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Comparison of Ten Creatinine-based Equations for Estimation of Glomerular Filtration Rate in Chinese Postmenopausal Women with Normal or Mildly Reduced Renal Function

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Abstract

Background and aim: The aim of the study was to compare the agreement of the commonly used creatinine-based equations with simple cystatin C (cysC) equation (100/serum cysC) for estimation of glomerular filtration rate (GFR) in Chinese postmenopausal women with normal or mildly decreased renal function.

Materials and methods: Total 936 twenty-four-hour urine and 837 fasting serum samples were tested for creatinine and serum cysC. GFR was estimated by 10 creatinine based equations which included the Cockcroft-Gault equation (CG), the Modification of Diet in Renal Disease equation (MDRD), the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI), 24 h urine creatinine clearance (CrCl), as well as six Asian equations (Asia, Japan, Korean, Thai, China1 and China2). The agreement of the creatinine based equations with cysC equation was assessed for correlation, bias, precision and accuracy.

Results: The equations of Korea (r=0.784), China2 (r=0.694), CKD-EPI (r=0.686) and CG (r=0.676) indicated higher intra-correlation with simple cysC GFR than other equations. CG and Korean formulas showed minimal bias from cysC GFR. Bland and Altman plot suggested a significant smaller limit of agreement to cysC GFR was achieved by Japan (52.7%), CKD-EPI (39%), Korean (45.2%) and China2 (46.3%) equations than CrCl (106.8%). Receiver operating characteristic (ROC) analysis indicated the better predictive performance in CG, CKD-EPI and China2 equations to cysC equation.

Conclusions: Estimation of GFR using the equations of CKD-EPI, Korean, China2 and Japan has comparable precision and accuracy with simple cysC calculated GFR among Chinese postmenopausal women with normal or mildly decreased renal function.

Keywords: Glomerular filtration rate; Creatinine; Cystatin C; Renal function

Introduction

Chronic kidney disease (CKD) is a worldwide health problem leading to a substantial risk for kidney failure, cardiovascular disease and mortality [1]. The Glomerular Filtration Rate (GFR) is a primary index of kidney function. Determining GFR is crucial for the prevention, diagnosis and treatment assessment of CKD.

Measurement of GFR is ideally performed using gold standards such as inulin, iohexol, ^{125}I-iothalamate, ^{51}Cr-EDTA or ^{99m}Tc DTPA clearance. These measures were also applicable in China. However, these techniques are often time-consuming, cumbersome and expensive, requiring specialized equipment and skills which are often not feasible in routine clinical practice. Serum creatinine is commonly used as a surrogate marker for filtration function of kidney; however its level can be affected by diet, muscle mass and tubular secretion. To overcome this deficiency, the Kidney Disease Outcome Quality Initiative (K/DOQI) recommended serum creatinine-based GFR equations with inclusion of demographic characteristics to estimate GFR [2].

Recently, serum cystatin C (cysC) has been proposed as a simple, accurate and sensitive marker of GFR in research and clinical practice with few circumstantial influences [3]. CysC is an endogenous inhibitor of proteases, produced at a constant rate and freely filtered by the glomerulus. It is neither secreted by the tubule nor reabsorbed into the systemic circulation [4], suggesting an ideal endogenous marker for GFR [5]. CysC is particularly useful for estimating kidney function when creatinine production is variable or unpredictable [6]. CysC is superior to serum creatinine in its greater specificity and sensitivity to detect mild changes in renal function even in individuals with normal and mildly reduced GFR [7,8]. Epidemiological studies also indicate that cysC estimated GFR has a consistently stronger and more linear association with all-cause mortality and cardiovascular events than creatinine based equations [9,10], and even a stronger predictor of end-stage renal disease (ESRD) than measured GFR [11].

The most frequently used creatinine formulae recommended by K/DOQI [12] include Cockcroft–Gault (CG) equation [13], the Modification of Diet in Renal Disease (MDRD) equation [14], CKD–Epidemiology Collaboration (CKD-EPI) equation [15] and 24 h Creatinine Clearance (CrCl). However, most of these equations were developed from non-Chinese population or patients with varying degrees of CKD. Recently, several creatinine based GFR equations

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in Asian populations (Asian, Korean, Japanese, Thai, and Chinese formulae) have been developed [16] which were either by adding a coefficient into the MDRD formula or developing a new equation using the same variables as the previous creatinine formula.

