

Original Article

Assessing the Diagnostic Power of Cystatin C and Creatinine in Detection of Chronic Kidney Disease

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Abstract

Introduction: In patients with renal disorders, a sudden decrease in glomerular filtration rate (GFR) would not result in rapid rise concentrations of Creatinine. The present study aimed to assess diagnostic accuracy of serum Cystatin C as an appropriate alternative to serum Creatinine for early detection of Chronic Kidney Disease (CKD).

Materials and Methods: In this study, 72 patients, 48 female and 24 male were selected. Serum Cystatin C and serum Creatinine were assayed, using enzyme-linked immunosorbent assay (ELISA) and routine methods, respectively. Glomerular filtration rate (eGFR) was estimated by Cockcroft and Gault formula. Receiver operating characteristics (ROC) analysis was adopted to evaluate diagnostic accuracy of serum Cystatin C and serum Creatinine.

Results: Using Pearson's Correlation Coefficient analysis among Creatinine, Cystatin C and eGFR showed Serum Cystatin C was better than Creatinine. The sensitivity, specificity and AUC for Serum Cystatin C were 0.88, 0.70 and 0.85, and for Serum Creatinine, they were 0.60, 0.80 and 0.68 respectively.

Conclusion: Our results showed that in early stages of CKD, Cystatin C is a more accurate biomarker for kidney function than Creatinine

Keywords: Creatinine, Cystatin C, Chronic Kidney Disease

1. Introduction

Chronic kidney disease (CKD) is a long-standing, progressive deterioration of kidney function with structural or functional abnormalities for 3 months or more. In advanced stages of CKD, permanent renal failure could be inevitable [1, 2]. By and large, factors which may increase the risk of chronic kidney disease are hypertension, diabetes and smoking [3]. High blood pressure affects kidney function which leads to kidney failure and approximately 40% of

adults more than 25 years old have hypertension (BP \geq 140 mmHg Systolic or 90 mmHg diastolic) [4]. Renal failure and its irreversible consequences can be prevented by early diagnosis and careful management of existing conditions[5].

Therefore, identification of reliable and accurate biomarkers will improve the CKD diagnosis and treatment methods. Serum Creatinine has been widely used as the kidney function measurement in common clinical practices and yet, Creatinine concentration is indicated as a biomarker of

glomerular filtration rate (GFR) and cannot remain as a magnificent diagnostic tool for kidney function. The reason is that the blood Creatinine will not increase until when 50% of kidney function is damaged; moreover, it is affected by muscle mass, age, gender and race. [6]. The common biomarker, Creatinine, inability to detect the early reduction of GFR is risky especially when detecting CKD at early stages is substantial.

Cystatin C has been proved to be the preferable biomarker compared to Creatinine in regard with renal function [7]. Cystatin C is a non-glycosylated 13-kD protein belonging to the cysteine superfamily of cysteine proteinase inhibitors and it is produced by all nucleated cells at a constant rate. Unlike Creatinine, the serum level of Cystatin C is not affected by age, sex, and muscle mass. Therefore, the plasma concentration of Cystatin C would be an accurate biomarker of subtle changes in renal function.[8]

Unlike the normal kidney, blood levels of Cystatin C starts to rise when GFR decreases and kidneys are not working well. The reason is that Cystatin C is passed freely across the normal Glomerular membrane and is then completely reabsorbed and degraded in tubular epithelial cells; the glomerular filtration rate controls the plasma Cystatin C concentration. [9] The aim of the present study was evaluating the diagnostic accuracy of Cystatin C and comparing the accuracy of Cystatin C with that of the Creatinine.

2. Materials and Methods

The study was carried out on 72 patients, aged between 40 to 70 years who referred to Shohada Tajrish Hospital for a check-up over their kidney function. Ethical approval for this study was obtained from Shahid Beheshti University of Medical Sciences, Tehran, Iran. Informed consent was obtained from all participants before the

study began, so records for age, height, weight and laboratory investigations were collected.

In order to reduce the confounding variables, patients were excluded from the study if they had any chronic disease or increased levels serum Creatinine and urea. The serum and plasma were obtained from blood samples when they were fast.

