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ORIGINAL RESEARCH

Performance of the estimated glomerular filtration rate creatinine and cystatin C based equations in Thai patients with chronic glomerulonephritis

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Background: Glomerular filtration rate (GFR) is considered the indicator of overall kidney function, and therefore, its assessment has become an important clinical tool in the daily care of chronic glomerulonephritis (CGN) patients. Currently, practical guidelines recommend using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations to assess GFR in CKD patients.

Methods: A cross-sectional study was performed in CGN patients. Standard GFR was measured using 24-hour urine creatinine clearance. GFR was estimated using the Cockcroft-Gault, Modification of Diet in Renal Disease, CKD-EPI equation based creatinine, cystatin C, and combined creatinine and cystatin C. The performance of GFR estimation equations were examined using bias, precision and accuracy and agreement between standard GFR and estimated GFR by calculating Cohen's *k*.

Results: A total of 125 patients (74 male, 59.2%) with mean age 56.1±18.1 years were included. Mean standard GFR was 51.6±32.2 mL/min per 1.73 m^2. A significant correlation was found between standard GFR and all estimated GFRs (r=0.573 to 0.660, $P<0.001$). CKD-EPI-creatinine-cystatin C equation had the smallest absolute bias and the significantly highest accuracy, although it was not significantly different from CKD-EPI-cystatin C equation (P=0.523). CKD-EPI-creatinine-cystatin C equation had the highest accuracy to classify CKD staging (Cohen's k=0.345), but it underestimated GFR in 32% and overestimated GFR in 18% of the CGN patients.

Conclusion: CKD-EPI-creatinine-cystatin C equation estimated GFR with little bias, and the highest accuracy among CGN patients. This equation gave a better estimate of GFR than the equation based on serum creatinine.

Keywords: serum cystatin C, CKD-EPI cystatin C, glomerulonephritis

Background

Creatinine clearance has been used to estimate glomerular filtration rate (GFR) and is often used for the initial evaluation of glomerular disease.[1,2] The estimated creatinine clearance rate can also be used to monitor the response to therapy and to initiate an early transition to dialysis therapy. However, this technique is complex, time-consuming, and difficult to perform in clinical practice.[3] Many equations to estimate GFR have been proposed, and estimated GFR based on serum creatinine or serum cystatin C is routinely used in the general population.[4] Recently, the Chronic Kidney Disease Epidemiology Collaboration has developed a new equation (CKD-EPI) based on serum creatinine

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and serum cystatin C.[5] CKD-EPI has greater precision and is preferred when estimating GFR for classified chronic kidney disease (CKD) stage.[6] However, to date, this equation has not been evaluated in chronic glomerulonephritis (CGN) patients.

Glomerulonephritis has a tendency to progress to CGN. The condition is characterized by irreversible and progressive glomerular and tubulointerstitial fibrosis, ultimately leading to a reduction in the GFR.[7] Currently, a subgroup of CKD patients such as CGN shows no clear-cut advice exists regarding which equation is the most precise for optimal estimation of GFR. Because most CGN patients receive corticosteroids treatment and present with a systemic inflammatory state, there is a potential opportunity to modify the production rate and release creatinine and cystatin C during therapy.[8,9] These are challenging issues for these patients. We assessed the performance of the creatinine and cystatin C based estimations of Cockcroft-Gault, Modification of Diet in Renal Disease (MDRD), and CKD-EPI equations compared to a 24-hour urine creatinine clearance measurement in a study consisting of CGN patients.

Methods

This cross-sectional study was approved by the Institutional Review Board, Royal Thai Army Medical Department, and all subjects participated in the study after giving informed consent. Serum samples were assayed for serum creatinine and cystatin C. CGN patients with stable renal function and proteinuria more than 0.5 g/day from the outpatient renal clinics of Phramongkutklao Hospital, Bangkok, Thailand, were recruited. All participants had their medical history reviewed with body weight, height, and body mass index measurement.

