Significant association between Cystatin C, Gensini score, and Potential biomarker for Increased Risk of coronary artery lesions

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Research article

Keywords: coronary artery disease, cystatin C, coronary artery lesions, Gensini score

Posted Date: June 11th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-34296/v1>

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Abstract

Objective: Cystatin C (Cys C) has been proposed as a useful biomarker of early impaired kidney function and predictor of mortality risk. The present analysis is to investigate the association of serum Cystatin C with the severity of coronary artery lesions, Gensini score (GS) and the risk of CAD.

Methods: 682 CAD patients (230 females, 452 males; mean age 62.6 ± 10.7 years, range from 31 to 86 years) and 135 healthy controls (41 females, 94 males; mean age 58.0 ± 10.3 years, range from 38 to 84 years) were recruited in the current study. ELISA was applied to measure serum Cystatin C levels. Estimated glomerular filtration rate (eGFR) and Gensini score were calculated.

Results: Serum TC, LDL-C, UA, Cystatin C and HCY were significantly elevated in CAD patients compared to healthy controls. There were significant differences regarding to Cystatin C, eGFR and Gensini score among different type of CAD patients, of which AMI group had an elevated serum Cystatin C, LDL-C, HCY and Gensini score than the other two groups. When stratified by the quartiles of Cystatin C, we found that age, proportion of male patients and hypertension and diabetes, HCY and Gensini score were increased in Quartile fourth groups than in other quartile groups. Spearman's correlation test revealed positive relationship between Cystatin C, HCY and Gensini score. Multivariate logistic regression analysis revealed that serum Cystatin C level, presence of hypertension and diabetes, HCY, age and male were the risk factors for coronary artery lesions.

Conclusions: In summary, our results suggested that Cystatin C is a promising clinical biomarker that provides complementary information to the established risk determinants. The serum Cystatin C level is strongly associated with Gensini score and could be used to evaluate the severity of coronary artery lesions.

Introduction

Coronary artery disease (CAD) is a prevalent disease and produces immense health and economic burdens in the United States and globally [1]. Cystatin C, a 13-kDa protein, is a member of a family of competitive inhibitors of lysosomal cysteine protease and an alternative endogenous surrogate parameter for assessment of glomerular filtration rate (GFR)[2]. Previous studies have proposed Cystatin C as a novel biomarker for serum creatinine in the evaluation of early impaired renal dysfunction, predominantly to distinguish small drops in GFR [3, 4]. Of interest, cystatin C has also been proposed as a useful biomarker for cardiovascular risk and associated with the mortality in diverse clinical scenarios [5-7].

Coronary angiography was an important tool for the assessment of coronary artery lesions in both clinical practice and scientific investigation in the past 30 years [8]. With the development of technology, Intravascular ultrasound (IVUS) is another powerful and accurate tool for the evaluation of atherosclerotic burden [9, 10]. The limitation of coronary angiography and IVUS were cost and availability and since most CAD registries continue to use angiography to measure atherosclerosis severity. Gensini

Score (GS), a widely used angiographic scoring system, have been defined and used for evaluation atherosclerotic burden and prognosis [11-13]. Ian J. Neeland et al. found that Gensini Score system was a valid estimate of CAD plaque burden through analyzing coronary angiographic data from 3600 patients and comparing with the IVUS results [14].

However, to date, limited research findings show the correlation between cystatin C, Gensini Score, and coronary artery lesions. Therefore, we implemented the present study to investigate the correlation of serum Cystatin C with the severity of coronary artery lesions, Gensini Score (GS) and the risk of CAD.

Method And Materials

Study subjects

We performed a prospective cohort study in the Second Hospital of Hefei City from January 2014 to December 2019. This study received ethical approval from the Ethical Committee of the Second Hospital of Hefei City (Hefei, China). 682 hospitalized patients diagnosed with CAD (230 females, 452 males; mean age 62.6 ± 10.7 years, range from 31 to 86 years) were recruited from the Department of Cardiology at the Second Hospital of Hefei City. 135 healthy volunteers (41 females, 94 males; mean age 58.0 ± 10.3 years, range from 38 to 84 years) without CAD were included as healthy controls. Patients and healthy controls with any history of infections, autoimmune diseases, metabolic disease (not including diabetes) and severe chronic diseases (such as cirrhosis, thyroid disease, and chronic renal insufficiency) were excluded.

