

# A Comparison of Serum Cystatin C and Creatinine with Glomerular Filtration Rate in Indian Patients with Chronic Kidney Disease

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## Abstract

**Objectives:** There is no literature available on the performance of cystatin C in Chronic Kidney Disease (CKD) patients of Indian population based on age group. Hence, this study is aimed to compare the diagnostic performance of serum cystatin C and creatinine with measured glomerular filtration rate (GFR) and estimated GFR (eGFR) in subjects of Indian origin.

**Methods:** The study was carried out at Tiruchirappalli, South India during the period of September 2010 to march 2011. One hundred and six CKD patients (82 males, 24 females) were enrolled and categorized into three groups based on age. The eGFR was calculated using Cockcroft-Gault (CG) and Modification of Diet in Renal Disease (MDRD) formulae. Serum cystatin C was measured with a particle-enhanced nephelometric immunoassay (PENIA) method. GFR was measured using  $^{99m}\text{Tc}$ -diethylene triamine penta acetic acid (DTPA) renal scan method.

**Results:** Serum cystatin C showed significant correlation with measured GFR in all the three groups ( $r=-0.9735$ ,  $r=-0.8975$  and  $r=-0.7994$  respectively) than serum creatinine ( $r=-0.7380$ ,  $r=-0.6852$  and  $r=-0.5127$  respectively).

**Conclusion:** Serum cystatin C showed a high correlation with measured GFR in young and older patients with CKD than creatinine. Thus, cystatin C is a good alternative marker to creatinine in CKD patients.

**Keywords:** GFR; eGFR; CKD; Cystatin C; Creatinine;  $^{99m}\text{Tc}$ -DTPA.

## Introduction

The glomerular filtration rate (GFR) is traditionally considered the best overall index of renal function in health and disease.<sup>1-3</sup> The gold standard for the evaluation of the GFR is insulin clearance but its widespread use is limited by several technical difficulties.<sup>4</sup> The  $^{99m}\text{Tc}$ -DTPA renography which was introduced by Gates,<sup>5</sup> is considered to be more accurate than 24 hours creatinine clearance and is recommended for clinical use in patients with reduced renal

function.<sup>6</sup> In  $^{99m}\text{Tc}$ -DTPA renography, the GFR is calculated without the need for blood or urine sampling.<sup>7</sup>

Calculation of GFR using an empirical mathematical formula has been encouraged as a simple, rapid and reliable means of assessing kidney function.<sup>8-10</sup> There are no fewer than 46 different prediction equations currently available, although the two most commonly used are the Cockcroft-Gault (CG),<sup>11</sup> and Modification of Diet in Renal Disease (MDRD) formulas.<sup>10</sup> Cystatin C is a 132-amino acid 13-kDa cysteine protease inhibitor produced by all nucleated cells and whose function is thought to be modulation of the intracellular catabolism of proteins.<sup>12</sup> It is formed at a constant rate and is freely filtered by the renal glomeruli and completely reabsorbed and catabolized by the proximal tubular cells.<sup>12-16</sup>

The objective of the present study was to investigate the usefulness of serum cystatin C compared with serum creatinine, estimated GFR using (CG & MDRD) and measured GFR.

## Methods

One hundred and six chronic kidney disease (CKD) patients (82 males, 24 females) with a mean age of  $50.61 \pm 15.25$  years (range: 21 to 85 years) were included in this study. There are no studies conducted on the Indian population comparing cystatin C and creatinine levels with GFR based on age groups. The patients were categorized into 3 groups based on age namely; group I ( $\leq 40$  years;  $n=26$ ), group II (41-59 years;  $n=54$ ) and group III ( $\geq 60$  years;  $n=26$ ). The etiology of CKD were chronic glomerular nephritis ( $n=46$ ; 43.3%), chronic tubular interstitial nephritis ( $n=24$ ; 22.6%), diabetes mellitus ( $n=18$ ; 6.9%), bilateral hydronephrosis ( $n=4$ ; 3.77%), analgesic nephropathy ( $n=2$ ; 1.88%) and undetermined ( $n=12$ ; 11.3%). (Table 1)

For measuring the GFR using the  $^{99m}\text{Tc}$ -DTPA Renography, the patients were made to lie down on a bed in the supine position and  $^{99m}\text{Tc}$ -DTPA was injected through an indwelling butterfly needle in an antecubital vein and was followed by infusion of 20 ml of normal saline. Frames of  $128 \times 128$  matrix were recorded with an online-computer, initially at one second for one minute and then at 10 seconds for 20 minutes.