Standard GFR measurements

All participants performed self-directed 24-hour urine collections and underwent creatinine clearance the next day, during which blood and spot urine samples were also collected. Serum and urine creatinine was analyzed using the enzymatic method, calibrated to be traceable to isotope dilution mass spectrometry. For comparison with estimated GFR equations, the measured GFR was normalized to 1.73 m^2 of the body surface area (BSA) by multiplying the measured GFR by 1.73/BSA. The BSA was calculated according to Du Bois and Du Bois.[10] All biochemical analyses of blood samples were conducted at the Phramongkutklao Hospital Laboratory. Stratification of measured GFR was based on the stages of CKD.

Estimated GFR equations

The prediction of GFR by the Cockcroft-Gault, MDRD, CKD-EPI equation based serum creatinine, serum cystatin C and combination of serum creatinine and cystatin C were calculated. The estimated renal functions using the (abbreviated) MDRD and the CKD-EPI equations were expressed as GFR in mL/min per 1.73 m^2. Serum cystatin C was analyzed using the immunonephelemetric technique (BN; Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA). Table 1 summarizes all of the equations used to estimate GFRs. Different equations estimating the GFRs were compared with the results of 24-hour urine creatinine clearance as standard GFR.

Statistical analysis

Data were expressed as mean ± standard deviation, median and its 25 to 75 interquartile for non-Gaussian variables (Kolmogorov–Smirnov test), or number and percentage. Bias, precision, accuracy, and Pearson's correlation coefficients with respect to standard reference were calculated. Calculation of the difference between standard GFR and estimated GFR represented bias value and the standard deviation of this difference represented precision value. Accuracy was evaluated by the percentage of patients with GFR within 30% of standard GFR. Differences in estimated GFR and absolute bias and accuracy between the equations were compared with Student's paired *t*-test or McNemar test, respectively. Bland–Altman plots were made to analyze whether differences between GFR and standard GFR were related to the magnitude of GFR. Patients were classified by stages of CKD according to level of standard GFR, as well as on the basis of each equation. Agreement between the standard GFR and each estimated GFR in the different stages of CKD was assessed by calculating Cohen's *k*. All statistical tests were two-sided, and $P<0.05$ was required to reject the null hypothesis. Statistical analysis was performed using SPSS for Windows, version 16.0 (SPSS Inc., Chicago, IL, USA).

Results

A total of 125 patients with CGN were evaluated, as summarized in Table 2. The participants were all Thais, 59.2% male with mean age 56.1±18.1 years. Body mass index was 23.8±4.4 kg/m^2. The cause of CGN with median proteinuria of 1.16 (interquartile range [IQR] 0.53, 2.68) g/day included the following: diabetic nephropathy (29.6%), lupus nephritis (26.4%), IgA nephropathy (14.4%), membranous nephropathy (10.4%), focal segmental glomerulosclerosis (10.4%), minimal change disease (4%) and IgM nephropathy

