Original Article

Comparison of Different Estimating Equations for Prediction of Glomerular Filtration Rate in Living Kidney Donors

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Abstract

Introduction: Assessment of renal function is a crucial step in evaluation of living kidney donors. The standard method for determining renal function is measurement of glomerular filtration rate (GFR) using I-123 iothalamate, Tc-99m Diethylene Triamine Pentaacetic Acid (DTPA) and 51Cr-Ethylene Diamine Tetraacetic Acid. As these methods are expensive and cannot be used in all clinical settings, it is common practice to estimate GFR by creatinine-based equations. The objective of this study is to compare commonly used estimating equations for the prediction of GFR in Living Kidney Donors.

Methods: In 75 healthy kidney donors, GFR estimated by Modification of Diet in Renal Disease Study equation(MDRD), Cockcroft-Gault formula(CG), Chronic Kidney Disease Epidemiology Collaboration(CKD-EPI) equation and 24 hour urinary creatinine clearance were compared to GFR measured by Tc-99m DTPA. Statistical analysis was done using Dunnett's test and Bland-Altman plot. Similarly, accuracy, precision and bias of each equation were assessed.

Results: Mean GFR calculated by DTPA clearance, CG, MDRD, CKD-EPI equations and 24 hour urine creatinine clearance were 83.35±8.59, 78.99±17.17, 93.30±17.12, 96.34±13.36 and 137.96±43.65 ml/min/1.73m^2 respectively. Applying Dunnett's test, GFR by CG equation minimally underestimated GFR measured by DTPA($p=0.612$) whereas GFR estimated by MDRD ($p=0.034$), CKD-EPI($p=0.03$) and 24 hour urine creatinine clearance($p<0.001$) were statistically significant. CG equation had the highest accuracy. Using Bland-Altman plot, the precision of CKD-EPI equation was the highest among all.

Conclusion: There is no single creatinine-based estimating equation to assess GFR with utmost accuracy and precision at the same time.

Keywords: creatinine clearance, Diethylene Triamine Pentaacetic Acid, living kidney donors

Introduction

Assessment of renal function measuring glomerular filtration rate (GFR) is an important part of routine evaluation for living kidney donor selection.[1,2,3] There are different methods available for assessment of GFR but measurement using an ideal filtration marker like inulin or alternative exogenous markers likeI-123 iothalamate, Tc-99m Diethylene Triamine Pentaacetic Acid (DTPA) and chromium-51 labeled Ethylene Diamine Tetraacetic Acid (^{51}Cr-EDTA) is considered standard.[4,5]However, these techniques being very expensive and complex, outweigh their high reliability and make them unsuitable for routine use, especially when it comes to regular assessment of GFR following live donor nephrectomy or regular monitoring of GFR in the intensive care unit setting and during course of nephrotoxic drugs.[3] Thus, creatinine-based GFR estimations have still been used widely for assessment of GFR.[6] Modification of Diet in Renal Disease (MDRD) Study equation, the Cockcroft- Gault (CG) formula and Chronic Kidney Disease Epidemiology Collaboration(CKD-EPI) equation are the most commonly used equations for estimating GFR.[7,8,9,10] Another method for assessment of renal function is urinary creatinine clearance (CrCl), which can be computed from a timed urine collection (24-hour urine collection) and blood sampling for serum creatinine.[11]

All these GFR-estimating equations have their own limitations, for instance MDRD and CG formula were developed using data from people with reduced renal function. Similarly, urinary creatinine clearance tends to overestimate GFR because of tubular secretion of creatinine as well as errors during timed collection of urine.[12,13]CKD-EPI equation is the recently developed creatinine-based equation validated in population with normal GFR.[10] Hence, it has been found to be the most precise and accurate in healthy population.[13] Nevertheless, the equation was extrapolated from the data studying western population Thus, the objective of our study was to compare commonly used GFR-estimating equations (24 hour urinary creatinine clearance, Cockcroft-Gault, Modification of Diet in Renal Disease and Chronic Kidney Disease Epidemiology Collaboration) for the prediction of GFR in Nepalese Living Kidney Donors.

