Comparison of Estimated Glomerular Filtration Rate with Both Serum Creatinine and Cystatin C (eGFRcr-cys) versus Single Analyte (eGFRcr or eGFRcys) Using CKD-EPI and MDRD Equations in Tertiary Care Hospital Settings

Usama Bin Khalid[1], Zujaja Hina Haroon[1], Muhammad Aamir[1], Qurat Ul Ain[1], Khurram Mansoor[2] and Syed Raza Jaffar[1]

[1]*Department of Chemical Pathology and Endocrinology, Armed Forces Institute of Pathology, Rawalpindi, Pakistan*
[2]*Department of Nephrology, Armed Forces Institute of Urology, Rawalpindi, Pakistan*

ABSTRACT

Objectives: To assess and compare the glomerular filtration rate (eGFR) estimated through MDRD and CKD-EPI$_{cr}$ equations in early and late stages of chronic kidney disease on biochemical marker creatinine (eGFR$_{cr}$), cystatin C (eGFR$_{cys}$); and combined (eGFR$_{cr\text{-}cys}$), using CKD-EPI equation.

Study Design: Observational, comparative cross-sectional study.

Place and Duration of Study: Chemical Pathology and Endocrinology Department, Armed Forces Institute of Pathology (AFIP), Rawalpindi in collaboration with Armed Forces Institute of Urology (AFIU), Rawalpindi from October 2019 to March 2020.

Methodology: GFR was assessed on the basis of creatinine clearance taking serum and 24-hour urinary specimens. MDRD and CKD-EPI equations were applied to calculate eGFR by serum creatinine (eGFR$_{cr}$), cystatin C (eGFR$_{cys}$), and combined (eGFR$_{cr\text{-}cys}$). Pearson correlation technique was used to compare eGFR calculated by different equations with creatinine clearance in different stages of CKD. Performance of equations was evaluated and compared in different stage of CKD.

Results: A total of 181 subjects were enrolled. Median age was 57 years (IQR, 25). Median (IQR) GFR (ml/min/1.73m^2) calculated by CrCl, MDRD, CKD-EPI$_{cr}$, CKD-EPI$_{cys}$ and CKD-EPI$_{cr\text{-}cys}$ equations were 45.1 (41.5), 50.6 (23.8), 52.0 (28.0), 43.0 (65.0) and 45 (47), respectively. eGFR calculated by CKD-EPI$_{cr}$ had positive and slightly higher correlation (r=0.880) than MDRD study equation (r=0.867). While comparing the markers, it was observed that CKD-EPI$_{cys}$ had better correlation in early stages of CKD (r=0.889); whereas, CKD-EPI$_{cr}$ performed better in late stages (r=0.896). CKD-EPI$_{cr\text{-}cys}$ had the highest correlation (r=0.984) at all stages of CKD.

Conclusion: eGFR calculated by CKD-EPI equation considered as better diagnostic efficient response than MDRD equation in diagnosis and staging of chronic kidney disease. While applying CKD-EPI equation for measurement of eGFR, eGFR$_{cr\text{-}cys}$ performs better than any of eGFR$_{cr}$ or eGFR$_{cys}$ at all stages of CKD.

Key Words: *Estimated glomerular filtration rate (eGFR), Cystatin C (Cys), Creatinine (Cr), Creatinine clearance (CrCl), CKD-EPI equation, MDRD equation.*

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INTRODUCTION

Chronic kidney disease (CKD) develops due to decreased renal functions along with irreversible morphological changes in kidney.[1] This devastating disease has high morbidity and mortality; nearly one million people die each year due to CKD-related causes.[2]

Correspondence to: Dr. Usama Bin Khalid, Department of Chemical Pathology and Endocrinology, Armed Forces Institute of Pathology, Rawalpindi, Pakistan
E-mail: usamakhalid89@hotmail.com

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With the burden of this disease rising globally, the developing countries are going to face the burnt as the prevalence is already high in these countries, and Pakistan is not an exception. In a recent study, the prevalence of CKD in a Metropolitan city Karachi (Pakistan) has been reported as 12.5%.[3]

