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ORIGINAL ARTICLE

Cystatin-C as a predictor for major adverse cardiac events in patients with acute coronary syndrome

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KEYWORDS

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Abstract Cystatin-C (CYS-C) has emerged as a highly sensitive marker of even a mildly impaired glomerular filtration rate. Experimental studies have suggested that its inhibitory effects on cysteine protease may help to prevent plaque destabilisation. We aimed to evaluate the predictive value of CYS-C level for major adverse cardiac events (MACE) including mortality and morbidity during the hospital stay and 3-month follow-up period.

Methods: Seventy-five patients were hospitalised for acute coronary syndrome (ACS). Another control group consisted of patients who were presented with chest pain but no evidence of ischaemic heart disease documented by laboratory markers and angiography. Serum CYS-C levels were measured during the first 24 h of admission. Patients with an abnormal creatinine-derived glomerular filtration rate (GFR) were excluded. Coronary angiography was performed for the entire study population.

Results: In group I, the mean CYS-C was 1.836 ± 0.782 mg/l vs. 0.991 ± 0.163 mg/l in the control group ($P < 0.000$). Cystatin-C showed a moderate correlation with total cholesterol in group I ($r = 0.5$) and with LDL ($r = 0.367$, $P < 0.01$). CYS-C showed a moderate positive correlation with the number of diseased vessels ($r = 0.419$, $P < 0.01$) and a moderate significant positive correlation with Killip classification ($r = 0.349$). Smoking was the only predictor associated with a high CYS-C level in the multivariate regression analysis ($P = 0.033$). CYS-C was an independent predictor of MACE and heart failure complications either in-hospital or during follow-up ($P < 0.05$).

Conclusions: CYS-C could be a useful marker for diagnosing coronary arteriosclerosis. An elevated CYS-C in patients with ACS is an independent predictor of MACE either in-hospital or during follow-up.

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1. Introduction

Cystatin-C (CYS-C) has emerged as a highly sensitive marker of even a mildly impaired glomerular filtration rate (GFR). Serum creatinine, an accepted marker of GFR, is limited by multiple factors including age, gender, muscle mass, physical activity and diet.[1] CYS-C is freely filtered by the glomerulus and is not secreted or reabsorbed by the tubular epithelial cells of kidneys because of its small size of 13 kilo Daltons (kDa). CYS-C is a member of the cystatin super family of endogenous cysteine protease inhibitors and is produced by all nucleated human cells. Notably, experimental studies have suggested that its inhibitory effects on cysteine protease might help prevent plaque destabilisation.[2]

Studies have demonstrated that elevated serum CYS-C is associated with a risk of cardiovascular events in asymptomatic elderly subjects and patients with heart failure or in acute coronary syndrome. However, the reasons for these associations are not fully understood.[3–8]

In this study, we assessed the prognostic value of CYS-C as a predictor of major adverse cardiac events (MACE) in patients with acute coronary syndrome in regards to mortality, heart failure, electrical or mechanical complications and the occurrence of ischaemic events during the hospital stay and within the three months following discharge from the hospital.

2. Methods

This was a non-randomised controlled trial that was prospectively conducted on 75 patients with acute coronary syndrome (ACS) and an equal number of controls. Patients included in this study presented with ACS, including acute myocardial infarction (AMI), non-ST-elevation myocardial infarction (NSTEMI) and unstable angina according to the definition established by the Joint European Society of Cardiology/American College of Cardiology Committee 2007.[9–13]

The control group comprised of 75 patients who presented with chest pain, which later proved to be unrelated to ischaemic heart disease (IHD) by ECG, laboratory tests (creatine kinase myocardial band fraction CK-MB and troponin I) and coronary angiography.

The exclusion criteria consisted of patients with neoplasia of any organ, pregnancy, thyroid dysfunction, altered mental status, cardiogenic shock, chronic renal failure, on haemodialysis, impaired kidney function on admission, suspected aortic dissection, old myocardial infarction (MI) within 6 months, currently receiving corticosteroid therapy and those who refused to participate.

Both groups were subjected to a complete history and thorough clinical examination assessing the type of ACS, Killip class to determine the degree of heart failure at the time of hospitalisation, blood pressure and heart rate.[14] Body weight (kg), height (cm), body mass index (kg/m^2) and waist circumference (cm) were recorded on admission.

