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Evaluation of 'CKD-EPI Pakistan' equation for estimated glomerular filtration rate (eGFR): a comparison of eGFR prediction equations in Pakistani population

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ORIGINAL ARTICLE

Evaluation of 'CKD-EPI Pakistan' Equation for estimated Glomerular Filtration Rate (eGFR): A Comparison of eGFR Prediction Equations in Pakistani Population

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ABSTRACT

Objective: To evaluate the results of 24-hour urinary creatinine clearance (CrCl) with estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), CKD-EPI Pakistan (CKD-EPI Pak), Cockcroft Gault (CG) and 4-variable Modification of Diet in Renal Disease (MDRD) equations.

Study Design: Descriptive, cross-sectional study.

Place and Duration of Study: Section of Clinical Chemistry, Department of Pathology and Laboratory Medicine, The Aga Khan University, Karachi, from June to October 2013.

Methodology: Laboratory data of subjects ≥18 years ordering 24-hour urinary CrCl from June to October 2013 was retrieved. Statistical comparison of eGFR using CKD-EPI, CKD-EPI Pak, CG and MDRD with the timed urine collection CrCl was done using regression analysis.

Results: The mean age of the group (n=670) was 51.3 ±15.4 years with a median of 53 (IQR:22.3) years, 55.7% being males. Median BMI of males and females was 26.98 kg/m^2 (IQR: 7.09) and 26.16 kg/m^2 (IQR: 6.97), respectively. Mean GFR using 24-hour creatinine clearance was 57.1 ±35.9 ml/min/1.73m^2 with a median of 51 ml/min/1.73m^2. Urinary creatinine clearance showed strong correlation with CG, MDRD, CKD-EPI and CKD-EPI Pak, showing r=0.78, r=0.79, r=0.82, and r=0.82, respectively. Sensitivity was highest for the CKD-EPI Pakistan (84.7%). Similarly, CKD-EPI Pakistan equation showed the highest agreement (88.7%) with CrCl compared to the other formulae.

Conclusion: The CKD-EPI Pak equation is more accurate and precise than the CG, CKD-EPI and MDRD in estimating GFR in Pakistani population.

Key Words: *GFR. Creatinine. Cockcroft Gault. Modification of Diet in Renal Disease. CKD-EPI*

INTRODUCTION

The prevalence of chronic kidney disease (CKD) is on the rise globally, which is now recognized as a global public health challenge with drastic effects on health and financial resources.[1] In Pakistan, overall prevalence of 12.5% has been reported.[2] Independent risk factors associated with CKD in the Pakistani population are reported to be hypertension, diabetes, elevated fasting glucose, higher triglyceride and stroke.[2-4]

Evaluation of kidney function in routine clinical practice is performed by measuring serum creatinine and 24-hour creatinine excretion (CrCl) as a measure of estimation of glomerular filtration rate (GFR).[5] Owing to the fact that eGFR is a more reliable marker for assessing the renal function compared to creatinine, the National Kidney Disease Education Program (NKDEP) has also recommended reporting eGFR whenever a serum Cr test is requested. In recent years, automatic calculation of eGFR using Cockcroft-Gault (CG) and the four-variable Modification of Diet in Renal Disease (MDRD) equation along with Cr result on laboratory reports is being increasingly provided. The MDRD equation was developed using the data of subjects that were already established cases of CKD; and furthermore, it suffers from certain limitations such as underestimation of eGFR at higher levels.[6,7]

In 2009, a new formula for estimation of GFR was proposed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) research group, termed as CKD-EPI.[8] A recent systematic review showed superior performance of CKD-EPI equation in comparison with MDRD in estimating measured GFR.[8] However, neither of these equations has been validated in Pakistani population where both muscle mass and meat consumption are lower as compared to Caucasians, which might lead to impreciseness of eGFR.[9]

The accuracy of CKD-EPI equation has been further improved by applying modification factors for slope and intercept.[10] This cross-sectional population based study evaluated the performance of CKD-EPI equation using Inulin clearance as gold standard, and reported it to be significantly more accurate than MDRD. Furthermore, the Pakistani correction factors in the CKD-EPI Pak equation reduced bias in estimating GFR compared to the original equation in the overall population.

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The aim of this study was to compare CKD-EPI, CKD-EPI Pak, CG and 4-variable MDRD formulae with creatinine clearance calculated through a timed urine collection in adult population.

