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ESTIMATING GLOMERULAR FILTRATION RATE IN BLACK SOUTH AFRICANS

by

H.E. van Deventer

A thesis submitted in partial fulfillment of the requirements for the degree of

Master of Medicine (Chemical Pathology)

University of the Witwatersrand

2009

Declaration

I, **H.E. van Deventer** declare that this thesis is my own work. It is being submitted for the degree of **Master of Medicine (Chemical Pathology)** in the University of the Witwatersrand, Johannesburg.

_____

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Publications and presentations arising from this study

Abstracts

1. H.E. van Deventer, J. George, I. Katz. Estimating Glomerular Filtration Rate in South Africa. Clinical Chemistry Supplement 2007;53:A36
2. H.E. van Deventer, J. George, I. Katz. Glomerular Filtration Rate Prediction Equations Based on Creatinine and Cystatin C. Clinical Chemistry and Laboratory Medicine Supplement 2007;45:S284
3. H.E. van Deventer, J. Paiker, I. Katz, J. George. A Simplified equation to predict Glomerular Filtration Rate. Clinical Chemistry Supplement 2008;54:A139

Poster Presentations

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2. H.E. van Deventer, J. George, I. Katz. Estimating Glomerular Filtration Rate in South Africa. American Association for Clinical Chemistry annual meeting 2007, San Diego, California, July 2007
3. H.E. van Deventer, J. Paiker, I. Katz, J. George. A Simplified equation to predict Glomerular Filtration Rate. American Association for Clinical Chemistry annual meeting 2008, Washington, District of Columbia, July 2008

Oral Presentations

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2. van Deventer H E, Vangu M D T, George J.A. Estimating Glomerular Filtration Rate in South Africa. South African Society of Nephrology, Windhoek, July 2008

Articles

1. H.E. van Deventer, J.A. George, J.E. Paiker, P. J. Becker, I.J. Katz. Estimating Glomerular Filtration Rate in Black South Africans Using the Modification of Diet in Renal Disease and Cockcroft-Gault Equations. Clinical Chemistry, July 2008

Awards:

2006:

Awarded Beckman postgraduate bursary; The South African Association of Clinical Biochemists

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Joint recipient of Faculty Research Prize, Faculty of Health Sciences, University of the Witwatersrand

Awarded a 2008 AACC International Travel Grant to attend AACC conference in Washington, DC

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Estimating Glomerular Filtration Rate in Black South Africans using the Modification of Diet in Renal Disease (MDRD) and Cockcroft-Gault equations

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Abstract

Background

The 4-variable Modification of Diet in Renal Disease (4-v MDRD) and Cockcroft-Gault (CG) equations are commonly used for estimating glomerular filtration rate (GFR); however, neither of these equations has been validated in an indigenous African population. The aim of this study was to evaluate the performance of the 4-v MDRD and CG equations for estimating GFR in black South Africans against measured GFR and to assess the appropriateness for the local population of the ethnicity factor established for African Americans in the 4-v MDRD equation.

Methods

We enrolled 100 patients in the study. The plasma clearance of chromium-51–EDTA (^{51}Cr-EDTA) was used to measure GFR, and serum creatinine was measured using an isotope dilution mass spectrometry (IDMS) traceable assay. We estimated GFR using both the reexpressed 4-v MDRD and CG equations and compared it to measured GFR using 4 modalities: correlation coefficient, weighted Deming regression analysis, percentage bias, and proportion of estimated GFR within 30% of measured GFR (P30).

Results

The Spearman correlation coefficient between measured and estimated GFR for both equations was similar (4-v MDRD $R^2 = 0.80$ and CG $R^2 = 0.79$). Using the 4-v MDRD equation with the ethnicity factor of 1.212 as established for African Americans resulted in a median positive bias of 13.1 (95% CI 5.5 to 18.3) mL/min/1.73m^2. Without the ethnicity factor median bias was 1.9 (95% CI -0.8 to 4.5) mL/min/1.73m^2.

Conclusion

The 4-v MDRD equation, without the ethnicity factor of 1.212, can be used for estimating GFR in black South Africans.

Introduction

Globally chronic kidney disease (CKD) is recognized as an important public health problem (1). In South Africa (SA) the high prevalence of hypertension, diabetes mellitus and infection with human immunodeficiency virus (HIV) results in a significant risk for CKD (2). It is therefore important to detect kidney dysfunction as early as possible in this population. Current guidelines define CKD as the presence, for three or more months, of either kidney damage as defined by structural or functional abnormalities of the kidney or a GFR < 60 mL/min/1.73m^2 (3, 4). GFR is an important component in the diagnosis of CKD and is also accepted as the best overall measure of kidney function (3, 5). Individuals with decreased GFR are not only at increased risk for the development of end stage renal failure (ESRD) but are also at increased risk for hospitalizations, cardiovascular disease (CVD) and other complications of decreased kidney function (6-10). It has been shown that early detection, appropriate evaluation and management of CKD improves outcome (1, 3, 4).

GFR can be measured as the renal clearance of exogenous markers such as Inulin, ^{51}Chromium ethylenediaminetetraacetic acid (^{51}Cr-EDTA), technetium-labeled diethylene-triamine-pentacetate (^{99m}Tc-DTPA) and Iohexol. However these exogenous markers are impractical for routine use. Endogenous GFR markers include creatinine and cystatin C. Creatinine is the most commonly used marker in the clinical laboratory to assess GFR, however it has multiple limitations (11). For example creatinine concentration is not only determined by GFR but is also affected by factors such as muscle mass, diet, gender and age (12, 13).

To overcome some of these limitations the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) and Kidney Disease: Improving Global

Outcomes (KDIGO) guidelines recommend the estimation of GFR (eGFR) using prediction equations based on serum creatinine (S-Cr) (3, 4). The two most commonly used prediction equations are the 4 variable Modification of Diet in Renal Disease (4-v MDRD) (14) and Cockcroft-Gault (CG) equation (15). The MDRD equation was derived in the United States from data from 1628 patients with known kidney-disease (651 women and 195 African-Americans) using ^{125}I-iothalamate clearance to measure GFR as the reference procedure (mean GFR 40 mL/min/1.73m^2) and was based on 6 variables: age, sex, serum creatinine, urea, albumin and ethnicity (16). Subsequently a 4-v MDRD equation, based on 4 variables: age, sex, serum creatinine and ethnicity was proposed to simplify its use in the clinical environment (14). An ethnicity factor of 1.212 was established for African Americans (14, 16).

Because of variability in serum creatinine assays the National Kidney Disease Education Program (NKDEP) Laboratory Working Group initiated a creatinine standardization program with creatinine calibration traceable to isotope dilution mass spectrometry (IDMS) creatinine measurement (17). The 4-v MDRD equation was re-expressed for use with the IDMS traceable creatinine measurements (18).

The Cockcroft-Gault (CG) equation was derived from 236 hospital in-patients in Canada (4 % women, ethnicity not stated) with measured creatinine clearance (CrCl) as the reference procedure (mean CrCl 73 ml/min) (15).

Neither of these formulae nor the ethnicity factor of 1.212 established for African Americans have been evaluated in African or non American black populations before. The applicability of these equations and the factor for ethnicity to black South Africans is therefore unknown.

The aim of this study was to examine the applicability of the 4-v MDRD and CG equations for estimating GFR in black South Africans against measured GFR and to evaluate whether the ethnicity factor established for African Americans is appropriate for black South Africans.

Methods

Participants

This study was a prospective study of patients seen at Chris Hani Baragwanath Hospital in 2006. Participants were recruited after being screened and counseled by their clinicians. These included participants with risk factors for developing CKD such as hypertension, diabetes mellitus and HIV as well as patients with established CKD. All participants were older than 18 years. Exclusion criteria were pregnancy, acute kidney injury and oedema. 100 black South Africans with varying degrees of renal function were enrolled in the study. Informed consent was obtained from all participants after being educated with regard to the potential benefits, risks and the study procedures. The study was approved by the Human Research Ethics Committee of the University of the Witwatersrand.

Test Methods

Age (years), standing height (centimeters), weight (kilogram) and gender were recorded for all participants. A 5 ml blood sample was collected for serum creatinine measurement prior to GFR measurement. Serum creatinine was measured using an alkaline picrate rate-blanked compensated kinetic assay (Roche Modular analyzer, Roche Diagnostics, Mannheim, Germany) with calibration traceable to IDMS. To assess possible calibration differences a calibration panel obtained from the Cleveland Clinic Foundation was used. This calibration panel consisted of 40 serum samples, with values assigned by a Roche enzymatic assay (Creatinine Plus, Roche Diagnostics) measured at the Cleveland Clinic Laboratories. This assay has been independently validated to be traceable to IDMS (19).

GFR Measurements

In this study ^{51}Cr-EDTA plasma clearance was used as a reference method for measuring GFR. GFR was measured according to guidelines adopted by the British Nuclear Medicine Society (20). GFR was calculated with the slope intercept method (21) corrected with the Brochner-Mortensen equation (22) and normalized to body surface area (BSA) using the DuBois method (BSA (m^2) = (71.84 weight (kg)$^{0.425}$ * height (cm)$^{0.725}$) / 10 000) (23). This measurement will be referred to as measured GFR (mGFR).

(For a detailed description of the GFR measurements see Supplemental File: GFR measurement protocol)

GFR Estimations

GFR was estimated using the following equations:

1. **The re-expressed 4-v MDRD equation** (18, 25):

eGFR (mL/min/1.73m^2) = 175 * (S-Cr (µmol/L) / 88.4) $^{-1.154}$ * (age) $^{-0.203}$ * (0.742 if female) * (1.212 if African American)

To assess the validity of the African American term in the black South African population GFR was estimated both with and without the African American ethnicity factor.

2. **The Cockcroft-Gault equation (15) normalized to 1.73 m^2**:

eGFR (mL/min/1.73m^2) = [(140 – age) * Weight (kg) * (0.85 if female) * 1.73 (m^2)] / [S-Cr (µmol/L) * 0.814 * BSA (m^2)]

The CG equation was normalized to 1.73m^2 to allow comparison with the 4-v MDRD equation and measured GFR. This is in keeping with most studies but is unlikely to reflect standard clinical practice (24). As the CG equation was developed with CrCl as the reference procedure and a creatinine assay not traceable to current IDMS values, bias is to be expected for the CG equation. To minimize this bias a correction factor for the CG equation was established. This correction factor was determined from the dataset of 100 patients by minimizing the sum of the squared residuals (the difference between eGFR and mGFR).

Statistical Methods

Statistical analysis was conducted using Analyse-it for Microsoft Excel. The Shapiro-Wilk test was used to test for normality. Continuous data variables are expressed as mean ± SD if parametric and median (IQR) if non parametric. The performance of the 4-v MDRD equation, both with and without the ethnicity factor and the Cockcroft-Gault equation normalized to 1.73m^2 were all assessed relative to that of mGFR by use of: (1) Spearman correlation coefficient, (2) weighted Deming regression analysis, (3) median percentage difference between estimated and measured GFR (percentage bias) and (4) proportion of eGFR within 30% of mGFR (P_{30}). Weighted Deming regression analysis was used to take into account random error in both measured GFR and serum creatinine measurement (25).

Results

Participants

Between August 2006 and November 2006, 100 black South Africans, 51 males and 49 females, were enrolled in the study. All participants were inpatients at the Chris Hani Baragwanath hospital or were being followed up at the renal unit outpatient department at the hospital. The study population had a median age of 47 (26), with an age range between 18 years and 86 years. Median weight was 67 (15) kg, and ranged between 46 and 119 kg. Participants included suffered from a wide range of different diseases. The most common of which included hypertension (n = 36), diabetes mellitus (n = 25) and HIV (n = 20). Other diagnoses included renal calculi, deep venous thrombosis, meningitis, multiple myeloma, nephrotic syndrome and epilepsy. Participants being worked up for possible kidney donation were also included (n = 7). The median mGFR was 61.7 (53.9) mL/min/1.73m^2 with a range between 3 and 132 mL/min/1.73m^2. (See Supplemental Data Table 1)

Test results

Creatinine Calibration

Evaluation of S-Cr calibration was based on 39 observations as one of the samples with a difference between the assigned value and the measured value more than 3 SDs from the mean difference was excluded from the analysis. The measurements were done in triplicate in three separate runs with measured S-Cr values ranging from 44 µmol/L to 398 µmol/L. The correlation between the Cleveland Clinic Foundation (CCF) assigned values and the South African measured values was high (R^2 = 0.999). Deming regression analysis was used to calculate the slope, 0.964 (95% CI 0.952 to 0.975) and intercept, 0.039 (95% CI 0.010 to 0.068) of the regression equation, with y = CCF assigned values and x = SA measured values. Because of this small but significant regression slope, measured S-Cr (SA) values were

standardized to CCF values. The resulting equation to standardize S-Cr (SA) was: Standardized S-Cr = 0.039 + 0.964 * S-Cr (SA). Standardized S-Cr values were used in all calculations.

