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Association of serum cystatin C levels with acute coronary syndrome in patients of advanced age

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Abstract

Objective: This study was performed to investigate the relationship between the serum cystatin C (Cys C) level and acute coronary syndrome (ACS) in patients of advanced age.

Methods: The study included 184 patients with ACS and 46 healthy control subjects. Statistical analysis was performed using SPSS version 14.0 (SPSS Inc., Chicago, IL, USA).

Results: The serum Cys C level was significantly higher in patients with than without ACS (1.24 ± 0.30 vs. 1.42 ± 0.46 mg/L, respectively). Patients with more stenotic coronary arteries were significantly more likely to have higher median serum Cys C and creatinine levels and a lower estimated glomerular filtration rate. The multivariate logistic regression analysis demonstrated that the serum Cys C level was independently associated with the presence of ACS and the quantity of stenotic coronary arteries after adjustment for confounding factors. Additionally, the serum Cys C level was positively correlated with age, the creatinine level, and the N-terminal pro-B-type natriuretic peptide level in all patients but was negatively correlated with the estimated glomerular filtration rate.

Conclusion: A high serum Cys C level was independently associated with ACS and the quantity of stenotic coronary arteries in patients of advanced age regardless of renal function.

Keywords

Acute coronary syndrome, serum cystatin C, advanced age, stenosis, estimated glomerular filtration rate, creatinine, N-terminal pro-B-type natriuretic peptide

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Introduction

Acute coronary syndrome (ACS), including unstable angina, non-ST-segment elevation myocardial infarction, and ST-segment elevation myocardial infarction, is a leading cause of death and disability worldwide.[1] Patients of advanced age constitute a large proportion of patients presenting with ACS.[2] In the United States, the median age at ACS presentation is 68 years (interquartile range, 56–79 years).[3] As the population grows older, especially in developing countries, increasing numbers of advanced-age patients present with ACS. However, patients of advanced age with ACS are more likely to have more comorbidities including chronic heart failure, arrhythmia, diabetes, cerebrovascular disease, chronic respiratory disease, and renal insufficiency.[2] The typical symptoms of angina are not always observed in patients with such conditions; additionally, the diagnostic specificity of cardiac troponins may be decreased. Therefore, early diagnosis and evaluation of the severity of ACS is sometimes difficult in older patients.

Cystatin C (Cys C) is a cysteine protease inhibitor produced by nearly all human cells and excreted into the bloodstream. With a low molecular weight of 13 kD, the protein is freely filtered by the renal glomerulus and then metabolized by the proximal tubule.[4] Compared with creatinine, Cys C may have a particular advantage for diagnosis in patients of advanced age because its level in the blood does not seem to be influenced by age, sex, race, or muscle mass.[5,6] The results of several cardiovascular health studies have demonstrated that Cys C has a much stronger and more linear association with the risk of mortality than does creatinine or creatinine-based estimates of the glomerular filtration rate (GFR).[4,6–8] Moreover, some evidence has suggested that Cys C can be influenced by inflammation and may be intricately involved in the pathogenesis of atherosclerosis.[9,10] All of these properties may render Cys C a potential biomarker in the early diagnosis of ACS and evaluation of its severity in patients of advanced age.

However, few data exist on the relationship between the serum Cys C level and ACS in patients of advanced age with or without chronic renal insufficiency. This study was performed to examine whether the serum Cys C level is associated with ACS and the number of stenotic coronary arteries in patients of advanced age regardless of the presence of renal insufficiency.

Methods

Patient population and study design

Patients of advanced age with suspected ACS who underwent diagnostic coronary angiography at North Huashan Hospital of Fudan University from January 2016 to December 2017 were enrolled in this study. After coronary angiography, the patients were divided into two groups: those who had been diagnosed with ACS and those who had no coronary stenosis. To evaluate the severity of ACS, the patients were further divided into three subgroups according to the number of stenotic coronary arteries (the 1-, 2, and 3-vessel groups). We only enrolled patients aged >60 years. We collected blood samples from each patient and recorded their age, sex, medical history, number of stenotic coronary arteries, and other clinical information. The study was performed according to the guidelines of the declaration of Helsinki and was approved by the ethics committee of North Huashan Hospital of Fudan University. All patients participating in the study provided verbal informed consent.

