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Evaluation of the CKD-EPI creatinine based glomerular filtration rate estimating equation in Black African and Indian adults in KwaZulu-Natal, South Africa

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ABSTRACT

Background: The estimation of glomerular filtration rate (GFR) plays a vital role in assessment of the renal function. This study evaluated the performance of the CKD-EPI$_{creat}$ and MDRD equations in the South African Kwa-Zulu Natal population.

Objectives: The objectives if the study were to compare the of CKD-EPI$_{creat}$ and MDRD equations in the selected population to the measured GFR using Sodium Technetium-99 m-diethylene-triamine-pentaacetate clearance derived GFR.

Method: Records of adult patients with measured GFR performed at the Nuclear Medicine Department at Inkosi Albert Luthuli Central Hospital, Durban, South Africa from 1 April 2014 to 31 March 2016 were reviewed. eGFR for all included patients was calculated using the MDRD equation without African American correction factor and the CKD-EPI$_{creat}$ equation with and without the African American correction factor for the Black African patients. Statistical comparison of the eGFR with measured GFR was performed with Bland Altman bias plots, Wilcoxon match pairs signed ranks test and accuracy within 10% and 30%.ROC curve analysis assessed the sensitivity and specificity at eGFR < 90 and < 60 ml/min/1.73m^2.

Results: After exclusion, 287 patients were included for analysis with sufficient numbers for only the Black African and Indian patients. None of the equations showed accuracy of eGFR within 30% of measured GFR for 90% of patients. In the Black African population, the CKD-EPI$_{creat}$ equation without the correction factor performed best. 17% and 14.4% of the Black African participants would be reclassified with the CKD-EPI$_{creat}$ equation without and with the African American correction factor respectively compared to mGFR at a cut-off of 60 mls/min/1.73m^2.

Conclusion: None of the evaluated equations attained the 2002 KDOQI benchmark of P_{30} > 90%. 11.1–17% of individuals would have been incorrectly classified using the CKD-EPI$_{creat}$ equation.

1. Introduction

Measured glomerular filtration rate (mGFR) remains the standard for assessing renal function [1]. However this method is invasive, expensive, cumbersome, may involve use of radio-isotopes and is not widely available. The use of equations for the estimation of Glomerular Filtration Rate (eGFR), despite several limitations still plays an important role in screening, diagnosing and staging of patients with renal impairment [2, 3].

Current Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend the use of the 2009 Chronic Kidney Disease Epidemiology Collaboration creatinine (CKD-EPI$_{creat}$) equation for eGFR [4]. The equation utilises the variables of serum creatinine, age, gender and race. Reports have demonstrated the equation to have improved accuracy, particularly at GFR > 60 ml/min/1.73m^2 when compared to the Modified Diet in Renal Disease (MDRD) equation which uses the four same variables but different coefficients [2, 3]. Additionally the CKD-EPI$_{creat}$ equation has been shown to be better predictor of risk than the MDRD Study equation in chronic kidney disease (CKD) cohorts as well as in cohorts with higher eGFR [5].

The National Health Laboratory Service (NHLS) in South Africa provides laboratory testing to all state health care facilities, catering for

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over 80% of the population. The MDRD equation is currently the equation used by the NHLS for the reporting of eGFR for adults. It has been developed in Caucasian adults with renal impairment and validated in the African American adult population [2]. Previous studies have shown that the MDRD equation without the African American correction factor performs better than with the correction factor for GFR estimation in Black South Africans [6, 7]. Hence the NHLS does not employ the African American correction factor when reporting MDRD in Black South Africans.

Both MDRD and CKD-EPI$_{creat}$ equations can only be used in patients 18 to 70 years old and are limited by the inaccuracy of creatinine as a marker of filtration (non-GFR determinants like muscle mass, diet and changes in excretion and/or secretion of creatinine can all affect levels). They were not validated in all populations and the influence of analytical imprecision of creatinine at low concentrations has not been well studied [2].

The KDIGO guidelines suggest measuring cystatin C in adults with eGFR of 45–59 ml/min/1.73 m^2 without markers of kidney damage for confirmation of Chronic Kidney Disease (CKD). The eGFR can then be calculated with the Cystatin C preferentially using the 2012 CKD-EPI cystatin C and 2012 CKD-EPI creatinine-cystatin C [4]. Cystatin C concentration is not affected by many of the patient related variables that affect creatinine for example, muscle mass and protein diet. Additionally, levels of cystatin C rise earlier in renal impairment when compared to serum creatinine [8]. However cystatin C testing is not readily available in most South African health care facilities and is a relatively expensive test when compared to serum creatinine.

