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# Clinical utility of serum cystatin C in predicting coronary artery disease

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## Abstract

**Background:** *There is limited data regarding the clinical utility of cystatin C in patients with stable coronary artery disease (CAD). The aim of this study was to determine the predictive value of cystatin C for the presence and severity of CAD and the association between this protein and other biochemical risk factors for atherosclerosis in patients with suspected CAD.*

**Methods:** *Ninety-four patients with CAD, and 92 patients without CAD but with cardiovascular risk factors, were included in this study. Echocardiography and other pertinent laboratory examinations were performed. Subjects were divided into four groups according to their cystatin C quartile. Cystatin C groups were analyzed for the association with CAD characteristics.*

**Results:** *The number of patients with CAD increased as the quartile of cystatin C increased, and there was a remarkable difference between quartiles ($p < 0.001$). Logistic regression analysis revealed independent predictors of incident CAD as cystatin C, hs-CRP, eGFR, HDL cholesterol and SBP ($p = 0.005$, $p = 0.027$, $p = 0.017$, $p = 0.014$ and $p = 0.001$, respectively). Moreover, cystatin C concentration was significantly correlated with CAD severity score ($\beta = 0.258$, $p < 0.01$). A cut-off value of 0.82 mg/L for cystatin C predicted incident CAD with a sensitivity and specificity of 75.5% and 75.0% respectively. Cystatin C concentration also correlated well with the atherosclerotic biochemical risk factors like homocysteine, creatinine and hs-CRP.*

**Conclusions:** *Cystatin C could be a useful laboratory tool in predicting the presence and severity of CAD in daily practice. It also correlates significantly with biochemical risk factors for CAD, namely homocysteine, low HDL and CRP.* (Cardiol J 2010; 17, 4: 374–380)

**Key words: cystatin C, coronary artery disease, markers of atherosclerosis**

## Introduction

Renal dysfunction has been identified as a risk factor for the onset and prognosis of coronary atherosclerosis, and is regarded as a coronary artery disease (CAD) equivalent [1–3]. Although glomerular filtration rate (GFR) is a sensitive method for assessing renal function, it has many drawbacks such as difficulties in collecting urine. Therefore, for practical reasons, estimated GFR (eGFR) is used widely in clinical settings, and this primarily depends on serum creatinine. However, serum creatinine is not sensitive enough to detect mild renal dysfunction [4]. Cystatin C is an endogenous glycosylated protein produced in all nucleotide cells in the human body and a novel marker for renal function [5]. It is more sensitive and specific for the estimation of GFR and less influenced by age, gender, race, muscle mass and medication, as compared to serum creatinine [4, 6, 7]. The use of cystatin C

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for the assessment of renal filtration function has recently been approved [8].

Previous studies have shown a close relationship between cystatin C and atherosclerotic disease [9–11]. Furthermore, a high level of cystatin C has been related to suspected or confirmed acute coronary syndrome [12]. In 2007, the European Society of Cardiology recommended the use of cystatin C for predicting myocardial infarction and long-term mortality in patients with non-ST elevation acute coronary syndrome [13]. The results of studies investigating the value of cystatin C in anticipation of atherosclerosis in suspected stable CAD patients are controversial [10, 14–16]. Therefore, the clinical utility of cystatin C in stable CAD patients merits further investigation.

The aim of this study was to investigate the predictive value of cystatin C level for the presence or severity of CAD and the association between this protein and other biochemical risk factors for atherosclerosis in patients with suspected CAD.

## Methods

### Study group

Ninety-four CAD patients (70 male, 24 female, mean age 57.8 ± 9.0 years) with significant coronary stenosis (> 50%) and 92 subjects without CAD but with cardiovascular risk factors (63 male, 29 female, mean age 55 ± 7 years) were included in this cross-sectional study. Patients with severe renal dysfunction (creatinine > 2 mg/dL), history of recent acute coronary syndrome, valvular heart disease, life-threatening arrhythmias, acute and chronic liver disease, infectious and inflammatory disease, and symptomatic heart failure were excluded. All patients were in a stable condition and taking optimal medical therapy for their cardiovascular risk factors. The local ethics committee approved the study and informed consent was obtained from all subjects.