Definition of ACS

All patients met the diagnostic criteria defined by 2014 American Heart Association/American College of Cardiology guideline for the management of patients with non-ST-segment elevation ACSs[3] and the 2013 American College of Cardiology Foundation/American Heart Association guideline for the management of ST-segment elevation myocardial infarction.[11]

Inclusion and exclusion criteria

The inclusion criteria were fulfillment of the above-mentioned diagnostic criteria, age of >60 years, and coronary artery stenosis of $\geq 50\%$ in at least one main coronary artery as confirmed by coronary angiography. Patients both with and without renal insufficiency were enrolled. The exclusion criteria were comorbid diseases including cardiomyopathy, valvular heart disease, myocarditis, acute cerebrovascular accident, acute infection, and advanced cancer and/or a medical history of a previous myocardial infarction, coronary stenting, and/or coronary bypass surgery.

Coronary angiography

The patients were evaluated by coronary angiography, and coronary artery disease was defined as visual stenosis of $\geq 50\%$ in at least one of the three major coronary arteries. The left anterior descending artery, left circumflex artery, and right coronary artery were examined to evaluate the number of stenotic coronary arteries and thus determine whether the patient had 0- to 3-vessel disease. Involvement of the left main trunk was evaluated as 2-vessel disease by itself.[12] The coronary angiography results were independently evaluated by two expert investigators.

Analysis of serum Cys C level

The concentration of serum Cys C was measured using a kit provided by Kyokuto Pharmaceutical Industrial (Tokyo, Japan), and the level is expressed in units of mg/dL.[13] The reference value of Cys C is ≤ 1.0 mg/L. In all patients, the serum Cys C concentration was measured within 24 h after admission.

Other data collection

The relevant data were collected from the patients' medical records. The levels of N-terminal pro-B-type natriuretic peptide, serum creatinine, fasting blood glucose, and low-density lipoprotein cholesterol (LDL-C) were measured by clinically approved assays on the same platform. The estimated GFR (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration creatinine-cystatin C equation, which can be expressed as follows:

$$\begin{aligned}\mathrm{eGFR} = {} & 135 \times \min(\mathrm{Scr}/\kappa, 1)^{\alpha} \\ & \times \max(\mathrm{Scr}/\kappa, 1)^{-0.601} \times \min(\mathrm{Scys}/0.8, 1)^{-0.375} \\ & \times \max(\mathrm{Scys}/0.8, 1)^{-0.711} \times 0.995^{\mathrm{age}} \\ & \times 0.969(\mathrm{if\,female}) \times 1.08(\mathrm{if\,black})\end{aligned}$$

where Scr is serum creatinine, Scys is serum cystatin C, κ is 0.7 for females and 0.9 for males, α is -0.248 for females and -0.207 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.[14]

Statistical analysis

Continuous variables are expressed as mean $\pm$ standard error of the mean or median [interquartile range], and categorical data are summarized as proportion and frequency as appropriate. If the parameters followed a normal distribution, the t-test was used to compare the differences

between two groups. One-way analysis of variance was used when there were more than two groups; otherwise, the Mann–Whitney U test and Kruskal–Wallis H test were used, respectively. The categorical variables were compared using the χ^2 test or Fisher's exact test. Factors considered to affect ACS and the number of stenotic coronary arteries were evaluated using a multivariate logistic regression model. Correlations between the serum Cys C level and creatinine level as well as other biochemical parameters (age, LDL-C concentration, and eGFR) were assessed with Pearson's correlation analysis. All tests were two-sided. P values of ≤ 0.05 were considered statistically significant. The statistical analysis was performed using SPSS version 14.0 (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

All patient characteristics are shown in Table 1. In total, 230 patients who underwent coronary angiography were enrolled in the study. Among the 230 patients, 184 were diagnosed with ACS and 46 had no coronary stenosis. There were no significant differences in clinical features such as age, medical history, N-terminal pro-B-type natriuretic peptide level, and renal function as measured by the serum creatinine level and eGFR among the groups. The patients in both groups were of advanced age. Compared with the controls, the patients with ACS had a higher proportion of men ($P = 0.032$) and a higher median LDL-C level ($P = 0.02$). Moreover, the serum Cys C level was significantly higher in patients with than without ACS (1.42 ± 0.46 vs. 1.24 ± 0.30 mg/L, respectively; $P = 0.015$) (Figure 1).