In this study, we compared the agreement of 10 creatinine-based formulas (CG, CKD-EPI, MDRD, CrCl and six Asian formulae) with a simple cysC formula (100/serum cysC) in Chinese postmenopausal women with normal or mildly decreased renal function. Although the combined creatinine-cystatin based GFR was suggested to be a useful test to estimate GFR than cystatin C or creatinine [17] alone among patients with chronic kidney disease, the findings have not been verified in subjects with relatively normal renal function. Owing to the substantial superiority of cystatin C and the simplicity of cystatin C equation, studies using cystatin C equation as reference would have great applicability especially in the setting of gold standards of GRF measurement unavailable.

Materials and Methods

Participants were recruited from community through advertisement on newspaper or health talks among postmenopausal women who were screened for a six-month randomized controlled trial to examine the effect of soy products supplementation on blood pressure. The initially eligible participants were given labeled and graduated urine collection bags to collect 24h urine. Women who have donated 24h urine samples were further invited for a clinic visit for blood taking, anthropometric measurements and questionnaire survey.

The study was conducted according to the guidelines of Declaration of Helsinki. The study protocol has been approved by the ethical committee of the Chinese University of Hong Kong and written informed consent has been obtained from all participants.

Inclusion and exclusion criteria

Subjects were Hong Kong Chinese women aged 48-70 y; at least 1 year after the cessation of menstruation; with mean SBP above 120~180 mmHg or DBP above 80~100 mmHg. Subjects were excluded if they were on anti-hypertensive medication, hormone therapy or hypoglycemic agents in recent 3 months; medical history or presence of cardiovascular diseases, severe liver and renal diseases and malignancies in recent 5 years. More details regarding subjects recruitment were published elsewhere [18].

Data collection

Overnight fasting (10-12h) venous blood samples and 24h urine samples were obtained during the period of April 2010 to June 2012. Serum was centrifuged at 3000g for 15 min at 4°C and isolated within 2h after collection. Each subject's serum samples was divided into several aliquots and stored at -85°C until analysis.

Serum biochemical tests were performed on Hitachi 7180 analyzer (Tokyo, Japan; reagents from Roche Diagnostics, Mannheim, Germany). Serum and urinary creatinine was measured by enzymatic methods by colorimetric assay. The calibrator of serum creatinine was isotope dilution mass spectrometry (IDMS) standardized [19]. Serum cysC was measured by particle-enhanced turbidimetric immunoassay (Gentian AS, Moss, Norway). The intra and inter coefficients of variations (CV) were 1.2% and 2.8% for serum creatinine, 1.1% and 2.1% for serum cysC, and 1.25% and 2.17% for urinary creatinine.

The equations used for GFR estimation

We used 10 creatinine based formulae to estimate GFR to compare with cysC based formula. Body surface area (BSA) was calculated according to the equation of $[(\text{height}^{*}\text{weight} / 3600)^{0.5}]$ [20]. The estimated GFR (except for MDRD and CKD-EPI equations) were standardized by BSA and expressed as $\text{ml}\cdot\text{min}/1/1.73\ \text{m}^2$. The following equations were used (SCr denoted as serum creatinine):

