



A Comparison of Glomerular Filtration Rate by Creatinine Based Equations and DTPA-Renogram in Healthy Adult Kidney Donors

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ABSTRACT

Introduction: Accurate determination of donor kidney function has important long-term implications for both donor health and recipient outcome. Many centers use 24 hour urinary creatinine clearance or creatinine-based GFR estimations to assess kidney function but their performance when compared with GFR measurements by isotope clearance remains inconclusive. We assessed the performance of creatinine based equations against DTPA GFR for evaluating Nepalese kidney donors.

Methods: All kidney donors who had undergone both DTPA GFR estimation and 24 hour urine CrCl were included. The performance of the urine-CrCl, CG-CrCl, modified MDRD GFR against DTPA GFR was evaluated by analyzing global bias, precision (R^2), Pearson correlation and accuracy percentage within 30% and 15%. The sensitivity and specificity of each predictive equation in selecting donor with GFR of ≥ 80 mL/min/1.73 m² was also calculated.

Results: Of 51 donors analysed, only 18 (35.29%) were male. The mean measured GFR was 102.752 ± 16.71 mL/min/1.73 m². Of all prediction equations, urine-CrCL has most precision ($R^2=0.207$) with the highest pearson correlation (0.455) and highest accuracy percentage within 30% and 15%. However, predictive performance was poor for all the equations. The urine CrCl had highest sensitivity of 100% for detecting donor with measured GFR > 80 mL/min/1.73 m² with positive predictive value of 92.1%.

Conclusions: The performance of all equations was disappointing and even the best performing equation urine-CrCl was suboptimal for donor selection. So considering the potential risk of living kidney donation, other more accurate methods of GFR estimation should be used.

Keywords: Cockcroft-Gault equation; creatinine clearance; glomerular filtration rate; modification of diet in renal disease formula; ^{99m}Tc-Diethylene-Triamine Pentaacetic Acid.

INTRODUCTION

Accurate estimation of donor Glomerular Filtration Rate (GFR) is essential both to ensure a donor's medical suitability and to predict future allograft performance as higher GFR of donors is independently associated with improved allograft outcomes.^{1,2} A wide approach is used to assess kidney function, with most centers using 24 hour urinary creatinine clearance (urine-CrCl) or creatinine-based GFR estimations such as Modification

of Diet in Renal Disease (MDRD) or Cockcroft-Gault (CG) equation.^{3,4} However, it has several deficiencies such as errors in collecting urine and tubular secretion of creatinine.⁵ In addition, race is an important determinant of GFR estimation.⁶ The performance of creatinine based estimates of GFR compared with the standard GFR measurements by isotope clearance

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remains inconclusive.² There is no comparative study that verifies the performance of creatinine based GFR in Nepalese healthy population. Our aim was to evaluate performance of creatinine based equations against DTPA GFR in kidney donors.

METHODS

A cross sectional study was conducted in the department of Nephrology, National Academy of Medical Sciences, Bir hospital, Kathmandu, Nepal from June 2011 to Feb 2013. Ethical approval was taken from Institutional Review Board, along with informed verbal consent from all subjects. All patients who came to the department of nephrology for kidney donor evaluation during the study period, with both 24 hour urine CrCl and ^{99m}Tc-Diethylene-Triamine Pentaacetic Acid (DTPA) renogram measurements were included whereas kidney donors without DTPA renogram were excluded.

Data regarding age, gender, place of residence, weight, height, body surface area (BSA), blood urea, serum creatinine and serum albumin for each subject were collected. Rest of investigations was done as per standard protocol for live kidney donor evaluation.

Modified Jaffe's method was used with auto analyzers to measure serum creatinine.⁷ Twenty four hour urine creatinine clearance was determined from a 24 hour urine collection by using formula: 24 hour urine-CrCl = UV/P , where U and P are urinary and plasma concentrations of creatinine and V are the urine flow rate.⁸ A creatinine clearance results were normalized to Body Surface Area (BSA) of 1.73 m²; BSA was calculated by Body Surface Area (Mosteller, square root method). $BSA = \sqrt{Height \times Weight / 3600}$.⁹ The Cockcroft-Gault equation was used to estimate creatinine clearance from the Serum Creatinine (SCr) as follows.¹⁰

$$CrCl \text{ (mL/min)} = \frac{(140 - \text{Age in year}) \times \text{Lean Body Weight [kg]}}{\text{Creatinine [mg/dL]} \times 72} \times 0.85 \text{ (if female)}$$

The calculated value was again adjusted for BSA of 1.73 m².