Comparison of measured GFR to the 4-variable MDRD equation

The Spearman correlation coefficient between mGFR and the 4-v MDRD equation was 0.90 (95% CI 0.85-0.93). Weighted Deming regression analysis showed a significant proportional bias 1.24 (95% CI 1.09 to1.38, p = 0.001) but no significant constant bias 0.24 (95% CI -5.91 to 5.43, p = 0.93) when the established ethnicity factor of 1.212 was used. Without the ethnicity factor weighted Deming regression analysis showed no significant proportional bias 1.02 (95% CI 0.90 to 1.14, p = 0.73) or constant bias 0.02 (95% CI -4.61 to 4.65, p = 0.99). The percentage bias (median percentage difference between eGFR and mGFR) for the 4-v MDRD equation with the established ethnicity factor of 1.212 was 27 %. Without the ethnicity factor, percentage bias was 5 %. With the ethnicity factor of 1.212 P_{30} for the 4-v MDRD equation was 52 % compared to 74 % without the ethnicity factor. (Fig. 1)

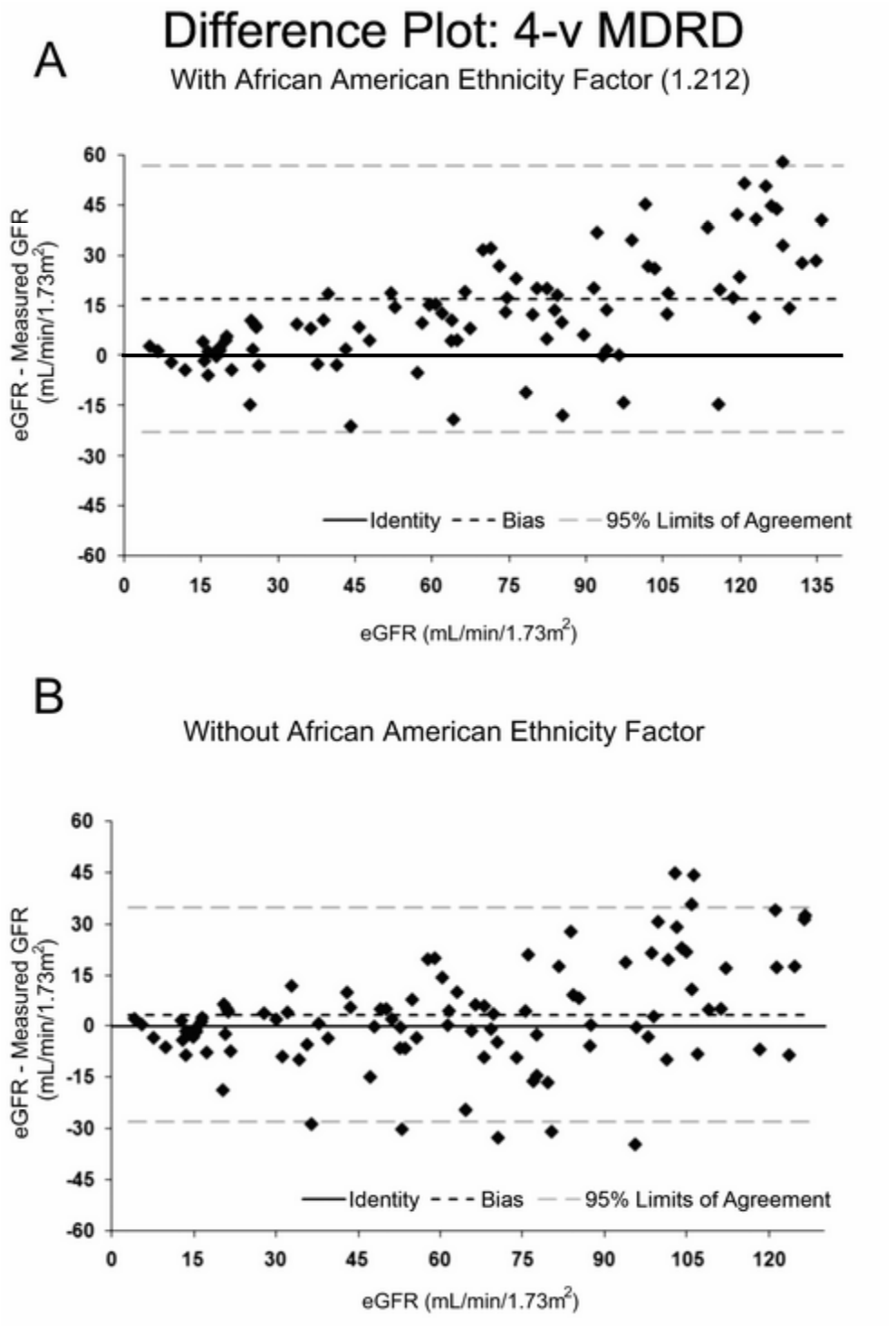


Fig 1: Difference Plot: 4-v MDRD equation and measured GFR

(A) Difference Plot, With African American Ethnicity Factor (1.212)

(B) Difference Plot, Without African American Ethnicity Factor

Comparison of measured GFR to the Cockcroft-Gault equation

The Spearman correlation coefficient between mGFR and CG normalized to 1.73m^2 was 0.89 (95% CI 0.85 to 0.93). Weighted Deming regression analysis comparing the CG equation to mGFR showed a significant proportional bias 1.13 (95% CI 1.03 to 1.23, p = 0.01) but no significant constant bias 2.38 (95% CI -1.37 to 6.13, p = 0.21). Percentage bias for the CG equation was 19 %. P_{30} for the CG equation was 58 %. The factor calculated to minimize bias of the CG equation in this dataset was 0.82 (95% CI 0.78 to 0.85). Correcting the CG equation for bias, eGFR (mL/min/1.73m^2) = 0.82 * CG (mL/min/1.73m^2), improved P_{30} to 71 %.

Performance of equations at different stages of renal disease

For each of the eGFR equations the dataset was split into three groups: eGFR < 30 mL/min/1.73m^2, eGFR 30-60 mL/min/1.73m^2 and eGFR > 60 mL/min/1.73m^2. In each of these groups median difference between eGFR and mGFR (bias), percentage bias, inter quartile range of the difference between eGFR and mGFR's (IQR) and root mean squared error (RMSE)were calculated. For each of the equations, bias, IQR and RMSE increased at higher levels of eGFR (Table 1).

Table 1: Performance of equations

eGFR	*N*	*Median bias (95 % CI) (mL/min/1.73m²)*	*Median percentage bias (%)*	*IQR [a] (mL/min/1.73m²)*	*RMSE [b] (mL/min/1.73m²)*	*P_{30} [c] (%)*
4-v MDRD (Ethnicity Factor 1.212)						
eGFR (< 30 mL/min/1.73m²)	20	1.7 (-1.7 to 4.4)	10.0	7.0	7.2	55
eGFR (30-60 mL/min/1.73m²)	15	8.8 (-2.2 to 14.8)	23.8	15.7	18.0	53
eGFR (> 60 mL/min/1.73m²)	65	20.4 (17.6 to 28)	28.8	28.6	35.1	51
Overall	100	13.1 (5.5 to 18.3)	27.0	25.2	28.5	52
4-v MDRD (Without Ethnicity Factor)						
eGFR (< 30 mL/min/1.73m²)	21	-1.4 (-4.0 to 2.2)	-6.7	7.0	7.2	67
eGFR (30-60 mL/min/1.73m²)	24	0.4 (-6.4 to 5.1)	1.4	11.8	11.8	75
eGFR (> 60 mL/min/1.73m²)	55	5.1 (-0.3 to 17.0)	8.8	26.3	26.8	76
Overall	100	1.9 (-0.8 to 4.5)	4.8	16.4	16.6	74
Cockcroft-Gault						
eGFR (< 30 mL/min/1.73m²)	19	4.1 (-0.1 to 6.2)	18.7	6.0	7.3	47
eGFR (30-60 mL/min/1.73m²)	18	6.0 (0.1 to 14.6)	17.4	15.0	16.1	67
eGFR (> 60 mL/min/1.73m²)	63	14.7 (10.6 to 22.7)	19.2	27.2	30.9	59
Overall	100	9.0 (5.1 to 12.1)	19.1	21.1	22.9	58
Cockcroft-Gault * 0.82						
eGFR (< 30 mL/min/1.73m²)	22	-0.7 (-3.3 to 3.0)	-2.7	6.5	6.5	59
eGFR (30-60 mL/min/1.73m²)	31	-2.0 (-8.0 to 1.7)	-5.0	16.5	16.6	74
eGFR (> 60 mL/min/1.73m²)	47	1.8 (-4.8 to 10.2)	1.9	31.8	31.9	74
Overall	100	-0.9 (-3.3 to 1.9)	-2.4	16.9	16.9	71

[a] IQR: Inter quartile range of the difference between estimated and measured GFR, [b] RMSE, root mean squared error, calculated as the square root of the [(median difference in estimate – measured)^2 + (inter quartile range of the difference)^2], [c] P30: Accuracy within 30 % of measured GFR.

Discussion

CKD is increasingly recognized as a global public health problem (1). The high prevalence of hypertension, diabetes mellitus and HIV in sub-Saharan Africa has resulted in a high risk for CKD (2). The early detection of CKD using simple laboratory tests and GFR prediction equations, such as the CG and 4-v MDRD equation is important for the prevention of long term complications.

Neither the CG nor the 4-v MDRD equation has previously been validated in Africa. The 4-v MDRD equation has also not been validated in a black population with a different body habitus to that of the African Americans. Our results show that both the CG, after correcting for bias, and the 4-v MDRD, without the ethnicity factor established for African Americans, can be used in black South Africans for estimating GFR.

Many recent articles have underscored the importance of creatinine standardization (17). For this study we used an alkaline picrate rate-blanked compensated kinetic assay (Roche Diagnostics) with calibration traceable to IDMS. In a study by Miller et al this method showed minimal bias compared to an IDMS value (26). In this study possible calibration differences were also assessed and corrected for by using a calibration panel with values assigned by the Roche enzymatic assay (Cleveland Clinic Foundation). As the S-Cr results were traceable to IDMS the re-expressed 4-v MDRD equation (14) was used.

The correlation coefficient for the 4-v MDRD equation was similar to studies done in other population groups (27-29). The 4-v MDRD equation using the ethnicity factor of 1.212 as suggested for African Americans overestimated mGFR in black South Africans. Without the ethnicity factor, thus using the same equation as established for Caucasians in the MDRD

study, median overestimation was minimal and there was no significant proportional bias. Accuracy within 30 % of mGFR, 52 % with the ethnicity factor of 1.212 and 74 % without the ethnicity factor also improved.

Goldwasser et al showed that African Americans have higher renal creatinine excretion per kilogram body weight than Caucasians and concluded that this may be related to differences in body composition, muscle metabolism, or diet (30). Lewis et al showed higher serum creatinine levels and urinary creatinine excretion rates for a given GFR in African Americans compared with non-African Americans (31). This may not be true for black South Africans as the two populations have different origins (32).

Creatinine generation is determined primarily by muscle mass and dietary intake (6). Differences in the ethnicity factor established for African Americans and black South Africans may be attributed to differences in muscle mass and body composition as well as differences in diet. Various studies have shown that West African athletes have less body fat and thicker thighs than Caucasians and this difference is even more striking between East and West Africans (33). Mean weight and body surface area for the MDRD study population was 79.6 ± 16.8 kg and 1.91 ± 0.23 m^2 respectively (16). Mean weight and body surface area for the MDRD African American study population were 84.1 kg and 1.96m^2 respectively (31). Mean weight and BSA for the African-American Study of Kidney disease and hypertension (AASK) was 90.2 kg and 2.02 m^2 respectively (31). As compared to our study which had a mean weight and mean BSA of 69.5 ± 13.8 kg and 1.76 ± 0.17 m^2 respectively. Differences in dietary intake are difficult to quantify it is possible that black South Africans consume less creatinine generating food than African Americans due to poorer socioeconomic circumstances (34).

The CG equation is still commonly used for estimating creatinine clearance as an indicator of GFR and was therefore included in the analysis. The correlation coefficient for the CG equation was similar to studies done in other population groups (27, 28). The positive bias observed for the CG equation may be attributed to the CG equation being established using creatinine clearance as a reference procedure which overestimates GFR due to the tubular secretion of creatinine (6). It may also be attributed to calibration biases between creatinine measurement for the original Cockcroft-Gault study and our present study as well as the CG equation being established in a different population group relative to our study.

The study population included 20 patients who were known to be infected with HIV. In South Africa the Nelson Mandela/Human Sciences Research Council survey estimated the prevalence of HIV in the adult population (aged 15 and 49 years old) to be 15.6% (35). Chronic kidney disease (CKD) is increasingly being recognized as an important complication of HIV Infection (36) and the estimation of GFR in this population group is therefore important. Further studies are needed to evaluate the performance of the 4-v MDRD equation in patients infected with HIV.

