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Original Research Article

Wide-ranging performance of different eGFR equations in stage determination of Chronic Kidney Disease patients from endemic areas for CKD in Sri Lanka

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ABSTRACT

Background: Chronic kidney disease of unknown etiology (CKDu) is a public health issue at epidemic proportions in North Central, Uwa and other provinces of Sri Lanka. The initial diagnosis and stage determination of the disease are based on estimated glomerular filtration rate (eGFR), and urine albumin to creatinine ratio (UACR) particularly at community level screening. In this context, harmony and performance of pertaining equations were verified.
Methods: Three hundred and ninety-nine (399) volunteer CKD patients were recruited from select CKDu high prevalence areas (Padaviya, Girandurukotte, and Mahiyanganaya). Performance of kidney dysfunction determinants; serum creatinine (SCr), and serum Cystatin C (CysC), as well as markers; UACR, and eGFR variants; SCr based MDRD, SCr based EPI, serum CysC based EPI and SCr and CysC based EPI were scrutinized in terms of kidney disease improving global outcomes (KDIGO) heat-map guidelines.
Results: Notable deviation was observed between SCr-based and CysC-based equations at early development of the disease (stage G1) suggesting that the latter may tend to under estimate disease development initially. UACR successfully confirmed diagnosis from eGFR equations including G1 proteinuric subjects (G1).
Conclusions: Comparative study of marker performances should improve eGFR based identification of initial CKDu cases in Sri Lanka.

Keywords: Chronic kidney disease, Chronic kidney disease of unknown etiology, Estimated glomerular filtration rate, Urine albumin to creatinine ratio

INTRODUCTION

Chronic kidney disease of unknown etiology (CKDu) is marked by renal failure with progressive loss of functional nephrons leading to end-stage renal disease (ESRD). The disease is at epidemic proportions in North Central and certain other provinces in Sri Lanka. The disease prevalence emphasizes the importance of kidney dysfunction markers of improved diagnostic value. Such indices should allow early detection of onset and determination of disease progression stage reliably. The clinically utilized markers in CKD screening and diagnosis include four variants of estimated glomerular filtration rate (eGFR) and urine albumin to creatinine ratio (UACR).[1,2] However, the eGFR equations have been developed to suit certain communities of the world.[3] For this reason, functional assessment of these indices in the local setting is important. The present paper was based on

data collected from CKDu endemic Padaviya, Girandurukotte, and Mahiyanganaya areas and an assessment in this regard.

The estimated glomerular filtration index (eGFR) is a widely used kidney dysfunction marker in the diagnosis of chronic kidney disease and in following up on its progression. Usually, decreased eGFR at or less than 60 ml/minute/1.73 m^2 over three-month period is considered the primary diagnostic criterion of the disease. However, eGFR is known to vary on a multitude of factors such as age, sex, race, and body mass.[3-5] Four eGFR variants have emerged to circumvent limitations mainly by employing indicators of kidney dysfunction such as serum creatinine (SCr), and serum cystatin C (CysC) or combinations of it and by accommodating the factors influencing eGFR.

The use of SCr to estimate eGFR is common as it offers a rapid and inexpensive marker of kidney dysfunction. It is universally used to diagnose and monitor both acute and chronic kidney diseases.[4] In 1999, the modification of diet in renal disease (MDRD) equation was introduced to calculate eGFR using SCr. The equation considers age, gender, and race while muscle mass and diet remain determinants of SCr level.[4,5] However, disadvantages occur as its validation is limited mostly to individuals of certain communities and non-diabetic subjects at the CKD stages G3 and G4.[3,6] In 2009, chronic kidney disease epidemiology collaboration (CKD EPI) equation was developed to overcome MDRD limitations. [3,6,7] Cystatin C, a small plasma protein of ~13 kDa that inhibits cysteine proteases, is produced by all nucleated cells of man and accumulates in blood when renal function is compromised.[8,9] Many authors suggest that CysC-based eGFR would be more accurate than the creatinine-based eGFR as CysC is not affected by age, gender, muscle mass, and diet.[2,3,10,11] Further, eGFR estimated using both creatinine and cystatin C was reported to be less vulnerable to factors influencing either measurement when both markers are included.[2,12,13] Urine albumin to creatinine ratio (UACR) involves two measurements affected by kidney failure and is mostly utilized as a marker that verifies renal health status suggested by eGFR measurements.[13,14] Present study was an effort of functional assessment of marker performance in the context of CKDu in Sri Lanka.

METHODS

Samples were collected in a cross-sectional study design from volunteer subjects who were long-term residents (more than 5 years) of CKDu endemic areas as Padaviya, and Girandurukotte (total subject participation, 399). The community level sample collection was performed from 27/06/2017 to 22/04/2018. A standard calculation was used to calculate the sample size, with the prevalence of the CKDu was assumed to be 5% of the population in the high prevalence area.

