

Assessment of accuracy of Cockcroft-Gault and MDRD formulae in critically ill Indian patients

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Abstract

Background: Cockcroft-Gault (CG) and Modification of Diet in Renal Disease (MDRD) formulae have not been validated in critically ill Indian patients. We sought to quantify the discrepancy, if any, in Glomerular Filtration Rate (GFR) estimated by CG and MDRD formulae with 24 hrs urine Creatinine Clearance (Cr Cl). **Materials and Methods:** Prospective cohort study in 50 adult patients in a mixed medical-surgical intensive care unit. Inclusion criteria: Intensive Therapy Unit (ITU) stay >48 hrs and indwelling urinary catheter. Exclusion criteria: Age <18 years, pregnancy, dialysis, urine output <400 ml/day and patients receiving ranitidine, cefoxitin, trimethoprim or diuretics. We estimated Creatinine Clearance by CG and MDRD formula and measured GFR by 24 hrs urine creatinine clearance. Bland Altman plot was used to find the difference between the paired observations. The association between the methods was measured by the product moment correlation coefficient. **Result:** The mean GFR as calculated by Creatinine Clearance was 79.76 ml/min/1.73 m² [95% Confidence Interval (CI) 65.79 to 93.72], that by CG formula was 90.05 ml/min/1.73 m² [95% CI: 74.50 to 105.60], by MDRD was 85.92 ml/min/1.73 m² [95% CI: 71.25 to 100.59]. The Bias and Precision between CG and Cr Cl were -4.5 and 140.24 respectively, between MDRD and Cr Cl was -6.1 and 122.52. The Correlation coefficient of CG formula as a measure of GFR was 0.65 ($P < 0.0001$), that of MDRD was 0.70 ($P < 0.0001$). **Conclusion:** We conclude that CG and MDRD formulae have a strong correlation with measured GFR but are not a reliable measure and overestimate GFR in critically ill Indian patients.

Key words: Cockcroft gault formula, glomerular filtration rate, modification of diet in renal disease, one hour urine creatinine clearance

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Introduction

Knowledge of the Glomerular Filtration Rate (GFR) is of vital importance, for adjusting doses of drugs and in planning the overall management of critically ill patients. GFR is most accurately measured by clearance of exogenous substances such as inulin, iothalamate or iohexol and radiolabelled isotopes: Technetium-^{99m} diethyl triamine penta- acetic acid (Tc^{99m} DTPA) or chromium 51 Ethylenediaminetetraacetic acid (EDTA) (Cr⁵¹ EDTA).^[1] These facilities are not available generally, in the intensive care unit. The serum

creatinine concentration is therefore commonly used as a surrogate marker of renal function, in this setting. Dose adjustments of drugs are often based on this, but the practice is often erroneous, as serum creatinine concentration is dependent on variables, some of them not related to the GFR. Independent variables like age, sex, race, muscle mass, drugs, diet, and creatinine secretion by the renal tubules may affect creatinine concentrations.^[2,3] Measurement of creatinine clearance by 24 hrs urine collection avoids some of these pitfalls, by annulling the variations due to muscle mass and concomitant creatinine generation, but it provides an overestimate of GFR because creatinine is filtered as well as secreted in the glomerulus. The time required in collection and analysis and the problems in ensuring complete urine collection makes this method of GFR estimation cumbersome and unreliable.

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Numerous equations have been developed to estimate GFR using serum bio- chemical parameters (usually serum creatinine concentration) along with demographic data. The CG formula and MDRD formulae are most commonly used for this purpose in adults to adjust dosages of drugs according to severity of renal impairment.^[1,2,4,5] There is a dearth of literature validating these formulae in critically ill patients. There are a number of issues unique to this group of patients, including sudden hemodynamic fluctuations, rapid deterioration of renal function, myriad medications and degrees of protein catabolic states resulting in varying loss of muscle mass. These factors may independently influence the accuracy of the formulae in this sub- group of patients. Extrapolation of data accumulated from stable patients, or indoor patients with normal serum creatinine may not be accurate in predicting renal function in the critically ill patients.^[1] The value and usefulness of these formulae in clinical practice would be dependent on the precision and bias of the calculated value in these patients.

This is a study to evaluate the precision, bias and correlation coefficient of these formulae in a critically ill patient population, across a range of renal function.

Some studies have suggested that creatinine clearance calculated on basis of short term urine collection may be equivalent to that done by 24 hrs urine collection.^[6-8] We compared creatinine clearance calculated on the basis of 1 hr urine collection with that of 24 hrs urine collection. We also tried to quantify the discrepancy in GFR, if any, as measured by 24 hrs urine collection as compared to 1 hour urine collection.

