

Cystatin C-based Formula is Superior to MDRD, Cockcroft-Gault and Nankivell Formulae in Estimating the Glomerular Filtration Rate in Renal Allografts

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Abstract

Objectives: There are conflicting reports on the reliability of the various glomerular filtration rate formula in renal allografts, to assess the performance of various glomerular filtration rate formula in estimating renal function of renal allografts.

Materials and Methods: Glomerular filtration rate was measured using an isotope Tc99m DTPA in 97 renal transplant patients and estimated using modification of diet in renal disease, Cockcroft-Gault formula, Nankivell, and a cystatin C-based formula. The overall performance of these formula was evaluated by calculating bias, accuracy and precision.

Results: Mean age was 39.8 years (± 12.7), body mass index was 26.9 (± 6.3) and serum creatinine was 114.5 $\mu\text{mol/L}$ (± 39.3). The mean measured glomerular filtration rate was 58.1 mL/min (± 25.6). The bias with modification of diet in renal disease was 7.7 ($P = .03$), with Cockcroft-Gault formula it was 3.2 ($P = .3$), with Nankivell it was 10.3 ($P = .0002$), and with cystatin C it was 0.31 ($P = .9$)

The precisions (r) for modification of diet in renal disease, Cockcroft-Gault formula, Nankivell, and cystatin C were 0.26 ($P = .01$), 0.26 ($P = .01$), 0.42

($P = .0001$), and 0.60 ($P < .0001$), respectively. We also investigated the impact of sex, age, body mass index, and glomerular filtration rate on the performance of these 4 formula.

Conclusion: The best correlation, highest precision, accuracy, and least bias were seen when using cystatin C. The largest bias was seen when using Nankivell and modification of diet in renal disease formula.

Key words: GFR, Renal allografts, Cystatin C, MDRD, Nankivell, Cockcroft-Gault Formulae

Estimation of glomerular filtration rate is important in assessing and following up renal function as serum creatinine is not reliable enough in reflecting the true glomerular filtration rate (1-3). Criterion standards for measuring glomerular filtration rate, using inulin or isotopes, are cumbersome and expensive. The performance of the modification of diet in renal disease study group and Cockcroft-Gault formula have been extensively assessed in native kidneys, but their accuracy in predicting renal function in renal allografts have not been well-established. Results using the Nankivell formula showed initial promise by some studies (4), but subsequent studies casted some doubt on their usefulness (5, 6).

Recently, formula for glomerular filtration rate estimation using cystatin C were developed (7, 8). Experience using such formula in renal allografts is limited (7, 8). Serum cystatin C, has been shown in several studies to be superior to serum in assessing renal function in native kidneys (4, 5), but it gave conflicting results when used in renal grafts (6, 9).

In 1 study, it was found that cystatin C-based calculation does not improve the glomerular filtration

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Experimental and Clinical Transplantation (2009) 4: 197-202

rate estimation accuracy over the use of abbreviated modification of diet in renal disease provided that nonconstant recalibration of creatinine is done (10). In another study, cystatin C-based glomerular filtration rate calculation formula performed better in renal transplant recipients than in creatinine-based equations (11). Thus, the objective of this study was to compare the performances of 3 creatinine-based formula and 1 cystatin C-based formula in estimating glomerular filtration rate in renal allograft

Patients and Methods

Adult patients with stable graft function were studied included (stable graft function was defined as less than 15% change in serum creatinine over the previous 2 months). The study was performed between January 2008 and October 2008 at King Abdulaziz Medical City Renal Transplant Centre, Riyadh, Iran. The immunosuppressive regimen consists of tacrolimus, mycophenolate mofetil, and steroids in 80% of the patients and cyclosporine. None of the patients were on cotrimaxazole (Siemens Healthcare Diagnostics, Deerfield, IL, USA).

Serum creatinine was measured by the modified kinetic Jaffe reaction, and a Hitachi D 2400 Modular Chemistry Analyzer thereafter (Roche Diagnostics Corp., Indianapolis, IN). Serum creatinine measurements were calibrated. Cystatin C was measured using N latex cystatin c kit by Dade Behring. On the same day that serum creatinine and cystatin C were measured, a radionuclide measurement of glomerular filtration rate was performed in a similar way as Kocabas and associates (12). Dynamic renal scintigraphy was performed in anterior projection over 40 minutes after intravenous administration of 10 mCi Tc99m DTPA. On 2- to 3-minute summed-image region of interests were delineated. Based on a Gates method, glomerular filtration rate normalized for body surface area, was estimated using computer software on Pegasus workstation (M/S ADAC) (12, 13).

