Research Article

Diagnostic Accuracy of Creatinine-Based Equations for eGFR Estimation in Pakistanis: Evaluation of the European Kidney Function Consortium Equation vs the CKD-EPI Pakistan Equation

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Keywords
Renal function; equations; eGFR; Pakistani

Abstract

Introduction
Chronic Kidney Disease (CKD) is prevalent in Pakistan, necessitating accurate diagnostic methods. This study evaluates the CKD-EPI 2009, CKD-EPI 2021, CKD-EPI Pak, MDRD, and EKFC equations against creatinine clearance (CrCl) to determine their diagnostic accuracy for CKD in the Pakistani population.

Methods
n a retrospective cross-sectional study, data from 2,310 participants aged 18-70 were analyzed at The Aga Khan University in Karachi. Serum creatinine (SCr) and CrCl were recorded, and eGFR was calculated using five equations. Statistical analyses compared eGFR equations with CrCl, assessing sensitivity, specificity, and predictive values.

Results
EPI-Pak exhibited the highest sensitivity (95.15%) and agreement (94.85%) followed by EPI-2009 and EPI-2021 which showed the closest agreement with CrCl. Bland-Altman plots also indicated that EPI-Pak had the best agreement with CrCl.
Discussion
EPI-Pak outperformed other equations in estimating eGFR for the Pakistani population, aligning with previous recommendations for South Asians. EKFC, although highly specific, was less effective overall.

Conclusion
EPI-Pak is the most accurate equation for diagnosing CKD in the Pakistani population. Its clinical implementation could improve CKD diagnosis and patient outcomes. Future studies should further validate these findings with larger, diverse samples.

Introduction

Chronic Kidney Disease (CKD) is a global health issue, leading to significant morbidity and mortality. The prevalence of CKD in Pakistan lies between 12.5% to 31.2% [1]. CKD progression eventually leads to kidney failure, resulting in the need for renal replacement therapy either by dialysis or by renal transplantation [2]. The most common etiologies for CKD, Diabetes Mellitus and Hypertension, are also the most common comorbidities in Pakistan. Moreover, CKD is also a risk factor for cardiovascular complications, thus highlighting the need for the early diagnosis and management of CKD [3].

Renal function can be assessed by estimating the glomerular filtration rate (GFR) using values of serum creatinine and 24-hour creatinine clearance (CrCl). Estimated GFR (eGFR) based upon serum creatinine is considered to be the most reliable indicator of kidney function. Serum creatinine (SCr) based eGFR is calculated using various equations which have been derived and validated in various populations [4]. The Modification of Diet in Renal Disease (MDRD) equation utilizes an individual's SCr, whereas the Cockcroft-Gault (CG) formula uses an individual's CrCl adjusted for the body surface area and weight although it is taken on average. This assumption limits the CG formula when applied to overweight individuals. The MDRD equation surpasses the CG although it still has its limitations due to significant bias and may not be optimum in mild CKD cases [5, 6]. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) created an equation (CKD-EPI 2009) in 2009 for eGFR. This outperformed MDRD because of lesser bias, better precision as well as greater accuracy. However, since participants of racial and ethnic minorities were very limited in the study, the population it takes into account is relatively limited [7]. Because of this restriction, in 2015, CKD-EPI Pakistan was made by making some alterations to the factors in CKD-EPI equation which allowed CKD-EPI Pakistan to factor in the South Asian demographics as well [8]. However, after using inulin clearance as a gold standard to see competence of CKD-EPI Pakistan in comparison to MDRD, CKD-EPI Pakistan came out to be more reliable when applied to the Pakistani population. In 2021, the coefficient for race was removed from the CKD-EPI eGFR equation and the modified version of that equation was accepted by the National Kidney Foundation and the American Society of Nephrology, although upon comparison, the difference in values of eGFR calculated by both equations was quite minor [9].