The obtained samples of serum and plasma were stored until the assessment time. For measurement of serum Cystatin C, an enzyme-linked immunosorbent assay (ELISA) method (Biovender, Norway) was used. Serum Creatinine was measured through standard method; moreover, the Cockcroft and Gault formula based on serum Creatinine concentration was used to calculate eGFR.

$$eGFR \text{ (ml/min)} = \frac{((140 - \text{age}) * \text{mass (kg)} * (0.85 \text{ if female}))}{(72 * \text{scr (mg/dl)})}$$

2.1. Statistical Analysis:

Statistical analysis of the study was performed through using SPSS software (version 25.0). The continuous data was presented with mean \pm SD and categorical data with frequencies. Difference between Non-CKD and CKD patients was compared by Chi-square and independent samples t tests and the association measurement between eGFR and other biomarkers were determined through using Pearson's coefficient. The best cut-off values of Cystatin C and Creatinine were calculated by Receiver operating characteristics (ROC) analysis to identify the CKD patients.

3. Results

The study sample included 72 patients aged 40–70 years (66.7% male and 33.3% women). The mean of serum Creatinine and serum Cystatin C levels, eGFR and other biological characteristics are shown in table 1. By using the independent samples t-test for age and weight, serum Cystatin C significant different level between non-CKD and CKD groups were obtained ($P < 0.05$).

Using the Pearson's correlation coefficient, the eGFR correlation with serum Cystatin C was ($r^2 = -0.451$, $p < 0.001$) and serum Creatinine was ($r^2 = -0.251$, $P = 0.033$) which are both regarded as significantly high values.

The best cut-off values based on the ROC analyses showed that the predictive power of serum Cystatin C is better than serum Creatinine for prediction of $GFR < 78$ ml/min/1.73. Table 2 shows the AUCs, best cut-off values, sensitivity and specificity.

Table 1. Characteristics of the patients

Characteristic	Non-CKD patient (n=47)	CKD Patient (n=25)	Total (n=72)	P-Value
Age	53.15 \pm 7.45*	57.04 \pm 8.68	54.51 \pm 8.06	0.048
Weight	82.68 \pm 13.60	72.89 \pm 11.47	79.28 \pm 13.65	0.002
Creatinine	0.99 \pm 0.14	1.09 \pm 0.18	1.02 \pm 0.17	0.184
Cystatin C	118.11 \pm 211.50	998.28 \pm 1014.52	423.72 \pm 744.96	<0.001
Sex (M)	17 (36.2)**	7 (28)	24 (33.3)	0.058

*mean \pm SD **no (%)

Table 2. The ROC analysis for prediction ability of Creatinine and Cystatin C

Biomarker	Sensitivity	Specificity	AUC	Cut Point
Creatinine	60.00	80.00	0.68	1.05
Cystatin C	88.00	70.00	0.85	100

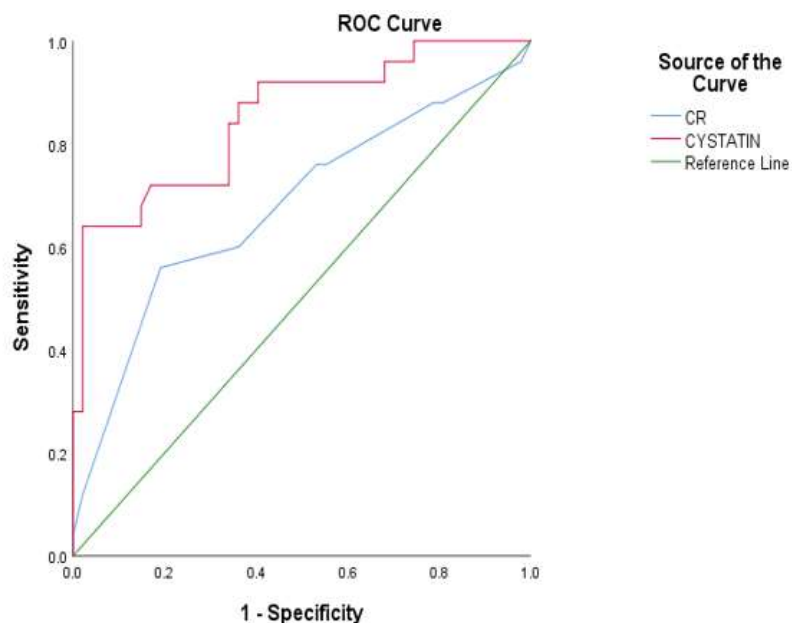


Figure1. ROC curve for estimating the accuracy of Creatinine and Cystatin C for detection of CKD

4. Discussion

Early detection and proper management of CKD can often help to prevent the kidney disease from getting worse [10]. Thus, by increasing the accuracy of biomarkers for early detection of individuals at progressive stage prediction and treatment of renal disease can be obtained.