Glomerular filtration rate was calculated using the following equations, and results were then adjusted for bovine serum albumin for the Nankivell and Cockcroft-Gault formulas (mL/min/1.73 m²):

1. Four-variable MDRD^[14]

$$eGFR_{MDRD} = 186 \times [SCr]^{-1.154} \times [age]^{-0.203} \times [0.742 \text{ if patient is female}]$$
2. Nankivell^[15] (eGFR_{NK})
 - a. For males: $eGFR_{NK} = 6.7 / SCr \text{ (mmol/L)} + \text{weight (kg)} / 4 - \text{urea (mmol/L)} / 2 - 100 / \text{height}^{[2]} \text{ (m)} + 35$
 - b. For females: $eGFR_{NK} = 6.7 / SCr \text{ (mmol/L)} + \text{weight (kg)} / 4 - \text{urea (mmol/L)} / 2 - 100 / \text{height}^{[2]} \text{ (m)} + 25$
3. Cockcroft-Gault^[16] (eGFR_{CG})
 - a. For males: $eGFR_{CG} = [(140 - \text{age}) \times \text{weight (kg)}] / SCr \times 72$
 - b. For females: $eGFR_{CG} = ([(140 - \text{age}) \times \text{weight (kg)}] / SCr \times 72) \times 0.85$
4. Cystatin-based glomerular filtration rate calculation 74.835 / cystatin C (mg/L) 1.333

Statistical Analysis

Population characteristics and subgroup comparisons were summarized by providing the number and percentage for categoric variables, and the mean and standard deviation (SD) for continuous variables.

Bias was evaluated as the mean difference between the measured and estimated glomerular filtration rate. Precision was assessed by Pearson correlation coefficient. Accuracy was defined as the percentage of calculated glomerular filtration rate lying within 30% to 50% of the measured glomerular filtration rate (17). The percentage of error in glomerular filtration rate prediction was calculated as (estimated value- measured value)/measured value $\times 100$. A value for *P* of $< .05$ was considered statistically significant.

The analysis was repeated after stratifying patients by age (< 40 and ≥ 40), estimated glomerular filtration rate (< 58 and ≥ 58 mL/min), sex, and body mass index (< 28 and ≥ 28).

Results

The mean age was 39.8 years (± 12.7), mean body mass index was 26.9 (± 6.3), and the mean serum creatinine was 114.5 $\mu\text{mol/L}$ (± 39.3). Of all the patients, 45.4% were males. The mean measured glomerular filtration rate was 58.1 mL/min (± 25.6). The calculated glomerular filtration rates using modification of diet in renal disease, Cockcroft-Gault formula, Nankivell, and cystatin C were 65.4 mL/min (± 24.7), 61.8 mL/min (± 26.0), 68.4 (± 22.3), and 57.4 mL/min (± 24.4), respectively (Table 1).

The bias and percentage error seen with modification of diet in renal disease were 7.7 ($P = .03$)

Table 1. Descriptive characteristics of the study sample.

Variable	n = 97	Minimum	Maximum
Sex			
Male	44 (45.4%)		
Female	53 (54.6%)		
Age, mean (SD), years	39.8 (12.7)	17	66
Weight, mean (SD), kg	70.1 (18.5)	22.9	120.0
Height, mean (SD), cm	160.7 (8.8)	143.0	186.0
BMI, mean (SD)	26.9 (6.3)	11.0	42.9
Urea	7.2 (3.4)	3.2	21.7
Plasma creatinine, mean (SD)	114.5 (39.3)	64.0	315.0
GFR Isotope	58.1 (25.6)	11.3	145.0
GFR CG, mean (SD)	61.8 (26.0)	11.7	141.0
GFR Cyst, mean (SD)	57.4 (24.4)	17.0	123.0
GFR MDRD, mean (SD)	65.5 (24.7)	14.6	133.5
GFR Nankivell, mean (SD)	68.4 (22.3)	9.6	113.7

Abbreviations: BMI, body mass index; CG, Cockcroft-Gault formula; GFR, Glomerular filtration rate; MDRD, modification of diet in renal disease; SD, Standard deviation.

