



Predictive value of elevated cystatin C in patients undergoing primary angioplasty for ST-elevation myocardial infarction

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Abstract

Objectives: The prognostic value of cystatin C (CysC) has been documented in patients with acute coronary syndrome without ST-segment elevation. However, its value in acute ST-segment elevation myocardial infarction (STEMI) remains unclear. The aim of this study was to evaluate the prognostic value of CysC in patients with STEMI undergoing primary percutaneous coronary intervention (PCI).

Methods: We prospectively enrolled 475 consecutive STEMI patients (mean age 55.6 ± 12.4 years, 380 male, 95 female) undergoing primary PCI. The study population was divided into tertiles based on admission CysC values. The high CysC group ($n = 159$) was defined as a value in the third tertile (>1.12 mg/L), and the low CysC group ($n = 316$) included those patients with a value in the lower two tertiles (≤ 1.12 mg/L). Clinical characteristics and in-hospital and one-month outcomes of primary PCI were analyzed.

Results: The patients of the high CysC group were older (mean age 62.8 ± 13.1 vs. 52.3 ± 10.5 , $P < .001$). Higher in-hospital and 1-month cardiovascular mortality rates were observed in the high CysC group (9.4% vs. 1.6%, $P < .001$ and 14.5% vs. 2.2%, $P < .001$, respectively). In Cox multivariate analysis; a high admission CysC value (>1.12 mg/L) was found to be a powerful independent predictor of one-month cardiovascular mortality (odds ratio, 5.3; 95% confidence interval, 1.25–22.38; $P = .02$).

Conclusions: These results suggest that a high admission CysC level was associated with increased in-hospital and one-month cardiovascular mortality in patients with STEMI undergoing primary PCI.

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1. Introduction

Cystatin C (CysC) is a cysteine protease inhibitor that is produced at a constant rate in all nucleated cells and freely filtered by the glomeruli without secretion and subsequent tubular reabsorption [1]. Many studies have shown that CysC is more reliable in determining renal function than the serum creatinine level and creatinine-based estimated glomerular filtration rate (GFR) formulas [2,3]. The CysC level is not affected by body muscle mass or diet [4]. CysC is superior to creatinine and estimated GFR for determining cardiovascular events and end-stage renal disease in the general population, the elderly, and individuals with coronary artery disease [4–9]. CysC is also released from myocardial cells, and hypoxia increases its production. CysC modulates inflammatory response, phagocytic functions, and degradation of the extracellular matrix by regulation of protease activity [10]. These physiological characteristics of CysC explain its strong associations with the development of atherosclerotic processes and vulnerable atherosclerotic plaques [11]. The prognostic value of CysC has been documented in patients with acute coronary syndrome (ACS) without ST-segment elevation with respect to in-hospital outcomes and long-term prognosis. However, its value in acute ST-segment elevation myocardial infarction (STEMI) remains unclear, and a limited number of studies are currently available [12,13]. The aim of this study was to evaluate the prognostic value of CysC regarding in-hospital and one-month outcomes in patients with STEMI.

2. Methods

2.1. Patient population

In this prospective observational study, we included 510 consecutive patients with acute STEMI presenting at the Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Center, Training and Research Hospital, between December 2010 and May 2012. The study inclusion criteria were as follows: electrocardiography (ECG) revealing STEMI, which was defined as >30 minutes of continuous typical chest pain and ST-segment elevation ≥ 2 mm in 2 contiguous electrocardiography leads within 12 hours of symptom onset or for up to 18 hours if there was evidence of continuing ischemia or hemodynamic instability. We excluded 35 patients from our analysis because they had no indication of PCI (n = 10), were not suitable for PCI (n = 10), had missing or unavailable data about admission CysC values (n = 14), or experienced chronic renal failure requiring dialysis (n = 1). Therefore, the final study population consisted of 475 patients. The population was divided into tertiles based on admission CysC values. A high CysC group (n = 159) was defined as a value in the third tertile (>1.12 mg/L), and a low CysC group (n = 316) was set as a value in the lower two tertiles (≤ 1.12 mg/L).