The detailed histories of patients, including demographics data and cardiovascular risk factors, were recorded. Serum cholesterols, homocysteine, high sensitive C-reactive protein (hs-CRP), blood urea nitrogen and creatinine levels were measured by routine laboratory methods. GFR was estimated by the Cockcroft-Gault formula:

[(140 age) × weight (kg)]/[72 × serum creatinine (mg/dL)] (× 0.85 for women) [17].

### Echocardiographic examination

All echocardiographic examinations were obtained at rest. Standard echocardiographic imaging was carried out by using a VIVID 7 machine (GE Healthcare, Little Chalfont, United Kingdom) with a 2.5 or 3.5 MHz phased array transducer. A single experienced cardiologist (M.K.) performed echocardiography and the mean of three consecutive cycles was used to drive the analysis. M-mode evaluation was made according to the recommendations of the American Society of Echocardiography [18]. The left ventricular ejection fraction was calculated via modified Simpson's technique. The left ventricular mass was calculated using the Devereux formula [19] and indexed to body surface area. The presence of left ventricular hypertrophy was accepted as left ventricular mass index (LVMI) > 134 g/m$^2$ for men and > 110 g/m$^2$ for women [20].

### Coronary angiography

All patients underwent coronary angiography, performed using standard Judkins techniques before the start of the study. Two expert investigators, blinded to the clinical data, analyzed the angiograms. The severity of coronary atherosclerosis was scored according to Gensini scoring [21] and three CAD groups were drawn up according to their CAD severity score: namely normal coronary arteries (normal coronary arteries or score 0), mild CAD (score = 1–20) and severe CAD (score > 20).

### Assessment of cystatin C

Venous blood was withdrawn from resting patients, and put into ethylenediamine-tetraacetic acid (EDTA)-containing tubes. Plasma was extracted after blood samples had been centrifuged at 3,000 g for 10 min at 0°C. Cystatin C was measured using the particle-enhanced nephelometric immunoassay (PENIA) method and N Lateks cystatin C kit (Dade Behring, Marburg, Germany) on a BN ProSpec protein analyzer (Dade Behring, Marburg, Germany) no more than 20 minutes after venipuncture.

### Statistical analysis

All analyses were performed using SPSS version 15.0 (SPSS Inc., Chicago, Illinois, USA). Categorical variables of cystatin C groups were compared by the chi-square test. Continuous variables were expressed as mean ± SD and compared by one-way analysis of variance. When indicated, a post hoc test (Scheffe or Tamhane) was performed. Correlations between continuous variables were assessed using Pearson's or Spearman's rank correlation analysis. Multivariate logistic regression analyses were performed to determine significant predictors of CAD. Significant variables in univariate analysis at a $p < 0.1$ level was entered in logis-