All patients underwent coronary angiography interpreted by two independent clinical observers with lesions recorded using a 17-segment modified AHA model [15]. All the patients should fulfill the diagnostic criteria of coronary artery disease defined by the American College of Cardiology/American Heart Association in 2014, and were confirmed by coronary angiography (CAG) to have stenosis $\geq 50\%$ in at least one coronary artery. Gensini score was calculated according to a modified Gensini scoring system [16].

Laboratory Investigation

Blood samples were drawn from subjects after an overnight fast before cardiac catheterization. The concentrations of cystatin C, FPG (fasting plasma glucose), TC (total cholesterol), TG (triglyceride), LDL-C (low-density lipoprotein cholesterol), BUN (blood urea nitrogen), UA (uric acid), HCY (homocysteine), and HDL-C (high-density lipoprotein cholesterol) were measured by using commercially available Human Elisa Kits (Biovendor Inc). The eGFR was calculated using the MDRD (modification of diet in renal disease) formula (eGFR MDRD) the CKD Epidemiology Collaboration (CKDEPI) equation.

Statistical analysis

All continuous variables were presented as mean $\pm$ SD and frequency for categorical variables. Continuous variables are presented as the means $\pm$ standard deviations, the intergroup comparisons were

made using the One-way ANOVA, and differences between two groups were evaluated by Student's t-test. The chi-square test or Fisher's exact test was used to assess differences in categorical data between the two groups. We performed multivariate logistic regression analysis to identify the independent risk factors for coronary artery lesions. Spearman's rank correlation method was used to determine correlation between cystatin C levels, HCY, eGFR and Gensini score.

Results

Comparison of baseline Clinical and laboratory characteristics between healthy Control and CAD Patients

Baseline demographics, physical exam characteristics, and laboratory characteristics were listed in **Table 1**. There were significant higher serum Cystatin C, HCY, UA, LDL-C, and FPG in CAD patients than in healthy controls (all $P < 0.05$). Although there was no significant difference in gender and hypertension distribution between CAD patients and healthy controls, CAD patients had a significant higher in age and diabetes proportion and lower serum HDL (high-density lipoprotein cholesterol) and eGFR compared to healthy controls (all $P < 0.05$). However, no significant difference was found in BUN, TC and TG (All $P > 0.05$).

Comparison of baseline Clinical and laboratory characteristics among different CAD patients

When comparing different variables among different type of CAD patients, the results showed that in AMI group, age, the proportion of male patients and hypertension and diabetes, TC, LDL-C, HCY, and Cystatin C were significant elevated than SAP group (all $P < 0.05$). The SAP group had the lowest mean levels of Cystatin C (1.1 ± 0.9) and AMI group had the highest levels (1.6 ± 0.6). HDL-C levels and eGFR were significantly higher in SAP group compared to AMI and UAP group ($P < 0.05$). However, no statistical differences were found in terms of SBP, DBP, FPG, BUN, UA, and TG (all $P > 0.05$) (Table 2).

In the UAP and AMI group, the serum Cystatin C level and HCY level were decreased with eGFR ($P < 0.05$). Further analysis showed that serum Cystatin C level was positively correlated with HCY level ($r=0.65$, $p=0.001$) and negatively correlated with eGFR ($r=-0.632$, $p=0.031$).

Baseline characteristics of CAD patients by Cystatin C Quartiles

Cystatin C grouping: The Cystatin C levels of all the CAD patients (682 cases) were divided into four subgroups according to the interquartile method: subgroup Q1, Cystatin C < 0.88 mg/L (161 cases); subgroup Q2, $0.88 \text{ mg/L} \leq \text{Cystatin C} < 1.09$ mg/L (172 cases); subgroup Q3, $1.09 \text{ mg/L} \leq \text{Cystatin C} < 1.29$ mg/L (178 cases); and subgroup Q4, Cystatin C ≥ 1.29 mg/L (171 cases).

The comparison of differences regarding Cystatin C quartiles among CAD patients revealed that the age, proportion of male patients and diabetes, HCY and Gensini score were significantly higher in Quartile fourth groups than in other groups (all $P < 0.05$) (Table 3). Of interesting, these data suggested that a remarkable increase in Gensini score with the increasing level of Cystatin C. Further analysis showed that serum Cystatin C level was positively correlated with Gensini score ($r=0.55$, $p=0.021$). These data

suggested that a remarkable increase in Gensini score with the increasing level of Cystatin C. Neither group showed any significant differences in terms of FBG, TC, TG, HDL, and LDL.

