Performance of Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations Versus ^{99}Tc-DTPA-Renogram for Glomerular Filtration Rate

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Abstract

Objectives: To evaluate the performance of Modification of Diet in Renal Disease equation ($MDRD_{186}$, $MDRD_{175}$), and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations in comparison to a gold standard method of Glomerular Filtration Rate (GFR) measurement (^{99}Tc-DTPA-renogram). Also, to correlate the three-equations in calculating estimated GFR, and their impacts on re-classifying CKD-stages in adult patients.

Methods: This cross-sectional study recruited two-groups of patients during a period of January to October 2021. The proportional differences between the prevalence of different CKD-stages according to both MDRD and CKD-EPI equations was 27% and 36%, respectively. Hence, a sample of 64 pairs is required to achieve a study power of 80% and a two-sided significance of 5% for detecting a difference of 0.11 between marginal proportions. The first group included 48 patients who underwent ^{99}Tc-DTPA-renogram procedure for GFR measurement, and the second group included only data of serum creatinine obtained from 30,348 adult patients who did not undergo the same procedure, and eGFR was calculated using the three-equations.

Results: The median of the reference GFR was 106.0(mL/min/1.73m2), whereas the median eGFR for the $MDRD_{175}$, $MDRD_{186}$, and CKD-EPI equations were 92.5, 98.3, and 102.1, respectively. All three-equations correlated moderately with the reference GFR (0.428, 0.428, 0.523), $p< 0.01$. The CKD-EPI showed lesser bias (3.7 vs 12.9 and 7.5 for $MDRD_{175}$ and $MDRD_{186}$, respectively) and more accuracy (95.8% vs 91.7% and 93.8%), however, it was the least precise (25.1 vs 22.3 and 23.8). The $MDRD_{186}$ performed similarly to the CKD-EPI equation at CKD stages 3a-5, and differed significantly at stages 1-2. Whereas the $MDRD_{175}$ differed significantly with both equations at stages 1 – 3b, however was similar to them at stages 4 – 5.

Conclusion: The CKD-EPI equation had the highest accuracy and the least bias and precision in the general population. The $MDRD_{186}$ CKD classification differed significantly from the CKD-EPI equation at CKD-stages 1 – 2 only. The CKD-EPI equation is preferred to MDRD for the detection and classification of early CKD-stages.

Keywords: CKD-EPI, Creatinine, GFR, MDRD

Introduction

kidney disease is the 8th leading cause of death in Oman, responsible for around 16.9 deaths per 100,000 Omani population in 2021.[1,2] Among kidney diseases, chronic kidney disease (CKD) stands out as a globally –

acknowledged significant cause of morbidity and mortality.[3] Hence, early diagnosis is of vital importance for early intervention and monitoring.

According to the Kidney Disease: Improving Global Outcome (KDIGO) clinical guidelines of 2012, CKD can be classified based on the cause, Glomerular Filtration Rate (GFR) category, and albuminuria category. Classification of CKD according to GFR (ml/min/1.73 m^2) is divided into five stages: Stage 1 (GFR ≥ 90), stage 2 (GFR 60 – 89), stage 3a (GFR 45 – 59), stage 3b (GFR 30 – 44), stage 4 (GFR 15 – 29), and stage 5 (GFR < 15).[4] The Glomerular Filtration Rate (GFR) is defined as the measure of how much plasma the kidneys filter in one minute (4). GFR is considered the best marker of kidney function. "True GFR", that is glomerular filtration, cannot be measured directly in humans and therefore, cannot be known with certainty.[5] However, GFR can be assessed by clearance measurements "mGFR or measured GFR" of exogenous filtration markers (such as inulin, iohexol, iothalamate, or ^{51}Cr-EDTA), or by serum levels of endogenous filtration markers "eGFR or estimated GFR" such as Cystatin C or creatinine. GFR measurement by clearance methods, though valuable, are not completely accurate and should be interpreted with caution, and they have a limited use in clinical settings due to practical difficulties, patients' inconveniences, and expense.[6-8]