**Table 1.** Variables of study population according to cystatin C quartiles.

| Variable | Serum cystatin C levels [mg/L] | | | | p (ANOVA) |
|---|---|---|---|---|---|
| | < 0.65 (n = 47) | 0.65–0.82 (n = 46) | 0.83–0.99 (n = 46) | ≥ 1.0 (n = 47) | |
| Age (years) | 54.2 ± 5.0* | 54.3 ± 8.9$^{\Delta}$ | 56.7 ± 8.8 | 59.1 ± 8.1 | 0.005 |
| Male/female | 39/8 | 29/17 | 34/12 | 31/16 | 0.170[a] |
| Hypertension (%) | 20 (42.6) | 17 (36.9) | 24 (52.2) | 32 (68.1) | 0.025[a] |
| Systolic blood pressure [mm Hg] | 130.6 ± 15.9$^{\dagger}$ | 125.5 ± 11.1 | 122.2 ± 14.3 | 124.7 ± 11.9 | 0.023 |
| Diastolic blood pressure [mm Hg] | 83.2 ± 10.0 | 79.8 ± 8.5 | 78.5 ± 9.6 | 80.0 ± 9.2 | 0.081 |
| Diabetes (%) | 22 (46.8) | 13 (28.3) | 17 (36.9) | 16 (34.1) | 0.344[a] |
| Smoking (%) | 14 (29.8) | 16 (34.8) | 15 (32.6) | 19 (40.4) | 0.337[a] |
| Heart rate [bpm] | 71.8 ± 8.8 | 73.1 ± 8.5 | 75.1 ± 13.1 | 75.3 ± 10.1 | 0.308 |
| Creatinine [mg/dL] | 0.77 ± 0.19$^{\dagger, *}$ | 0.84 ± 0.14$^{\Delta}$ | 0.93 ± 0.15¶ | 1.15 ± 0.39 | < 0.001 |
| eGFR (%) | 115 ± 33$^{\dagger, \ddagger, *}$ | 106 ± 24 | 100 ± 22 | 78 ± 28 | < 0.001 |
| Total cholesterol [mmol/L] | 200 ± 52$^{\ddagger}$ | 169 ± 32 | 186 ± 45 | 187 ± 46 | 0.010 |
| HDL cholesterol [mmol/L] | 52 ± 10$^{\dagger, \ddagger, *}$ | 43 ± 10 | 42 ± 9.7 | 40 ± 11 | < 0.001 |
| LDL cholesterol [mmol/L] | 115 ± 47 | 101 ± 29 | 116 ± 37 | 109 ± 35 | 0.211 |
| Triglycerides [mmol/L] | 170 ± 106 | 132 ± 54$^{\Delta}$ | 168 ± 82 | 181 ± 80 | 0.026 |
| Homocysteine [$\mu$g/dL] | 1.8 ± 0.7$^{\dagger, \ddagger, *}$ | 2.0 ± 0.8 | 2.2 ± 0.5 | 3.2 ± 1.2 | < 0.001 |
| hs-CRP [mg/L] | 5.3 ± 4.0* | 5.6 ± 5.4 | 6.3 ± 7.1 | 8.7 ± 7.7 | 0.037 |
| CAD severity score | 1.5 ± 5.3$^{\dagger, \ddagger, *}$ | 10.0 ± 18.5$^{\Delta}$ | 18.7 ± 19.2 | 25.2 ± 21.3 | < 0.001 |
| Normal coronary arteries (score 0) (%) | 42 (89.3) | 27 (58.7) | 13 (28.3) | 10 (21.3) | |
| Mild CAD (score 1–20) (%) | 3 (6.3) | 9 (19.7) | 15 (32.6) | 10 (21.3) | < 0.001[a] |
| Severe CAD (score > 20) (%) | 2 (4.4) | 10 (21.7) | 18 (39.1) | 27 (57.4) | |
| LV end-diastolic volume [mL] | 115 ± 38* | 118 ± 23 | 125 ± 47 | 146 ± 76 | 0.022 |
| LV end-systolic volume [mL] | 46 ± 18* | 41 ± 19$^{\Delta}$ | 52 ± 36 | 66 ± 56 | 0.012 |
| LV ejection fraction (%) | 62.5 ± 6.8* | 65.1 ± 6.8$^{\Delta}$ | 61.9 ± 7.8 | 55.9 ± 9.7 | < 0.001 |
| LV mass index [g/m$^2$] | 112 ± 32* | 120 ± 35 | 117 ± 40 | 146 ± 58 | 0.001 |
| LV hypertrophy (%) | 11 (23.4) | 16 (34.8) | 16 (34.8) | 22 (46.8) | 0.024[a] |

Data is expressed as mean ± SD or number; eGFR — estimated glomerular filtration rate; hs-CRP — high sensitive C reactive protein; CAD — coronary artery disease; LV — left ventricle; ‡p < 0.05 between patients in cystatin C < 0.65 and 0.65–0.82; †p < 0.05 between patients in cystatin C < 0.65 and 0.83–0.99; *p < 0.05 between patients in cystatin C < 0.65 and ≥ 1.0; §p < 0.05 between patients in cystatin C 0.65–0.82 and 0.83–0.99; $^{\Delta}$p < 0.05 between patients in cystatin C 0.65–0.82 and ≥ 1.0; ¶p < 0.05 between patients in cystatin C 0.83–0.99 and ≥ 1.0; [a]p value from $\chi^2$ test

tic regression analysis. Moreover, a linear regression analysis was applied for CAD severity score, homosysteine and hs-CRP levels. A receiver-operating characteristic (ROC) curve analysis was performed to identify the optimal cut-off points of cystatin C and CRP levels (to determine maximal sensitivity and specificity) for predicting CAD. The area under the curve value was calculated to determine accuracy of the test. A p value of < 0.05 was considered as statistically significant.