To further analyze the severity of ACS, the 184 patients with ACS were divided into 3 subgroups (1-, 2-, and 3-vessel disease) according to the number of stenotic coronary arteries. As demonstrated in Table 2, significant differences were found in the serum Cys C concentration, creatinine

Table 1. Baseline clinical characteristics in participants with and without ACS.

Characteristic	non-ACS n = 46	ACS n = 184	*P*-value
Age, years	72.6 (67.75–78.25)	72.8 (66–79)	0.968
Sex, male	21 (45.7)	116 (63.0)	0.032
History of CHF	4 (8.7)	26 (14.1)	0.463
History of HBP	31 (67.4)	131 (71.2)	0.613
History of DM	8 (17.4)	57 (31.0)	0.067
LDL-C, mg/dL	2.38 ± 0.72	2.72 ± 0.92	0.02
Cystatin C, mg/L	1.24 ± 0.30	1.42 ± 0.46	0.015
Creatinine, μmol/L	79.52 ± 20.45	83.82 ± 24.78	0.278
eGFR, mg/mL/1.73 m^2	65.11 ± 14.73	60.75 ± 16.72	0.107
NT-proBNP, pg/mL	523.47 ± 494.94	827.10 ± 1140.24	0.064
Angiography			
1-vessel disease	–	101 (54.9)	–
2-vessel disease	–	69 (37.5)	–
3-vessel disease	–	14 (7.6)	–

Data presented as mean ± standard deviation, median (interquartile range), or n (%). ACS, acute coronary syndrome; CHF, chronic heart failure; HBP, high blood pressure; DM, diabetes mellitus; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide

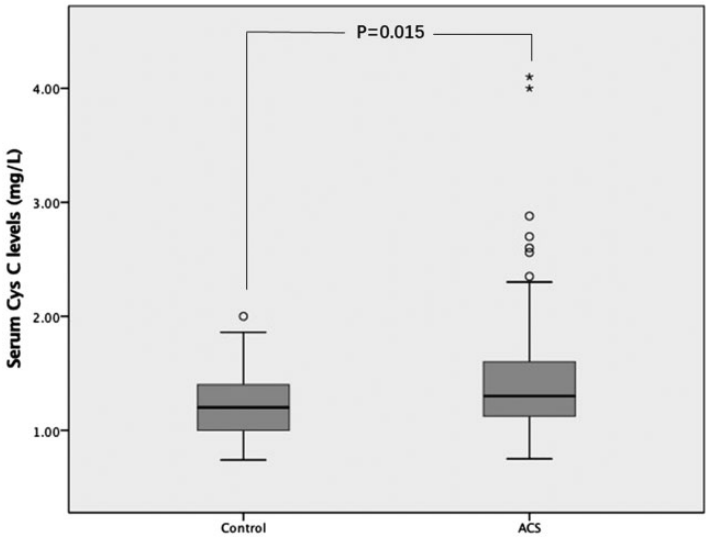

Figure 1. Differences in serum Cys C level between participants with and without ACS. Cys C, cystatin C; ACS, acute coronary syndrome.

Table 2. Baseline clinical characteristics of participants according to the quantity of stenotic coronary arteries.

		ACS			
Characteristic	non-ACS (n = 46)	1 vessel (n = 101)	2 vessels (n = 69)	3 vessels (n = 14)	*P*-value
Age, years	72.60 ± 6.30	71.54 ± 7.34	74.09 ± 7.62	75.00 ± 8.75	0.098
Sex, male	21 (45.7)	67 (66.3)	40 (58.0)	9 (64.3)	0.121
History of CHF	4 (8.7)	11 (10.9)	12 (17.4)	3 (21.4)	0.319
History of HBP	31 (67.4)	69 (68.3)	51 (73.9)	11 (78.6)	0.767
History of DM	8 (17.4)	26 (25.7)	24 (34.8)	7 (50.0)	0.052
LDL-C, mg/dL	2.38 ± 0.72	2.70±0.93	2.74 ± 0.82	2.77 ± 1.29	0.133
Cystatin C, mg/L	1.24 ± 0.30	1.28 ± 0.30	1.50 ± 0.40	2.04 ± 1.00	<0.001
Creatinine, μmol/L	79.52 ± 20.45	78.29 ± 20.57	87.64 ± 25.75	104.93 ± 33.60	<0.001
eGFR, mg/mL/1.73 m^2	65.11 ± 14.73	66.52 ± 15.39	55.45 ± 14.40	45.25 ± 18.00	<0.001
NT-proBNP, pg/mL	523.47 ± 494.94	704.20 ± 927.55	933.55 ± 1374.83	1189.10 ± 1215.89	0.076