All primary PCI procedures were performed in a single high-volume tertiary care center (>3000 PCI/year) by expert operators who carry out an average of >75 PCI/year. The study protocol was approved by the hospital's Ethics Committee.

2.2. Analysis of patient data

At admission, the patients' medical histories and a special questionnaire on lifestyle and risk factors were taken. Reperfusion time and door-to-balloon time were also recorded.

On admission, venous blood was obtained from all patients. CysC was measured using a Cobas 6000 (Roche, Germany) analyzer series module c 501 with the immunoturbidimetric method. A 12-lead ECG was recorded in each patient just after hospital admission, and the myocardial infarction type was also obtained from the ECGs. At 24 to 72 hours after revascularization, a transthoracic echocardiographic study was performed using a Vivid S5 prob 3S-RS (GE Healthcare) with a 1.7/3.4 MHz phased-array transducer, and the left ventricular ejection fraction (LVEF) was calculated using the biplane Simpson method [14].

The GFR was estimated by the simplified Modification of Diet in Renal Disease (MDRD) equation [15].

2.3. Coronary angiography, primary angioplasty, and stenting

All patients received a chewable 300 mg aspirin and clopidogrel (600 mg loading dosage) before coronary angiography. Angiographic data of the patients were evaluated from catheter laboratory records. Emergency coronary angiography and angioplasty were performed by the percutaneous femoral approach. A nonionic, low-osmolality contrast media was used in all patients. The artery that was presumed to be unobstructed was injected first. Blood flow in the infarct-related artery (IRA) was graded according to the Thrombolysis in Myocardial Infarction classification [16]. Heparin (100 IU/kg) was administered when the coronary anatomy was first defined.

After visualizing the left and right coronary arteries, 2.5 μ g of nitrate was selectively injected into the IRA to rule out a possible coronary spasm. An angiographic evaluation was made by visual assessment. Primary angioplasty (including balloon angioplasty and/or stent implantation) was performed only for IRA according to lesion type. For each procedure, interventional success at the acute phase was defined as reducing to <30% of obstruction and stenosis of the IRA with Thrombolysis in Myocardial Infarction 3 flow just after primary angioplasty. After angioplasty, all patients were admitted to the coronary care unit, where 100 mg aspirin and 75 mg clopidogrel were continued in all patients. The use of glycoprotein IIb/IIIa inhibitors was left to the discretion of the operator.

2.4. Definition

Reperfusion time was measured as the time from symptom onset until coronary reperfusion was obtained with balloon inflation. The door-to balloon time was defined as the time between hospital admission and balloon inflation. Patients were evaluated according to the Killip clinical examination classification [17]. Advanced heart failure was defined as New York Heart Association classification ≥ 3 . Anemia was set as a baseline hemoglobin concentration < 13 mg/dL in males and < 12 mg/dL in females. Renal failure was defined as a GFR < 60 mL/min per 1.73 m², which was estimated by the MDRD equation [15]. Patients with diabetes mellitus (DM) were determined to be those with documented DM currently using either oral hypoglycemic agents or insulin treatment at admission. Cardiovascular mortality was defined as unexplained sudden death, death due to acute STEMI, heart failure, or arrhythmia. We set the repeat target vessel revascularization (TVR) as the need for PCI or coronary surgery because of restenosis or reocclusion of the IRA. Reinfarction was described as an elevation of serum creatinine kinase-MB enzyme levels at least 2 times of the upper limit of normal and ST-segment re-elevations.

2.5. Follow-up

Follow-up data were obtained from hospital records or by interviewing (directly or by telephone) patients, their families, or their personal physicians. Major adverse cardiac events (MACE) were defined as cardiovascular mortality, reinfarction, or repeat TVR (percutaneous or surgical).

