Section: General Medicine

Original Research Article

RELIABILITY OF ESTIMATING GLOMERULAR FILTRATION RATE IN CHRONIC KIDNEY DISEASE PATIENTS: A COMPARATIVE ANALYSIS OF 24-HOUR URINE CREATININE CLEARANCE WITH MDRD (MODIFICATION OF DIET IN RENAL DISEASE), COCKCROFT–GAULT, AND CKD-EPI (CHRONIC KIDNEY DISEASE EPIDEMIOLOGY) EQUATIONS

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ABSTRACT

Background: Chronic kidney disease (CKD) is a global public health crisis that has been linked to higher rates of cardiovascular disease, progression to end-stage renal disease, and earlier death. Accurate estimation of the glomerular filtration rate (GFR) is necessary to establish an accurate diagnosis, stage the disease, make therapeutic decisions, and adjust drug dosages in CKD. Even though the standard reference method for measuring GFR, 24-hour creatinine clearance urine (CrCl), is still widely used, the method suffers from collection error and compliance issues. Thus, serum creatinine–based estimating equations (MDRD, Cockcroft-Gault, and CKD-EPI) have emerged, but the reliability of these equations can vary based on population. The purpose of this study was to compare the estimated glomerular filtration rate (GFR) derived from three different formulae (MDRD, Cockcroft-Gault, and CKD-EPI) to actual CrCl measured by 24-hour collection in patients with chronic renal insufficiency (CKD) and to determine which of the formulas exhibited the greatest correlation with measured CrCl results.

Materials and Methods: An observational study was performed over 13 months at one individual tertiary hospital with 150 adults with chronic kidney disease who were diagnosed using the 2012 KDIGO criteria. Patients who had Acute Kidney Injury (AKI), patients on Dialysis for ESRD, pregnant females and patients who did not collect all of their urine were excluded from this study. For this study, various statistical analyses were used, including Pearson correlation, Bland-Altman analysis, and subgroup comparisons based on age, gender, and CKD stages.

Results: The average CrCl amount measured over 24 hours was 26.77 ± 10.76 mL/min. The average GFR amounts calculated using the methods listed below were as follows: 25.93 ± 10.05 mL/min (MDRD), 30.98 ± 12.73 mL/min (Cockcroft-Gault), and 27.64 ± 11.06 mL/min/1.73 m2 (CKD-EPI). CKD-EPI had the lowest bias and narrowest limits of agreement by all three methods compared to the measured CrCl result across all age groups, both genders, and all CKD stage patients. MDRD underestimated the GFR amount in the early stages; whereas, Cockcroft-Gault overestimated the GFR amount in the later stages of CKD.

Conclusion: CKD-EPI had the highest correlation with 24hr creatinine clearances and showed the greatest consistency among different CKD stages and demographic groups; therefore it is the preferred equation for estimating GFR in patients with CKD.

Keywords: Chronic kidney disease, Estimated glomerular filtration rate, Creatinine clearance, MDRD, Cockcroft–Gault, CKD-EPI.

INTRODUCTION

Chronic kidney disease (CKD) is a major global public health problem characterized by a progressive and irreversible decline in kidney function. It is defined by the presence of kidney damage or a persistent reduction in glomerular filtration rate (GFR) to less than 60 mL/min/1.73 m² for at least six months. Accurate estimation of GFR is critical to the diagnosis, staging and follow-up of CKD and is essential for directing treatment decisions, adjusting the doses of renally excreted medications and predicting long-term clinical outcomes.[1,2]

The most accurate approach to assessing GFR is via the direct measurement of a small amount of filtration markers such as inulin, iohexol injection and radionuclide tracers (Chromium-51 ethylenediaminetetraacetic acid). However, the direct measurement approach can be very expensive, complicated, time-consuming and not available to routine clinical practice. This can be especially true in developing countries where resources are limited. Thus 24-hour creatinine clearance (CrCl) has traditionally been accepted as a surrogate measure of GFR.[3] This is because creatinine is normally freely filtered at the glomerulus, and can be quantitatively determined using most standard laboratory assays or methods. Although this method has been widely used, 24-hour urine collection can pose several challenges for patients, including being an inconvenient method to perform, having inconsistent collection, patients not complying with the proper protocol, or the presence of pre-analytical errors. In addition, creatinine is also secreted in the tubules, which may also lead to an overall higher value than what the actual GFR is, particularly in patients with advanced CKD.[4]