Serum creatinine remains the most routinely used endogenous marker of kidney function in clinical laboratories worldwide. Creatinine is affected by several factors including age, gender, ethnicity, muscle mass, diet, and exercise.[9,10] The KDIGO 2012 clinical guidelines recommends calculating eGFR using the CKD epidemiology collaboration (CKD-EPI 2009) equation, or with an alternative eGFR equation comparable to it. The serum creatinine measurement should be done using a specific assay with calibration traceable to the international standard reference materials with minimal bias compared to IDMS reference methodology.[4] Because of the aforementioned limitations of GFR measurement, estimated GFR equations have been used in clinical practice as they are easier for routine use. Three equations have been developed in the past decades to assess the GFR and help in the diagnosis and classification of CKD. These equations are the Cockcroft-Gault formula developed in 1976,[11] the Modification of Diet in Renal Disease (MDRD) equation developed in 1999,[12] and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation developed in 2009.[13] The Cockcroft-Gault equation estimates the creatinine clearance (mL/min) and requires weight, age, gender, and serum creatinine.[11] Hence, the creatinine clearance (CrCl) may overestimate eGFR depending on the patient's weight. This equation was developed using the Jaffe method for creatinine measurement and therefore, using it with other methods of creatinine measurement might create bias.[14,15] Due to these disadvantages, the use of Cockcroft-Gault equation in clinical practice is limited.[16]

The MDRD and CKD-EPI equations on the other hand, estimate GFR (mL/min/1.73m^2) rather than CrCl and require serum creatinine, age, gender, and ethnicity but not weight as the results are adjusted to the body surface area. The original MDRD equation was developed using 1628 patients with CKD, and it contained a constant factor of 186 which was replaced later on in the re-expressed four – variable MDRD equation by a coefficient factor of 175, as the serum creatinine assay was standardized to the IDMS reference method.[12,17] The MDRD equation was found to perform well in patients with lower levels of GFR (≤ 60 mL/min/1.73m^2), but it underestimated GFR considerably at GFR values higher than that.[12] This underestimation created bias at GFR ranges above 60 mL/min/1.73m^2, and it called for a new equation that works better in this range. In 2009, Levey et al derived a new formula from the MDRD equation that showed greater accuracy than MDRD when compared with measured GFR using urinary clearance of iothalamate.[13] The CKD-EPI formula was found to show lower bias at estimated GFR values greater than 60 mL/min/1.73m^2, which led to a 1.6% lower prevalence estimate of CKD in the United States population compared to MDRD.[13] Just like MDRD, the CKD-EPI formula relied on age, gender, and race as surrogates for non-GFR determinants of serum creatinine. Interestingly, while the MDRD equation yielded higher prevalence estimates of CKD in women, Whites, and elderly populations, the CKD-EPI equation showed reduced prevalence in women and Whites, but not in the elderly.[13]

Many laboratories around the globe embraced the change from MDRD to the CKD-EPI equation. Several studies highlighted the effects of CKD-EPI implementation in changing the CKD stages in a significant portion of patients into higher eGFR stages.[18-21] When compared to a gold standard method of GFR measurement, the CKD-EPI equation was also found in several studies to be the most accurate, precise, and least biased among other eGFR equations.[22,23] In Oman, a study by Al Maqbali[24]was done in 2013 to compare $MDRD_{186}$, $MDRD_{175}$, and CKD-EPI in the Omani diabetic population. It was shown in this study that the performance of $MDRD_{186}$ was comparable to CKD-EPI, whereas the $MDRD_{175}$ was found to underestimate GFR and hence increase the prevalence of CKD in the diabetic population.[24] Therefore, the current healthcare system continues to use the conventional $MDRD_{186}$ for GFR estimation.

No local validation study was done before to assess the performance of CKD-EPI and MDRD equations in comparison with a gold standard method of GFR measurement in the general Omani population. Furthermore,

whether implementing the CKD-EPI equation in Oman would yield a significant difference in CKD stages re-classification is unknown. This study aimed to evaluate the performance (bias, precision, accuracy) of MDRD and CKD-EPI equations in comparison to a standard method of GFR measurement (99Tc-DTPA renogram) using data from a tertiary hospital in Oman. It also aimed to correlate the performance of MDRD and CKD-EPI equations on CKD stages re-classification in Omani adult patients.