2.6. Statistical analysis

Quantitative variables were expressed as mean value \pm SD, and qualitative variables were shown as a percentage (%). The comparison of parametric values between the two

groups was performed using a two-tailed Student's *t* test. Categorical variables were compared by the likelihood-ratio χ^2 test or the Fisher's exact test. A backward stepwise multivariate logistic regression analysis, which included variables with $P < .1$, was performed to identify independent predictors of one-month cardiovascular mortality. Age, female sex, DM, hypertension, currently smoking, CysC > 1.12 mg/L, Killip class > 1 , anemia at admission, renal failure, three-vessel disease, unsuccessful procedure, LVEF $< 40\%$, tirofiban usage, and creatinine > 1.5 mg/dL were entered into the model. A $P < .05$ was considered statistically significant. All statistical studies were carried out with the Statistical Package for the Social Sciences (SPSS) software program (version 15.0, SPSS, Chicago, Illinois, USA).

3. Results

3.1. Baseline characteristics

The baseline characteristics are listed in Table 1. The baseline CysC level of the study population was 1.1 ± 0.4 mg/L (range: 0.35 to 6.9). The high CysC group was older than the low CysC group (mean age 62.8 ± 13.1 vs. 52.3 ± 10.5 , $P < .001$). Compared to the low CysC group, DM, hypertension (HT), myocardial infarction (MI) history and higher Killip class at admission were more prevalent in the high CysC group. Anterior MI and female gender were not statistically different between the 2 groups. However, being a current smoker was more frequent in the low CysC group patients.

3.2. Laboratory findings

Table 2 lists the patients' laboratory data. Baseline GFR values were lower in the high CysC group. Baseline blood creatinine and glucose values were higher in the high CysC group (1.14 ± 0.48 vs. 0.84 ± 0.16 , mg/dL, $P < .001$; $183.7 \pm$

Table 1 Baseline characteristics of study patients

Variables	CysC ≤ 1.12 (n = 316)	CysC > 1.12 (n = 159)	P
Age, years (SD)	52.3 ± 10.5	62.8 ± 13.1	$< .001$
Age > 70 years, n (%)	18 (5.7)	52 (32.7)	$< .001$
Female gender, n (%)	56 (17.7)	39 (24.5)	.07
DM, n (%)	52 (16.4)	42 (26.4)	.007
Hypertension, n (%)	93 (29.4)	71 (44.7)	.001
By-pass history, n (%)	6 (1.9)	4 (2.5)	.63
PCI history, n (%)	35 (11.1)	29 (18.2)	.02
MI history, n (%)	43 (13.6)	34 (21.3)	.03
Current smoker, n (%)	249 (78.8)	95 (59.7)	$< .001$
Anterior MI, n (%)	146 (46.2)	60 (37.7)	.07
Killip class > 1 n (%)	19 (6)	30 (18.9)	.001
Reperfusion time, min (SD)	246.7 ± 143.8	250.3 ± 147.6	.8
Door-to-balloon time, min (SD)	41.2 ± 15.8	43.2 ± 18.6	.3

Table 2 Laboratory Findings and angiographic and procedural characteristics of patients

Variables	CysC ≤ 1.12 (n = 316)	CysC > 1.12 (n = 159)	P
Baseline creatinine, mg/dL (SD)	0.84 ± 0.16	1.14 ± 0.48	<.001
Baseline glucose, mg/dL (SD)	160.5 ± 66.5	183.7 ± 103.7	.004
Anemia at admission, n (%)	27 (8.5)	35(22)	<.001
Baseline hemoglobin, g/dL (SD)	15 ± 7.1	13.9 ± 2.9	.05
Baseline GFR, mL/min per 1.73 m ² (SD)	98.1 ± 22.8	70.6 ± 24.3	<.001
Renal failure	2(0.6)	46 (28.9)	<.001
Peak CK-MB, IU/L (SD)	140.7 ± 135.5	149.1 ± 140.6	.5
Total-cholesterol, mg/dL (SD)	199.6 ± 44	191.9 ± 51.9	.1
LDL-cholesterol, mg/dL (SD)	135 ± 34.9	126.2 ± 38.9	.01
HDL-cholesterol, mg/dL (SD)	40.8 ± 9.9	42.1 ± 11.1	.26
Triglyceride, mg/dL (SD)	126.1 ± 85.2	130.1 ± 90.1	.72
CysC, mg/L (SD)	0.92 ± 0.12	1.4 ± 0.42	<.001
Culprit lesion			.59
LMCA, n (%)	0 (0)	0 (0)	
LAD, n (%)	149 (47.1)	64 (40.2)	
CX, n (%)	36 (11.4)	19 (11.9)	
RCA, n (%)	129 (40.8)	75 (47.2)	
Others, n (%)	2(0.6)	1 (0.6)	
No. of diseased vessels			.08
1	146 (46.2)	56(35.2)	
2	100 (31.6)	54 (33.9)	
3	66 (20.9)	47 (29.6)	
Unsuccessful procedure, n (%)	16 (5.1)	13 (8.2)	.18
Stent usage, n (%)	281 (88.9)	140 (88.1)	.79
Stent length, mm (SD)	23.6 ± 10.1	23.2 ± 8.9	.71
Stent diameter, mm (SD)	3.31 ± 1.67	3.37 ± 1.77	.67
Tirofiban usage, n (%)	110 (34.8)	46 (28.9)	.17