Laboratory investigation included a complete blood count, and random blood glucose, urea and creatinine,[15] total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol tests. Cardiac enzymes, including troponin I, creatine kinase (CK), CK-MB and lactic dehydrogenase (LDH), were measured. Laboratory tests, which were performed on admission, were repeated three times on the subsequent three days. The estimated glomerular filtration rate (GFR) (millilitres per minute per 1.73 square metres) was calculated using the simplified Modification of Diet in Renal Disease (MDRD) equation:

$$86.3 \times (\text{serum creatinine}\,[\text{mg/dl}]) - 1.154 \times (\text{age}\,[\text{years}]) - 0.203 \times (0.742 \text{ if female})$$[16].

The estimated creatinine clearance (millilitres per minute) was calculated using the Cochcroft–Gault equation:

$$(140 \text{ age}\,[\text{years}]) \times \text{body weight}\,[\text{kg}] \times (0.85 \text{ if female})/(72 \times \text{serum creatinine}\,[\text{mg/dl}])$$[16].

Human CYS-C ELISA is a sandwich enzyme immunoassay for the quantitative measurement of human CYS-C in serum, plasma, cerebrospinal fluid and tissue culture medium. The surface of the wells in the microtitration plate is coated with polyclonal, anti-human, CYS-C-specific antibody, which agglutinates with serum CYS-C, and the concentration is determined according to colour changes. Serum CYS-C samples were drawn within the first 24 h of admission after at least 8 h of fasting. The normal serum CYS-C concentration reference in adult, using the nephelometric method, is 0.51–1.21 mg/l.[17–19]

All populations were evaluated by transthoracic echocardiography and diagnostic coronary angiography, which were interpreted by two independent experts in the coronary interventions. Maximal medical therapy and invasive management were given to all patients, and additional investigations performed during the patient's hospital stay were based on the clinical decisions of the attending physician. All patients were followed up during the hospital stay and for three months after hospital discharge.

3. Statistical analyses

The data were coded and computed on a statistical package for Social Sciences SPSS version 17 for Windows. Continuous variables were evaluated using the *t*-test and categorical variables using χ^2. The Pearson correlation coefficient (r) was calculated to examine the strength and direction of the correlation between two variables. The correlation was weak if $r < 0.3$, moderate if $0.3 < r < 0.6$ and strong if $r > 0.6$. A receiver operating characteristic curve (ROC) analysis was used to determine the optimal cutoff that provided the greatest sensitivity and specificity for the predicting variables. The results were considered to be significant if the area under the curve (AUC) $> 0.5\,\text{cm}^2$ and $P < 0.05$. Binary logistic multivariate regression analysis explored how much variation in the dependent variable could be explained by variability in two or more independent variables. $P < 0.05$ was considered to be significant.

4. Results

This study was conducted from January to October 2010. We divided the study population into two groups. Group I included patients with ACS, and group II included control patients. The demographic data of the studied populations are presented in Table 1.

CYS-C level ranged from 0.775 to 4.216 mg/l with a mean of 1.836 ± 0.782 in group I vs. 0.666–1.660 mg/l with a mean of 0.991 ± 0.163 mg/l in the control group ($P = 0.000$). All laboratory results are shown in Table 2.

Transthoracic echocardiography showed a mean EF of 51.7 ± 11.3%, LVEDD of 5.5 ± 0.9, and LVESD of 3.7 ± 0.9 in group I vs. 62.1 ± 7.5, 4.6 ± 0.7 and 3.00 ± 0.6 in the control group, respectively. Seventy-one (94.6%) patients in group I had significant regional wall motion abnormalities (RWMA), whereas there was no RWMA in the control group. All echocardiographic findings in group I were statistically significant compared with the control group ($P < 0.001$).