Materials and Methods

A prospective cohort study was conducted in 50 adult patients in a mixed medical-surgical intensive care unit in a tertiary referral center. Inclusion criteria were: ITU stay > 48 hrs and <1 week and indwelling urinary catheter. Exclusion criteria were age less than 18 years, pregnancy, hemodialysis or peritoneal dialysis, hemodynamically unstable patients or those on vasoactive drugs like dobutamine, dopamine or noradrenaline, urine output < 400 ml/day and patients receiving cimetidine, ranitidine, cefoxitin, trimethoprim or diuretics. Urine was collected for 24 hrs of which the last hour urine was analyzed separately. Serum creatinine was measured during the last hour of urine collection. Cr Cl was calculated from urine creatinine as measured in 24 hrs and the 1 hr urine sample. The 24 hrs urine creatinine clearance was calculated by the formula: Urine creatinine conc X days volume X1.73/Plasma creatinine

conc X 1440 X Body surface area. The 1 hr urine creatinine clearance was calculated by: Urine creatinine conc × 1 hr volume × 1.73/Plasma creatinine clearance X 60 X BSA. We estimated Creatinine Clearance by CG and MDRD formula and from 24 hrs and 1 hr urine collections. As the CG formula allows calculation as per lean body weight, it was estimated from equations based on the measured height. The body surface area was also calculated from the measured height and lean body weight. The MDRD equation calculates the GFR corrected for body surface area (ml/min per 1.73 m²). To allow comparison, the Cockcroft-Gault (CG) equation and measured Cr Cl were also normalized to 1.73 m². All the biochemical parameters were measured by an auto analyzer- Dade Dimension RXL. S. creatinine was measured by modified Jaffe reaction, albumin by Bromocresol purple and urea was measured by urease. All the calculations were done on Medcalc 3000 complete edition software.

Statistical analysis

Bland-Altman analysis was used to evaluate the relationship between the Creatinine clearance and the values calculated using the two formulae by determining the mean bias and the precision between the different figures.^[9] Bias was assessed as the mean percentage error (MPE) calculated as the mean percentage difference between the estimated clearances and the measured creatinine clearance. The precision was assessed by the mean absolute percentage error (MAPE) so that the results could be directly compared with those of other recent studies.^[7,10] The association between the methods was measured by the product moment correlation coefficient.

The procedure mentioned above was also followed for comparison between 1 hr and 24 hrs creatinine clearances. Statistics were performed with the help of Statistical software packages Medcalc[®] (version 8.1) from MedCalc[®] Belgium.

Results

Basic characteristics

A convenience sample of 50 patients (26 male and 24 female) average age 63 (95% CI 58 to 68 years) and Simplified Acute Physiology Score (SAPS) score 33 (95% CI 30-37). The study was performed on an average on 2.88th day of ITU stay. Mean serum creatinine 1.06 mg/dl (95% CI 0.76 to 1.37). Mean lean body weight was 59.01 ± 09.61 kg. Mean Body surface area was 1.62 + 0.19 m² The 24 hrs urine obtained on the day of study was comparable to the urine volume obtained by extrapolation of the final 1 hr urine volume to a 24 hrs urine volume [Table 1]. 24 patients (48%) were on mechanical ventilation.

Table 1: Epidemiological data

Demographic data	Mean	SD	95% CI
Age (yrs)	63	17.32	58 – 68
Gender ratio	13:12		
Lean body weight (Kg)	59.01	09.61	(56.28—61.74)
BSA m ²	1.62	0.19	(1.57—1.68)
SAP score	33	12	30-37
Length of stay in ITU before study (days).	2.88	1.1	2.57 – 3.19
Renal data.			
Serum creatinine.(mg/dl)	1.06	1.07	.76 – 1.37
BUN (mg/dl)	22.46	17.65	17.44 – 27.47
S.albumin (mg/dl)	2.29	0.66	2.10 – 2.48
1 hr urine volume (ml)	94.38	63.97	76.20 – 112.56
24 hr urine volume (ml)	1924.44	1063.01	1622.33 – 2226.55
Urine creatinine conc 1 hr. (mg/dl)	51.91	34.67	42.05 – 61.76
Urine creatinine conc 24 hr. (mg/dl)	50.61		
No of patients on mechanical ventilation	24 (48%)		