METHODOLOGY

Laboratory results of subjects above 18 years; tested for CrCl from 1st June to 31st October 2013 were reviewed at the Section of Clinical Chemistry, Department of Pathology and Laboratory Medicine, The Aga Khan University Hospital, Karachi. The clinical laboratory of AKUH is the national reference laboratory with laboratories in various cities, more than 250 phlebotomy stations across Pakistan and a tertiary laboratory at main AKUH campus in Karachi. Before the commencement of study, exemption was sought from the institutional ethical review committee.

Printed patient instructions for 24-hour urine collection were routinely provided to the individuals ordering CrCl test along with sterile leak resistant urine collection containers with tightly-fitted lid at the time of requisition by the patient. Serum samples for Cr estimation were collected when the patient delivered the 24-hour urine sample to the phlebotomy center or the main laboratory. At the same time, weight and height of the subjects, for calculation of body surface area (BSA), was noted by phlebotomists. Subjects with CrCl not adjusted for BSA were excluded. Furthermore, samples coming from outside Pakistan were also not included in the final data analysis.

Serum and urine Cr were assayed with the rate-Jaffe reaction on Siemens analyzer, ADVIA 1800. This assay was calibrated daily by two-point calibration, using calibrators provided by the manufacturer (Siemens Diagnostics Corp.), which is traceable to an isotope dilution mass spectrometry (IDMS) reference method, using the National Institutes of Standards and Technology (NIST) Standard Reference Material 967. For the calibration of urine specimens, urine calibrator was used daily. The system was monitored by routine internal quality control procedures and participation in College of American Pathologists (CAP) external quality assurance surveys. Normal reference range for males and females was taken as 0.8-1.3 mg/dl and 0.6-1.2 mg/dl, respectively.

Estimation of GFR was done using the CrCl, MDRD, CG, CKD-EPI and CKD-EPI Pak formulae as shown in Table I. The 4-variable MDRD, which requires serum Cr, age, gender, and ethnicity was used but the ethnicity factor which is for Black Americans was not applied.

Statistical analysis of the data was performed using Statistical Package of Social Sciences (SPSS) version 20 and EP evaluator version 10.3.0.556 (Data innovations, LLC). Quantitative variables were expressed in terms of mean and standard deviation (SD); and medians with intraquartile range for non-parametric variables. Shapiro Wilk test was used to check normality of data. Deming regression analysis was used to obtain slopes adjusted for measurement error and regression to the mean for each equation in comparison with CrCl. Performance of equations was compared by using a cutoff value for CrCl <60 ml/min/1.73m^2. The data was stratified into the five stages of CKD as follows: Stage I: eGFR ≥90 ml/min per 1.73 m^2, Stage II: eGFR 60--89 ml/min per 1.73m^2, Stage III: eGFR 30-59 ml/min per 1.73 m^2, Stage IV: eGFR 15-29 ml/min per 1.73 m^2 and Stage V: eGFR <15 ml/min per 1.73 m^2. Kruskal-Wallis test is used to compare medians of Cr, CrCl, MDRD, CG, CKD-EPI and CKD-EPI Pak among the different stages of CKD. Sensitivity, specificity, positive predictive and negative predictive values were calculated for CrCl, MDRD,CG, CKD-EPI and CKD-EPI Pak. Two-tailed p-values < 0.05 were considered significant and <0.01 as highly significant.

Table I: Equations for estimating glomerular filtration rate in adults.

Method of GFR calculation	Equations
CrCl (ml/min/1.73m^2)	Urinary Cr x volume x 1.73/ serum Cr x1440 x BSA
MDRD (mL/min/ 1.73 m^2)	175 x Cr -1.154 x Age -0.203 x (0.742 if female)
CG (mL/min)	(140 - age) x weight / serum Cr x 72 x (0.85 for females)
CKD-EPI	If SCr < 0.9 (for male): 141 x (SCr/0.9)-0. 411 x 0.993^{Age}
	If SCr > 0.9 (for male): 141 x (SCr/0.9) -1.209 x 0.993^{Age}
	If SCr < 0.7 (for female): 144 x (SCr/0.7)-0.329 x 0.993^{Age}
	If SCr > 0.7 (for female): 144 x (SCr/0:9)-1.209 x 0.993^{Age}
CKD-EPI Pak	0.686 x CKD-EPI 1.059

GFR = Glomerular filtration rate; CrCl = Creatinine clearance; Cr = Creatinine; BSA = Body surface area; MDRD = Modification of diet in renal disease; exp = exponential; CG= Cockcroft Gault.
Serum Cr in mg/dL, weight in kg, height in meters, age in years, and BSA in meter square.