Limitations of the study were as follows: 1) The relative small sample size of the study. 2) The study was conducted at only one geographical site which does not adequately represent all population groups in South Africa. Further studies for these population groups are needed. 3) The characteristics of the study population differed from that of the MDRD study population. The study population included hospitalized patients and participants who were known to be infected with HIV. In these participants creatinine production may differ and they may have reduced creatinine excretion compared to the MDRD study population which

consisted out of outpatients with CKD who were otherwise healthy. 4) In this study plasma sampling was done at 2 and 4 hours for patients with eGFR > 30mL/min/1.73m^2 and at 3 and 5 hours for patients with eGFR < 30 mL/min/1.73m^2. Using the renal clearance of ^{51}Cr-EDTA as a reference procedure Brochner-Mortensen et al showed that in patients with advanced chronic kidney disease (GFR range: 3 – 13 mL/min) plasma sampling done at 4 and 24 hours after injection is more reliable (0.5 mL/min ± 0.5 mL/min) than plasma sampling done between 3 and 5 hours (3.7 mL/min ± 2.2 mL/min) (37). However in the SA context delayed plasma sampling may have resulted in patients being lost to follow up. 6) The Cleveland Clinic calibration panel and participant samples were run at different times. A residual calibration error is therefore still possible.

In summary, our study confirms that both the 4-v MDRD equation, without the ethnicity factor of 1.212, and the Cockcroft-Gault equation, after correcting for bias, can be used for estimating GFR in black South Africans.

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Appendix I: GFR Measurement Protocol

In this study ^{51}Cr-EDTA plasma clearance was used as a reference method for measuring GFR. A close correlation between plasma clearance of ^{51}Cr-EDTA and inulin clearance has been demonstrated (1, 2).

GFR was measured according to guidelines adopted by the British Nuclear Medicine Society (3). 3.7 MBq ^{51}Cr-EDTA (Amersham, UK) was injected intravenously in an antecubital vein and the line flushed with 10 ml 0.9 % saline. Blood samples were then collected from the contralateral arm at 120 and 240 minutes post injection for patients with eGFR > 30 mL/min/1.73m^2 and at 180 and 300 minutes post injection for patients with eGFR < 30 mL/min/1.73m^2. The exact time of sample collection was noted and used in the calculation of GFR. After centrifugation (3000 g for 10 min) the radioactivity in all plasma samples was counted on a gamma counter (Cobra, Auto-Gamma counter, Packard Biosciences) for 5 min with appropriate standards and blanks. All counting was done in triplicate. GFR was then calculated with the slope intercept method (2) corrected with the Brochner-Mortensen equation (4). GFR was normalized to body surface area (BSA) using the DuBois method (BSA (m^2) = (71.84 weight (kg)$^{0.425}$ * height (cm)$^{0.725}$) / 10 000) (5). This measurement will be referred to as measured GFR (mGFR).

^{51}Cr-EDTA plasma clearance using the slope intercept method corrected with the Brochner-Mortensen equation provides a good compromise between accuracy and reliability on the one hand and simplicity on the other hand (3). This method has been independently validated by Fleming et al (6). Picciotto et al showed that ^{51}Cr-EDTA total plasma clearance can be

accurately calculated using the slope-intercept method corrected with the Brochner-Mortensen equation for clearance values as low as 10 mL/min/1.73m^2 (7).

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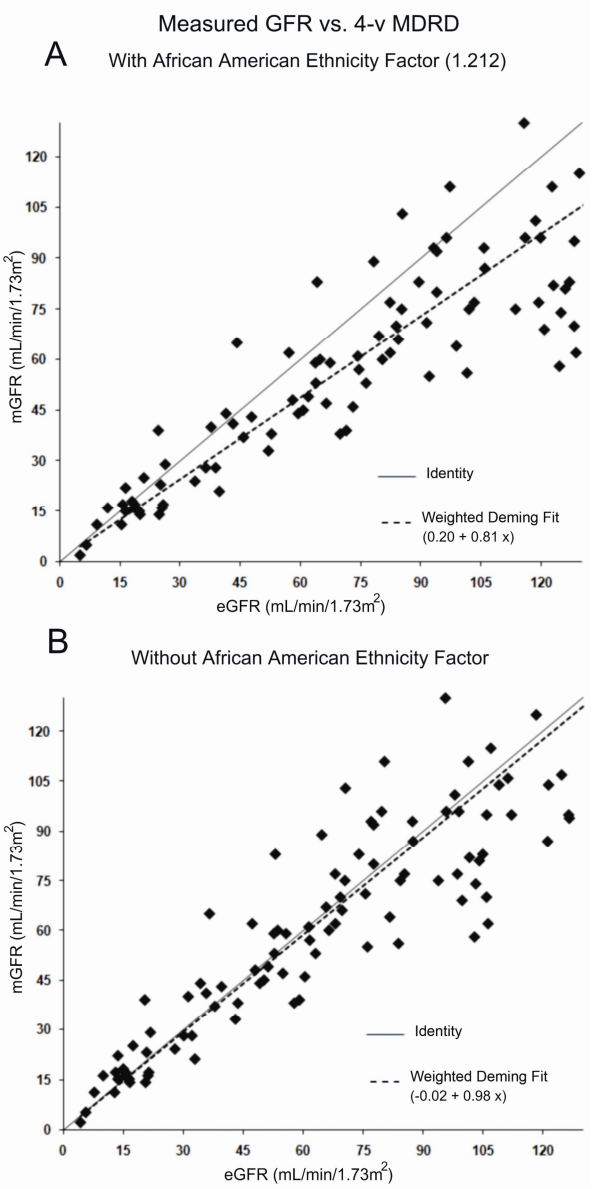
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Appendix II: Supplemental Table

Table: Participant Characteristics

	Median (IQR)
Age, years	47 (26)
Males	40 (27)
Females	49 (25)
Weight, kg	67 (15)
Males	67 (16)
Females	67 (15)
Height, cm	168 (12)
Males	171 (7)
Females	161 (12)
Body surface area, m^2	1.75 (0.19)
Males	1.79 (0.20)
Females	1.69 (0.17)
Standardized S-Cr, µmol/L	97 (91)
Males	102 (103)
Females	80 (84)
Measured GFR, mL/min/1.73m^2	62 (49)
Males	62 (58)
Females	61 (48)

Appendix III: Supplemental Figure



Supplemental Fig: Weighted Deming Regression Analysis between 4-v MDRD equation and measured GFR:

(A) Weighted Deming regression analysis , With African American Ethnicity Factor: 1.212

(B) Weighted Deming regression analysis, Without African American Ethnicity Factor

Appendix IV: Analysis of Participants known to be HIV positive

A limitation to this study is that the study population included hospitalized patients and participants who were known to be infected with HIV. In these participants creatinine production may potentially differ and they may have reduced creatinine excretion compared to the MDRD study population which consisted out of outpatients with CKD who were otherwise healthy.

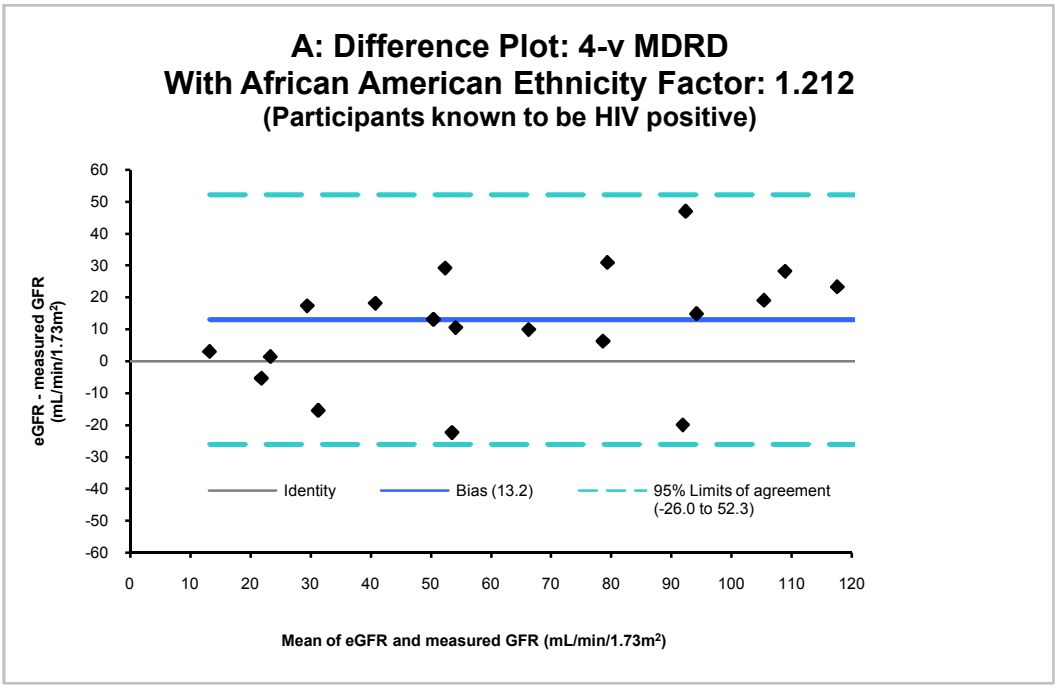
Analysis of this subset of participants is therefore of importance. The study population included 20 patients who were known to be HIV positive.

Participants known to be HIV positive

This study population had a median age of 35 (10), with an age range between 27 years and 54 years. Median weight was 60 (9) kg, and ranged between 49 and 92 kg. The Mann-Whitney test showed a significant difference in weight in participants known to be infected with HIV and the remaining participants, 68 (16) kg ($P < 0.05$). The Mann Whitney test did not show a significant difference between median S-Cr results for the group known to be HIV positive 106 (106) μmol/L and the remaining participants 93 (87) μmol/L (P=0.68). The median mGFR was 66 (57) mL/min/1.73m^2 with a range between 11 and 103 mL/min/1.73m^2. The Mann Whitney test did not show any significant difference between mGFR for this group known to be HIV positive and the remaining participants (mGFR = 60 (48) mL/min/1.73m^2) (P=0.64).

Comparison of measured GFR to the 4-variable MDRD equation in subset of participants known to be HIV positive

The Spearman correlation coefficient between mGFR and the 4-v MDRD equation was 0.87 (95% CI 0.69-0.95). Proportional bias and constant bias, calculated using weighted Deming Regression analysis, was 1.23 (95% CI 0.98 to1.49, p = 0.07) and -1.35 (95% CI 11.28 to 8.58, p = 0.78) respectively when the established ethnicity factor of 1.212 was used. Without the ethnicity factor proportional bias was 1.01 (95% CI 0.82 to 1.20, p = 0.91) and constant bias was -0.49 (95% CI -7.11 to 6.12, p = 0.88). The percentage bias (median percentage difference between eGFR and mGFR) for the 4-v MDRD equation with the established ethnicity factor of 1.212 in this subset of patients was 22 %. Without the ethnicity factor, median percentage bias was 1 %. With the ethnicity factor of 1.212 P_{30} for the 4-v MDRD equation was 60 % compared to 70 % without the ethnicity factor.



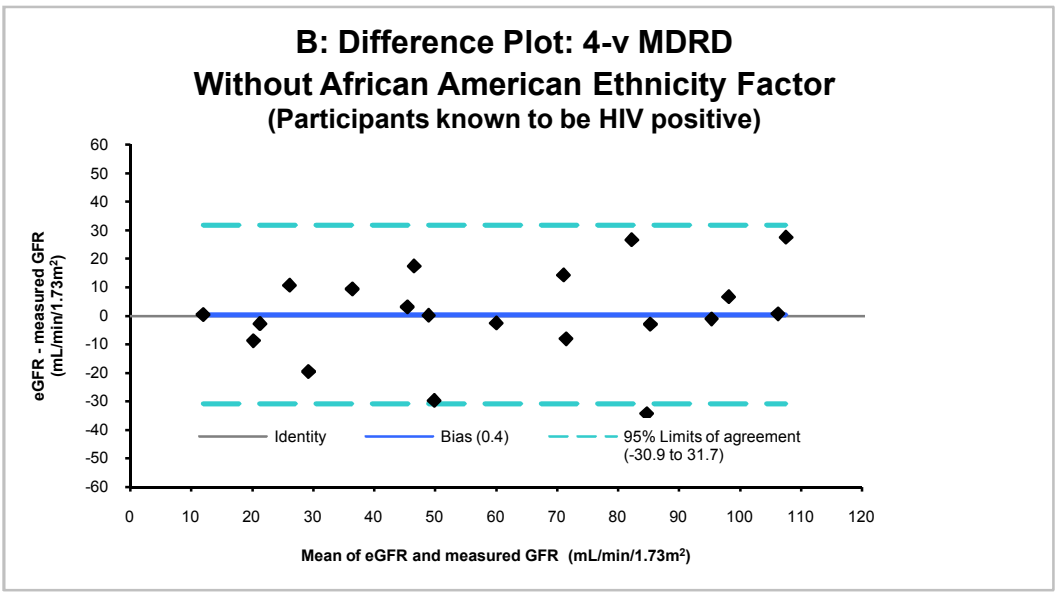


Fig 1: Difference Plot: 4-v MDRD equation and measured GFR (Participants known to be HIV positive)

(A) Difference Plot, With African American Ethnicity Factor (1.212)

(B) Difference Plot, Without African American Ethnicity Factor

Discussion

Stohr et al reported, as part of the Development of Antiretroviral Therapy in Africa (DART) study, that moderate renal impairment in HIV infected adults in Africa, was more frequently identified using Cockcroft-Gault eGFR than 4-v MDRD eGFR (with the established African American ethnicity factor) (1). However no "gold standard" GFR measurement was used. A potential reason for this is that using the African American ethnicity factor in the African population results in an overestimation of true GFR. In this study the percentage bias (median percentage difference between eGFR and mGFR) for the 4-v MDRD equation with the established ethnicity factor of 1.212 for all participants was 27 %. Without the ethnicity factor, percentage bias was 5 %. The percentage bias (median percentage difference between eGFR and mGFR) for the 4-v MDRD equation with the established ethnicity factor of 1.212 in the subset of patients known to be infected with HIV was 22 %. Without the ethnicity factor, median percentage bias was 1 %.

