Original article:

Comparison of Chronic Kidney Disease Epidemiology Collaboration Equations with Other Accepted Equations for Estimation of Glomerular Filtration Rate in Indian Chronic Kidney Disease Patients

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Abstract

Background and Aim: In routine clinical practice, the estimation of glomerular filtration rate (GFR) based on serum creatinine has been followed. However, the reliability of creatinine in estimation of GFR is biased and imprecise, leading to the misdiagnosis of chronic kidney disease (CKD). The serum cystatin C is an alternative marker for estimating GFR. Hence, we aimed to compare the newly proposed Chronic Kidney Disease Epidemiology Collaboration Equations (CKD-EPI) with four approved equations based on both creatinine and cystatin C with reference to Tc-99m-diethylenetriamine pentaacetate (Tc-99m-DTPA) considered as a standard. ***Materials and Methods:***Two hundred and one patients were enrolled in the study from a private nephrology outpatient clinic(OPD), Tiruchirappalli, India. The serum creatinine and cystatin C were measured along with routine biochemistry tests. The measurement of GFR was done by Tc-99m-DTPA gates method. The estimated GFR (eGFR) were calculated using serum cystatin C and creatinine based formulae along with the new CKD-EPI formulae. All eGFR estimations were compared with the measured GFR by gates method. ***Results:*** The average measured GFR of end stage, severe, moderate, mild renal disease and normal patient groups were 10.17±2.47, 22.58±4.40, 39.05±7.06, 69.62±24.64 and 118.06±29.23 respectively. When comparing the diagnostic accuracy for predicting GFR using well established formulae, the cystatin C based formulae have shown to be highly accurate in all stages of CKD than creatinine based formulae. Among cystatin C based formulae, CKD-EPI $_{\text{Cystatin C}}$ had relatively better diagnostic accuracy for predicting GFR in all stages of CKD. ***Conclusion:*** CKD-EPI $_{\text{Cystatin C}}$ formula has unbiased and more accurate to predict GFR in all stages of CKD.

Keywords: CKD; GFR; CKD-EPI; eGFR; Tc-99m-DTPA

Bangladesh Journal of Medical Science Vol. 16 No. 02 April'17. Page : 238-244

Introduction

Chronic kidney disease (CKD) is a devastating disease and universally it becomes more predominant[1].Assessment of the kidney function by measurement of glomerular filtration rate in routine clinical practice is a part of follow up of kidney diseases. Though, the measurement of GFR by using exogenous markers clearance are accurate, they are unsuitable due to their inconvenience, high cost, laborious and cumbersome [2].Under this situation, we are in a position to estimating the GFR by using various calculations. Conventionally, number of equations have been considered for GFR estimation. Among these equations, the Modification of Diet in Renal Disease (MDRD)[3], Cockcroft-Gault[4] and Chronic Kidney Disease Epidemiology collaboration (CKD-EPI)[5] have been accepted for creatinine based equations to estimate the GFR. However, there are a number of disadvantages in using serum creatinine itself as a filtration marker [6,7]. Hence, identifying an alternative filtration marker is vital for accurate, reproducible and unbiased estimation of GFR.

Serum cystatin C is a one such marker produced from all nucleated cells at a constant rate and freely filtered by glomerulus[8]. The cystatin C has been completely metabolised and 99% reabsorbed in the peroximal tubules[9,10]. Because of these key factors, serum cystatin C has been proposed and proved as

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a superior marker for predicting GFR than serum creatinine[11]. Even though its superiority over serum creatinine is well known, its role in predicting glomerular filtration rate and validation of cystatin C based formulae are still conflicting[12-16]. Hence, the present study aimed to determine the efficiency of cystatin C and its formulae for estimating eGFR and creatinine based formulae compare with measured GFR (Tc-99m-DTPA) in all stages of Indian CKD patients.