Table 2. Bias, percentage error, and accuracy of the 4 formula in the whole group.

Differences	Mean (SD) (P value)	% Error	Values falling within 30% 50%
With CG	3.2 (31.3) (P = .3)	27.1%	24.2% 41.1%
With Cyst	-0.31 (22.4) (P = .9)	10.4%	42.4% 62.0%
With MDRD	7.7 (33.5) (P = .03)	48.2%	25.0% 38.1%
With Nankivell	10.3 (26.1) (P = .0002)	40.7%	27.1% 36.5%
Correlations	Correlation coefficient	P value	
With CG Cockcroft-Gault	0.26	.01	
With Cyst	0.60	< .0001	
With MDRD modification of diet in renal disease	0.12	.2	
With Nankivell	0.42	< .0001	

Abbreviations: CG, Cockcroft-Gault formula; MDRD, modification of diet in renal disease.

and 48.2% with Cockcroft-Gault formula were 3.2 ($P = .3$) and 27.1%, with Nankivell were 10.3 ($P = .0002$), and 40.7%, and with cystatin C were 0.31 ($P = .9$) and 10.4%, respectively. The percentage of calculated glomerular filtration rate values falling within 30% and 50% of measured glomerular filtration rate using cystatin C were 42.4% and 62.0%, respectively, modification of diet in renal disease, were 25.0% and 38.1% respectively, Cockcroft-Gault formula were 24.2% and 41.1%, respectively, and Nankivell were 27.1% and 36.5%, respectively (Table 2). The correlation precisions (r) for modification of diet in renal disease, Cockcroft-Gault formula, Nankivell, and cystatin C were 0.26 ($P = .01$), 0.26 ($P = .01$), 0.42 ($P = .0001$), and 0.60 ($P < .0001$), respectively (Table 2).

When stratifying for sex, age, body mass index, and glomerular filtration rate, the bias with cystatin C-based formula remains unchanged, whereas there is slight improvement in the 3 creatinine-based formula, higher glomerular filtration rate, lower body mass index, and males. Bias is also reduced

Table 3. Bias in the 4 formula as stratified by different variables.

Variable	CG Mean, SD (P value)	Difference with Cyst Mean, SD (P value)	MDRD Mean, SD (P value)	Nankivell Mean, SD (P value)
Sex				
Male	10.1, 34.3 (.06)	1.6, 27.6 (0.7)	21.7, 32.5 (< .0001)	17.5, 28.0 (.0002)
Female	-2.9, 27.3 (.5)	-1.9, 17.0 (0.4)	-4.3, 29.8 (.3)	4.1, 22.9 (.2)
Age				
< 40	0.5, 34.0 (.9)	-3.2, 20.2 (.3)	10.9, 32.9 (.03)	5.0, 27.1 (.2)
≥ 40	5.9, 28.6 (.2)	2.6, 24.2 (.5)	4.6, 34.1 (.04)	15.5, 24.3 (< .0001)
GFR				
< 58	18.2, 28.3 (< .0001)	6.1, 19.1 (.04)	27.3, 28.2 (< .0001)	23.0, 21.6 (< .0001)
≥ 58	-11.8, 26.8 (.004)	-6.5, 23.8 (.007)	-12.3, 25.9 (.0003)	-2.6, 24.1 (.05)
BMI				
< 28	-10.0, 25.0 (.0008)	-3.8, 23.4 (.03)	5.7, 32.1 (.02)	2.8, 25.5 (.04)
≥ 28	16.9, 31.6 (.00007)	3.3, 20.9 (.03)	9.8, 35.1 (.007)	18.4, 24.5 (< .0001)

Abbreviations: BMI, body mass index; CG, Cockcroft-Gault formula; GFR, Glomerular filtration rate; SD, Standard deviation.

Table 4. The correlations in the 4 formulas as stratified by different variables.

