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Automated Reporting of Estimated Glomerular Filtration Rate: A Comparison of Creatinine Clearance, Modification of Diet in Renal Disease and Cockcroft Gault Equations from Pakistan

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Research Article

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ABSTRACT

Objectives: To facilitate early detection of chronic kidney disease, many organizations now recommend reflex reporting of estimated glomerular filtration rate (eGFR) whenever serum creatinine (Cr) is measured. To compare two widespread eGFR equations with creatinine clearance (CrCl) calculated through a timed urine collection.
Methodology: Laboratory data of subjects' ≥ 18 years tested for CrCl from October 2010 to December 2010 was retrieved from laboratory information system of Aga Khan University Hospital. Statistical comparison of eGFR using Cockcroft Gault (CG) and 4-variable Modification of Diet in Renal Disease (MDRD) formulae with CrCl was performed.
Results: Six hundred and seventy subjects with CrCl were studied. Mean age of the group was 51 ±15 years, 55.7 % being males. Mean glomerular filtration rate using CrCl, MDRD and CG were 57.1 (±35.9), 57.8 (±33.6) and 68.7 (±41.5) ml/min respectively. Deming regression analysis generated MDRD = 5.23 + 0.92 (CrCl) and CG = 0.23 + 1.2 (CrCl) for comparison of CrCl results with those of MDRD and CG respectively. Comparing MDRD and CrCl, Bland Altman revealed acceptable agreement with a minimal bias of 0.65 ml/min.

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Conclusion: We suggest that automatic reporting of eGFR using MDRD can be implemented in clinical laboratories when serum Cr is reported.

Keywords: Kidney; creatinine; glomerular filtration rate; laboratories;

ABBREVIATIONS

Estimated glomerular filtration rate (eGFR); creatinine (Cr); creatinine clearance (CrCl);Cockcroft Gault (CG); Modification of Diet in Renal Disease (MDRD); chronic kidney disease (CKD); glomerular filtration rate (GFR); College of American Pathologists (CAP); body surface area (BSA); Statistical Package of Social Sciences (SPSS); body mass index (BMI); National Kidney Disease Education Program (NKDEP)

1. INTRODUCTION

The growing prevalence of chronic kidney disease (CKD) has implications on health and economic output. Literature from United States, Australia and China reports the prevalence of CKD from 11 -13% (Coresh et al., 2003; Chadban et al., 2003; Zuo et al., 2005). Prevalence of CKD in apparently healthy adult Indians and Iranians was also reported between 12 to15 percent (Varma et al., 2010; Safarinejad, 2009). Literature for the migrant populations of South Asian origin shows a higher risk for CKD than the native whites (Hall and Hsu, 2006; Fischbacher et al., 2003). However exact prevalence of CKD in Pakistan is not known but the burden of risk factors of CKD like diabetes and hypertension is high in this part of the world (Hamid et al., 1995; Hameed et al., 1995). In a population-based cross-sectional study in Karachi on 262 individuals above 40 years, 29.9 % had reduced glomerular filtration rate (GFR) (Jafar et al., 2005).

The best means to assess kidney function is by GFR. Determination of GFR, with “inulin” is technically demanding; therefore, GFR is measured in medical practice by estimating creatinine clearance (CrCl). The two major limitations affecting the accuracy of CrCl include an inaccurately collected urine specimen and Cr secretion by renal tubules. As collection of urine is a hassle in clinical practice, health care providers commonly rely on serum creatinine (Cr) alone as a measure of GFR. However, rise in Cr levels occur when 50-70% of nephrons are destroyed and the differentiation of normal from abnormal kidney function is often inadequate as it can miss 20 to 25% of those with CKD (Levey et al., 2006).

In recent years, automatic calculation of estimated GFR (eGFR) using empirical mathematical formulae has been recommended along with Cr result on laboratory reports as a simple, rapid and reliable means of assessing kidney function and (Mathew, 2005; K/DOQI Guidelines, 2002; Akbari et al., 2004; Lin et al., 2003; Warren et al., 2007). Currently the trend to incorporate eGFR with serum Cr is on rise as is evident from College of American Pathologists (CAP) Surveys, which shows an increases of 74% in 2009 in participating labs from North America from 20% in 2005 (Levey et al., 2006; Miller, 2009). This initiative helps to identify and treat CKD at earlier stage thus preventing or delay kidney failure with improve patient outcomes.