The sample selection criteria included adults between 30 and 75 years of age, with the majority of them being field farmers by occupation. Patients under 30 and over 75, as well as those with known etiologies for CKD such as diabetes and hypertension, were excluded. Following the informed consent, about 5ml peripheral whole blood and 15 ml of spot urine samples were collected. Answers to questionnaires on demography were collected at pre-organized indoor centers in high prevalence areas from each subject. Ethical clearance was obtained (RP/2015/04, RP/2017/03) from the ethical review committee at the Faculty of Medicine, General Sir John Kotelawala Defence University, Sri Lanka before sampling.

Sample collection and processing

Serum was prepared from clotted whole blood by centrifugation at 3000 rpm for 5 minutes. Spot urine was collected in standard disposable containers. All samples were kept on dry ice during sample transportation and later stored at -80ºC in the laboratory until analysis.

Sample analyses and estimation of kidney dysfunction markers

Urine albumin (mg/l) and urine creatinine (mg/dl) were measured, and urine albumin to creatinine ratio (mg/gm of creatinine) was calculated. Serum creatinine (mg/dl), and urine creatinine (mg/dl) analyses were conducted with Mindray BS-200 chemistry analyzer using the modified Jaffe method. Urine albumin was measured by Bromcresol green, endpoint method, and UACR was estimated in the above system. Serum cystatin C (mg/l) was determined by HEALES- QR100 protein analyses system by turbidometry. GFR levels (ml/minute/1.73 m^2) were estimated for all subjects individually by alternative equations, MDRD equation according to Leavy et al, and SCr-EPI, CysC-EPI, as well as SCr and CysC, combined EPI equations in compliance with Inker et al. Subjects were identified in terms of the CKD stages, G1, G2, G3a, G3b, G4, and G5 (ESRD) using eGFR obtained from the equations. Further, based on eGFR and UACR, subjects were again classified into CKD categories on KDIGO "heat map" guidelines.[14]

eGFR and UACR data and their serum and urinary determinants were subjected to multivariate statistical analysis. The ANOVA was performed to identify the variations among results produced by each eGFR equation. ANOVA and multivariate Cluster analyses was performed using SPSS 24 and Minitab Software (version 17) respectively.

RESULTS

Demographic information

In the current study, demographic data were summarized in Table 1. Male predominance was evident and it has

been reported that over 80% of CKDu patients were farmers in the endemic areas.[15] In the study, over 50% of patients consumed water from shallow dug wells and about one-thirds of them had CKD patients among family members.

Table 1: Demography of CKDu subjects of Padaviya and Giradurukotte area (n=399).

Demographic data	% of subjects (N)
Gender	
Male	77 (307)
Female	33 (92)
Occupation	
Farmers	82 (327)
Civil defence force	6 (24)
Others	12 (48)
Family history of CKD	
Yes	32 (128)
No	68 (271)
Drinking water source	
Tank water	38 (152)
Tap water	4 (16)
Rainwater	1 (4)
Dug well	54 (215)
Tube well	3 (12)
Mean age±SD (years)	55±5.5 (399)

Variations of EGFR measurements

Repeated measures ANOVA (with a Greenhouse-Geisser correction) determined that the mean eGFR measures of the same patient differed significantly ($p<0.05$) among the four equations considered. Post hoc analysis (with a Bonferroni adjustment) revealed that eGFR was significantly decreased from SCr based MDRD to CyC-based EPI ($p<0.05$), and from SCr-based MDRD to SCr and CysC-based EPI ($p<0.05$). However, eGFR measures of SCr based MDRD to SCr based EPI ($p>0.05$) did not show any significant difference. Apparent inter-subject variations among eGFRs were high in SCr-based MDRD whereas low in CysC-based EPI in CKD patients (Figure 1).

Multivariate cluster analyses showed a distinct behavior of UACR from all four eGFR measures of CKD patients (Figure 2) where eGFR measures were clustered together at a similarity level about 75%.

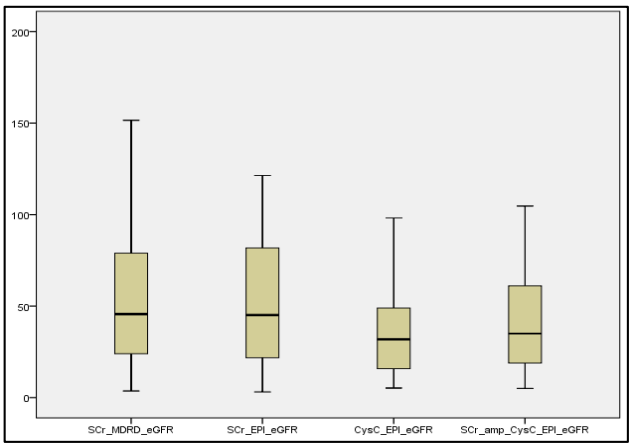

Figure 1: Comparison of the median of eGFR in different equations among CKDu subjects from Padaviya and Girandurukotte areas (n=399).

