Validation of equations to estimate glomerular filtration rate in South Africans of mixed ancestry

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Background. The Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations are two commonly used formulae to estimate glomerular filtration rate (GFR) in adults. The CKD-EPI equation is recommended in current international and local guidelines for the diagnosis and management of chronic kidney disease (CKD), unless an alternative equation has been shown to have superior accuracy. Validation and comparison of the equations in local populations are therefore required. Previous studies have reported on the accuracy of these prediction equations in black South Africans and those of Indian ancestry.

Objectives. To evaluate the performance of the MDRD and CKD-EPI equations in South African (SA) adults of mixed ancestry.

Methods. In all participants, GFR was measured (mGFR) from plasma clearance of 99mTc-diethylenetetraaminepenta-acetic acid (99mTc-DTPA), using a standardised technique. Serum creatinine assays were isotope dilution mass spectrometry traceable. GFR was estimated (eGFR) using the MDRD and CKD-EPI equations, and with and without the black ethnicity factor. The agreement, bias, precision and accuracy of each equation was determined.

Results. Eighty adults were included (30 male, median age 39 years, median GFR 59 mL/min/1.73 m²). Sixty-eight had a diagnosis of CKD, 10 were potential kidney donors, and 2 were healthy volunteers. Both equations, without the black ethnicity factor, had good agreement with measured GFR. The equations tended to overestimate GFR, with bias of 1.6 and 7.9 mL/min/1.73 m² for the MDRD and CKD-EPI equations, respectively. The interquartile ranges of the differences were 15.9 and 20.2 mL/min/1.73 m², and as a measure of accuracy, the percentages of estimates that fell within 30% of the mGFR (P30) were 80% and 72.5% (p=0.18). For identification of individuals with a GFR <60 mL/min/1.73 m², the sensitivity of MDRD eGFR was 97.3% and that of CKD-EPI eGFR was 97.1%.

Conclusions. The MDRD and CKD-EPI equations have shown satisfactory and comparable performance in this SA mixed-ancestry adult population, with the MDRD equation marginally less biased than the CKD-EPI.

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Chronic kidney disease (CKD) is defined by the presence of abnormalities of kidney structure or function (such as a glomerular filtration rate (GFR) <60 mL/min/1.73 m²) present for >3 months, with implications for health.10 The Kidney Disease: Improving Global Outcomes (KDIGO) guideline recommends using a creatinine-based equation to estimate GFR in the initial assessment of CKD and for monitoring disease progression.11 The two most commonly used equations in adults are the Modification of Diet in Renal Disease (MDRD) equation12-13 and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.10 Unless an alternative equation has been shown to have superior accuracy, use of the CKD-EPI equation is recommended.10,13

A 2012 systematic review found that neither the MDRD nor the CKD-EPI equation performed well in populations outside North America, Europe or Australia, and it concluded that neither equation could be used routinely across all populations and all GFR ranges.16 Studies conducted in various South African (SA) populations support this, and although the findings varied, the equations tended to have unacceptable bias, precision and/or accuracy.17-11 The poor performance of the equations in SA populations is concerning. SA is a developing country with limited centres that are able to measure GFR. Even where the service is available, the large number of CKD patients attending renal clinics precludes routine GFR measurement, compelling physicians to rely on estimated GFR (eGFR). Furthermore, GFR estimates are essential in epidemiological studies, specifically to determine CKD prevalence.

The mixed-ancestry (coloured) population group is estimated to comprise 8.8% of SA’s population12 and almost 49% of the Western Cape Province population.13 Its origins are Khoisan (32 - 43%), Bantu-speaking African (20 - 36%), European (21 - 28%) and Asian (9 - 11%).14 No previous studies have evaluated GFR-estimating equations in this group, despite the fact that it has a high prevalence of CKD.13,14 Considering the population group’s genetic diversity, it is hypothesised that accuracy of the commonly used equations will be poor.

Objectives

To evaluate the performance of the MDRD and CKD-EPI equations in mixed-ancestry SA adults.