LMCA, left main coronary artery; LAD, left anterior descending coronary artery CX, circumflex coronary artery; RCA, right coronary artery; CK-MB, creatinine kinase-MB; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

103.7 vs 160.5±66.5, mg/dL, $P = .004$, respectively). Anemia at admission was also lower in the low CysC group (8.5 % vs 22%, $P < .001$).

3.3. Angiographic and procedural characteristics

Angiographic and procedural characteristics are depicted in Table 2. Culprit lesions were similar in the two groups. An unsuccessful procedure, stent use, number of diseased vessels, and tirofiban usage were not statistically different between the 2 groups.

3.4. In-hospital and one-month outcomes

Table 3 presents the in-hospital outcomes after primary PCI. The high CysC group had a significantly higher incidence of in-hospital cardiovascular mortality than the low CysC group (9.4% vs. 1.6%, respectively, $P < .001$). MACE, advanced heart failure, cardiopulmonary resuscitation, inotrop usage, cardiogenic shock, intra-aortic balloon pump usage, atrial fibrillation, and a transient pace were more frequent in patients in the high CysC group.

One-month outcomes are depicted in Table 3. The high CysC group had a significantly higher incidence of cardiovascular mortality than the low CysC group (14.5% vs 2.2%,

respectively, $P < .001$). Kaplan-Meier survival curves of high and low CysC groups are presented in Fig. 1. Advanced heart failure, fatal reinfarction, and MACE were also more frequently observed in the high CysC group. Independent predictors of one-month cardiovascular mortality were determined by a backward stepwise multivariate logistic regression. These predictors of cardiovascular mortality are depicted in Table 4. Killip class > 1 at admission, unsuccessful procedure, and CysC > 1.12 mg/L were found to be independent predictors of one-month cardiovascular mortality. In a receiver operating characteristic (ROC) curve analysis, a CysC value of 1.12 was identified as an effective cut-point in the STEMI of 1-month cardiovascular mortality (area under curve = 0.79, 95% confidence interval [CI] 0.7-0.89, $P < .001$). A CysC of > 1.12 yielded a sensitivity of 80% and a specificity of 71%. The ROC curve analysis was also performed for GFR < 60 mL/min per 1.73 m² (area under curve = 0.75, 95% CI, 0.65-0.85; $P < .001$), and for creatinine > 1.5 mg/dL (area under curve = 0.71, 95% CI, 0.6-0.82; $P < .001$) (Fig. 2). Among patients with a baseline creatinine of < 1.5 mg/dL, CysC > 1.12 mg/L presented with a greater risk for 1-month cardiovascular mortality (odds ratio: 5.76, 95% CI, 2.29-14.5; $P < .001$).