Barraclough et al recently reported in a small (n=27) study, using the renal clearance of Tc-99m Pentetate as GFR measurement, that the 4-v MDRD equation performed with a level of accuracy and precision sufficient for clinical decision making (2). Ravasi et al reported that the 4-v MDRD equation showed a satisfactory correlation with creatinine clearance (3).

Further studies evaluating GFR estimation equations in patients with HIV are necessary.

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Appendix V: Limitations of Glomerular Filtration Rate estimation equations

Limitations of eGFR equations are well described and various articles caution against the indiscriminate use of eGFR equations.

Currently the 4-v MDRD equation is not recommended for drug dosing adjustment. Creatinine calibration to ID-MS reference methods results in lowering of creatinine results compared to creatinine measurements performed to establish drug dosing adjustment guidelines (1). Current drug dosing guidelines use the Cockcroft-Gault equation to estimate creatinine clearance and these estimation equations have not been adjusted for use with ID-MS traceable creatinine measurements (1). It is also important to note that the Cockcroft Gault equation estimates creatinine clearance (2) and the 4-v MDRD equation estimates GFR (3). In a recent study Roblin et al showed significant differences in estimates obtained by the Cockcroft-Gault equation and 4-v MDRD equation and concludes that the4-v MDRD equation cannot replace the Cockcroft Gault equation for drug dose adjustment (4).. Kallner et al caution that the 4-v MDRD equation does not include any body size marker and is thus a dangerous marker for guiding drug administration (5).

Use of the 4-v MDRD equation is not recommended for acutely ill patients. Poggie et al reported accuracy within 50 % of measured GFR to be only 49 % for the 4-v MDRD equation in sick patients with renal dysfunction (6).

The performance of the 4-v MDRD equation in patients without CKD is unclear (7). Current recommendation state that eGFR for these patients should be reported as "> 60 mL/min/1.73m^2" (8). It has also been shown that eGFR present a significant underestimation compared to "gold standard" measured GFR in diabetic patients with hyperfiltration (9).

Little evidence exists validating the 4-v MDRD equation in older people (> 75 years) (7). Lamb et al reported that in a group of patients aged 69 – 92 years that the 4-v MDRD equation performed reasonably well in this population but that further larger studies are needed (10).

Application of 4-v MDRD eGFR may lead to errors in GFR estimation on persons with extremes of body size, muscle mass or nutritional status (11, 12).

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Appendix VI: Glomerular Filtration Rate estimation equations in other population groups

The MDRD equation was developed in the United States and included both Caucasian and African American participants with chronic kidney disease, for the African American population an ethnicity factor was established for use with the MDRD equation (1). The validity of the MDRD study in other population groups needs to be evaluated (2). Various studies have been done evaluating the MDRD equation in different population groups (Table 1). Most of these studies found the MDRD equation to be valid, a notable exception being the study by Ma et al which established a modified MDRD equation for the Chinese population (3).

Table 1: Characteristics of some studies in which the MDRD equation has been evaluated

Author	Population	Participant characteristics	Reference GFR measurement
Lewis et al. 2001 (4)	United States - African Americans	Presumed hypertensive nephrosclerosis	^{125}I-iothalamate clearance
Ma et al. 2006 (3)	Chinese	Chronic Kidney Disease	^{99m}Tc-DTPA clearance
Imai et al. 2007 (5)	Japanese	Chronic Kidney Disease	Inulin clearance
Jafar et al. 2005 (6)	Pakistan	Age > 40 years	Creatinine clearance
Mahajan et al. 2005 (7, 8)	India	Renal donors	^{99m}Tc-DTPA clearance
Jones et al. 2009 (9)	Australia	Patients routinely referred for GFR measurement	^{99m}Tc-DTPA clearance
Nobrega et al. 2006 (10)	Brasilia	Chronic kidney disease	Creatinine clearance
Ibrahim et al. 2008 (11)	Egypt	Renal donors	^{99m}Tc-DTPA clearance
Bostom et al. 2002 (12)	Germany and Austria	Chronic Kidney Disease	Iohexol clearance
Van Den Noortgate et al. 2002 (13)	Belgium	Geriatric (> 70 years) hospital inpatients	^{51}Cr-EDTA clearance
Mariat et al. 2002 (14)	France	Renal transplant recipients	Inulin clearance

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1197–1202 (2008)

Estimating Glomerular Filtration Rate in Black South Africans by Use of the Modification of Diet in Renal Disease and Cockcroft-Gault Equations

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BACKGROUND: The 4-variable Modification of Diet in Renal Disease (4-v MDRD) and Cockcroft-Gault (CG) equations are commonly used for estimating glomerular filtration rate (GFR); however, neither of these equations has been validated in an indigenous African population. The aim of this study was to evaluate the performance of the 4-v MDRD and CG equations for estimating GFR in black South Africans against measured GFR and to assess the appropriateness for the local population of the ethnicity factor established for African Americans in the 4-v MDRD equation.

METHODS: We enrolled 100 patients in the study. The plasma clearance of chromium-51–EDTA (^{51}Cr-EDTA) was used to measure GFR, and serum creatinine was measured using an isotope dilution mass spectrometry (IDMS) traceable assay. We estimated GFR using both the reexpressed 4-v MDRD and CG equations and compared it to measured GFR using 4 modalities: correlation coefficient, weighted Deming regression analysis, percentage bias, and proportion of estimated GFR within 30% of measured GFR (P_{30}).

RESULTS: The Spearman correlation coefficient between measured and estimated GFR for both equations was similar (4-v MDRD $R^2 = 0.80$ and CG $R^2 = 0.79$). Using the 4-v MDRD equation with the ethnicity factor of 1.212 as established for African Americans resulted in a median positive bias of 13.1 (95% CI 5.5 to 18.3) mL/min/1.73 m^2. Without the ethnicity factor, median bias was 1.9 (95% CI −0.8 to 4.5) mL/min/1.73 m^2.

CONCLUSIONS: The 4-v MDRD equation, without the ethnicity factor of 1.212, can be used for estimating GFR in black South Africans.

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Globally, chronic kidney disease (CKD)[4] is recognized as an important public health problem *(1)*. In South Africa, the high prevalence of hypertension, diabetes, and infection with HIV results in a significant risk for CKD *(2)*; it is therefore important to detect kidney dysfunction as early as possible in this population. Current guidelines define CKD as the presence, for 3 or more months, of either kidney damage as defined by structural or functional abnormalities of the kidney or a glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 *(3, 4)*. GFR, an important component in the diagnosis of CKD, is also accepted as the best overall measure of kidney function *(3, 5)*. Individuals with decreased GFR are at increased risk not only for the development of end-stage renal failure, but also for hospitalizations, cardiovascular disease, and other complications of decreased kidney function *(6–10)*. It has been shown that early detection, appropriate evaluation, and management of CKD improves outcome *(1, 3, 4)*.

GFR can be measured as the renal clearance of exogenous markers such as inulin, chromium-51–EDTA (^{51}Cr-EDTA), technetium-labeled diethylene-triaminepentacetate (^{99m}Tc-DTPA), and iohexol. These exogenous markers are impractical for routine use, however. Endogenous GFR markers include creatinine and cystatin C. Creatinine is the most commonly used marker in the clinical laboratory to assess GFR, but it

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[4] Nonstandard abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate; ^{51}Cr-EDTA, chromium-51–EDTA; eGFR, estimated GFR; S-Cr, serum creatinine; 4-v MDRD, 4-variable Modification of Diet in Renal Disease; CG, Cockcroft-Gault; IDMS, isotope dilution mass spectrometry; CrCl, creatinine clearance; BSA, body surface area; mGFR, measured GFR; IQR, interquartile range.

has multiple limitations *(11)*—for example, it is also affected by factors such as muscle mass, diet, sex, and age *(12, 13)*.

To overcome some of these limitations, the National Kidney Foundation–Kidney Disease Outcomes Quality Initiative and Kidney Disease: Improving Global Outcomes guidelines recommend the estimation of GFR (eGFR) using prediction equations based on serum creatinine (S-Cr) *(3, 4)*. The 2 most commonly used prediction equations are the 4-variable Modification of Diet in Renal Disease (4-v MDRD) *(14)* and Cockcroft-Gault (CG) *(15)* equations. The MDRD equation was derived in the United States by analysis of data from 1628 patients (651 women and 195 African-Americans) with known kidney disease using ^{125}I-iothalamate clearance to measure GFR as the reference procedure (mean GFR 40 mL/min/1.73 m^2) and was based on 6 variables: age, sex, serum creatinine, urea, albumin, and ethnicity *(16)*. Subsequently, a 4-v MDRD equation based on 4 variables—age, sex, serum creatinine, and ethnicity—was proposed to simplify its use in the clinical environment *(14)*. An ethnicity factor of 1.212 was established for African Americans *(14, 16)*.

Because of variability in serum creatinine assays, the National Kidney Disease Education Program Laboratory Working Group initiated a creatinine standardization program with creatinine calibration traceable to isotope dilution mass spectrometry (IDMS) creatinine measurement *(17)*. The 4-v MDRD equation was reexpressed for use with the IDMS traceable creatinine measurements *(18)*.

The Cockcroft-Gault equation was derived from 236 hospital inpatients in Canada (4% women, ethnicity not stated) with measured creatinine clearance (CrCl) as the reference procedure (mean CrCl 73 mL/min) *(15)*.

Neither of these formulae nor the ethnicity factor of 1.212 established for African Americans has yet been evaluated in African or non-American black populations. The applicability of these equations and the factor for ethnicity to black South Africans is therefore unknown. The aim of this study was to examine the applicability of the 4-v MDRD and CG equations for estimating GFR in black South Africans against measured GFR and to evaluate whether the ethnicity factor established for African Americans is appropriate for black South Africans.

Materials and Methods

PARTICIPANTS

We conducted a prospective study of patients seen at Chris Hani Baragwanath Hospital in 2006. Participants, who were recruited after being screened and counseled by their clinicians, were older than 18 years and had established CKD or risk factors for developing CKD, such as hypertension, diabetes, and HIV. Exclusion criteria were pregnancy, acute kidney injury, and edema. We enrolled 100 black South Africans with varying degrees of renal function. All participants gave informed consent after being educated with regard to potential benefits, risks, and study procedures. The study was approved by the Human Research Ethics Committee of the University of the Witwatersrand.

TEST METHODS

Age (years), standing height (centimeters), weight (kilograms), and sex were recorded for all participants. Before GFR measurement, we collected a 5-mL blood sample for serum creatinine measurement using an alkaline picrate rate-blanked compensated kinetic assay (Roche Modular analyzer; Roche Diagnostics) with calibration traceable to IDMS. To assess possible calibration differences, we used a calibration panel of 40 serum samples (Cleveland Clinic Foundation), with values assigned by a Roche enzymatic assay (Creatinine Plus; Roche Diagnostics), that has been independently validated as traceable to IDMS *(19)*.

GFR MEASUREMENTS

We used ^{51}Cr-EDTA plasma clearance as a reference method for measuring GFR. GFR was measured according to guidelines adopted by the British Nuclear Medicine Society *(20)* and calculated with the slope intercept method *(21)*, corrected with the Brochner-Mortensen equation *(22)*, and normalized to body surface area (BSA) using the DuBois method: BSA (m^2) = [71.84 × weight (kg)$^{0.425}$ × height (cm)$^{0.725}$]/10 000 *(23)*. This value is referred to as measured GFR (mGFR). (For a detailed description of the GFR measurements, see the Data Supplement that accompanies the online version of this article at www.clinchem.org/content/vol54/issue7.)