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**Table 1:** Characteristic of patients with CKD. Data are presented as mean  $\pm$ SD and mean (%).

Characteristic	n=106
Age (yrs)	50.6 $\pm$ 15.25
Body surface area (m <sup>2</sup> )	1.72 $\pm$ 0.20
Body mass index (kg/m <sup>2</sup> )	23.49 $\pm$ 4.57
Serum creatinine (mg/dl)	3.44 $\pm$ 2.03
Serum cystatin C (mg/l)	3.04 $\pm$ 1.19
Measured iGFR (ml/min/1.73m <sup>2</sup> )	31.31 $\pm$ 17.58
eGFR <sub>CG</sub> (ml/min/1.73m <sup>2</sup> )	31.81 $\pm$ 22.40
eGFR <sub>MDRD</sub> (ml/min/1.73m <sup>2</sup> )	29.32 $\pm$ 21.21
Causes of renal disease	n (%)
Chronic glomerular nephritis	46(43.3)
Chronic tubular interstitial nephritis	24(22.6)
Diabetes Mellitus	18 (16.9)
Bilateral hydronephrosis	4(3.77)
Analgesic nephropathy	2(1.88)
Undetermined	12(11.3)

Region of interest (ROI) over each kidney was assigned manually on the frame 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 uptake of individual kidney for one minute from 2 to 3 minutes after the injection was calculated. The GFR was automatically estimated by a commercially available computer program (E. CAM, Siemens, USA) according to the Gate's algorithm.

GFR Estimation and Normalization of GFR were calculated using the following equations:

$$\text{CG Method: GFR (ml/min/1.73m}^2\text{)} = \left[ \frac{(140 - \text{age}) \times \text{weight (kg)}}{72 \times \text{S.Cr (mg/dl)}} \right]$$

For women, multiply with 0.85

The GFR (ml/min) is obtained by CG method normalized for a body surface area of 1.73m<sup>2</sup> according to Haycock's Equation.<sup>17</sup>

$$\text{MDRD method: GFR (ml/min)} = 186 \times (\text{S.Cr in mg/dl})^{-1.54} \times \text{age}^{-0.203}$$

For women, multiply with 0.742

Serum cystatin C was measured using particle enhanced nephelometric immunoassay (PENIA) kit (Dade Behring, Marburg, GmbH, Germany). While serum creatinine was measured by Jaffe's method using an autoanalyser (Biosystems, USA). Written consent was obtained from all the study participants.

Statistical significance among the groups was determined using the Medcalc 8.1 statistical software (Belgium). Values are given as mean  $\pm$  standard deviation. The association between cystatin C and creatinine with isotopic GFR and estimated GFR was assessed

by Pearson correlation and stepwise multiple regression analysis. A value  $p < 0.05$  was considered statistically significant.

## Results

In terms of the correlation between cystatin C and creatinine with measured GFR and eGFR in this study, the results showed that as the age of the CKD patient's increased, the GFR slightly decreased and the cystatin C levels significantly increased. Table 2 shows the measured GFR, eGFR<sub>CG</sub>, eGFR<sub>MDRD</sub>, cystatin C and creatinine levels of the three groups based on age. The stepwise multiple regression between cystatin C with measured GFR showed significant correlation with measured GFR ( $r = -0.9735$ ;  $p < 0.001$ ) than serum creatinine with measured GFR in group 1, (Fig. 1). Serum creatinine correlates well with eGFR<sub>CG & MDRD</sub> ( $r = -0.8516$ ;  $p < 0.0001$  and  $r = -0.8157$ ;  $p < 0.0001$ , respectively) than cystatin C with eGFR<sub>CG & MDRD</sub> ( $r = -0.7894$ ;  $p < 0.0001$  and  $r = -0.7777$ ;  $p < 0.0001$ , respectively) in the same group. The receiver operating curve (ROC) analysis indicates that the cystatin C has (AUC: 0.753; sensitivity: 73.1%) higher sensitivity than creatinine (AUC: 0.655; sensitivity: 48.3%). (Fig. 2)