RESULTS

After excluding those without weight and height measurement, 670 cases were included in final data analysis. Majority of the subjects were male (55.7%). Median BMI of males and females was 26.98 kg/m^2 (IQR: 7.09) and 26.16 kg/m^2 (IQR: 6.97), respectively. Mean age of the group was 51.3 ±15.4 years with a median of 53 years (IQR: 22.3).

For both genders, inverse reciprocal non-linear relationship was noted between serum creatinine and eGFR estimated by all other CKD-EPI Pak equation, such that a reduction in GFR produces an increase in serum creatinine as shown in Figures 1a and 1b.

Overall 126 (42.4%) females out of 297, and 203 (54.4%) males out of 373 had elevated serum Cr values. A strong positive correlation between serum Cr and GFR staging was noted as mean Cr levels were significantly higher with climbing GFR stages. Out of the total 670 subjects, 394 (58.8%) subjects had CrCl <60 ml/min. Among these 49.1% (n=329) had high serum Cr values based on gender specific reference intervals and 61.7% were males. Whereas, eGFR equations performed better than

serum Cr alone and showed higher agreement with respect to CrCl in identifying patients with impaired renal function (MDRD: 83.9%, CG: 82.5%, CKD-EPI: 83.5% and CKD-EPI Pak: 84.7%).

Strong correlation was noted between CrCl and CG (r=0.78), MDRD (0.79) and CKD-EPI Pak (0.82) and CKD-EPI (0.82). Confidence interval for slope and intercept were 0.829 (0.791 to 0.867) and 5.688 (3.105 to 8.272), respectively for CKD-EPI Pak equation. Results are summarized in Figure 2a, b, c and d.

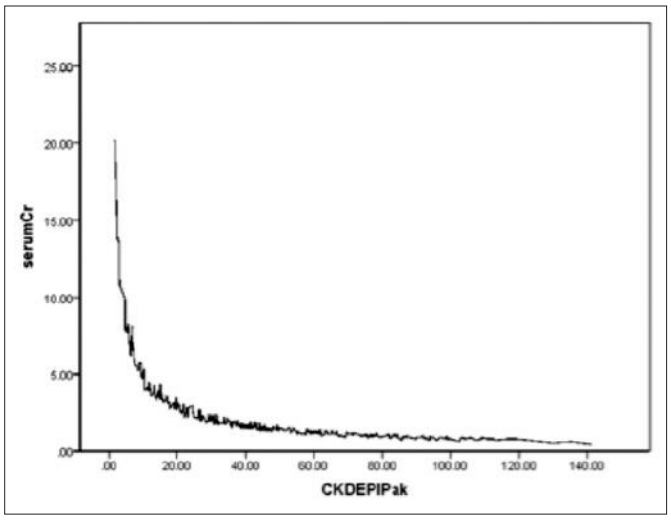

Figure 1a: Showing relationship between CKD-EPI Pak and Serum Creatinine in males.
Line graph showing relationship between Serum Cr and CKD-EPI Pak equation. As depicted, there is an inverse relationship between Serum Cr and CKD-EPI Pak; r = - 0.6 (p-value 0.01).

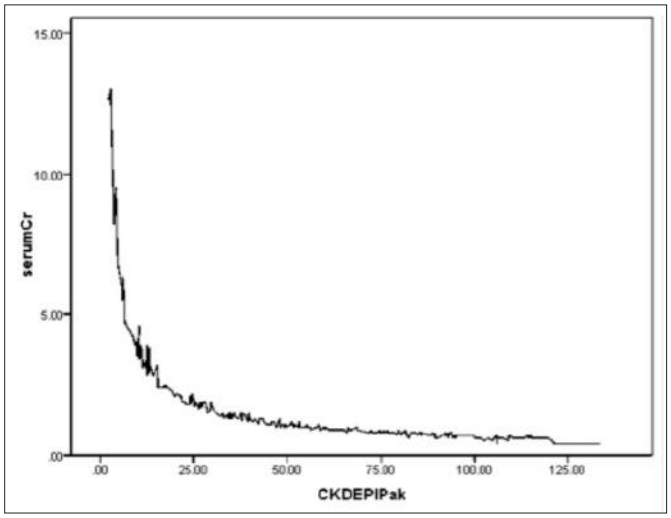

Figure 1b: Showing relationship between CKD-EPI Pak and Serum Creatinine in females.
Line graph showing relationship between Serum Cr and CKD-EPI Pak equation. As depicted there is an inverse relationship between Serum Cr and CKD-EPI Pak; r = - 0.6 (p-value: <0.01).

