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Predictive Performance of Renal Function Equations Among Ghanaians Presenting with Chronic Kidney Disease

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This study specifically evaluate the predictive performance and accuracy of the six renal function equations in patients presenting with CKD in our community. The results of these predictive equations for 50 patients using stage of CKD and/or with serum creatinine $>200 \mu\text{mol L}^{-1}$ were compared with the recommended methods (4v-MDRD and CG). Another 55 subjects with similar age group and sex distributions but without kidney pathology were studied as control. The most accurate results were obtained with the reference equations (4v-MDRD and CG) with CG having a slight edge over 4v-MDRD equation. The sensitivity and specificity of the 4v-MDRD equation to detect Glomerular Filtration Rate (GFR) values $< 60 \text{ mL/min/1.73 m}^2$ were 67.3 and 63.9%, respectively; that of CG was 62.9 and 71.3%, respectively. These results suggest that measurement of GFR with predictive equations might be a prudent strategy for the assessment of renal function among the CKD population.

Key words: Chronic kidney disease, predictive equations, creatinine, BUN, GFR, Ghana

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INTRODUCTION

Chronic kidney disease is a major health problem worldwide with dramatically increasing incidence and prevalence (Levey *et al.*, 2007). The prevalence rates of chronic kidney disease have been increasing in Ghana over the years thus necessitating the establishment of dialysis centres at the three leading teaching hospitals to manage patients with End Stage Kidney Disease (ESKD). Early detection and stratification of chronic kidney disease helps in providing interventions to reduce morbidity and mortality. There is therefore, the need to identify the best tool for diagnosis. Determination of GFR, however, involves the measurement of the renal clearance of exogenous markers such as inulin (gold standard), chromium-51-Ethylene diamine tetracetic acid (⁵¹Cr-EDTA), technetium labeled diethylene-triamine-pentacetate (99 m Tc-DPTA), iohexol and cystatin C (National Kidney Foundation, 2002). These methods are however expensive, not readily available and impractical for routine use especially in Africa and in Ghana for that matter. Thus the endogenous clearance of creatinine (creatinine clearance) remains the most widely used method to estimate the GFR since it is widely available, relatively inexpensive and not technically demanding. However, since the creatinine clearance (Ccr) estimation relies on timed urine collection it becomes unreliable as it is difficult to obtain and is subject to errors during collection. Also, this method overestimates GFR as the creatinine is both filtered and secreted. Furthermore, the use of creatinine has multiple limitations (Herget-Rosenthal *et al.*, 2007) since creatinine is affected by the age, sex, diet, certain drugs (e.g., isoniazid) and the muscle mass of the individual (Levey, 1990; Perrone *et al.*, 1992). This has led to the development of predictive equations which have been demonstrated to compare well with results of inulin clearance (Guignard *et al.*, 1980; Ocheke and Agaba, 2006; Schwartz *et al.*, 1976). In developing countries where Ccr determination is available only in specialized centres, predictive equations would be useful in GFR estimation since it would allow for early detection, stratification and prompt management of patients with chronic kidney disease. The aim of this study, therefore, was to examine the applicability of six predictive equations in the estimation of GFR for the stratification of CKD.

MATERIALS AND METHODS

Subjects: Fifty consecutive patients with various chronic kidney diseases and/or with serum creatinine >200 µmol L⁻¹ from the medical unit and the diabetic clinic

of the Tamale Teaching Hospital, in the Northern Region of Ghana were recruited for this study. The aetiology ranged from diabetic nephropathy, chronic glomerulonephritis, adult polycystic kidney disease and hypertensive nephropathy as well as chronic kidney disease of unknown aetiology. Another 55 subjects with similar age and sex distribution without chronic kidney disease were studied as controls. The participation of the respondents who are all indigenes of Ghana was voluntary and informed consent was obtained from each of them. The study was approved by the local Committee on Human Research Publication and Ethics.

Sample collection and preparation

Biochemical analysis: Venous blood samples were collected after an overnight fast (12-16 h). About 5 mL of venous blood was collected and dispensed into vacutainer® plain tubes. After clotting, it was then centrifuged at 500 g for 15 min. The serum was stored at -80°C until assayed. Serum biochemistry was performed with ATAC® 8000 Random Access Chemistry System (Elan Diagnostics, Smithfield, RI, USA). Parameters that were determined include: Blood Urea Nitrogen (BUN) (mmol L⁻¹), creatinine (CRE) (µmol L⁻¹) and Albumin (g L⁻¹). The methods adopted by the automated instrument for the determination of the above parameters are according to the reagent manufacturer's instruction - JAS™ diagnostics, Inc. (JAS Diagnostics, Inc. Miami Florida, USA).