Methods

Participants

Participants were recruited from the outpatient clinics of the Division of Nephrology at Tygerberg Hospital, Cape Town, between June 2015 and October 2018. Patients attending routine outpatient
appointments or individuals being worked up for potential kidney donation were screened by a renal physician to exclude acute renal failure, concurrent illness, cancer, expanded extracellular fluid volumes (ascites, oedema or pleural effusions), pregnancy or breastfeeding. After screening, adult patients (≥18 years) who self-classified as South Africans of mixed ancestry were invited to participate. All participants provided written informed consent. The study was approved by the Stellenbosch University Health Ethics Research Committee (ref. no. S14/10/217).

**GFR measurement**

GFR was measured in the Nuclear Medicine Division of Tygerberg Hospital following our departmental protocol, which is based on the methodology in the 2004 British Nuclear Medicine Society GFR guideline.[17] On arrival, the height and weight of the participant was recorded. Approximately 40 MBq of $^{99m}$Tc-diethylenetriaminepenta-acetic acid ($^{99m}$Tc-DTPA) was injected through an intravenous catheter. Extravasation was excluded by imaging the injection site using a gamma camera. A similar dose of $^{99m}$Tc-DTPA was used for preparation of the standard. Patient and standard doses were calibrated accurately by weighing the syringes before and after administration of the doses on a Precisa 620C balance (precision = 0.005 g) (Precisa Balances Ltd, UK). In order to avoid excessively high count rates, a double dilution reaction was used (Siemens ADVIA 1800; Siemens Healthineers, Germany). In September 2016, the analyser was replaced with a Roche Cobas 6000 (Roche Diagnostics, Basel, Switzerland). In 46 individuals, Scr was measured using the Jaffé (alkaline picrate) method, and in 34 the enzymatic method on the new

\[ eGFR = 141 \times \min\left(\frac{\text{Scr}}{\kappa,1}\right)^{1.209} \times \max\left(\frac{\text{Scr}}{\kappa,1}\right)^{-1.023} \times g \times e, \]

where Scr is serum creatinine in µmol/L, $\kappa$ is 61.9 for females and 79.6 for males, $a$ is –0.329 for females and –0.411 for males, $\min(x,y)$ and $\max(x,y)$ indicate the minimum and maximum of $x$ and $y$, respectively, $g$ is a gender factor (male = 1, female = 1.108), and $e$ is an ethnicity factor (African American = 1.159, other ethnic groups = 1).

**Data analysis**

Bias was calculated as the median difference between eGFR and measured GFR (mGFR). Precision was expressed as the interquartile range (IQR) of the differences, and as the root mean square error of the regression of eGFR vs. mGFR. As measures of accuracy, the root mean square error (RMSE) values (calculated as the square root of mean ($\log eGFR - \log mGFR$))^2 and percentages of GFR estimates that fell within 30% ($P_{30}$) and 20% ($P_{20}$) of the mGFR were calculated. Bland-Altman analyses[21] were used to determine the agreement between eGFR and mGFR. The sensitivity, specificity and positive predictive value for identifying individuals with an mGFR <60 mL/min/1.73 m² were calculated for each equation. The Shapiro-Wilk test was used to test for normality. The McNemar test was used to compare proportions.

Statistical analysis was performed using MedCalc Statistical Software for Windows v.18.10.2 (MedCalc Software, Belgium [https://www.medcalc.org], 2018).

**Results**

In total, 80 participants were included (30 male, median age 39 years, full age range 18 - 68 years). Sixty-eight had a diagnosis of CKD, 10 were potential kidney donors, and 2 were healthy volunteers. The median mGFR was 59 mL/min/1.73 m² (full range 10 - 126 mL/min/1.73 m²) (Fig. 1 and Table 1).

In 46 individuals, Scr was measured using the Jaffé (alkaline picrate) method, and in 34 the enzymatic method on the new
The analyser was used. There was no significant difference in bias or precision of the equations between the alkaline picrate and enzymatic groups (data not shown).

