied population was good, as the prevalence rates of severe diseases, such as stroke (1.97%) and cancer (0.10%), were very low.

Table 1: Clinical characteristics of the participants in this study (*N* = 966).

Characteristics	Values
Male/female, *n*	175/791
Age (years), median (Q1, Q3)	102 (101, 104)
BMI (kg/m^2), median (Q1, Q3)	18.06 (15.79, 20.22)
Waist-hip ratio, median (Q1, Q3)	0.89 (0.85, 0.93)
Ethnic Han, *n* (%)	839 (86.85)
SBP (mmHg), median (Q1, Q3)	150.5 (136.0, 173.0)
DBP (mmHg), median (Q1, Q3)	76.0 (67.0, 83.0)
Hemoglobin (g/L), mean±SD	113.11 ± 16.76
Red blood cells ($\times 10^{12}$/L), mean±SD	4.01 ± 0.61
MCV (fl), mean±SD	90.40 ± 8.95
Total protein (g/L), mean±SD	68.67 ± 6.26
Albumin (g/L), median (Q1, Q3)	38.7 (36.0, 41.3)
Serum homocysteine (μmol/L), median (Q1, Q3)	23.5 (18.6, 29.4)
Serum uric acid (μmol/L), median (Q1, Q3)	318.0 (261.75, 386.0)
Serum urea (mmol/L), median (Q1, Q3)	5.9 (4.6, 7.5)
Serum creatinine (μmol/L), median (Q1, Q3)	78.0 (65.0, 99.0)
Diseases, *n* (%)	
Hypertension	227 (23.50)
Cardiovascular disease	39 (4.04)
Stroke	19 (1.97)
Diabetes	48 (4.97)
Dyslipidaemia	4 (0.41)
Cancer	1 (0.10)

BMI: Body mass index; DBP: Diastolic blood pressure; MCV: Mean corpuscular volume; SBP: Systolic blood pressure; SD: Standard deviation.

Agreement of the three equations in the whole study population

The Bland-Altman plots showed comparisons of kidney function estimates with the MDRD, CKD-EPI, and BIS1 equations [Figure 2]. The mean difference between the MDRD and CKD-EPI estimates was only 6.0 mL·min^{-1}·1.73 m^{-2}, and the 95% limits of agreement were –14.8 and 26.8 mL·min^{-1}·1.73 m^{-2}. There were 4.55% of points beyond the 95% limits of agreement. In addition, the MDRD equation yielded higher eGFR value than the CKD-EPI equation in patients with CKD stage 1 and healthy people. For comparisons between the MDRD and BIS1 estimates, the mean difference was 18.0 mL·min^{-1}·1.73 m^{-2}, and the 95% limits of agreement were –3.0 and 38.9 mL·min^{-1}·1.73 m^{-2}. There were 4.04% of points beyond the 95% limits of agreement. In addition, the MDRD equation almost always yielded higher eGFR value than the BIS1 equation. The mean difference between the CKD-EPI and BIS1 equation was 12.0 mL·min^{-1}·1.73 m^{-2}, with 95% limits of agreement of –0.4 and 24.4 mL·min^{-1}·1.73 m^{-2}. There were 5.90% of points beyond the 95% limits of agreement. In addition, the CKD-EPI equation yielded higher eGFR value than the CKD-EPI equation in patients with CKD stages 2 and 3.

The results of the classification and κ analysis are shown in Table 2. The strength of agreement was substantial between the MDRD and CKD-EPI equations ($\kappa = 0.610$, $P < 0.050$) and was fair between the CKD-EPI and BIS1 equations ($\kappa = 0.253$, $P < 0.050$) and between the MDRD and BIS1 equations ($\kappa = 0.381$, $P < 0.050$). Staging based on the MDRD- and CKD-EPI-derived eGFR was the most consistent in 691 (71.53%) patients, staging with the CKD-EPI and BIS1 equations was consistent in 593 (61.39%) patients, while staging with the MDRD and BIS1 equations was the least consistent, with only 429 (44.41%) subjects. Overall, relative misclassification of CKD stage 2 was more frequent than misclassification of other CKD stages with these three equations. Furthermore, misclassification of CKD stages 2 and 5 was more frequent with the CKD-EPI equation than with the MDRD and BIS1 equations, and misclassification of CKD stage 3 was more frequent with the BIS1 equation than with the CKD-EPI and MDRD equations.