Urinalysis: Early morning urine was collected in plastic containers from the respondents and urine protein was determined using the dip-stick qualitative method (CYBOW™ DFI Co Ltd, Gimhae-City, Republic of Korea).

Anthropometric variables: Anthropometric measurements included height to the nearest meter without shoes and weight to nearest 0.1 kg in light clothing. Subjects were weighed on a bathroom scale (Zhongshan Camry Electronic Co. Ltd, Guangdong, China) and their height measured with a wall-mounted ruler. BMI was calculated by dividing weight (kg) by height squared (m²).

Renal function equation and staging of CKD: The six renal function equations evaluated are listed below; all equations use serum creatinine (SCr) levels to predict renal function.

$$\text{Cockcroft gault} = \frac{(140 - \text{age}) \times \text{weight}}{72 \times \text{SCr}} (\times 0.85 \text{ if female}) \quad (1)$$

$$4v - \text{MDRD} = 186 \times \text{SCr}^{-1.154} \times \text{age}^{-0.204} \times (1.212 \text{ if black}) \times (0.742 \text{ if female}) \quad (2)$$

$$\text{Jelliffe 1} = \frac{98 - 0.8(\text{age} - 20)}{72 \times \text{SCr}} (\times 0.90 \text{ if female}) \quad (3)$$

$$\begin{aligned} \text{Jelliffe 2} = & \text{Male: } 100/\text{Scr}-12 \\ & \text{Female: } 80/\text{Scr}-7 \end{aligned} \quad (4)$$

$$\begin{aligned} \text{Bjornson} = & \text{Male: } \frac{[27 - (0.173 \times \text{age})] \times \text{weight} \times 0.07}{\text{Scr}} \\ & \text{Female: } \frac{[25 - (0.175 \times \text{age})] \times \text{weight} \times 0.07}{\text{Scr}} \end{aligned} \quad (5)$$

$$\begin{aligned} \text{Gate} = & \text{Male: } (89.4 \times \text{Scr}^{-1.2}) + (55 - \text{age}) \times (0.447 \times \text{Scr}^{-1.1}) \\ & \text{Female: } (60 \times \text{Scr}^{-1.1}) + (56 - \text{age}) \times (0.3 \times \text{Scr}^{-1.1}) \end{aligned} \quad (6)$$

Body Surface Area (BSA) was estimated according to the method of Du Bois and Du Bois, (1989):

$$\text{BSA} = \text{weight (kg)}^{0.425} \times \text{height (m)}^{0.7250} \times 20247$$

The GFR results from the various renal function equations were used to divide the study population into 5 categories corresponding with the five stages of CKD in the K/DOQI CKD classification (National Kidney Foundation, 2002). The staging classified GFR ≥ 90 mL/min/1.73 m² as stage 1, 60-89 mL/min/1.73 m² as stage 2, 30-59 mL/min/1.73 m² as stage 3, 15-29 mL/min/1.73 m² as stage 4 and <15 mL/min/1.73 m² as stage 5.

Statistical analysis: The results are expressed as Means \pm SEM. Unpaired t-test was used to compare means. Agreement between the predictive equations was assessed by the Bland-Altman statistic (Bland and Altman, 1986). Correlation was assessed by the Pearson's rank method. Sensitivity and specificity values for the prediction equations in detecting subnormal GFR (i.e., GFR <60 mL/min/1.73 m²) were also calculated using Receiver Operator Characteristic (ROC) analysis. A level of $p < 0.05$ was acceptable as statistically significant. GraphPad Prism version 5.00 for windows was used for statistical analysis (GraphPad software, San Diego California USA, www.graphpad.com).