Methods

The study protocol was reviewed by the ethical committee at the Royal hospital with approval numberSRC#91/2021. This was a cross-sectional study recruited two-groups of patients during a period of January to October 2021. The first group included patients who underwent ^{99}Tc-DTPA-renogram procedure for GFR measurement, and the second group included data of serum creatinine obtained from 30,348 adult patients, and eGFR was calculated using the three-equations.

For both groups, the inclusion criteria were all patients attending the hospital in the specified time period aged 18-70 years. The exclusion criteria included patients less than 18 years of age, elderly more than 70 years of age, and pregnant women.

MDRD equations used:

- $MDRD_{186}$ equation: eGFR (mL/min/1.73 m^2) = 186 (S.Cr in µmol/L x 0.011312)$^{-1.154}$ x (age)$^{-0.203}$ x (0.742 if female) x (1.212 if African American/black)

- $MDRD_{175}$ equation: eGFR (mL/min/1.73 m^2) = 175 (S.Cr in µmol/L x 0.011312)$^{-1.154}$ x (age)$^{-0.203}$ x (0.742 if female) x (1.212 if African American/black)

CKD-EPI equations (2009):

- Female with Cr < 62 µmol/L: eGFR (mL/min/1.73 m^2) = 144 x (Cr/61.6)$^{-0.329}$ x (0.993)^{age}

- Female with Cr > 62 µmol/L: eGFR (mL/min/1.73 m^2) = 144 x (Cr/61.6)$^{-1.209}$ x (0.993)^{age}

- Male with Cr < 80 µmol/L: eGFR (mL/min/1.73 m^2) = 141 x (Cr/79.2)$^{-0.411}$ x (0.993)^{age}

- Male with Cr > 80 µmol/L: eGFR (mL/min/1.73 m^2) = 141 x (Cr/79.2)$^{-1.209}$ x (0.993)^{age}

Sample size for the comparison of MDRD and CKD-EPI equations to ^{99}Tc-DTPA renogram as calculated using data from 3 studies from the literature,[12,18,25] where the correlation between measured GFR and estimated GFR was found to be 0.83 – 0.88. The proportional differences between the prevalence of different CKD stages (mainly stages 1 and 2) according to both MDRD and CKD-EPI equations was 27% and 36%, respectively. Hence, when using a sample calculator, it was found that a sample of 64 pairs is required to achieve a study power of 80% and a two-sided significance of 5% for detecting a difference of 0.11 between marginal proportions.

Data entry and analysis was done using Microsoft Excel Office 2019. The prevalence of each CKD stage by both MDRD and CKD-EPI equations was calculated using pre-determined cut-off value to indicate the abnormal levels (taken from the international guidelines for each parameter), and the number of abnormal results was divided by the population size in that group and then multiplied by 100 to yield the prevalence percentage. The comparison between both equations to a reference method was assessed using Bland-Altman plot.

The accuracy, precision, and bias were determined using the following methods:

- Accuracy was calculated as the percentage of estimated GFR within 30% of measured GFR

- Precision was calculated as the IQR (Q3-Q1)

- Bias was calculated as the mean of the bias percentage which is calculated as = (mGFR-eGFR by specified equation/mGFR) x 100%

Results

The first group (99Tc-DTPA renogram), of which 35.4% were females and 64.5% were males, with a mean age of 38 ± 10.4 years. The median GFR (mL/min/1.73m^2) measured by 99Tc-DTPA renogram was 106.0 (104.0 – 112.0), while the median eGFR calculated by $MDRD_{175}$, $MDRD_{186}$, and CKD-EPI was 92.5 (81.8 – 104.1), 98.3 (86.9 – 110.6), and 102.1 (92.3 – 117.4), respectively (Table 1). As for the second group, 58.4% were females and 41.5% were males, with a mean age of 43.2 ± 13.6 years. And their mean GFR calculated by $MDRD_{175}$, $MDRD_{186}$, and CKD-EPI was 100.4 (± 40.2), 106.7 (± 42.7), and 99.5 (± 29.2) mL/min/1.73m^2, respectively.