1. CG-GFR [13] $=[(140 - \text{age}) \times \text{weight (kg)}]/(\text{SCr} \times 72) \times 0.85$;
2. MDRD-GFR [14] $= 175 \times \text{SCr}^{-1.154} \times \text{age}^{-0.203} \times 0.742$;
3. CKD-EPI-GFR [15] $= 141 \times \text{Min}(\text{SCr}/0.7, 1)^{-0.329} \times \text{Max}(\text{SCr}/0.7, 1)^{-1.209} \times 0.993^{\text{age}} \times 1.018$;
4. 24h CrCl $= (\text{urine Cr} \times \text{urine volume})/\text{SCr}$;
5. Asia-GFR [21] $= (1.086 \times 175 \times \text{SCr})^{-1.154} \times \text{age}^{-0.203} \times 0.742$;
6. Japna-GFR [22] $=194 \times \text{SCr}^{-1.094} \times \text{age}^{-0.287} \times 0.739$;
7. Korean-GFR [23] $= 87.832 \times \text{SCr}^{-0.882} \times \text{age}^{0.01} \times 0.653$;
8. Thai-GFR [24] $=1.129 \times 175 \times \text{SCr}^{-1.154} \times \text{age}^{-0.203} \times 0.742$;
9. China1-GFR [25] $=175 \times \text{SCr}^{-1.234} \times \text{age}^{-0.179} \times 0.79$;
10. China2-GFR [26] $= 234.96 \times \text{SCr}^{-0.926} \times \text{age}^{-0.280} \times 0.828$;
11. Simple cysC GFR [27] $=100/\text{serum cysC}$;

Statistical analysis

Statistical analyses were performed using SPSS for Windows version 17.0 and MedCalc for Windows, trial version 12.7.5. (MedCalc Software, Mariakerke, Belgium). All the tests were 2-tailed, and the results were considered significant when P value was below 0.05. The agreement of the creatinine based formulae and simple cysC formula were assessed in terms of four factors – correlation, bias, precision and accuracy.

Data were presented as mean ± SD for continuous variables. Intra-correlation coefficients (ICC) were used to describe the correlation between creatinine-based GFR and cysC estimated GFR. The mean difference between creatinine-based GFR and the simple cysC GFR was used to determine the bias. Paired samples **t**-test was used to compare the difference of GFR formulae. The width of the SD of the mean difference was an estimation of precision [28]. Accuracy was calculated as the percentage of creatinine based GFR within 30% of the simple cysC based GFR(2), which was compared with chi-square tests. In addition, performance of the equations for two subgroups, defined by cysC GFR ≥90 or <90 $\text{ml}\cdot\text{min}^{-1}\cdot 1.73\ \text{m}^{-2}$, was also investigated.

Bland-Altman method [29] was used to assess the agreement of creatinine based GFR with cysC calculated GFR by the regression of mean difference against the average of the two methods. The precision was represented as the width between the 95% limits of agreement (± 2SD). Relative differences were calculated as percentage difference from the cysC GFR.

Receiver Operating Characteristic (ROC) analysis was also conducted to determine the contribution of creatinine based formula to cystatin C-based formula. The area under the curve, sensitivity and specificity were compared for the test of overall agreement.

Finally, the 10 creatinine based equations were compared and ranked for their overall performance with respect to bias, precision, correlation and accuracy and final rank for each equation was calculated by adding up individual ranks.

Results

In this study, 936 twenty-four hours urine samples and 837 fasting serum samples were tested. 824 were included in final analysis. The characteristics of participants included in this study were presented in Table 1. The mean age of participants was 57.8 ± 4.8 years with average 8.5 years after menopause. The mean Body Mass Index (BMI) was 23.2 ± 2.3 kg/m^2. The mean serum creatinine and cysC levels were 55.3 ± 8.1µmol/L and 1.139 ± 0.136 mg/L respectively.

The ICC between various creatinine estimated GRF and simple cysC estimated GRF were shown in Table 2. The correlations coefficients (r) varied from 0.324 to 0.784 (all p<0.001). The formula of Korea (r=0.784), China2 (r=0.694), CKD-EPI (r =0.686) and CG (r=0.676) indicated higher correlation with simple cysC GFR than other equations.

Table 3 indicated the results for the bias, precision and accuracy of the creatinine based equations against simple cysC GFR. In overall participants, most of creatinine based GFRs were positively biased except for Japan formula (P<0.001). CG (1.37 ml/min/1.73m^2) and Korean (2.74 ml/min/1.73m^2) formulas showed minimal bias from cysC-GFR while China1 formula had the largest bias (30.67 ml/min/1.73m^2). A better precision (lower SD of mean bias) was observed with CKD-EPI, Korean, Japan and China2 than other equations, while the 24h CrCl indicated poorest precision among the equations. The best accuracy within 30% was reached with the Korean formula (97.6%) and the next were CKD-EPI (94.7%), Japan (93.0%) and China2 formulae (92.8%). The China1 (36.2) and Thai (58.0) equations deviated from cysC estimated GFR the most. Except for China1, Thai and Asia formulae, other equations had 30% accuracy up to the acceptable tolerance of 70%.