Data presented as mean ± standard deviation or n (%). ACS, acute coronary syndrome; CHF, chronic heart failure; HBP, high blood pressure; DM, diabetes mellitus; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide

concentration, and eGFR among these groups. Patients with more stenotic coronary arteries were likely to have a higher median serum Cys C concentration ($P = 0.001$) (Figure 2) and creatinine concentration ($P < 0.001$) and a lower eGFR ($P < 0.001$). No significant differences existed in other clinical parameters.

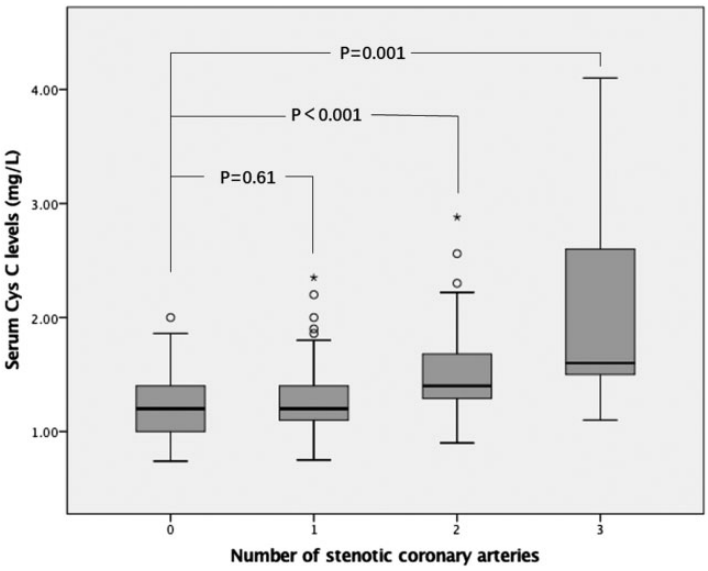

Figure 2. Differences in serum Cys C level among patients with acute coronary syndrome with different numbers of stenotic coronary arteries. Cys C, cystatin C.

Table 3. Multivariate logistic regression analysis model for prediction of ACS.

Variables	Odds ratio	95% CI	*P*
Sex	2.006	1.012–3.973	0.046
History of DM	2.536	1.074–5.988	0.034
LDL-C	1.706	1.117–2.605	0.013
Cystatin C	4.016	1.242–12.986	0.02

ACS, acute coronary syndrome; CI, confidence interval; DM, diabetes mellitus; LDL-C, low-density lipoprotein cholesterol.

Multiple logistic regression analysis

We conducted a multivariate logistic regression analysis to evaluate the potential predictors of ACS in the entire study population. As shown in Table 3, the multivariate logistic regression analysis revealed that the serum Cys C concentration was independently associated with ACS after adjustment for confounding factors (odds ratio [OR], 4.016; 95% confidence interval [CI], 1.242–12.986; $P = 0.02$).

Table 4. Multivariate logistic regression analysis model for prediction of the quantity of stenotic coronary arteries.

Variables	Odds ratio	95% CI	*P*
Age	0.999	0.958–1.043	0.986
Sex	0.674	0.342–1.328	0.255
History of CHF	0.708	0.318–1.571	0.395
History of HBP	1.063	0.607–1.861	0.832
History of DM	0.453	0.257–0.799	0.006
LDL-C	1.342	0.997–1.806	0.052
Cystatin C	5.646	1.250–25.508	0.024
Creatinine	0.990	0.969–1.010	0.314
eGFR	0.984	0.938–1.033	0.513
NT-proBNP	1.000	0.999–1.001	0.091

CI, confidence interval; CHF, chronic heart failure; HBP, high blood pressure; DM, diabetes mellitus; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

We further evaluated the potential predictors of the severity of ACS using multivariate logistic regression analysis. As shown in Table 4, the multivariate

Table 5. Correlations between serum cystatin C level and other parameters.

	r	P
Age, years	0.294	<0.001
LDL-C, mg/dL	0.121	0.068
Creatinine, μmol/L	0.626	<0.001
eGFR, mL/min/1.73 m^2	−0.830	<0.001
NT-proBNP, pg/mL	0.159	0.016

LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide

logistic regression analysis revealed that the serum Cys C concentration was independently associated with the number of stenotic coronary arteries after adjustment for confounding factors (age, sex, medical history, LDL-C concentration, creatinine concentration, and eGFR) (OR, 5.646; 95% CI, 1.250–25.508; $P = 0.024$).