The calculation of the GFR using modified four variables formula, the abbreviated MDRD equation was used as follows.¹¹

$$GFR(\text{mL/min per } 1.73 \text{ m}^2) = 186.3 \times (SCr^{-1.154}) \times (\text{Age}^{-0.203}) \times 0.742 \text{ (if female)} \times 1.21 \text{ (if black)}$$

Measurement of GFR by DTPA renogram (DTPA GFR) was Camera-based, Gates (low dose) method, performed in the nuclear medicine laboratory at Bir Hospital and Magnetic Resonance Imaging (MRI) Centre, Kathmandu. The subjects were orally hydrated with 0.5 L of fluid for the ^{99m}Tc- DTPA renogram study and ^{99m}Tc-DTPA dosed at 50 Ci/kg was injected intravenously. Dynamic images were obtained for 30 min using a dual headed variable angle Gamma camera. The total and individual kidney GFR was calculated using the Gates method and the values were normalized to BSA of 1.73 m².^{12,13}

All data were analyzed using the statistical program SPSS(PC+) version 20.0. Results were expressed as means \pm SD. The student t-test was used for comparison of means. Bias was defined as mean of difference between estimated GFR and measured GFR. The percentage of estimated GFR obtained from each equation falling within 15% and 30% of measured GFR were calculated and used as a measure of accuracy of the prediction equation. The precision was measured by R² statistics, which was derived by simple linear regression analysis. Pearson's correlation was used to measure the correlation between estimated GFR and measured GFR. The three prediction equations were compared and ranked for their performance with respect to global bias, precision, correlation and accuracy and final rank for each equation was given after adding up each rank. The best performance in each category was ranked as one and the worst as five. Equal performances for two or more equations were given the same rank. The sensitivity and specificity of each equation in selecting a donor with DTPA-GFR of ≥ 80 mL/min/1.73 m² was also calculated, and their relative accuracies were measured by area under Receiver Operating Characteristic (ROC) curves. P value < 0.05 was considered as significant.

RESULTS

There were total 51 cases during the study period. The mean age of kidney donors was 40.84 ± 2.1 years with age range of 20 to 65 years and male to female ratio of 0.53:1. The mean measured GFR was 102.752 ± 6.71 mL/min/1.73 m² with higher GFR in female than male donor (Table 1).

Table 1. The demographic profiles of healthy kidney donors.

Variables	Total N = 51	Male N = 18	Female N = 33
Age (years \pm SD)	40.84 \pm 12.108	42.33 \pm 11.391	40.03 \pm 12.578
Weight (kg)	54.02 \pm 9.511	58.89 \pm 8.670	51.36 \pm 8.989
Height (cm)	156.63 \pm 11.105	166.78 \pm 8.286	151.09 \pm 8.164
Body surface area (m ²)	1.53 \pm 0.16651	1.6478 \pm 0.14289	1.4658 \pm 0.14287
Serum creatinine (mg/dL)	0.9294 \pm 0.17583	1.0611 \pm 0.15770	0.8576 \pm 0.14149
Blood urea (mg/dL)	42.892 \pm 6.9508	24.889 \pm 6.5340	24.894 \pm 7.2670
Serum albumin (gm/dL)	4.8333 \pm 0.48894	4.8722 \pm 0.45349	4.8121 \pm .51281
DTPA-GFR (mL/min)	102.7520 \pm 16.71871	97.5094 \pm 12.15367	105.6115 \pm 18.28602

Mean calculated CrCl or GFR was highest by urine CrCl followed by CG CrCl and MDRD GFR (Table 2).

Table 2. Mean calculated CrCl or GFR, mean bias, precision (R²), correlation and accuracy of various prediction equations.

Estimated GFR (mL/min/ 1.73 m ²)	Mean (\pm SD) GFR/CrCl	Bias (mean \pm SE)	Precision (R ²)	Pearson correlation	Accuracy: percentage within 30%	Accuracy: percentage within 15%
Urine CrCl	116.5231 \pm 18.31526	13.7712 \pm 2.56737	0.207	0.455	51	29.4
CG CrCl	83.9247 \pm 20.51966	-18.8273 \pm 3.40926	0.025	0.157	27.5	15.7
MDRD GFR	82.9225 \pm 19.46338	-19.8294 \pm 3.35997	0.016	0.127	29.4	7.8

The percentage of estimated GFR falling within 30% of measured GFR was 51, 27.5 and 29.4 and within 15% was 29.4, 15.7 and 46.4 for urine CrCl, CG CrCl and MDRD GFR equations, respectively. Only donor weight was associated significantly (P value=0.027) influencing measured GFR in our study population in regression analysis (Table 3).