Table 1: The median, bias, precision, and accuracy of measured GFR and GFR calculated by $MDRD_{175}$, $MDRD_{186}$, and CKD-EPI in the first group.

GFR	Median (range)	Bias (mean %)	Precision	Accuracy p (30)
Measured GFR (^{99}Tc-DTPA renogram)	106.0 (104.0-112.0)	-	-	-
$MDRD_{175}$	92.5 (81.8-104.1)	12.9	22.3	91.7
$MDRD_{186}$	98.3 (86.9-110.6)	7.5	23.8	93.8
CKD-EPI	102.1 (92.3-117.4)	3.7	25.1	95.8

Performance of the equations in comparison to 99Tc-DTPA renogram. The estimated GFR by both $MDRD_{186}$, $MDRD_{175}$, and CKD-EPI equations correlated moderately well with the measured GFR by ^{99}Tc-DTPA renogram (r=0.4, 0.4, and 0.5, respectively with p value <0.01), and all lied within the accepted limits of agreement. Figure 1 shows the Bland Altman plots of the three equations in comparison with the reference GFR measured by DTPA renogram.

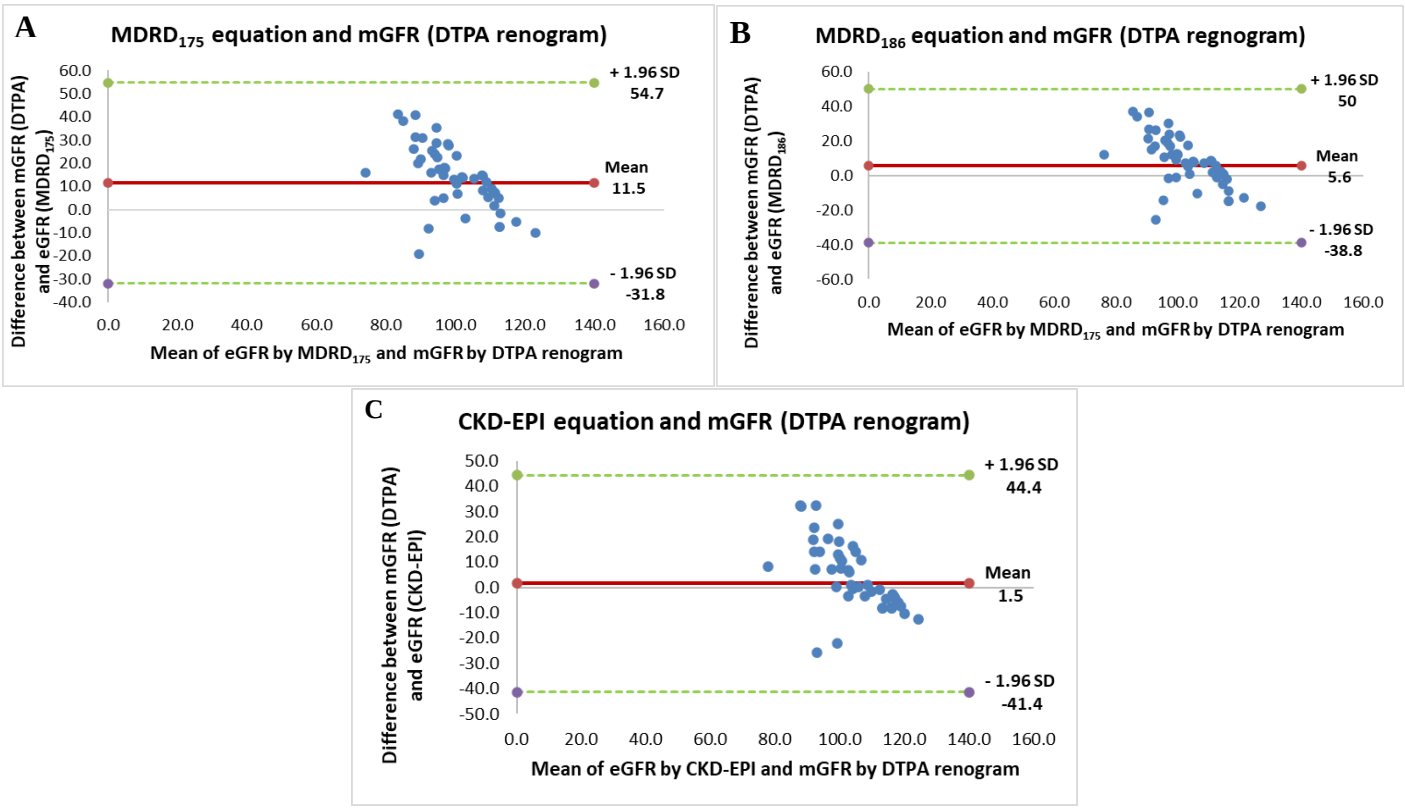

Figure 1: Bland Altman plots comparing the calculated GFR with the measured GFR by ^{99}Tc-DTPA renogram in the first group. A) $MDRD_{175}$ equation with DTPA renogram, B) $MDRD_{186}$ equation with DTPA renogram, and C) CKD-EPI equation with DTPA renogram.