Methods

A total of 75 healthy adults who were being worked up for kidney donation were prospectively studied from August 2015 to July 2016 in Tribhuvan University Teaching Hospital. All cases had laboratory evaluation with serum creatinine and 24 hours urine creatinine using automatic biochemistry analyzer (BT1500, Biotecnica instruments). GFR was assessed by Tc-99mDTPA clearance(mGFR) as renogramwith gamma camera (Siemens E.CAM) as a part of routine work up. Similarly, estimated GFR (eGFR) were calculated using the following GFR-estimating equations:

Creatinine clearance (CrCl) based on 24-hour urine creatinine:[11]

$eGFR_{CrCl}$(ml/min)= urine creatinine x urine volume/ serum creatinine

Cockcroft-Gaultformula:[7]

$eGFR_{CG}$(mL/min)=(140-Age) x Weight in kg(x 0.85if female)/Serum creatinine(umol/L)

MDRD Study Equation:[8]

$eGFR_{MDRD}$(mL/min/1.73m^2)=186 x (Serum Creatinine/ 88.4)$^{-1.154}$ x (Age)$^{-0.203}$ x (0.742 if female) x (1.210 if black)

CKD-EPI equation:[10]

$eGFR_{CKDEPI}$(mL/min/1.73m^2) =141 x min(S_{Cr}/κ, 1)$^{\alpha}$ x max(S_{Cr} /κ, 1)$^{-1.209}$ x0.993^{Age} x1.018 [if female] x1.159 [if Black];where

S_{Cr} (standardized serum creatinine) = mg/dL

κ = 0.7 (females) or 0.9 (males)

α = -0.329 (females) or -0.411 (males)

min = indicates the minimum of S_{Cr}/κ or 1

max = indicates the maximum of S_{Cr}/κ or 1

age = years

Body surface area(BSA) was calculated using Mosteller formula:[14]

BSA=√(height (cm) x weight (kg)/ 3600)

GFR measured from DTPA (mGFR) andeGFR estimated from CG formula and 24 hour urine creatinine clearance were standardized according to BSA. The study was ethically approved by Institutional Review Board of Institute of Medicine (Ref:354(6-11-E)/073/073) and consent was obtained from all the participants of the study.

All variables were presented as their mean± Standard Deviation (SD) or percentages. Each estimating equation for GFR was compared with mGFR using Dunnett's test and all were compared with each other using univariate analysis and ANOVA test. P-value of less than 0.05 was considered statistically significant. The mean differences between each eGFR and mGFR were used to determine bias. In addition, the accuracy within 10% and 30% of mGFR was determined for each eGFR. The precision of the estimates was determined as SD of the mean difference between mGFR and eGFR. Finally, the agreements between mGFR and the estimating equations used for eGFR were assessed according to Bland and Altman plot.[15] The limits of agreement of each eGFR were calculated as mean difference (mGFR-eGFR)± two standard deviations and errors of each eGFR as double standard deviation divided by the mean of the measurements from the two methods in relation to mGFR.The between-method

error of 30% or less was determined as acceptable, as suggested by Critchley and Critchley.[15]