Table 2: Classification of the study population according to renal function equation

RFE	Total GFR	Stage 1 (= 90)	Stage 2 (60-89)	Stage 3(30-59)	Stage 4 (15-29)	Stage 5 (<15)
4v-MDRD	92.66 \pm 10.56(100%)	153.00 \pm 9.26(50.0%)	69.38 \pm 2.67(17.4%)	53.91 \pm 2.00(2.2%)	22.91 \pm 3.38(6.5%)	5.99 \pm 0.83(23.9%)
CG	76.44 \pm 8.94(100%)	149.90 \pm 11.93(32.6%)	69.49 \pm 1.03(24.5%)	54.32 \pm 3.05(14.3%)	18.10 \pm 1.86(6.1%)	7.17 \pm 0.97(22.4%)
Jelliffe 1	67.43 \pm 6.76(100%)	121.40 \pm 4.34(34.7%)	73.39 \pm 2.04(20.4%)	50.55 \pm 2.87(14.3%)	25.47 \pm 1.48(4.1%)	7.85 \pm 1.03(26.5%)
Jelliffe 2	77.22 \pm 8.88(100%)	137.90 \pm 6.89(42.8%)	75.14 \pm 3.27(14.3%)	52.76 \pm 2.81(12.2%)	20.58 \pm 5.93(4.1%)	0.26 \pm 0.96(26.5%)
Bjornson	78.96 \pm 9.18(100%)	157.60 \pm 12.38(30.6%)	72.26 \pm 2.45(34.7%)	45.68 \pm 6.32(6.1%)	23.37 \pm 3.23(4.1%)	7.72 \pm 1.15(24.5%)
Gates	69.13 \pm 7.55(100%)	129.10 \pm 6.16(34.7%)	74.01 \pm 2.63(22.4%)	44.38 \pm 2.63(12.2%)	22.55 \pm 5.59(4.1%)	5.16 \pm 0.71(26.5%)

Data are presented as Mean \pm SEM. RFE: Renal Function Equation, CG: Cockcroft-Gault, 4v-MDRD: Four variable modification of diet in renal disease

RESULTS

The aetiology of the CKD ranged from diabetic nephropathy, 25(50%) patients; chronic glomerulonephritis, 4(8%) patients; Adult polycystic kidney disease, 1(2%) patient; hypertensive nephropathy, 6(12%) patients and chronic kidney disease with unknown aetiology, 14(28%) patients.

The mean age of the subjects [48.23 \pm 2.51 (49.52 \pm 3.33 for males and 46.50 \pm 3.88 for females)] was significantly higher than that of the control group (34.89 \pm 2.22). Apart from serum Albumin which showed a significantly lower value when the CKD subjects were compared to the control group, Proteinuria, Blood Urea Nitrogen (BUN) and Creatinine (CRE) showed significantly higher values when CKD subjects were compared to the control group (Table 1).

To assess the consequences of the limitations of the various renal function equations we applied the K/DOQI guidelines which recommended defining a clinical action plan for each patient with CKD on the basis of the stage of disease as defined by the K/DOQI CKD classification (National Kidney Foundation, 2002) (Table 2). This analysis was based solely on results of the renal function equations applied and all the 50 subjects with CKD were considered. Though there are wide variations in the mean value and percentage subject with mild CKD (Stage 1 and 2), the 4v-MDRD and CG equations gave similar mean values. The 4v-MDRD equation gave the highest percentage value of 50.0 whilst the Jelliffe 2 equation gave the lowest percentage of 14.3 (Table 2). For

Table 1: Demographic and clinical characteristics of study population

Parameters	Control	CKD
Age (years)	34.89 \pm 2.22	48.23 \pm 2.51***
Weight (kg)	65.45 \pm 2.43	68.61 \pm 2.68
Height (m)	1.63 \pm 0.01	1.64 \pm 0.01
BMI (kg m ⁻²)	24.63 \pm 0.81	25.41 \pm 0.89
Proteinuria (mg L ⁻¹)	0.04 \pm 0.02	1.17 \pm 0.26***
BUN (mmol L ⁻¹)	3.52 \pm 0.17	15.51 \pm 2.86***
Creatinine (μ mol L ⁻¹)	105.90 \pm 3.97	341.60 \pm 68.32***
Albumin (g L ⁻¹)	41.50 \pm 1.22	36.38 \pm 1.21**
BSA (m ²)	1.69 \pm 0.03	1.73 \pm 0.03

Data are presented as Mean \pm SEM, BUN: Blood Urea Nitrogen, BSA: Body Surface Area, CKD: Chronic Kidney Disease. * $p < 0.05$; ** $p < 0.001$ and *** $p < 0.0001$ where the CKD are compared to the control group

Table 3: Pearson correlation coefficients clinical variables and renal function equation for control group (upper right-hand side) and kidney disease group (lower left-hand side)

