INTRODUCTION

Chronic kidney disease (CKD) is a global problem with rising prevalence worldwide. The situation in Asian countries is also very alarming due to high prevalence of diabetes, hypertension and nephrolithiasis in this region.\(^1\) Due to the lack of a central registry in Pakistan the exact prevalence of CKD is not known.\(^2,3\) In a recent survey conducted on 300 adults, 30 years or older from a community in Karachi, an alarming 25.3% had reduced GFR, with only 2.3% individuals being aware of their disease.\(^4\)

GFR is considered the best diagnostic test for the diagnosis and staging of CKD.\(^5-7\) The level of GFR and its magnitude of change over time is not only important for assessing the level of kidney damage but also for making decisions about diagnosis, prognosis and management of CKD.\(^5\) The old conventional method of measuring GFR by 24 hours urinary creatinine clearance involved a cumbersome method of collecting timed urine sample which was prone to errors and was not accurate for estimating the GFR since it over-estimated the true GFR.\(^5,6\) Clearance of inulin and radiopharmaceuticals such as iothalamate,\(^5\) Chromium-ethylene-diamine-tetra-acetic acid (\(^{51}\)Cr-EDTA) and \(^{99m}\)Tc-DTPA are the standard methods for measurement of GFR, but these are complex to implement, very costly and available at only selected centres.\(^8,9\)

In clinical practice, GFR is typically estimated (eGFR) from the serum concentration of creatinine, which is now the first line test of kidney function.\(^5\) There are multiple eGFR equations available, but most commonly used are the Cockcroft-Gault and the MDRD equations.\(^5\) The abbreviated or 4 variable MDRD equation is considered to be more practical and most widely used equation which has been validated in different populations worldwide.\(^10-13\) Race is an important determinant of GFR estimation by the MDRD equation and a racial coefficient of 1.21 was included for African-American population in the original MDRD study equation. In Asian countries, this equation was previously applied without the inclusion of this factor. But due to population variations, several Asian countries have modified the MDRD equation by adding a new ethnic factor for their respective population with CKD.

In these modification of MDRD equation studies researchers have used either Inulin or DTPA renal scan as the reference method, both the Chinese and Thai
ethnic factors were derived using $^{99m}$Tc-DTPA scan as the reference method for GFR measurement. No such study of modification of the MDRD equation has so far been conducted in Pakistani population.

The aim of this study was to compare diagnostic performance of the modified equation with the original one in various stages of CKD, against the reference method of GFR i.e. renal dynamic imaging by $^{99m}$Tc-DTPA scan using Gates method.

**METHODOLOGY**

This cross-sectional study was conducted at the Department of Chemical Pathology and Endocrinology, AFIP, Rawalpindi, from July 2011 to July 2012 after approval of the institutional review committee. Sample size was calculated by the WHO sample size calculator formula 7.1.1 based on a pilot study carried out by the trainee researcher on 80 patients with CKD. The mean (SD) of ethnic factor derived in the pilot study samples was 0.960 (±0.24). Based on this mean (SD), a total of 139 patients were required for the study at a confidence level of 95.

A total of 200 patients were recruited by non-probability consecutive sampling technique for the study after their informed consent for the workup of CKD. All had undergone renal DTPA scan for GFR. Analysis of serum creatinine was done on same day. Out of these, 47 subjects with normal renal function and 13 outliers were excluded, whereas 140 subjects fulfilling the inclusion criteria were selected for the study. Inclusion criteria were CKD patients of either gender aged 18 – 75 years and inhabitants of Pakistan. Exclusion criteria was healthy individuals, kidney transplant patients and patients with acute renal failure, Nephrotoxic drug use before or during study period, pregnancy, oedematous disorders leading to CKD. Correlation and bivariate regression were applied to compare the original eGFR and later the means of rGFR with mGFR. Paired samples t-test was used to compare first the means of reference GFR (rGFR) with original eGFR and later the means of rGFR with modified GFR (mGFR). Mean difference between both the groups calculated by Bland Altman analysis was used for estimating the bias. Accuracy was measured as the percentage of eGFR results not deviating more than 15%, 30%, and 50% from rGFR results. A p-value of < 0.05 was considered significant.