GFR ESTIMATIONS

GFR was estimated using the following equations:

- reexpressed 4-v MDRD equation *(18, 24)*: eGFR (mL/min/1.73 m^2) = 175 × [S-Cr (μmol/L)/88.4]$^{-1.154}$ × age (years)$^{-0.203}$ × (0.742 if female) × (1.212 if African American)

- Cockcroft-Gault equation *(15)* normalized to 1.73 m^2: eGFR (mL/min/1.73 m^2) = [(140 − age in years) × weight (kg) × (0.85 if female) × 1.73 (m^2)]/[S-Cr (μmol/L)× 0.814 × BSA (m^2)]

To assess the validity of the 4-v MDRD equation with the African American factor in the black South African population, GFR was estimated both with and without this factor. The CG equation was normalized to 1.73 m^2 to allow comparison with the 4-v MDRD equation and measured GFR. This is in keeping with most studies but is unlikely to reflect standard clinical practice *(25)*. Because the CG equation was developed with CrCl as the reference procedure and a creatinine assay not traceable to current IDMS values, bias is to be expected for the CG equation. To minimize this bias, we established a correction factor for the CG equation, determined from the dataset of 100 patients by minimizing the sum of the squared residuals (the difference between eGFR and mGFR).

STATISTICAL METHODS

Statistical analysis was conducted using Analyze-it for Microsoft Excel. We used the Shapiro-Wilk test to test for normality. Continuous data variables are expressed as mean (SD) if parametric and median [interquartile range (IQR)] if nonparametric. We assessed the performance of the 4-v MDRD equation, both with and without the ethnicity factor, and the Cockcroft-Gault equation normalized to 1.73 m^2 relative to that of mGFR by use of Spearman correlation coefficient, weighted Deming regression analysis, median percentage difference between estimated and measured GFR (percentage bias), and proportion of eGFR within 30% of mGFR (P_{30}). We used weighted Deming regression analysis to take into account random error in both measured GFR and serum creatinine measurement *(24)*.

Results

PARTICIPANTS

Between August 2006 and November 2006, 100 black South Africans (51 men and 49 women) were enrolled in the study. All participants were inpatients at the Chris Hani Baragwanath hospital or were being followed up at the renal unit outpatient department at the hospital. The study population had a median (IQR) age of 47 (26) years, range 18–86 years. Participants suffered from a wide range of different diseases, the most common of which included hypertension (n = 36), diabetes (n = 25), and HIV (n = 20). Other diagnoses included renal calculi, deep venous thrombosis, meningitis, multiple myeloma, nephrotic syndrome, and epilepsy. Participants being worked up for possible kidney donation were also included (n = 7). The median mGFR was 61.5 (49.6) mL/min/1.73 m^2, range 3–132 mL/min/1.73 m^2. (See Supplemental Table 1.)

CREATININE CALIBRATION

Evaluation of S-Cr calibration was based on 39 observations, after excluding one of the samples with a difference between the assigned value and the measured value of >3 SDs from the mean difference. The measurements were done in triplicate in 3 separate runs, with measured S-Cr values ranging from 44 to 398 μmol/L. The correlation between the Cleveland Clinic Foundation (CCF) assigned values and the South African (SA) measured values was high ($R^2 = 0.999$). Deming regression analysis was used to calculate the slope, 0.964 (95% CI 0.952 to 0.975), and intercept, 0.039 (95% CI 0.010 to 0.068), of the regression equation, with y = CCF-assigned values and x = SA-measured values. Because of this small but significant regression slope, measured S-Cr (SA) values were standardized to CCF values with the following equation: standardized S-Cr = 0.039 + [0.964 × S-Cr (SA)]. Standardized S-Cr values were used in all calculations.

COMPARISON OF MEASURED GFR TO THE 4-v MDRD EQUATION

The Spearman correlation coefficient between mGFR and the 4-v MDRD equation was 0.90 (95% CI 0.85 to 0.93). Weighted Deming regression analysis showed a significant proportional bias of 1.24 (95% CI 1.09 to 1.38, $P = 0.001$) but no significant constant bias [0.24 (95% CI −5.91 to 5.43, $P = 0.93$)] when the established ethnicity factor of 1.212 was used. Without the ethnicity factor, weighted Deming regression analysis showed no significant proportional bias [1.02 (95% CI 0.90 to 1.14, $P = 0.73$)] or constant bias [0.02 (95% CI −4.61 to 4.65, $P = 0.99$)]. The percentage bias (median percentage difference between eGFR and mGFR) for the 4-v MDRD equation with the established ethnicity factor of 1.212 was 27%. Without the ethnicity factor, percentage bias was 5%. With the ethnicity factor of 1.212, P_{30} for the 4-v MDRD equation was 52% vs 74% without the ethnicity factor (Fig. 1).

COMPARISON OF MEASURED GFR TO THE CG EQUATION

The Spearman correlation coefficient between mGFR and CG normalized to 1.73 m^2 was 0.89 (95% CI 0.85 to 0.93). Weighted Deming regression analysis comparing the CG equation to mGFR showed a significant proportional bias of 1.13 (95% CI 1.03 to 1.23, $P = 0.01$) but no significant constant bias [2.38 (95% CI −1.37 to 6.13, $P = 0.21$)]. Percentage bias for the CG equation was 19%, and P_{30} was 58%. The factor calculated to minimize bias of the CG equation in this dataset was 0.82 (95% CI 0.78 to 0.85). Correcting the CG equation for bias, eGFR (mL/min/1.73 m^2) = 0.82 × CG (mL/min/1.73 m^2), improved P_{30} to 71%.

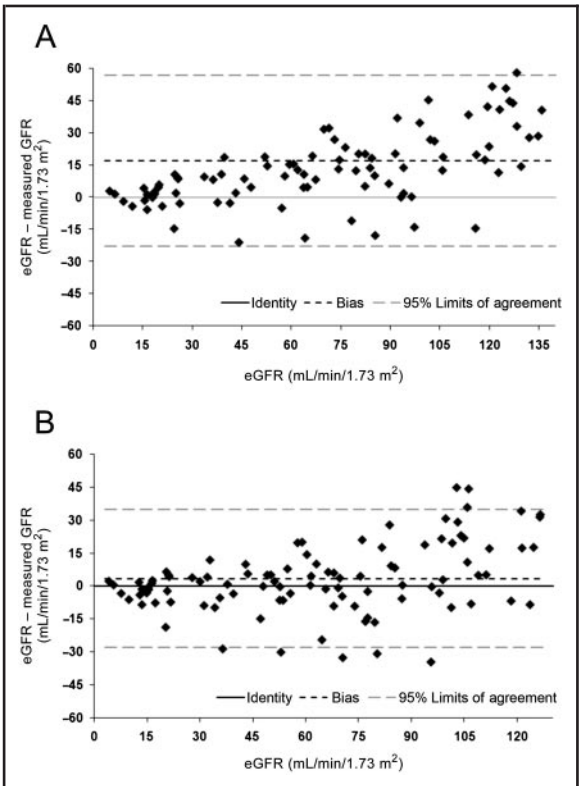


Fig. 1. Difference plot: 4-v MDRD equation and measured GFR.

(A), With African American ethnicity factor (1.212). (B), Without African American ethnicity factor.

PERFORMANCE OF EQUATIONS AT DIFFERENT STAGES OF RENAL DISEASE

For each of the eGFR equations, the dataset was split into 3 groups: eGFR <30, 30–60, and >60 mL/min/1.73 m^2. In each of these groups, the median difference between eGFR and mGFR (bias), percentage bias, IQR of the difference between eGFR and mGFRs, and root mean squared error were calculated. For each of the equations, bias, IQR, and root mean squared error increased at higher levels of eGFR (Table 1).

Discussion

CKD is increasingly recognized as a global public health problem *(1)*. The high prevalence of hypertension, diabetes, and HIV in sub-Saharan Africa has resulted in a high risk for CKD *(2)*. Early detection of CKD using simple laboratory tests and GFR prediction equations, such as the CG and 4-v MDRD equations, is important for the prevention of long-term complications.

Neither the CG nor the 4-v MDRD equation has previously been validated in Africa. The 4-v MDRD equation has also not been validated in a black population with a different body habitus than that of African Americans. Our results show that both the CG (after correcting for bias) and the 4-v MDRD (without the ethnicity factor established for African Americans) can be used for estimating GFR in black South Africans.

Many recent articles have underscored the importance of creatinine standardization *(17)*. For this study, we used an alkaline picrate rate-blanked compensated kinetic assay (Roche Diagnostics) with calibration traceable to IDMS. In a study by Miller et al. *(26)*, this method showed minimal bias compared with an IDMS value. We also assessed and corrected for possible calibration differences by using a calibration panel with values assigned by the Roche enzymatic assay (Cleveland Clinic Foundation). Because the S-Cr results were traceable to IDMS, we used the reexpressed 4-v MDRD equation *(14)*.

The correlation coefficient for the 4-v MDRD equation was similar those of studies done in other population groups *(27–29)*. The 4-v MDRD equation using the ethnicity factor of 1.212 as suggested for African Americans overestimated mGFR in black South Africans. Without the ethnicity factor (thus using the same equation as established for whites in the MDRD study), median overestimation was minimal and there was no significant proportional bias. Accuracy within 30% of mGFR was 52% with the ethnicity factor of 1.212 and 74% without the ethnicity factor.

Goldwasser et al. *(30)* showed that African Americans have higher renal creatinine excretion per kilogram body weight than whites and concluded that this may be related to differences in body composition, muscle metabolism, or diet. Lewis et al. *(31)* showed higher serum creatinine levels and urinary creatinine excretion rates for a given GFR in African Americans compared with non-African Americans. This may not be true for black South Africans, as the 2 populations have different origins *(32)*.

Creatinine generation is determined primarily by muscle mass and dietary intake *(6)*. Differences in the ethnicity factor established for African Americans and black South Africans may be attributed to differences in muscle mass and body composition as well as differences in diet. Various studies have shown that West African athletes have less body fat and thicker thighs than whites, and this difference is even more striking between East and West Africans *(33)*. Mean weight and BSA for the MDRD study population were 79.6 (16.8) kg and 1.91 (0.23) m^2, respectively *(16)*; for the MDRD African American study population, 84.1 kg and 1.96 m^2 *(31)*; for the African-American Study of Kidney disease and hypertension (AASK), 90.2 kg and 2.02 m^2

Table 1. Performance of equations.[a]

eGFR	n	Median bias, mL/min/1.73 m^2 (95% CI)	Median percentage bias, %	IQR, mL/min/1.73 m^2	RMSE, mL/min/1.73 m^2	P_{30}, %
4-v MDRD with ethnicity factor of 1.212						
eGFR <30 mL/min/1.73 m^2	20	1.7 (−1.7 to 4.4)	10.0	7.0	7.2	55
eGFR 30–60 mL/min/1.73 m^2	15	8.8 (−2.2 to 14.8)	23.8	15.7	18.0	53
eGFR >60 mL/min/1.73 m^2	65	20.4 (17.6 to 28)	28.8	28.6	35.1	51
Overall	100	13.1 (5.5 to 18.3)	27.0	25.2	28.5	52
4-v MDRD without ethnicity factor						
eGFR <30 mL/min/1.73 m^2	21	−1.4 (−4.0 to 2.2)	−6.7	7.0	7.2	67
eGFR 30–60 mL/min/1.73 m^2	24	0.4 (−6.4 to 5.1)	1.4	11.8	11.8	75
eGFR >60 mL/min/1.73 m^2	55	5.1 (−0.3 to 17.0)	8.8	26.3	26.8	76
Overall	100	1.9 (−0.8 to 4.5)	4.8	16.4	16.6	74
CG						
eGFR <30 mL/min/1.73 m^2	19	4.1 (−0.1 to 6.2)	18.7	6.0	7.3	47
eGFR 30–60 mL/min/1.73 m^2	18	6.0 (0.1 to 14.6)	17.4	15.0	16.1	67
eGFR >60 mL/min/1.73 m^2	63	14.7 (10.6 to 22.7)	19.2	27.2	30.9	59
Overall	100	9.0 (5.1 to 12.1)	19.1	21.1	22.9	58
CG × 0.82						
eGFR <30 mL/min/1.73 m^2	22	−0.7 (−3.3 to 3.0)	−2.7	6.5	6.5	59
eGFR 30–60 mL/min/1.73 m^2	31	−2.0 (−8.0 to 1.7)	−5.0	16.5	16.6	74
eGFR >60 mL/min/1.73 m^2	47	1.8 (−4.8 to 10.2)	1.9	31.8	31.9	74
Overall	100	−0.9 (−3.3 to 1.9)	−2.4	16.9	16.9	71

[a] IQR is the difference between estimated and measured GFR. RMSE (root mean squared error) was calculated as the square root of [(median difference in estimate − measured)^2 + (IQR of the difference)^2]. P_{30} is accuracy within 30% of measured GFR.

(31); and for our study, 69.5 (13.8) kg and 1.76 (0.17) m^2. Differences in dietary intake are difficult to quantify, but it is likely that black South Africans consume less creatinine-generating food than African Americans owing to poorer socioeconomic circumstances.

The CG equation is still commonly used for estimating creatinine clearance as an indicator of GFR and was therefore included in the analysis. The correlation coefficient for the CG equation was similar to those of studies done in other population groups *(27, 28)*. The positive bias observed for the CG equation may be attributed to the CG equation being established using creatinine clearance as a reference procedure, which overestimates GFR owing to the tubular secretion of creatinine *(6)*. It may also be attributed to calibration biases between creatinine measurement for the original CG study and this study, as well as the CG equation being established in a different population group.