Parallel to this, another equation was developed by the European Kidney Function Consortium (EKFC) in 2021. This equation surpasses the limitations of its predecessors while also given to laboratories to be incorporated without needing changes which makes it more convenient to use [10]. Given the limitations of existing GFR estimation equations in accurately diagnosing CKD in diverse populations, there is a need to evaluate their applicability to the Pakistani population. This is because the existing solutions fail to completely weigh in the Pakistani correction factors with regards to the environment and life style can only be corrected if there is an measuring tool specific to the Pakistani demographics [11]. Therefore, the objective of our study is to compare EKFC, CKD-EPI 2021, CKD-EPI 2009, CKD-EPI Pak and MDRD equations taking CrCl as gold standard in order to evaluate these equations and understand which equation holds the greatest value when it comes to diagnosing CKD in the Pakistani population.

Materials and Methods

Study Design and Settings

This study was a retrospective cross-sectional study conducted at the Chemical Pathology branch of the Department of Pathology and Laboratory Medicine and the Nephrology unit at The Aga Khan University in Karachi.

The integrated laboratory management system (iLMS) provided consecutive CrCl test results for individuals above the age of 18 for the three months of December 2021 to February 2022.

Study Participants

After excluding individuals below 18 years of age and those above 70 years of age, a total of 2310 results were evaluated in the final dataset. Participants included individuals above the age of 18, and demographic characteristics such as age and gender were noted. The rationale behind the selection of the age criteria was based on the reasoning that the CKD-EPI Pak equation was originally made and validated for this age group [11]. Biochemical results of SCr and CrCl were also recorded. The study sample was obtained from laboratory records, and the data was analyzed retrospectively. The eGFR values for each patient was calculated using the five different equations as described in Table 1.

Laboratory Analysis

The rate-Jaffe reaction was employed for SCr analysis using the Siemens ADVIA 1800 analyzer, which can be linked to a reference method for isotope dilution mass spectrometry (IDMS). The laboratory was accredited by the College of American Pathologists (CAP), and analysis was performed following CLSI guidelines. Normal reference intervals for SCr were determined as 0.9–1.3 mg/dL for males and 0.6–1.1 mg/dL for females.

Data Analysis

Version 22 of the Statistical Package of Social Sciences (SPSS) was used for data analysis. Deming regression analysis was conducted in contrast with CrCl. A threshold of CrCl < 60 mL/minute/1.73 m2 was employed to evaluate the effects of the formulas. The Kruskal-Wallis test was used to compare the medians of Cr, CrCl, MDRD, CKD-EPI 2009, CKD EPI 2021, CKD-EPI Pak & EKFC across various GFR stages. Sensitivity, specificity, positive predictive values, and negative predictive values were determined for each equation. Mean differences

between CKD EPI 2021, CKD EPI 2009, CrCl & EKFC were examined using the Bland-Altman plot.

Table 1: Equations for estimating glomerular filtration rate in adults.

Type of Equation	Formula and criteria		
CrCl	Urine Cr Conc x urinary volume x 1.73/serum Cr x 1440 x BSA		
MDRD	175 x SCr-$^{1.154}$ x age$^{-0.203}$ x (0.742 if female)		
CKD-EPI 2009	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/0.7)$^{-1.209}$ x 0.993^{age}		
CKD-EPI Pak	0.686 x CKD-EPI$^{1.059}$		
CKD-EPI 2021	142 x minute (S_{cr}/κ, 1)$^{\alpha}$ x max (S_{cr}/κ, 1)$^{-1.200}$ x 0.9938^{age} x 1.012 [if female] where: S_{cr} = standardized serum creatinine in mg/dLκ = 0.7 (females) or 0.9 (males) α = -0.241 (female) or -0.302 (male) min (S_{cr}/κ, 1) is the minimum of Scr/κ or 1.0 max (S_{cr}/κ, 1) is the maximum of Scr/κ or 1.0. age (years)		
EKFC	Age (years)	SCr/Q	Equation for eGFR
	2 – 40	<1	107.3 × (Scr/Q)$^{-0.322}$
		≥1	107.3 × (Scr/Q)$^{-1.132}$
	>40	<1	107.3 × (Scr/Q)$^{-0.322}$ × 0.990$^{(Age-40)}$
		≥1	107.3 × (Scr/Q)$^{-1.132}$ × 0.990$^{(Age-40)}$

BSA: Body surface area

For EKFC Equation:

Scr: Serum creatinine concentration

Q value calculations for ages 2–25 years:
Males: $\ln(Q) = 3.200 + 0.259 \times Age - 0.543 \times \ln_{(Age)} - 0.00763 \times Age^2 + 0.0000790 \times Age^3$
Females: $\ln(Q) = 3.080 + 0.177 \times Age - 0.223 \times \ln_{(Age)} - 0.00596 \times Age^2 + 0.0000686 \times Age^3$

Q value calculations for ages >25 years:
Males: Q = 80 µmol/L (0.90 mg/dL)
Females: Q = 62 µmol/L (0.70 mg/dL)

Results

In this retrospective cross-sectional study, a cohort of 2310 participants, comprising 1,075 females (46.5%) and 1,235 males (53.5%), with a median age of 52 years, was analyzed. The study evaluated CrCl and its comparison with six equations (EPI-2009, MDRD, EPI-2021, EPI-Pak, CKD-EPI 2012, and EKFC) for estimating Glomerular Filtration Rate (GFR) across five stages of kidney function (GFR stages I-V).

Table 2: Comparison of CrCl and the 6 formulae in the 5 GFR stages (n = 2,310).

GFR Stages	N	CrCl (mL/minute)	EPI-2009 (mL/minute)	MDRD (mL/minute)	EPI-Pak (mL/minute)	EPI-2021 (mL/minute)	EGFR (EKFC) (mL/minute)	p-value
	2,310	60.00 (34.00-89.60)	71.07 (42.53-100.32)	63.87 (39.34-91.33)	62.77 (36.40-90.32)	72.28 (43.25-102.07)	69.72 (42.72-95.83)	<0.001
I	578	111.00 (100.00-131.00)	109.11 (99.94-122.43)	106.61 (90.09-131.69)	98.78 (90.06-111.66)	110.11 (96.74-121.47)	105.38 (96.07-116.48)	<0.001
II	578	75.00 (67.00-81.00)	87.99 (78.98-100.32)	75.97 (67.18-87.15)	78.70 (70.19-90.32)	86.73 (68.21-102.06)	85.77 (77.15-95.83)	<0.001
III	669	45.00 (37.00-52.00)	54.23 (46.15-62.73)	50.17 (42.07-57.67)	47.14 (39.73-55.00)	56.48 (44.18-73.58)	53.37 (46.34-61.15)	<0.001
IV	281	22.00 (19.00-26.00)	28.52 (24.85-33.33)	26.90 (22.72-32.64)	23.87 (20.60-28.12)	30.55 (23.76-41.77)	29.31 (25.45-34.52)	<0.001
V	204	9.00 (6.00-12.00)	11.17 (7.71-14.95)	11.08 (7.61-14.89)	8.84 (5.97-12.04)	11.16 (7.52-16.84)	12.11 (8.66-16.06)	<0.001

Results presented in Table 2 indicate that EPI-2009 and EPI-2021 exhibit the closest agreement with CrCl across all stages, as evidenced by their smallest mean differences compared to CrCl within each stage. It is noteworthy that as GFR stages decrease, indicating lower kidney function, mean differences between CrCl and all formulas tend to increase, suggesting potential decline in formula accuracy in individuals with reduced kidney function.

Table 3: Diagnostic ability of CrCl versus MDRD, EPI 2009, EPI-Pak, EPI 2021 & EKFC.

	MDRD	EPI 2009	EPI-Pak	EPI 2021	EKFC
Sensitivity	90.99%	95.15%	95.15%	83.10%	94.63%
Specificity	88.58%	94.55%	94.55%	83.22%	95.07%
PPV	88.83%	94.57%	94.57%	83.17%	95.04%
NPV	90.78%	95.13%	95.13%	83.15%	94.66%
Agreement (%)	89.78%	94.85%	94.85%	83.16%	94.85%
R^2 value	0.5834	0.8433	0.8439	0.4564	0.8386

Next, we assessed the diagnostic ability of the six equations and compared it with CrCl for all the individuals. Among the equations assessed, EPI-Pak demonstrates the highest percentage of agreement and sensitivity of 94.85% and 95.15% respectively, while EKFC exhibits the highest specificity and positive predictive value (PPV) of 95.07% and 95.04% respectively, and EPI 2009 shows the highest negative predictive value (NPV) of 95.13%. Remarkably, the EPI-Pak equation emerges with the highest R2 value, indicating superior assessment of kidney function compared to other formulas as depicted in Table 3. Finally, we also highlighted the agreement between CrCl and individual equations in the form of Bland-Altman plots in Figures 1-5 which also highlights that EPI-Pak is perhaps the most suited when it comes to assessing the renal function in the Pakistani population. In figures 6 and 7, we try to compare the median values of the three important equations i.e., EPI-Pak, EPI2009 and EPI2021 with factors like gender, CKD stage and age-groups which can help us draw important conclusions.