Medians of calculated and measured GFR in different CKD stages are shown in Table II. Kruskal-Wallis test to compare medians of Cr, CrCl, MDRD, CG, CKD-EPI and CKD-EPI Pak showed that there is statistically significant difference among the different stages of CKD (p<0.01, Table III).

Among the 4 formulae tested against CrCl, CKD-EPI Pak showed the highest sensitivity, negative predictive

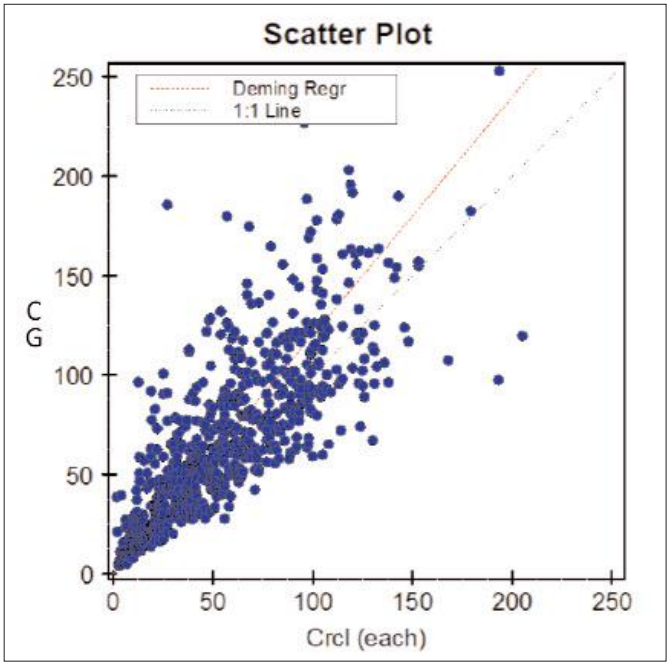

Figure 2a: Showing comparison of CrCl with CG. The Deming Regression analysis demonstrates close agreement between the CrCl and CG. The solid line indicates the slope of observed measurements (slope = 1.2) plotted against the perfect-fit line for which slope = 1.
y = 0.23+ 1.2(x)
r = 0.78

Table III: Diagnostic ability* of CrCl versus MDRD, CG, CKD-EPI and CKD-EPI Pak.

	MDRD	CG	CKD-EPI	CKD-EPI Pak
Sensitivity	84.3%	76.6%	81.8%	88.7%
Specificity	83.2%	90%	86.1%	79%
Positive predictive value	87%	91%	89%	85.4%
Negative predictive value	79%	73%	77.3%	83.4%
Agreement (%)	83.9%	82.5%	83.5%	84.7%

**Calculated for a threshold cut-off of 60 ml/min/1.73 m² taking CrCl as the reference.*

Table II: Difference between CrCl and the 4 formulae in the 5 stages of CKD (n=670).

GFR stages	n	Median Cr (mg/dl)	Median eGFR using the different formulae (ml/min)					p-value
			CrCl	MDRD	CG	CKD-EPI	CKD-EPI Pak	
I	135 (20.1%)	0.8 (IQR:0.3)	105 (IQR:25)	89 (IQR:28)	112.2 (IQR49.6)	99.3 (IQR:26.2)	89.3 (IQR:25)	< 0.0001
II	141 (21%)	1.0 (IQR: 0.5)	72 (IQR:16)	67.7 (IQR:24.4)	80.1 (IQR:36.8)	73.8 (IQR:30.5)	65.3 (IQR:28.6)	< 0.0001
III	219 (32.7%)	1.4 (IQR: 0.7)	44 (IQR:14)	47 (IQR:21.6)	53.3 (IQR: 27.3)	47.2 (IQR: 25.3)	40.7 (IQR:23.1)	< 0.0001
IV	103 (15.3%)	2.4 (IQR: 1.5)	22 (IQR:6.0)	26 (IQR: 19.2)	33.1 (IQR:20.7)	26.2 (IQR:18.4)	21.8 (IQR: 16.3)	< 0.0001
V	72 (10.8%)	4.4 (IQR: 3.9)	9.5 (IQR:6)	12.1 (IQR: 11.6)	14.9 (IQR: 14.6)	12.4 (IQR:11.0)	9.8 (IQR: 9.3)	< 0.0001

**p-value <0.01 = highly significant.*

value being 88.7% and 83.4%, respectively. The calculated sensitivity, specificity, positive and negative predictive values of MDRD, CG, CKD-EPI and CKD-EPI Pak are shown in Table III.