CYS-C showed a moderate positive correlation with the number of diseased vessels ($r = 0.419$, $P < 0.01$) and a moderate positive correlation with Killip classification ($r = 0.349$, $P < 0.01$). However, CYS-C showed a weak negative correlation ($r = -0.066$) with peak troponin I ($P > 0.05$) (Tables 3 and 4). There was a weak correlation between CYS-C and the degree of left main artery stenosis ($r = 0.265$, $P = 0.002$). Additionally, there was a moderate significant correlation to the degree of circumflex artery stenosis ($r = 0.312$) and to diagonal branch stenosis ($r = 0.517$), but there was a weak correlation in left anterior descending artery, obtuse marginal branch and right coronary artery stenosis without any statistical significance ($P > 0.05$) (Table 5).

The patients in group I were further subdivided according to the type of acute coronary syndrome into 19 patients (25.3%) with unstable angina, 12 patients (16%) with NSTEMI and 44 patients (58.6%) with STEMI. Comparing the CYS-C level among these three groups, CYS-C level ranged from 0.775 to 4.108 mg/l with a mean of 1.634 ± 0.992.4 mg/l in unstable angina patients. In the NSTEMI group, it ranged from 1.748 to 4.216 mg/l (mean 2.218 ± 0.659 mg/l), and in the STEMI group, it ranged from 0.966 to 3.823 mg/l (mean 1.805 ± 0.705 mg/l) with no significant difference between these groups ($P = 0.129$). Additionally, we subdivided group I into two groups according to the CYS-C level, using a cutoff point of 1.141 mg/l; this point had the maximum sensitivity and specificity. Subgroup A consisted of 27 patients (36%) with a CYS-C level below 1.141 mg/l, and subgroup B consisted of 48 patients (64%) with a CYS-C level above 1.141 mg/l. We found a statistically significant difference in CYS-C level between subgroup B compared with subgroup A ($P < 0.01$). Table 6 illustrates that patients in subgroup B had a significantly higher number of diseased vessels compared with patients in subgroup A ($P = 0.005$). Additionally, subgroup A showed a significantly lower number of patients who presented with thrombus in the culprit lesion (seven patients (25%) vs. 25 patients (52%) in subgroup B, $P = 0.028$). Patients in subgroup A were only Killip class 1–2, whereas subgroup B presented with Killip class 1–4 ($P = 0.045$) (Table 7). Comparing patients regarding the number and location of the lesions and CYS-C level showed no significant differences between lesion site and number between subgroups A and B ($P > 0.05$) (Table 8).

According to the total incidence of MACE during hospital stay, subgroup B showed a significantly higher incidence of complications (43 patients (89%) vs. 18 patients (66%) in subgroup A, $P = 0.014$). Mechanical complications were significantly higher in subgroup B compared with subgroup A (37 patients (77%) vs. 11 patients (40%), $P = 0.002$). Additionally, subgroup B had a significantly higher incidence of heart failure (30 patients (62%) vs. three patients (11%) in subgroup A, $P = 0.000$). However, regarding other complications in subgroup A, it was found that electrical complications occurred in 11 patients (40%) and re-infarction complications occurred in one patient (3.7%) vs. 27 (56%) and seven (14%) patients, respectively, in subgroup B, with no statistically significant differences ($P > 0.05$) (Table 9).

Concerning MACE during the follow-up according to CYS-C level, subgroup B showed a significantly higher incidence of total MACE, which occurred in 38 (92.7%), whereas MACE occurred in 18 patients (66.7%) in subgroup A ($P = 0.006$) (Table 10). Subgroup B showed a significantly higher percentage of total mortality (18 patients (37%)) compared with subgroup A, which had no mortality ($P < 0.05$) (Table 11).

In a multivariate regression analysis between the prevalence of high CYS-C and traditional risk factors for IHD, including hypertension (HTN), diabetes mellitus (DM), smoking and low levels of HDL cholesterol, we found that if all risk factors were present, the patient had a high CYS-C level. The only risk

Table 1 Demographic data of the study population.