**Table 2:** Laboratory data for participants stratified by Age Groups (n = 106). Data are presented as mean  $\pm$ SD.

Laboratory data	Age Groups		
	$\leq 40$ Years	41-59 Years	$\geq 60$ Years
N	26	54	26
Age (Years)	30.54 $\pm$ 7.97	51.26 $\pm$ 5.76	69.31 $\pm$ 7.07
BMI (kg/m <sup>2</sup> )	21.61 $\pm$ 4.60	24.47 $\pm$ 3.95	23.32 $\pm$ 5.19
BSA (m <sup>2</sup> )	1.65 $\pm$ 0.25	1.74 $\pm$ 0.19	1.73 $\pm$ 0.16
S.Creatinine (mg/dl)	3.13 $\pm$ 1.95	3.51 $\pm$ 2.29	3.6 $\pm$ 1.46
S.Cystatin C (mg/l)	2.69 $\pm$ 1.09	3.21 $\pm$ 1.28	3.33 $\pm$ 1.03
GFR (ml/min/1.73 m <sup>2</sup> )	39.74 $\pm$ 19.27	28.80 $\pm$ 16.96	28.09 $\pm$ 14.35
eGFR <sub>CG</sub> (ml/min/1.73 m <sup>2</sup> )	40.23 $\pm$ 22.24	33.06 $\pm$ 24.60	20.81 $\pm$ 10.33
eGFR <sub>MDRD</sub> (ml/min/1.73 m <sup>2</sup> )	35.47 $\pm$ 22.24	30.30 $\pm$ 23.30	21.12 $\pm$ 10.68

In group II, the stepwise multiple regression between cystatin C with measured GFR showed significant correlation ( $r = -0.8975$ ,  $p < 0.0001$ ) than creatinine with measured GFR ( $r = -0.6852$ ), as shown in Fig. 3. The cystatin C correlates well with eGFR<sub>CG & MDRD</sub> ( $r = -0.7649$ ;  $p < 0.0001$  and  $r = -0.7753$ ;  $p < 0.0001$ ) than creatinine with eGFR<sub>CG & MDRD</sub> ( $r = -0.7460$  and  $r = -0.7673$ , respectively). The ROC analysis demonstrated that cystatin C (AUC: 0.725; sensitivity: 84.5%) exhibits higher sensitivity than creatinine (AUC: 0.571; sensitivity: 33.9%). (Fig. 4)

In Group III, the stepwise multiple regression between cystatin C with measured GFR showed that cystatin C significantly correlates with measured GFR ( $r = -0.7994$ ;  $p < 0.0001$ ) than

creatinine with measured GFR ( $r=-0.5127$ ) as shown in Fig. 5. Serum creatinine correlates with  $eGFR_{CG \&MDRD}$  ( $r=-0.9018$ ;  $p<0.0001$  and  $r=-0.9504$ ;  $p<0.0001$ ) than cystatin C ( $r=-0.6010$  and  $r=-0.5668$ ). The ROC analysis indicated that cystatin C (AUC: 0.767; sensitivity: 96.8%) exhibits higher sensitivity than creatinine (AUC: 0.586; sensitivity: 61.3%). (Fig. 6)

For the correlation between cystatin C and creatinine with age, Body Mass Index (BMI) and Body Surface Area (BSA), the results showed no significant correlation with cystatin C ( $r=0.0350$ ,  $r=-0.0934$  and  $r=-0.0358$ , respectively;  $p>0.05$ ). Creatinine also exhibited no correlation with age and BSA ( $r=-0.1136$ ,  $r=-0.1049$ , respectively;  $p>0.05$ ) but a correlation was observed creatinine and BMI ( $r=-0.4228$ ;  $p=0.0314$ ) in group I.

In group II, the age, BMI and BSA did not correlate with cystatin C ( $r=0.1719$ ,  $r=0.0883$  and  $r=-0.2257$ , respectively;  $p>0.05$ ). Similarly, there was no correlation between age and BMI with creatinine but a correlation was observed between BSA and creatinine ( $r=-0.2580$ ;  $p=0.0596$ ).

