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SERUM CREATININE BASED ESTIMATED GFR EQUATIONS: DO THEY PREDICT MEASURED GFR IN HEALTHY KIDNEY DONORS?

Nephrology

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ABSTRACT

Aims: To evaluate serum creatinine based estimated GFR equations for predicting measured GFR in healthy kidney donors.

Methodology: In this retrospective observational study we compared serum creatinine based eGFR equations such as MDRD, CKD-EPI,MAYO and Cockroft-Gault equations with measured GFR by DTPA renogram in 150 healthy kidney donors. The Bias, the correlation and the accuracy were calculated for these eGFR equations

Results: Out of 150 study cohort 75% were females. Mean age was 44.77±9.75. Mean measured GFR was 105.72±9.39. Correlation coefficient was 0.443,0.557,0.374,0.449 respectively for MDRD, CKD-EPI,MAYO and Cockroft-Gault equations and R2 , a measure of accuracy was 19.6%,31%,14%,20.2% respectively for MDRD, CKD-EPI,MAYO and Cockroft-Gault equations

Conclusions: Available estimated GFR equations are neither precise nor accurate compared to measured GFR by DTPA renogram in our healthy kidney donors. we need adequately powered studies to develop either a new equation for estimating GFR or a correction factor for the available equations in the Indian population.

KEYWORDS

Serum creatinine, eGFR, DTPA renogram

INTRODUCTION:

Glomerular filtration rate (GFR) is the single best measure of overall kidney function[1]. In principle, GFR is the product of the number of nephrons(N) and the average single nephron GFR (SNGFR). Neither can be measured directly, but variation in either can cause variation in GFR. The number of nephrons(N) appears to be lower in people with CKD, older age, or a history of prematurity[2,3]. Variation in SNGFR may be affected by the time of day, dietary protein intake, exercise, pregnancy, obesity, hyperglycemia, use of antihypertensive drugs, an excess or deficit of extracellular fluid, as well as chronic and acute kidney disease[4].

Direct measurement of GFR is not possible in humans. However, GFR can be assessed by clearance of an ideal filtration markers such as inulin or an alternative exogenous marker such as iothalamate, EDTA, diethylene triamine pentaacetic acid (DTPA), and iohexol. Measuring clearance with the use of exogenous markers is complex, expensive, and difficult to do in routine clinical practice[5].

Urinary clearance of an endogenous filtration marker such as creatinine can be computed from a timed urine collection. However, this method has several deficiencies such as errors in collecting urine and tubular secretion of creatinine, which can substantially overestimate the true GFR[6].

GFR can be estimated by endogenous filtration markers in a steady-state condition without urine collections. Estimating equations include variables such as age, sex, race, and body size, in addition to serum creatinine, as surrogates for muscle mass, and therefore, they can overcome some of the limitations of the use of serum creatinine alone. An estimating equation is derived with the use of regression techniques to model the observed relation between the serum level of the marker and the measured GFR in a study population.

The first attempt to estimate GFR was by the Cockcroft and Gault (C-G). They developed a formula to estimate GFR in 1976 with the data from 249 men with creatinine clearances (Ccr) from 30 to 130 ml per minute[7]. In this equation, they used age, body weight, serum creatinine, and sex.

Later The Modification of Diet in Renal Disease (MDRD) study equation was developed in 1999 with the use of data from 1628 patients with chronic kidney disease. It estimates GFR adjusted for body-surface area[8]. The MDRD equation was compared against a gold standard, urinary clearance of iothalamate.

The CKD-EPI equation was derived in 2009 in 8254 subjects (a further 3896 subjects pooled from 16 studies were used for validation), with the urinary clearance of iothalamate again as a gold standard[9]. It has less bias and greater accuracy than the MDRD equation, especially at higher GFR[10].

The Mayo Clinic Quadratic Equation (MCQE) was proposed to give a more accurate estimation of true GFR in those subjects without renal disease. This equation was derived in 2004 in 900 subjects both with CKD and healthy people (potential donors) compared with the urinary clearance of iothalamate as a gold standard[11].

None of these equations were used Indian population either in the derivation cohort or in the validation cohort, and there is paucity of data for validation of these equations in the Indian population.

We undertook this study to compare the estimated equations derived GFR to measured GFR by DTPA renogram in healthy kidney donors.

MATERIAL AND METHODS:

It is a retrospective observational study.

The study was conducted at the Institute of Nephro-urology, Bangalore.

The records of all healthy adult, living, related kidney donors between January 2010 to August 2019 were reviewed and 150 of them who had adequate data were included in the study.

Data regarding age, gender, place of residence, weight, serum creatinine (S Cr), and measured GFR by DTPA renogram for each subject were collected and entered in an excel sheet.

Measurement of serum creatinine:

Kinetic alkaline picrate method was used which is the improvised version of Jaffe's chemistry. The assay was carried out through the Abbott architect ci4100 integrated system. A periodic external quality assessment was done for this assay through Randox Laboratories Ltd.UK.