Risk factors for coronary artery lesions

The multivariate logistic regression analysis was used to identify the independent risk factors for coronary artery lesions. The results showed that the significant risk factors included age ($P = 0.042$; OR = 2.33), the proportion of patients with hypertension ($P = 0.001$; OR = 2.17) and diabetes ($P = 0.003$; OR = 2.78) and Male ($P = 0.004$; OR = 2.27), as well as HCY ($P = 0.03$; OR = 1.43) (Table 4).

For the Cystatin C level, the ORs and 95% confidence intervals for coronary artery lesions were analyzed by Cystatin C quartiles. We adjusted for age, sex, distribution of hypertension and diabetes, and HCY before compared with the first (lowest) quintile. The odds ratios (CI95%, P value) for coronary artery lesions were as follows: second quintile, 1.28 (0.89-1.85, $p = 0.18$); third quintile, 1.52 (0.94-2.49, $p = 0.09$); and fourth quintile, 2.28 (1.24-2.85, $p = 0.003$). These data strongly suggested that increased serum Cystatin C levels were related with the severity of coronary artery lesions.

Discussion

This cross-sectional study of 682 China's patients with CAD or 145 healthy controls revealed the relationship between serum cystatin C levels and the prevalence of CAD, the severity of atherosclerotic burden of the coronary arteries. Our data disclosed that the high level of Cystatin C closely and independently associated with CAD and its severity. The most important findings of the current study are the facts that Cystatin C levels were not only negatively associated with eGFR but also significantly and positively related to Gensini score. The higher levels of Cystatin C, the higher score of Gensini score, which means higher severity of atherosclerotic burden of the coronary arteries.

Past studies have disclosed the strong relationship between high serum levels of Cystatin C and the stable coronary artery disease [7], acute coronary syndrome (ACS), non-ST-elevation acute coronary syndrome (NSTEMI) [17] and ST elevated myocardial infarction (STEMI) [6]. The aim of current study was to investigate the relationship between the serum level of cystatin C and coronary artery lesions in CAD patients. Our results are consistent with some past studies, which have proved the severity of CAD and worse clinical outcomes were related with high Cystatin C levels [18-20]. Thus, the level of Cystatin C could be a promising and clinical biomarker for predicating the severity of CAD and its prognosis.

The association between Gensini score and prognosis of CAD such as mortality and disease progression were proved in several previous studies [21-24]. Unfortunately, few researchers put their attention on the role of cystatin C in predicting the severity of atherosclerotic plaque burden of the coronary arteries. Rainer P. Woitas and co-workers analyzed data from 2998 patients of the LURIC (Ludwigshafen Risk and Cardiovascular Health) study with a median follow-up of 9.9 years and a strong relationship was revealed between the concentration of Cystatin C and long-term all-cause and cardiovascular mortality in individuals undergoing coronary angiography [24]. Another multicenter trial in 2162 patients with the

whole spectrum of CAD and cystatin C measurements, Keller T et al. found an increased mortality in CAD patients with elevated cystatin C levels [25]. High level of Cystatin C and risk of mortality and morbidity had also been revealed in other different cohorts [26-29]. Our current study results strongly implied that the serum level of cystatin C may be a promising biomarker for the evaluation of atherosclerotic plaque burden. Therefore, Cystatin C has a stronger and more linear relationship in predicting adverse outcomes of CAD.

Till now, the mechanism of how Cystatin C put an impact on the progression of coronary artery disease is still unclear. Following factors could be used to explain the mechanism. First, Cystatin C is a cysteine protease inhibitor that is produced at a constant rate by all nucleated cells and freely filtered by glomeruli owing to its low molecular weight. Therefore, Cystatin C is not only a useful marker in judging the early renal insufficient, but also could be an important tool for predicting long-term prognosis of renal dysfunction [30, 31]. Several studies have revealed that early renal dysfunction was a strong and independent risk of CAD [32, 33]. Systemic micro-inflammation response or oxidative stress would accelerate the progression of atherosclerosis in CAD patients with early renal impairment [34, 35]. The risk for CAD Patients with high serum of Cystatin C is much higher than those with normal level of Cystatin C, suggesting those patients had preexisting renal insufficiency. Secondly, past studies have proved that smoking, obesity, and chronic inflammation affect the production of cystatin C, all those factors were risk of CAD [36-38]. In our present study, high serum levels of Cystatin C mean high Gensini score, suggesting that Cystatin C has an active role in biological process leading to format atherosclerotic plaque. Thirdly, Cystatin C is a key endogenous cathepsins inhibitor and its main function is to keep the balance between proteases and their main inhibitor [38-40]. Increased serum levels of Cystatin C lead to break the balance between Cystatin C and cysteine cathepsins. Thus, the atherosclerosis formation and development will be further accelerated in CAD patients [41, 42].