Glomerular filtration rate (GFR) is one of the parameters to evaluate glomerular function of the kidneys. It is ideally measured on substances which are filtered freely from glomerulus and neither secreted nor re-absorbed. Exogenous substances like inulin, iohexol and iothalamate are used for GFR measurement.[4] Creatinine clearance is taken as alternative using endogenous creatinine, but it is cumbersome for the patients in routine laboratory testing as it involves 24-hour urine collection.[5] Estimated glomerular filtration rate (eGFR) is widely used to evaluate

kidney filtration function by using endogenous markers for GFR calculation. It has better compliance and can be used effectively for diagnosis, treatment and monitoring of glomerular function.[6] CKD is more common in old age; and eGFR estimation is challenging in elderly group of masses. Lower muscle mass and decreased consumption of nutrients in older people might cause bigger bias in GFR estimates based on creatinine as its serum concentration is influenced by issues like muscle mass, physical activity, protein diet *etc*. Cystatin C, produced by all nucleated cells of the body and freely filtered from glomerulus, is not influenced by muscle mass and nutrients intake. It is reported to be an improved and more sensitive filtration marker than creatinine, especially in elderly people.[7]

Various formulae have been derived for calculation of eGFR. The formulae used in current study for calculating eGFR are summarised in Table I. Each equation has certain advantages and limitations; and there is still a debate regarding the accuracy and efficiency of these equations. Change of food in renal disease (MDRD) equation is extensively applied in most laboratories of Australia and United Kingdom for estimating GFR. Criticism is on its underestimation of GFR in healthy individuals, *i.e.* GFR ≥60ml/min.[8] Chronic kidney disease-epidemiology consortium equation (CKD-EPI) is a relatively new equation for estimating GFR; and is thought to give better estimates, especially at higher GFR (≥90 ml/min).[9] The use of new markers like cystatin C, either as independent or in conjunction with creatinine in eGFR calculation formulae, have been hypothesised to perform better having better sensitivity and specificity.[10] However, there are few studies available to evaluate which equation is more reliable and closely correlated with accurate measurement of disease, especially on Pakistani population.

Current study aims to compare eGFR measurements using MDRD and CKD-EPI equations for choosing better equation corresponding to CKD staging done on the basis of creatinine clearance. Furthermore, a comparison of eGFR estimates calculated on the basis of creatinine ($eGFR_{cr}$), cystatin C ($eGFR_{cys}$) and a combination of creatinine and cystatin C ($eGFR_{cr\text{-}cys}$) was also carried out on a Pakistani population.

METHODOLOGY

An observational, comparative cross-sectional study was conducted in the Department of Chemical Pathology and Endocrinology, Armed Forces Institute of Pathology, Rawalpindi, in collaboration with Armed Forces Institute of Urology, Rawalpindi from October 2019 to March 2020, after getting ethical approval from the institution. For sample size calculation, WHO sample size calculator was used taking prevalence of CKD at 12.5% with 95% confidence interval and 5% margin of error.