Table 1 Equations used for the estimation of glomerular filtration rate

Cockcroft-Gault formula	(140 − age) × body weight/SCr ×72 (×0.85 if female)		
MDRD	$175 \times SCr^{-1.154} \times age^{-0.203}$ (×0.742 if female)		
2009 CKD-EPI creatinine equation	Female		
	– SCr ≤0.7 mg/dL	– $(SCr/0.7)^{-0.329} \times (0.993)^{age}$	
	– SCr >0.7 mg/dL	– $(SCr/0.7)^{-1.209} \times (0.993)^{age}$	
	Male		
	– SCr ≤0.9 mg/dL	– $(SCr/0.9)^{-0.411} \times (0.993)^{age}$	
	– SCr >0.9 mg/dL	– $(SCr/0.9)^{-1.209} \times (0.993)^{age}$	
2012 CKD-EPI cystatin C equation	– SCysC ≤0.8 mg/L	– $133 \times (SCysC/0.8)^{-0.499} \times (0.996)^{age}$ (×0.932 if female)	
	– SCysC >0.8 mg/L	– $133 \times (SCysC/0.8)^{-1.328} \times (0.996)^{age}$ (×0.932 if female)	
2012 CKD-EPI creatinine-cystatin C equation	Female		
	– SCr ≤0.7 mg/dL	SCysC ≤0.8 mg/L	$130 \times (SCr/0.7)^{-0.248} \times (SCysC/0.8)^{-0.375} \times (0.995)^{age}$
	Female		
	– SCr ≤0.7 mg/dL	SCysC >0.8 mg/L	$130 \times (SCr/0.7)^{-0.248} \times (SCysC/0.8)^{-0.711} \times (0.995)^{age}$
	Female		
	– SCr >0.7 mg/dL	SCysC ≤0.8 mg/L	$130 \times (SCr/0.7)^{-0.601} \times (SCysC/0.8)^{-0.375} \times (0.995)^{age}$
	Female		
	– SCr >0.7 mg/dL	SCysC >0.8 mg/L	$130 \times (SCr/0.7)^{-0.601} \times (SCysC/0.8)^{-0.711} \times (0.995)^{age}$
	Male		
	– SCr ≤0.9 mg/dL	SCysC ≤0.8 mg/L	$135 \times (SCr/0.7)^{-0.207} \times (SCysC/0.8)^{-0.375} \times (0.995)^{age}$
	Male		
	– SCr ≤0.9 mg/dL	SCysC >0.8 mg/L	$135 \times (SCr/0.7)^{-0.207} \times (SCysC/0.8)^{-0.711} \times (0.995)^{age}$
	Male		
	– SCr >0.9 mg/dL	SCysC ≤0.8 mg/L	$130 \times (SCr/0.7)^{-0.601} \times (SCysC/0.8)^{-0.375} \times (0.995)^{age}$
	Male		
	– SCr >0.9 mg/dL	SCysC >0.8 mg/L	$130 \times (SCr/0.7)^{-0.601} \times (SCysC/0.8)^{-0.711} \times (0.995)^{age}$

Abbreviations: MDRD, Modification of Diet in Renal Disease; SCr, serum creatinine (mg/dL); SCysC, serum cystatin C (mg/L); CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.

(2.4%) and miscellaneous CGN (2.4%). Seventy-three patients (47%) received corticosteroid, and 84 (54.2%) ACE inhibitor or angiotensin 2 receptor antagonist. Mean and median serum creatinine, and serum cystatin C levels were 2.59±2.37 (1.9, IQR 1.2, 2.8) mg/dL and 1.89±1.02 (1.6, IQR 1.15, 2.38) mg/L, respectively. Mean standard GFR was 51.6±32.2 mL/min per 1.73 m^2.

Table 2 Clinical features in the study population

Characteristic	Value (N=125)
Age (years)	56.1±18.1
Male (N, %)	74 (59.2%)
Female (N, %)	51 (40.8%)
Body weight (kg)	67.4±14.8
Body mass index (kg/m^2)	23.8±4.4
Serum albumin (g/dL)	3.7±0.6
Urine protein 24-hour (g/day)	1.16 (0.53, 2.68)
Serum creatinine (mg/dL)	1.9 (1.2, 2.8)
Serum cystatin C (mg/dL)	1.89±1.02
Creatinine clearance (mL/min/1.73 m^2)	51.6±32.2
Etiology	
– Diabetic nephropathy	37 (29.6%)
– Lupus nephritis	33 (26.4%)
– IgA nephropathy	18 (14.4%)
– Focal segmental glomerulosclerosis	13 (10.4%)
– Membranous nephropathy	13 (10.4%)
– Minimal change disease	5 (4%)
– IgM nephropathy	3 (2.4%)
– Miscellaneous	3 (2.4%)

Absolute bias, absolute precision, accuracy within 30%, and correlation coefficient between estimated GFRs and standard GFR are summarized in Table 3. A significant correlation was found between CKD-EPI-creatinine (r=0.619), CKD-EPI-cystatin C (r=0.649), CKD-EPI-creatinine-cystatin C (r=0.660), Cockcroft-Gault (r=0.573), and MDRD equation (r=0.617) with standard GFR. All equations significantly underestimated standard GFR ($P<0.001$) except CKD-EPI-cystatin C equation. CKD-EPI-creatinine-cystatin C equation had the smallest significant absolute bias when compared with CKD-EPI-creatinine, Cockcroft-Gault and MDRD equation ($P<0.01$) (Figure 1). It also showed the significantly highest accuracy when compared with CKD-EPI-creatinine, Cockcroft-Gault and MDRD equation ($P<0.01$), although it did not significantly differ from CKD-EPI-cystatin C equation (P=0.523).