Incidence at various stages of CKD staging calculated by different equations

The distributions of CKD stages according to eGFR calculated by the MDRD, CKD-EPI and BIS1 equations were as follows: The incidence rate was highest in stages 2 and 3, while the other 3 stages were relatively rare. The results of CKD staging calculated by the MDRD and CKD-EPI equations were very similar. However, there were fewer patients with CKD stage 2 (7.56% *vs.* 37.06% and

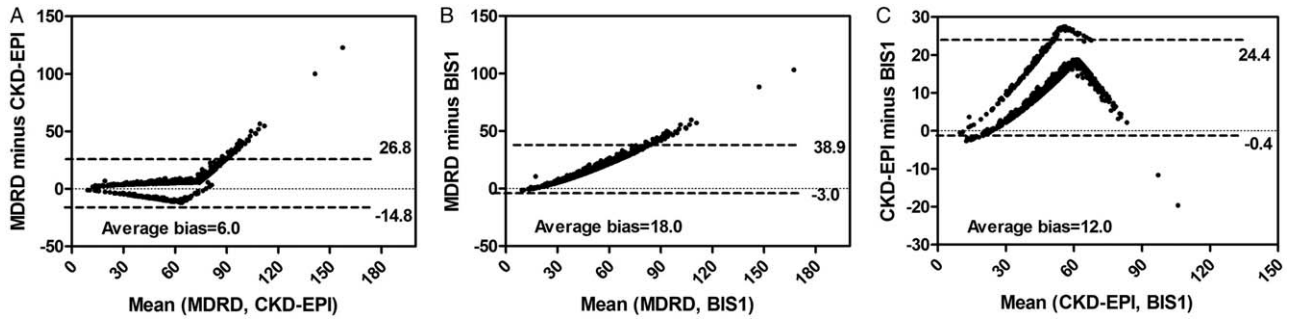

Figure 2: Bland-Altman plots of comparisons of kidney function estimates with the MDRD, CKD–EPI and BIS1 equations. Dashed lines represent the 95% limits of agreement. BIS1: Berlin Initiative Study 1; CKD–EPI: Chronic Kidney Disease Epidemiology Collaboration; MDRD: Modification of diet in renal disease.

Table 2: Agreement of three equations in the whole study population.

	MDRD						
Items	**Stage 1**	**Stage 2**	**Stage 3**	**Stage 4**	**Stage 5**	κ	***P***
CKD-EPI						0.610	0.001
Stage 1	2 (2.13)*	0	0	0	0		
Stage 2	92 (97.87)	247 (69.99)*	32 (6.94)	0	0		
Stage 3	0	111 (31.01)	404 (87.64)*	7 (15.22)	0		
Stage 4	0	0	25 (5.42)	33 (71.74)*	2 (28.57)		
Stage 5	0	0	0	6 (13.04)	5 (71.43)*		

	MDRD						
Items	**Stage 1**	**Stage 2**	**Stage 3**	**Stage 4**	**Stage 5**	κ	***P***
BIS1						0.253	0.002
Stage 1	2 (2.13)*	0	0	0	0		
Stage 2	73 (77.66)	0*	0	0	0		
Stage 3	19 (20.21)	358 (100.00)	375 (81.34)*	0	0		
Stage 4	0	0	86 (18.66)	45 (97.83)*	0		
Stage 5	0	0	0	1 (2.17)	7 (100.00)*		

	CKD-EPI						
Items	**Stage 1**	**Stage 2**	**Stage 3**	**Stage 4**	**Stage 5**	κ	***P***
BIS1						0.381	0.001
Stage 1	2 (100.00)*	0	0	0	0		
Stage 2	0	73 (19.68)*	0	0	0		
Stage 3	0	298 (80.32)	454 (86.97)*	0	0		
Stage 4	0	0	68 (13.03)	58 (96.67)*	5 (45.45)		
Stage 5	0	0	0	2 (3.33)	6 (54.55)*		

The data were shown as *n* (%). *Patients in whom chronic kidney disease classification with different equations was consistent. BIS1: Berlin Initiative Study 1; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; MDRD: Modification of diet in renal disease.

38.41%) and more patients with stages 3 (77.85% *vs.* 47.72% and 54.04%) and 4 (13.56% *vs.* 4.76% and 6.21%) when using the BIS1 equation than when using the MDRD and CKD-EPI equations. There were more patients with stage 1 CKD when using the MDRD equation than when using the CKD-EPI and BIS1 equations (9.73% *vs.* 0.21% and 0.21%). In addition, the incidence rates of stage 5 were rare (0.72%, 1.14%, and 0.83%) when using the MDRD, CKD-EPI and BIS1 equations, respectively.

Important factors for the differences in CKD staging based on different equations

Spearman correlation coefficients, partial correlation coefficients, and coefficients of partial determination are shown in Table 3. Δ(MDRD, CKD-EPI), Δ(MDRD, BIS1) and Δ(CKD-EPI, BIS1) were all significantly correlated with Scr, serum uric acid (SUA), urea and homocysteine levels ($P<0.050$), but not with albumin ($P>0.050$). However, age was significantly correlated with Δ(MDRD,

Table 3: Spearmen correlations and partial correlations of differences between GFR estimates obtained with MDRD, CKD-EPI, BIS1 equations, and other parameters.