Baseline variables	Mean ± SD
Age (y)	57.8 ± 4.8
Menopausal age (y)	50.3 ± 4.3
Years after menopause (y)	8.5 ± 5.6
Height (cm)	155.5 ± 5.7
Body weight (kg)	56.4 ± 8.8
BMI	23.2 ± 2.3
WC (cm)	77.8 ± 6.5
WHR	0.837 ± 0.048
Body fat%	29.8 ± 5.6
SBP (mmHg)	129.3 ± 15.5
DBP (mmHg)	79.2 ± 9.8
Body surface area (m^2)	1.56 ± 1.13
Serum creatinine (µmol/L)	55.3 ± 8.1
Serum urea nitrogen (mmol/l)	5.531 ± 1.014
Serum cys-C (mg/l)	1.139 ± 0.136
24h urine volume (ml)	2099.7 ± 634.7
Urinary creatinine (mmol/l)	4.3 ± 1.8
Urinary creatinine excretion (mmol/24h)	8.2 ± 2.5
Urinary sodium excretion (mmol/L)	5.699 ± 2.284
Urinary potasium excretion (mmol/L)	1.453 ± 0.492
CysC_Simple	79.9 ± 10.6
CysC_DAKO	65.4 ± 11.6
CysC_Gentian	67.3 ± 10.1

Data were presented as mean ± standard deviation. BMI: Body Mass Index; WC: waist circumference; WHR: Waist to Hip Ratio; SBP and DBP: Systolic and Diastolic Blood Pressure; CrCl: Creatinine Clearance; CG: Cockcroft-Gault; MDRD: Modification of Renal Disease; cysC: cystatin C; CysC_Simple: simple cysC equation estimated GFR; CysC_DAKO: cysC estimated GFR by DAKO equation; CysC_Gentian: cysC estimated GFR by Gentian equation.
The conversion factor for creatinine concentration in mmol/L is mg/dL×88.40.

Table 1: Characteristics of participants.

		ICC with simple cysC estimated GFR	
		Absolute agreement	Consistency
CG-GFR	r	0.676	0.677
	P	<0.001	<0.001
MDRD-GFR	r	0.526	0.718
	P	<0.001	<0.001
CKD-EPI-GFR	r	0.686	0.823
	P	<0.001	<0.001
24h CrCl	r	0.324	0.367
	P	<0.001	<0.001
Asia-GFR	r	0.491	0.713
	P	<0.001	<0.001
Japan-GFR	r	0.626	0.788
	P	<0.001	<0.001
Korean-GFR	r	0.784	0.796
	P	<0.001	<0.001
Thai-GFR	r	0.431	0.703
	P	<0.001	<0.001
China1-GFR	r	0.330	0.659
	P	<0.001	<0.001
China2-GFR	r	0.694	0.789
	P	<0.001	<0.001

ICC: intra-correlation coefficient; CysC: cystatin C; CysC_Simple: simple cysC equation estimated GFR; r: correlation coefficient; CrCl: creatinine clearance; CG: Cockcroft-Gault; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration equation; MDRD: Modification of Renal Disease; GFR: glomerular filtration rate

Table 2: Intra-correlation coefficients (ICC) between 10 creatinine estimated GFR and simple cysC GFR (n=824).

In 669 women with cysC estimated GFR ≥90 ml/min/1.73m^2, Korean and CKD-EPI formulae showed a relatively less bias than other equations. In precision, CKD-EPI, Korean and China2 showed superior value as compared to 24h CrCl and CG equation (P<0.05). Among the 10 equations, Korean (97.3%), Japan (93.2%), China2 (91.8%) and CKDEPI (90.2%) showed higher accuracy within 30% of cys estimated GFR than the other equations. Similar findings were observed in 155 women with mildly reduced renal function at cysC GFR ≤90 ml/min/1.73m^2. The CG and Korean GFR showed little bias, while Thai and China1 GFR significantly overestimated cysC GFR (P<0.001). Korean (97.9%), CKD-EPI (97.0%), Japan (92.7%) and China2 (91.8%) indicated better accuracy than other equations.