	Group I		Group II		*P*-value
	Range	Mean ± SD	Range	Mean ± SD	
Gender (male)	39	52%	40	53.3%	0.875
Age	22–70	50.3 ± 8.1	29-69	49.09 ± 8.1	0.367
DM[a]	28	37.3%	30	40.0%	0.737
HTN[a]	34	45.3%	33	44.0%	0.870
Smoker	39	52.0%	33	44.0%	0.327
Dyslipidaemia	51	68%	26	34.7%	0.000
High level of LDL	46	61.3%	25	33.3%	0.001
Low level of HDL	38	50.7%	9	12.0%	0.000
CVS[a]	3	4%	5	6.7%	0.467
Weight (kg)	60–115	78.7 ± 10.3	58–97	79.5 ± 10.2	0.624
Height (cm)	152–190	174.7 ± 10.2	156–188	174.2 ± 8.9	0.747
BMI (kg/m^2)	19–41	25.1 ± 3.8	20.1–34.8	25.9 ± 2.6	0.138
Waist circumference (cm)	59–106	80.6 ± 10.08	55–100	82.9 ± 9.9	0.160

[a] DM: diabetes mellitus, HTN: hypertension, CVS: cerebrovascular stroke.

Table 2 Laboratory investigations in groups I and II.

	Group I		Group II		*P*-value
	Range	Mean ± SD	Range	Mean ± SD	
RBS (mg/dl)[a]	85–370	158.7 ± 65.7	65–217	108.1 ± 27.2	0.000
HB (g/dl)[a]	11.5–16.1	13.3 ± 0.9	11.1–16.9	13.4 ± 1.4	0.195
HCT (%)[a]	27–47	39.9 ± 3.6	32–52	41.4 ± 6.6	0.081
Peak troponin I (IU/L)	0.01–7.00	0.7 ± 1.1	0.01-0.31	0.02 ± 0.03	0.000
CK-MB (U/L) on admission[a]	7–250	51.7 ± 52.1	5–19	11.7 ± 4.1	0.000
Total cholesterol (g/dl)	120–337	209.4 ± 39.9	120–300	183.3 ± 33.3	0.000
LDL cholesterol (g/dl)	49–233	116.7 ± 36.6	45–170	92.5 ± 27.9	0.000
HDL cholesterol (g/dl)	24–99	45.05 ± 13.3	45–170	57.97 ± 14.7	0.000
Serum cystatin-C (mg/l)	0.775–4.216	1.836 ± 0.782	0.666–1.660	0.991 ± 0. 163	0.000
Creatinine (mg/dl) on admission	0.5–1.2	0.89 ± 0.12	0.58–1.3	0.87 ± 0.14	0.209
UREA (mg/dl) on admission	16–130	38.9 ± 21.07	22–56	36.6 ± 8.03	0.375
Creatinine clearance on admission (ml/min)	75–133	101.4 ± 15.5	85–142	103.8 ± 11.2	0.290
GFR (ml/min/1.73 m^2) on admission[a]	67.2–121	91.8 ± 13.9	82–126	93.5 ± 7.6	0.139

[a] RBS: random blood sugar, HB: haemoglobin, HCT: haematocrit, CK-MB: creatine kinase myocardial band fraction, GFR: glomerular filtration rate.

Table 3 Correlation of CYS-C in group I with number of diseased vessels, peak troponin and Killip class.

	Serum cystatin-C	
	r	*P*-value
Number of diseased vessels	0.419	< 0.001
Peak troponin I level (IU/L)	−0.066	0.575
Killip class on admission	0.349	0.002

Table 5 Correlation of CYS-C with the degree of stenosis in group I.

	Serum cystatin-C	
	r	*P*-value
LM stenosis (%)	0.265	0.022
LAD stenosis (%)[a]	0.190	0.103
D stenosis (%)[a]	0.517	0.000
CX stenosis (%)[a]	0.312	0.006
OM stenosis (%)[a]	−0.216	0.063
RCA stenosis (%)[a]	0.015	0.897

[a] LM: left main artery, LAD: left anterior descending artery, D: diagonal artery, CX: circumflex artery, OM: obtuse marginal artery, RCA: right coronary artery.

factor that correlated significantly to CYS-C was smoking ($P < 0.05$). In contrast, in a multivariate regression analysis between the prevalence of high CYS-C and other traditional risk factors, including DM, HTN, smoking and high LDL cholesterol, if all risk factors were present, the patient had a high CYS-C level. The only independent risk factor was a high LDL-cholesterol level ($P < 0.01$).