Results

Baselines characteristics of 75 participants as well as their GFR measured by DTPA and estimated GFR by different equations are presented in Table 1. All eGFR were found to be significantly different ($p<0.001$) when compared to mGFR using ANOVA test.$eGFR_{CG}$ minimally underestimated GFR ($p=0.612$) using Dunnett's test while $eGFR_{MDRD}$ ($p=0.034$), $eGFR_{CKDEPI}$ ($p=0.03$) and $eGFR_{CrCl}$ ($p<0.001$) were statistically significant when compared to mGFR as shown in Table 2. Similarly, using univariate analysis, $eGFR_{CG}$ did not significantly differ from mGFR ($p=0.256$) and $eGFR_{CKDEPI}$ was comparable to $eGFR_{MDRD}$ ($p=0.428$) as presented in Table 3. Mean differences(bias) between each eGFR and mGFR, their standard deviation and the mean of mGFR and eGFRare shown in Table 4. Mean bias was lowest for $eGFR_{CG}$. The precision of $eGFR_{CKDEPI}$was the highest among all.Except eGFRCG, all eGFRshowed significant bias ($p<0.001$) when compared to mGFR as depicted by Table 3. In addition, the accuracy of $eGFR_{CG}$within 30% of mGFR was 92%, which was significantly higher than other equations ($p<0.001$). The Bland and Altman plots of all estimating equations are presented in Figure (1-4). The errors were 35.77%, 32.98%, 26.11% and 73.17% for $eGFR_{CG}$, $eGFR_{MDRD}$, $eGFR_{CKDEPI}$ and $eGFR_{CrCl}$ respectively when compared to mGFR. Similarly, the limits of agreement were 57(-24.38 to 32.62), 58.28(-39.09 to 19.19), 46.95(-36.46 to 10.49) and 161.26(-134.22 to 26.98) ml/min/1.73 $m^2$for $eGFR_{CG}$, $eGFR_{MDRD}$, $eGFR_{CKDEPI}$ and $eGFR_{CrCl}$ respectively when compared to mGFR.

Table 1. Baseline Characteristics and Glomerular Filtration Rate (GFR) estimated by different techniques

Female	52(69.3%)
Male	23(30.7%)
Age (years)	44.72±11.42
Weight (kg)	59.72±8.09
Body Surface Area (m^2)	1.59±.13
Body Mass Index (kg/m^2)	25.07±4.02
Serum Creatinine (umol/L)	71.2±11.14
99mTc DTPA mGFR ($ml/min/1.73m^2$)	83.35±8.59
$eGFR_{CG}$ ($ml/min/1.73m^2$)	78.99±17.17
$eGFR_{CKDEPI}$ ($ml/min/1.73m^2$)	96.34±13.36
24 hour urine CrCl ($ml/min/1.73m^2$)	137.96±43.65
$eGFR_{MDRD}$ ($ml/min/1.73m^2$)	93.30±17.12

Table 2. Comparison between estimated GFR(eGFR) by different equations and measured GFR(mGFR) by DTPA using Dunnett's test

eGFR	p-value
$eGFR_{CG}$	0.612
$eGFR_{MDRD}$	0.034*
$eGFR_{CKDEPI}$	0.003*
$eGFR_{CrCl}$	<0.001*

*p<0.05

Table 3. Comparison among estimated GFR (eGFR) by different equations and measured GFR (mGFR) by DTPA using univariate analysis

GFR	GFR	Mean difference	Significance	95% Confidence Interval for Difference	
				Lower Bound	Upper Bound
mGFR	$eGFR_{CG}$	4.36	0.256	-3.16	11.88
	eGFRMDRD	-9.95*	0.010	-17.47	-2.42
	$eGFR_{CKDEPI}$	-12.98*	0.001	-20.51	-5.46
	$eGFR_{CrCl}$	-54.60*	<0.001	-62.13	-47.08
$eGFR_{CG}$	mGFR	-4.35	0.256	-11.88	3.16
	$eGFR_{MDRD}$	-14.30*	<0.001	-21.83	-6.78
	$eGFR_{CKDEPI}$	-17.34*	<0.001	-24.87	-9.82
	$eGFR_{CrCl}$	-58.96*	<0.001	-66.49	-51.44
$eGFR_{MDRD}$	mGFR	9.95*	0.010	2.42	17.47
	$eGFR_{CG}$	14.30*	<0.001	6.78	21.83
	$eGFR_{CKDEPI}$	-3.03	0.428	-10.56	4.48
	$eGFR_{CrCl}$	-44.65*	<0.001	-52.18	-37.13
$eGFR_{CKDEPI}$	mGFR	12.98*	0.001	5.46	20.51
	$eGFR_{CG}$	17.34*	<0.001	9.82	24.87
	$eGFR_{MDRD}$	3.03	0.428	-4.48	10.56
	$eGFR_{CrCl}$	-41.62*	<0.001	-49.14	-34.09
$eGFR_{CrCl}$	mGFR	54.60*	<0.001	47.08	62.13
	$eGFR_{CG}$	58.96*	<0.001	51.44	66.49
	$eGFR_{MDRD}$	44.65*	<0.001	37.13	52.18
	$eGFR_{CKDEPI}$	41.62*	<0.001	34.09	49.14