Classification of all patients according to CKD staging is summarized in Table 4. The CKD-EPI-creatinine, CKD-EPI-cystatin C, CKD-EPI-creatinine-cystatin C, Cockcroft-Gault and MDRD equation classified 33% (Cohen's k=0.192), 43% (Cohen's k=0.300), 50% (Cohen's k=0.345), 38% (Cohen's k=0.195), and 38% (Cohen's k=0.205) of the CGN patients

Table 3 Comparison of estimation of the different GFR equations to the standard GFR (24-hour urine creatinine clearance 51.59±32.24 mL/min/1.73 m^2)

	CKD-EPI-creatinine	CKD-EPI-cystatin C	CKD-EPI-creatinine-cystatin C	Cockcroft-Gault	MDRD
Estimated GFR (mL/min/1.73 m^2)	43.78±32.07[a]	48.41±31.92	44.95±31.43.2[a]	45.37±32.2[a]	41.28±28.82[a]
Absolute bias	20.36	18.35[c]	17.99[b]	21.08	20.14
Absolute precision	20.78	19.82	20.21	21.85	20.53
Accuracy 30% (%)	44.0	51.2[c]	54.4[b]	40.0	43.2
Correlation coefficient	0.619[d]	0.649[d]	0.660[d]	0.573[d]	0.617[d]

Notes: [a]$P<0.01$, versus standard GFR; [b]$P<0.01$ versus CKD-EPI-creatinine, Cockcroft-Gault and MDRD equation; [c]$P<0.05$ versus Cockcroft-Gault equation; [d]$P<0.001$ correlated with standard GFR.

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

correctly, respectively. CKD-EPI-creatinine-cystatin C equation classified most patients correctly. It underestimated GFR in 32% and overestimated GFR in 18% of the patients.

Discussion

The validity of estimated GFR equations based on serum creatinine and/or cystatin C was evaluated in our cross-sectional study of CGN patients. Most of the study population included diabetic nephropathy, lupus nephropathy, and IgA nephropathy with persistent proteinuria, and received corticosteroid therapy, confirming the need for validating GFR equations in this setting. An agreement was established between standard GFR versus all equations, whereas overall mean estimated GFR equations were underestimated. This study, conducted in a clinical CGN setting, also showed that the smallest absolute bias and the highest accuracy was present in the CKD-EPI-creatinine-cystatin C equation. Our finding showed that the CKD-EPI-creatinine-cystatin C equation improved accuracy and agreement after classification in subgroups of CKD.

The CKD-EPI creatinine and/or cystatin equation has been developed and proposed to estimate GFR in CKD