In a multivariate regression analysis to predict the occurrence of MACE in subgroup B, we found that if patients with MACE had a high CYS-C, DM, HTN and low HDL cholesterol, the only parameter that correlated with MACE was a high CYS-C level ($P < 0.05$). Therefore, a high CYS-C is an independent risk factor for MACE. Additionally, in a multivariate regression analysis concerning the occurrence of heart failure complications in-hospital, a high CYS-C level was significantly associated with the occurrence of heart failure ($P < 0.05$), and a low HDL cholesterol had no significance.

Table 4 Correlation of CYS-C in group I and the control group with age, lipid profile, ejection fraction, creatinine, creatinine clearance and GFR.

	Correlation of cystatin-C			
	Cystatin-C in group I		Cystatin-C in group II	
	r	P-value	r	P-value
Age	0.252	0.029	0.360	0.002
Total cholesterol	0.511	0.000	−0.05	0.668
LDL cholesterol	0.367	0.001	0.02	0.868
HDL cholesterol	−0.06	0.654	−0.177	0.128
Triglycerides	0.124	0.290	−0.093	0.427
Ejection fraction %	−0.241	0.037	−0.053	0.649
Creatinine	0.164	0.161	0.165	0.157
Creatinine clearance	−0.402	0.000	−0.313	0.006
MDRD GFR[a]	−0.536	0.000	−0.330	0.004

[a] MDRD GFR: glomerular filtration rate using the simplified Modification of Diet in Renal Disease (MDRD) equation.

Table 6 Patient subgroups according to CYS-C level, which illustrate descriptive data in both subgroup.

	Subgroup A (Mean ± SD)	Subgroup B (Mean ± SD)	*P*-value
Cystatin-C			
Range	0.775–1.141	1.142–4.216	
Mean ± SD	1.042 ± 0.067	2.282.5 ± 0.63	0.000
Total cholesterol	184.2 ± 32.7	223.6 ± 36.7	0.000
LDL cholesterol	98.9 ± 28.1	126.6 ± 37.3	0.001
HDL cholesterol	46.7 ± 10.5	44.1 ± 14.7	0.425
Triglyceride	156.2 ± 50.7	161.7 ± 41.7	0.611
EF %[a]	54.9 ± 10.6	49.9 ± 11.3	0.067
LVEDD[a]	5.4 ± 0.6	5.5 ± 1.1	0.368
LVESD[a]	3.6 ± 0.8	3.7 ± 1.1	0.505
Number of diseased vessels	1.7 ± 0.775	2.2 ± 0.8	0.005
Thrombus in the culprit vessel	7 (25.7%)	25 (52.1%)	0.028

[a] EF: ejection fraction, LVEDD: left ventricular end-diastolic diameter, LVESD: left ventricular end-systolic diameter.

Table 7 Killip classification in subgroups A and B.

	Killip class on admission								*P*-value
	Class 1		Class 2		Class 3		Class 4		
Subgroup A	18	66.7%	9	33.3%	0	0%	0	0%	0.045
Subgroup B	17	35.4%	26	54.2%	4	8.3%	1	2.1%	

A receiver operator characteristic (ROC) curve was used to determine the sensitivity and specificity for predicting the in-hospital occurrence of MACE. The CYS-C sensitivity was 85.2% and specificity 71.4% at a serum value greater than 1.041 mg/l (Fig. 1). Additionally, CYS-C sensitivity was 100%, and specificity was 77.2% at a serum level greater than 1.041 mg/ml for predicting in-hospital mortality in patients with ACS (Fig. 2).

5. Discussion

CYS-C is a cysteine protease inhibitor that is believed to play an essential role in tissue remodelling. Low levels of cystatin-C in atherosclerotic plaques could be a risk factor for ischaemic events, as immunostaining of CYS-C has shown low expression of this protein in atherosclerotic plaques.[20,21]

Our study found a significantly higher level of cardiac enzymes, CYS-C and all parameters of the lipid profile, including total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides, in group I compared with the control group ($P < 0.05$). This result was consistent with those of Sekizuka et al.,[22] who investigated 88 outpatients suspected of having ischaemic heart disease. Serum CYS-C was measured within 3 months before coronary angiography, and they concluded that CYS-C itself could possibly be used to screen for coronary artery disease in patients with suspected coronary arteriosclerosis. Eriksson et al.[23] have stated that high cholesterol or LDL-cholesterol levels are risk factors of IHD, but CYS-C reflects more precisely the presence or absence of coronary artery disease.