*p<0.05

Table 4. Mean difference between measured GFR(mGFR)by DTPA and estimated GFR(eGFR) by different equations

Mean difference(bias)	Mean	Standard Deviation	Accuracy % within	
			10% of mGFR	30% of mGFR
$mGFR\text{-}eGFR_{CG}$	4.12	14.54	41.33	92
$mGFR\text{-}eGFR_{MDRD}$	-9.95	14.58	33.33	85.33
$mGFR\text{-}eGFR_{CKDEPI}$	-12.99	11.73	28	84
$mGFR\text{-}eGFR_{CrCl}$	-53.63	40.31	8	20

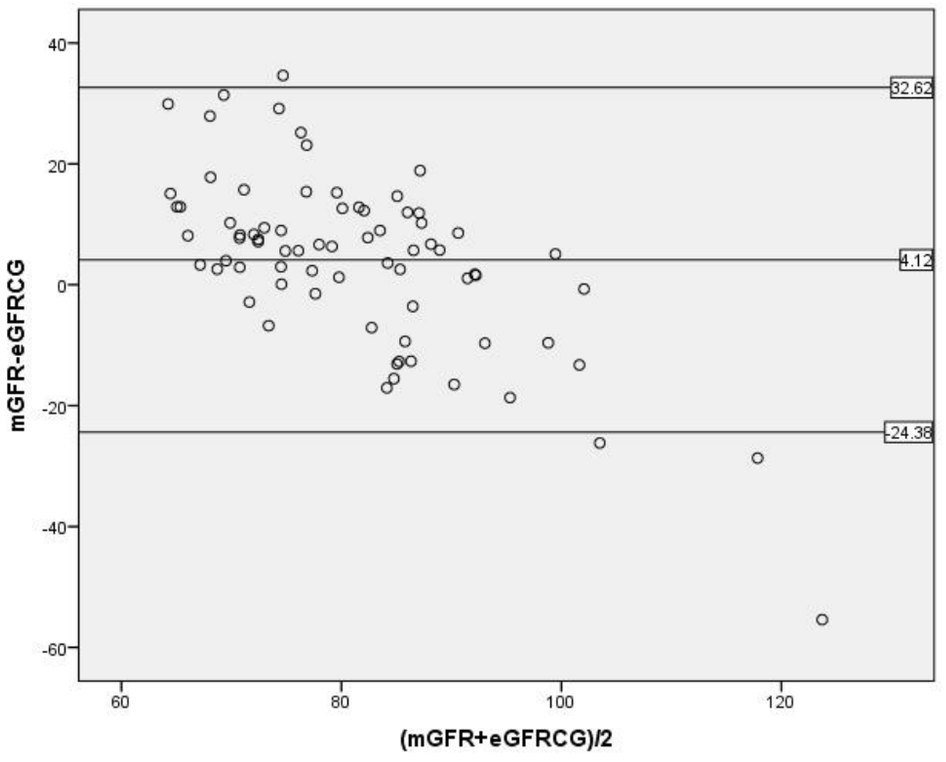

Figure 1. Bland-Altman Plot. Comparison of agreements between measured GFR (mGFR) by DTPA and estimated GFR (eGFRCG) by Cockcroft-Gault formula