Table 3. Multiple linear regression analysis to identify factors affecting measured GFR in healthy renal donors.

	β - coefficient	P value	95% confidence interval
Constant	126.477	0.017	24.151 to 228.803
Age	-0.292	0.056	-0.817 to 0.011
Sex	-0.160	0.439	-19.905 to 8.796
Weight	-0.341	0.027	-1.128 to 0.071
Height	0.117	0.538	-0.397 to 0.751
Urea	-0.200	0.181	-1.193 to 0.233
Creatinine	-0.001	0.994	-31.516 to 31.273
Albumin	0.069	0.615	-7.082 to 11.827

24 hour urine CrCl fared the best cumulative ranking among all the creatinine based equations with respect to global bias, precision, correlation and accuracy (Table 4).

Table 4. Ranking of performance of various prediction equations with respect to global bias, precision, correlation and accuracy.

Equations	Bias	Precision	Correlation	Accuracy	Cumulative rank
Urine CrCL	1	1	1	1	4
CG CrCL	2	2	2	2	8
MDRD GFR	3	3	3	3	12

Besides the predictive performance, the ability of an equation to safely exclude potential donors with GFR < 80 mL/min/1.73 m² is critical. The area under ROC

curves illustrated that CG-CrCl equation had the highest accuracy (among the three equations compared) in correctly identifying cases with GFR ≥ 80 mL/min/1.73 m² (Table 5).

Table 5. Sensitivity and specificity of each equation in selecting a donor with a DTPA GFR ≥ 80 mL/min/1.73 m² and positive and negative predictive values and area under the ROC curve.

Equation	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Area under ROC curve
Urine CrCl	100	0	92.1	0	0.468
CG CrCl	53.2	100	100	15.4	0.883
MDRD GFR	55.3	100	100	16	0.838

Utilization of the CG-CrCl equation to estimate GFR was not very sensitive for selecting a donor with a GFR ≥ 80 mL/min/1.73 m² (sensitivity 53.2%), but was sensitive enough to detect a donor with mild renal dysfunction (specificity 100%). Three donors had GFR < 80 mL/min/1.73 m² based on DTPA clearance; but all these patients had urine CLCr > 80 mL/min/1.73 m² and so were chosen for donor nephrectomy. The urine CrCl had highest sensitivity of 100% for detecting donor with measured GFR > 80 mL/min/1.73 m² but specificity was 0% with positive predictive value of 92.1% and accuracy of 0.468 (area under ROC curve) only.

DISCUSSION

Function of a donor kidney has a significant long-term impact on both the donor health and the allograft function in recipient. GFR is the generally accepted marker for overall renal function and can be precisely measured by using the filtration marker ^{99m}Tc-DTPA. However, the cost and equipment required for DTPA-GFR estimation prevent its widespread use in developing countries.¹⁴ For example, most kidney transplant centers in Nepal use urine-CrCl as an index of GFR. However, data from several large clinical trials have shown that urine-CrCl is inaccurate and lacking in precision as an estimate of GFR and serum creatinine itself is affected by multiple factors other than GFR, such as muscle mass and meat product consumption.¹⁵⁻¹⁷ Therefore several GFR estimating equations have been developed to estimate GFR based on serum creatinine concentration, age, gender, and body size. The CG equation and MDRD study equation are widely used and recommended by the National Kidney Foundation and American Society of Nephrology for use in clinical practice in patients with chronic kidney disease.¹⁸ However these formulae are limited by the lack of validation in the full range of GFR and in different ethnic groups and both equations have lower precision in high GFR populations and GFR estimates are less useful in the normal range of GFR.¹⁹ None of the currently available estimating equations had been

validated in Nepalese healthy kidney donors. This is the first study from Nepal to check the validity of these equations in kidney donors.

In our study, mean measured GFR was within normal range but higher in female kidney donor than male counterpart which is contrary to general population and this may be due to most of the female donors were younger. The only factor affecting measured GFR was donor's weight. Two donors were > 60 years of age with measured GFR < 80 mL/min/1.73 m² but their urine CrCl was > 80 mL/min/1.73 m² without alternative suitable donor so went for donor nephrectomy. Four donors had hypertension stage 1 with reasonably controlled blood pressure with single antihypertensive agent and all were having measured GFR > 80 mL/min/1.73 m².