There are several limitations should be acknowledged in the current study. First, the present study is hospital-based observational study, of which study subjects participated in our study came for medical treatment, these patients payed more attention to their health, and this may lead to a selection bias. Second, only CAD patients were included in the present study, so our results cannot be applied to the other study population. Third, Cystatin C levels were measured only once, we could not discriminate if an elevated Cystatin C level was influenced by acute kidney injury or chronic kidney disease. Furthermore, the sample size is relatively small in our study, especially for the healthy controls. The small sample size may reduce the statistical power and cause a contradictory result. Further well-designed and follow-up studies with larger samples are still needed to determine the precise relationships between Cystatin C and CAD.

In summary, serum Cystatin C is higher in CAD patients than in healthy controls, and exerts a clinical severity among different type of CAD patients. Our results suggested that the serum Cystatin C level is strongly associated with Gensini score and could be used to evaluation the severity of Coronary artery disease. An elevated Cystatin C concentration could be an independent factor associated with the

progression of CAD, and be a useful clinical marker that provides complementary information to the established risk determinants.

Declarations

Acknowledgements

This research was founded by Hefei Municipal Health and Family Planning Commission (No. hwk2017yb012). We would like to thank all participants for their technical assistance and advice regarding statistical analysis.

Conflict of Interest:

There are no conflicts of interests.

All studies on humans described in the present manuscript were carried out with the approval of the responsible ethics committee and in accordance with national law and the Helsinki Declaration of 1975 (in its current, revised form). Informed consent was obtained from all patients included in studies.

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Tables

Table 1 Basic clinical characteristic between CAD patients and control groups

	CAD patients (n=682)	Healthy Control (n=135)	<i>P</i> -value
Age (years)	62.6±10.7	58.0±10.3	0.001
Males (%)	66.3	69.6	0.114
Hypertension (%)	45.7	43.7	0.683
Diabetes (%)	20.1	11.1	0.010
SBP (mmHg)	138.4±20.9	120.8±21.8	0.341
DBP (mmHg)	88.9±62.9	84.4±12.5	0.075
FPG (mmol/L)	6.4±4.3	5.2±0.2	0.001
BUN (mmol/L)	5.3±1.5	5.2±4.4	0.238
UA (μmol/L)	379.2±88.6	286.3±78.4	0.001
HCY (mmol/L)	10.7±4.2	9.1±5.1	0.02
TC (mmol/L)	4.2±1.1	4.0±1.1	0.053
TG (mmol/L)	2.0±1.6	2.0±1.4	0.668
HDL-C (mmol/L)	1.2±0.6	1.4±0.3	0.003
LDL-C (mmol/L)	2.6±1.1	2.4±0.8	0.010
eGFR (ml/min/1.73m ²)	82.6±17.3	92.3±16.7	0.001
Cys C (mg/L)	1.2±0.8	0.8±1.0	0.031

Cys C: cystatin C; SBP: systolic blood pressure; DBP: diastolic blood pressure; FPG: fasting plasma glucose; BUN: blood urea nitrogen; UA: uric acid; HCY: homocysteine; TC: total cholesterol; TG: triglyceride; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; eGFR: estimating glomerular filtration rate

Table 2 Comparison of clinical characteristics among different type of CAD patients