Figure 1: Bland Altman plot comparing CrCl and MDRD equation.

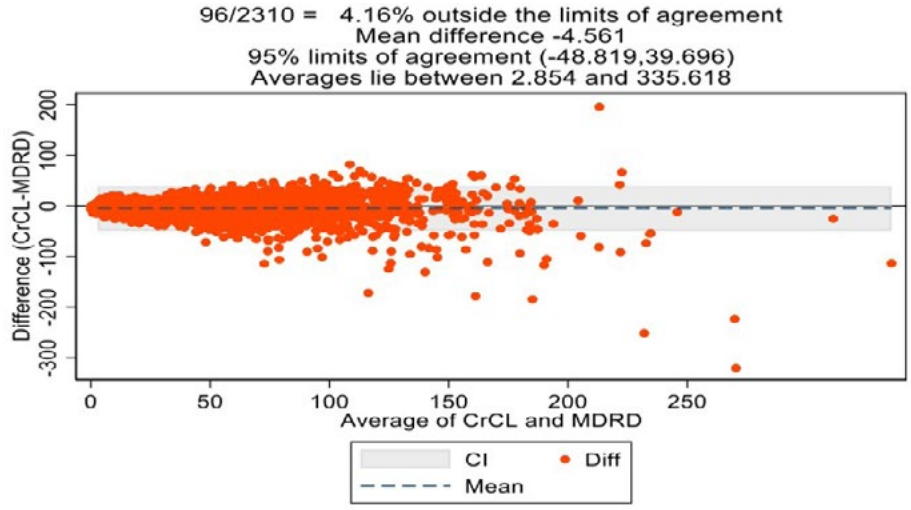


Figure 2: Bland Altman plot comparing CrCl and EPI 2009 equation.

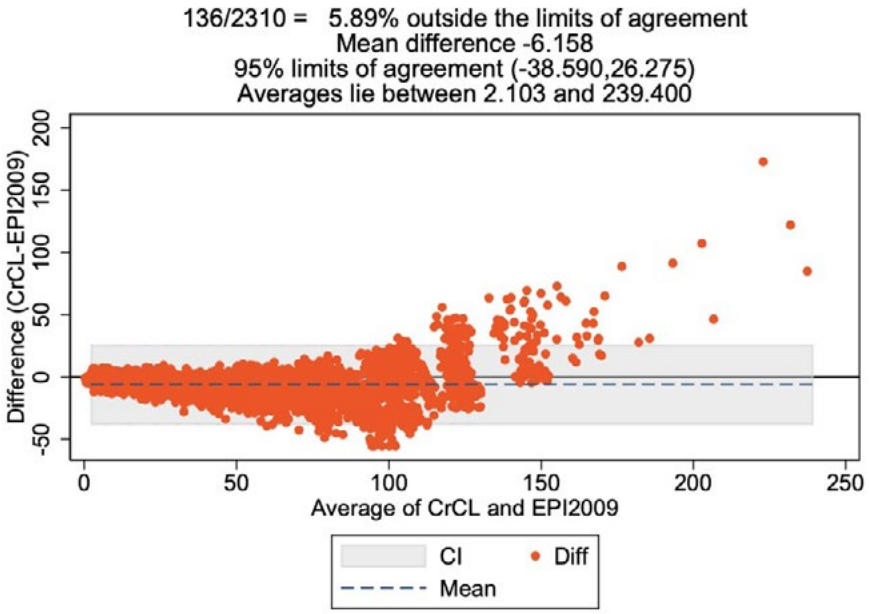


Figure 3: Bland Altman Plot comparing CrCl and EPI-Pak equation.