A total of 181 subjects of different age, gender, ethnicity and socioeconomic status were included in the study after screening, and employing convenient non-probability sampling technique. Inclusion criteria were the patients diagnosed as chronic kidney disease (CKD) and disease-free subjects; while, patients with cancer, thyroid diseases, tuberculosis and patients taking steroids were excluded from the study, as it alters the steady state concentration of cystatin C. All participants reported to the Endocrine Clinic of AFIP where informed written consents were taken from all the participants. Before taking sample, for estimation of body surface area (BSA), weight and height of each individual were measured. All enrolled patients were provided printed instructions for 24-hour urine collection who has requested for creatinine clearance test along with sterile urine collection containers with tightly-fitted lid. After the receipt of sample of 24-hour urine in the laboratory, three milliliters (3ml) venous blood was collected in yellow top gel tubes. Serum was separated by centrifugation at 3500 rpm for three minutes and analysis was completed within four hours of sample collection. Spectrophotometric technique was used for serum creatinine assay by using the modified Jaffe enzymatic principle on fully automated chemistry analyser, ADVIA® 1800 by Siemens. Cystatin C was analysed on semi-automated Nephstar™ system, based on immunonephalometric technique. GFR was assessed on the basis of creatinine clearance taking serum creatinine and 24-hours urinary specimens. CKD staging was done on the basis of glomerular filtration rate (GFR) as, stage 1 (GFR ≥90 ml/min/1.73m^2), stage 2 (GFR 60-89 ml/min/1.73m^2), stage 3a (GFR 45-59 ml/min/1.73m^2), stage 3b (GFR 30-44 ml/min/1.73m^2), stage 4 (GFR 15-29 ml/min/ 1.73m^2), and stage 5 (GFR ≤15 ml/min/1.73m^2) after Takahashi *et al*.[11] Those samples having GFR >60ml/min/1.73m^2 were categorised in early stage and the samples with GFR ≤60ml/min/1.73m^2 were labelled as late stage. Estimated glomerular filtration rate (eGFR) was calculated by applying MDRD and CKD-EPI equations based on creatinine ($eGFR_{cr}$), and CKD-EPI equation based on Cystatin C ($eGFR_{cys}$), and both ($eGFR_{cr\text{-}cys}$) according to the formulae shown in Table I. Data were analysed through Statistical Package for the Social Sciences (SPSS) software version 21. Test of normality performed before data analysis was through Shapiro-Wilk test. The parameters having continuous variation and normally distributed have been reported as mean ± SD; whereas, median (IQR) were used for non-parametric data. Categorical data were expressed as frequencies and percentages. Tests of significance and Pearson's correlation technique were applied to find out correlation and any significant difference between the equations. P-value <0.01 was taken as significant. Correlation graph was plotted between clinical CKD staging and eGFR calculated by different equations.

RESULTS

A total of 181 subjects were enrolled, of which 104 (57.5%) were males and 77 (42.5%) were females. Mean age was 54.5 ±17.74 years [median 57 (IQR, 25) years].

Table I: Representative GFR estimating equations for use in adults.

Abbreviation	GFR Equation
CrCl (ml/min)	Urinary creatinine x Volume/ serum creatinine x 1440
MDRD[12] (ml/min/1.73m^2)	GFR (mL/min/1.73 m2) = 175 × (Scr × 0.01131)$^{-1.154}$ × (age)$^{-0.203}$ × (1.210 if patient is black) × (0.742 if patient is female)
CKD-EPI$_{creat}$[13] (ml/min/1.73m^2)	141 × min (Scr × 0.01131/κ, 1)α × max(Scr × 0.01131/κ, 1)$^{-1.209}$ × 0.993age × 1.018 [if female] × 1.159 [if black], Where, κ is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.
CKD-EPI$_{cys}$[14] (ml/min/1.73m^2)	133 × min (Scys/0.8, 1)$^{-0.499}$ × max (Scys/0.8, 1)$^{-1.328}$ × 0.996Age × 0.932 [if female], where min indicates the minimum of Scys/κ or 1, and max indicates the maximum of Scys/κ or 1.
CKD-EPI$_{creat-cys}$[14] (ml/min/1.73m^2)	135 × min (Scr × 0.01131/κ, 1)α × max (Scr × 0.01131/κ, 1)$^{-0.601}$ × min (Scys/0.8, 1)$^{-0.375}$× max (Scys/0.8, 1)$^{-0.711}$ × 0.995Age × 0.969 [if female] × 1.08 [if black], Where, κ is 0.7 for females and 0.9 for males, α is −0.248 for females and −0.207 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.

Age is given in years, serum creatinine in µmol/L, serum cystatin C (Scys) in mg/L, and weight in kilograms. CrCl, Creatinine Clearance CKD-EPI, Chronic Kidney Disease–Epidemiology Consortium; ID-MS, isotope dilution-mass spectrometry; MDRD, modification of diet in renal disease; Scr, serum creatinine; Scys, serum cystatin C.

Table II: Descriptive statistics of biochemical parameters and eGFR (n=181).