Among the 47 different prediction equations; the two most commonly use equations are the Cockcroft–Gault (CG) and the four-variable Modification of Diet in Renal Disease (MDRD). However, both have not been validated in South Asian population who has a smaller physique compared to Caucasians. The aim of this study is to evaluate the performance of the 4-variable MDRD and CG equations for eGFR for reflex reporting with every serum Cr being ordered in the clinical laboratory at Aga Khan University.

2. MATERIALS AND METHODS

2.1 Samples

An analysis of laboratory data of subjects ordering CrCl was performed at the Section of Chemical Pathology, Department of Pathology and Microbiology, Aga Khan University (AKU), Karachi. AKU is a tertiary care, private hospital situated in Karachi. The AKU clinical laboratory caters samples from all over Pakistan through its one hundred and ninety four phlebotomy centers. Samples from all over the country are transported in ice and analyzed at the main hub in Karachi. The study population hence was reflective of geographical distribution of Pakistan.

Subjects more than 18 years of age, tested for CrCl from 1st October 2010 to 31st December 2010 were included. Subjects with CrCl not adjusted for body surface area (BSA) were excluded.

2.2 Collection of Urine Specimen

Printed patient instructions for 24 hour urine collection were provided to the subjects at every phlebotomy center along with sterile leak resistant urine collection containers with tightly fitted lid. Patient instructions were according to the universal recommendations for 24 hour urine collection.

2.3 Method for Cr Measurement

Serum samples for Cr estimation were collected when the patient delivered the 24 hour urine sample to phlebotomy center or main laboratory. At the same time, weight and height of the subjects was noted (for calculation of BSA) by phlebotomist. Normal reference range for males and females was taken as 0.8 -1.3 mg/dl and 0.6 -1.2 mg/dl, respectively.

Serum and urine Cr were assayed with the rate-Jaffe reaction on Synchron analyzer (Beckman Coulter Analyzer). This assay was calibrated daily by two point calibration using calibrators provided by the manufacturer (Beckman Diagnostics Corp.) For the calibration of urine specimens, urine Calibrator was used daily. The system was monitored by routine internal quality control procedures and biweekly participation in external quality control system (External quality assurance services program for clinical chemistry; EQAS by Bio-Rad). The coefficient of variation of Cr assay used were <5% that is within the accuracy criterion (<15%). CrCl was computed from serum and urine Cr and expressed per 1.73 m2 of BSA.

2.4 GFR Estimation

Estimation of GFR was done using the MDRD and CG formulae (Table 1). The 4 variable MDRD which requires serum Cr. age, gender and ethnicity was used but the ethnicity factor which is for Black Americans was not applied.

Table 1. Equations for estimating glomerular filtration rate in adults

Method of GFR calculation	Equations
CrCl (ml/min/1.73m^2)	urinary Cr x volume x 1.73/ serum Cr x1440 x BSA
MDRD (mL/min/ 1.73 m^2)	175 x Cr (exp[-1.154]) x Age (exp[-0.203]) x (0.742 if female)
CG (mL/min)	(140 - age) x weight / serum Cr [mg/dL] x 72 x (0.85 for females)

GFR= glomerular filtration rate; CrCl= creatinine clearance; Cr= creatinine; BSA= body surface area; MDRD= modification of diet in renal disease; exp= exponential; CG= Cockcroft Gault. Serum Cr in mg/dL, weight in kg, height in meters, age in years, and BSA in meter square.

2.5 Statistical Analysis

Statistical Package of Social Sciences (SPSS) version 19 and Analyze-it for Microsoft Excel was used for statistical analysis of the data. Two-tailed p values < 0.05 were considered significant and <0.01 as highly significant. Mean ± SD for quantitative variables was computed. Comparison was done by applying paired t test between CrCl and the two formulae. Regression analysis taking measurement errors for both methods into account was done using Deming procedure. Deming regression was used to obtain slopes adjusted for measurement error and regression to the mean. The Pearson's correlation coefficient was used to compare the overall precision of GFR by CrCl and the 2 formulae. Agreement between the two methodologies was assessed using graphical plot as described by Bland and Altman.

The data was stratified into the 5 stages of CKD in the following manner: Stage I, GFR >90 ml/min; Stage II, GFR 60-90 ml/min; Stage III, GFR 30-59 ml/min; Stage IV, GFR 15-29 ml/min; Stage V GFR <15 ml/min (17).