Materials and Methods

Participants

Totally 201 Indian participants greater than 18 years, with CKD at the private nephrology outpatient clinic were consecutively enrolled in the study. All participants in this study signed the informed consent. The participants with severe heart failure, acute renal failure, pleural or abdominal effusion, serious edema or malnutrition, skeletal muscle atrophy, amputation, ketoacidosis were excluded. Patients who were taking trimethoprim or cimetidine or ACEI/ARB and those who had recently received glucocorticoid andhemodialysis therapy were also excluded. The patients are classified in to five groups based on the GFR levels namely group 1-End stage kidney disease (<15 ml/min/1.73m^2; N= 32), Group 2- Severe stage kidney disease (16-29 ml/min/1.73m^2; N= 58), Group 3- Moderate stage kidney disease (30-59 ml/min/1.73m^2; N= 70), Group 4 – Mild stage kidney disease (60-89 ml/min/1.73m^2; N= 22) and Group 5- Normal patients (>90 ml/min/1.73m^2; N= 19).

Measurement and Estimation of GFR

GFR Measurement using ^{99m}Tc-DTPA Renography

The patients are made to lie down on a bed in the supine position. 99mTc-DTPA was injected through an indwelling butterfly needle in to anticubital vein and followed by infusion of 20 ml of normal saline. Frames of 128 x 128 matrix were recorded with an online- computer, initially at one second for one minute and then at 10 seconds for 20 minutes.

Region of interest (ROI) over each kidney assigned manually on the frame was added from 1 to 3 minutes following injection. The semi lunar background ROI around each kidney was defined and was modified for the inferior ROI's in the original gates. The background corrected time-activity curve was generated and the renal update of individual kidney for one minute period from 2 to 3 minutes after the injection was calculated. The GFR was automatically estimated by a commercially available computer programme (E. CAM, Siemens, USA) according to the Gate's[17] algorithm.

Creatinine and Cystatin C assay

All creatinine measurements were performed in the same laboratory. Blood samples were obtained simultaneously with the GFR measurement. Serum creatinine was measured by Jaffe's method using auto analyser (A 15, Bio systems, USA). Serum cystatin C was measured by particle enhanced nephelometricimmuno assay (PENIA) (Dade Behring, Germany).

Creatinine Based Estimation of GFR

The two formulae studied to predict GFR from serum creatinine were the one proposed by Cockcroft and Gault[4].

GFR_{CG} = [(140-age) × weight (kg)] / 72 × S.Cr (mg/dl)

(for women, multiply with 0.8) and the one simplified from the MDRD formula [18].

$GFR_{MDRD} = 186 \times (S.Cr \text{ in mg/dl})^{-1.54} \times age^{-0.203}$

(for women, multiply with 0.742)

Where S.cr is serum creatinine concentration.

A correction for body surface area (BSA) was necessary for the CG formula. This was performed using estimated BSA according to Haycock's equation [19].

If female: $144 \times (Scr/0.7)^{-1.209} \times 0.993^{age}$ (×1.159,if black)

If male: $141 \times (Scr/0.7)^{-1.209} \times 0.993^{age}$ (×1.159,if black)

Cystatin C based estimation of GFR

GFR estimated using two equations that were based on serum cystatin C one proposed by Hoek[13]:

GFR_{Hoek} = -4.32 + (80.35 x 1/ cystatin C)

and the another proposed by Lebricon[14]:

$GFR_{LeBricon}$ = [(78) x (1/cystatin C)] + 4

GFR was measured using 99mTc-DTPA and all formulae were compared with it. In this study isotope GFR was considered gold standard and all calculated formulae were compared with it, in the absence of inulin clearance.

CKD $EPI_{Cystatin\ C}$: If Female:$133 \times (Scys/0.8)^{-1.328} \times 0.996^{age} \times 0.932$: If Male: $133 \times (Scys/0.8)^{-1.328} \times 0.996^{age}$

CKD-$EPI_{Creatinine\text{-}Cystatin\ C}$: If Female:$130 \times (Scr/0.7)^{-0.248} \times (Scys/0.8)^{-0.711} \times 0.995^{age}$ (×1.08,if black)

If Male: $135 \times (Scr/0.9)^{-0.601} \times (Scys/0.8)^{-0.711} \times 0.995^{age}$ (× 1.08,if black)

Statistical analysis

Correlation coefficients and stepwise regression analysis were carried out using Medcalc 8.1 statistical software (Belgium). A P Value <0.05 was considered statistically significant. The receiver operating characteristic (ROC) curve was depicted toanalyse the diagnostic value of 7 equations.The largerarea under the ROC curve (ROC AUC) usually

means a better diagnostic value. Bias, precision and accuracy were used toevaluate the performance of each equation. Bias was defined as the median results of differences between eGFR and measured GFR (eGFR-GFR).