	Δ(MDRD, CKD-EPI)			Δ(MDRD, BIS1)			Δ(CKD-EPI, BIS1)		
Items	**Spearmen cc**	**Partial cc**	**Partial R^2**	**Spearmen cc**	**Partial cc**	**Partial R^2**	**Spearmen cc**	**Partial cc**	**Partial R^2**
Age (years)	0.230*	0.100†	1.00%	0.038	0.123†	0.02%	−0.020	−0.018	0.03%
Scr (μmol/L)	−0.826*	−0.331*	10.96%	−0.997*	−0.645*	41.60%	−0.563*	−0.413*	17.06%
BMI (kg/m^2)	−0.155*	−0.083‡	0.69%	−0.123†	−0.030	0.09%	0.027	0.098†	0.96%
WHR	−0.018	0.052	0.27%	−0.055	0.033	0.11%	−0.098†	−0.048	0.23%
SUA (μmol/L)	−0.502*	−0.191*	3.65%	−0.574*	−0.233*	5.43%	−0.271*	0.036	0.13%
Albumin (g/L)	<0.001	−0.036	0.13%	0.015	−0.029	0.08%	0.016	0.026	0.07%
Serum urea (mmol/L)	−0.349*	0.137*	1.88%	−0.503*	0.122†	1.49%	−0.364*	−0.085‡	0.72%
HCY (μmol/L)	−0.340*	−0.049	0.24%	−0.442*	−0.084‡	0.71%	−0.262*	−0.019	0.04%

*Significantly different from controls ($P<0.001$). †Significantly different from controls ($P<0.010$). ‡Significantly different from controls ($P<0.050$). Δ: Difference value of equations; BIS1: Berlin Initiative Study 1; BMI: Body mass index; cc: correlation coefficient; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; HCY: Homocysteine; MDRD: Modification of diet in renal disease; Scr: Serum creatinin; SUA: Serum uric acid; WHR: Waist-hip ratio.

Table 4: Differences between GFR estimates obtained with MDRD, CKD–EPI, BIS1 equations stratified by gender.

Items	**Men ($n=175$)**	**Women ($n=791$)**	***Z***	***P***
Δ (MDRD, CKD-EPI)	−7.46 (−8.98, −5.63)	5.67 (4.98, 7.64)	20.60	<0.001
Δ (MDRD, BIS1)	10.09 (6.47, 13.58)	18.03 (12.23, 24.97)	11.49	<0.001
Δ (CKD-EPI, BIS1)	18.29 (12.47, 23.89)	11.42 (6.87, 15.19)	11.51	<0.001

The data were shown as median (Q1, Q3). Δ: Difference value of equations; BIS1: Berlin Initiative Study 1; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; MDRD: Modification of diet in renal disease.

CKD-EPI), but not with other comparisons. Δ(MDRD, CKD-EPI) and Δ(MDRD, BIS1) were significantly correlated with body mass index (BMI) ($P<0.05$), but Δ(CKD-EPI, BIS1) was not correlated with it ($P>0.05$), while waist-hip ratio showed the opposite trends. Partial correlation analysis demonstrated that Scr and SUA had the most important influences on variability in Δ(MDRD, CKD-EPI) (partial R^2: 10.96% and 3.65%, respectively) and Δ(MDRD, BIS1) (partial R^2: 41.60% and 5.43%, respectively). Scr had the most important influence on variability in Δ(CKD-EPI, BIS1) (partial R^2: 17.06%). The proportions of variability in differences between GFR estimation equations determined from the relationship with other indexes were relatively low for all comparisons (partial R^2: 0.02–1.88%). Table 4 showed that Δ(MDRD, CKD-EPI) and Δ(MDRD, BIS1) were greater in women than men, while Δ(CKD-EPI, BIS1) showed the opposite trends ($P<0.001$).

Discussion

With the acceleration of the ageing process, the prevalence of CKD in the elderly population has increased year by year.[1] Accurate estimation of GFR is important for detecting and staging CKD, determining drug dosages, stratifying risk, and tailoring the dosages of several drugs to kidney function.[12] There is currently no guideline that explicitly recommends which equation we should use when calculating GFR for the elderly. From the perspective of the practicing clinician, the aim of this study was to investigate the differences between the MDRD, CKD-EPI, and BIS1 equations in terms of CKD staging, explore whether they can be considered interchangeable and analyze the sources of discrepancy.