There were 30 deaths after one-month of follow-up. Of these patients, mortality ratios were more frequent in the high CysC group (n = 23, 76.7%) than in the low GFR (< 60 mL/

Table 3 In-hospital and 1-month cardiac events of all study patients

Variables	CysC ≤ 1.12 (n = 316)	CysC > 1.12 (n = 159)	P
Cardiovascular mortality, n (%)	5 (1.6)	15 (9.4)	<.001
Reinfarction, n (%)	19 (6)	9 (5.7)	.87
Target-vessel revascularization, n (%)	20 (6.3)	8 (5)	0.56
MACE, n (%)	24 (7.6)	22 (13.8)	.03
Stroke, n (%)	3 (0.9)	0 (0)	.22
Cardiopulmonary resuscitation, n (%)	9 (2.8)	17 (10.7)	<.001
Dialysis, n (%)	1 (0.3)	2 (1.2)	.22
Advanced heart failure, n (%)	17 (5.4)	28 (17.6)	<.001
Cardiogenic shock, n (%)	6 (1.9)	17 (10.7)	<.001
Inotrop usage, n (%)	11(3.5)	24(15.1)	<.001
IABP usage, n (%)	5 (1.6)	11 (6.9)	.002
Atrial fibrillation, n (%)	5 (1,6)	8 (5)	.03
Transient pace, n (%)	3 (0.9)	11(6.9)	<.001
Gastrointestinal bleeding, n (%)	0 (0)	2 (1.3)	.04
LVEF, % (SD)	49.2 ± 9.2)	44 ± 11.1)	<.001
1-month cardiovascular mortality, n (%)	7 (2.2)	23 (14.5)	<.001
1-month target-vessel revascularization, n (%)	20 (6.3)	13 (8.2)	<.43
1-month stroke, n (%)	3 (0.9)	0 (0)	<0.22
1-month advanced heart failure, n (%)	57 (18)	41 (25.8)	<.04
1-month fatal reinfarction, n(%)	5 (1.6)	16 (10.1)	<.001
1-month MACE, n (%)	27 (8.5)	34 (21.4)	<.001

IABP, intra-aortic balloon pump.

min per 1.73 m²) (n = 13, 43.3%) and high creatinine (> 1.5 mg/dL) (n = 8, 26.7%) groups (Fig. 3).

4. Discussion

The main findings of the present single-center study are as follows: (1) patients in the high CysC group were older and had a higher prevalence of DM, HT, PCI, MI, lower LVEF, and advanced Killip class; 2) high CysC levels are associated with a remarkable increase in one-month cardiovascular mortality; and 3) after adjustment for potential confounders, high CysC (but not a low GFR and high creatinine) was one of the independent predictors of one-month cardiovascular mortality (Fig. 3).

There is an important, close correlation between cardiac and renal diseases [18]. Go et al [19] found that there was an inverse association between GFR and cardiovascular events. Shiba et al [20] examined GFR in heart failure patients and showed that all-cause deaths were significantly higher in patients with reduced GFR. Creatinine was also shown to be a risk factor for unfavorable in-hospital events in patients with acute heart failure [18]. Serum creatinine and creatinine clearance (Cockcroft-Gault and MDRD equations) are used to evaluate renal function. However, serum creatinine levels are influenced by age, gender, muscle mass, physical activity, and diet and therefore are not sensitive enough to detect mild renal dysfunction [21,22].

High CysC levels identify early GFR abnormalities and are known to be highly sensitive markers for detecting

preclinical kidney dysfunction [23]. CysC is a cysteine protease inhibitor produced at a constant rate in all nucleated cells and also freely filtered by the glomeruli without secretion or subsequent tubular reabsorption [1]. Studies have shown that CysC is a good marker for renal dysfunction, especially in patients with creatinine levels within the normal range [24]. In our study, we observed that admission creatinine ≥ 1.5 mg/dL and GFR < 60 mL/min per 1.73 m² are two of the strongest risk factors for one-month