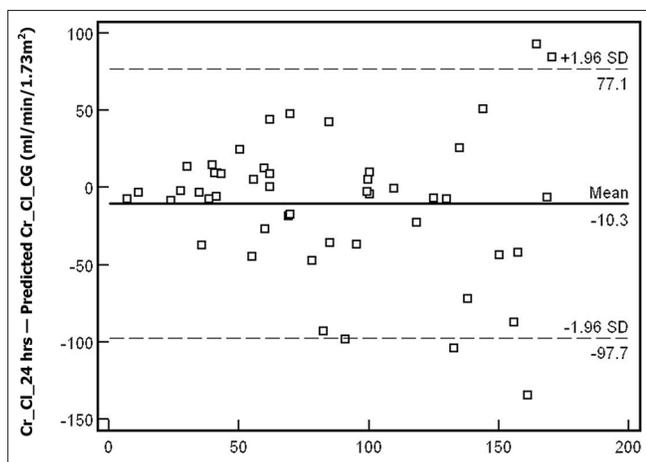


Figure 1: Bland and Altman plot of 24 hrs Cr Cl and predicted Cr Cl by CG (Differences)

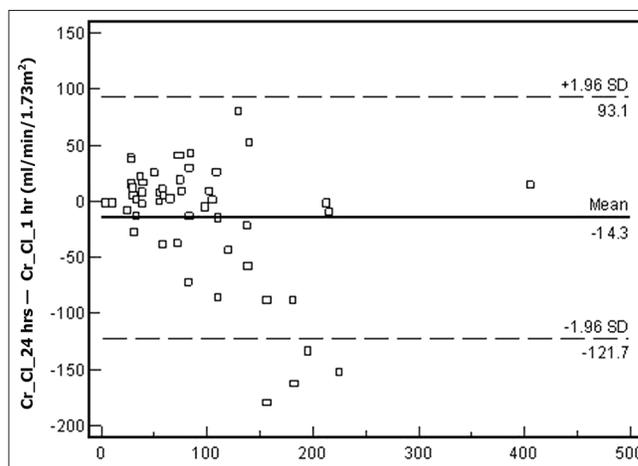


Figure 2: Bland and Altman plot of 24 hrs Cr Cl and Cr Cl 1 hour (Difference)

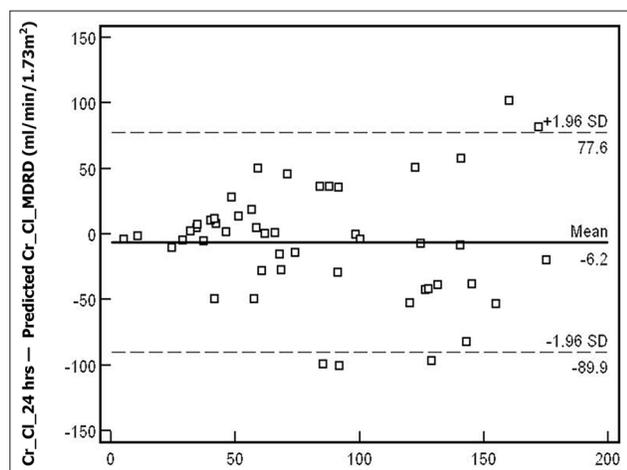


Figure 3: Bland and Altman plot of 24 hrs Cr Cl and predicted Cr Cl by MDRD (Differences)

The median GFR estimated by CG formula was 78.19 ml/min (95% CI: 74.50 to 105.60), by MDRD was 74.40 ml/min (95% CI: 71.25 to 100.59) by 24 hrs urine

Creatinine clearance 66.38 ml/min (95% CI: 65.79 to 93.72) and that by 1 hr urine creatinine clearance was 94.56 ml/min.

The mean GFR as calculated by 24 hrs urine was 79.76 ml/min/1.73 m² (95% CI 65.79 to 93.72) and that by 1 hr urine was 94.56 ml/min/1.73 m² (95% CI 72.4 to 116.72). The mean GFR estimated by CG formula was 90.05 ml/min/1.73 m² (95%CI: 74.50 to 105.60), by MDRD was 85.92 ml/min/1.73 m² (95% CI: 71.25 to 100.59).

The percentages of patients whose estimated GFR lay within 25% confidence interval of measured GFR by CG were 42% and that by MDRD were 40%.

The bias and precision between 24 hrs urine Creatinine clearance and 1 hr urine Creatinine clearance is -14.30 and 107 [Figure 1]. The Bias and Precision between CG and 24 hrs urine Creatinine Clearance were -10.3

Table 2 : Bias, precision and correlation coefficient of CG, MDRD and 1 hour vs 24 hour urine creatinine clearance

	Bias	Precision	Correlation coefficient
Cr CL (24 hr /1 hr)	-14.3	107	0.78 ($P < 0.0001$)
CG/24 hr Urine Cr CL	-10.3	87.4	0.6278 ($P < 0.0001$)
MDRD / 24hr Urine CrCL	-5.2	83.7	0.6335 ($P < 0.0001$)

and 87.4 respectively while that between MDRD and 24 hrs urine Cr Cl was -6.2 and 83.70 [Figures 2 and 3] [Table 2]. The Correlation coefficient of 1 hr urine Creatinine clearance as a measure of 24 hour urine creatinine clearance was 0.78 ($P < 0.0001$). The Correlation coefficient of CG formula as a measure of GFR was 0.6278 ($P < 0.0001$) and that of MDRD was 0.6335 ($P < 0.0001$).