There are a variety of serum creatinine-based estimating equations to calculate creatinine clearance, in order to make measuring the actual creatinine clearance easier. As one of the most commonly used and recognized formulae for estimating GFR, The MDRD equation first calculates serum creatinine and adjusts for age, sex, and race. Through the use of the MDRD equation, the clinical determination of GFR has increased, since it excludes the need for timed urine collections, although the MDRD equation continues to underestimate GFR at higher values (>60 mL/min/1.73 m2) and is less reliable in patients with near-normal renal function.[5]

1. MDRD (Modification of Diet in Renal Disease) Equation (4-variable)

$$eGFR = 175 \times (\text{Serum Creatinine})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female})$$

- Serum creatinine in mg/dL
- Age in years
- Result expressed as mL/min/1.73 m²

The Cockcroft: Gault (CG) formula to estimate creatinine clearance was developed in 1976 based on age, sex, weight, and serum creatinine level. The CG formula was generally utilized as part of the guidelines to help with drug dosing in pharmacokinetics; however the CG formula contains several deviations that may cause inaccuracies for patients who have chronic kidney disease or CKD (i.e., variations between body composition, obesity, muscle mass, and malnutrition).[6]

2. Cockcroft–Gault (CG) Formula

$$CrCl = \frac{(140 - Age) \times Weight\ (kg)}{72 \times Serum\ Creatinine}$$

- Multiply by 0.85 if female
- Serum creatinine in mg/dL
- Result expressed as mL/min

If normalized to BSA (1.73 m²):

$$Adjusted\ CrCl = \frac{CrCl \times 1.73}{BSA}$$

The CKD-EPI, introduced in 2009, was created with the intent to allow for more precise estimates of GFR among patients with a wider range of GFR due to its derivation from several large diverse cohorts of populations; because of its design and derivation, the CKD-EPI equation has been shown to be more precise and have less bias than both MDRD & Cockcroft-Gault, especially when GFR was higher. The 2021 revision removed the coefficient for race, making the equation more equitable and universally applicable than previously. Even with the development of advance estimating equations, in many clinical situations where a direct measurement (mGFR) cannot be made the 24-Hour Creatinine Clearance continues to be a reference method. Prior studies comparing the modified MDRD (Modifying of Diet in Renal Disease), Cockcroft-Gault (CG), and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) estimates to the 24-Hour CrCl have had conflicting results. These varying results may be influenced by a variety of factors, including patient age, nutritional status, associated comorbidities, and characteristics unique to the population being tested. The misclassification of CKD stage may have a major impact on the decisions made regarding treatment, therefore underscoring the need for population-specific validation (7–10).

3. CKD-EPI 2021 Creatinine Equation (Race-free)

$$eGFR = 142 \times \min\left(\frac{Scr}{\kappa}, 1\right)^{\alpha} \times \max\left(\frac{Scr}{\kappa}, 1\right)^{-1.200} \times 0.9938^{Age} \times (1.012 \text{ if female})$$

Where:

- Scr = Serum creatinine (mg/dL)
- κ (kappa) = 0.7 (female), 0.9 (male)
- α (alpha) = –0.241 (female), –0.302 (male)
- Age in years
- Result expressed as mL/min/1.73 m²

For many patients with CKD in a tertiary care setting (i.e. Government Omandurar Medical College and Hospital, Chennai) the burden of CKD is high and access to exogenous marker study is limited, making the comparison of the reliability of commonly used eGFR estimating equations against the 24-Hour Creatinine Clearance both feasible and clinically relevant. The aim of this analysis is to identify the

estimating equation that correlates most highly with CrCl to facilitate accurate CKD staging and optimal management of patients.

The objectives of this study were to evaluate the estimated glomerular filtration rate based on the MDRD, Cockcroft-Gault and CKD-EPI formulas against a 24-hour urine creatinine clearance in patients suffering from chronic kidney disease and to determine which of these formulas yields values that are most comparable to measured creatinine clearance.