Correlation analysis

As illustrated in Table 5 and Figure 3, the serum Cys C level was positively correlated with age and creatinine in all patients ($r = 0.294$, $P < 0.001$ and $r = 0.626$, $P < 0.001$, respectively), while it was negatively correlated with the eGFR ($r = -0.830$, $P < 0.001$).

Discussion

In the present study, the serum Cys C level was significantly higher in advanced-age patients with ACS regardless of renal function. Furthermore, the number of stenotic coronary arteries was associated with the expression level of Cys C in serum. Moreover, the multivariate logistic regression analysis indicated that an increased serum Cys C concentration could be an independent variable for ACS and the number of stenotic coronary arteries after adjustment. The data also showed that the serum Cys C concentration was significantly and positively correlated with the creatinine level but negatively correlated with the eGFR. Thus, measurement of the serum Cys C level could be useful for identifying individuals at risk of ACS and predicting the severity of ACS in patients of advanced age.

ACS is the leading cause of death and disability worldwide, and its prevalence increases with age.[1,15] ACS is induced by the rupture of an atherosclerotic plaque and subsequent luminal thrombosis.[16] The diagnostic approach to suspected ACS includes three major components: assessment of the clinical profile or symptoms, electrocardiographic examination, and measurement of cardiac biomarkers (especially troponins). However, these three evaluations can be difficult to perform in patients of advanced age, hindering the timely diagnosis of ACS. Cardiac troponins are significantly more often elevated in older patients in the absence of ACS because of impaired renal function, arrhythmias, and diastolic and/or systolic heart failure. Therefore, exploring a new potential biomarker to assist in the diagnosis of ACS in patients of advanced age is very important.

Cys C is an endogenous cysteine proteinase inhibitor produced by nucleated cells. Under conditions of ischemia and hypoxia, cardiomyocytes produce Cys C and release it into the blood.[17] Studies have demonstrated that a high Cys C concentration is directly related to both inflammation and atherosclerosis.[18] Therefore, this marker could be associated with the development and progression of atheroma plaques.[19] Because of its low molecular weight, Cys C is freely filtrated by the glomeruli and reabsorbed by the renal tubules and less strongly influenced by sex, age, and muscle mass. Therefore, Cys C has been proposed as an early and sensible marker of glomerular function and a better marker for detection of mild renal impairment.[20] Previous clinical studies have