Variable	CG	Cockcroft-Gault	Correlation with cystatin	MDRD modification of diet in renal disease	Nankivell
		Coefficient (<i>P</i> value)	Coefficient (<i>P</i> value)	Coefficient (<i>P</i> value)	Coefficient (<i>P</i> value)
Sex	Male	0.21 (.0206)	0.45 (.0003)	0.27 (.09)	0.37 (.001)
	Female	0.35 (.001)	0.75 (< .0001)	-0.05 (.8)	0.51 (.0001)
Age	< 40	0.24 (.01)	0.71 (< .00001)	0.29 (.5)	0.46 (.001)
	≥ 40	0.30 (.04)	0.51 (.0003)	-0.12 (.41)	0.41 (.004)
GFR	< 58	0.21 (.1)	0.42 (.005)	-0.11 (.4)	0.37 (.009)
	≥ 58	0.11 (.4)	0.18 (.2)	0.37 (.01)	0.11 (.5)
BMI	< 28	0.53 (.0001)	0.64 (< .0001)	0.35 (.02)	0.54 (< .0001)
	≥ 28	0.13 (.4)	0.58 (< .0001)	-0.25 (.1)	0.32 (.03)

Abbreviations: BMI, body mass index; CG, Cockcroft-Gault formula; GFR, Glomerular filtration rate.

Table 5. Accuracy in the 4 formula as stratified by glomerular filtration rate and body mass filtration (expressed as percentage of patients with estimated glomerular filtration rates within 30% of the measured glomerular filtration rate).

	CG	Cyst	MDRD	Nankivell
GFR < 58	20.8	43.5	17.0	20.4
≥ 58	27.7	41.3	33.3	31.0
BMI < 28	27.1	45.7	21.7	30.6
≥ 28	21.3	39.1	28.3	23.4

Abbreviations: BMI, body mass index; CG, Cockcroft-Gault formula; GFR, Glomerular filtration rate.

with younger age in the Cockcroft-Gault formula, Nankivell formula (Table 3).

Precision improves further with cystatin C formula in the females and the young, in Cockcroft-Gault formula with higher body mass index, in modification of diet in renal disease with lower glomerular filtration rate and higher body mass index and in Nankivell in females and lower body mass index (Table 4).

Table 5 shows that accuracy improves with higher glomerular filtration rate in Cockcroft-Gault formula, modification of diet in renal disease, and Nankivell formula but this accuracy still remains inferior when compared with that of cystatin C formula. Low body

mass indexes are associated with improved accuracy in Cockcroft-Gault formula and Nankivell formula and reduced accuracy in modification of diet in renal disease formula.

Discussion

Creatinine-based estimations of glomerular filtration rate have revealed conflicting reports (18-20). This variation may be related to the methodology and accuracy of creatinine estimation and whether creatinine was calibrated (21, 22). Many of the studies using creatinine-based formula were criticized for lack of proper calibration of serum creatinine (18, 19, 21-23). Our study revealed that cystatin C-based equation is the best formula for estimating glomerular function in kidney transplant recipients who have reasonably good renal function (mean measured glomerular filtration rate was 58.1 [STD, 25.6]. The bias, precision, and percentage of error using this formula were found to be -0.31 ($P = .9$), 0.60 ($P < .0001$), and 10.4%, respectively. The cystatin C formula maintained its good performance regardless of age, sex, glomerular filtration rate level, or body mass index.

The second best performance was seen with the Cockcroft-Gault formula with bias, precision, and percentage of error of 3.2% ($P = .3$), 0.26% ($P = .01$), and 27.1% respectively. The precision of the Cockcroft-Gault formula improved in women (0.35) ($P = .0$), and have body mass index of > 28 (0.53) ($P = .0001$). We found that the accuracy improves slightly with glomerular filtration rates > 58 mL/min in Cockcroft-Gault formula.

The lowest correlation and largest bias was seen with the Nankivell and modification of diet in renal disease formula both of which overestimated the glomerular filtration rate by 10.3 ($P = .0002$) and 7.7 mL/min ($P = .03$) respectively. Raju and associates also found a significant bias of 11.5 mL/min and 36.5 mL/min when using modification of diet in renal disease and Nankivell equations, respectively, with 30% accuracy of 66% and 15% respectively (5). In this study, they also found that Cockcroft-Gault formula performed better than modification of diet in renal disease and Nankivell equations (5).