## Results

Cystatin C concentration was significantly elevated in the CAD group compared to normal coronary arteries patients (1.04 ± 0.38 and 0.70 ± ± 0.25 mg/L respectively, p < 0.001). Clinical, laboratory, angiographic and echocardiographic variables of cystatin C quartile groups are presented in Table 1. Only ten (0.54%) patients' creatinine levels were higher than 1.3 mg/dL.

The number of CAD patients increased as the quartile of cystatin C increased, with a remarkable statistical difference between cystatin C groups ($\chi^2$: 59.7 and p < 0.001). Independent predictors of incident CAD determined by logistic regression were: cystatin C, hs-CRP, eGFR, HDL cholesterol and systolic blood pressure, after adjustments for age, creatinine, eGFR, gender, presence hypertension and diabetes mellitus, LDL cholesterol, diastolic blood pressure and homocysteine (Table 2). Every 0.1 mg/L increase in cystatin C, 1 mg/L increase in hs-CRP, 0.1 mmol/L decrease in HDL and 10% decrease in eGFR caused a 32%, 12%, 6.1% and 23% increase in the risk of having CAD, respectively.

In ROC curve analyses, among the parameters investigated for the prediction of CAD, cystatin C had the most discriminatory power for the occur-

**Table 2.** Multivariate logistic regression analysis for predicting the presence of coronary atherosclerosis.

| Variable | Odds ratio | 95% CI | P |
|---|---|---|---|
| Cystatin C (for each 0.1 mg/L) | 1.316 | 1.086–1.594 | 0.005 |
| hs-CRP [mg/L] | 1.124 | 1.013–1.248 | 0.027 |
| eGFR (%) | 0.977 | 0.958–0.996 | 0.017 |
| HDL cholesterol [mmol/L] | 0.950 | 0.911–0.989 | 0.014 |
| Systolic blood pressure [mm Hg] | 0.940 | 0.906–0.975 | 0.001 |

CI — confidence interval; eGFR — estimated glomerular filtration rate; hs-CRP — high sensitive C reactive protein

**Table 3.** Receiver-operating characteristic analyses for cystatin C, creatinine, eGFR, hs-CRP, HDL cholesterol levels and systolic blood pressure in predicting coronary atherosclerosis.

| Variable | Area under curve (95% CI) | P | Cut-off | Sensitivity | Specificity |
|---|---|---|---|---|---|
| Cystatin C | 0.811 (0.748–0.873) | < 0.001 | 0.82 mg/L | 75.5% | 75.0% |
| Creatinine | 0.746 (0.676–0.815) | 0.001 | 0.90 mg/dL | 74.7% | 71.2% |
| eGFR | 0.742 (0.671–0.813) | < 0.001 | 95% | 72.8% | 69.1% |
| hs-CRP | 0.637 (0.556–0.717) | 0.001 | 4 mg/L | 62.8% | 62.0% |
| HDL cholesterol | 0.713 (0.639–0.787) | < 0.001 | 42 mmol/L | 71.7% | 62.7% |
| Systolic blood pressure | 0.652 (0.574–0.729) | < 0.001 | 125 mm Hg | 60.9% | 54.3% |

CI — confidence interval; eGFR — estimated glomerular filtration rate; hs-CRP — high sensitive C reactive protein

rence of CAD across the entire population. The AUCs in predicting CAD were 0.811, 0.746, 0.742, 0.637, 0.713 and 0.652 for cystatin C, creatinine, eGFR, hs-CRP, HDL cholesterol and systolic blood pressure, respectively (Table 3). The ROC curves for cystatin C, creatinine, eGFR, hs-CRP are shown in Figure 1. As well as between cystatin C and creatinine, significant AUC differences were found between other variables ($p < 0.05$). The ROC curve analysis for cystatin C and hs-CRP had the highest and smallest AUC value respectively. Therefore, the most significant AUC difference was found between cystatin C and hs-CRP ($p < 0.01$). A 0.82 mg/L cut-off value of cystatin C predicted CAD with a sensitivity and specificity of 75.5% and 75.0%, respectively. Cut-off value, sensitivity and specificity of other variables are shown in Table 3.