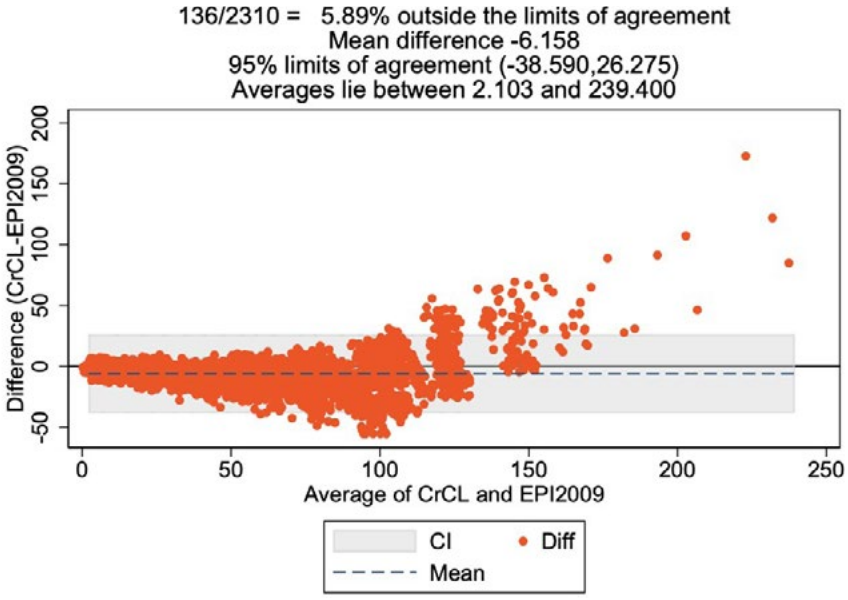


Figure 4: Bland Altman Plot comparing CrCl and EPI2021 equation.

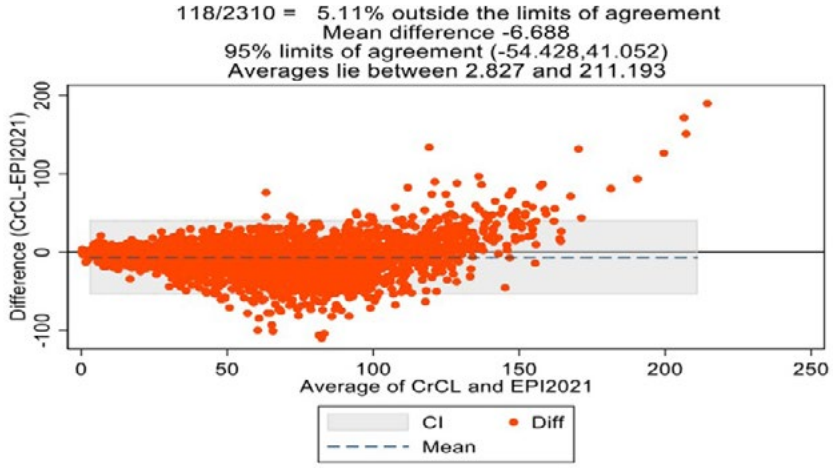


Figure 5: Bland Altman Plot comparing CrCl and EKFC equation.

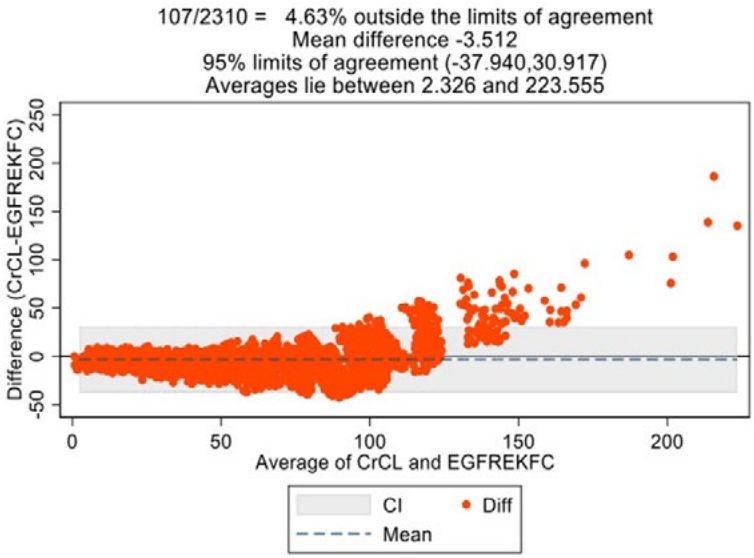


Figure 6: Comparison of median values of EPI-Pak, EPI2009 and EPI2021 equations with gender and CKD stage.