MATERIALS AND METHODS

Study Design and Setting: This prospective, observational, comparative Research Study was performed at the Department of General Medicine Government Omandurar Medical College and Hospital in Chennai a tertiary care teaching hospital. To assess the reliability of estimated glomerular filtration rate (eGFR) by comparing commonly used estimating equations with 24-hour urine creatinine clearance in patients with chronic kidney disease (CKD).

Study Duration and Participants: Conducted over 13 months (June 2024 - June 2025), patients ≥18 years of age with a CKD diagnosis based on KDIGO 2012 guidelines were included in this study. Patients with Acute Kidney Injury, ESRD requiring dialysis, pregnancy or who were critically ill, and those unable to provide a complete 24-hour urine sample were excluded from the study. Eligible patients were enrolled consecutively into the study after providing written informed consent.

Sample Size: To determine the required number of subjects to find at least a 0.80 correlation coefficient (correlate) between 24 hours of creatinine clearance and eGFR (estimated glomerular filtration rate), based on 90% power and a significance level of (0.05). It was decided that a total of 150 subjects would be recruited, taking into consideration a potential loss to follow up. Data were obtained on 149 subjects for all variables, which were included in the final analysis.

Study Parameters and Procedure: Participants collected urine for 24 hours to determine creatinine clearance in their urine. Their serum creatinine levels were measured during the 24-hour urine collection time. Creatinine clearance was determined using three methods: the MDRD equation, the Cockcroft-Gault formula adjusted by body surface area (BSA) and the CKD-EPI 2021 creatinine equation. Creatinine clearance values were normalized to BSA expressed as milliliters per minute (mL/min) per 1.73 square meters (m^2) of BSA. Measured creatinine clearance was used to stratify patients into the different stages of chronic kidney disease (CKD).

Statistical Analysis: SPSS version 26 analysed the data. A Pearson correlation between creatinine clearance vs eGFR equation results assessed the agreement, as well as Bland-Altman analysis, concordance correlation coefficients, and root mean square errors. Statistical significance was defined as $p < 0.05$ for all analyses.

Ethical Considerations: The study received ethical approval from the Institutional Ethics Committee and conducted according to the Declaration of Helsinki. Patient confidentiality and safety were maintained at all times during the study.

RESULTS

Study Population Characteristics: The study [Table 1] consisted of a total of 150 people who had been diagnosed with chronic kidney disease (CKD). The average age was 55.7 (± 14.6) years; 59.3% were younger than 60 and 40.7% were over 60 years old. The distribution by gender was fairly equal; 49.3% female, 50.7% male. An overwhelming proportion of the sample was Asian (98%). Of the participants, 62.7% reported having developed CKD from either having Diabetes alone or from having Hypertension as well as diabetes. Most study participants were receiving CKD Treatment (90%).

Table 1: Baseline Characteristics of Study Population

Variable	Value
Age (years), mean ± SD	55.7 ± 14.6
Female, n (%)	74 (49.3)
Male, n (%)	76 (50.7)
Asian ethnicity, n (%)	147 (98.0)
Diabetes ± Hypertension, n (%)	94 (62.7)
On CKD treatment, n (%)	135 (90.0)

[Table 2] provides Serum creatinine on average was equal to 2.52 ± 0.70 mg/dL. The average of 24-hour determined creatinine clearance (CrCl) was equal to 26.77 ± 10.76 mL/min and was therefore, the standard reference.

Table 2: Biochemical Parameters and Measured Renal Function

Parameter	Mean ± SD
Serum creatinine (mg/dL	2.52 ± 0.70
Urine creatinine (mg/dL)	110.8 ± 41.0
24-h urine volume (mL)	876 ± 252
24-h CrCl (mL/min)	26.77 ± 10.76

The mean (with standard deviation) estimated GFR for each method of calculation is listed below [Table 3]:
MDRD: 25.93 ± 10.05 mL/min/1.73m²
Cockcroft-Gault: 30.98 ± 12.73 mL/min
CKD-EPI: 26.91 ± 11.06 mL/min/1.73m²
Cockcroft-Gault generally gave higher estimates of GFR than the other two methods, and CKD-EPI had the highest numerical correlation to CrCl measured by the hourly urine collection method.