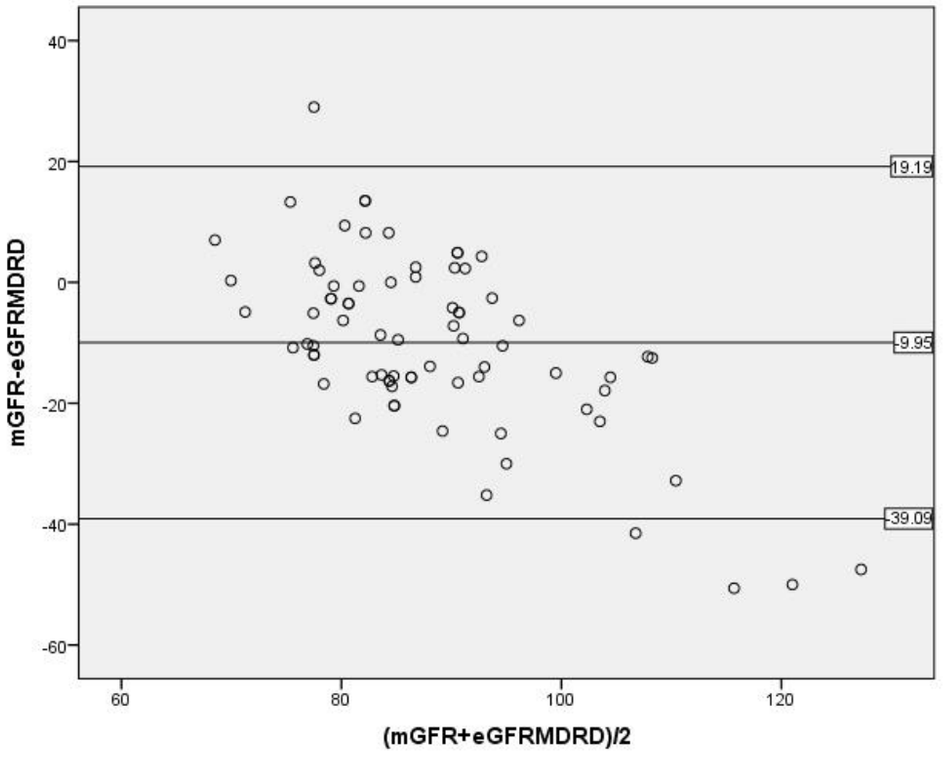

Figure 2. Bland-Altman Plot. Comparison of agreements between measured GFR(mGFR) by DTPA and estimated GFR (eGFRMDRD) by Modified Diet in Renal Disease Study Equation

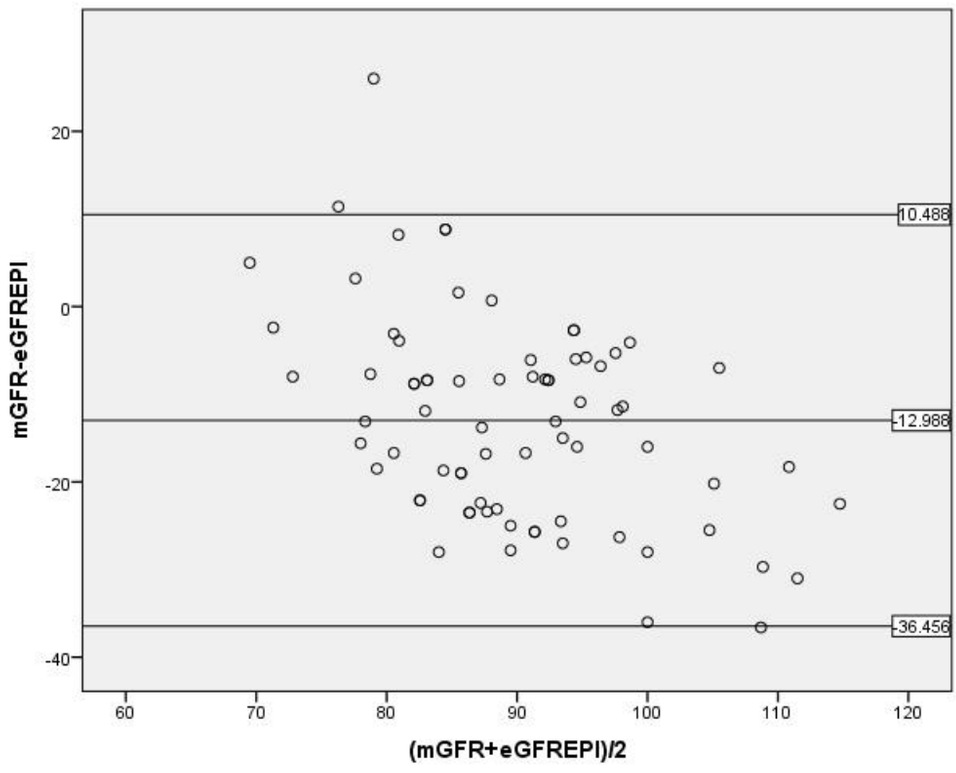

Figure 3. Bland-Altman Plot. Comparison of agreements between measured GFR (mGFR) by DTPA and estimated GFR (eGFREPI) by Chronic Kidney Disease Epidemiology Collaboration Equation