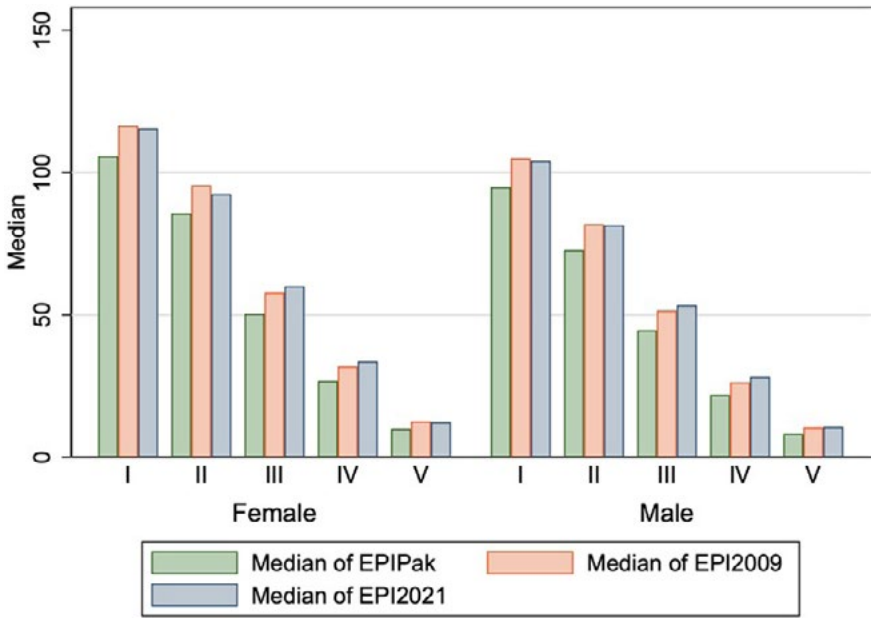
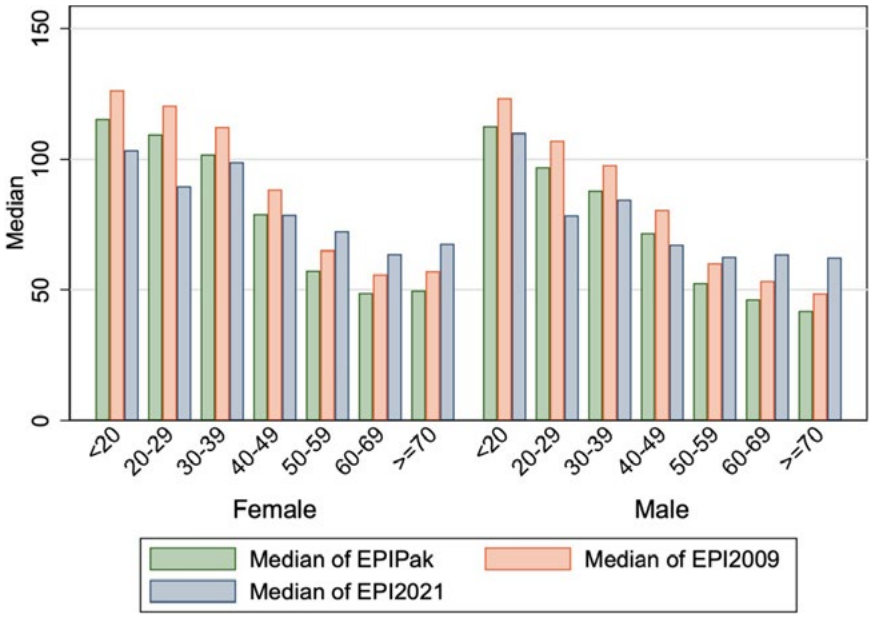


Figure 7: Comparison of median values of EPI-Pak, EPI2009 and EPI2021 equations with gender and age-group.