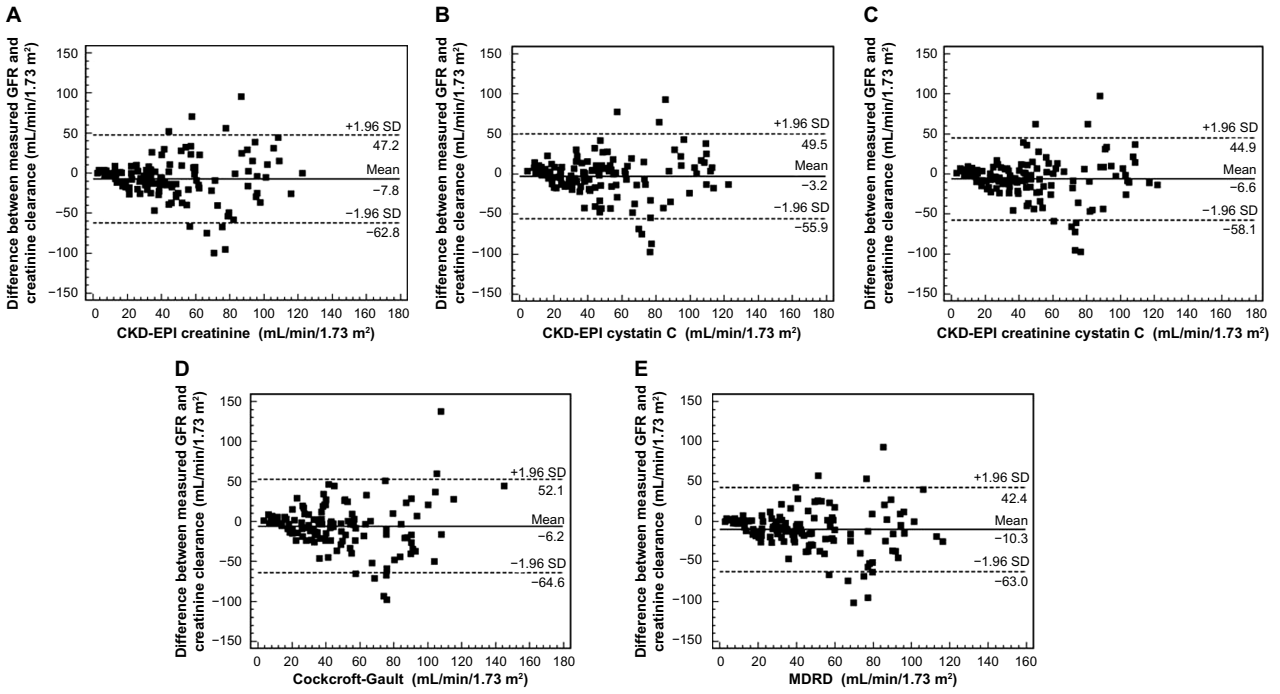

Figure 1 Bland–Altman plots of the different estimated GFR equations in comparison with 24-hour urine creatinine clearance or standard GFR.

Notes: The difference between the estimated GFR and standard GFR is plotted against the standard GFR. A positive difference shows an overestimation, whereas a negative difference shows an underestimation. (**A**) CKD-EPI-creatinine equation. (**B**) CKD-EPI-cystatin C equation. (**C**) CKD-EPI-cystatin C-creatinine equation. (**D**) Cockcroft-Gault equation. (**E**) MDRD equation.

Abbreviations: GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; SD, standard deviation; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.

Table 4 Comparison of classification of patients in stages of CKD according to different GFR equations with the standard GFR

	Standard GFR or 24-hour urine creatinine clearance (mL/min/1.73 m²)					
	≥90	60–89	30–59	15–29	≤15	Total
CKD-EPI-creatinine (mL/min/1.73 m², Cohen's *k*=0.192 [95% CI; 0.082–0.302])						
≥90	**7**	6	2	1	0	16
60–89	4	**2**	8	1	0	15
30–59	6	11	**18**	6	0	41
15–29	4	2	15	**6**	1	28
≤15	0	0	5	6	**14**	25
CKD-EPI-cystatin C (mL/min/1.73 m², Cohen's *k*=0.300 [95% CI; 0.186–0.414])						
≥90	**11**	4	2	1	0	18
60–89	4	**7**	5	2	0	18
30–59	5	7	**25**	5	0	42
15–29	1	3	15	**9**	9	37
≤15	0	0	1	3	**6**	10
CKD-EPI- creatinine-cystatin C (mL/min/1.73 m², Cohen's *k*=0.345 [95% CI; 0.231–0.459])						
≥90	**11**	5	2	0	0	18
60–89	2	**6**	5	3	0	16
30–59	6	7	**24**	5	0	42
15–29	2	3	13	**8**	2	28
≤15	0	0	4	4	**13**	21
Cockcroft-Gault (mL/min/1.73 m², Cohen's *k*=0.195 [95% CI; 0.083–0.306])						
≥90	**4**	5	2	0	0	11
60–89	9	**6**	5	2	0	22
30–59	5	8	**21**	9	1	44
15–29	3	2	18	**5**	2	30
≤15	0	0	2	4	**12**	18
MDRD (mL/min/1.73 m², Cohen's *k*=0.205 [95% CI; 0.095–0.315])						
≥90	**5**	4	2	0	0	11
60–89	6	**4**	6	2	0	18
30–59	6	11	**18**	5	0	40
15–29	4	2	17	**7**	1	31
≤15	0	0	5	6	**14**	25
Total	21	21	48	20	15	125

Note: The bold represents the number of patients classified in the same CKD stage from both estimated GFR methods.