As CKD is defined as a GFR level of <60 ml/min per 1.73 m2 which represents loss of half or more of the adult level of normal kidney function, performance of equations was also compared by using a cutoff value for CrCl <60 ml/min/1.73m2 (cutoff value for defining CKD). Sensitivity, specificity, positive predictive and negative predictive values were calculated for CrCl, MDRD and CG.

Data was stratified into three groups based on age in years. Comparison of mean and SD for GFR equations was done between the three groups. Agreement of eGFR with CrCl in older age group was done.

3. RESULTS

Nine hundred and eighty five subjects ordered CrCl in the three month period (from 1st October 2010 to 31st December 2010). After excluding those without weight and height measurement; 670 cases were included in final data analysis. Mean age of the group was 51 ± 15 years (Range= 18-55 years).

Majority of the subjects were male (55.7%). Mean age of males and females were 51.5(±16.1) and 51.1 (±14.5) years respectively. Mean BMI of males and females was 27.8 (±13) and 27.6 (± 5.8) kg/m^2, respectively.

Out of the entire group raised serum Cr was seen in 500 (74.6%) males (Cr >1.3 mg/dL) and 489 (72.9%) females (serum Cr >1.2mg/dL).

Mean GFR using CrCl, MDRD and CG were 57.1 (± 35.9), 57.8 (± 33.6) and 68.7 (± 41.5) ml/min respectively. Bias between calculated and measured GFR in different CKD stages is shown in Table 2.

Table 2. Mean comparison of CrCl and estimated glomerular filtration rate in different stages of CKD. (N=670)

Stage of CKD (n)	CrCl Mean ±SD ml/min/1.73m^2	MDRD Mean ±SD ml/min/1.73m^2	CG Mean ±SD ml/min	Bias between MDRD/CrCl	Bias between CG/CrCl
Stage 1 (135)	112.3 ± 21.2	96.95 ± 27.9	118.3 ± 37.6	-15.35	6
Stage 2 (146)	73 ± 9.1	71.5 ± 22.1	85.1 ± 25.9	-1.5	12.1
Stage 3 (214)	44.5 ± 8.4	50.7 ± 19.9	58 ± 24.1	6.2	13.5
Stage 4 (103)	22.1 ± 3.9	32.3 ± 21.3	38.5 ± 23.8	10.2	16.4
Stage 5 (72)	8.8 ± 3.5	15.7 ± 15.8	19.4 ± 14.7	6.9	10.6

