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Comparison of CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula based eGFR (estimated glomerular filtration rate) with C-G (Cockcroft-Gaul) and MDRD (Modification of Diet in Renal Disease) formula based eGFR in adult Bangladeshi population

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Abstract

Glomerular filtration rate (GFR) is the most important and accurate measure of overall kidney functions both in good health and disease because it is the sum of the filtration rates in each of the functioning nephrons .Different GFR measuring methods have some limitations.The objective of this study was to compare the CKD-EPI formula based eGFR with that of Cockcroft- Gault formula & 4 variable MDRD formula based eGFR.This Cross-sectional analytical study was done in the Department of Biochemistry & Molecular biology, BSMMU September during the period of July 2017 to August 2018. Serum creatinine was measured and eGFR by MDRD, CKD-EPI and Cockcroft-Gault formula was calculated using the respective equations on online calculator. Comparison of eGFR values between CKD-EPI & MDRD formula and between CKD-EPI & Cockcroft-Gault formula were done among different groups. Comparison was done by Bland Altman agreement test to see the agreement on the measurement of GFR between three equation based eGFR method. Pearson's correlation test revealed a positive correlation between C-G and CKD-EPI (r = 0.779), but a stronger correlation between MDRD and CKD-EPI (r = 0.934). Bland-Altman plot showed strong agreement between CKD-EPI & 4–variable MDRD than between CKD-EPI & C-G formula. From this study we may conclude CKD-EPI and MDRD formula showed better agreement than between CKD-EPI and Cockcroft-Gault formula. So, this study suggests that CKD-EPI and MDRD equations can be used to estimate GFR more effectively than Cockcroft-Gault equation in Bangladeshi population.

Introduction

Chronic kidney disease is defined as either the presence of kidney damage or GFR less than 60 mL/min/1.73 m^2 for three or more months.[1] National Kidney Foundation recommended estimation of GFR is essential for monitoring of chronic kidney disease (CKD) or to detect CKD among those with risk factors.[2]

Serum creatinine alone fails to identify many patients whose kidney function is reduced.[3] Measurements of creatinine clearance is reported with some the errors.[4] Hence, The National Kidney Disease Education Program recommends calculating glomerular filtration rate (GFR) from serum creatinine based predictive equations.[5]

The urinary or plasma clearance of an ideal filtration marker, such as inulin and Technetium-99m DTPA is the gold standard for the measurement of GFR.[6] But they are time consuming, expensive and troublesome than e GFR by prediction equation. The most commonly used equations are Cockroft-Gault equation, four-variable modification of diet in renal disease (MDRD) equation,and the recently described CKD-epidemiology collaboration (CKD-EPI) equation.[7] The CKD-EPI equation is based on the same four variables as the MDRD Study equation, but uses a 2-slope spline to model the relationship between estimated GFR and serum creatinine, and a different relationship for age, sex and race.[8]

The CKD-EPI and MDRD Study equations estimate GFR adjusted forbody surface area. eGFR derived from the CKD-EPI and MDRD Study equations can, therefore, be applied to determine the level of kidney function,

regardless of a patient's size. But bias regarding MDRD and CKD-EPI equations have been reported to overestimate GFR in obese patients.[9] Again, the Cockcroft-Gault equation estimates creatinine clearance and is not adjusted for body surface area, hence it can be used for drug dosage recommendations.[10] But it tends to overestimate renal function at lower levels, particularly when obesity or fluidoverload is present because it includes body weight as variable.[11]

However, these equations have been validated in the Caucasianpopulation and patients with CKD. Several researchers found that the MDRD equation, consistently underestimate GFR, whereas the C-G equations consistently overestimate measured GFR in people with normal renal function. In potential kidney donors, these two prediction equations may not be sufficient for estimating GFR. Previous several studies also recognized that the CKD-EPIequation permits more accurate GFR estimation, fewer false-positive diagnosesof CKD, lower prevalence estimates for CKD, and more accurate risk prediction for adverse outcomes.[12]

Some studies in Bangladesh showing a higher accuracy of eGFR derived from MDRD compared to others.[13] In India a recent study found best predicting equation was CKD-EPI over others. Still, there are very limited data on the performance of the newer CKD-EPI equation in the Asian population, especially in Bangladesh.

The aim of this study was to predict eGFR based on these three serum creatinine based equations and to evaluate CKD-EPI based estimated GFR with respect to Cockcroft-Gault (C-G) and 4-variable MDRD among adult Bangladeshi population attending outpatient department of BSMMU.

Methods

It was a cross sectional analytical study. Adult individuals of both sexes were included and subjects with cancer, chronic disease, pregnancy were excluded. A total of 460 adult individuals with their apparently healthy attendants were selected from Bangabandhu Sheikh Mujib Medical University (BSMMU) outpatient department (OPD) .