Table 3: Comparison of eGFR Equations with 24-Hour Creatinine Clearance

Method	Mean ± SD (mL/min)
24-h CrCl	26.77 ± 10.76
MDRD	25.93 ± 10.05
Cockcroft–Gault	30.98 ± 12.73
CKD-EPI	26.91 ± 11.06

[Table 4] shows MDRD and Cockcroft–Gault methods of estimation for creatinine clearance (CrCl) in patients <60 years differ significantly from measured CrCl ($p < 0.0001$), whereas CKD-EPI does not appear to have a significant bias from measured CrCl.

In patients ≥60 Years, CKD-EPI was statistically consistent with measured CrCl ($p = 0.749$), while Cockcroft–Gault showed a significant bias from measured CrCl.

Table 4: Renal Function by Age Category

Method	<60 yrs (Mean ± SD)	p-value	≥60 yrs (Mean ± SD)	p-value
24-h CrCl	28.43 ± 12.06	-	24.36 ± 8.02	-
MDRD	26.74 ± 11.13	<0.0001	24.76 ± 8.18	0.069
Cockcroft–Gault	34.41 ± 14.25	<0.0001	25.98 ± 7.88	0.039
CKD-EPI	28.61 ± 12.42	0.335	24.43 ± 8.19	0.749

[Table 5] evaluating that female's CrCl was lower than males'. The MDRD and Cockcroft-Gault equations demonstrated a statistically significant gender bias while the CKD-EPI showed no statistically significant gender bias with a consistent CrCl for both genders.

Table 5: Renal Function by Gender

Method	Females (Mean ± SD)	p-value	Males (Mean ± SD)	p-value
24-h CrCl	22.38 ± 7.17	-	31.05 ± 11.94	-
MDRD	21.44 ± 6.86	<0.0001	30.31 ± 10.75	0.0068
Cockcroft–Gault	27.63 ± 9.59	<0.0001	34.25 ± 14.51	0.0005
CKD-EPI	22.32 ± 7.45	0.784	31.38 ± 12.17	0.133

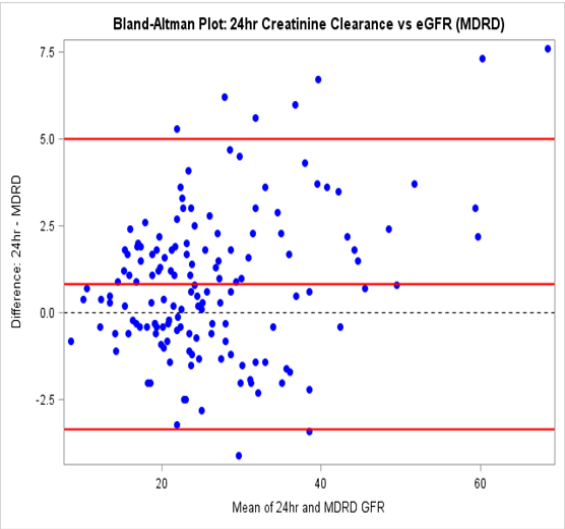

Figure 1: The Bland–Altman plot comparing 24-hour creatinine clearance with MDRD eGFR

The Bland-Altman plot shows how well measured 24-hour creatinine clearance and the GFR estimated by the MDRD correlation are in agreement showed in [Figure 1]. The thick red line in the middle of the plot is the mean difference (bias) between the two methods. The thin red lines above and below the midpoint line are the 95% limits of agreement. The spread of the individual data points around the bias line indicates only moderate agreement, particularly at higher mean GFR values, which demonstrate considerable variability (decreased precision) of the MDRD equation compared to measured creatinine clearance.
[Figure 2] demonstrates how well measured 24-hour creatinine clearance corresponds with estimated GFR (Cockcroft-Gault), using a Bland-Altman plot as a visual representation of agreement. If a measurement were perfect, all points would fall on the middle red line, with corresponding limits of agreement set by the outer red lines (95%) and all point spread equally about the mean. The significant degree of deviation, especially in the ranges above the mean for GFR, indicates that the Cockcroft-Gault equation has a larger degree of systematic error and lower precision than does the measured value using creatinine clearance.