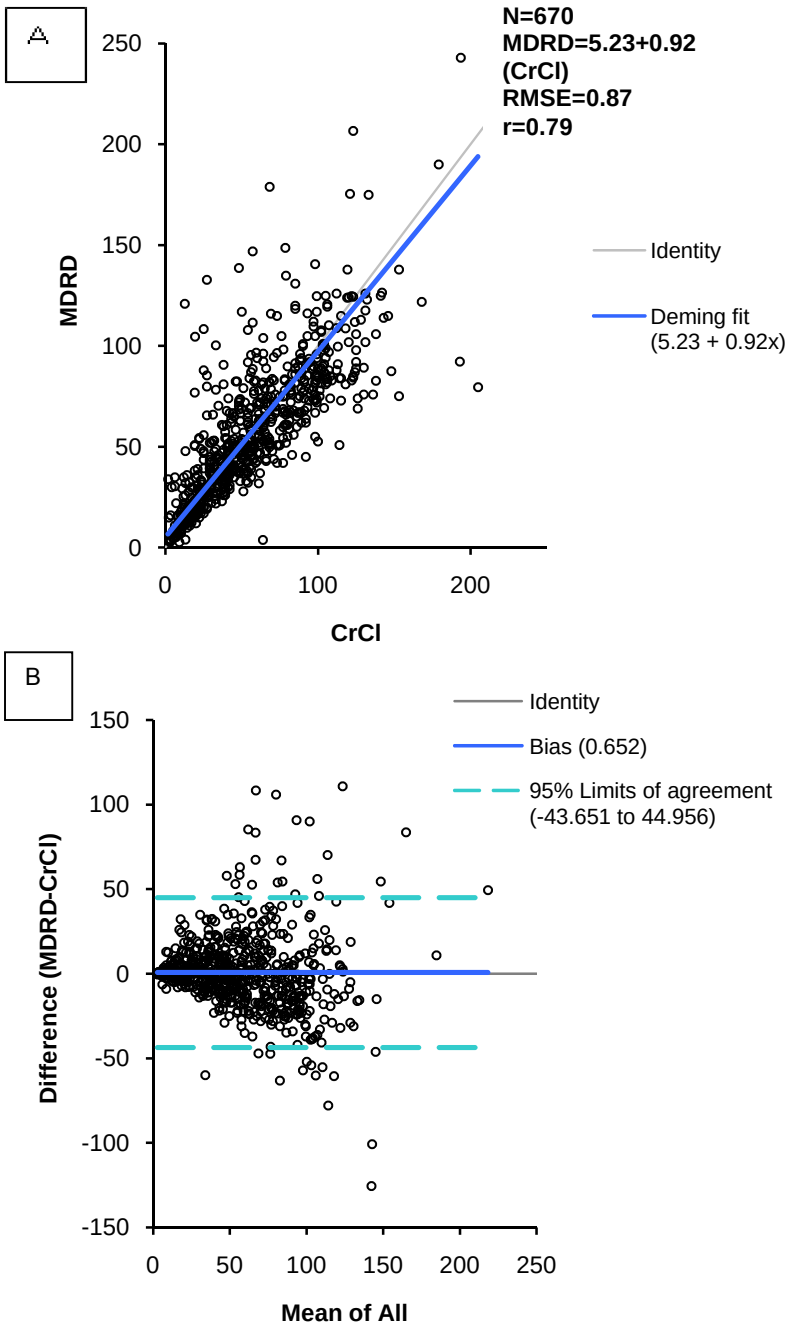
N = total sample size, n=number of subjects, CKD= chronic kidney disease, CrCl= creatinine clearance, MDRD= Modification of Diet in Renal Disease, CG= Cockcroft Gault.

3.1 Comparison of CrCl and MDRD

Non- significant difference between the means of CrCl and MDRD was seen (t=-0.74, p>0.05). A very slight constant bias existed between CrCl and MDRD (Confidence interval 1.56 – 8.89) but there was no significant proportional bias between the two methods (Confidence interval 0.84 – 1.0). Bland Altman revealed agreement with a minimal bias of 0.65ml/min/1.72m2 between CrCl and MDRD (CI -1.06 to 2.37) (Figures 1A and 1B).

3.2 Comparison of CrCl and CG

Significant difference between the means of CrCl and CG values was noted (t=11.4, p<0.05). No significant constant bias and minimal proportional bias existed between CrCl and CG (Confidence interval for intercept and slope was -4.3 to 4.78 and 1.1 to 1.3 respectively) (Figure 1C). Bland Altman revealed agreement with a minimal bias of 11.58 ml/min between CrCl and CG (Confidence interval 9.6 to 13.5) (Figure 1D).


A
N=670
MDRD=5.23+0.92 (CrCl)
RMSE=0.87
r=0.79
MDRD
CrCl
Identity
Deming fit (5.23 + 0.92x)
B
Difference (MDRD-CrCl)
Mean of All
Identity
Bias (0.652)
95% Limits of agreement (-43.651 to 44.956)