The study population included 20 patients who were known to be infected with HIV. In South Africa, the Nelson Mandela/Human Sciences Research Council survey estimated the prevalence of HIV in the adult population (15–49 years old) to be 15.6% *(34)*. Chronic kidney disease is increasingly being recognized as an important complication of HIV infection *(35)*, and the estimation of GFR in this population group is therefore important. Further studies are needed to evaluate the performance of the 4-v MDRD equation in patients infected with HIV.

Limitations of the study were as follows: *a*) The study has a relatively small sample size. *b*) It was conducted at only one geographical site, which does not adequately represent all population groups in South Africa. Further studies for these population groups are needed. *c*) The characteristics of the study population differed from that of the MDRD study population. The study population included hospitalized patients and participants who were known to be infected with HIV. In these participants, creatinine production may differ and they may have reduced creatinine excretion compared with the MDRD study population, which consisted of outpatients with CKD who were otherwise healthy. *d*) In this study, plasma sampling was done at 2 and 4 h for patients with eGFR >30 mL/min/1.73 m^2

and at 3 and 5 h for patients with eGFR <30 mL/min/1.73 m^2. Using the renal clearance of ^{51}Cr-EDTA as a reference procedure, Brochner-Mortensen and Freund *(36)* showed that in patients with advanced chronic kidney disease (GFR 3–13 mL/min) plasma sampling done at 4 and 24 h after injection is more reliable [0.5 (0.5) mL/min] than that done between 3 and 5 h [3.7 (2.2) mL/min]. In the South African context, however, delayed plasma sampling may have resulted in patients being lost to follow up. *e*) The Cleveland Clinic calibration panel and participant samples were run at different times. A residual calibration error is therefore still possible.

In summary, our study confirms that both the 4-v MDRD equation, without the ethnicity factor of 1.212, and the Cockcroft-Gault equation, after correcting for bias, can be used for estimating GFR in black South Africans.

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Appendix VIII: Ethics Clearance

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 van Deventer

CLEARANCE CERTIFICATE	**PROTOCOL NUMBER M060137**
PROJECT	Assessing Renal Fnction: Evaluating the Use of tge Modification of Diet in Renal Disease (MDRD) Equationin the SA Pop.....
INVESTIGATORS	Dr HE van Deventer
DEPARTMENT	Chemical Pathology
DATE CONSIDERED	06.01.27
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 06.01.31 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Dr J George

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10005, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix IX: Abstracts and Posters Arising from Study

Glomerular Filtration Rate Prediction Equations Based on Creatinine and Cystatin C. 17th IFCC - FESCC European Congress of Clinical Chemistry and Laboratory Medicine, Amsterdam, The Netherlands, June 2007

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Background: The Modification of Diet in Renal Disease (MDRD) equation is commonly used for estimation of glomerular filtration rate (GFR). The aim of this study was to develop and evaluate a cystatin C-based prediction equation for estimation of GFR.

Methods: GFR was measured for 100 patients with various degrees of renal function. GFR was measured as the plasma clearance of ^{51}Cr-EDTA. Serum creatinine was measured using an alkaline picrate assay traceable to isotope dilution mass spectrometry (IDMS). Cystatin C was measured using an immunoturbidimetric assay. GFR was estimated using the re-expressed 4-variable MDRD equation [GFR = 175 *S-Cr (mg/dl)$^{-1.154}$ *Age$^{-0.203}$ *0.742 if female]. Stepwise multiple linear regression analysis was used to develop a cystatin C-based prediction equation.

Results: Age was statistically significant (P<0.0001) for inclusion in the cystatin C-based equation [GFR = 200 $*10^{\wedge Cystatin\ C*-0.31}$ $*10^{\wedge Age*-0.0025}$]. The correlation between estimated and measured GFR using the cystatin C-based equation (R^2 0.87) and the MDRD equation (R^2 0.79) was not significantly different (P=0.1). Proportion of estimated GFR within 30% of measured GFR (P_{30}) for the MDRD equation (P_{30}=75%) was not significantly different from the cystatin C-based equation (P_{30}=83%) (P=0.2). For patients with GFR > 60 ml/min/1.73m^2 precision (standard deviation of the difference between estimated and measured GFR) was significantly better for the cystatin C-based equation (13ml/min/1.73m^2) than for the MDRD equation (19ml/min/1.73m^2) (P=0.007).

Conclusion: The use of cystatin C-based prediction equations as a more precise indicator of GFR for those patients with a GFR > 60 ml/min/1.73m^2 needs to be further investigated.

Glomerular filtration rate prediction equations based on Creatinine and Cystatin

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1. Background

The Modification of Diet in Renal Disease (MDRD) equation[1] is commonly used for estimation of glomerular filtration rate (GFR).[2] The aim of this study was to develop and evaluate cystatin C-based prediction equations for estimation of GFR and to compare their performance to that of the MDRD equation.

2. Methods

GFR was measured in 100 patients with various degrees of renal function by means of the plasma clearance of ^{51}Cr-EDTA.[3] Serum creatinine was measured using an alkaline picrate assay traceable to isotope dilution mass spectrometry (IDMS). Cystatin C was measured using an immunoturbidimetric assay (DAKO). GFR was estimated using the re-expressed 4-variable MDRD equation.[4]

[GFR = 175 *S-Cr (mg/dl)$^{-1.154}$ *Age$^{-0.203}$ * 0.742 if female]

3. Statistical analysis

Multiple linear regression analysis was used to develop two cystatin C-based equations to predict GFR:

To assess the reliability of each of the equations the intraclass correlation and maximum likelihood estimation[5] for each equation was calculated using a leave-one-out cross validation procedure.

To assess the performance of the equations, both equations were evaluated using 500 random bootsrap samples from the dataset used to derive the equations. Correlation coefficient (R^2), bias, standard deviation (SD), combined root mean squared error (CRMSE) and accuracy within 30 % (P_{30}) were used to assess the performance of the cystatin C equations and MDRD equation relative to that of GFR. **(Table 1)**

Results were then ranked according to GFR and the dataset split into three groups: GFR < 30 ml/min/1.73m^2, GFR 30-60 ml/min/1.73m^2 and GFR > 60 ml/min/1.73m^2. Bias, SD and CRMSE were then caluculated in each of these groups. **(Table 2)**

4. Results

Intraclass correlation and maximum likelihood estimation for cystatin C equation 1 and cystatin C equation 2 were 0.92 and 0.89 respectively.

When compared to measured GFR the correlation coefficient for the MDRD equation and cystatin C equation 1 was R^2 = 0.79 and R^2 = 0.87 respectively.

The MDRD equation performed significantly better when no factor for race was included (P_{30} = 61 % vs. P_{30} = 75 %; P < 0.05). **(Figure 1 and Table 1)**

For patients with a GFR < 30 ml/min/1.73m^2 there was no significant difference in SD for cystatin C equation 1 and 2 when compared to the MDRD equation (5.2 ml/min/1.73m^2 and 4.0 ml/min/1.73m^2 vs. 4.8 ml/min/1.73m^2). However for patients with GFR > 60 ml/min/1.73m^2 the SD was significantly better for cystatin C equation 1 when compared to the MDRD equation (13 ml/min/1.73m^2 vs. 19 ml/min/1.73m^2; P < 0.05). This difference was not noted for Cystatin C equation 2.

For patients with GFR > 60 ml/min/1.73m^2 CRMSE for the MDRD equation (26 ml/min/1.73m^2) was 59 % higher than for cystatin C equation 1 (16 ml/min/1.73m^2) **(Figure 3 and Table 2)**

5. Conclusion

Cystatin C-based prediction equations are a better indicator of GFR than that of the MDRD equation for those patients with a GFR > 60 ml/min/1.73m^2. However for those patients with severe renal impairment, namely GFR < 30 ml/min/1,73m^2, there does not appear to be any significant difference.

Cystatin C equation 1

Log GFR	Coefficient (95 % CI)	SE[#]
Intercept	2.30 (2.24 to 2.36)	0.030
Cystatin C (mg/l)*	-0.31 (-0.33 to -0.29)	0.01
Age*	-0.0025 (-0.0037 to -0.0014)	0.0006

[#] SE: Standard error * P < 0.0001

$$y = a + bx + cx$$

$$\text{Log GFR} = 2.30 - 0.31 * \text{Cystatin C} - 0.0025 * \text{Age}$$

$$\text{GFR} = 10^{2.30} * 10^{(-0.31 * \text{Cystatin C})} * 10^{(-0.0025 * \text{Age})}$$

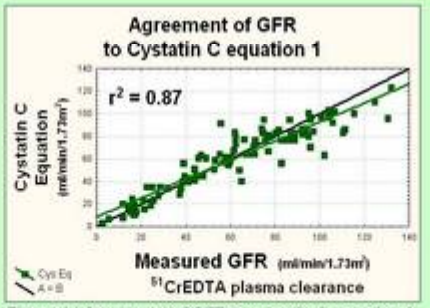


Figure 1 | Agreement of GFR to cystatin C equation 1

Cystatin C equation 2

Log GFR	Coefficient (95% CI)	SE[#]
Intercept	2.18 (1.95 to 2.42)	0.12
Log Cystatin (mg/l)*	-1.25 (-1.35 to -1.15)	0.052
Log Age*	-0.20 (-0.34 to -0.053)	0.072

[#] SE; Standard error * P < 0.0001

$$y = a + bx + cx$$

$$\text{Log GFR} = 2.18 - 1.25 * \text{Log Cys C} - 0.20 * \text{Log Age}$$

$$\text{GFR} = 10^{2.18} * \text{Cys C}^{-1.25} * \text{Age}^{-0.20}$$

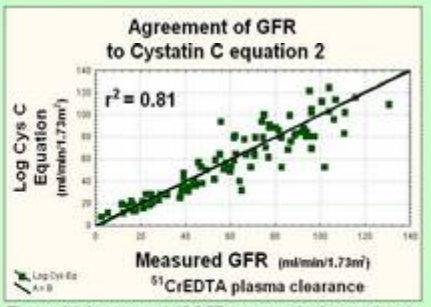


Figure 2 | Agreement of GFR to cystatin C equation 2

Table 1 | Agreement of GFR to MDRD and cystatin C equations for all patients

	R^2 (95% CI)	Bias [a] (95% CI)	SD [b] All stages	IQR [c] All stages	CRMSE [d] All stages	Accuracy within 30%
MDRD (Factor for race: 1.212)	0.79 (0.76 to 0.82)	8.9 (8.4 to 10.1)	18.9	20.6	22.5	61%
MDRD (Factor for race: 1.00)	0.79 (0.76 to 0.82)	0.1 (-1.6 to 0.7)	15.5	14.7	14.7	75%
Cystain C equation 1	0.87 (0.85 to 0.89)	-0.3 (-1.0 to 0.7)	11.6	11.4	11.4	83%
Cystain C equation 2	0.81 (0.77 to 0.83)	-1.8 (-3.3 to 0.0)	15.8	13.7	13.8	87%

[a] Bias is defined as the median difference between estimated and measured GFR, [b] SD: standard deviation of the difference between estimated and measured GFR, [c] IQR: interquartile range of the difference between estimated and measured GFR, [d] CRMSE: (combined root mean squared error) is calculated as the square root of the [(median difference in estimated – measured GFR)^2 + (inter quartile range of the difference)^2]

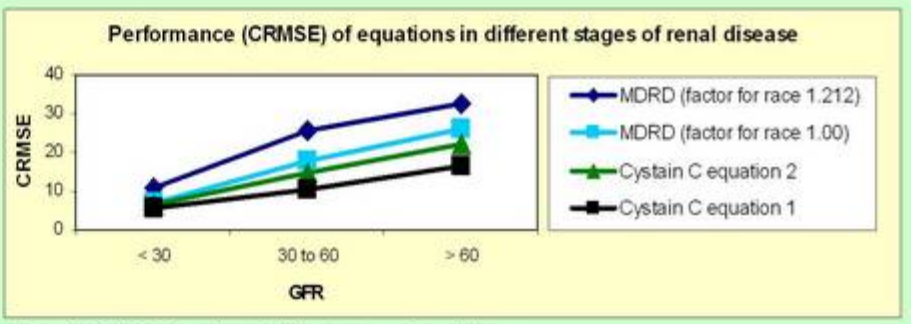


Figure 3 | CRMSE of equations in different stages of renal disease

Table 2 | Performance of equations in different stages of renal disease

	GFR < 30 ml/min/1.73m^2				GFR 30 to 60 ml/min/1.73m^2				GFR > 60 ml/min/1.73m^2			
	Bias [a]	SD [b]	IQR [c]	CRMSE [d]	Bias [a]	SD [b]	IQR [c]	CRMSE [d]	Bias [a]	SD [b]	IQR [c]	CRMSE [d]
MDRD (Factor for race: 1.212)	2.4	5.7	10.4	10.7	13.6	16.1	21.8	25.7	14.9	22.1	28.9	32.5
MDRD (Factor for race: 1.00)	0.5	4.8	7.0	7.1	2.2	13.0	17.7	17.9	-2.5	19.0	25.8	26.0
Cystain C equation 1	1.5	5.2	5.5	5.7	1.2	9.5	10.6	10.6	-5.4	12.9	15.5	16.4
Cystain C equation 2	1.1	4.0	6.5	6.6	-6.2	11.0	13.5	14.9	-3.5	20.3	21.7	22.0

[a] Bias is defined as the median difference between estimated and measured GFR, [b] SD: standard deviation of the difference between estimated and measured GFR, [c] IQR: interquartile range of the difference between estimated and measured GFR, [d] CRMSE: (combined root mean squared error) is calculated as the square root of the [(median difference in estimated – measured GFR)^2 + (inter quartile range of the difference)^2]

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Estimating Glomerular Filtration Rate in South Africa. American Association for Clinical Chemistry annual meeting 2007, San Diego, California, July 2007

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Background: Glomerular filtration rate (GFR) is accepted as the best overall measure of renal function. The Cockcroft-Gault and Modification of Diet in Renal Disease (MDRD) equations are commonly used for estimating GFR. The MDRD equation includes a correction factor of 1.212 for the African American population.