Our results are also consistent with those of Luc et al.,[24] who confirmed the association of plasma CYS-C with the incidence of myocardial infarction, coronary death and angina in 9756 patients in the case-control PRIME study during the 5-year follow-up. In their study, creatinine and GFR were not different between the cases and the controls; whereas total cholesterol, LDL cholesterol and triglycerides were significantly higher and HDL cholesterol was lower in the experimental group. Additionally, the prevalence of smoking, HTN and DM was significantly higher in these patients. In contrast, our study showed no difference between the experimental and control groups regarding DM, HTN and smoking. Thus,

Table 8 Distribution of significant lesions in subgroups A and B.

	Lesion site and number														Total lesions (Mean ± SD)
	LM		LAD				CX		OM		RCA				
	One lesion		One lesion		Two lesions		One lesion		One lesion		One lesion		Two lesions		
Subgroup A	0	0%	10	37%	1	3.7%	1	3.7%	4	14.8%	8	29.6%	2	7.4%	1.48 ± 0.72
Subgroup B	4	8.3%	25	52.1%	2	4.2%	8	16.7%	5	10.4%	7	14.6%	0	0%	1.66 ± 0.75
P-value	0.123	0.430	0.097	0.574	0.36	0.627									

Table 9 Incidence of in-hospital MACE in subgroups A and B.

	Serum cystatin-C				*P*-value
	Subgroup A		Subgroup B		
Total MACE	18	66.7%	43	89.6%	0.014
Mechanical complications	11	40.7%	37	77.1%	0.002
Heart failure	3	11.1%	30	62.5%	0.000
Electrical complications	11	40.7%	27	56.3%	0.197
Re-infarction	1	3.7%	7	14.6%	0.143

Table 10 Incidence of re-hospitalisation and MACE in both subgroups during the follow-up period.

	Serum cystatin-C				*P*-value
	Subgroup A		Subgroup B		
Total MACE[a]	18	66.7%	38	92.7%	0.006
Heart failure	13	48.1%	38	79.2%	0.006
Electrical complications	11	40.7%	32	66.7%	0.029
Ischaemic complications	5	18.5%	21	43.8%	0.028
Total re-hospitalisations	2	7.4%	35	72.9%	0.000

[a] MACE: major adverse cardiac events.

Table 11 Total survival and death either in-hospital or during the follow-up period.

Outcomes	Serum cystatin-C				*P*-value
	Subgroup A		Subgroup B		
Total survival	27	100.0%	30	62.5%	0.000
Total mortality	0	0%	18	37.5%	
Hospital mortality	0	0%	8	16.7%	0.025
Mortality during the follow-up period	0	0%	10	20.8%	0.011

it is apparent that risk prediction models relying on traditional risk factors account for only approximately half of the variability in coronary heart disease risk.[22]

Animal studies have shown that the balance between protease activities and their inhibitors has an important role in vascular disease.[25] Luc et al.[24] have suggested that ischaemic events are the consequence of a relative insufficiency of protease inhibitors, such as CYS-C, in relation to increased expression of matrix proteinases in inflammatory atherosclerotic lesions, even if the inflammatory process increases serum CYS-C expression. Increased plasma levels in subjects with coronary ischaemic events could indicate an overexpression of CYS-C in cells outside of the arterial wall, which could create a balance with the decreased arterial atherosclerotic expression of CYS-C.

Koenig et al.[26] demonstrated a positive association between the incidence of coronary artery disease (CAD) and cystatin-C in a German cohort including 1033 subjects with ischaemic heart disease in secondary prevention of fatal and non-fatal cardiovascular events during 33 months of follow-up. Additionally, Kilic et al.[27] investigated 160 patients hospitalised with ACS and demonstrated that the admission serum CYS-C level was significantly associated with future cardiovascular complications and mortality during 12 months of follow-up.