Our results showed that urine CrCl method overestimated GFR with bias of 13.77 ± 2.56 mL/min/1.73 m² but both CG CrCl and MDRD GFR equations underestimated GFR by bias of -18.82 ± 3.4 and -19.94 ± 3.35 mL/min/1.73 m² respectively. Urine CrCl was most precise and the least scattered. Thus all equations were more or less biased when compared with the measured GFR. Except urine CrCl, no other equations are advantageous for Nepalese populations as it has highest sensitivity of 100% for detecting donor with GFR ≥ 80 mL/min/1.73 m². We compared various prediction equations with respect to degree of global bias, precision, correlation and accuracy, and ranked them according to their performance. Overall, urine CrCl fared the best, followed by CG CrCl and then MDRD GFR equation. The urine CrCl method gives higher GFR estimates with accuracy percentage within 30% and 15% of measured GFR only 51 and 29.4. Zhao WY et al also found the similar type of result like Urine-CrCl tended to overestimate GFR, with a bias of 14.2 mL/min/1.73 m² and precision (R²) estimate of 0.22. Urine-CrCl fell within 30% and 50% of the DTPA-GFR in 75.9% and 89.3% of the cases respectively.¹⁴ So even it may not

be useful for routine screening of renal function in kidney donors.

In our study, all derived GFR from creatinine, CG CrCl and MDRD GFR formulae underestimated actual kidney function. This is similar to the findings of previous studies that also reported under estimation of MDRD GFR formula by 9 to 29 mL/min/1.73 m².^{5,20-22} The CG-CrCl equation had the highest accuracy in correctly identifying suitable kidney donor with GFR \geq 80 mL/min/1.73 m² followed by MDRD GFR equation and least for urine CrCl and had specificity of 100% that is not selecting donors with impaired GFR. Positive predictive value for selecting donors with normal GFR were 100% for both CG CrCl and DTPA GFR equations and only 92.1% for urine CrCl thus showing none of these creatinine based method for estimation of GFR clinically accurate in selecting normal donor in Nepalese populations.

Other studies looking at the performance of these equations in Asian populations have also yielded inconsistent results. Zuo et al. reported that the abbreviated MDRD equation performed poorly in a Chinese population with CKD when compared with DTPA GFR estimation.²³ But Kang et al. found that the CG and MDRD study equations had greater accuracy and precision with measured GFR in healthy Korean populations.²⁴ However, both the equations severely underestimated GFR similar to our result. Mahajan et al. reported the MDRD study equation is the most precise and accurate, whereas CG-GFR is the least biased in Indian population.²⁵ A racial difference in renal function of patient populations can explain these discrepancies in different studies. The CG equation was designed to predict CrCl and not GFR.¹⁰ CrCl usually exceeds GFR by 10–15% because of urinary creatinine that is derived from tubular secretion also.²⁶ The MDRD equation was also derived from Caucasians with mild to moderate renal failure.²⁷ As both the equations were

designed to predict 24-h CrCl or GFR in Caucasian populations, it is not surprising that it performed poorly when used to estimate GFR in Asian populations. Race is an important determinant of GFR estimation. Urinary Creatinine excretion may be lower in Mongolians than in Caucasians and African Americans because both muscle mass and lesser protein intake.^{28,29} Accurate estimation of GFR in subjects with mild to normal renal function is very difficult, because small changes in serum creatinine may result in a substantial change in calculated GFR. Considering that living kidney donation carries a substantial risk for donors with even mildly renal function, these equations are suboptimal. Thus, every donor should undergo a more accurate GFR measurement, such as insulin, ¹²⁵I-iothalamate, ⁵¹Cr-EDTA, and ^{99m}Tc-DTPA or iohexol clearance. Even though these methods are cumbersome and expensive, but they are worthwhile to know the potential risk of living kidney donation and transplant outcome.

CONCLUSIONS

The mean measured GFR in healthy adult donors in our study was 102.752 ± 16.718 mL/min/1.73 m². The performance of urine-CrCl and the other equations is disappointing as urine CrCl overestimates but CG CrCl and MDRD GFR underestimates the true GFR. Urine CrCl estimation performed better in terms of global bias, precision, correlation and accuracy, when compared with CG CrCl, MDRD GFR. Their poor ability to identify donors with renal dysfunction makes them unsuitable for clinical use.

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