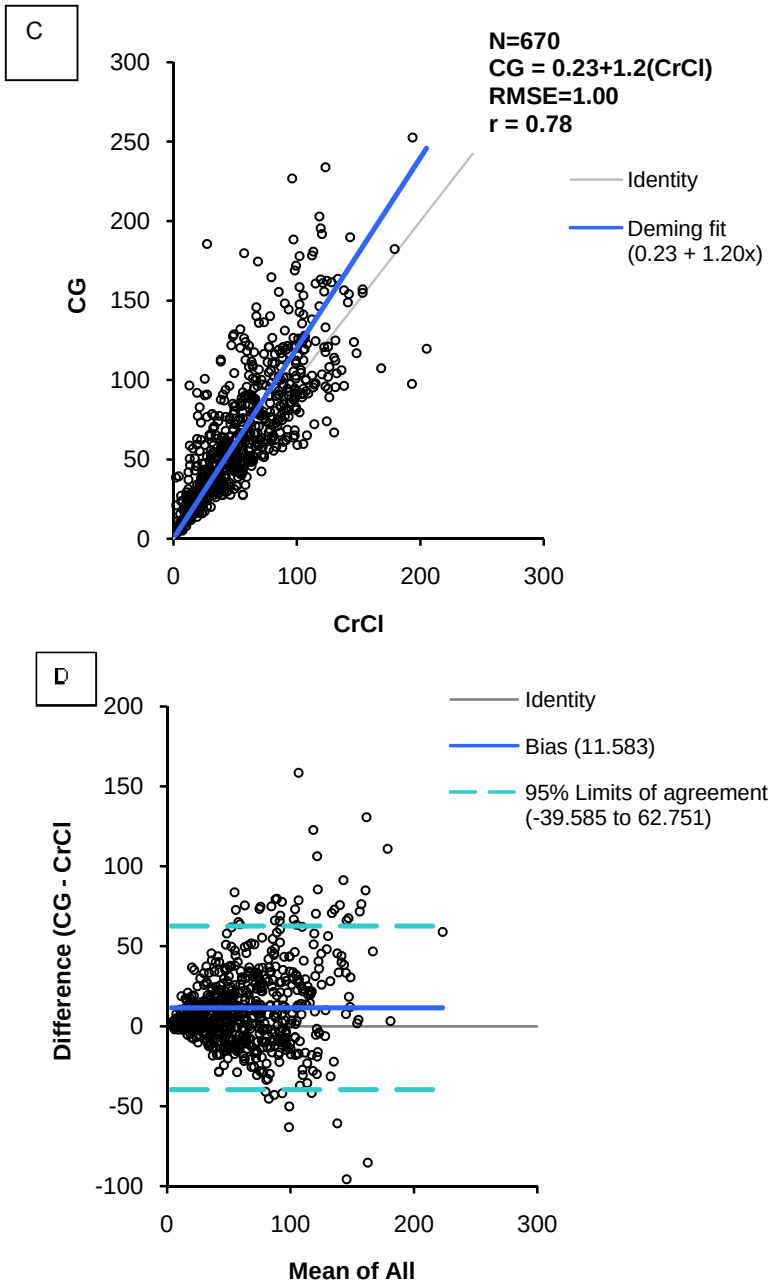


Fig. 1. Comparison of Creatinine Clearance with Modification of Diet in Renal Disease and Cockcroft Gault Equations

Figure 1. Graphs showing comparison of CrCl with MDRD and CG values for GFR:

(A) the Deming Regression analysis demonstrates close agreement between the CrCl and MDRD. The solid line indicates the slope of observed measurements (slope= 0.92) plotted against the perfect-fit line for which slope = 1.

(B) Bland Altman between CrCl and MDRD reveals majority of values lying around 0 and within confidence interval. The solid line indicates the mean difference among the methods, and the 95% confidence intervals for the differences are indicated by dashed lines. Bias of 0.65 shows acceptable agreement between values of CrCl and MDRD.

(C) The Deming Regression analysis demonstrates close agreement between CrCl and CG. The solid line indicates the slope which is = 1.2 plotted against the perfect-fit line for which slope = 1 and

(D) Bland Altman between the CrCl and CG reveals majority of values lying between the confidence interval with bias=11.5. The solid line indicates the mean difference among the methods, and the 95% confidence intervals for the differences are indicated by dashed lines. (CrCl= creatinine clearance, MDRD= modification of diet in renal disease, CG= Cockcroft Gault, N= number of samples, RMSE= root mean square error, r=correlation coefficient.)

3.3 Relation of Serum Cr to CrCl

The reciprocal relation of serum Cr concentration to CrCl was observed (r= -0.54). Similarly inverse relationship was seen when serum Cr was plotted with MDRD and CG, respectively (Figure 2 A, B and C).

3.4 Diagnostic Ability of CrCl versus MDRD and CG

Three hundred and ninety four (58.8%) subjects out of the total had CrCl <60 ml/min. There were 170 males and 181 females who had serum Cr within the reference interval. Amongst them 20% males and 35.3% females had CrCl<60ml/min. The calculated sensitivity, specificity, positive and negative predictive values of MDRD and CG are shown in Table 3.