	Age	WT	HT	BMI	PRT	BUN	CRE	ALB	BSA	MDRD	CG	JL 1	JL 2	BJ	Gates
Age		0.10	-0.10	0.14	0.54	0.20	0.08	0.07	0.06	-0.33*	-0.41**	-0.48**	-0.17	-0.23	-0.27
WT	0.33*		0.50***	0.94***	-0.15	0.13	0.29*	0.10	0.97***	-0.34*	0.37**	-0.32*	-0.33*	-0.27	-0.21
HT	0.19	0.44**		0.18	-0.32*	0.06	0.21	-0.23	0.69***	-0.05	0.37**	-0.08	-0.11	-0.05	-0.12
BMI	0.29	0.91***	0.03		-0.05	0.13	0.27	0.19	0.83***	-0.40**	0.27	-0.36*	-0.36**	-0.31*	-0.22
PRT	-0.14	0.09	-0.06	0.15		0.09	-0.12	0.18	-0.20	-0.05	-0.24	-0.14	0.06	0.112	0.02
BUN	-0.09	-0.18	-0.18	-0.11	0.09		0.37*	-0.08	0.13	-0.34*	-0.30	-0.34*	0.06	-0.40**	-0.35**
CRE	-0.08	-0.16	-0.06	-0.14	0.11	0.92***		-0.24	0.31*	-0.78***	-0.58***	-0.77***	-0.87***	-0.78***	-0.81***
ALB	0.13	0.22	0.13	0.15	-0.26	0.10	0.06		0.01	0.05	0.14	0.07	0.11	0.08	0.02
BSA	0.34*	0.97***	0.65***	0.78***	0.06	-0.19	-0.14	0.21		-0.33*	0.39**	-0.32*	-0.33*	-0.26	-0.24
MDRD	-0.20	-0.08	0.07	-0.15	0.08	0.04	0.18	0.04	-0.06		0.68***	0.98***	0.97***	0.81***	0.92***
CG	-0.05	-0.06	0.08	-0.11	0.20	0.01	0.18	-0.10	-0.02	0.86***		0.71***	0.66***	0.56***	0.69***
JL 1	-0.12	-0.03	0.02	-0.06	0.14	-0.02	0.09	0.01	-0.02	0.97***	0.87***		0.94***	0.79***	0.91***
JL 2	-0.19	-0.10	0.02	-0.16	0.14	0.01	0.13	0.05	-0.09	0.97***	0.85***	0.95***		0.82***	0.92***
BJ	-0.02	-0.05	0.09	-0.11	0.19	-0.03	0.11	-0.10	-0.01	0.81***	0.98***	0.86***	0.83***		0.84***
Gates	-0.15	-0.10	-0.01	-0.13	0.14	-0.04	0.05	0.00	-0.09	0.88***	0.80***	0.93***	0.93***	0.85***	

*Correlation is significant at the 0.05 level (2-tailed), **Correlation is significant at the 0.01 level (2-tailed), ***Correlation is significant at the 0.0001 level (2-tailed). WT: Weight, HT: Height, BMI: Body mass index, PRT: Proteinuria, BUN: Blood Urea Nitrogen, CRE: Creatinine, BSA: Body Surface Area

those with moderate CKD (Stage 3), all the equations gave close mean GFR values apart from the Bjornson and Gates equations which turned out lower values. The 4v-MDRD gave the lowest percentage for stage 3(2.2%) as only one subject fitted that classification whilst the Jelliffe 1 and Gates equations gave the highest GFR 14.3% (Table 2). Interestingly, all the renal function equations generated similar percentage for subjects with severe CKD (Stage 4 and 5). The 4v-MDRD and CG however, gave closer but higher percentage values for stage 4 (Table 2).

From the Pearson rank correlation analysis in Table 3, there are significant positive correlations among the various renal function equations and between BUN and CRE for both the control group and subjects presenting with CKD. However, the relationship between BUN and CRE is stronger within the CKD than the control. Apart from age which shows significant positive correlation with BSA in only the CKD subjects, weight (WT), height (HT) and Body Mass Index (BMI) indicate significant positive correlation with BSA within both the control group and CKD group. WT also showed significant positive correlation with HT and BMI within both study groups. Conversely, the renal function equations generally gave negative but significant correlation with BUN, CRE, BMI, WT and age within only the control group.