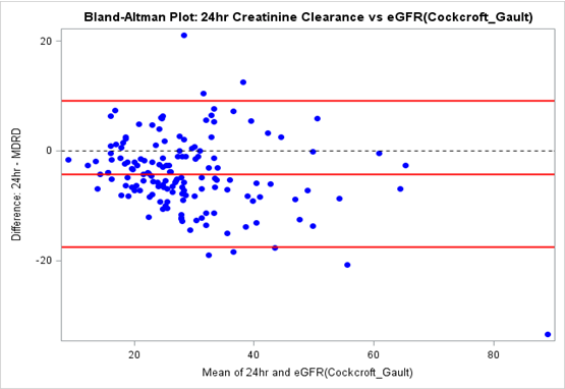

Figure 2: The Bland–Altman plot comparing 24-hour creatinine clearance with Cockcroft–Gault eGFR

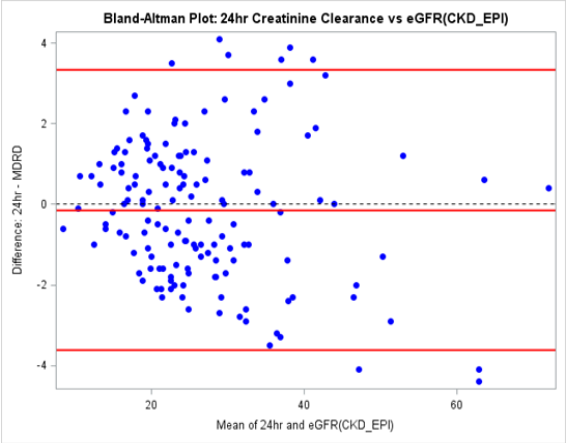

Figure 3: The Bland–Altman plot comparing 24-hour creatinine clearance with CKD-EPI eGFR

According to Bland–Altman plotting shown in [Figure 3], 24-hr creatinine clearance had a significant correlation with CKD-EPI estimated GFR. The mean difference (central red line) represents the bias, while the upper and lower bounding red lines suggests that CKD-EPI provides a more closely correlated estimate of GFR than measured creatinine clearance because more of the (zero-difference) points are clustered closer together and the limits of agreement are smaller in distance from the mean difference compared to those of creatinine clearance.

In patients with chronic kidney disease (CKD), [Table 6] gives both the MDRD and Cockcroft-Gault equations have been shown to underestimate the glomerular filtration rate (GFR) in stages 2 through 4 and overestimate the GFR in advanced stages (4 through 5) respectively. In contrast, CKD-EPI closely tracked measured creatinine clearance (CrCl) across all CKD stages without significant bias beyond Stage 2.

Table 6. Renal Function by CKD Stage (Mean ± SD)

Stage of CKD	Stage 2			Stage 3a			Stage 3b			Stage 4			Stage 5		
	Mean	Std Dev	p-value	Mean	Std Dev	p-value	Mean	Std Dev	p-value	Mean	Std Dev	p-value	Mean	Std Dev	p-value
24hr Creatinine Clearance	64.4	5.41		48.22	3.38		35.76	4.37		22.32	3.8		12.4	2.02	
eGFR MDRD	59.38	3.57	0.0378	46.4	2.75	0.0106	34.25	4.45	0.0055	21.85	4.08	0.0066	12.37	1.99	0.8941
eGFR Cockcroft Gault	75.3	20.48	0.2497	52.97	8.13	0.282	37.79	8.8	0.19	26.91	6.56	<.0001	17.1	3.9	0.0002
eGFR CKD EPI	66.28	3.77	0.2655	50.12	2.25	0.0481	35.41	4.16	0.4179	22.46	4.25	0.3422	12.41	2.02	0.9643

DISCUSSION

Accurate measurement of glomerular filtration rate (GFR) is one of the most important steps in diagnosing, staging, and treating chronic kidney disease (CKD). The traditional method for measuring GFR is a 24-hour urine creatinine collection (CrCl); however, many errors can occur in producing this number because of collection errors, non-compliance by the patient, and physiologic interference from other variables like renal tubular secretion of creatinine. Because of these considerations, it is common practice to use a serum creatinine–based estimate of GFR when making routine clinical assessments. This study has compared GFR estimates with 24-hour measured CrCl calculated with the MDRD, Cockcroft-Gault, and CKD-EPI equations in a mostly Asian CKD population and has shown that the CKD-EPI equation differs the least by way of bias to measured 24-hour CrCl among CKD patients of all ages and genders at all CKD stages.[6,11,12]