Table 3. Diagnostic performance of equations using CrCl <60 ml/min/1.73m^2 as a diagnostic cutoff in all the subjects and in those with normal serum creatinine

	Patients with normal and abnormal Cr N=670		Patients with normal Cr n=351	
	MDRD	**CG**	**MDRD**	**CG**
Sensitivity%	87.2	76.6	37.7	40.8
Specificity%	83.2	89.8	94.4	92.4
Positive predictive value %	87.8	91.5	72.5	67.7
Negative predictive value %	79	72.9	79.6	80.1

N = total sample size, n=number of subjects, CrCl= creatinine clearance, serum Cr= creatinine, MDRD= Modification of Diet in Renal Disease, CG= Cockcroft Gault.

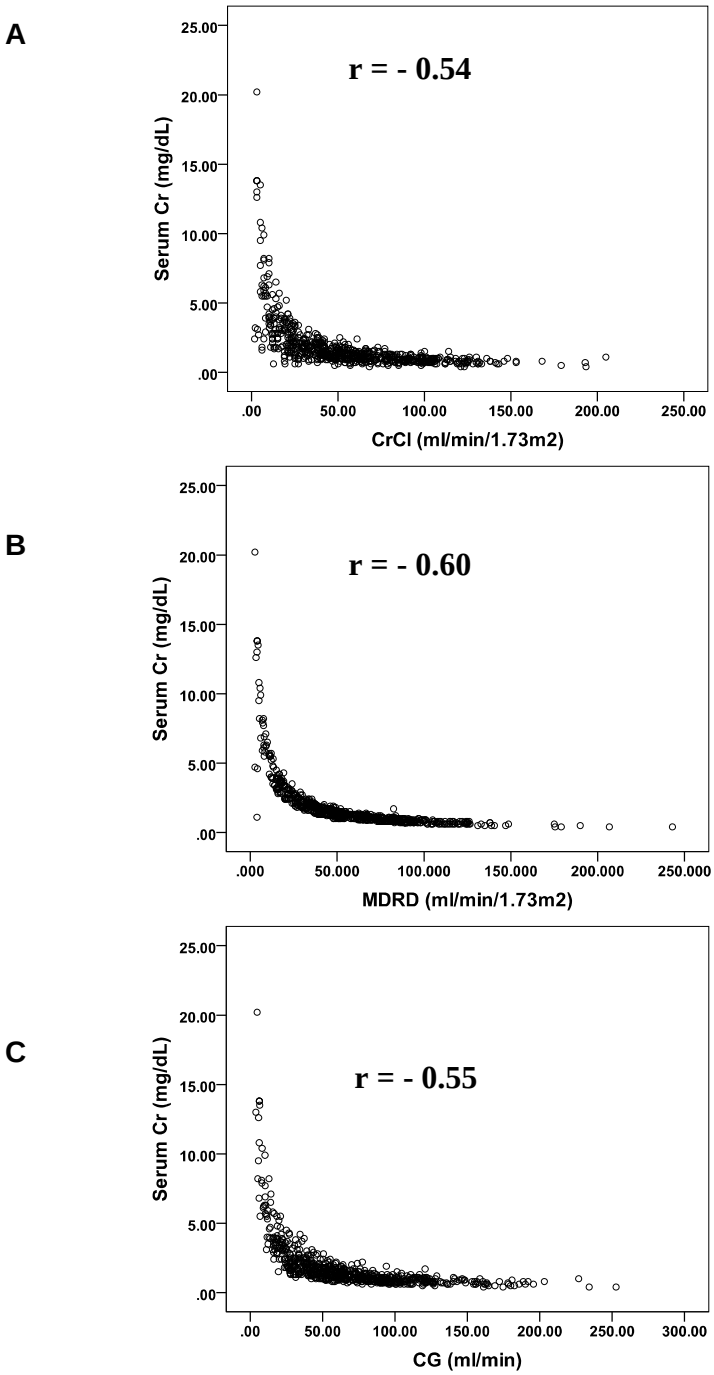


Fig. 2. Relationship of Serum Creatinine with Different Equations for Estimating Glomerular Filtration Rate.

Figure 2: Relation of serum Cr concentration to (A) CrCl measured, (B) eGFR by MDRD and (C) eGFR by CG. Each point represents the measurement for one patient. All three graphs depict the inverse and curvilinear relationship of Cr to CrCl, MDRD and CG results.

3.5 Impact of Age on EGFR

There were 168 subjects (25.1%) who were between 18-40 years, 313 (46.9%) between 40 to 60 years and 188(28.1%) who were older than 61. Mean CrCl was 71.3 ± 43.5, 58.6 ± 34 and 41.9 ± 24 ml/min/1.73m2 for the young, middle aged and old respectively (Figure 3).