The association between cystatin C and CAD severity score is depicted in Figure 2. Linear regression analysis showed that cystatin C, hs-CRP and HDL cholesterol levels were the most significant predictors of CAD severity ($\beta = 0.258$, $p < 0.001$; $\beta = 0.249$, $p < 0.001$ and $\beta = -0.227$, $p = 0.001$, respectively; the explained variance for the CAD severity score [$R^2$] was 0.309).

Cystatin C was significantly correlated with serum creatinine, homocysteine, hs-CRP, HDL cholesterol and eGFR ($p < 0.01$ for each). The most significant predictors of serum homocysteine level were cystatin C level and CAD severity score ($\beta = = 0.450$, $p < 0.001$ and $\beta = 0.176$, $p = 0.031$, adjusted for hs-CRP, eGFR, age and blood pressure; and the explained variance of homocysteine ($R^2$) was 0.268]. Although hs-CRP significantly correlated with cystatin C, only CAD severity score and creatinine concentration predicted hs-CRP ($\beta = 0.297$, $p < 0.001$ and $\beta = 0.210$, $p = 0.003$ respectively).

Since impaired renal function constitutes a substantial risk for CAD, we analyzed various tests that reflect renal function to predict CAD. Among these tests, cystatin C was found to be superior to creatinine or eGFR for its sensitivity and specificity in predicting CAD (Fig. 1).

## Discussion

Our study has shown a strong correlation between cystatin C and the presence or severity of CAD, low HDL, creatinine and homocysteine levels in patients with suspected CAD. However, the correlation was weak between cystatin C and hs-CRP.

Several lines of study have demonstrated an association between renal impairment and atherosclerotic vascular disease [1–3, 22]. Wang et al. [15] reported that mild renal impairment, determined by elevated cystatin C, was associated with the occur-

| | AUROC | Confidence interval |
|---|---|---|
| Cystatin C | 0.811 | 0.748–0.873 |
| Creatinine | 0.746 | 0.676–0.815 |
| eGFR | 0.742 | 0.671–0.813 |
| hs-CRP | 0.637 | 0.556–0.717 |

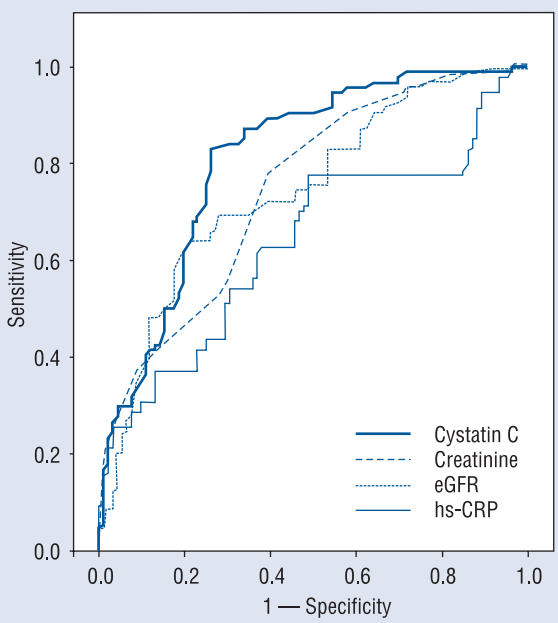


**Figure 1.** Receiver-operating characteristic (ROC) curve analyses and the area under ROC curves (AUROC) for cystatin C, creatinine, estimated glomerular filtration rate (eGFR) and high sensitive C reactive protein (hs-CRP) in predicting the presence of coronary artery disease (CAD).