Ethical consideration: Permission for the study was given by the local ethical Committee

Results

Baseline characteristics

A total of 201 CKD patients (Male: 149; Female: 52) were enrolled in the present study and they were categorised in to five groups based on GFR and other baseline characteristicsaccording to the CKD stages are summarized in Table 1.

Table.1. Baseline Characteristics of study population

	< 15 ml/ min/1.73m²	**16-29 ml/ min/1.73m²**	**30-59 ml/ min/1.73m²**	**60-89 ml/ min/1.73m²**	**>90 ml/ min/1.73m²**
	(N: 32 M: 20 F:12)	(N: 58 M: 48 F: 10)	(N: 70 M: 50 F:20)	(N: 22 M: 18 F: 4)	(N: 19 M: 13 F:6)
Age years	51.38 ±15.6	52.48 ± 12.35	53.54 ± 12.47	47.73 ± 18.54	30.33 ± 8.97
Urea mg/dl	126.25 ±60.86	88.17 ± 38.61	78.76 ± 55.39	42.09 ± 28.12	19 ± 8.71
Creatinine mg/ dl	6.2 ± 2.55	3.90 ± 1.6	2.99 ± 1.54	1.34 ± 0.28	1.2 ± 0.64
	r = -0.3953	r = -0.2389	r = -0.1369	r = 0.02365	
	P = 0.0251	*P* = 0.0710	*P* = 0.2583	*P* = 0.9168	
Cystatin C mg/l	4.86 ± 0.93	3.67 ± 0.28	2.31 ± 0.46	1.16 ± 0.16	0.74 ± 0.16
	r = -0.5162	r = -0.5489	r = -0.7241	r = -0.7933	
	P = 0.0025	*P* = <0.0001	*P* = <0.0001	*P* = <0.0001	
Measured GFR (99 m DTPA)	10.17 ± 2.47	22.58 ± 4.40	39.05 ± 7.06	69.62 ± 24.64	118.06 ± 29.23
$eGFR_{MDRD}$	12.6 ± 8.48	21.72 ± 12.73	28.34 ± 16.36	61.46 ± 23.29	76.83 ± 32.84
	r = 0.3485	r = 0.3365	r = 0.2562	r = 0.2078	
	P =0.0506	*P* =0.0098	*P =0.3230*	*P* = 0.3535	
$eGFR_{Lebricon}$	20.45 ± 2.35	23.96 ± 3.22	40.38 ± 11.09	72.57 ± 10.57	117.85 ± 34.23
	r = 0.2137	r = 0.7942	r = 0.6546	r = 0.7520	
	P =0.0958	*P =<0.0001*	*P =<0.0001*	*P* = 0.0010	
$eGFR_{Hoek}$	12.62 ± 2.42	17.41 ± 2.37	33.15 ± 11.43	66.31 ± 10.88	111.91 ± 33.48
	r = 0.5180	r = 0. 0.6708	r = 0.4546	r = 0.6884	
	P =0.0024	*P* =0.0001	*P =0.7385*	*P* = 0.0004	
CKD-EPI Creatinine	11.25 ± 7.40	20.84 ± 13.49	28.78 ± 17.65	63.54 ± 23.09	83 ± 37.24
	r = 0.3601	r = 0.3445	r = 0.2720	r = 0.1999	
	P = 0.0429	*P* = 0.0081	*P* = 0.0228	*P* = 0.3725	
$CKD\text{-}EPI_{Cystatin\ C}$	9.97 ± 1.76	23.32 ± 1.70	39.4 ± 8.71	68.36 ± 13.95	117.86 ± 19.29
	r = 0.8180	r = 0.9990	r = 0.8040	r = 0.8270	
	P<0.0001	*P*<0.0001	*P*<0.0001	*P* = <0.0001	
CKD-EPI Creatinine-Cystatin C	9.44 ± 3.25	25.63 ± 4.88	36.31 ± 11.05	64.45 ± 15.68	99.33± 32.47
	r = 0.4458	r = 0.3976	r = 0.1482	r = 0.1716	
	P =0.0106	*P =0.0020*	*P* = 0.2208	*P* = 0.4451	

Performance of Various formulae in End Stage Chronic Kidney Disease

The measured GFR using 99m-DTPA renal scan had compared with the serum cystatin C with its formulae and Creatinine with its formulae in the end stage chronic kidney disease patients. The relationship was checked by doing correlation analyses with the above said parameters. Among serum creatinine and cystatin C compared with the measured GFR, the cystatin C had better negative correlation (r = - 0.5162; p=0.0025) than creatinine (r = -0.3953; p=0.0251) with measured GFR. Similarly, the various formulae based on both cystatin C and Creatinine used for estimation of GFR were compared with measured GFR (Fig.1).