Discussion

CKD is a growing concern in middle- and low-income countries and more importantly, in Pakistan. Timely analysis, clinical staging and outcomes are used to decide on the mode of therapy for the patient on a case-by-case basis. All these modes of treatment have relevant financial concerns associated with them and therefore timely diagnosis of the disease and its extent has become very important [12]. To achieve these values as accurately as possible, a plethora of equations and formulas have been derived, as mentioned earlier more, and each successive method was aimed at addressing the gaps in their predecessor methods.

In this retrospective cross-sectional study, we used a Pakistani sample to analyze all the mentioned equations to gauge the sensitivity and specificity in diagnosing CKD and its staging when it comes to the demographics of Pakistan. It is quite evident from Table 3 and the Bland Altman plots that EPI-Pak outperforms all the equations and more importantly, the newly presented, EKFC formulae owing to its better reliability and better assessment of kidney function and having the highest R2 value. On the other hand, EKFC excels when it comes to a higher specificity and better positive predictive value while keeping up with EPI-PAK and EPI-2009 when it comes to agreement percent. This shows it is just as reliable for sorting

out people without CKD or End-Stage Renal Disease (ESRD) and for being used as an evaluation standard by using creatinine clearance. Our findings align with those Safdar et al and Ahmed et al, who pointed out that the EPI-Pak equation is perhaps the most accurate and precise equation when it comes to estimating eGFR in the South-Asians and appropriate measures should be taken for its implementation in the clinical laboratories [8, 11].
When talking about relatively older equations such as MDRD, it is evidently clear through many other studies as well that it has been outperformed by all its successors, and compared to MDRD, CKD-EPI gave the best estimation of eGFR [13]. Once in the top tiers, the CKD-EPI equations were put to question by another Pakistani study, namely Ahmed et al which proved that the EPI-Pak equation was perhaps more suitable to assessing CKD in the Pakistani population than the CKD-EPI 2021 equation [14]. Finally, the recently developed equation of EKFC attempted to estimate the eGFR using a creatinine-based equation and literature shows that this equation improved the accuracy of eGFR assessment in cohorts from Europe, the United States, and Africa [15]. Our study, with its results, shows that this might not apply the same way to a Pakistani cohort. EPI-Pak, which had a sensitivity of 93.2% in the study by Ahmed et al. now had a sensitivity of 95.15% in our study, with EKFC's sensitivity at 94.63%. Although the difference might be negligible, these results assert importance of EPI-Pak equation being the best option when it comes to estimating eGFR for a Pakistani cohort. Implementing the EPI-Pak equation in clinical laboratories could enhance the accuracy of CKD diagnosis and improve patient outcomes in Pakistan

Finally, like all other studies, there are some limitations to this study as well. These limitations involve the inherent restrictions when it comes to using eGFR because when compared with the results of measured GFR (mGFR) which shows a concerning 38% subjects being misclassified in their GFR groups based on their CKD stage. Furthermore, factors such as finite data on mGFR boundaries for age, ethnicity and gender along with variations in markers of mGFR also create a gap in arriving at an actual 100% reliable value [16]. The study's retrospective cross-sectional design may introduce several potential biases. For instance, selection bias is a concern, as the sample only includes participants from a single institution, possibly limiting the generalizability of the findings to the broader Pakistani population. Additionally, information bias could arise from the reliance on existing medical records, which may contain inaccuracies or incomplete data. Finally, our study also used the 24-hour urine CrCl as the gold standard which actually tends to overestimate the GFR [17].

As evident by the findings in this study, we can conclude that an automated reporting of eGFR using CKD-EPI Pak equation in laboratories across Pakistan will prove beneficial for the physicians as well as the patients for an accurate and timely diagnosis. These findings 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. In order to overcome the possible bias associated with retrospective designs, future studies should consider a prospective design and include a larger, more diverse sample to validate these findings.

Declaration of Conflict of interests

The authors of this article declare that there is no conflict of interest with regard to the content of this manuscript.

Ethical Considerations

The study was conducted in accordance with ethical guidelines and was approved by the institutional ethical review committee (Approval No: 2022-7451-21323). Anonymity of participants was preserved by coding the study identifiers into medical record numbers.

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