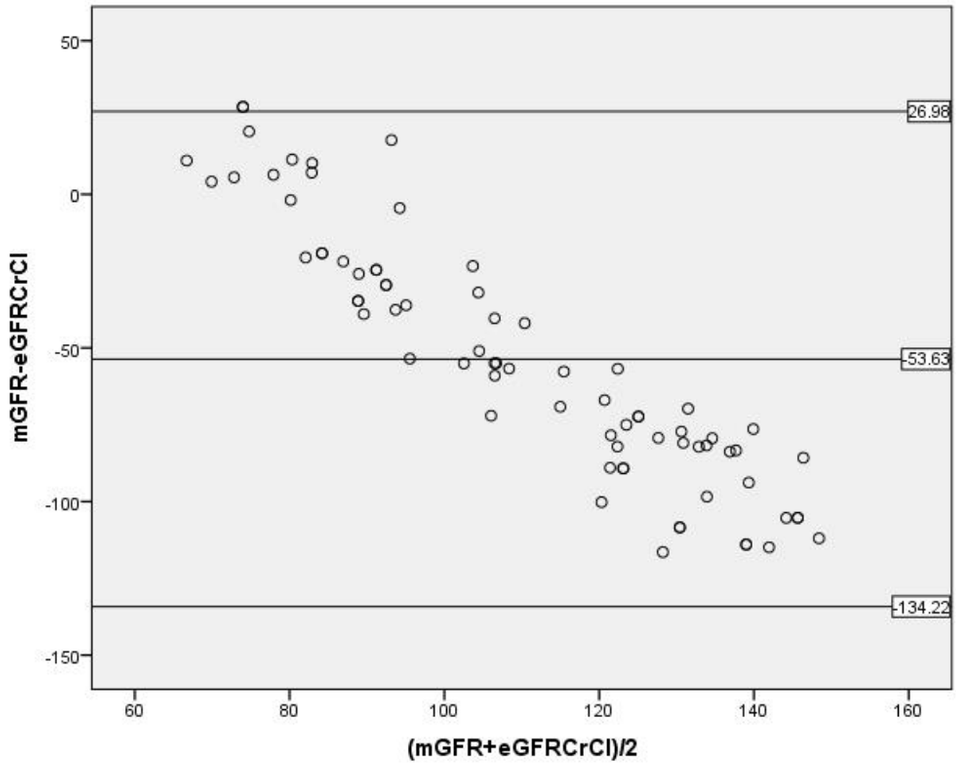

Figure 4. Bland-Altman Plot. Comparison of agreements between measured GFR (mGFR) by DTPA and estimated GFR(eGFRCrCl) by 24 hour urine Creatinine Clearance

Discussion

Measurement of GFR is an essential part of living kidney donor evaluation as both the donor and recipient are affected by the function of donated kidney.[1] GFR measured by Tc-99mDTPA is one of the standard methods of measurement of GFR.[4]The creatinine-based equations are frequently used in clinical practice to estimate GFR because they are easy to calculate, less costly, can be repeated and are very useful in critical care setting.[3] In this study, GFR calculated by various formulae like CG, MDRD, CKD-EPI and 24 hour creatinine clearance were compared to GFR measured from DPTA renogram.