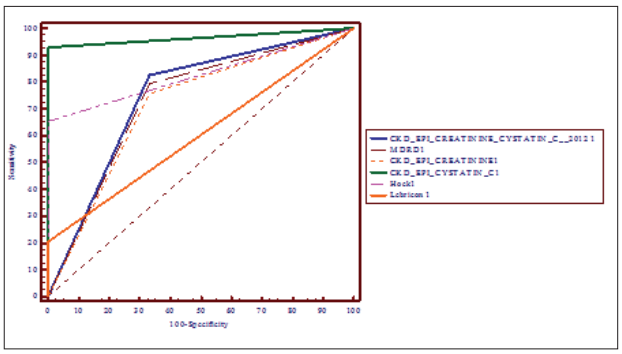

Fig.1. Performance of Various formulae in End Stage Chronic Kidney Disease

Among the various formulae, CKD EPI $_{cystatin\ C}$ showed significant correlation (r = 0.8180; *P*<0.0001) with measured GFR than MDRD (r = 0.3485; *P* =0.0506), LeBricon (r = 0.2137; *P* =0.0958), Hoek (r = 0.5180; *P* =0.0024), CKD EPI $_{Creatinine}$ (r = 0.3601; *P* = 0.0429) and CKD EPI $_{Creatinine\text{-}Cystatin\ C}$ (r = 0.4458; *P =0.0106).*The ROC analysis of various formulae had been compared and the CKD EPI $_{Cystatin\ C}$ showed higher AUC (0.966) and higher sensitivity (92.3 %) & specificity (100 %) than other formulae (Table 2).

Performance of Various formulae in Severe Stage Chronic Kidney Disease

The measured GFR using 99m-DTPA renal scan had compared with the serum cystatin C with its formulae and Creatinine with its formulae in the severe stage chronic kidney disease patients. The relationship was checked by doing correlation analyses with the above said parameters. Among serum creatinine and cystatin C compared with the measured GFR, the cystatin C had better negative correlation (r=- 0.5489; p≤0.0001) than creatinine (r = -0.2389; p=0.0710) with measured GFR. Similarly, the various formulae based on both cystatin C and Creatinine used for estimation of GFR were compared with measured GFR (Fig.2).