	SAP group (n=248)	UAP group (n=237)	AMI group (n=197)	P-value
Age (years)	61.1±10.2	64.6±10.8	65.3±10.0	0.000
Males (%)	60.5	69.2	75.1	0.002
Hypertension (%)	56.0	59.9	67.7	0.001
Diabetes (%)	15.7	23.2	27.8	0.000
SBP (mmHg)	137.6±21.4	139.0±18.8	139.0±22.3	0.860
DBP (mmHg)	83.2±12.8	93.2±81.7	93.9±89.6	0.170
FPG (mmol/L)	5.8±2.0	6.6±6.1	6.6±2.8	0.320
BUN (mmol/L)	5.1±1.5	4.2±1.2	5.4±1.3	0.256
UA (μmol/L)	289.1±77.1	295.1±82.1	301.2±78.5	0.179
HCY (mmol/L)	9.1±6.4	10.2±5.5	11.4±4.9	0.03
TC (mmol/L)	3.8±1.1	4.1±1.1	4.4±1.2	0.006
TG (mmol/L)	2.0±1.7	1.8±1.4	2.2±2.0	0.113
HDL-C (mmol/L)	1.3±0.4	1.2±0.9	1.1±0.3	0.029
LDL-C (mmol/L)	2.1±0.9	2.4±0.8	2.9±1.5	0.000
eGFR (ml/min/1.73m ²)	92.2±19.2	84.8±17.5	77.4±20.1	0.032
Cys C (mg/L)	1.1±0.9	1.3±0.7	1.6±0.6	0.030
Gensini score	17.1±18.9	37.6±31.8	58.3±40.8	0.000

Cys C: cystatin C; SBP: systolic blood pressure; DBP: diastolic blood pressure; FPG: fasting plasma glucose; BUN: blood urea nitrogen; UA: uric acid; HCY: homocysteine; TC: total cholesterol; TG: triglyceride; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; eGFR: estimating glomerular filtration rate; SAP: stable angina group; UAP: unstable angina group; AMI: acute myocardial infarction group.

Table 3 Baseline characteristics of CAD patients and laboratory variables according to cystatin C concentration quartiles

Variables	Serum cystatin C levels (mg/L)				<i>P</i>
	Quartile 1 (<0.88)	Quartile2 (0.88~1.09)	Quartile 3 (1.09~1.29)	Quartile 4 (>1.29)	
	(n=161)	(n=172)	(n=178)	(n=171)	
Age (years)	58.0±10.6	61.7±8.5	63.9±10.8	66.6±10.7	0.000
Males (%)	56.7	60.6	73.1	74.3	0.000
Hypertension (%)	54.7	56.1	63.5	64.3	0.321
Diabetes (%)	13.9	12.6	22.1	31.0	0.001
TC (mmol/L)	4.0±1.1	4.2±0.97	4.2±1.2	4.2±1.1	0.243
TG (mmol/L)	2.0±1.5	1.8±1.3	2.1±1.6	2.1±2.0	0.450
HDL-C (mmol/L)	1.2±1.9	1.2±2.4	1.2±1.3	1.2±1.4	0.612
LDL-C (mmol/L)	2.5±0.9	2.6±1.2	2.6±1.1	2.7±1.4	0.438
HCY (mmol/L)	8.2±5.2	8.7±4.7	9.6±5.1	10.8±4.6	0.001
eGFR (ml/min/1.73m ²)	98.2.2±12.9	91.3±15.7	82.6±13.8	75.8±16.9	0.000
Gensini score	23.4±29.3	35.8±30.5	44.8±35.6	59.0±35.9	0.000

SBP: systolic blood pressure; DBP: diastolic blood pressure; FPG: fasting plasma glucose; TC: total cholesterol; TG: triglyceride; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; eGFR: estimating glomerular filtration rate.

Table4 Risk factors for coronary artery lesions by multivariate logistic regression analysis

	S.E.	Wald	<i>P</i>	OR	95% CI for OR	
					Lower	Upper
Age	0.21	7.22	0.042	2.33	0.40	4.35
Male	0.15	8.51	0.004	2.27	1.37	7.14
Hypertension	0.23	11.51	0.001	2.17	1.39	3.45
Diabetes	0.27	10.56	0.003	2.78	1.61	4.54
HCY	0.131	8.02	0.03	1.43	1.12	1.82
Cys C (mg/L)						
Q1(<0.88)				1.00		
Q2 (0.88~1.09)	0.19	1.78	0.18	1.28	0.89	1.85
Q3(1.09~1.29)	0.25	2.91	0.09	1.52	0.94	2.49
Q4(>1.29)	0.21	8.74	0.003	2.28	1.24	2.85

Cys C: serum Cystatin C; CI: confidence interval; HCY: homocysteine