The results of rGFR were divided with that of the MDRD eGFR to get the ethnic factor for each individual patient. Mean and SD values of all the ethnic factors was calculated and used for further modification of the original MDRD eGFR equation, i.e., the mean ethnic factor was included in the original equation instead of the African-American factor, thus the formula for modified equation was 175 x S. Cr$^{-1.154}$ x age$^{-0.203}$ x (0.742 if female) $\times$ (0.742 if female)

The modification of original MDRD equation was performed in steps as follows:

- The ethnic factor for MDRD eGFR was derived as under:
  - $rGFR^* = eGFR (MDRD) \times EF$
  - $rGFR = 175 \times (S \text{ Cr})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times EF$

- $rGFR^* = rGFR / 175 \times (S \text{ Cr})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) x (0.742 \text{ if female})$

*where rGFR is reference GFR, and EF is for ethnic factor.

All the study data was entered in Statistical Package for Social Sciences (SPSS) version 19 (SPSS Inc, Chicago, IL, USA) and MedCalc statistical software version 10.2. Mean value and SD were calculated for quantitative variables like age, height, weight, serum creatinine, GFR, and ethnic factor. Frequencies and percentages were calculated for qualitative variables like gender and disorders leading to CKD. Correlation and bivariate regression were applied to compare the original eGFR and mGFR with rGFR. Paired samples t-test was used to compare first the means of reference GFR (rGFR) with original eGFR and later the means of rGFR with modified GFR (mGFR). Mean difference between both the groups calculated by Bland Altman analysis was used for estimating the bias. Accuracy was measured as the percentage of eGFR results not deviating more than 15%, 30%, and 50% from rGFR results. A p-value of < 0.05 was considered significant.
RESULTS

A total of 140 patients were studied for GFR analysis comprising 99 (71%) males and 41 (29%) females, with mean age of 55 ± 13 years, age ranging from 23 – 75 years. Mean values were 32.91 ± 14.96 for rGFR, 34.89 ±16.45 for original eGFR, 0.971 ± 0.20 for ethnic factor and 33.87 ± 15.97 for mGFR (Table I). Majority of the patients (57%, n=80) were in CKD stage 3, whereas 29% (n=39) were in stage 4 and 14% (n=21) in stage 5. There was a predominance of patients belonging to the Punjab belt (64%, n=90) followed by Pakhtoons (28%, n=39) and only a few patients were from Kashmir and other provinces (8%, n=11). In correlation and bivariate regression analysis both the eGFR methods correlated well with rGFR. Regression equation for eGFR was $y = 2.1598 + 0.9944 x$ with correlation coefficient $r = 0.904$ and $r^2 = 0.817$ ($p < 0.0001$), and regression equation for mGFR was $y = 2.0973 + 0.9655 x$ with correlation coefficient $r = 0.904$ and $r^2 = 0.817$ ($p < 0.0001$). Paired samples t-test showed a significant difference between the rGFR and original eGFR ($p = 0.001$), whereas the difference between rGFR and mGFR was not significant ($p = 0.099$). In CKD stages 3 and 4 there was significant difference between original eGFR and rGFR ($p = 0.033$ and 0.014 respectively) whereas it was not significant between mGFR and rGFR ($p = 0.474$ and 0.065 respectively). The difference was not significant in both the pairs in CKD stage 5 or advanced kidney disease ($p = 0.136$ and 0.317 respectively). Eighty one percent of eGFR values and 87% of mGFR values were within 30% accuracy of rGFR. Generally both the eGFR equations performed well in diagnosis of CKD in our population with more than 80% of eGFR values lying within 30% accuracy, and mGFR was closer to the rGFR in accuracy as compared to the original eGFR in all CKD stages (Table II). Performance of eGFR formulae against rGFR on the basis of Bland-Altman bias and accuracy within 15%, 30% and 50% of rGFR is as shown in Table III. A linear relationship was found between mGFR and rGFR with $r^2$ value of 0.817 at a significance level of < 0.001 (Figure 1).