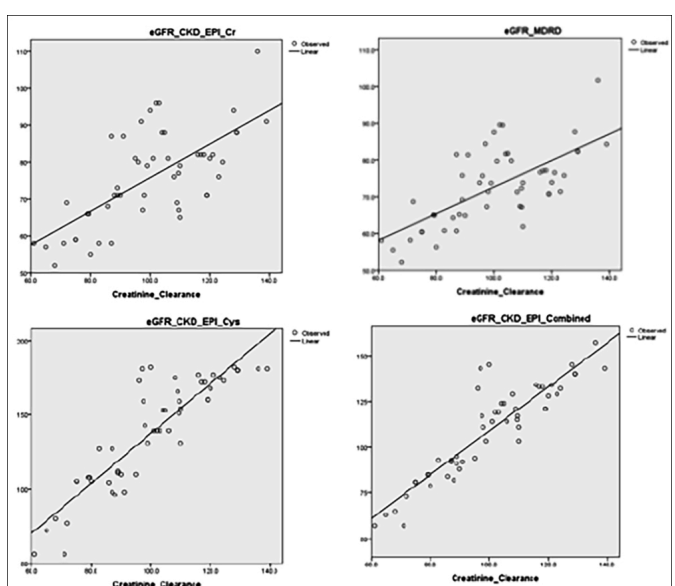
Parameter	Median	IQR
Urea (mmol/L)	6.0	3.7
Creatinine (µmol/L)	113	31.0
Cystatin C (mg/dl)	1.53	0.97
CrCl (ml/min)	45.1	41.5
eGFR MDRD (ml/min/1.73m^2)	50.6	23.8
eGFR$_{cr}$ CKD-EPI (ml/min/1.73m^2)	52.0	28.0
eGFR$_{cys}$ CKD-EPI (ml/min/1.73m^2)	43.0	65.0
eGFR$_{cr-cys}$ CKD-EPI (ml/min/1.73m^2)	45	47

Data were age wise categorized into 4 groups i.e. group 1(16-25 years), group 2 (26-40 years), group 3 (41-60 years) and group 4 (>60 years). Fifty-two (28.7%) were having early stage of CKD (GFR >60ml/min/1.73m^2) and 129 (71.3%) were at late stage of CKD (GFR<60ml/min/1.73m^2). Descriptive statistics on biochemical variables (urea, creatinine, cystatin C, CrCl and eGFR) are presented in Table II.

Age-wise categorisation revealed that late stage CKD (n=129) was more prevalent in group 4 (>60 years) *i.e.* 64 cases (49.6%), followed by 50 cases (38.8%) in group 3, 10 cases (7.8%) in group 1 and 5 cases (3.9%) in group 2. Comparison of CrCl with eGFR calculated by different equations showed significant difference (p ≤0.01) shown in Table III.

Pearson's correlation (r) analysis was carried out to see the relationship between CrCl and eGFR calculated by different equations. Relationship between these variables in early stages is shown in Figure 1.

In later stages in Figure 2. In initial stages (stage 1 &2) of CKD, equation based on cystatin C had higher correlation with 24-hours creatinine clearance (r=0.889). In late stages of CKD, creatinine based CKD-EPI$_{cr}$ equation better correlated to CrCl (r=0.896). However, equation based on both analytes *i.e.* creatinine and cystatin C (CKD-EPI$_{cr-cys}$) had the highest correlation (r=0.984) with CrCl at all stages of CKD.