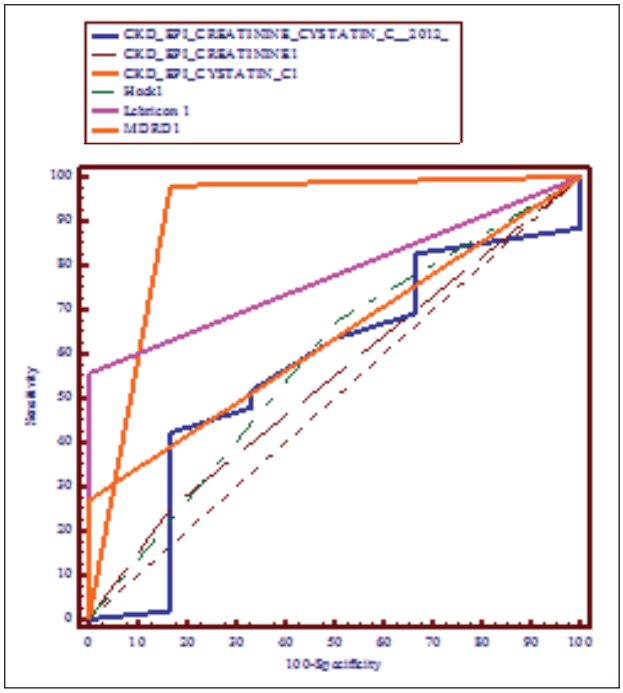

Fig 2: Performance of Various formulae in Severe Stage Chronic Kidney Disease

Among the various formulae, CKD EPI $_{cystatin\ C}$ showed significant correlation (r=0.9990; p<0.0001) with measured GFR than MDRD (r = 0.3365; p=0.0098), LeBricon (r=0.7942; p< 0.0001), Hoek (r= 0.6708; p=0.0001), CKD EPI$_{Creatinine}$ (r = 0.3445; p= 0.0081) and CKD EPI $_{Creatinine\text{-}Cystatin\ C}$ (r=0.3976; p*=0.0020).*The ROC analysis of various formulae had been compared and the CKD EPI$_{CystatinC}$ showed higher AUC (0.907) and higher sensitivity (98.1%) than other formulae (Table 2).

Performance of Various formulae in Moderate Stage Chronic Kidney Disease

The measured GFR using 99m-DTPA renal scan had compared with the serum cystatin C with its formulae and Creatinine with its formulae in the moderate stage chronic kidney disease patients. The relationship was checked by doing correlation analyses with the above said parameters. Among serum creatinine and cystatin C compared with the measured GFR, the cystatin C had better negative correlation (r = -0.7241; p<0.0001) and creatinine did not significantly correlate (r = -0.1369; p=0.2583) with measured GFR. Similarly, the various formulae based on both cystatin C and Creatinine used for estimation of GFR were compared with measured GFR (Fig.3). Among the various formulae, CKD

EPI $_{cystatin\ C}$ showed significant correlation (r= 0.8040; p<0.0001) with measured GFR than LeBricon (r=0.6546; p<0.0001) and CKD EPI$_{Creatinine}$ (r=0.2720; p=0.0228). Moreover, Hoek (r=0.4546; p=0.7385), MDRD (r=0.2562; p=0.3230) and CKD EPI $_{Creatinine\text{-}Cystatin\ C}$ (r=0.1482; p=*0.2208)* did not significantly correlate with the measured GFR. The ROC analysis of various formulae had been compared and the CKD EPI$_{Cystatin\ C}$ showed higher AUC (0.833) and higher sensitivity (93.3 %) &specificity (100 %) than other formulae (Table 2).

Table 2: Comparison of specificity and sensitivity of various formulae using ROC analysis

	GFR < 15 ml/ min/1.73m²			GFR 16 – 29 ml/ min/ 1.73m²			GFR 30 – 59 ml/ min/ 1.73m²			GFR 60- 89 ml/min/ 1.73m²		
	AUC	Sensitivity	Specificity	AUC	Sensitivity	Specificity	AUC	Sensitivity	Specificity	AUC	Sensitivity	Specificity
CKD-EPI-Cystatin C	**0.966**	**92.3**	**100**	**0.907**	**98.1**	**100**	**0.833**	**93.3**	**100**	**0.974**	**96.8**	**100**
CKD-EPI-Creatinine-Cystatin C 2012	0.747	33.1	83.3	0.569	28.8	83.3	0.575	13.4	100	0.570	16.1	100
CKD-EPI-Creatinine	0.713	75.9	66.7	0.542	25	83.3	0.622	91	33.3	0.553	9.7	100
MDRD	0.730	79.3	66.7	0.635	26.9	100	0.567	13.4	100	0.579	16.1	100
Hoek	**0.828**	**85.5**	**100**	0.587	55.8	50	0.577	58.2	33.3	0.684	**38.7**	66.7
LeBricon	0.603	20.7	100	**0.779**	**67.3**	**100**	**0.624**	**82.1**	**66.7**	**0.728**	**77.4**	**100**