In subjects who were ≥ 61 years statistical correlation between CrCl and MDRD and CrCl and CG revealed strong correlation (r=0.78, p<0.01 and r=0.73, p<0.01 respectively.)

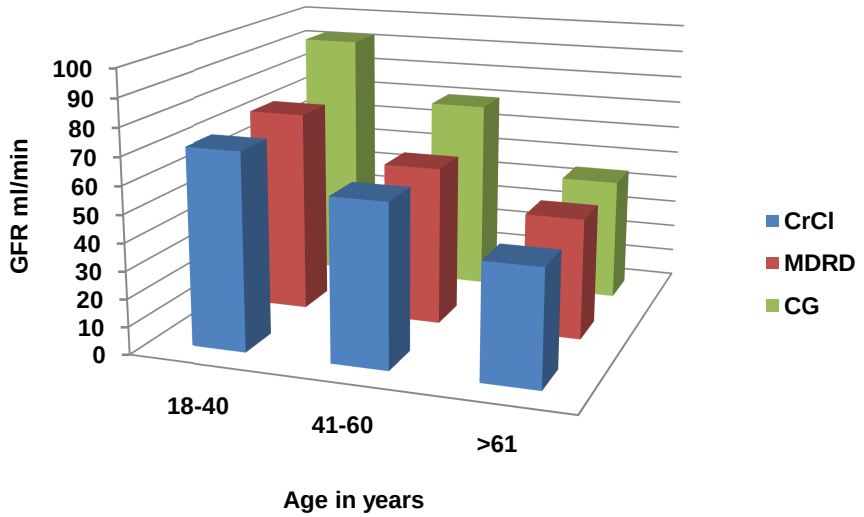


Fig. 3. Impact of Age on Estimated Glomerular Filtration Rate

Graph showing decline in creatinine clearance with increasing age depicted by all three equations. Cockcroft gault overestimated GFR more in young subjects. GFR= glomerular filtration rate; CrCl= creatinine clearance; MDRD= modification of diet in renal disease; CG= Cockcroft Gault.

4. DISCUSSION

Efforts for early detection of impaired kidney function are needed to reduce complications and new cases of CKD. This data analysis was done with the primary aim of evaluating the performance of two most common eGFR equations to start automatic reporting of eGFR on every serum Cr report generated by a clinical laboratory. Acceptable agreement between CrCl and MDRD and CrCl and CG was noted. MDRD equation was found to be better in determining GFR than CG as reflected by RMSE values (Figure 1A). Bland Altman plots for CrCl/MDRD and CrCl/CG revealed MDRD to be more accurate than CG with a minimal bias of 0.65ml/min/1.73m2. CrCl revealed strong correlation with both MDRD and CG. This correlation is comparable to another study done in similar population (Zubairi and Hussain, 2008).

Both the equations performed better in subjects with elevated serum Cr as compared to the group with normal serum Cr. This is understandable as the MDRD equation was derived in study participants who had moderate to severe renal failure. Creatinine clearance identified

34 males and 64 females with low GFR but with normal serum Cr. Along with CrCl both MDRD and CG performed better than serum Cr alone and indicates its inadequacy for assessing a kidney function. Jafar TH et al also reported that CG and MDRD outperformed serum Cr in identifying cases with depressed kidney function in a population based study done in Karachi Pakistan (Jafar, 2005). The reason behind this could be that eGFR eliminates some of the disadvantages of serum Cr by taking age and weight of the subjects into account.

It is important to keep in mind that improper collection of urine samples could be a potential bias and could be the cause of underestimation of CrCl. Other factors causing underestimation of GFR include spillage of urine and degradation of urinary Cr. These concerns were catered by providing written instructions, leak proof urine containers with tight lids and transporting the specimens in ice. Another factor which can contribute to underestimation of GFR is low muscle mass which was taken care of by adjusting CrCl to BSA.

As expected mean CrCl declined with advancing age and was the lowest in subjects >61 years. Both MDRD and CG revealed strong correlation with CrCl in the elderly group in this data. MDRD was observed to be more sensitive than CG for detection of a GFR < 60 ml/min per 1.73 m^2. However CG was found to be more specific but it over estimated GFR in quite a few cases.