The performance of the GFR estimation equations is shown in Table 2. The bias of the MDRD equation was 1.6 mL/min/1.73 m², whereas the CKD-EPI equation overestimated GFR by 7.9 mL/min/1.73 m². The RMSE values of the regression of MDRD and CKD-EPI v. mGFR were 15.1 and 13.5 mL/min/1.73 m², respectively, whereas the IQR of the differences was narrower for the MDRD equation than the CKD-EPI (15.9 v. 20.2 mL/min/1.73 m²). The $P_{30}$ values did not differ significantly (MDRD 80.0%, CKD-EPI 72.5%; $p=0.18$). When the black ethnicity factor was applied, bias, precision and accuracy of both equations deteriorated. The Bland-Altman analyses are shown in Fig. 2. Both equations had non-significantly higher $P_{30}$ values in the subgroup of individuals with a GFR ≥60 mL/min/1.73 m² (MDRD 84.6%, CKD-EPI 82.1%) than in the GFR <60 mL/min/1.73 m² subgroup (MDRD 75.6%, CKD-EPI 63.4%). For identification of individuals in whom the GFR was <60 mL/

### Table 1. Participant characteristics (N=80)

| Characteristic                          | Median (Full Range) |
|-----------------------------------------|---------------------|
| Age (years)                             | 39 (18 - 68)        |
| Scr (µmol/L), median (full range)       | 92 (66 - 191)       |
| Scr (mg/dL), median (full range)        | 1.0 (0.5 - 7.9)     |
| Measured GFR (mL/min/1.73 m²), median (full range) | 59 (10 - 126) |
| Sex (male), n (%)                       | 30 (37.5)           |
| GFR (mL/min/1.73 m²), n (%)             |                     |
| ≥90                                     | 27 (33.7)           |
| 60 - 89                                 | 12 (15.0)           |
| 30 - 59                                 | 19 (23.8)           |
| <30                                     | 22 (27.5)           |
| Diagnosis/reason for participation, n (%) |                     |
| Glomerular disease                      | 41 (51.3)           |
| Lupus nephritis                         | 17 (21.3)           |
| Focal segmental glomerulosclerosis      | 7 (8.7)             |
| IgA nephropathy                         | 4 (5.0)             |
| Membranous nephropathy                  | 3 (3.8)             |
| Other glomerulonephritis                | 10 (12.5)           |
| CKD of unknown cause                    | 8 (10.0)            |
| Autosomal dominant polycystic kidney disease | 5 (6.2)          |
| Malignant hypertension                  | 4 (5.0)             |
| Solitary kidney                         | 3 (3.8)             |
| Obstructive nephropathy                 | 2 (2.5)             |
| Other specified renal disease           | 5 (6.2)             |
| Potential kidney donor                  | 10 (12.5)           |
| Healthy volunteer                       | 2 (2.5)             |
| Chronic use of trimethoprim*            | 4 (5.0)             |

Scr = serum creatinine; GFR = glomerular filtration rate; CKD = chronic kidney disease.

*In 4 of the patients with lupus nephritis.

### Table 2. Bias, precision, accuracy, and 95% limits of agreement of the MDRD and CKD-EPI GFR estimation equations

|                      | MDRD                         | CKD-EPI                        | MDRD with black ethnicity factor | CKD-EPI with black ethnicity factor |
|----------------------|------------------------------|--------------------------------|----------------------------------|------------------------------------|
| Bias                 | Median difference* (95% CI)  | 1.6 (–0.3 - 7.5)               | 7.9 (5.4 - 11.5)                 | 15.3 (11.1 - 20.3)                 | 20.3 (14.6 - 24.0)               |
| Precision            | IQR of the differences*†     | 15.9                            | 20.2                            | 25.9                               | 28.1                              |
| RMSE                 | 15.1                         | 13.5                            | 18.2                            | 15.7                               |
| Accuracy             | RMSE*‡                        | 0.239                           | 0.257                           | 0.331                              | 0.347                             |
| $P_{30}$, % (95% CI) | 80.0 (69.6 - 88.1)           | 72.5 (61.4 - 81.9)              | 51.3 (39.9 - 62.6)               | 47.5 (36.2 - 59.0)                |
| $P_{20}$, % (95% CI) | 60.0 (48.4 - 70.8)           | 55.0 (43.5 - 66.2)              | 36.3 (25.8 - 47.8)               | 31.3 (21.4 - 42.6)                |
| Agreement            | 95% LOA*                     | –24.9 – 34.4                    | –17.9 – 35.7                    | –21.6 – 60.0                      | –14.5 – 55.2                     |