South Africa with its high incidence of communicable diseases such as Human Immunodeficiency Virus (HIV) and Tuberculosis (TB) and non-communicable diseases has a significant disease burden related to renal pathologies. South African Kwa-Zulu Natal (KZN) patients are a high risk population for kidney disease due to the high prevalence of HIV infection, Diabetes Mellitus and Hypertension [9–11]. About 20% of patients on renal replacement therapy in South Africa are from KZN and it is the province with the second highest amount of patients on renal replacement therapy [12]. According to Census 2011 statistics, KZN consisted of 86.81% Black African, 7.37% Indian or Asian, 4.18% white, 1.38% mixed race and 0.26%other race category thus making KZN unique in terms of population diversity when compared to the rest of South Africa [13]. Therefore determining the performance of the available creatinine-based equations (since Cystatin C is not widely available in South Africa) as well as their suitability for use in this specific population is important.

Previous studies performed in South African populations include a study assessing the predictive performance of the MDRD eGFR equation which found no statistical difference in measured GFR (mGFR) between Black African and Indian patients. They concluded that the MDRD equation without the African American correction factor should be used for African CKD patients,which has already been suggested in another study [6].Use of the MDRD formula in South African Indian population may not be appropriate and a correction factor or a new equation is needed to improve prediction in this ethnic group [14]. Another study performed in the Bellville-South community in the metropolitan city of Cape Town South Africa compared the performance of the Cockcroft-Gault, MDRD and CKD-EPI$_{creat}$ equation in this population which consists predominantly of mixed race individuals. They found the MDRD and CKD-EPI$_{creat}$ to be comparable in this population and concluded that CKD-EPI$_{creat}$ equation should be used for eGFR and CKD staging [15].

Other international studies have found differences in performances of these equations in different populations and racial groups [15–18]. Of note, the CKD-EPI$_{creat}$ equation eGFR has been found to be lower in Asians and higher in Native Americans and Hispanics compared with Whites and others [16]. It has also been found to overestimate GFR as compared to mGFR in South Africans [16].

The aim of the study was to assess the performance of the CKD-EPI$_{creat}$ against mGFR in the different adult population groups in the South African Kwa-Zulu Natalpopulationand compare its performancetothe currently in use MDRD equation.

2. Methods

This was a retrospective, observational, cross sectional study.The study was performed at the Inkosi Albert Luthuli Central Hospital (IALCH), an academic hospital servicing the province of KZN in South Africa. It is the only public hospital in KZN that performs mGFR. Inclusion criteria were South African patients > 18 years old admitted to or attending IALCH clinics (for more than one visit) during the period of 1 April 2014 to 31 March 2016 who had a mGFR done with age, gender, race and serum creatinine available. Exclusion criteria were serum creatinine > 24 h after measured GFR, pregnant patients and race groups with < 200 patients during the study period of 1 April 2014 to 31 March 2016.

mGFR testing records in the Nuclear Medicine Department at IALCH,together with medical records from the hospital information system (Meditech) and laboratory information system(Trakcare) were reviewed and clinical history, age, gender, race and serum creatinine results (measured within 24 h of the measured GFR) for patients > 18 years old were obtained for the period from 1 April 2014 to 31 March 2016. The Biomedical Research Ethics Committee (BREC) of the University of Kwa-Zulu Natal (Clearance certificate number BE 290/17) approved this study, in accordance with the Declaration of Helsinki.

2.1. Measured GFR

mGFR was performed at the Nuclear Medicine Department using the estimation of the plasma clearance of Sodium Technetium-99 m-diethylene-triamine-pentaacetate (^{99m}Tc-DTPA). During the period of the study, there were no changes to the formulation used. The dosage is patient specific and is prepared as per their body weight along with a standard that were both measured under the same conditions. All doses are measured by activity in the dose calibrator. Background reading on the calibrator is noted and subtracted. Plasma samples are collected 1 and 3 h after dosage injected and counted in a well counter with appropriate standards and blanks for background. The Dubois and Dubois slope intercept method with correction for body surface area was used for mGFR calculation [19]. This mGFR was then compared to adult criteria for chronic kidney disease classification [4].

2.2. Serum creatinine measurement

Serum creatinine samples were analysed on the Siemens Advia 1800 analyser (Siemens Healthcare Diagnostics, Tarrytown, USA) using the modified Jaffe kinetic method, which is traceable to an isotope dilution mass spectrometry (IDMS) reference creatinine method (laboratory bias = 5%, total CV = 3% derived from verification data during period of study).The methodology did not change during the study period.

2.3. Estimation of GFR

The MDRD eGFR equation without the African American correction factor and 2009 CKD-EPI$_{creat}$eGFR equations (correction factor added for the Black African participants) were used [2].

$$\text{MDRD eGFR equation:GFR (ml/min/1.73 m}^2) = 175 \times [\text{serum creatinine } (\mu\text{mol}/l) \times 0.011312]^{-1.154} \times [\text{age}]^{-0.203} \times [0.742 \text{ if female}]$$

$$2009\ \text{CKD} - \text{EPI}_{creat}\ \text{eGFR equation: GFR} = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018\ [\text{if female}] \times 1.159\ [\text{if black}]$$