Objective: The aim of this study was to assess the accuracy of the Cockcroft-Gault and MDRD equations in the black South African population and to see whether the correction factor of 1.212 is appropriate for the black South African population.

Methods: GFR was measured for 100 patients with various degrees of renal function (Mean GFR: 61 ± 32 ml/min/1.73 m^2). GFR was measured as the plasma clearance of ^{51}Cr-EDTA. Serum creatinine (S-Cr) was measured using an alkaline picrate rate-blanked compensated kinetic assay with calibration traceable to isotope dilution mass spectrometry (IDMS) creatinine measurement. GFR was estimated using the Cockcroft-Gault equation normalized to 1.73m^2 and the re-expressed 4-variable MDRD equation [GFR = 175 * S-Cr (mg/dl)$^{-1.154}$ *

$Age^{-0.203}$ * 0.742 if female]. Estimated GFR was compared to measured GFR using correlation coefficient (R^2), mean percentage difference between estimated and measured GFR (percentage bias) and proportion of estimated GFR within 30% of measured GFR (P_{30}).

Results: The correlation between estimated and measured GFR for the MDRD and Cockcroft-Gault equation was the same (R^2 0.79). The correlation between estimated and measured GFR (MDRD equation) was significantly better for those patients with chronic kidney disease (GFR < 60 ml/min/1.73m^2) than for those patients with slightly decreased renal function (GFR > 60 ml/min/1.73m^2), R^2 0.78 and R^2 0.29 respectively ($p<0.001$). ROC curve analysis for detection of GFR <60ml/min/1.73m^2 showed no significant different in the area under the curve for the Cockcroft-Gault (0.956) and the MDRD (0.955) equations. Percentage bias for the Cockcroft-Gault equation was 15.4%. P_{30} for the Cockcroft-Gault equation was 64%. Correcting the Cockroft-Gault equation for bias (Corrected Cockcroft-Gault = 0.85 * Cockcroft-Gault) improved P_{30} to 70%. Percentage bias for the MDRD equation using the correction factor of 1.212 as suggested for the African American population was 22.5%. Percentage bias improved to 1.1% when no correction factor was used. P_{30} for the MDRD equation was also significantly better when no correction factor was used (P_{30} = 75%) than when the correction factor of 1.212 was used (P_{30} = 61%) ($p<0.05$).

Conclusion: In our study there was no significant difference between the performance of the MDRD and Cockcroft-Gault equations. The MDRD equation using the correction factor of 1.212 as suggested for the African American population overestimates measured GFR in the black South African population. This difference may be attributed to a lower proportional

muscle mass in the black South African population compared to the African American population. The validity of the MDRD equation needs to be further evaluated in different population groups.

Estimating Glomerular Filtration Rate in South Africa

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Background

GFR is accepted as the best overall measure of renal function.[1] The Modification of Diet in Renal Disease (MDRD)[1] and Cockcroft-Gault[2] equations are commonly used for estimating glomerular filtration rate (GFR). The MDRD equation includes a factor of 1.212 which was calculated for the African American population. The aim of this study was (1) to evaluate the performance of the MDRD and Cockroft-Gault equations for estimating GFR in the black South African population against measured GFR and (2) to evaluate whether the factor established for the African American population is accurate for the black South African population.

Methods

100 black South Africans with varying degrees of renal function were enrolled in the study. GFR was measured using one of the gold standards of GFR measurement namely the plasma clearance of ^{51}Cr-EDTA.[4] Serum creatinine (S-Cr) was measured using an alkaline picrate rate-blanked compensated kinetic assay (Roche Modular) with calibration traceable to isotope dilution mass spectrometry (IDMS). GFR was estimated using two equations, the re-expressed 4-variable MDRD equation [GFR = 175 * S-Cr (mg/dl)$^{-1.154}$ * Age$^{-0.203}$ * 0.742 if female][5] and the Cockcroft-Gault equation [GFR = [(140 - age) * weight] / (S-Cr (mg/dl) * 72) (* 0.85 if female)] normalized to 1.73m^2. A modified Cockcroft-Gault equation (Cockcroft Gault * 0.85) was also evaluated.

The performance of the MDRD equation, both with and without the factor for race, and the Cockcroft-Gault equation relative to that of GFR was assessed by :

(1) Mean percentage difference between estimated and measured GFR (percentage bias)
(2) Accuracy within 30 % of measured GFR (P_{30})
(3) Correlation coefficient (R^2)
(4) Performance at different stages of renal disease
(5) ROC analysis

Results

Table 1 | Population Characteristics

	Male (n = 51)	Female (n = 49)	Total (n =100)
Age, years	40 (24)	49 (26)	47 (26)
Weight, kg	67 (15)	67 (15)	67 (15)
Height, m	171 (7)	161 (12)	168 (12)
Body surface area, m^2	1.79 (0.20)	1.69 (0.15)	1.75 (0.19)
Body mass index, kg/m^2	23 (7)	25 (9)	24 (6)
Serum creatinine, mg/dl	1.20 (1.18)	0.94 (0.94)	1.14 (1.08)
Measured GFR, ml/min/1.73m^2	60.6 ± 31.6 *	61.6 ± 32.8 *	61.1 ± 32.0 *

Data expressed as Median (IQR) and * Mean ± SD

(1) Percentage Bias and (2) Accuracy within 30 % of measured GFR

Table 2 | Percentage Bias and Accuracy of MDRD and Cockcroft-Gault equations

	% Bias [a]	Accuracy within 15 %	Accuracy within 30%	Accuracy within 50 %
MDRD (Factor for race: 1.212)	22.5 %	31 %	61 %	80 %
MDRD (Factor for race: 1.00)	1.1 %	51 %	75 %	95 %
Cockcroft-Gault	15.4 %	41 %	64 %	79 %
Cockcroft-Gault * 0.85 (Corrected for bias)	-1.9 %	46 %	70 %	95 %

[a] mean percentage difference between estimated and measured GFR

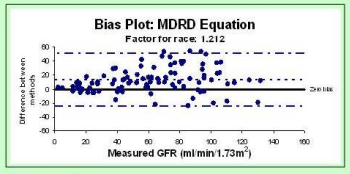


Figure 1 |

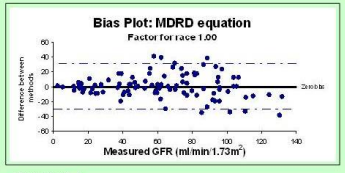


Figure 2 |

The **MDRD equation** performed better without the factor of 1.212 which adjusted for race as evidenced by:
(1) Percentage bias which was 22.5 % with the factor and 1.1 % without the factor. **(Figure 1 & 2).**
(2) Accuracy within 30 % of measured GFR (P_{30}) which was significantly better when no factor was used (P_{30} = 75%) than when the correction factor of 1.212 was used (P_{30} = 61%) (p<0.05). **(Table 2)**

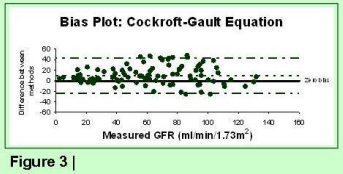


Figure 3 |

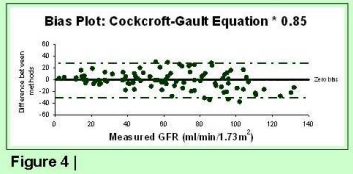


Figure 4 |

Cockcroft-Gault equation:
(1) Percentage bias for the Cockcroft-Gault equation was 15.4% **(Figure 3).**
(2) P_{30} for the Cockcroft-Gault equation was 64%. Correcting the Cockroft-Gault equation for bias (Corrected Cockcroft-Gault = 0.85 * Cockcroft-Gault) improved P_{30} to 70%. **(Table 2)** There was no significant difference betweeen P_{30} for the MDRD equation (factor for race 1.00) and the Cockroft-Gault equation corrected for bias.

(3) Correlation Coefficient

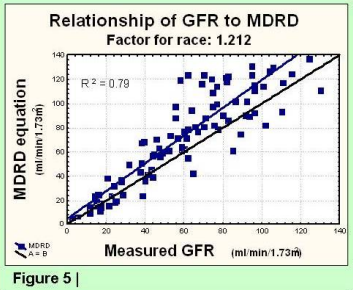


Figure 5 |

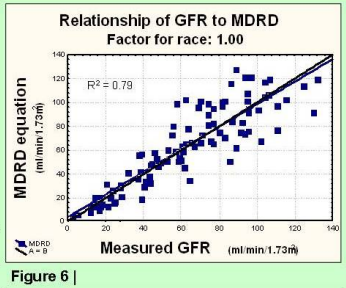


Figure 6 |

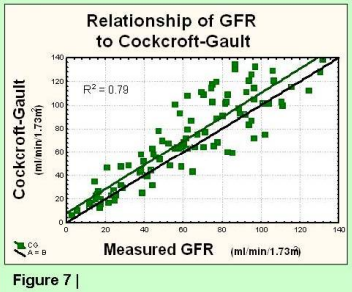


Figure 7 |

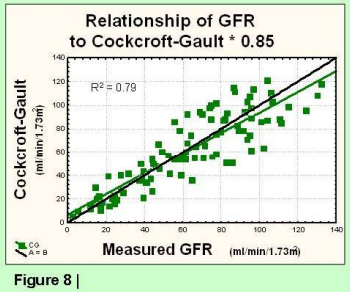


Figure 8 |

When compared to measured GFR the correlation coefficient for the MDRD and Cockcroft-Gault equations was similar (R^2 0.79) **(Figure 5, 6, 7 & 8).**

(4) Performance at Different stages of renal disease

Table 3 |

	GFR < 30 ml/min/1.73m² (n = 23)			GFR 30 to 60 ml/min/1.73m² (n = 25)			GFR > 60 ml/min/1.73m² (n=52)		
	Bias [a]	IQR [b]	CRMSE [c]	Bias [a]	IQR [b]	CRMSE [c]	Bias [a]	IQR [b]	CRMSE [c]
MDRD (Factor for race: 1.212)	1.5	10.3	10.4	12.3	17.5	21.4	16.0	30.3	34.3
MDRD (Factor for race: 1.00)	-1.0	6.8	6.8	2.2	15.1	15.3	-0.3	27.3	27.3
Cockcroft-Gault	3.5	6.5	7.4	8.3	15.9	17.9	8.7	30.2	31.4
Cockcroft-Gault * 0.85	0.2	7.5	7.5	-1.3	15.2	15.3	-3.3	28.0	28.2

[a] median difference, [b] IQR: Inter quartile range of the difference between estimated and measured GFR, [c] CMRSE, combined root mean squared error, calculated as the square root of the [(median difference in estimate – observed)^2 + (inter quartile range of the difference)^2]

The MDRD equation performed better for those patients with GFR < 30 ml/min/1.73m^2 (CRMSE = 6.8 ml/min/1.73m^2) and GFR 30 - 60 ml/min/1.73m^2 (CRMSE = 15.3 ml/min/1.73m^2) than for those patients with GFR > 60 ml/min/1.73m^2 (CRMSE = 27.3 ml/min/1.73m^2). The correlation between estimated and measured GFR (MDRD equation) was also significantly better for those patients with chronic kidney disease (GFR < 60 ml/min/1.73m^2) than for those patients with slightly decreased renal function (GFR > 60 ml/min/1.73m^2), R^2 0.78 and R^2 0.29 respectively (p<0.001). The Cockcroft-Gault equation also performed better for those patients with GFR < 30 ml/min/1.73m^2 (CRMSE = 7.5 ml/min/1.73m^2) and GFR 30-60 ml/min/1.73m^2 (CRMSE = 15.3 ml/min/1.73m^2) than for those patients with GFR > 60 ml/min/1.73m^2 (CRMSE = 28.2 ml/min/1.73m^2). **(Table 3)**

(5) ROC Analysis

Table 4 |

	GFR < 30 ml/min/1.73m²	GFR < 60 ml/min/1.73m²	GFR < 90 ml/min/1.73m²
	AUC (95% CI)	AUC (95% CI)	AUC (95% CI)
MDRD equation	0.994 (0.983 to 1.000)	0.955 (0.916 to 0.994)	0.899 (0.840 to 0.959)
Cockcroft Gault Equation	0.987 (0.971 to 1.000)	0.956 (0.920 to 0.991)	0.892 (0.830 to 0.954)

ROC analysis for detection of GFR <60ml/min/1.73m2 showed no significant different in the area under the curve for the Cockcroft-Gault (0.956) and the MDRD (0.955) equations. **(Table 4)**

Conclusion

This study showed that the MDRD equation performed well for those patients with a GFR < 60 ml/min/1.73m^2 but not for those patients with a GFR > 60 ml/min/1.73m^2. There was no significant difference between the performance of the MDRD and Cockcroft-Gault equations. The MDRD equation using the factor of 1.212 as suggested for the African American population overestimates GFR in the black South African population when compared to measured GFR. For the black South African population the equation performed best when using a factor of 1.00. The validity of the MDRD equation needs to be evaluated in different population groups.