We, however, found that the bias in both modification of diet in renal disease and Nankivell formula improves with glomerular filtration rate > 58 mL/min (to -12.3 and -2.6, respectively), with body mass index < 28 (to 5.7 and 2.8, respectively),

and in women (to -4.3 and 4.1 respectively). Bias improves in older patients using the modification of diet in renal disease formula (to 4.6) and in younger patients using the Nankivell formula (to 5.0). The Nankivell formula was developed specifically for assessing glomerular filtration of the transplanted kidney (15). Earlier reports indicated that the Nankivell equation was superior (4). Subsequent studies, however, showed modification of diet in renal disease formula to be more accurate and revealing that the Nankivell equation tends to overestimate glomerular filtration rate (5). Gaspari and associates (23) have shown that modification of diet in renal disease was superior to Nankivell and Cockcroft Gault equations. It was associated with least bias (2.7 mL/min), and highest precision when used in transplant patients, compared with 11 other creatinine-based prediction equations. In their study, the Cockcroft-Gault formula and Nankivell biases were 8.5 and 10.0, respectively. However, even with the modification of diet in renal disease equation, only 45% of the results were within 10% error. The authors conclude that none of the formula is of sufficient accuracy to be used in clinical trials. Poggio and associates (6) also found superiority of modification of diet in renal disease over Nankivell and Cockcroft-Gault formula in transplant patients. As with our study, the authors that found that Nankivell and Cockcroft-Gault formula overestimated the glomerular filtration rate. Another study by Gera and associates (24) also confirmed that modification of diet in renal disease was superior to Cockcroft-Gault formula in terms of having less bias and more accuracy and precision. In this study, it was noted that the Cockcroft-Gault formula overestimates the glomerular filtration rate, particularly with lower renal functions.

The discrepancy between our reports and the other reports with us showing superior performance of Cockcroft-Gault formula over modification of diet in renal disease could be explained that our patients had good renal function. The Cockcroft-Gault formula, which has been devised to measure CrCl, can be expected to overestimate glomerular filtration rate in lower levels of renal function.

As cystatin C is thought not to be affected by sex, age, or weight, most cystatin C-based formula do not include consideration of sex, weight, or age. There is very small number of reports on the use of cystatin C to estimate glomerular filtration rate in renal

transplant patients that shows promise (25, 26). In 1 study, it was found that cystatin-based estimation gave a better indication of renal function than creatinine-based formula especially with glomerular filtration rate < 60 mL/min (21, 22). We found slight improvement in precision using cystatin C formula in patients with glomerular filtration rate < 58 mL/min (0.42) ($P = .005$) as compared to those with glomerular filtration rate > 58 mL/min (0.18) ($P = .2$). However, its accuracy and bias were equally good in glomerular filtration rates above and below 58 mL/min.

Both of these studies (25, 26) used serum cystatin concentration rather than cystatin-based calculation of glomerular filtration rate. In 1 study that used estimated cystatin C-based glomerular filtration rate (10), the bias was found to be -4.7 . This compares to our findings of -0.31 mL/min.

White and associates (27) found that cystatin C-based equations had more accuracy and precision and less bias than creatinine-based equations. Although cystatin C has been reported as not being affected by age and weight, White and associates (27) found that the cystatin-based glomerular filtration rate estimation in transplanted patients was more accurate in patients with lower muscle mass. Further, in a large number of patients it was found that serum cystatin C was higher in older and heavier patients independently of renal function (28). We found no significant impact of age or body mass index on bias, precision, or accuracy of the cystatin C formula. Steroids are known to raise the cystatin level (29). However, our patients used small dosages of steroids (< 7.5 mg/day)

A weakness of this study is that most of the patents included have good renal function. Nevertheless, subanalysis, according to glomerular filtration rate still showed the superiority of the cystatin C-based formula.

Conclusion

Until now, there has been no consensus on what is the best formula to use to asses glomerular filtration rate in renal transplant recipients. Our preliminary data would suggest that best correlation, highest precision and least bias was seen when using cystatin C formula. This remained consistent regardless of age, sex, glomerular filtration rate, or body mass index. Cg, a modification of the diet in renal disease

and Nankivell formula performed poorly. The least correlation and largest bias was seen when using Nankivell and modification of diet in renal disease.

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