The differences between creatinine estimated GFR and cysC GFR were assessed by Bland and Altman method (Table 4). Of the 10 equations, 1.5% in relative difference was found for the CG formula, 3.1% for Korean formula and 9.8% for China2 formula, significantly lower than China1 (31.0%) and Thai (23.5%) formulae. A significant smaller limit of agreement (higher precision) was achieved with the Japan (52.7%), CKD-EPI (39%), Korean (45.2%) and China2 (46.3%) equations than 24h CrCl (106.8%).

ROC curve analysis (Table 5 and Supplemental Figure) was conducted among creatinine based equations with simple cysC calculated GFR at cut-off value of 90 mL/min/1.73 m^2. The better agreement to cysC formula was indicated in CG, CKD-EPI and China2 with area under the curve (AUC) of 0.874, 0.871 and 0.872 respectively. The 24h CrCl had the poorest AUC of 0.761 among the 10 equations (p<0.001).

The overall agreement by ranking of various prediction equations with respect to bias, precision, correlation and accuracy are shown in Supplemental Table. The Korean, CG, CKDEPI, Japan and China2 equations had higher ranking scores than others.

Creatinine-estimated GFR	Mean ± SD (ml/min/1.73m^2)	Bias Mean of difference (ml/min/1.73m^2)	Precision Standard deviation (ml/min/1.73m^2)	Accuracy within 30% (%)
All (n=824)				
CG-GFR	81.3 ± 24.1	1.37	18.42	85.9
MDRD-GFR	96.2 ± 18.7	16.27	14.28	75.1
CKD-EPI-GFR	88.6 ± 10.4	8.72	8.19	94.7
24h CrCl	95.1 ± 36.1	15.30	33.13	85.9
Asia-GFR	98.3 ± 19.1	18.37	14.62	69.7
Japan-GFR	69.0 ± 12.9	-10.94	9.90	93.0
Korean-GFR	82.7 ± 12.7	2.74	9.64	97.6
Thai-GFR	102.2 ± 19.9	22.26	15.25	58.0
China1-GFR	110.6 ± 22.8	30.67	17.93	36.2
China2-GFR	88.5 ± 14.5	8.59	10.63	92.8
>=90 ml/min/1.73m^2 (n=669)				
CG-GFR	108.6 ± 25.6	12.3	23.6	87.9
MDRD-GFR	116.2 ± 19.6	19.8	17.8	73.7
CKD-EPI-GFR	99.8 ± 8.4	3.5	7.6	90.2
24h CrCl	117.1 ± 32.0	20.9	30.2	87.9
Asia-GFR	118.7 ± 20.0	22.3	18.2	67.6
Japan-GFR	83.0 ± 13.3	-13.4	11.8	93.2
Korean-GFR	96.5 ± 12.6	0.2	11.1	97.3
Thai-GFR	123.4 ± 20.8	27.0	19.0	54.8
China1-GFR	134.6 ± 24.3	38.2	22.4	32.9
China2-GFR	104.6 ± 14.4	8.3	12.7	91.8
<90 ml/min/1.73m^2 (n=155)				
CG-GFR	74.9 ± 18.6	-1.2	15.9	83.4
MDRD-GFR	91.6 ± 15.2	15.4	13.2	76.7
CKD-EPI-GFR	86.1 ± 9.1	9.9	7.9	97.0
24h CrCl	90.1 ± 35.0	14.0	33.5	83.7
Asia-GFR	93.6 ± 15.5	17.4	13.5	71.8
Japan-GFR	65.8 ± 10.5	-10.4	9.3	92.7
Korean-GFR	79.5 ± 10.4	3.3	9.2	97.9
Thai-GFR	97.3 ± 16.1	21.1	14.0	54.8
China1-GFR	105.1 ± 18.5	28.9	16.3	32.9
China2-GFR	84.8 ± 11.8	8.6	10.1	91.8

CrCl: creatinine clearance; CG: Cockcroft-Gault; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration equation; MDRD: Modification of Renal Disease; cysC: cystatin C; GFR: glomerular filtration rate.
The conversion factor for creatinine concentration in mmol/L is mg/dL×88.40.