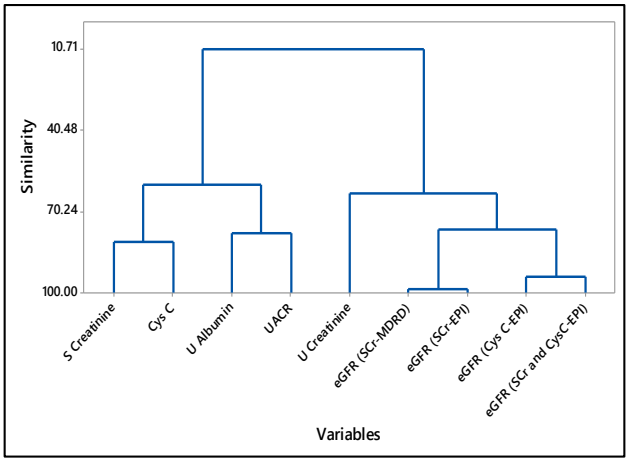

Figure 2: Relationship among eGFR variants, UACR, and their determinants of CKDu subjects in Padaviya and Girandurukotte areas (n=399).

Table 2: Mean and median levels of eGFR in different formulas and primary parameters such as SCr, CysC, and UACR among CKDu patients from Padaviya and Girandurukotte areas (n=399).

	SCr_MDRD ml/min/1.73 m^2	SCr_EPI_ ml/min/1.73 m^2	CysC_EPI ml/min/1.73 m^2	SCr_and_CysC_EPI ml/min/1.73 m^2	SCr_ mg/l	CysC mg/dl	UACR mg/gm of creatinine
Mean (SD)	52.06* (33)	51.56 (33)	35.5* (22)	40.6 (25)*	2.20 (1.8)	2.4 (1.4)	95.6 (238)
Median	45.6	45	31	34.8	1.6	1.9	37.6

*$p<0.05$ (significant at 0.05 level).

Table 3: Placement of patients in different CKD stages based on alternative eGFR equations (n=399).

eGFR equation used ml/min/1.73 m^2	UACR mg/gm of creatinine				
	Stage	<30	30-299	≥300g	Total (%)
	G1	51	17	0	68 (17)
	G2	66	26	2	94 (24)
SCr/MDRD	G3a	22	19	4	45 (11)
	G3b	15	36	4	55 (14)
	G4	21	63	4	88 (22)
	G5	3	39	7	49 (12)
	G1	52	19	0	71 (17)
	G2	47	26	2	75 (19)
SCr/CKD-EPI	G3a	22	17	3	42 (10)
	G3b	10	51	5	66 (17)
	G4	25	63	3	91(23)
	G5	3	43	8	54 (13)
	G1	12	5	0	17 (4.2)
	G2	36	22	0	58 (15)
S.Cystatin C/CKD-EPI	G3a	38	18	0	56 (14)
	G3b	42	36	7	85 (21)
	G4	25	65	4	94 (24)
	G5	23	56	10	89 (22)
	G1	16	6	0	22 (5.5)
	G2	62	32	0	94 (24)
SCr + Cystatin C/ CKD-EPI	G3a	40	19	3	62 (15)
	G3b	23	28	4	55 (14)
	G4	25	68	7	100 (25)
	G5	10	49	7	66 (17)
Colour scale		Low risk	Mild risk	Moderate risk	High risk

Identification of CKD stage

After confirming renal health status shown by eGFR with UACR, it was observed that different stages were assigned for the same patients based on different eGFR equations. Therefore, the study attempted to identify the differences in the staging with different eGFR equations. Three hundred and ninety-nine (399) confirmed CKD/CKDu patients were also considered for the second section of the study. Patients were classified into stages using KDIGO "heat map" guidelines (Table 3). Creatinine-based equations (MDRD, EPI) identified 17% of patients as stage G1 whereas Cys C EPI and SCr and Cys C EPI identified only around 5 % at G1. However, SCr MDRD and SCr EPI identified 34%, and 36% consequently in stages G4 and G5 together. Cys C-based equations identified 46% and 42% in G4 and G5. Although, sizable differences in subject numbers were noticed in the early stages among different formulas, differences were reduced in the middle and late stages. A further high number of low-risk patients were identified in MDRD compared with other equations. In summary, the kidney dysfunction markers based on four eGFR equations did not perform similarly in diagnosing and categorizing CKD patients into stages in the study (Figure 3 and Table 3) particularly as a high variation of subject numbers was evident at stage G1 among the estimates.