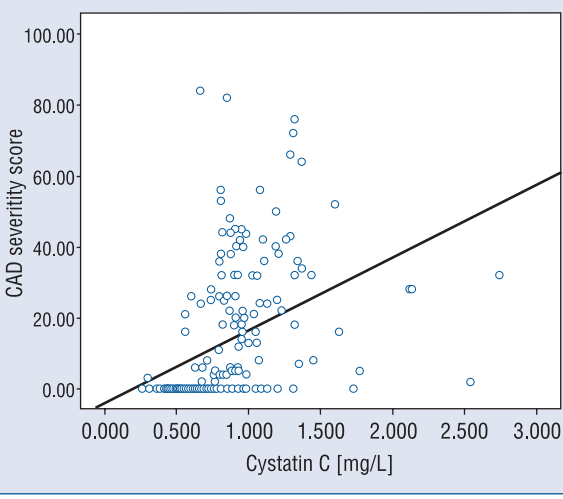


**Figure 2.** The relation between cystatin C and coronary artery disease (CAD) severity score.

rence and severity of CAD; however creatinine and eGFR were not able to predict CAD occurrence in their study. Likewise, Koenig et al. [10] reported that cystatin C was superior to creatinine or eGFR for predicting cardiovascular events. A prospective cohort study by Luc et al. [14], showed an association between cystatin C and the incidence of CAD. However, when CRP was included in the analyses, cystatin C lost its significance. This suggests the predictive value of cystatin C is not independent. In another study, cystatin C independently predicted smooth CAD lesions, but not complex lesions or CAD severity [16]. Our study is in accordance with the findings of Wang et al. [15] and Koenig et al. [10] that, among markers of renal function, cystatin C and eGFR are significantly and independently related to the presence of CAD, but only cystatin C predicts CAD severity. Additionally, results of our study are consistent with the observation that creatinine is not sensitive to detect mild impairments in renal function, since we observed no association between serum creatinine and the presence or severity of CAD. Moreover, we found that cystatin C is more sensitive and specific than CRP in identifying CAD.

A cut-off value of cystatin C to anticipate the presence of CAD has not been suggested to date. We analyzed the optimal cut-off value of cystatin C in our study, which revealed optimal cut-off as 0.82 mg/L with a 75.5% and 75% sensitivity and specificity respectively.

A number of previous studies reported a positive correlation between cystatin C and certain inflammatory markers such as fibrinogen, hs-CRP, IL-6 and TNF-$\alpha$ [9, 10, 14] and they hypothesized that alterations of serum cystatine C levels could be due to the inflammatory response which is evident in atherosclerosis. However, few studies have not found an association between CRP and cystatin C in both stable and unstable CAD [12, 16]. Singh et al. [23] investigated the association between renal function markers and inflammatory parameters; this revealed an independent association between eGFR and CRP or fibrinogen. Although there was an association between cystatin C and CRP or fibrinogen in this study, this association was lost following the inclusion of eGFR into the analyses.

Our results confirm previous studies [12, 23] that demonstrate the positive correlation between cystatin C and CRP. However, in our study, the most significant predictors of CRP were found to be CAD severity and serum creatinine.

Elevated homocysteine level is a well-known cardiac risk factor for the development of athero-

sclerosis [24]. In contrast to serum creatinine, serum cystatin C has independently predicted fasting total homocysteine level in both stable CAD and renal transplantation patients with normal serum creatinine [25, 26]. Likewise, the most significant parameters in our study in predicting serum homocysteine were serum cystatin C level and CAD severity score.

### Limitations of the study

There were a number of limitations to our study. Firstly, the sample size of our study was relatively small and we did not consider medication in our analyses. Secondly, renal function is closely related to the outcome of stable [10, 22] and unstable CAD [12, 13] patients and we did not evaluate cardiovascular events that warrant prospectively designated studies. Finally, we did not collect 24-hour urine for true GFR, which is the 'gold standard' method of assessing renal function.

## Conclusions

The results of our study indicate that serum cystatin C is as relevant as CRP (which is currently widely used in predicting CAD). Moreover, cystatin C is superior to other markers of renal function in anticipating CAD risk. There is a considerable association between serum cystatin C and biochemical cardiovascular risk factors such as homocysteine, low HDL and CRP. With these results, we suggest that cystatin C could be used as a marker in daily practice to predict the presence or severity of atherosclerosis in suspected stable CAD patients.

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