The CKD-EPI showed the highest accuracy with a p(30) of 95.8%, and the least bias compared to the conventional and revised MDRD equations (Table 1). However, the CKD-EPI equation also demonstrated the least precision compared to the MDRD equations. Table 1 shows the median, bias, precision, and accuracy of all equations in comparison the reference method of GFR measurement.

Re-classification of CKD stages according to the equations. The MDRD and CKD-EPI equations remained in close agreement in GFR estimation at stages 3b, 4, and 5. However, the $MDRD_{175}$ equation started deviating from the remaining two equations at stage 3a at around GFR 50 mL/min/1.73m^2, while the $MDRD_{186}$ started deviating from the CKD-EPI equation at stage 2 at around GFR 69 mL/min/1.73 m^2 (figure 2).

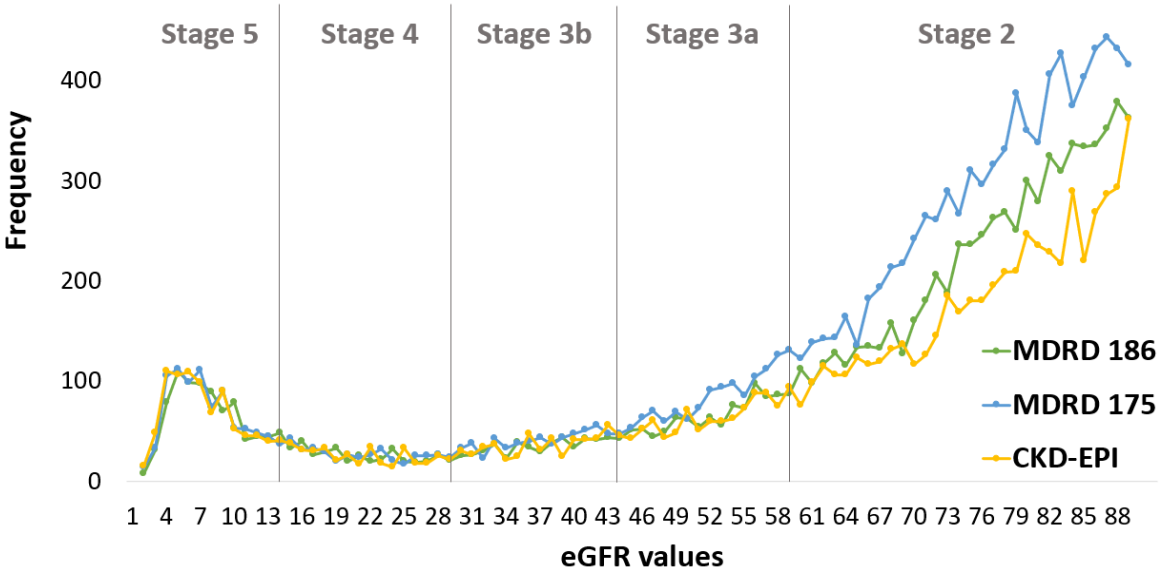

Figure 2: Distribution of eGFR results calculated by both MDRD and CKD-EPI equations and classified into KDIGO CKD stages in the second group.