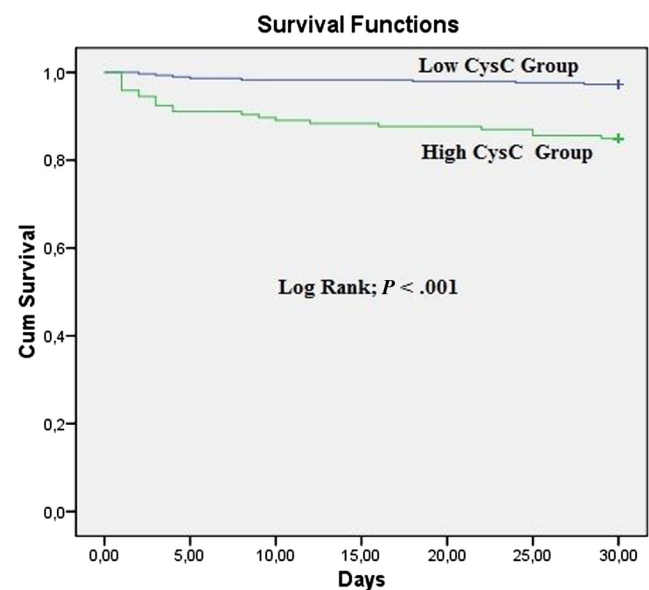


Fig. 1 Kaplan-Meier survival curve of high and low CysC groups.

Table 4 Effects of multiple variables on the one-month cardiovascular mortality in univariate and multivariate Cox regression analyses

	Univariate OR	95% CI	P	Multivariate OR	95% CI	P
Age	1.089	1.057-1.121	<.001			
Female gender	2.96	1.41-6.2	.004			
DM	3.4	1.62-7.16	.001			
Hypertension	2.68	1.28-5.6	.009			
Killip class > 1	43.9	17.9-78	<.001	27.5	7.9-95.4	<.001
CysC > 1.12 mg/L	5.9	2.6-13.3	<.001	4.66	1.3-16.6	.017
Anemia at admission	3.5	1.61-7.4	.001			
Renal failure	4.9	1.7-13.7	.003			
No-reflow	10.7	4.7-24	<.001			
Three-vessel disease	3.8	1.86-7.8	<.001			
Unsuccessful procedure	12	5.7-25.3	<.001	4.77	1.2-18.8	.0025
LVEF<%40	10.4	4.4-24.9	<.001			

cardiovascular mortality. However, neither creatinine levels on admission nor the GFR values were independent risk factors. Instead, CysC levels have independently distinguished the one-month cardiovascular mortality, and CysC was also found to be useful in identifying patients with a risk of cardiovascular mortality among those with an admission creatinine of <1.5 mg/dL. Our findings were compatible with the study by Silva et al [13].

Over the last few years, studies have focused on the association of CysC with cardiovascular risk and mortality [12,25]. In 2004, Jernberg et al [26] found that a single measurement of CysC was independently associated with mortality but not with the risk of subsequent MI in patients with non-ST elevation acute coronary syndrome (NSTE-

ACS). In another small study by Kilic et al [27], CysC was found to be the most powerful predictor for MACE in ACS. Taglieri et al [8] assessed 525 patients taking part in the Systemic Inflammation Evaluation in Patients with NSTEMI-ACS (SIESTA) study and showed that serum creatinine and GFR were not predictors for the study end-point, but increased levels of CysC were an independent predictor of cardiac events at one-year follow-up.

Recently, Sun et al [28] reported that increased CysC was an independent predictor of MACE in patients with ACS treated with PCI. The *in vivo* study using intravascular ultrasound by Gu et al [29] reported that CysC was higher in ACS than in stable angina, and plasma CysC was also positively correlated with the plaque area and plaque burden, which may offer clues for the larger atherosclerotic burden.

Including the present study, three studies have evaluated CysC in patients undergoing primary PCI for acute STEMI. A retrospective study by Ichimoto et al [12] reported that a higher incidence of rehospitalization for heart failure was observed in patients with higher CysC levels. However, there was no significant difference in death, reinfarction, stroke, and TVR, but the study population was small (n = 71). The other study was by Silva et al [13]. They included 153 consecutive patients. The patients who progressed to cardiogenic shock or who died during hospitalization had significantly greater CysC levels. A high baseline CysC level