All of them mixed-in together, the Chronic kidney disease epidemiology collaboration (CKD-EPI) method (GFR) exhibited the highest total perfusion error (+0.14 mL/min) and displayed the greatest consistency in limits of agreement compared to both the Modification of diet in renal disease (MDRD) and Cockcroft 2.0 methods; this is consistent with previous validation studies that demonstrated chronic kidney disease epidemiology collaboration provide equal accuracy and reproducibility when estimating GFR across the full range of GFRs studied. The results of the study suggest that the estimations of GFR from CKD-EPI were superior to those from MDRD, particularly at high GFR (> 60 mL/min); this

leads to improved risk stratification for people with stage 2-4 chronic kidney disease. Likewise, Inker et al. documented multiple studies where CKD-EPI outperformed MDRD in all positive clinical assessments in groups of 1 or more "normal" or diseased persons measured for their GFR at multiple clinical facilities.[13]

The current study demonstrated that there is significant bias in estimating patient's GFR using the MDRD and Cockcroft-Gault equations for patients aged <60 years of age vs measured CrCl while the CKD-EPI formula has shown consistent results with both younger and older cohorts. This has been demonstrated in other studies (Hapsari and Anniwati on the accuracy of CKD-EPI and the MDRD for CKD patients in Asian populations) where the MDRD estimated GFR for patients aged <60 was significantly overestimated when compared to CrCl while the CKD-EPI formula had a more stable/consistent accuracy regardless of the age of the patient. The impact of advancing age on muscle mass and therefore creatinine generation in this older cohort also may be responsible for the inaccuracy of both the MDRD and Cockcroft-Gault equations and favors the use of the CKD-EPI equation.[14,15]

The gender analysis indicated that both the MDRD and the Cockcroft-Gault methods both had significant bias against females, meaning that their kidney function estimate was much lower than it should be. On the other hand, The CKD-EPI equation did not show significant bias based on sex. Results in these studies are similar to what is reported in the literature by both Bonjoch et al. and Vega et al., who indicated that there was better sex neutrality with the use of the CKD-EPI equation compared to the MDRD and Cockcroft-Gault equations. Because of the importance of accurate classification for women, particularly with respect to dosing and staging of CKD, the use of CKD-EPI may allow for more equitable and accurate treatment.[16,17]

Cockcroft–Gault has commonly overpredicted GFRs during advanced CKD whereas in the earlier stages, GFRs were predicted to be underestimated by the MDRD equation and represented their generally known limitations in calibrating GFRs accurately. In contrast, GFRs obtained by the CKD-EPI method were shown to have a high degree of agreement with CrCl as measured throughout all stages (i.e., II, III, IV and V). Many similar findings have been previously published (Ali et al. 2010, El-Minshawy and Ali 2011) where CKD-EPI consistently provided a better agreement with both measured clearance and isotopic GFR methods. The consistency noted with the CKD-EPI method in late-stage CKD patients is particularly applicable in tertiary care centres where a vast majority will be receiving treatment for late-stage CKD.[18,19]

The current cohort displays a high prevalence of diabetic nephropathy, which reflects current epidemiological trends seen globally. In addition, our results indicate that CKD-EPI displayed little bias compared with diabetic CKD, which is consistent with previous findings showing that both MDRD and Cockcroft-Gault are more likely to have their results impacted by variability in metabolic and anthropometrics. With the increasing prevalence of diabetes-related CKD throughout the world, the use of CKD-EPI will have important implications for more accurate staging and making therapy decisions.[3,20]

CONCLUSION

This study provides compelling evidence that CKD-EPI is the most accurate creatinine-based equation for estimating Glomerular filtration rate among patients with CKD when compared to MDRD and Cockcroft-Gault by demographic subgroups and stages of disease respectively. In addition to supporting guideline recommendations to use the CKD-EPI for routine reporting of estimated GFR, these findings also indicate that CKD-EPI is appropriate to use in the care of Asian CKD patient populations by reducing the need for burdensome 24-hour urine collection and achieving clinically validated levels of accuracies.

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