The reclassification of CKD stages based on the three equations showed that the $MDRD_{175}$ differed significantly from both $MDRD_{186}$ and CKD-EPI at stages 1-3b, classifying more patients into stages 2-3b compared to the remaining two. The CKD EPI equation yielded different CKD classification at stages 1 and 2 compared to the $MDRD_{186}$ equation (p value < 0.001) but had a similar performance at stages 3a – 5, with the CKD-EPI equation classifying more patients into stage 1 (figure 3).

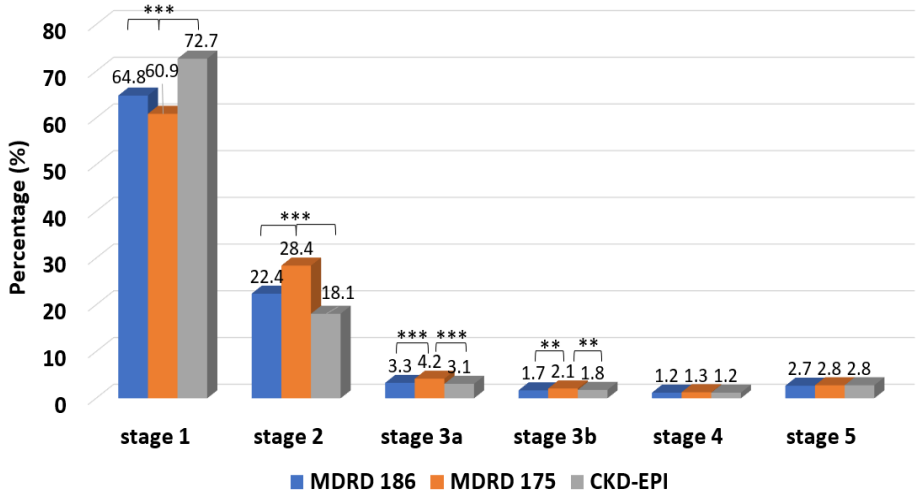

Figure 3: Distribution of CKD stages by eGFR calculated by MDRD175, MDRD186, and CKD-EPI equations in the second group. *** (P value < 0.001), ** (P value < 0.01).

Discussion

This study revealed that the CKD-EPI equation had the highest accuracy, the least bias, and the least precision in comparison to the conventional and revised MDRD equations in the Omani population. It also showed that the GFR estimated by the conventional MDRD equation deviated from the GFR estimated by the CKD-EPI equation at CKD stage 2, while the revised MDRD equation started deviating at CKD stage 3a. The use of CKD-EPI equation classified more patients to a higher GFR stage, mainly CKD stage 1, as compared to the conventional and revised MDRD equations. However, it had similar performance to the conventional MDRD equation at stages 3a – 5.

The findings correlate with a recent study from Ireland which compared both equations in 300,000 samples of inpatients, outpatients, and General Practice (GP) patients.[18] Their results showed that the CKD-EPI equation performed better at high GFR levels compared to the revised MDRD equation, but the change in CKD re-classification occurred mostly from stage 2 to 1 and from 3a to 2. The study concluded that changing from MDRD to CKD-EPI will have little impact in most patients' eGFR and CKD stages, however for the rest of the patients it will reduce the number of cases identified as CKD and therefore, reduce unnecessary nephrology referrals.[18] Similar conclusions were observed in the Kidney Early Evaluation Program (KEEP) in the US[19] and in another study by Korhonen et al.[20]

As for a closer Asian-based population, the comparison between both equations was studied in a multi-ethnic Malaysian population with a comparison to a gold standard method of GFR measurement, namely ^{51}Chromium EDTA plasma clearance. The study highlighted the superiority of CKD-EPI equation in terms of accuracy and precision as compared to MDRD.[22] Similar findings were obtained in a Saudi Arabia – based study that compared both equations to inulin clearance.[23]

In Oman, a previous study done by Al Maqbali[24] compared the performances of $MDRD_{186}$, $MDRD_{175}$, and CKD-EPI (2009) in the Omani diabetic population seen in primary care, specifically looking at their CKD re-classification based on eGFR.[24] The study concluded that the performance of $MDRD_{186}$ and CKD-EPI was in accordance with each other and relayed comparable results. It is noted however that the study did not compare the performances with a gold standard GFR measurement method. The study also demonstrated that compared with the aforementioned formulae, $MDRD_{175}$ underestimated GFR especially at stages 2-3, increasing CKD diagnosis.[24]