Measurement of GFR by DTPA renogram:

The subjects were orally hydrated with 0.5 L of fluid for the 99mTcDTPA renogram study and 4mcu of 99mTc-DTPA was then injected intravenously. The study was carried out in a supine position to negate the effect of gravity. Dynamic images were obtained for 30 min using a dual-headed variable angle Gamma camera with SPECT facility (Siemens, E-CAM). The total and individual kidney GFR was calculated using the Gates method and the values were normalized to BSA.

Estimation of GFR by prediction equations:

- Cockcroft-Gault equation(C-G GFR)(corrected for body surface area)[7]: (140 - age) x weight in kg/(SCr x 72) (x0.85, if female)x0.84
- MDRD modified 4 variable equation (MDRD GFR)[8]: 186 (SCr)-1.154 x (age)-0.203 (x0.742, if patient is female) (x1.212, if patient is black)
- EPI equation for eGFR(CKD-EPI GFR)[9]:141 × min(SCr/κ, 1)α × max(SCr/κ, 1)−1.209 × 0.993age × 1.018 (if female) × 1.159 (if black) where: κ is 0.7 for females and 0.9 for males,α is −0.329 for females and −0.411 for males, min indicates the minimum of SCr/κ or 1 ,max indicates the maximum of SCr/κ or 1
- The Mayo Clinic Quadratic Equation (MAYO GFR)[11]: exp {1.911 + (5.249/SCr) - (2.114/ SCr2) - (0.00686 x Age) - 0.205 (if female)}; If SCr < 0.8 mg/ dL, use 0.8 for Scr

Statistical Analysis:

Results on continuous measurements are presented on Mean ±SD (Min-Max) and results on categorical measurements are presented in Number (%).

Student t-test has been used to find the significance of study parameters on a continuous scale and Chi-square/ Fisher Exact test has been used to find the significance of study parameters on a categorical scale between two or more groups respectively.

We defined Bias as the mean difference between mGFR and eGFR (mGFR-eGFR).

Pearson correlation between study variables is performed to find the degree of relationship, Pearson correlation coefficient ranging between -1 to 1, -1 being the perfect negative correlation, 0 is the no correlation and 1 means perfect Positive correlation.

r values ranges 0.00-0.10 ; Negligible correlation, 0.10-0.39 Weak correlation,0.40-0.69 Moderate correlation, 0.70-0.89 Strong correlation, 0.90-1.00 Very strong correlation

Accuracy was measured by r2 statistics, which was derived by simple linear regression analysis.

Statistical software: Statistical software namely SPSS 22.0, and R environment ver.3.2.2 were used for the analysis of the data, and Microsoft Word and Excel have been used to generate graphs, tables, etc.

RESULTS:

The Study included 150 subjects. The mean age of the study population was 44.77±9.75 (Table1). The majority of study subjects belonged to female sex 75% (Figure1). The mean weight of the study population and serum creatinine were significantly lower in females compared to males(Table1). However there was no significant difference in measured GFR across sexes(Table1).

Figure 1: Sex distribution of study cohort

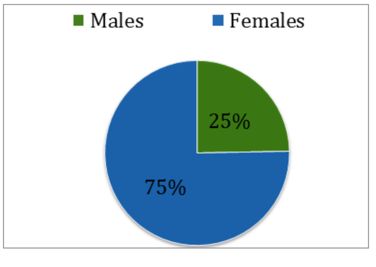

Table 1: Baseline clinical variables of study cohort

variables	Gender		Total	P value
	Male	Female		
Age in years	46.89±10.72	44.08±9.35	44.77±9.75	0.128
Weight (kg)	63.11±10.73	59.28±9.88	60.22±10.19	0.047*
Serum Creatinine (mg/dl)	0.89±0.10	0.70±0.11	0.74±0.13	<0.001**
Split GFR Left	51.40±5.53	52.83±5.37	52.48±5.43	0.164
Split GFR Right	52.6±5.48	53.47±5.19	53.25±5.26	0.384
Measured GFR	103.95±10.33	106.30±9.03	105.72±9.39	0.186

GFR: Glomerular filtration rate, * Moderately significant, ** Strongly significant

When measured GFR was compared with estimated GFR equations, all the equations underestimated the GFR except for the Mayo Clinic Quadratic equation (Table 2). When the Bias was assessed between measured GFR and estimated GFR, CKD-EPI equation had the least bias compared to the other equations(Table 2).

Table 2: Bias values for estimated GFR equations

GFR	Total	Bias (Mean difference)
MDRD GFR	100.88±20.52	-4.84
CKD- EPI GFR	102.21±13.42	-3.51
MAYO GFR	109.32±11.23	4.4
C-G GFR	97.47±23.60	-8.25

GFR: Glomerular filtration rate, MDRD: Modified diet renal disease, CKD-EPI: Chronic kidney disease Epidemiology Collaboration, MAYO: The Mayo Clinic Quadratic Equation, C-G: Cockcroft-Gault equation

When measured GFR compared with estimated GFR by Pearson's correlation all estimated GFR equations had mild to moderate correlation with measured GFR. Among all estimated GFR equations CKD-EPI equation had the best correlation with measured GFR yet correlation was moderate (Table 3).