In our study, there was no significant difference between serum CYS-C among ACS patients, including STEMI, NSTEMI or unstable angina ($P > 0.05$), because all patients had the

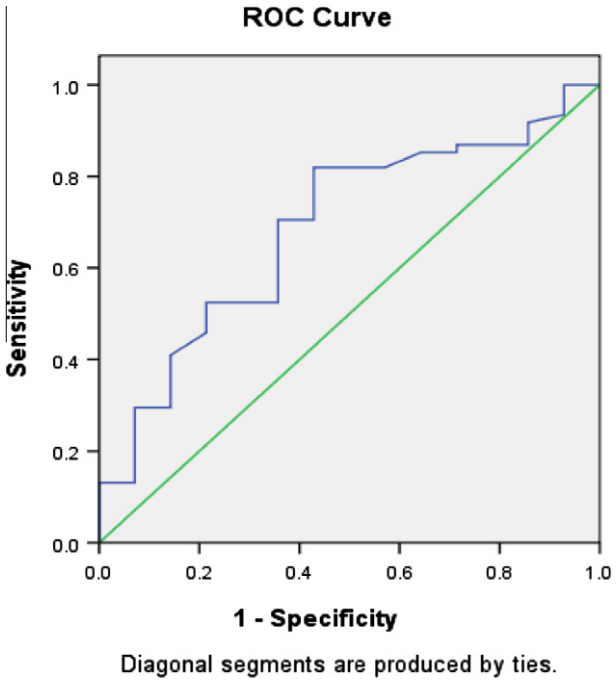

Figure 1 ROC curve to predict the sensitivity and specificity for the occurrence of in-hospital MACE. The area under the curve was 0.686 ($P = 0.031$).

same pathophysiology concerning plaque rupture or fissuring due to an imbalance between the synthesis and degradation of the fibrous cap leading to coronary events. This result was consistent with Akerblom et al.,[28] who also concluded that CYS-C level was not different between the types of ACS in 16,402 patients because CYS-C functions as an important inhibitor of proteases and a decrease in atherosclerotic plaques could have a role in the onset of ischaemic events.[20]

CYS-C is not only a parameter that measures kidney function, but it is also an independent cardiovascular risk factor. Mild or severe chronic renal insufficiency is associated with atherosclerosis and CYS-C is recognised as an accurate endogenous marker of the glomerular filtration rate that is probably superior to creatinine.[29–31] In our study, the higher CYS-C level in group I compared with the controls was not due to a decrease in GFR, as patients with renal impairment were excluded from the study. Additionally, Luc et al.[24] concluded that a decreased glomerular filtration rate would not justify the higher CYS-C levels in patients with ACS compared with the controls.[24,32,33] Furthermore, Koening et al.[26] noted that CYS-C, independent of creatinine level or GFR, was associated with the risk of future coronary vascular disease in patients with CAD.

Our results showed that the CYS-C level tended to increase as the number of diseased arteries increased. This result was consistent with Sekizuka et al.,[22] who concluded that the CYS-C level tended to increase as the number of diseased arteries increased. Nicholls et al.[34] showed in their study that the association between CYS-C and CAD severity was independent of traditional risk factors, including diabetes, which is known to be a strong predictor of atherosclerotic burden.

In our results, we failed to demonstrate an association between serum CYS-C and the number of significant stenoses in coronary vessels. These results were consistent with those of Eriksson et al.,[23] who failed to demonstrate in young survivors of myocardial infarction an association between serum CYS-C and the number of stenoses in the diseased vessels.

Plasma CYS-C value may have a greater capacity to stratify patients at a high risk of cardiovascular complications during the first hours of hospitalisation compared with other methods of assessing renal function.[26] We found that an elevated CYS-C level was associated with a poorer cardiovascular prognosis. Nevertheless, our study patients had a normal glomerular filtration rate. When the patients were divided into two groups (CYS-C < 1.141 mg/l or $\geqslant 1.141$ mg/l), the incidence of MACE either in-hospital or during follow-up was significantly higher in patients with a high CYS-C, in addition to a worsening of Killip class on admission. Our results showed that a high serum CYS-C level was a risk factor for MACE or heart failure independent of traditional risk factors, such as low HDL cholesterol. These results are consistent with those of García Acuña et al.,[33] who indicated that an elevated serum CYS-C level predicted the development of heart failure, myocardial infarction and cardiovascular death in 203 patients hospitalised with high-risk ACS, independent of other classic risk factors either in-hospital or during a 6-month follow-up period. Sarnak et al.[6] observed that when patients were divided according to serum CYS-C, there were no significant differences in traditional risk factors, such as diabetes mellitus and disorders of lipid metabolism, which possibly accelerate the progression of arteriosclerosis. Jernberg et al.[7] claimed that serum CYS-C was independently associated with mortality in 726 NSTEMI population, but not with a risk of subsequent MI. Kilic et al.[27] proposed that in all of the study groups, including STEMI, NSTEMI and unstable angina, serum CYS-C was significantly higher in patients with MACE compared with patients without MACE. Additionally, Moran et al.[35] concluded that CYS-C can be a marker of heart failure, and its combination with N-terminal pro-B-type natriuretic peptide (Nt–Pro-BNP) was a better marker than CYS-C alone for predicting cardiovascular mortality, especially in elderly patients with heart failure.[36,37]