Similar to groups I and II, in group III there was also no correlation between age, BMI and BSA with cystatin C ( $r=0.1762$ ,  $r=0.3261$ ; and  $r=0.2357$ , respectively;  $p>0.05$ ) and with creatinine ( $r=-0.2541$ ,  $r=0.2837$  and  $r=-0.0796$ , respectively;  $p>0.05$ ).

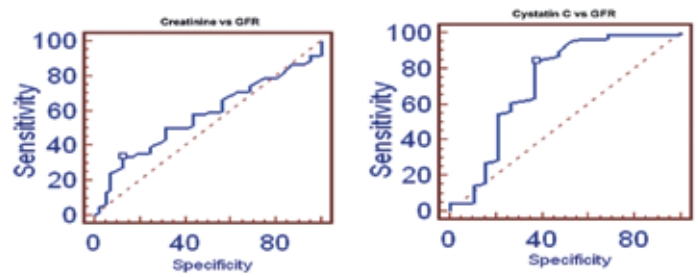


Figure 4: ROC of Creatinine and Cystatin C with GFR.

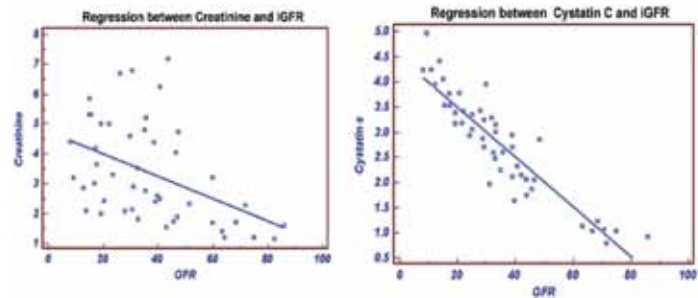


Figure 5: Regression of Creatinine and Cystatin C with GFR.

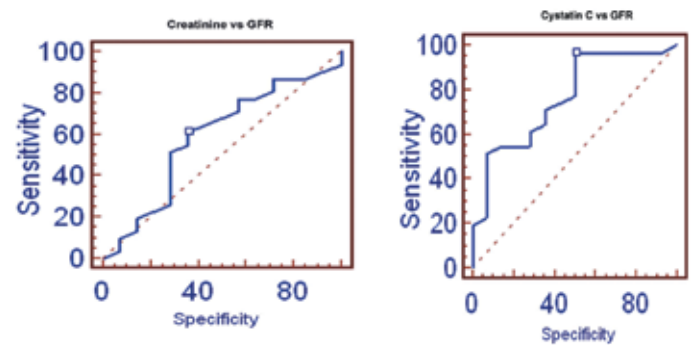


Figure 6: ROC of Creatinine and Cystatin C with GFR.

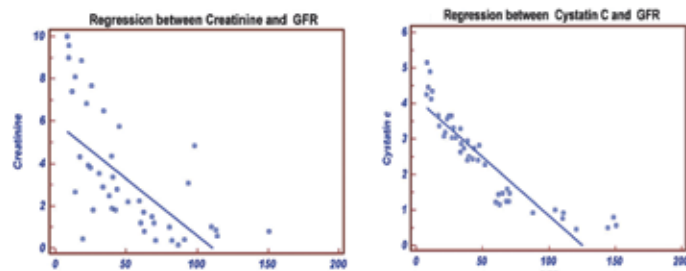


Figure 1: Regression of Creatinine and Cystatin C with GFR.

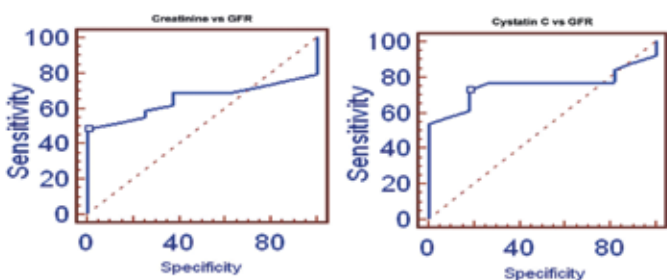


Figure 2: ROC of Creatinine and Cystatin C with GFR.