Table 3: Bias, precision and accuracy of creatinine based GFR related to simple cysC based GFR (all, <90 and >=90 ml/min/1.73m^2).

Discussion

In this study, we compared various creatinine based formulae with cystatin C for estimation of GFR in postmenopausal Chinese women with normal or mildly decreased renal function. The results showed that the equations of CKD-EPI, Korean, Japan and China2 compared well with simple cysC GFR with less bias, higher precision and accuracy than other equations.

Several factors could account for the discrepancies among estimations. First, different reference standards for developing GFR equations may lead to the inconsistencies [30]. Reference method varied considerably across studies. For example, ^{125}I-iothalamate clearance was used for developing MDRD [14] and CKD-EPI [15] equations, inulin clearance was used for Korean [23] and Japan [22] equations, while ^{99m}Tc-DTPA clearance was used for Asian [21], Thai [24] and China equations [25,26]. The inconsistent references may bias the true GFR values. Second, the population studied in equation generation may also account for the discrepancies. Intrinsic factors such as the loss of muscle mass with aging [31] could affect the evaluation of GFR in elderly. The estimating equations developed primarily based on western populations may show different performance when used in Asian. Third, the differences in the calibration of serum creatinine assays could also contribute to the inaccuracy of the estimated GFR [32].

Our findings are consistent with previous reports that Korean and CKD-EPI equations performed better in subjects with higher GFR [12,33]. In this study, we found that CG equation showed less bias to

	Mean difference and %difference	95% CI	Precision (limit of agreement)
CG-GFR	1.4	-34.7~37.5	72.2
	(-1.5%)	(-42.4~39.5%)	(81.9%)
MDRD-GFR	16.3	-11.7~44.3	56.0
	(17.5%)	(-9.9~44.9%)	(54.8%)
CKD-EPI-GFR	8.7	-7.3~24.8	32.1
	(10.5%)	(-9.0~30.0%)	(39.0%)
24h CrCl	15.3	-49.6~80.2	129.8
	(12.9%)	(-40.5~66.3%)	(106.8%)
Asia-GFR	18.4	-10.3~47.0	57.3
	(19.6%)	(-7.7~46.9%)	(54.6%)
Japan-GFR	-10.9	-3.04~8.5	11.54
	(-15.4%)	(-41.7~11.0%)	(52.7%)
Korean-GFR	2.7	-16.1~21.6	37.7
	(3.1%)	(-19.5~25.7%)	(46.2%)
Thai-GFR	22.3	-7.6~52.2	59.8
	(23.5%)	-3.7~50.6%	(54.3%)
China1-GFR	30.7	-4.5~65.8	70.3
	(31.0%)	2.4~59.5%	(57.1%)
China2-GFR	8.6	-12.2~29.4	41.6
	(9.8%)	-13.4~32.9%	(46.3%)

CG: Cockcroft-Gault equation; MDRD: modification of diet in renal disease equation; CrCl: creatinine clearance; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration equation; GFR: glomerular filtration rate

Table 4: Bland and Altman analysis on mean difference (ml/min/1.73m^2), % difference and limit of agreement to simple cysC GFR