Shlipak et al.[3] demonstrated that an elevated serum CYS-C in 279 patients was associated with an increased risk of death, cardiovascular complications and incidence of heart failure in outpatients with chronic coronary disease. In this study, although appropriate invasive management and maximal medical therapy were given to all patients, the occurrence of MACE among patients with higher CYS-C levels could not be prevented. An elevated serum CYS-C level was associated with a significant incidence of death either in-hospital or during follow-up. CYS-C had the greatest sensitivity in predicting death, with 77% specificity. These data were consistent with those of Koenig et al.,[26] Jernberg et al.,[7] García Acuña et al.,[33] and Keller et al.,[8] who reported the prognostic value of CYS-C in predicting death in predominately male patients with stable CAD or ACS in a cohort of the Athero Gene study. Akerblom et al.[28] concluded that the CYS-C level contributes independently in predicting the risk of cardiovascular death or MI in NSTEMI and showed no difference in all types of ACS.

6. Conclusions

Elevated serum CYS-C in the first few hours of hospitalisation for ACS is an independent predictor of MACE, especially of

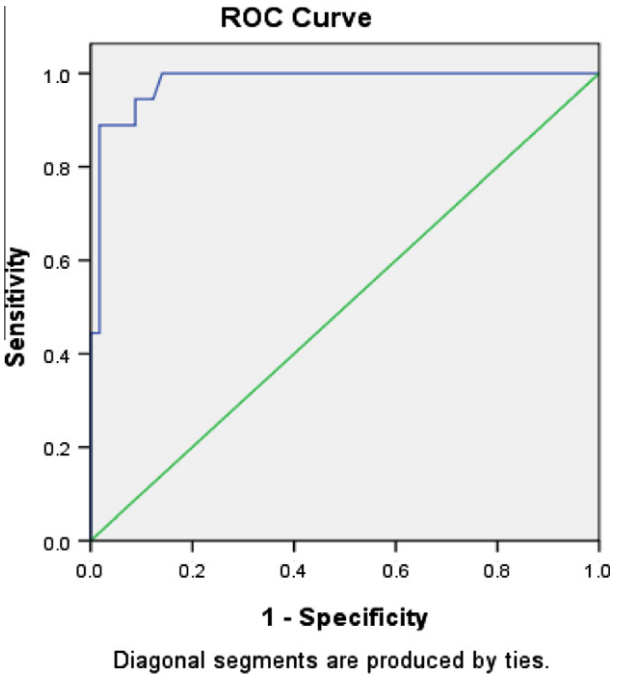

Figure 2 ROC curve to predict in-hospital mortality in patients with ACS. The area under the curve was 0.980 ($P = 0.000$).

heart failure, either in-hospital or during follow-up. High total cholesterol or LDL cholesterol and low HDL cholesterol are risk factors of IHD, but CYS-C could be a useful marker for diagnosing coronary arteriosclerosis. CYS-C was associated with the risk of future coronary vascular disease in patients with CHD, independent of serum creatinine or GFR. Serum CYS-C tended to increase as the number of diseased arteries increased.

7. Study limitations

The small sample size and the relatively short period of follow-up are the main limitations of this study. We aimed to investigate the role of CYS-C in ACS, so we excluded patients with renal impairment, although several studies have considered renal impairment as a risk factor for MACE. Further studies are needed to confirm the efficacy of CYS-C for predicting adverse outcomes.

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