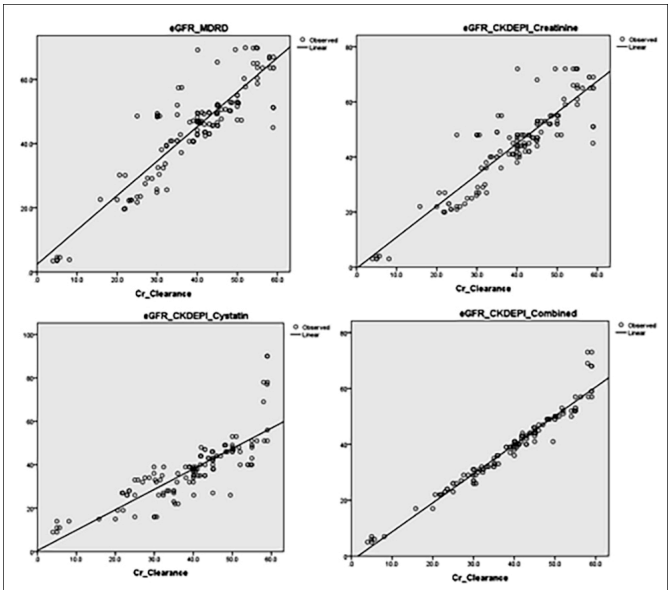


Equation	Correlation (r)	Significance (p)
MDRD	0.677	<0.001
CKD-EPI$_{cr}$	0.689	<0.001
CKD-EPI$_{cys}$	0.889	<0.001
CKD-EPI$_{cr-cys}$	0.904	<0.001

Figure 1: Correlation of different equations with creatinine clearance in early stages of CKD (n=52).

Table III: Comparison of different equations with CrCl (n=181).

Stage	n	Creatinine Median (IQR)	Cystatin C Median (IQR)	Median (IQR) eGFR using different formulae					p-value
				CrCl	eGFR MDRD	eGFR CKD-EPI$_{cr}$	eGFR CKD-EPI$_{cys}$	eGFR CKD-EPI$_{cr-cys}$	
Stage 1	35	99.0 (6)	0.345 (0.225)	109.5 (20)	76.6 (10.9)	81.0 (12)	160 (38)	124 (20)	<0.01
Stage 2	17	102 (18.5)	0.794 (0.228)	79.4 (16.0)	64.3 (7.7)	66 (13)	105 (32)	84 (23)	<0.01
Stage 3a	43	113 (26)	1.456 (0.172)	51 (7)	52.9(13)	55 (13)	47 (8)	50 (8)	<0.01
Stage 3b	63	121 (24)	1.752 (0.456)	40 (8.4)	46.1 (8.2)	44 (8)	35 (11)	39 (9)	<0.01
Stage 4	17	246 (74)	2.328 (0.325)	23.5 (3.6)	22.6 (6.9)	22 (4)	27 (14)	23 (4)	<0.01
Stage 5	6	1088.5 (367.5)	4.851 (1.579)	5 (1.6)	3.75 (1)	3 (1)	11 (5)	6 (2)	>0.01



Equation	Correlation (r)	Significance (p)
MDRD	0.893	<0.001
CKD-EPI$_{cr}$	0.896	<0.001
CKD-EPI$_{cys}$	0.823	<0.001
CKD-EPI$_{cr-cys}$	0.977	<0.001

Figure 2: Correlation of different equations with creatinine clearance in late stages of CKD (n=129).

DISCUSSION

Chronic kidney disease (CKD) also known as chronic renal failure, is gradual loss of kidney function (nephron damage) which cause decrease in glomerular function (GFR <60ml/min per 1.73m^2) for at least 3 months, as per guidelines of Kidney Disease: Improving Global Outcomes (KDIGO). What may be causes, when there is loss of nephrons and reduction of utilitarian renal mass arrives at a specific point, the rest of the nephrons start a procedure of irreversible sclerosis that prompts a dynamic decay in the GFR.[15] Estimated glomerular filtration rate (eGFR) is calculated using endogenous markers such as creatinine and cystatin C. eGFR can be effectively used for establishing diagnosis, monitoring of CKD progression and treatment and prognosis of disease, along with albuminuria.[16] In the newer guidelines of CKD classification system, it is recommended that both (GFR and albuminuria levels) may be used in combination, rather than alone, to improve prognostic accuracy in the assessment of CKD.[17] The guidelines recommend, in a more specific manner, to include estimated GFR and urine albumin levels (CGA) during assessment of the risks of overall mortality, morbidity, complications and the progression of CKD for patients with a low GFR (<60 mL/min/1.73 m^2) or very high albuminuria (>300 mg/24 h).[18]

In current study, comparison between two eGFR equations (MDRD and CKD-EPI) as well as markers (creatinine, cystatin C and combined creatinine and cystatin C) was done to adopt the better performing equation for diagnosis and follow-up of CKD patients. While comparing the equations, CKD-EPI equation better corresponds the clinical diagnosis and staging. Comparison of markers showed that combined markers, i.e. cystatin C in collaboration with creatinine (eGFRcr-cys) was the one which correlates with the clinical diagnosis, staging and the outcomes of the disease with follow-up.