GFR = glomerular filtration rate (m = measured, e = estimated); MDRD = Modification of Diet in Renal Disease; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; CI = confidence interval; IQR = interquartile range; RMSE = root mean square error; $P_{30}$ and $P_{20}$ = percentages of GFR estimates that fell within 30% and 20%, respectively, of the mGFR; LOA = limits of agreement.

*Units mL/min/1.73 m²
†The differences were calculated as eGFR – mGFR.
‡RMSE of the regression of eGFR v. mGFR.
§RMSE calculated as the square root of mean (log eGFR – log mGFR)².
min/1.73 m², the sensitivities of the MDRD and CKD-EPI equations were >90% in the three subgroups analysed (Table 3).

**Discussion**

The performance of both equations was satisfactory in this mixed-ancestry SA population. The MDRD equation was less biased than the CKD-EPI equation, over-estimating mGFR by 1.6 mL/min/1.73 m² compared with 7.9 mL/min/1.73 m² ($p<0.001$). The IQRs of the differences were 15.9 mL/min/1.73 m² for the MDRD equation and 20.2 mL/min/1.73 m² for the CKD-EPI equation, and the RMSE values were 16.0 and 16.4 mL/min/1.73 m², respectively. Accuracy was not significantly different, with $P_{30}$ values of 80% and 72.5% ($p=0.18$). In the original CKD-EPI study, the CKD-EPI equation was compared with the MDRD equation using a large validation set of 6 646 individuals. Although the majority of participants were white and had CKD, the population was fairly diverse in terms of ethnicity (19% black, ~4% Asian/Hispanic) and pathology (29% diabetes, 19% transplant recipients, 14% healthy kidney donors). The mean GFR was 68 mL/min/1.73 m². The median difference, IQR and $P_{30}$ of the MDRD equation were –5.5 mL/min/1.73 m², 18.3 mL/min/1.73 m² and 80.6%. The CKD-EPI equation performed marginally better, with a bias of 2.5 mL/min/1.73 m², an IQR of 16.6 mL/min/1.73 m² and a $P_{30}$ of 84.1%. In an earlier study, the MDRD equation was evaluated in a large population pooled from 10 studies (mean GFR 68 mL/min/1.73 m², 32% black, 5% Asian/Native American, 29% diabetes, 5% transplant recipients). Median bias was –2.7 mL/min/1.73 m², IQR 16.4 mL/min/1.73 m² and $P_{30}$ 83%. The results in our study, specifically for the MDRD equation, are comparable to these and some of the other large validation studies from North American, European and Australian populations.

For identification of individuals with a GFR <60 mL/min/1.73 m², both equations performed well, with sensitivities >97% and specificities and positive predictive values >80%. This is useful information for screening programmes or for researchers conducting epidemiological studies on the prevalence of CKD in local communities. Although sensitivity decreased slightly when individuals with a GFR <30 mL/min/1.73 m² were excluded from the analysis, it remained >90% for both equations. For the GFR subgroups analysed, the MDRD equation tended to perform better than the CKD-EPI; however, as expected from the small numbers in each group, the differences were not significant.

A few investigators have evaluated the MDRD and CKD-EPI equations in other SA populations. One consistent finding across all the studies in black South Africans was that incorporation of an African American ethnicity factor resulted in a substantial increase in bias and a decrease in precision and accuracy. It is therefore not surprising that similar results were found in our mixed-ancestry population (Table 2).