Creatinine is a common biomarker of kidney function which is produced in a constant rate by the body. However, it has several limitations one of which is not being a sensitive biomarker of GFR. Therefore, identification of early biomarker for kidney damage is imperative. Several studies have demonstrated that among the other biomarkers, Cystatin C is the most accurate biomarker for early diagnosing of CKD. [11]

Serum Cystatin C as a magnificent biomarker of renal functions rises rapidly during minor glomerular damage. In addition, elevated levels of Cystatin C are associated with increased cardiovascular risk. In normal kidneys, Cystatin C levels are 0.8–1.1 mg/L and 0.6–1.1 mg/L for men and women, respectively. [12]

In the present study, the predictive accuracy of Cystatin C for individuals was shown in early stages of CKD as an improved diagnostic marker of GFR in comparison with the current marker. It was revealed that the mean of serum Cystatin C level was significantly increased in patients with renal impairment in comparison with the non-CKD patients.

These findings are in accordance with the research of Michele Mussap et al who also reported early and significantly higher Serum Cystatin C levels than serum Creatinine in 52 CKD patients.[13]

While Serum Cystatin C had higher correlation with eGFR than serum Creatinine, the present study revealed that inverse association with eGFR and Serum Cystatin C is significant ($r^2 = -0.451$, $p < 0.001$). Similar findings were reported by Weihong Zhao et al which demonstrated

the significant correlation between eGFR and Serum Cystatin C. [14]

In a study conducted by Kumaresan et al, the ROC analysis showed that the AUC for Cystatin C and Creatinine was 0.77 and 0.59, respectively [15]. In this study, the AUC of 85% demonstrated that Cystatin C has a higher accuracy for predicting $GFR < 78$ ml/min than Creatinine (auc= 68%).

The optimal cut-off points of Cystatin C and Creatinine for detecting early stage of CKD were determined. Cutoff value for Cystatin C was 100 ng/ml (sensitivity= 0.88; specificity= 0.70) and for Creatinine was 1.05 mg/dl (sensitivity= 0.60; specificity= 0.80). In Gerbes et al study the optimal cut off concentrations for Cystatin C and Creatinine were 1.0 mg/l (sensitivity= 0.69; specificity= 0.56) and 0.9 mg/100 ml (sensitivity= 0.45; specificity= 0.70), respectively [16]. These results are consistent with the present study's finding which proved the higher sensitivity for Cystatin C in comparison with Creatinine.

5. Conclusion

This study's findings indicated that the diagnostic power of serum Cystatin C for early detection of CKD is higher than Creatinine. Therefore, Cystatin C with or without Creatinine could be used as an appropriate diagnosing marker of CKD.

Conflict of Interest

The authors declare no conflict of interest.

References

1. Levey, A.S., et al., Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). 2005. 67(6): p. 2089-2100.
2. Levey, A.S., L.A. Inker, and J.J.J. Coresh, Chronic kidney disease in older people. 2015. 314(6): p. 557-558.
3. Yamagata, K., et al., Risk factors for chronic kidney disease in a community-based population: a 10-year follow-up study. 2007. 71(2): p. 159-166.

4. Abebe, S.M., et al., Prevalence and associated factors of hypertension: a cross-sectional community based study in Northwest Ethiopia. 2015. 10(4): p. e0125210.
5. Braun, L., et al., High burden and unmet patient needs in chronic kidney disease. 2012. 5: p. 151.
6. Mula-Abed, W.-A.S., K. Al Rasadi, and D.J.O.m.j. Al-Riyami, Estimated glomerular filtration rate (eGFR): a serum creatinine-based test for the detection of chronic kidney disease and its impact on clinical practice. 2012. 27(2): p. 108.
7. Lee, S.H., et al., Cystatin C as a predictive marker of renal dysfunction and mid-term outcomes following off-pump coronary artery bypass grafting. 2015. 101(19): p. 1562-1568.
8. Faraji, M.A.H., et al., Serum Cystatin C as an Endogenous Marker of Renal Function in Patients with Chronic Kidney Disease (CKD). 2017. 4(1): p. 3-12.
9. Pan, Y., et al., A Meta-analysis on diagnostic value of serum cystatin C and creatinine for the evaluation of glomerular filtration function in renal transplant patients. 2014. 14(4): p. 1025-1035.