Bland-Altman analysis which shows the performance of the various renal function equations in comparison with 4v-MDRD and CG equations are as shown in Fig. 1 and 2, respectively. The bias (i.e., the mean difference) in GFR estimation by the JL 1, JL 2, BJ and Gates equations in relation to 4v-MDRD were 24.3, 12.7, 11.7 and 21.6%, respectively. Also, the bias (i.e. the mean difference) in GFR estimation by the JL 1, JL 2, BJ and Gates equations

in relation to CG were 9.0, -0.8, -2.5 and 7.3%, respectively. Apart from the agreement between JL 1 and Gates in relation to 4v-MDRD which were not so good, all the rest gave good agreement in accordance with the results from the Pearson rank correlation described in Table 3. Apart from that, there is also good agreement between 4v-MDRD and CG equation (bias of 14.3) as shown in Fig. 3.

Considering the various renal function equations, at least 32.6% of the subjects had GFR < 60 mL/min/1.73 m² (Table 2). As a result of that we sought to calculate the sensitivity and specificity of these predictive equations to detect GFR values below 60 mL/min/1.73 m² using ROC analysis. The sensitivity and specificity of the 4v-MDRD equation to detect GFR values less than 60 mL/min/1.73 m² were 67.3 and 63.9%, respectively; that of CG were 62.9 and 71.3% respectively; that of JL1 were 44.9 and 69.3%, respectively; that of JL2 were 59.2 and 69.4%, respectively; that of BJ were 34.5 and 70.9% respectively; that of BJ were 57.1 and 53.1%, respectively.

DISCUSSION

The significant increase in age of the CKD group relative to the control group indicates that the risk of CKD increases as one grows older which is in conformity with the findings of other studies (Coresh *et al.*, 2002; National Kidney Foundation, 2002). This observation confirms a significant trend of decreasing estimated GFR with increasing age. Apart from that, the result of this study shows a significant decrease in plasma albumin with concomitant increase in proteinuria (Table 1). This is in line with the study of Levey *et al.* (2003), which indicated that persistently increased protein excretion is usually a marker of kidney damage. Physiologically normal persons