The results of the present study are substantiated by earlier studies. In a study conducted at Agha Khan Hospital Karachi in 2017 by Sibtain *et al*.,[19] CKD-EPI equation better correlated with CrCl in patients with CKD (r=0.82) than Cockcroft Gault equation (r=0.78) and MDRD study equation (r=0.79). Matsushita *et al.* carried out a meta-analysis of data from 1.1 million adults from 25 general cohorts and 7 high risk cohorts,[20] and compared the risk prediction using CKD-EPI and MDRD study equations and found CKD-EPI equation as more precisely ordered the hazard for mortality and ESRD than did MDRD study condition over a wide scope of population. In this way, the unwavering quality of CKD-EPI condition in conclusion, the reliability of CKD-EPI equation in diagnosis, staging and risk prediction for CKD patients is far higher than MDRD equation and can be effectively used in clinical setting.

In comparison of makers either independently or in combination, the results of this study showed that equation based on cystatin C had high correlation in early stages, while equation based on creatinine had better correspondence to CrCl in late stages of CKD. In a study conducted by Tidman *et al.* in Sweden in 2004-05, comparison between creatinine, cystatin C and combination was done in 644 patients using mean MDRD and Orebro-cyst Gentian formulae.[21] The inclusion of both creatinine and cystatin C in equation was the best matched with measured GFR by iohexol. In a study conducted by Kilbride *et al*. in United Kingdom, [22] CKD-EPI$_{cr\text{-}cys}$ equation showed the lowest bias (Median difference=0.8), and the highest accuracy (P_{30}= 86) as compared to MDRD, CKD-EPI$_{cr}$ and CKD-EPI$_{cys}$. A study carried out in South India by Kumaresan *et al*. in 2011,[23] reported that serum cystatin C had significantly higher correlation (r=0.9735) with measured GFR than creatinine in 106 patients of CKD. Stevens *et al*. analysed the data collected on 3,418 CKD patients, tests of diagnostic accuracy were applied on different markers taking measured GFR by iohexol as gold standard.[10] Serum cystatin C levels provided accurate results independent of factors like muscle mass, dietary intake or race. While, another study conducted in 2015 by Fan

et al. reported that comparison between CKD-EPI equations based on different markers was done on 805 CKD patients in Iceland.[24] They further reported that estimation of eGFR$_{cr\text{-}cys}$ by CKD-EPI equation was proved to be better than eGFR$_{cr}$ in four metrics and similar to eGFR$_{cys}$ by two metrics.

The diagnosis, staging and prognosis of CKD is of paramount importance in dealing the overall burden of disease globally. The findings of the present investigation are in well agreement with various studies conducted in variety of environments in which inclusion of both creatinine and cystatin C has been recommended for calculation of eGFR. Although the study provides guidance for choosing the better equation for calculating eGFR, a mulicentered approach with larger sample size will further strengthen the results. Advance study with exogenous gold standard marker is required, which could not be used because of financial constraints.

CONCLUSION

eGFR calculated by CKD-EPI showed better clinical correlation in comparison to MDRD equation in diagnosis and staging of chronic kidney disease. While, applying CKD-EPI equation for calculation of eGFR, eGFR$_{cr\text{-}cys}$ proved to be better than any of eGFR$_{cr}$ or eGFR$_{cys}$ alone and is equally good for diagnosis and staging as of creatinine clearance at all stages of CKD.

ETHICAL APPROVAL:
The study was granted ethical approval before commencement of study by Institutional Review Board of AFIP Rawalpindi.

PATIENTS' CONSENT:
Informed written consents were taken from all participants of the study for research and publication purposes.

CONFLICT OF INTEREST:
Authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
UBK: Idea conception, data collection, data analysis, results, discussion and literature review.
ZHH: Idea conception, data analysis, results, discussion and literature review.
MA: Review of article and discussion.
QUA: Data analysis and results writing.
KM: Data collection and literature review.
SRJ: Discussion and literature review.

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