Discussion

There are many clinical scenarios in the ITU, where an assessment of renal function is important for planning patient management, as in patients with declining renal function, in those with altered muscle mass, when taking a decision regarding renal replacement therapy, and when administering drugs predominantly eliminated by the kidneys.^[10,11] To avoid drug related toxicity, doses of all drugs eliminated by the renal route need to be adjusted regularly in accordance with the degree of loss of renal function. This assumes particular importance in the intensive care unit where patients are often on multiple drugs with their interactions and different metabolic pathways.

For widespread clinical application, the tool for assessment of renal function needs to be accurate, convenient and inexpensive. An accurate, non-invasive formula-based method that does not require multiple blood samples or tedious urine collection would be ideal. The CG and MDRD formulae are used routinely in practice, but their accuracy has not been validated in critically ill patients.^[4,12,13]

The CG equation was derived from a cohort of 249 stable white men from serum creatinine, age, weight, and sex to estimate creatinine clearance (*not actual GFR*). All of these were inpatients in a veterans' hospital creatinine clearance varying from $30-130$ ml/m, It was not adjusted for body surface area. Although no females were included in the cohort, the CG method assumed a reduction in GFR of 15% for this population, which is based on expert opinion. The MDRD formula was derived from a stable cohort of 1628 outpatients with a mean age of 50 years and mean GFR of 39.8 ml/m.^[13,14] Other studies have evaluated the formulae in critically ill patients, but in patients with normal serum creatinine.^[1,8] All these scenarios and the patient population are far removed from critically ill patients in an intensive therapy unit in a developing country.

Serum creatinine is the result of generation, distribution and excretion of creatinine. A lower generation will therefore result in a lower serum concentration for the same GFR, if distribution and excretion remain the same. Major source of serum creatinine is the release from endogenous muscles and exogenous nutritional intake of protein. As exogenous intake of protein is often inadequate and the patient is in negative nitrogen balance, the muscle mass in critically ill patients may be reduced, leading to a decreased production of creatinine. This may be one of the reasons of overestimation of creatinine clearance if one relies on serum creatinine concentration only. Moreover, secretion of creatinine varies substantially both in the same individual over time and between individuals. In addition, serum creatinine and GFR are not linearly but hyperbolically related. In critically ill patients, who are in a non-steady state it has been shown, that changes of GFR are poorly reflected by daily changes in serum creatinine concentrations in the presence of acute renal failure.^[1] A 24 hrs creatinine clearance is therefore normally used as a marker of renal function.

This study may be criticized on the grounds that we have not compared the estimated creatinine clearance against the gold standard of GFR calculation, such as Inulin or Iohexol clearance. In developing countries, creatinine clearance calculated on basis of 24 hr urine collection is still used as the gold standard. As recently as 2005 Vila *et al.*, have termed creatinine clearance as the 'gold standard' for clinically monitoring renal functions.^[15] A lot of interest has been generated recently by cystatin C levels for monitoring of renal functions.^[16-19] But even that may not be applicable to critically ill patients as most patients with critical illness have low tri-iodothyronine values.^[20]

Inulin clearance and radioisotope studies are rarely available and this study was conducted in the usual setting. In our study we found that both CG and MDRD formulae overestimated the creatinine clearance significantly though both had a good correlation between them.

The critically ill patient population has a dynamic milieu, where the hemodynamic status and renal function change rapidly. It is not practical to wait for

24 hrs, for a creatinine clearance report on the basis of which drug dosing is adjusted. During this period the renal function may change. We therefore tried to evaluate a 1 hr urine creatinine clearance against the 24 hrs urine creatinine clearance. Our results showed that there was a good correlation between them. There is significant difference between them however, when bias and precision were analyzed. This is in concordance with other studies in the critically ill population.^[6] This is because renal perfusion may be affected by factors other than blood pressure that may change rapidly over a few hours.

The fundamental question regarding the use of these formulae in the ITU is "What degree of bias is acceptable in clinical practice?" It is difficult to answer this question and provide guidelines, as it is dependent on a particular clinical situation and the relevant treatment objective. It may not be clinically significant, say for adjusting drug dosage, in patients with normal or mild renal impairment, where mild overestimation may be acceptable. However, in patients with moderate to severe renal impairment the creatinine clearance may be significantly overestimated leading to a higher drug dosage and toxicity.

We recommend that for initial assessment creatinine clearance should be measured, but estimation by formulae can be used for subsequent follow up.

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