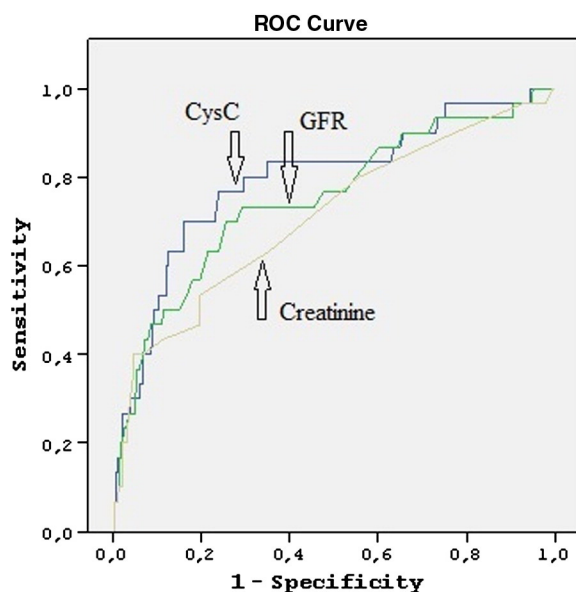


Fig. 2 The receiver-operating characteristic (ROC) curve with regard to death at one-month for high Cystatin C (CysC), low glomerular filtration rate (GFR) (> 60 ml/min/1.73m²), and high creatinine (<1.5 mg/dl) with area under curve of 0.79 (95% CI, 0.69 to 0.89), 0.75 (95% CI, 0.65 to 0.85), and 0.71 (95% CI, 0.6 to 0.82), respectively.

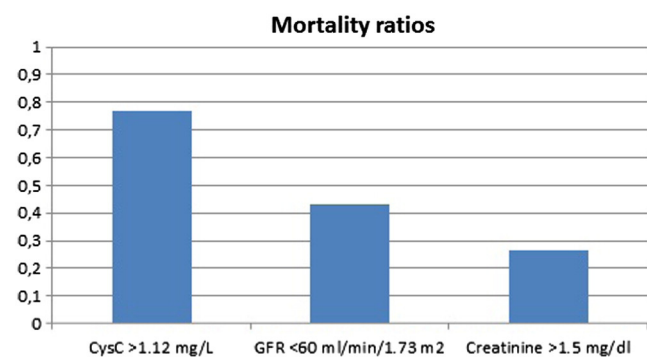


Fig. 3 Mortality ratios of subgroups in one-month follow-up.

was associated with an increased risk of death or reinfarction in long-term follow-up. To our knowledge, our study has been the largest prospective study of patients with STEMI that evaluated the short-term follow-up of these patients.

Not surprisingly, CysC levels were higher in the older patients in our study. This finding was likely because older patients more commonly had a higher inflammatory burden, HT, anemia, poor nutritional status, and age-associated diseases, including DM and renal failure. Higher DM, HT, renal failure, and admission anemia rates were more commonly observed in patients with high CysC. These findings were correlated with the study by Taglieri et al [8].

The precise mechanism for these findings is not clear. Cathepsin S has elastolytic and collagenolytic properties and plays a role in extracellular matrix remodeling by degradation of matrix proteins. CysC is an inhibitor of Cathepsin L and S [30]. It has been speculated that inflammatory cytokines stimulate the production of cathepsins, and increased CysC levels may reflect a counterbalance activity. Higher Killip, lower LVEF, and renal failure are indicators of higher inflammation, so it is not unexpected to see higher CysC levels.

4.1. Study limitations

This study was a single-center study. It is non-randomized and thus subject to selection bias. However, we were careful to include consecutive patients. We did not look at high-sensitivity C-reactive protein, B-type natriuretic peptide, other pro-inflammatory cytokines, or markers of oxidative stress. Despite adjusting for multiple risk factors, it is possible that there might have been residual confounding conditions and medications. We have no data on any changes in CysC levels during the course of the hospital stay. In addition, we have no long-term follow-up data.

5. Conclusion

Our study showed that patients with high CysC had worse clinical outcomes and higher mortality both while they were still hospitalized and during the next one-month period, than patients with low CysC. In summary, CysC is a powerful prognostic factor in patients undergoing primary PCI for STEMI. Larger studies will be needed to reveal the pathophysiologic link between increased CysC levels and mortality in patients with STEMI.

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