In a study of 100 black South Africans with CKD, the bias, precision and accuracy of the MDRD equation were similar to our values. In half of the same population (i.e.

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**Table 3. Diagnostic performance of the MDRD and CKD-EPI GFR equations in detecting patients with a GFR <60 mL/min/1.73 m²**

|                        | Sensitivity, % (95% CI) | Specificity, % (95% CI) | PPV, % (95% CI) | NPV, % (95% CI) |
|------------------------|-------------------------|-------------------------|----------------|----------------|
| All patients (N=80)    |                         |                         |                |                |
| MDRD                   | 97.3 (91.0 - 99.6)      | 88.4 (79.3 - 94.5)      | 87.8 (78.6 - 94.1) | 97.4 (91.1 - 99.7) |
| CKD-EPI                | 97.1 (90.7 - 99.6)      | 82.6 (72.7 - 90.3)      | 80.5 (70.1 - 88.5) | 97.4 (91.1 - 99.7) |
| GFR 45 - 90 mL/min/1.73 m² (n=31) | |                         |                |                |
| MDRD                   | 93.8 (78.9 - 99.3)      | 73.3 (54.4 - 87.5)      | 78.9 (60.6 - 91.4) | 91.7 (76.1 - 98.5) |
| CKD-EPI                | 92.3 (76.9 - 98.8)      | 61.1 (42.0 - 78.0)      | 63.2 (44.1 - 79.7) | 91.7 (76.1 - 98.5) |
| GFR >30 mL/min/1.73 m² (n=58) | |                         |                |                |
| MDRD                   | 93.8 (84.2 - 98.4)      | 90.5 (79.7 - 96.6)      | 78.9 (66.2 - 88.5) | 97.4 (89.4 - 99.8) |
| CKD-EPI                | 92.3 (82.2 - 97.7)      | 84.4 (72.5 - 92.6)      | 63.2 (49.5 - 75.5) | 97.4 (89.4 - 99.8) |

GFR = glomerular filtration rate; MDRD = Modification of Diet in Renal Disease; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; GFR = glomerular filtration rate; PPV = positive predictive value; NPV = negative predictive value; CI = confidence interval.
50 black South Africans), the CKD-EPI equation had a median bias of 4.9 mL/min/1.73 m² and a P₃₀ of 74%, values also very similar to ours.[6] In a separate study of 91 black South Africans with CKD, bias of the MDRD equation was negligible but the precision was poor as reflected by the wide 95% limits of agreement in the Bland-Altman analyses (−37.9 - 40.0 mL/min/1.73 m²).[10] The P₃₀ of the MDRD equation in this study ranged between 36% and 69% depending on the GFR. In a more recent study of 188 black South Africans, the P₃₀ value of the MDRD equation was 53 - 54% and that of the CKD-EPI equation 53 - 54%, whereas the P₃₀ values in 99 Indian South Africans were 49 - 66% and 54 - 66% for the MDRD and CKD-EPI equations, respectively.[13] This population included individuals with malignancy (58%) and CKD (38%).

Possible reasons for the poorer performance of eGFR in previous SA studies include differences in ethnicity, mean GFR, pathology and/or methodology. Many other studies in populations outside the USA, Europe and Australia have shown similarly poor results, and in most cases these have been attributed to ethnic differences.[6] Although South Africans of mixed ancestry are genetically diverse, with Khoisan (32 - 43%), Bantu-speaking African (20 - 36%), European (21 - 28%) and Asian (9 - 11%) ancestral components,[14] this diversity did not significantly limit eGFR performance in this population. Furthermore, the fact that some studies in black Africans with CKD had similar results suggests that ethnicity may be less important than other factors.[7,8]