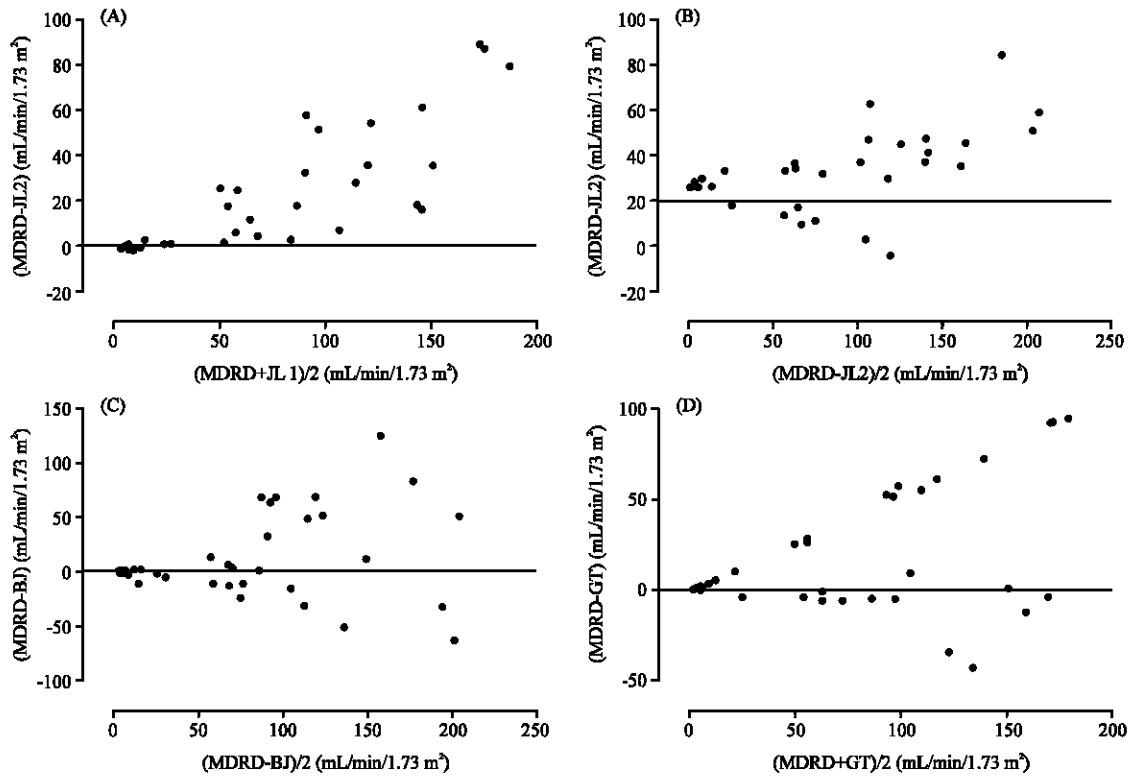


Fig. 1: Bland-Altman plot showing the agreement between (A) 4v-MDRD and JL 1, (B) 4v-MDRD and JL 2, (C) 4v-MDRD and BJ and (D) 4v-MDRD and Gate

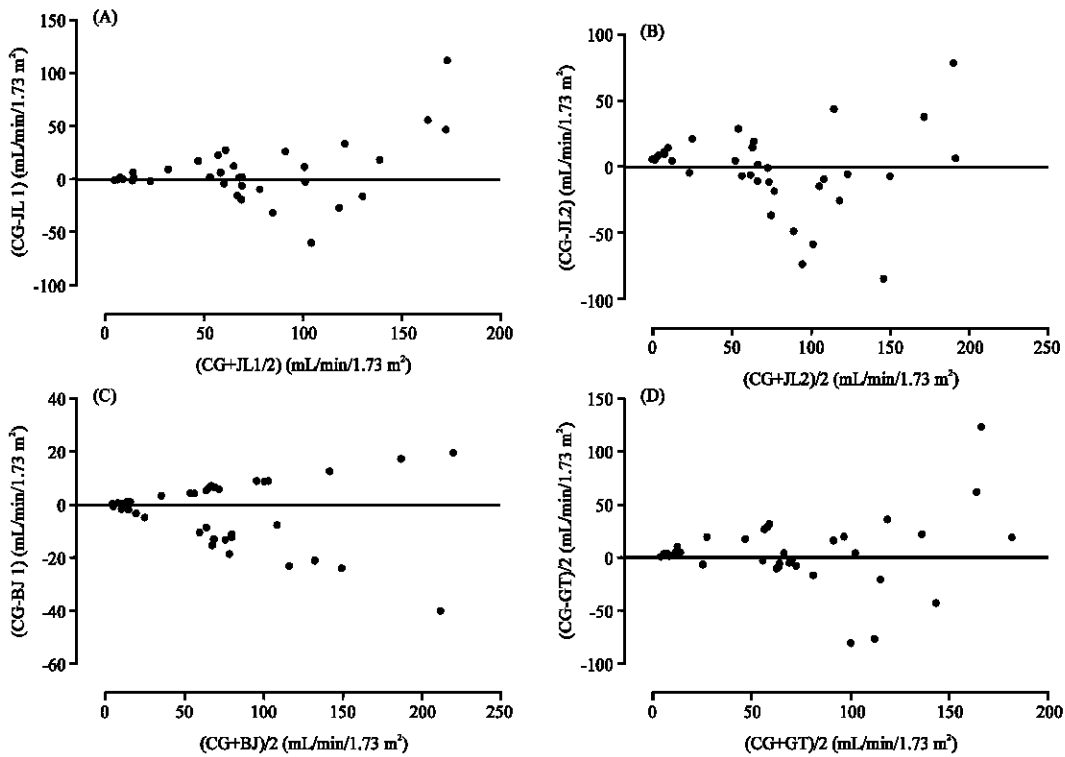


Fig. 2: Bland-Altman plot showing the agreement between (A) CG and JL 1, (B) CG and JL 2, (C) CG and BJ and (D) CG and Gate

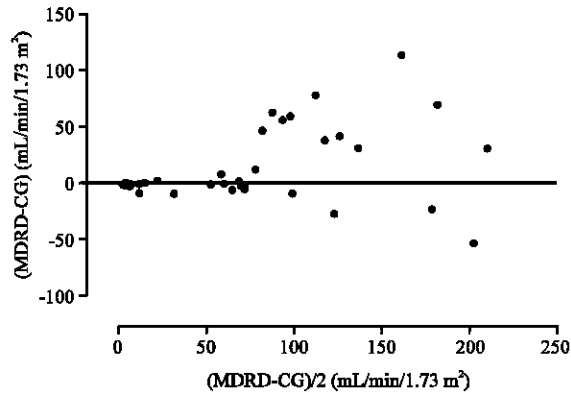


Fig. 3: Bland-Altman plot showing the agreement between 4v-MDRD and CG

usually excrete routinely undetectable amounts of protein in the urine. Increased excretion of albumin is a sensitive marker for chronic kidney disease and may be due to diabetes, glomerular disease and hypertension. Proteinuria implies that there is an increased urinary excretion of albumin or any other specific protein (Levey *et al.*, 2003).