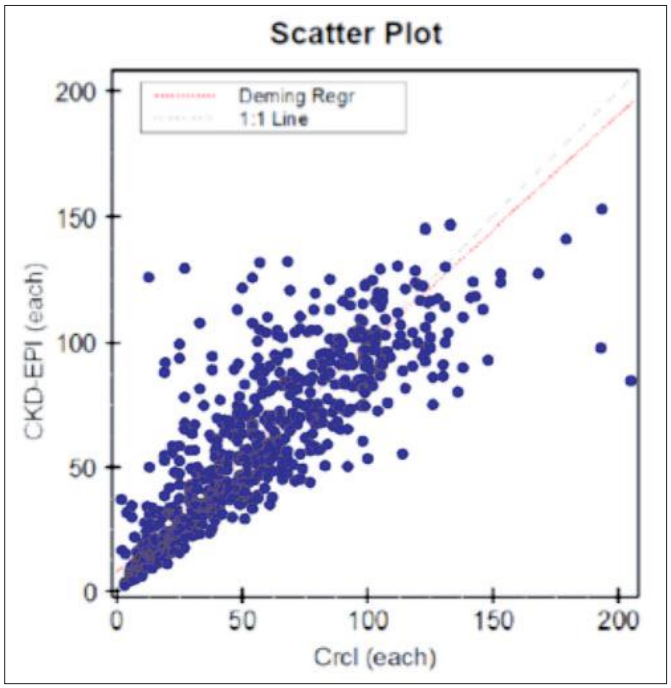

Figure 2b: Showing comparison of CrCl with CKD-EPI. The Deming Regression analysis demonstrates close agreement between the CrCl and CKD-EPI. The solid line indicates the slope of observed measurements (slope = 0.83) plotted against the perfect-fit line for which slope = 1.
y = 5.7 + 0.83(x)
r = 0.82

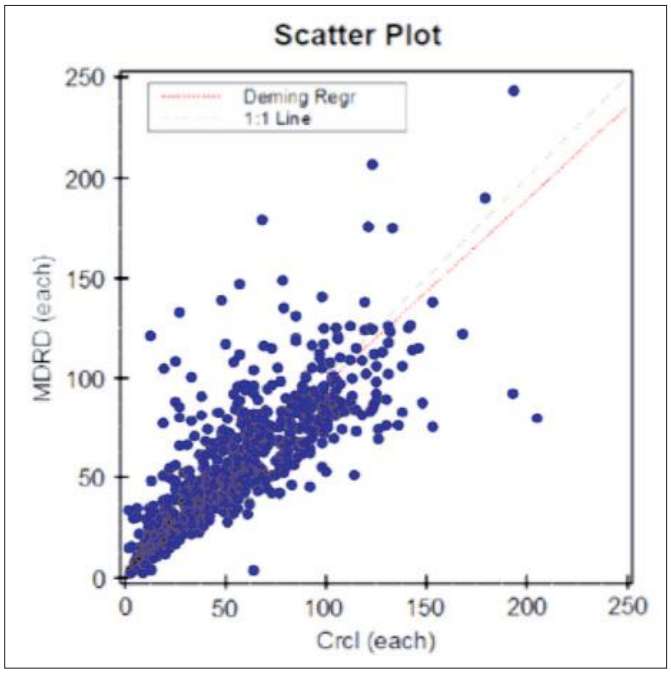

Figure 2c: Showing comparison of CrCl with MDRD. The Deming Regression analysis demonstrates close agreement between the CrCl and MDRD. The solid line indicates the slope of observed measurements (slope = 0.92) plotted against the perfect-fit line for which slope = 1.
y = 5.23 + 0.92(x)
r = 0.79