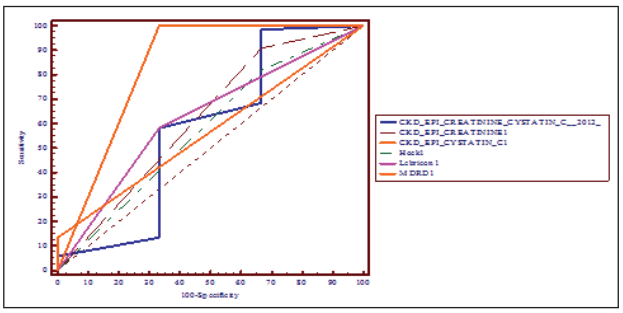

Fig.3. Performance of Various formulae in Moderate Stage Chronic Kidney Disease

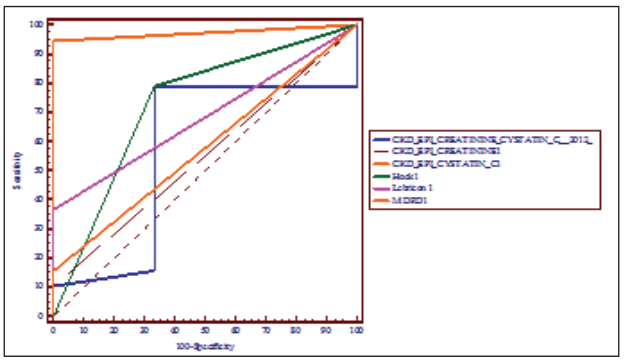

Fig.4.Performance of Various formulae in Mild Stage Chronic Kidney Disease

Performance of Various formulae in MildStage Chronic Kidney Disease

The measured GFR using 99m-DTPA renal scan had compared with the serum cystatin C with its formulae and Creatinine with its formulae in the mild stage chronic kidney disease patients. The relationship was checked by doing correlation analyses with the above said parameters. Among serum creatinine and cystatin C compared with the measured GFR, the cystatin C had better negative correlation (r=- 0.7933; p<0.0001) than creatinine (r = 0.02365; p=0.9168) with measured GFR. Similarly, the various formulae based on both cystatin C and Creatinine used for estimation of GFR were compared with measured GFR (Fig.4). Among the various formulae, CKD EPI$_{cystatin\ C}$ showed significant correlation (r=0.8270; p<0.0001) with measured GFR than LeBricon (r=0.7520; p=0.0010), Hoek (r=0.6884; p=0.0004). Moreover, MDRD (r=0.2078; p=0.3535), CKD EPI$_{Creatinine}$ (r=0.1999; p=0.3725) and CKD EPI$_{Creatinine\text{-}Cystatin\ C}$ (r= 0.1716; p=*0.4451)* did not significantly correlate with measured GFR. The ROC analysis of various formulae had been compared and the CKD EPI$_{Cystatin\ C}$ showed higher AUC (0.974) and higher sensitivity (96.8 %) and specificity (100%) than other formulae (Table 2).

Discussion

Estimation of the glomerularfiltration rate (GFR) is themost important step in the diagnosis of chronic kidney disease(CKD), and significant research has been directed towarddeveloping the most accurate, convenient, and reproducibleequation.

Traditionally, the Modification of Diet in RenalDisease (MDRD)[1], Cockcroft–Gault[2], and Chronic KidneyDisease Epidemiology Collaboration (CKD-EPI)[3]equationshave been considered the most acceptable creatinine-basedequations for estimating GFR.However, there are a number of disadvantages in using serumcreatinine itself as afiltration marker[6,7]. Therefore, identifying a new endogenous filtration marker is necessary for theaccurate and convenient estimation of GFR. Since cystatin C is less affected by muscle mass and diet than is creatinine [24-26] it has been widely anticipated thatcystatin C wouldprovide a more accurate estimate of GFR than would creatinine. The advantage of the cystatin C–based equation over the creatinine–based equation is that it is less subject to the effects of age, sex, and race.

Accurate estimation of GFR is important for interpreting the symptoms and laboratory abnormalities that may specify the kidney disease; for therapeutic dosing; and for detecting and managing chronic kidney disease and assessing the prognosis. A reduction in GFR to less than 60 ml/min/1.73m^2 for 3 months or longer is a diagnostic criterion for chronic kidney disease and is associated with an increased risk of adverse outcomes, including death[20-23]. Bias with the new, combined creatinine–cystatin C equation and with the average of the new cystatin C equation and the creatinine equation was similar to that with the individual creatinine and cystatin C equations, but they had greater precision and accuracy and resulted in more accurate classification of measured GFR as less than 60 ml/min/1.73m^2 the threshold for the diagnosis of chronic kidney disease.

The present study compared the sensitivity and specificity of new formulae with other existing equations in 201 participants with normal to advanced stages of kidney diseases. The vital conclusion of the study was that CKD-EPI$_{CystatinC}$ formula had better diagnostic value towards higher sensitivity and specificity in the entire participants including normal to advanced kidney disease participants.

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