Table 3: Comparision and correlation of measured GFR vs estimated GFR Pearson correlation

Pair	Total	
	r value	P value
Measured GFR vs MDRD GFR	0.443	<0.001**
Measured GFR vs CKD-EPI GFR	0.557	<0.001**
Measured GFR vs MAYO GFR	0.374	<0.001**
Measured GFR vs C-G GFR	0.449	<0.001**

GFR: Glomerular filtration rate, MDRD: Modified diet renal disease, CKD-EPI: Chronic kidney disease Epidemiology Collaboration, MAYO: The Mayo Clinic Quadratic Equation, C-G: Cockcroft-Gault equation, ** Strongly significant

When regression analysis was used to measure the accuracy of estimated GFR equations compared to measured GFR, none of the estimated GFR equations had good predictive value, however, among them, CKD-EPI equation fared better than the rest of estimated GFR equations (Table 4).

Table 4: Regression analysis to predict measured GFR

Sl no	Prediction Equation	R^2	SE	P value
1	Measured GFR=85.29+0.203 x MDRD_GFR	19.6%	8.44	<0.001**
2	Measured GFR=65.935+0.389 x CKD-EPI_GFR	31.0%	7.82	<0.001**
3	Measured GFR=71.54+0.313 x MAYO_GFR	14.0%	8.73	<0.001**
4	Measured GFR=88.32+0.179 x C-G_GFR	20.2%	8.41	<0.001**

GFR: Glomerular filtration rate, MDRD: Modified diet renal disease, CKD-EPI: Chronic kidney disease Epidemiology Collaboration, MAYO: The Mayo Clinic Quadratic Equation, C-G: Cockcroft-Gault equation, ** Strongly significant

When the cumulative rank of all three variables that assess the predictive value of estimated GFR equations compared to measured GFR was added, the CKD-EPI estimated GFR fared best among other estimated equations (Table 5).

Table 5: Overall performance ranking of various estimated equations

Sl no	e GFR equation	Pearsons correlation	Bias	R^2	Correlation Rank	Bias Rank	Accuracy Rank	Net Rank

1	MDRD eGFR	0.443	-4.84	19.6%	3	3	3	9
2	EPI eGFR	0.557	-3.51	31.0%	1	1	1	3
3	Mayo eGFR	0.374	4.4	14.0%	4	2	4	10
4	C-G eGFR	0.449	-8.25	20.2%	2	4	2	8

GFR: Glomerular filtration rate, MDRD: Modified diet renal disease, CKD-EPI: Chronic kidney disease Epidemiology Collaboration, MAYO: The Mayo Clinic Quadratic Equation, C-G: Cockcroft-Gault equation

DISCUSSION:

This study results showed that all estimated equations had only mild to moderate correlation with measured GFR and were less accurate when compared with measured GFR in healthy kidney donors.

Srinivas S et al.[12] studied the performance of estimated GFR equations in 599 kidney donors and found that none of the equations had accuracy and precision when compared with measured GFR by DTPA renogram. Jessani S et al.[13] studied the performance of eGFR equations in 581 subjects when compared to GFR measurement by urinary clearance of inulin suggested that all estimated equations were inaccurate and less precise compared to measured GFR, furthermore, they suggested correction factor for CKD-EPI equation to enhance accuracy and precision. Suchada P et al.[14] in their systemic review of comparisons of GFR estimation using the CKD Epidemiology Collaboration (CKD-EPI) equation and other creatinine-based equations in Asian population concluded that these estimated GFR equations were not accurate enough in Asian population and emphasized the need for correction factor or new equation for Asian population to estimate GFR.

In our study among the estimated GFR equations, CKD-EPI equation fared better than other estimated equations to predict measured GFR.

Thestudy published by Srinivas S et al.[12] showed that the Cockcroft-Gault equation(C-G GFR) fared better than the rest of estimated equations to predict measured GFR. However, the CKD- EPI equation to estimate GFR was not used in that study. Kumar et al.[15] in their study of 130 patients composed of both patients with CKD as well as healthy kidney donors have shown that CKD EPI by cystatin c had the best predictive value for measured GFR by urinary Inulin clearance when compared to therest. Similar to our study Jessani S et al.[13] in their study shown that CKD-EPI had the best predictive value for measured GFR compared to the MDRD equation.

Our study has several limitations. The sample size of the study population was small. Only healthy kidney donors were included in our study , so we could not extrapolate our findings in disease states like chronic kidney disease(CKD). Study design being retrospective in nature means we need to rely on available data in medical records resulting in absence of anthropometric data, nutrition status of study participants, and dietary habits. Because all these factors can independently affect the creatinine levels in the blood irrespective of GFR. All these estimated equations except the C-G equation in their derivation cohort were compared to measured GFR by renal clearance of Iothalmate whereas the C-G equation was compared against urinary clearance of creatinine. However, in our study, we measured GFR by DTPA renogram.

CONCLUSIONS:

Available estimated GFR equations are neither precise nor accurate compared to measured GFR by DTPA renogram in our healthy kidney donors. An appropriately powered prospective study that includes both healthy people and patients with CKD is required to either develop a new equation for estimating GFR or a correction factor for the available equations in the Indian population.

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