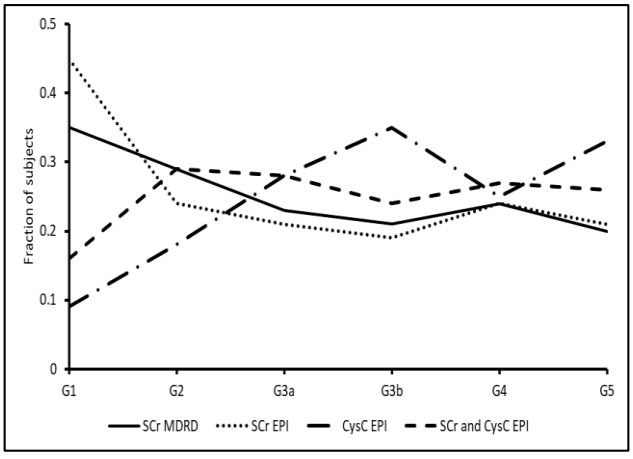

Figure 3: Fraction of eGFR variants in CKDu subjects in Padaviya and Giradurukotte areas (n=399).

DISCUSSION

The most commonly used serum creatinine-based equations include Cockraft and Gault (1976),

modification of diet in renal disease (MDRD, 1999), and chronic kidney disease epidemiology collaboration (CKD-EPI, 2009). These equations particularly the MDRD have elevated the standards of patient diagnosis and management in CKD as many guidelines in North America and Europe adopted it.[16-8] eGFR equations incorporate certain race specificities. However, none has been developed to suit many other communities in the world. Asians usually have a smaller build, and their dietary patterns are also different on account of cultural trends. The impact of these differences on the performance of the equations is not known.[17] Further, in Sri Lanka CKDu prevalence in endemic areas is rural where community screening, diagnosis, and patient management heavily depend on the accuracy of eGFRs. In this context, a comparative assessment of eGFR approaches remains important.

Many reports maintain that SCr-MDRD and SCr-EPI are more accurate at early stages 1 and 2 while CysC-EPI eGFR and SCr and Cys-C combined eGFR is more accurate in identifying stages 3 and 4.[2,8,19] In this study, data application to KDIGO format which essentially cross-checks eGFR outcome with UACR values showed that SCr- MDRD and SCr-EPI weakly performed in the above context. But Cystatin C-based EPIs identified the early stages better. When the middle and later stages of chronic kidney disease stages are considered, all the equations did not show a notable difference in performance. In Padaviya and Giradurukotte areas the majority of the subjects were paddy farmers (Table 1) who were undergoing occupational dehydration in fields. It is plausible that an increase in serum creatinine levels in such conditions may have led false diagnosis of some of the subjects at stage 1 in the study. However, many authors reported an intrinsic tendency of SCr-based eGFRs in identifying subjects at early CKD development without attribution to dehydration or any other modulatory effect.[20-23] In this context, the validity of SCr as a marker determinant remains the same. In contrast, cystatin C-based eGFR does not rely on age, sex, and body mass and dehydration status does not affect Cystatin C levels in serum.[23] It is advisable to use Cys C-based e-GFR for screening and diagnosis purposes predominantly in farming communities in CKD endemic areas of Sri Lanka. Studies have shown that the calculation of eGFR with a combination of creatinine and Cys C could yield more acceptable results.[11] The workers further maintain that the enhanced accuracy might be due to the lesser overall effects of age, sex, and body mass-like factors when both markers, CysC and SCr are considered. However, these implications remain to be assessed in local conditions.

Results from the cluster analyses essentially support a notion of comparable performance among eGFR variants as the variables emerged related particularly as compared to a distinct UACR (Figure 2). It has to be noted the cluster dendrogram did not incorporate stage-wise data as variables. This together with the non-comparable performance of eGFR variants in early diagnosis (Table 3 and Figure 3) suggests that the differences among eGFR variants could be limited to sorting stages rather than identifying the disease.

No standardized equations have been developed to estimate eGFR for CKD patients among community in Sri Lanka. Thus, all available equations world-wide were used in the current study to identify the variations of each equation rather than to define the accuracy.

CONCLUSION

In conclusion, the study provides evidence that CysC-based and Cr-based eGFR equations may behave differently during early CKD development (G1). Comparative study of marker performances should improve eGFR based identification of initial CKDu cases in Sri Lanka.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Faculty of Medicine, General Sir John Kotelawala Defence University, Sri Lanka (RP/2015/04, RP/2017/03)

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