All subjects were briefed about the study properly and after taking written consents, their anthropometric measurements and blood pressures (BP) were recorded. Blood samples were collected from each subject with full aseptic precautions. Serum creatinine and eGFR were measured in the Department of Biochemistry and Molecular Biology, BSMMU. eGFR was calculated by MDRD formula in the Department of Biochemistry and Molecular Biology, BSMMU. eGFR by CKD-EPI formula and Cockcroft-Gault formula was calculated by using the respective equations on online calculator. Comparison of eGFR values between CKD-EPI & MDRD formula and between CKD-EPI & Cockcroft-Gault formula were done among different groups.

According to elevated serum creatinine level, 5.0% subjects were categorized as high creatinine group among the total study subjects. Pearson's correlation test revealed a positive correlation between C-G andCKD-EPI , then between MDRD and CKD-EPI. Bland-Altman plot showed strong agreement between CKD-EPI & 4–variable MDRD than between CKD-EPI & C-G formula as limit of agreement was lower in case of MDRD formula within 95% limit.

Results

A total 460 patients of both male and female were enrolled in the study to find out estimsted GFR by CKD-EPI formula , Cockcroft-Gault formula & MDRD formula. Comparison of eGFR values between CKD-EPI & MDRD formula and between CKD-EPI & Cockcroft-Gault formula were done among different groups.Demographic and other factors influencing GFR were also considered in the study procedure and study outcome.

Pearson's Correlation of CKD-EPI formula with MDRD formula and Cockcroft-Gault formula for calculating eGFR among the study subjects (n=460) was done to measure the level of significance (Table-I)

Table-I

Correlation of CKD-EPI formula with MDRD formula and Cockcroft-Gault formula (N=460)

One group variable	Other group variable	r value	p value
CKD-EPI	MDRD	0.934	<0.001
	Cockcroft-Gault	0.779	<0.001

Bland-Altman agreement plot shows better agreement of the MDRD Formula withCKD-EPI equation than Cockcroft–Gault formula for all study subjects as limit of agreement was lower in case of MDRD formula (40.36) than Cockcroft- Gault formula (80.00) within 95% limit (Table - II).

Pearson's correlation was done to measure the level of significance between CKD- EPI, MDRD formula and CKD-EPI, Cockcroft- Gault (C-G) formula in high creatinine group.(Table - III)

Bland-Altman agreement plot shows better agreement of the MDRD Formula than Cockcroft– Gault formula with CKD-EPI equation in high creatinine group as limit of agreement was lower in case of MDRD formula (8.02) than Cockcroft- Gault formula (42.15) within 95% limit (Table - IV).

Pearson's correlation was done to measure the level of significance between CKD- EPI, MDRD formula and CKD-EPI, Cockcroft- Gault (C-G) formula in normal creatinine group whichshows significant positive correlation (Table - V).

Table-II

Bland-Altman agreement plot between CKD-EPI, MDRD formula and CKD-EPI, Cockcroft-Gault formula for calculating eGFR (N=460)

e GFR	Mean difference	Std. Deviation	Upper limit of agreement	Lower limit of agreement	Limits of agreement
CKD-EPI Vs MDRD	0.74	10.09	20.93	-19.44	40.36
CKD-EPI Vs Cockcroft - Gault	-0.38	20.00	39.62	-40.39	80.00

Table-III

Pearson's Correlation of CKD-EPI formula with MDRD formula and Cockcroft-Gault formula (N=460)

One group variable	Other group variable	r value	p value
CKD-EPI	MDRD	0.993	<0.001
	Cockcroft-Gault	0.780	<0.001

Table-IV

Bland-Altman agreement plot between CKD-EPI, MDRD formula and CKD-EPI, Cockcroft-Gault formula for calculating eGFR in high creatinine group.

e GFR	Mean difference	Std. Deviation	Upper limit of agreement	Lower limit of agreement	Limits of agreement
CKD-EPI Vs MDRD	1.26	2.00	5.27	-2.75	8.02
CKD-EPI Vs Cockcroft - Gault	-0.26	10.53	20.81	-21.33	42.15

Table-V

Pearson's Correlation of CKD-EPI formula with MDRD formula and Cockcroft-Gault formula for calculating eGFR in normal creatinine group (n=437)

One group variable	Other group variable	r value	p value
CKD-EPI	MDRD	0.920	<0.001
	Cockcroft-Gault	0.740	<0.001

In normal creatinine group Bland-Altman agreement plot shows better agreement of the MDRD Formulathan Cockcroft– Gault formula with CKD-EPI equation as limit of agreement was lower in case of MDRD formula (41.37) than Cockcroft-Gault formula (81.54) within 95% limit (Table - VI).