Possibly one of the most important determinants of the effectiveness of eGFR equations is patient pathology. The population in our study comprised CKD patients (85%) and healthy individuals (15%), a composition similar to the development populations of the MDRD and CKD-EPI equations, which is likely to have contributed towards the good performance of the equations in our study. In contrast, in the most recent of the SA studies, 58% of patients had cancer.[11] A lower average Scr concentration in this population[11] may explain the positive bias found for both MDRD and CKD-EPI equations, as cancer and other chronic illnesses are known to reduce creatinine generation through muscle wasting.[24]

In the measurement of GFR, factors such as the use of a different filtration marker or method to calculate GFR will result in systematic differences in mGFR; however, provided measurement of GFR is performed correctly, the effect should be small. This is because the error on eGFR = mGFR is equal to \( \sqrt[3]{[ \text{error on eGFR}^3 + \text{error on } m\text{GFR}^3]} \), so if the error in mGFR << error in eGFR, the latter would contribute little to the error on the difference. In the present study, meticulous care was paid to methodology for GFR measurement. Our departmental guideline adheres strictly to the 2004 British Nuclear Medicine Society GFR guideline,[15] and we perform rigorous quality control checks on each GFR study. Furthermore, an analysis of measurement errors in our unit, taking into account error in all aspects of the investigation (e.g. measuring patient height and weight, preparation of the standard, measuring of doses, recording of time, pipetting technique and counting of samples), revealed an error in mGFR of −2 mL/min/1.73 m².[25]

All participants in the present study were screened meticulously by a renal physician, a factor that may contribute to the relatively good performance of eGFR. Patients with expanded extracellular fluid volumes (ascites, oedema or pleural effusions), acute renal failure, any acute concurrent illness, or any other reason to suspect unstable kidney function were not considered for inclusion. Furthermore, GFR and Scr were measured on the same day in every patient. Although fluctuations in Scr may to a degree mirror fluctuations in GFR, with coefficients of variation (CV) for repeat measurements of −8 - 10% for GFR and 6% for Sct,[17,26] measurement of these parameters on different days will limit the precision that is attainable. Use of a Jaffe assay rather than an enzymatic method for creatinine measurement will further limit the precision considering analytical CVs of −5.5% and 2%, respectively.[24]

**Study limitations**

The main limitation of this study is the sample size; however, the study was sufficiently powered to draw conclusions about the performance of the equations in the population. The primary outcome variable is the P₃₀ proportion. A sample size of 80 is sufficient to estimate the true population value of P₃₀ using a 95% confidence interval (CI) to within 10% of the true value (i.e. a CI width of 20%), given that the P₃₀ is 70 - 80%. While a better estimation of P₃₀ is ideal, an estimation within 10% can be regarded as acceptable. On the other hand, a sample size of −150 would be required to detect a significant difference between the MDRD and CKD-EPI equations at P₃₀ values of 80% and 72.5%, respectively. It therefore cannot be concluded that the MDRD equation outperformed the CKD-EPI equation in this study. Ideally, more patients with normal kidney function would have been included. This might have resulted in better performance of the CKD-EPI equation, as (i) the MDRD equation has been shown to have poorer accuracy at higher GFR levels,[23] and (ii) the CKD-EPI equation was found to be more accurate than the MDRD in most GFR subgroups.[27] Based mainly on a CKD population, our results are not necessarily generalisable to other populations, e.g. patients with cancer. Four of the patients with lupus nephritis who were included used trimethoprim chronically. Trimethoprim is known to interfere with the tubular secretion of creatinine, thus raising Scr levels.[24] However, the effect of this factor on the overall results of the study is thought to be minimal.

**Conclusions**

The MDRD and CKD-EPI equations have both shown satisfactory performance in this SA mixed-ancestry adult population, with comparable accuracy. This information is reassuring to physicians treating patients with CKD and to researchers conducting epidemiological studies.

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**Author contributions.** JLH: data analysis, manuscript preparation. KB: participant recruitment, manuscript review. MRD: co-supervisor, manuscript review. JMW: supervisor, manuscript review.

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**Conflicts of interest.** None.

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