DISCUSSION

Under recognition of its earlier stages and risk factors may be one of the reasons for the rise in CKD progressing to End Stage Renal Disease (ESRD). GFR measurement is a critical method for the diagnosis and evaluation of CKD. The normal mean value for GFR in healthy young men and women is approximately 130 mL/min per 1.73 m² and 120 mL/min per 1.73 m²,
respectively, and it declines by approximately 1 mL/min per 1.73 m² per year after 40 years of age. Accurate values of GFR are necessary for effective decision making in the management of CKD patients. Presently GFR estimated equations based on serum creatinine are widely employed for screening and staging of CKD. The National Kidney Foundation of USA has recommended that all laboratories should report a calculated GFR using the MDRD formula. By doing so, the laboratory helps in early detection, treatment and prevention of CKD. The formula can be incorporated into the Laboratory Information System with automatic calculation and reporting of eGFR with every serum creatinine measured in adult patients.

The abbreviated MDRD equation, including only four variables - S Cr, gender, age, and ethnicity is the most widely used in clinical practice today, and provided an acceptable level of accuracy (at least 70% of eGFR values lying within 30% deviation from the rGFR) in advanced stages of CKD and is recommended by Kidney Disease Outcome Quality Initiative (K/DOQI) clinical practice guidelines. Many studies have shown that MDRD equation performed well in populations with lower levels of GFR (< 60 ml/min/1.73 m²), but variable performance in those with higher levels (> 60 ml/min/1.73 m²). Recently, researchers have proposed a new MDRD equation in which the assay for serum creatinine is traceable to the standard method, Isotope Dilution Mass Spectrometry (IDMS). This IDMS traceable standardized serum creatinine assay eliminates the error introduced by variability among clinical laboratories in calibration of serum creatinine assays.

Estimation of GFR has also assumed greater importance in the Asian countries due to increased emphasis given by many studies on early detection and management of CKD. Race was an important factor in determination of eGFR, and an ethnic factor of 1.21 was used for the African-American population of the MDRD study. Over the years, Asian countries have been using this equation without the ethnic factors, and it was constantly felt that the equation did not perform better without the ethnic factor since there was a lot of difference in the body mass of Asians as compared to the African-Americans. Therefore, several countries in this region have attempted to use their own ethnic factors and have modified the MDRD equation in their respective population with CKD. Asian countries as China, Japan, Korea and Thailand have derived the ethnic factors for their representative population and validated the MDRD equation for GFR estimation after its modification.

In this study, the authors first calculated the ethnic factor of our local population based on the values of rGFR and original MDRD eGFR. Secondly, the original MDRD eGFR was modified by inclusion of the mean ethnic factor of the local population. Performance of both the original and modified eGFR equations against the rGFR was demonstrated in this study. The modified MDRD equation showed improvement in the mean and SD as compared to the original equation. In general, the MDRD equation demonstrated minimum bias and reasonable precision and accuracy in our local population with CKD in all its stages. The overall performance of the modified equation was superior to that of the original equation by showing decreased bias, and improved accuracy compared with rGFR. Studies by Ying-Chun et al., Lee et al., Praditpornsilpa and Matsuo et al. also showed similar results with improved performance of the modified equations in CKD stages 3 – 5 in their respective population.

The limitation of the study was that the study population was small to represent the entire population of the country. In future, multicentre studies will be required to find a common ethnic factor representing the entire Pakistani population.

**CONCLUSION**

This study confirmed that MDRD equation is a suitable and valid equation for estimating GFR in CKD patients of Rawalpindi. Moreover, with the inclusion of ethnic factor for the Pakistani population, it further improves the accuracy of the GFR estimation and eliminates bias. Furthermore, we recommend future studies to validate the MDRD equation in Pakistani population using the same GFR measurement protocol and eligible criteria along with derivation of a common ethnic factor for the entire population.

**REFERENCES**