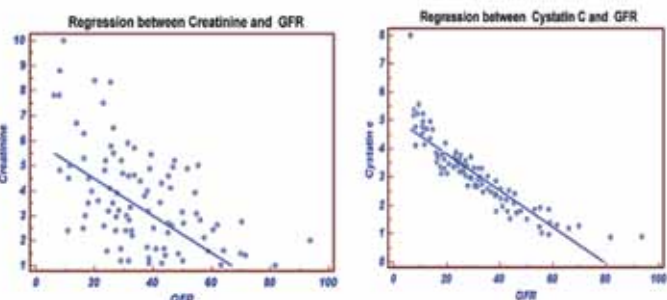


Figure 3: Regression of Creatinine and Cystatine with GFR.

## Discussion

Low molecular weight proteins are eliminated mainly through glomerular filtration which renders their measurements potential markers of renal function.<sup>18</sup> The substances most extensively studied in this respect are  $\alpha_1$ -microglobulin,<sup>14,19</sup> and  $\beta_2$ -microglobulin,<sup>14,19-21</sup> both of which have their limitations. Serum  $\alpha_1$ -microglobulin, which is of hepatic origin, is largely bound to IgA and albumin and thus not freely filtered. The production rate of  $\beta_2$ -microglobulin varies considerably with immune reactions as it is a part of the histocompatibility antigen complex and produced predominantly by lymphocytes.<sup>19,21</sup> These limitations do not apply to cystatin C for which both a constant production rate and free glomerular filtration have been documented.<sup>22-24</sup>

It has been unambiguously proved that creatinine varies with age, gender and body mass. But in the case of cystatin C, there are conflicting views, some evidence supporting,<sup>25</sup> and certain other evidence opposing,<sup>26,27</sup> the influence of age, gender and body mass on cystatin C levels. To investigate this conflict, the present study was conducted in Indian patients with CKD.

The results of this study showed that serum cystatin C is the most useful endogenous marker of GFR in all age groups. In this study, we compared the diagnostic value of cystatin C, creatinine, CG and MDRD formulae for GFR in assessment of renal function based on age groups. The correlation of cystatin C with GFR was comparable to that of creatinine, CG and MDRD formulae in all age groups. These results suggest that cystatin C is a good marker of renal function in patients with renal impairment, as has been reported in non-diabetic patients,<sup>28-32</sup> patients with renal transplant,<sup>33</sup> and in healthy patients.<sup>34</sup>

Cystatin C is proposed to reflect GFR independent of age and body composition.<sup>21,35,36</sup> Also in the present study, similar findings have been observed. In addition, it was found that serum creatinine may be influenced with body composition up to 60 years. Serum creatinine correlated well with GFR than serum cystatin C, which may be due to the eGFR being calculated using the creatinine levels. Whereas, in middle aged group the cystatin C correlated well with eGFR than creatinine. This may be due to the increased amount of BMI in that group.

This is also evidence that confirms the influence of creatinine with body mass. In the study by O'Riordan et al. among 53 geriatric outpatients aged >70 years, cystatin C was considerably more accurate than creatinine in estimating GFR, with values greater than reference range having a 97% sensitivity in detecting GFR <60 ml/min/1.73m<sup>2</sup> compared with a sensitivity of only 37% for creatinine.<sup>37</sup> Similarly, the present study also revealed that cystatin C is found to be more accurate than creatinine in estimating GFR with 96.8% sensitivity, compared with a sensitivity of 61.3% for creatinine in patients >60 years. The other two age groups also showed similar findings. An increased serum cystatin C concentration may provide a clinically important indication of a decreased GFR, even if serum creatinine concentration remains unchanged.<sup>38</sup> Similar findings were observed in the present study, but cystatin C tends to increase in patients up to 60 years and then significantly decreased. This fact confirms that cystatin C is less dependent on age groups.

## Conclusion

Cystatin C seems to be a promising alternative to creatinine as an endogenous marker of GFR in CKD patients in adults and older age groups. Serum cystatin C is directly related with GFR but not with age, and is also not influenced by BMI and body surface area, whereas serum creatinine is influenced by body mass. These findings may improve the utility of cystatin C as a laboratory diagnosis test for assessment of renal function.

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