Equations	AUC	SD (ml/min/1.73m^2)	Sensitivity (%)	Specificity (%)	Youden index	P value*	P value**
CG-GFR	0.874	0.0136	97.3	34.2	0.619	0.874	
MDRD-GFR	0.860	0.0156	91.2	55.9	0.581	<0.0001	0.287
CKD-EPI-GFR	0.871	0.0142	94.2	50.0	0.603	0.896	0.457
24h CrCl	0.761	0.0232	95.8	28.8	0.453	<0.0001	<0.0001
Asia-GFR	0.860	0.0156	91.2	55.9	0. 581	<0.0001	0.232
Japan-GFR	0.865	0.0152	91.3	55.9	0.591	<0.0001	0.401
Korean-GFR	0.866	0.0151	96.7	33.6	0.602	0.069	0.434
Thai-GFR	0.860	0.0156	91.2	55.9	0. 581	<0.0001	0.168
China1-GFR	0.856	0.0159	92.1	52.6	0.576	<0.0001	0.180
China2-GFR	0.872	0.0147	98.2	28.3	0.608		0.874

AUC: area under the curve; SD: standard deviation; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; GFR: glomerular filtration rate; MDRD: modification of diet in renal disease; CrCl, creatinine clearance; CG: Cockcroft-Gault; ROC: receiver operating characteristic. P* compared with China2-GFR; P** compared with CG-GFR.

Table 5: ROC curves analysis on the creatinine based equations at a simple cysC estimated GFR cut-off of 90 ml/min/1.73m^2

cysC equation in decreased renal function than that in normal renal function, while CKD-EPI equation performed with less bias and greater accuracy than other equations in both subgroups. The discrepancy of performance according to renal function level may result from differences in the process of equation development. CG equation were developed based on CKD patients with reduced renal function, while CKD-EPI equation was developed based on data from participants with diverse clinical characteristics, with and without CKD [34,35]. Therefore, applicability of the CKD-EPI equation is more general than that of other equations.

In our analysis, 24h urine CrCl indicated significant bias and poor precision from cysC GFR. The findings are consistent with previous reports [16,28]. CrCl is determined from urinary creatinine as well as serum creatinine. It has several deficiencies such as errors in collecting urine and tubular secretion of creatinine, which could bias the true GFR [28]. In our study, 24 hour urine was adequately collected in 74.8% of participants according to the normal range of creatinine excretion (7-18μmol/24h) [36] and CrCl did not underestimate cysC- GRF. Thus, the inaccuracy of CrCl may not be due to inadequate urine collection. However, the urine and serum creatinine were analyzed in different labs without unified calibration in our study, thus a systemic bias may have been introduced and it could be one reason for the poorer performance of ClCr.

Several limitations of this study should be noted. First, in this study, we did not use the reference standards for measuring GFR due to resource limitation. However, previous studies indicated that the simple cysC GFR values were numerically similar and strongly correlated with measured GFR values [27,37-40]. Despite the advantages of the cysC, cysC-based equation may not completely replace the reference standard for GFR measurement. However, cysC is a simple and less labor-intensive marker that approximates direct measures of GFR and is independent of muscle mass, diet, age or sex [7]. CysC has been accepted as a reliable endogenous marker for evaluation of renal function especially in the elderly population and for those with normal or mildly impaired kidney function [39,41]. In addition, even using gold standards, different methods for GFR measurement have difference precision and accuracy. Overestimation of inulin clearance by radioisotopic filtration markers was often reported [42]. For example, ^{125}I-iothalamate exceeded inulin measurements by 14.6 to 25.9 [42] and ^{99m}Tc-DTPA overestimated inulin clearance by 3.5 to 13.5 ml/min/1.73 m^2 [43]. Reference methods for GFR measurement are not highly correlated with each other since the degree of bias, precision and accuracy varied notably. Therefore, the various qualities of the GFR measurements may not make them unified and reliable "gold standard." Our analysis using cysC as an approximate reference could also provide some exploratory information for researchers. Second, the study only included Chinese postmenopausal women with relatively normal renal function, thus the findings may not be generalizable to male or other ethnic or age groups.

Despite these limitations, it is the first study that various creatinine derived formulae were compared with cysC estimated GFR in Chinese postmenopausal women without chronic kidney disease. In this study, we used standard method traceable to IDMS to measure serum creatinine. The analyses were performed on a relatively large sample size.

Conclusions

Estimation of GFR using the equations of CKD-EPI, Korean, Japan and China2 has comparable precision and accuracy with simple Cys-C calculated GFR among Chinese postmenopausal women with normal or mildly decreased renal function.

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