The baseline characteristics of this study population are comparable to Indian healthy kidney donors studied by Mahajan et al[17]. The mean body weight and body surface area in his study were 59.04±10.07 kg and 1.58±0.15 m^2 respectively. Similarly, the mean age of his study population was 44.7 years with 72.2% being female. This is contrary to European studies which have different baseline characteristics than our study.[12,18]

In this study, population has lower measured GFR than the western population.[13,19]Mahajan et al in his study in Indian population had mean GFR calculated by DTPA of 83.4 ml/min/ 1.73m^2 which was comparable to our study whereas Lin et al. showed mean GFR calculated by DTPA to be 125.1±20.3 ml/min/1.73 m^2 in 100 potential kidney donors.[13,17] The demonstration of a lower GFR value in healthy living Nepalese potential kidney donors as in Indian healthy donors can have significant impact in selection of kidney donors. Many potential donors may be excluded due to apparently low GFR following western reference ranges. With the availability of indigenous data, those donors with an apparently low GFR value by western standards but a normal GFR value by Nepalese standards can be considered.

This study showed that $eGFR_{CG}$ minimally underestimated mGFR and had minimal bias. The precision was highest for $eGFR_{CKD-EPI}$. Similarly, the limits of agreement was highest for CKD-EPI and lowest for 24 hour creatinine clearance. As defined by Critchley and Critchley, $eGFR_{CKD-EPI}$ had acceptable error when compared to mGFR whereas eGFR determined using other equations had error greater than 30%.[16] In our study, GFR estimated by MDRD, CKD-EPI and 24 hour urine creatinine clearance significantly overestimated mGFR. Among all equations, 24 hour urine creatinine had the least accuracy, precision and bias.

Chung et al in his study population of 207 healthy kidney donors found that CG showed minimal bias, while 24 hour urine-CrCl and MDRD equation significantly underestimated GFR determined by DTPA with $eGFR_{CKD-EPI}$ showing the highest precision and limits of agreement.[20] Similarly, Lujan et al observed $eGFR_{CKD-EPI}$ to be the most precise and accurate with minimal bias in his study enrolling 85 kidney donors.[19] Mahajan et al reported CG equation to be the least biased and MDRD equation to be the most accurate but with significant positive bias, overestimating true GFR whereas 24 hour urine creatinine clearance performed most poorly in terms of accuracy, precision and bias.[17]As seen in our study, Rule et al in his study of 274 renal donors observed that $eGFR_{CG}$ had more accuracy, correlation and less bias than $eGFR_{MDRD}$when compared with the iothalamate clearance.[21] Vervoort et al, in his study, reported MDRD to be the most poorly performing of all the prediction equations when MDRD, CG and 24 hour urine-CrCl were compared to inulin clearance.[18] Contrary to our study, Lin et al concluded that MDRD equations were more precise and accurate than CG when compared to DTPA and iothalamate GFR estimation in 100 renal donors.[11]

Most studies have shown $eGFR_{CKDEPI}$ to have greater precision and accuracy compared to those of the MDRD and CG formula, especially for subjects with normal GFR.[6,7,8,22,23] This is because development of CKD-EPI formula included many healthy participants while CG and MDRD formula were developed from the data set of patients with reduced renal function. Significant overestimation of GFR by CKD-EPI in our study may be due to the fact that this equation was developed primarily based on western population data with significantly different anthropometric measurements than that of Asian population.[24,25,26] Similarly, the highest bias with 24 hour creatinine clearance as seen in several studies may be due to errors in collection of urine sample and tubular secretion of creatinine.[10,11]

Different conclusions regarding GFR-estimating equations have shown them to be misleading when it comes to critical decision-making like living kidney donor selection.[19,22]There are several limitations in our study. Inulin clearance which is the gold standard method for measuring GFR was not used.[27] Nevertheless, Tc-99m DTPA clearance has been accepted as the accurate method for the measurement of GFR though it slightly underestimates true GFR.[28,29,30] A large sample sized multicenter study is still needed to validate the GFR-estimating equations in Nepalese population.

Conclusion

Though GFR estimated by CG formula was found to underestimate GFR measured by DTPA with minimal bias, CKD-EPI equation showed the greatest precision and limits of agreement. Therefore, there is no single creatinine-based equation to assess GFR with utmost accuracy and precision at the same time.

Conflict of Interest: None declared

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