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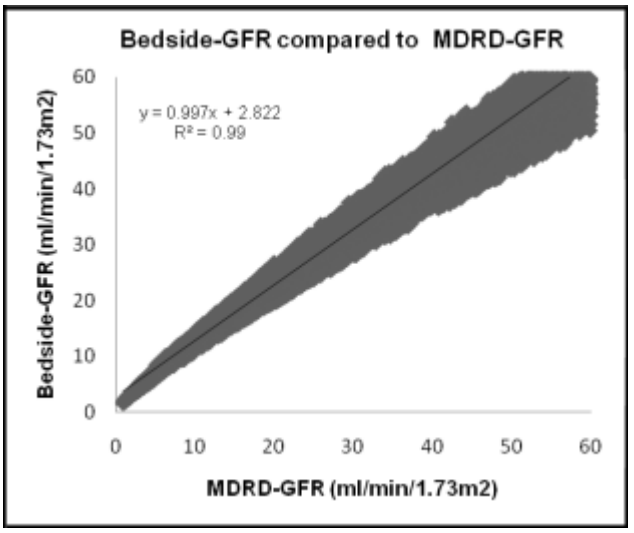
A Simplified equation to predict Glomerular Filtration Rate. American Association for Clinical Chemistry annual meeting 2008, Washington, District of Columbia, July 2008

Authors: H.E. van Deventer[1], J. Paiker[1], I. Katz[2], J. George[1]

Background: The 4-variable Modification of Diet in Renal Disease (MDRD) equation is commonly used for estimating glomerular filtration rate (GFR) and provides unbiased and reasonably accurate estimates of GFR when GFR is <60 ml/min/1.73 m^2. However it is difficult to calculate without the use of computers, which may not be freely available in developing countries. The aim of this study was to develop a simplified equation for estimating GFR that can be used at the bedside and to evaluate its performance against the MDRD equation.

Methods: GFR was measured in 100 patients using one of the "gold standards", namely the plasma clearance of ^{51}Cr-EDTA. Serum creatinine (S-Cr) was measured using an isotope dilution mass spectrometry (ID-MS) traceable assay (Roche Alkaline Picrate). Linear regression analysis was used in this cohort to develop the simplified equation: **Bedside-GFR = 7000/S-Cr (µmol/l) * gender,** where gender is 1 for males and 0.75 for females. This equation was then compared to the re-expressed MDRD equation (S-Cr assay traceable to ID-MS) in an independent dataset consisting of 63 304 S-Cr results, of which 20 580 had a MDRD-GFR< 60ml/min/1.73m^2, collected from patients who attended Johannesburg Hospital in 2007. The bedside-GFR equation was evaluated using the following modalities: sensitivity and specificity for detecting MDRD-GFR< 60ml/min/1.73m^2, correlation coefficient, bias and precision.

Results: Using the entire dataset the sensitivity and specificity of the bedside GFR equation to detect MDRD-GFR< 60ml/min/1.73m^2 was 94% and 98% respectively. For those patients with MDRD-GFR< 60ml/min/1.73m^2 the Spearman correlation coefficient between the MDRD and bedside-GFR equation was $R^2 = 0.99$ and bias was 2.82 ml/min/1.73m^2. In these patients 79% of bedside-GFR results were within 5 ml/min/1.73m^2, 97% within 7ml/min/1.73m^2 and 100% within 10 ml/min/1.73m^2 of MDRD-GFR.



Conclusion: The simplified bedside-GFR equation correlates well with the MDRD equation for the estimation of GFR < 60ml/min/1.73m^2.

A Simplified Equation to predict Glomerular Filtration Rate

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1) Background

Glomerular filtration rate (GFR) is accepted as the best overall measure of renal function[1]. The 4 variable Modification of Diet in Renal Disease (4-v MDRD) equation [2] is commonly used for estimating GFR (eGFR) and provides unbiased and reasonably accurate estimates of GFR when GFR is < 60 mL/min/1.73m^2. However, as the calculation incorporates many variables, it is difficult to calculate without the use of computers, which may not be freely available in developing countries.

2) Aim

The aim of this study was:

(1) to develop a simplified equation for estimating GFR that can be used at the bedside

(2) to evaluate its performance against the 4-v MDRD equation.

3.1) Methods

A 100 patients with varying renal function were enrolled in this study [3]. GFR was measured (mGFR) using a "gold standard" method, namely the plasma clearance of ^{51}Cr-EDTA [4]. Serum creatinine (S-Cr) was measured using an alkaline picrate rate-blanked compensated kinetic assay (Roche Modular) with calibration traceable to an isotope dilution mass spectrometry (ID-MS) method.

Linear regression analysis was applied to this dataset (Development dataset) to develop a bedside equation for estimating GFR (bedside-eGFR). To simplify the equation only the predictor variables S-Cr and gender, were included in the equation. The relationship between Log (GFR) and Log (S-Cr) was found to be linear [2]. In the 4-v MDRD study the coefficient for S-Cr was –1.154. This was rounded to –1 to make the final equation easy to calculate on a handheld calculator.

$$Y = a + bX_1 + cX_2$$

Where: a = intercept coefficient, b = coefficient for Log (S-Cr) and c = coefficient for age

Log (GFR) = a – 1 * Log (S-Cr) + c * Gender

Log (GFR) + 1 * Log (S-Cr) = a + c * Gender

The intercept and gender coefficient (where gender is 0 if male and 1 if female) was calculated for predicting [Log (GFR) + Log (S-Cr)].

Table 1 | Coefficients for predicting Log (GFR) + Log (S-Cr)

	Coefficient	95 % CI	SE
Intercept	3.84	3.81 to 3.87	0.02
Coefficient for gender	-0.13	-0.17 to -0.08	0.02

Log (GFR) = 3.84 - Log (S-Cr) –0.13 * Gender

GFR = $10^{3.84}$ * S-Cr^{-1} * $10^{-0.13 * Gender}$

This was rounded to:

eGFR = 7000 / S-Cr if male and eGFR = 7000 / S-Cr * 0.75 if female

3.2) Methods

The bedside-eGFR equation was then compared to the re-expressed 4-variable (4-v MDRD) [5] equation for S-Cr assays traceable to ID-MS.

eGFR = 175 * S-Cr (µmol/L / 88.4)$^{-1.154}$ * Age$^{-0.203}$ * 0.742 if female

This dataset consisted of 63 304 S-Cr results from patients who attended Johannesburg Hospital in 2007 (Verification dataset).

The performance of the bedside-eGFR equation relative to that of the 4-v MDRD-eGFR was assessed by:

(1) Sensitivity and specificity for detecting 4-v MDRD-eGFR < 60 mL/min/1.73m^2

(2) Correlation coefficient (R^2)

(3) Mean difference between bedside-eGFR and 4-v MDRD-eGFR (Bias)

(4) Accuracy within 5 mL, 7 mL, 10 mL and 30 % (P_{30}) of 4-v MDRD-eGFR

4.1) Results: Population Characteristics

Table 2 | Population Characteristics

Development dataset	Male (n = 51)	Female (n = 49)	Total (n =100)
Age, years	40 (27)	49 (25)	47 (26)
Serum creatinine, µmol/L	106 (107)	83 (87)	101 (95)
mGFR, mL/min/1.73m^2	62 (58)	61 (48)	62 (49)
Verification dataset (All Patients)	**Male (n = 29 170)**	**Female (n = 34 134)**	**Total (n = 63 304)**
Age, years	44 (26)	42 (28)	43 (27)
Serum creatinine, µmol/L	91 (73)	70 (42)	79 (57)
Verification dataset (eGFR < 60 mL/min/1.73m^2)	**Male (n = 10 087)**	**Female (n = 10 493)**	**Total (n = 20 580)**
Age, years	49 (25)	51 (28)	55 (27)
Serum creatinine, µmol/L	211 (318)	144 (197)	177 (254)

Data expressed as Median (IQR)

4.2) Results: Evaluation of bedside-eGFR equation

Table 3 | Evaluation of bedside-eGFR equation

Verification dataset (All Patients)	
Sensitivity*	93.5 (93.2 to 93.9) %
Specificity*	98.3 (98.2 to 98.4) %
*detection of 4-v MDRD-eGFR < 60 mL/min/1.73m^2	
Verification dataset (eGFR < 60 mL/min/1.73m^2)	
Spearman Correlation Coefficient (R^2)	0.99
Bias (bedside-eGFR - 4-v MDRD-eGFR)	2.82 (2.79 to 2.87) mL/min/1.73m^2
Accuracy within 5 mL, 7 mL, 10 mL and 30 % (P_{30}) of 4-v MDRD-eGFR	
Within 5 mL/min/1.73m^2 of 4-v MDRD-eGFR	79 %
Within 7 mL/min/1.73m^2 of 4-v MDRD-eGFR	97 %
Within 10 mL/min/1.73m^2 of 4-v MDRD-eGFR	100 %
Within 30 % (P_{30}) of 4-v MDRD-eGFR	83 %

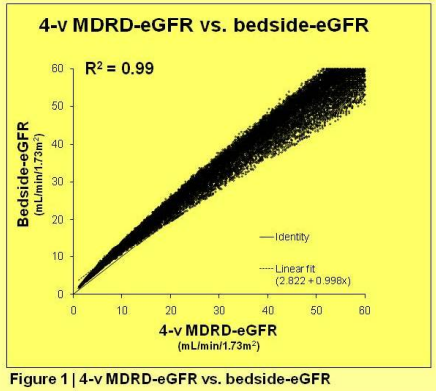


Figure 1 | 4-v MDRD-eGFR vs. bedside-eGFR

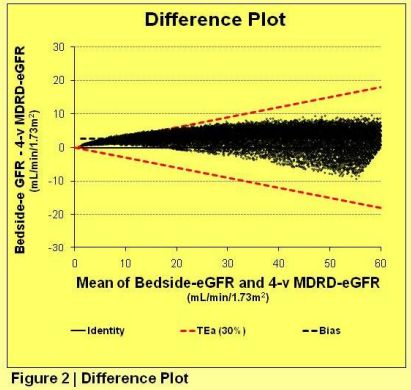


Figure 2 | Difference Plot

5) Discussion

In South Africa (SA) the high prevalence of hypertension, diabetes mellitus and infection with human immunodeficiency virus (HIV) results in a significant risk for chronic kidney disease (CKD) [6]. The early detection of CKD through screening and educational efforts should therefore be a priority. Our results show that the bedside-eGFR equation can be used for the detection of CKD (eGFR < 60 mL/min/1.73m^2) and give results that correlate very well with the 4-v MDRD equation. One variable not included in the bedside-eGFR equation is age. The bedside-eGFR equation overestimates GFR in elderly subjects and underestimates GFR in younger subjects when compared to the 4-v MDRD equation [Figure 3]. The clinical significance of this is uncertain.

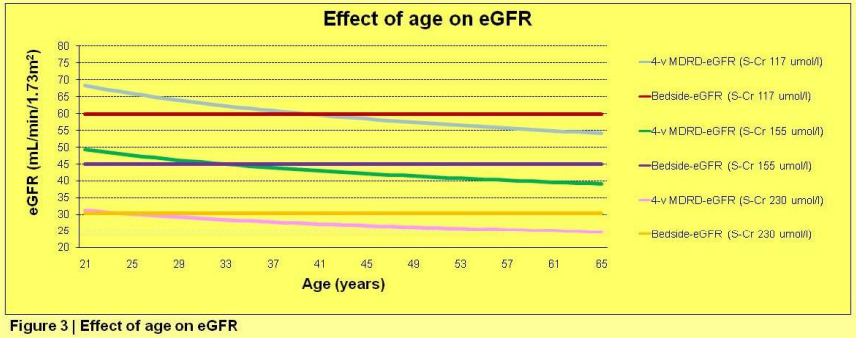


Figure 3 | Effect of age on eGFR

6) Conclusion

We have developed a simplified equation for the estimation for GFR. This equation correlates well with the 4-v MDRD equation for patients with a eGFR < 60 mL/min/1.73m^2 and can be used to simply screen for CKD.

7) References

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