Given that the CKD-EPI equation was developed in a largely young – middle aged population with a mean measured GFR of 68 mL/min/1.73m^2, the equation has a risk of underestimating GFR in older populations. A study done in the Netherlands looked into the consequences of introducing CKD-EPI equation in a west Caucasian population of older age.[21] It has shown that the equation yielded higher GFR values in younger age groups and revealed a steeper GFR decline with ageing as compared to the MDRD equation. Hence, younger people were classified mores into higher GFR stages whereas older people, especially males, into lower GFR stages.[21] Similar conclusions were found in the study done by Al Maqbali in Oman,[24] and were observed as well in the present study.

The eGFR equation in use in Royal hospital at the time of this study, Oman was the $MDRD_{186}$ equation. This study confirmed the superior accuracy and least bias of the CKD-EPI equation as compared to $MDRD_{186}$ equation, rendering a possible implication for shifting to CKD-EPI for GFR estimation in Oman for better CKD detection and classification. It is worthy to note that at the time the study was conducted, CKD-EPI 2021 equation was just newly released.[26] Afterwards our data was recalculated using the 2021 equation, and an agreement of 99.7% was found between the 2009 and 2021 CKD-EPI equations (data not shown).

In the recent years, concerns regarding utilizing race as one of determinants for GFR estimation were discussed and analyzed. As race can be seen as a social or political factor rather than a biological construct, the CKD-EPI 2021 equation was developed in order to provide estimates of GFR in an unbiased yet reliable manner. Several papers discussed the change in the CKD-EPI 2021 equation as compared to its 2009 version. A study by Munch et al compared eGFR calculated using CKD-EPI 2009 (assuming Non-Black race; CKD-EPI09 - NB) and CKD-EPI 2021 with 51 Chromium EDTA clearance as the gold standard method of GFR measurement. The study looked at the bias, accuracy, precision, and CKD stages reclassification according to the equations, and it predominantly did so in a mostly white population. The study concluded that, to a small degree, the CKD-EPI 2021 equation performed better compared to the CKD-EPI 09-NB equation, however the CKD-EPI09-NB was superior in terms of CKD stages reclassification at GFR < 60 mL/min/1.73m2.[27] Another paper by Gasevoort et al discussed the argument of

whether the European nephrologists should start using the 2021 version of CKD-EPI equation or not, given its effect on reclassifying high-risk patients with diabetes or cardiovascular disease into lower risk categories, and it concluded with the preference not to as to avoid missing diagnosing CKD in this high risk category.[28] Similar findings were noted in a study that looked into the effect of changing to CKD-EPI 2021 in the Spanish population, which is mostly Caucasian.[29]

Although this study was limited by its relatively small sample size used with the reference GFR measurement method, and the fact that most of the patients included in the first group were healthy kidney donors who had GFRs or CKD 1-2 only, it was empowered by the inclusion of more than 37,000 patients in the second group, who were all from the general Omani population with different comorbidities and covering all CKD stages.

As a consequence of the outcome of our study, the $MDRD_{186}$ – in use in the Royal hospital, Ministry of Health, Oman – was substituted with the CKD-EPI equation. Future prospective studies in such a population can further confirm the superiority and advantageousness of the CKD-EPI equation over the MDRD equation.

Conclusion

This study evaluated the performance of $MDRD_{186}$, $MDRD_{175}$, and CKD-EPI equations in comparison to ^{99}Tc-DTPA renogram and correlated their impacts on re-classifying CKD stages in adult patients. It has shown that the CKD-EPI equation was the most accurate and the least biased and precise in the general population, with the differences in CKD reclassification appearing in CKD stages 1 – 2 only. Hence, the CKD-EPI equation is preferred to MDRD for the detection and classification of early CKD stages. Future studies of prospective nature and with larger sample sizes can give further information regarding the performance of CKD-EPI equation versus the MDRD equation in comparison to a gold standard technique of GFT measurement.

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The authors have no conflicts of interest to declare

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