Table-VI

Bland-Altman agreement plot between CKD-EPI, MDRD formula and CKD-EPI, Cockcroft-Gault formula for calculating eGFR in normal creatinine group (N=460).

e GFR	Mean difference	Std. Deviation	Upper limit of agreement	Lower limit of agreement	Limits of agreement
CKD-EPI Vs MDRD	0.72	10.34	21.41	-19.97	41.37
CKD-EPI Vs Cockcroft - Gault	-0.39	20.38	40.38	-41.16	81.54

Discussion

The GFR is considered as the best overall index of kidney function. Age related loss of renal function reflects the presence of a variety of different risk factors for CKD.[14] Recently, a study showed an alarmingly high rate of CKD roughly one in five among urban middle- income Bangladeshis.[1]

Serum creatinine is used as a marker of kidney function, though this method may be fraught with errors. In our study, when decreased kidney function was defined as elevated serum creatininelevel ≥1.4 mg/dl for male or ≥1.2 mg/dl for female, the percentage of high creatinine group was 5% among the total study subjects.

However MDRD is used by most of the laboratories for calculating eGFR, but it might underestimate and sometimes overestimates eGFR compared to CKD-EPI derived eGFR. In our study mean±SD of eGFR values by CKD-EPI, 4- variable MDRD & Cockcroft-Gault (C-G) were 100.43±21.96, 99.68±26.85 & 100.82±31.61 respectively. After correlating eGFR from the 3 equations, our study showed a positive correlation between C-G and CKD-EPI (r=0.779), but a stronger correlation between MDRD and CKD-EPI (r=0.934) among the study subjects. The correlation between CKD-EPI and C-G was less strong comparedto MDRD equation. Uche and Osegbe also reported similar findings wherestrong positive correlation was seen between CKD-EPI versus MDRD (r=0.93) with a weaker correlation was observed with CG (r=0.76).[15] In our study we observed that the correlation

was strong in high creatinine group where r=0.99 than normal creatinine group (r=0.92) between CKD-EPI & MDRD formulas. This observation is supported by several researchers.[16,17] However, the CKD-EPI equation was more accurate than MDRD in a subgroup of people with normal kidney function with eGFR between 60-120 mL/min/1.73 m^2.

The Bland-Altman plot is useful to reveal a relationship between the differences and the averages, to look for any systematic bias represented by the limits of agreement (mean difference ± 2 SD of difference) and to identify possible outliers.[18] The narrow limit of agreement indicates strong agreement between methods. In our study Bland-Altman plot showed strong agreement between CKD-EPI & 4–variable MDRD than between CKD-EPI & C-G formula in total (40.36 vs 80.00), high creatinine group (8.02 vs 42.15) and normal creatinine group (41.37 vs 81.54) as limit of agreement was lower in case of MDRD formula within 95% limit. Our study result was in consistent with various previous studies. In Thailand, it was found that agreement between the CKD-EPI and C-G equation was (70.9%) in comparison to CKD-EPI and MDRD it was 93.9%. [19]

Our study result demonstrated that the agreement between CKD-EPI & MDRD equations was better in high creatinine group compared to normal creatinine group as limit of agreement were 8.02 vs 41.37 between them. Lujan et al. reported that the MDRD equation underestimated GFR> 60ml/min/1.73 m^2 in healthy population compared to CKD-EPI and suggested that CKD-EPI to be applied instead of MDRD, in subjects or candidates for kidney donation to avoid wrong GFR underestimates, which might lead to an inappropriate exclusion of candidates.[20] From the study of pooled clinical populations by Levey et al, who developed CKD-EPI equation found that MDRD and CKD-EPI were in good agreement in the CKD patients (eGFR < 60ml/min/1.73 m^2) than the patients with eGFR > 60ml/min/1.73 m^2.

Recently Mulay and Gokhale confirmed better performance of CKD-EPI equation compared to MDRD equation and C-G equation. However in contrast to our study, Kumar and Mohan showed that MDRD formula to be in good approximation at values greater than 60 ml/min/1.73 m^2 than CKD-EPI and Cockcroft- Gault formulas in estimating GFR.[21] Hence they recommended MDRD equation in calculating eGFR, drug dosing, detection of CKD, and estimating prognosis of CKD in clinical field.

The better performance of CKD- EPI equation at normal creatinine group (eGFR >60ml/min/1.73 m^2) were consistent across studies. Therefore, CKD-EPI is a more appropriate equation to use for healthy or stable individuals with normal kidney function.

Due to the absence of a gold standard method of GFR measurement, it was hard to comment which method was more accurate when compared with different equations. Finally this study recommends that CKD-EPI and MDRD equations can be used to estimate GFR more effectively than Cockcroft-Gault equation. CKD-EPI is the best choice for stable patients with normal creatinine.

Conclusion

This study found that agreement was good between CKD-EPI and MDRD formula than between CKD-EPI and Cockcroft-Gault formula. So, this study suggests that CKD-EPI and MDRD equations can be used to estimate GFR more effectively than Cockcroft-Gault equation.

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Ethical Issue

The protocol for this study was approved by the Institutional Review Board of Bangabandhu Sheikh Mujib Medical University.

Conflict of Interest : Authors declare no conflict of interest.

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