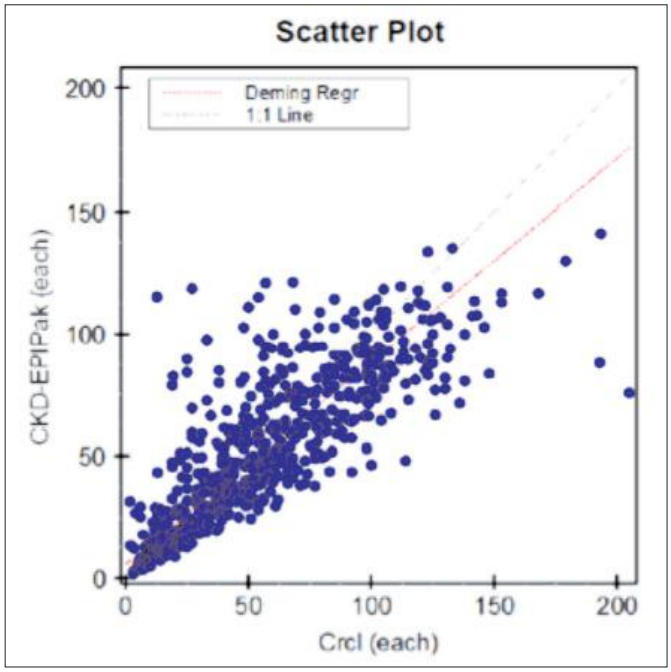

Figure 2d: Showing comparison of CrCl with CKD-EPI Pak. The Deming Regression analysis demonstrates close agreement between the CrCl and CKD-EPI Pak. The solid line indicates the slope of observed measurements (slope = 0.92) plotted against the perfect-fit line for which slope = 1.
y = 7.9 + 0.92(x)
r = 0.82

DISCUSSION

Statistics from Pakistan show that the prevalence of risk factors of CKD is higher in this region including hypertension, which is found to be exhibiting an escalating trend more in the older age group and in females.[11,12] Similarly, the incidence of diabetes is on the rise in Pakistan, its prevalence being 6.8%.[13]

A community-based survey held in 2011 in Karachi, reported that 25.3% (n=300) of study participants presented with low estimated glomerular filtration rate (eGFR) based on serum creatinine (Cr). An alarming finding of this survey was that only 2.3% individuals were aware of their declining renal function.[14] This large scale under detection of early stages of CKD in Pakistan is a potential contributor to end stage renal disease, inviting large increases in resources to combat treatment expenditures. Keeping in mind the high cost of dialysis and scarcity of services for dialysis, it is not at all surprising that only 10% patients with CKD in Pakistan are able to afford therapy.[15]

Considering the importance of early recognition of falling eGFR, this study was designed in order to compare various eGFR equations in Pakistani population and to evaluate the accuracy and reliability of CKD-EPI Pak equation in the local setup. College of American Pathologists mandatory recommend reporting eGFR along with every creatinine test ordered.[16] There has been a rising trend in reporting of eGFR as evident by the CAP general chemistry C-B Survey 2013, that reported use of eGFR by 90% laboratories out of 3,696

laboratories as compared to 83% in 2012. The various eGFR equations including the CKD-EPI and MDRD have been established, based on data collected from Caucasian and African-American populations.[17]

Furthermore, published literature has highlighted the fact that the calculation of eGFR for Asian population using these equations without validation could result in inaccuracies.[18-20]

The study population in this study was reflective of geographical distribution of Pakistan. In this context, the current study was undertaken to evaluate the performance of the different eGFR estimating equations in Pakistani population. Compared to the original CKD-EPI equation, the improvements in accuracy for the CKD-EPI Pak equation makes it a potential marker for eGFR reporting and this has been the corner stone of our study. The findings suggest that modification of the CKD-EPI equation with a Pakistan correction factor is the most accurate and practicable creatinine-based GFR estimating equation for the South Asian population, at least in Pakistan compared to CrCl.

CKD is usually silent until extensive kidney damage has befallen. The public health objective of the NKDEP is to achieve timely identification of patients with CKD so treatment regimens can be brought into play. Therefore, the NKDEP has recommended reporting eGFR along with Cr for adults as eGFR value is a more precise indicator of renal function deterioration compared to stand alone Cr values.[21] Thus to accomplish this, spontaneous reporting of eGFR can provide a cost effective way to identify people with CKD, especially in resource-limited under-developed countries in the earlier stages of declining renal function.

CONCLUSION

The results of this study support automated reporting of eGFR using CKD-EPI Pak equation in laboratories across Pakistan. The findings of this study can also be shared with clinical laboratories in Pakistan and neighboring countries, to facilitate reporting of eGFR when serum creatinine is measured, which will pave the way for better clinical outcomes and will prove to be beneficial for the physicians as well as patients.

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