As MDRD gave best agreement with CrCl automatic reporting of eGFR using MDRD with every serum Cr ordered can be initiated by clinical laboratories in our setup. The advantages of the MDRD over CG as a screening tool for CKD are that it only requires knowledge of four simple indices that are easily available by clinical laboratories, does not require knowledge of the patient's weight and height, making it suitable for automated laboratory reporting. The MDRD formula yields an eGFR normalized to 1.73m2 BSA. Adjusting for BSA is necessary when comparing a patient's eGFR with normal values or when determining the stage of CKD.

The MDRD study equation developed in 1999 is a thoroughly validated equation derived from primarily white subjects who had non diabetic kidney disease (Levey et al., 2006; Levey et al 1999). There has been extensive evaluation of the performance of the equation in different populations with non-diabetic kidney disease, diabetics with and without kidney disease, patients with liver disease, kidney transplant recipients, and potential kidney donors (Stevens et al., 2007; van Deventer et al., 2008). This equation has not been validated in South Asian population which generally have different muscle mass than Caucasians. A Chinese study revealed that the 4 variable MDRD did not perform well in Chinese CKD patients (Zuo et al., 2005). Mahajan et al. reported that both the MDRD study equation and the 4 variable MDRD study equation overestimated GFR measured by 99m diethylene triamine penta-acetic acid plasma clearance.

On the other hand CG equation takes into account the increase in Cr production with increasing weight, and the decline in Cr production with age. The formula requires multiplication by 0.85 to account for smaller muscle mass compared to men (Cockcroft and Gault, 1976). CG requires additional information such as weight and height leading to additional complexities for eGFR reflex reporting by laboratories. The formula recommended by National Kidney Disease Education Program (NKDEP) for automatic eGFR reporting is also MDRD and not CG (Narva and Briggs, 2009).

Serum Cr is one of the most frequent tests being ordered in a clinical laboratory. But most of the time it is ordered as a part of routine investigations and not to assess kidney function. Primary aim in providing additional information about kidney function is early detection of CKD in a low income country like ours where the cost of therapy whether dialysis or renal transplant is unaffordable for majority of the people. Automatic reporting of eGFR will result in timely detection of CKD, a disease which has intense effects on morbidity and mortality as well as negative social implications (Kagoma et al., 2010; Davey, 2006). Jafar et al. recommended in 2005 that laboratories should report values of eGFR in addition to serum Cr levels.

It is important to consider here that NKDEP recommends reporting eGFR values greater than or equal to 60 ml/min/1.73 m2 simply as ≥ 60 mL/min/1.73 m2 and not as an exact number. For values below 60 ml/min/1.73 m2, the report should give the numerical estimate rounded to a whole number. Reasons for not giving the exact number in those with eGFR ≥ 60 are as follows. Firstly MDRD is less accurate for persons with normal or mildly impaired kidney function. Secondly inter-laboratory differences in calibration of Cr assays, and the imprecision of the assays, have their greatest impact in the near-normal range and therefore lead to greater inaccuracies for values >60 mL/min/1.73 m. Lastly eGFR values of ≤60 mL/min/1.73 m2 have more clinical significance.

There are few limitations of this study, first being that we have not used the gold standard inulin clearance for comparing MDRD and CG. Results of CrCl are user dependent and we cannot guarantee complete emptying of bladder by subjects and proper urine collection though a brochure was given to all which had the instructions for proper urine collection. Secondly we do not have the clinical data of the subjects included. The results in the study are based on a single measurement of CrCl while the diagnosis of CKD requires reduction in GFR for at least 3 months. For research purpose single measurements of serum Cr are considered appropriate. It is important to keep in mind the limitations of this automatic reporting.

The MDRD equation has not been validated in children and is valid for the adult population only. The NKDEP Laboratory Working Group report states that the MDRD Study equation should only be used in individuals age 18 and older (Myers et al., 2006).

5. CONCLUSION

In conclusion automatic laboratory reporting of eGFR will enhance early identification of kidney dysfunction and is a fairly cost effective method of identifying patients with CKD especially in a developing country with financial restraints. Keeping in mind the sensitivity and the specificity of the test the result of eGFR should be interpreted in the clinical context. This routine reporting of eGFR requires awareness amongst health care providers and educating clinicians. It is suggested that laboratories report eGFR for all patients in whom serum Cr is ordered and let the clinicians to decide reliability and correlate the results with the patient's clinical condition.

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