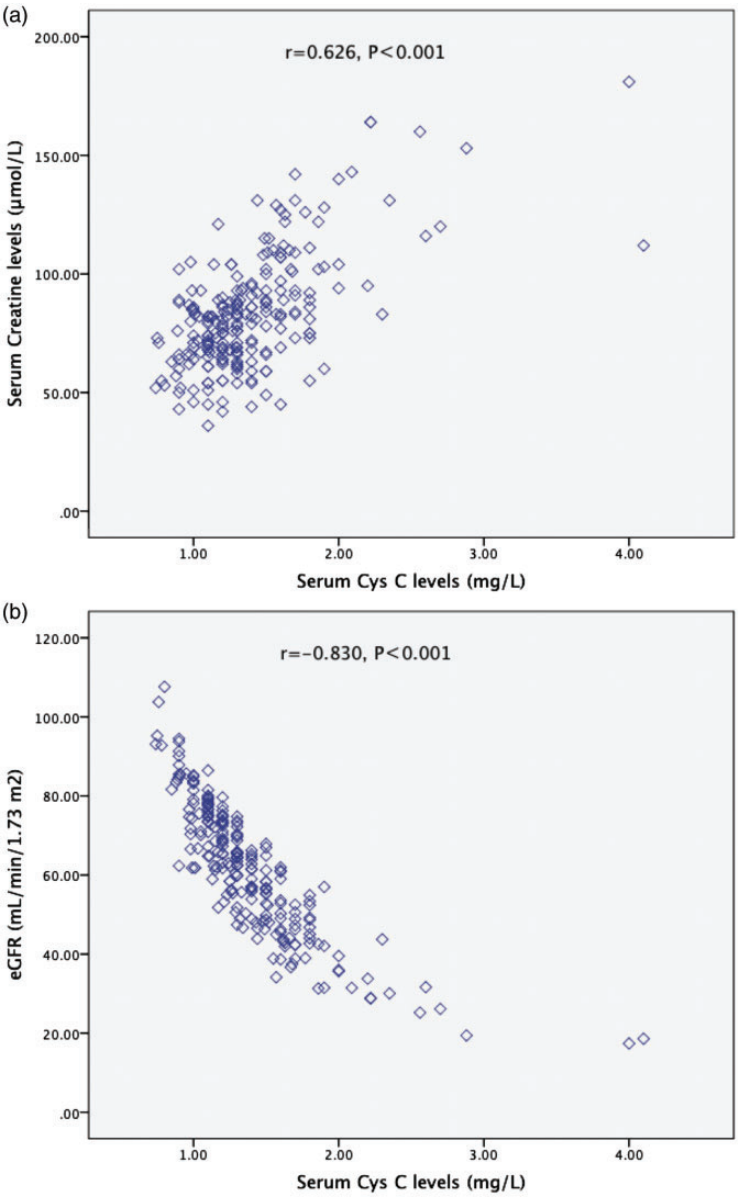

Figure 3. (a) Correlation between serum levels of Cys C and creatinine. (b) Correlation between serum Cys C level and eGFR. Cys C, cystatin C; eGFR, estimated glomerular filtration rate.

confirmed that Cys C is a predictor of cardiovascular events in patients with impaired renal function.[21–23] In the current study, we assessed the association between Cys C and ACS in patients of advanced age regardless of their kidney function to avoid the well-known effect of overt renal insufficiency on coronary artery disease. Our study demonstrated that the serum level of Cys C, but not the serum creatinine level or eGFR, was

independently associated with the presence of ACS, although the serum Cys C level was positively correlated with the creatinine level and negatively correlated with the eGFR.

In part, the results of this study are consistent with some previous studies that demonstrated that a high Cys C level is a risk factor for ACS (OR, 1.002; 95% CI, 1.00029–1.004; $P = 0.02$) and ST-segment elevated myocardial infarction (OR, 1.0009; 95% CI, 0.99–1.002; $P = 0.04$) and that it could play an important role in the early diagnosis and prevention of adverse cardiovascular events.[24] Similar observations were made by Alhusseiny et al.,[25] who found that the serum Cys C level in patients with AMI was significantly increased at the time of the admission (1296.0 ± 431.8 ng/mL) and discharge (1244.6 ± 482 ng/mL) compared with the reference level in healthy subjects (0.7 ± 0.2 ng/mL). Lodh et al.[26] also found that the serum Cys C level was significantly higher in patients with ACS than in healthy controls. However, few studies have focused on patients of advanced age with ACS. The mean age of the patients with ACS in the present study was 72.8 years (interquartile range, 66–79 years). This mean age is higher than that in previously published research. In addition, when the association between the Cys C level and severity of ACS was evaluated, we found a positive relationship between the serum cystatin C level and the number of diseased vessels.

The present study has several limitations. First, the findings of this study only suggest an association between the serum Cys C level and ACS. Because of the limited sample sizes in the subgroups, we did not further explore the relationships between the serum Cys C level and the types of ACS (unstable angina, non-ST-segment elevation myocardial infarction, and ST-segment elevated myocardial infarction). Second, angiographic information was limited to the number of stenotic coronary arteries. To ensure consistence with clinical practice worldwide, experienced angiographers assessed coronary stenosis by visual estimation rather than by quantitative evaluation. Third, this was a single-center study with a relatively small number of patients. The sample size should be increased to enhance the power of the statistical analysis. Thus, further studies with a larger sample size are needed to confirm the results and to validate the clinical implication of serum Cys C as a diagnostic biomarker of ACS.

Conclusions

In conclusion, our findings demonstrate that a high serum Cys C level is independently associated with ACS and the quantity of stenotic coronary arteries in patients of advanced age regardless of renal function. Thus, serum Cys C may be a potential biomarker of ACS. Measurement of the serum Cys C level might be useful for identifying individuals at risk of ACS and predicting the quantity of stenotic coronary arteries in patients of advanced age.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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