Abbreviations: GFR, glomerular filtration rate; CKD, chronic kidney disease; CI, confidence interval; MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.

populations.[11,12] Recently, an equation combining filtration markers of serum creatinine and serum cystatin C provided greater accuracy and may be useful.[13] The estimation of GFR in CGN remains challenging in daily practice. Initially, serum cystatin C appears to have high sensitivity for a screening test for renal injury in patients with nephrotic syndrome.[14] Corticosteroid therapy in glomerulonephritis influences serum and urine cystatin C levels in patients with nephrotic syndrome.[15] In addition, systemic inflammatory response may alter creatinine production and increase serum cystatin C levels, which could influence both the CKD-EPI creatinine and/or cystatin equation.[16] Our results confirmed that CKD-EPI-creatinine-cystatin C and CKD-EPI-cystatin C indicated the best option for evaluating GFR in a CGN population with 47% receiving corticosteroid treatment. In addition, the CKD-EPI-creatinine-cystatin C equation had a higher performance than the CKD-EPI-creatinine equation. This agrees with the results of Ma et al who reported that using combined equations based on serum creatinine and serum cystatin C in an Asian CKD population significantly improved GFR estimation.[17] Using these equations in children, young adults, the elderly, and people with cirrhosis and HIV also confirmed the high diagnostic performance.[18–21] With our results, we can probably conclude that the CKD-EPI-creatinine-cystatin C can be used reliably in CGN patients.

The accuracy within 30% of the estimated gold standard values demonstrated the superiority of CKD-EPI-creatinine-cystatin C compared with CKD-EPI-creatinine, Cockcroft-Gault and MDRD equation. Moreover, stage misclassification was reduced by the equation based on CKD-EPI-creatinine-cystatin C. The misclassification of CKD by the combined equation was decreased from 67% to 50% compared with CKD-EPI-creatinine, and it also decreased from 62% to 50% compared with Cockcroft-Gault and MDRD equation. The results were similar in the paper published by Bevc et al, evaluating the cystatin C-based equations in comparison with 51Cr-EDTA clearance in adult patients with diabetic kidney disease.[22] This will help physicians to diagnose CKD more correctly, and treat CKD properly. However, the performance of CKD-EPI-creatinine-cystatin C was limited and was only slightly superior to all equations. All equations could not completely replace the "24-hour urine creatinine clearance" to estimate GFR in a population of CGN patients. These results demonstrated that the accuracy of estimated GFR formulas might not be as precise as a GFR marker in CGN with inflammatory condition and treatment with systemic corticosteroids.

The study had a few limitations. First, we should have standard GFR with insulin clearance or iohexol clearance. Endogenous creatinine clearance is correlated well with standard GFR, but creatinine is variably secreted by the proximal tubule. Therefore, endogenous creatinine clearance might overestimate true GFR, depending on the rate of tubular secretion of creatinine. Second, the stable renal function in CGN patients was considered by the nephrologists who took care of the patients, but only 78% of subjects had previous serum creatinine within 3 months of treatment. Third, our study only analyzed a Thai population, but all serum creatinine and cystatin C-based equations were developed from

studies involving participants of all races. Finally, a relatively small number of patients were enrolled in the subgroups of CKD stage.

In conclusion, this study demonstrated a correlation of all estimated GFR equations in CGN patients. CKD-EPI-creatinine-cystatin C had high accuracy for estimated GFR, although the performance was close to that of CKD-EPI-cystatin C. These equations should help physicians in daily practice to assess renal function in their CGN patients.

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Disclosure

The authors have no conflicts of interest to declare.

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