In this study, we evaluated the performances of the 6 renal function formulae for estimating GFR in 50 subjects with CKD. These formulae are commonly used in daily clinical practice elsewhere and decisions regarding the care of CKD patients are based on the estimated GFR, but their accuracy is still disputable (National Kidney Foundation, 2002). Furthermore, none of these six equations has been validated among Africans and for that matter Ghanaian adult CKD subjects. However, K/DOQI recommends the use of the 4v-MDRD and the CG equations which are presumed to be the most accurate. Accurate assessment of renal function among patients with CKD is important for diagnostic and interventional purposes, adequate therapeutic management, interpretation of symptoms that might be ureamic in nature and decision-making regarding when the initiation of dialysis might be appropriate. Because of the numerous disadvantages of using creatinine clearance and other markers, predictive equations are typically used, to estimate renal function (Cockcroft and Gault, 1976; Gates, 1985; Jelliffe and Jelliffe, 1972; Levey *et al.*, 1999a, b).

Present results show that among the six equations the most accurate renal function estimates were derived by using the CG and 4v-MDRD equations with the CG having a slight edge over the 4v-MDRD in terms of the specificity. The 4v-MDRD and CG equations gave sensitivity and specificity of 67.3 and 63.9%, respectively and 62.9 and 71.3%, respectively to detect GFR values less 60 mL/min/1.73 m².

Analysis of bias, a measure of systematic error, generally showed a very good global agreement between the renal function equations. A similar bias of 14.3 was observed when the CG formula was compared with the GFR estimated by 4v-MDRD. In contrast, to the 4v-MDRD, the JL 1 and Gate formula were shown largely to underestimate measured GFR. The reasons for this discrepancy are not clear, but it may be due to differences in patient characteristics and may warrant further investigation.

Analysis of the ability of a formula to classify patients into different subgroups depends on the characteristics of the population. In particular, it depends on the proportion of patients who happen to be near the boundaries of the subgroups. In our study, analysis of the performance of all the formulae to classify patients according to the K/DOQI CKD classification showed that, all the formulae classified approximately the same percentage of subjects into the severe stage (stage 4) and end stage renal disease (stage 5) (Table 2). Though there are greater variations as one moves closer to stage 1, the 4v-MDRD and CG either have similar mean values or similar percentage values thus confirming their superiority over the other equations and also highlights the limitations of the other formulae. The better agreement between the 4v-MDRD and CG equation at a more advanced stage of CKD in this study is in conformity with other reports elsewhere (Fontseré *et al.*, 2006), as their performance improves when GFR declines.

The most important practical utility of a GFR predictive formula is to diagnose and stratify chronic kidney disease in patients with kidney disease. According to Levey *et al.* (1999a) the 4v-MDRD equation shows better diagnostic accuracy than the CG formula as it does not require body weight. This, however, appears not to be the case in our study where the CG appeared to have a slight edge over the 4v-MDRD with a specificity of 71.3% against 63.9% to detect GFR values less than 60 mL/min/1.73 m². The 4v-MDRD formula in comparison to the CG seems to overestimate low GFR, because the relationship between serum creatinine and GFR in severe kidney disease is not simple as the clearance of creatinine does not depend solely on GFR (Perrone *et al.*, 1992). In this study the 4v-MDRD stratified 30.4% of the subjects in stages 4 and 5 compared to the CG equation which stratified 28.5% of the subjects in stages 4 and 5.

CONCLUSION

In conclusion, the CG and 4v-MDRD are the most accurate equations among the six predictive equations for

renal dysfunction even though they seem to have their limitations. Whereas the sensitivity and the accuracy of the CG formula cannot be overlooked due to the influence of weight, the 4v-MDRD equation is also difficult to calculate in clinical practice and probably underestimates GFR at high levels, but in contrast to our findings, other studies have found it to have better accuracy in diagnosing and stratifying chronic kidney disease which is an important advantage for a prediction formula. Further studies are therefore, warranted prior to the generalization of these findings for patients presenting with chronic kidney disease.

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