The general health status of our studied population was good, and the present study did not have subject selection bias. In this study, patients with CKD stages 1 and 2 were more prevalent when using the MDRD equation compared with the CKD-EPI and BIS1 equations. Similarly, the Bland-Altman plots showed that the MDRD equation yielded higher eGFR values than the CKD-EPI and BIS1 equations for patients with CKD stages 1 and 2. This might result in optimistic eGFR estimates for some elderly individuals. In addition, this study found that the agreement between the CKD-EPI and BIS1 equations was fair in the upper and lower ranges of eGFR, whereas it was worse in the middle range. In addition, the CKD-EPI equation yielded higher eGFR values than the BIS1 equation in CKD stages 2–3. The diagnosis of these CKD stages is very important for determining the specific diagnostic and therapeutic measures to be recommended.[9] These findings were similar to those of a previous study reported by Corsonello *et al*[10] involving elderly individuals approximately 80 years old. The CKD-EPI equation classified more patients with CKD stage 5 than the BIS1 equation. This might result in more individuals undergoing dialysis and can cause differences in patient prognosis. This result was quite different from that in a previous report by Corsonello *et al*,[10] possibly because of the ages, ethnicities, and gender ratios in the

study populations were different. Evidently, selecting older adults for diagnostic and therapeutic interventions related to CKD stage changes depending on which equation was used.[13] However, misclassification of the stage of CKD also caused problems for managing medications that were cleared by the kidneys, especially among older patients with multiple chronic diseases treated with polypharmacy regimens.[9]

This study reported the incidence rates at various stages of CKD staging, calculated according to different equations. The incidence rates were highest in stages 2 and 3; thus, we should pay attention to these individuals. The results of CKD staging calculated by the MDRD and CKD-EPI equations were very similar. However, there were fewer patients with CKD stage 2 and more patients with stages 3 and 4 when using the BIS1 equation than when using the MDRD and CKD-EPI equations. There were more patients with CKD stage 1 when using the MDRD equation than when using the CKD-EPI and BIS1 equations. Thus, the incidence rates at various stages of CKD staging were quite different and these equations cannot be considered interchangeable.

There are several important factors that affect differences between GFR estimates obtained with the MDRD, CKD-EPI, and BIS1 equations. We took into account kidney and metabolic disease-related indicators, including age, Scr, BMI, WHR, SUA, albumin, urea, and homocysteine levels. Ultimately, we observed strong negative correlations between Scr levels and all three comparisons, especially for Δ(MDRD, BIS1) and Δ(CKD-EPI, BIS1), which explained 41.60% and 17.06% of the variability in these two comparisons, respectively. In addition, we found that Δ(MDRD, CKD-EPI) and Δ(MDRD, BIS1) were greater in women than men, but Δ(CKD-EPI, BIS1) showed the opposite trends. This finding could be explained by the fact that many elderly people, especially elderly women, had sarcopenia and multiple comorbidities that cause a loss of muscle mass and, thus, low Scr levels.[14,15] These three equations were not developed in a large number of healthy people, resulting in worse performance in elderly people with low Scr levels.[5-7] In addition, we found an interesting phenomenon: SUA levels and all 3 comparisons had negative correlations, which was significant, especially for Δ(MDRD, CKD-EPI) and Δ(MDRD, BIS1), which explained 3.65% and 5.43% of the variability in these 2 comparisons, respectively. Perhaps we should pay attention to the SUA factor when building a new equation for the elderly. We were still unclear about the specific reasons for this phenomenon. A possible reason might be that the prevalence of hyperuricemia gradually increased with increasing age; thus, elderly people, especially centenarians, have a higher incidence of hyperuricemia.[16] However, we found that age had a weak correlation with this factor. The possible reason might be that the individuals of this study were all centenarians and, thus, were of similar age.

The present study had some advantages. There was no doubt that our sample of centenarians was very large, and this information was very important in the world. Indeed, the centralized and standardized serum analyses utilized in this study guaranteed the quality of the data. Furthermore, the variety of collected variables allowed the identification of sources of divergence between these 3 equations.

The limitations of this study also deserved consideration. We did not measure GFR directly because some centenarians were weak and could not undergo the invasive, complex gold standard diagnostic method. Furthermore, given that some centenarians were unable to have their weight accurately measured due to weakness, we did not study the Cockcroft-Gault equation. Last, serum cystatin C levels were unavailable for many centenarians due to the expensive measurement costs involved in such a large patient cohort. Therefore, we did not compare cystatin C-based equations.

In conclusion, these 3 equations could not be considered interchangeable for assessing eGFR in centenarians. The eGFR diverged significantly in the range of GFR corresponding to CKD stages 2 and 3, which might dramatically impact clinical decision making. Scr, SUA, and gender had the most important influences on the differences in these 3 equations for centenarians. Thus, Scr, SUA, and gender should be considered when we decide which equation to use for elderly people in order to avoid over- or underestimating GFR. Disagreement between equations might significantly impact the applications of stage-specific measures for managing CKD among centenarians. Therefore, we need to build a new equation that is more suitable for the elderly.

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Conflicts of interest

None.

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