May cystatin-c be associated with post-myocardial infarction complications?

Postmyocardial infaction complication associated with cystatin C

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Abstract

Aim: Decreased cystatin C increases proteolytic effects of cathepsin contributing to plaque rupture. We aimed to investigate the association of cystatin C levels with in-hospital and post-discharge cardiac events in patients with acute myocardial infarction (AMI). Material and Method: We included 85 patients with AMI. Patients with cancer, systemic diseases, increased creatinine, active infection or aortic aneurysm were excluded. Demographic data, laboratory and echocardiographic parameters were analyzed. Serum cystatin C levels were measured in before coronary angiography. Results: Non-ST elevation myocardial infarction was determined in 32.94% of the patients. There were no differences between the normal and high cystatin C groups in terms of gender, diagnosis, obesity, hypertension, hyperlipidemia, cigarette smoking, Killip classification, preference of primary percutaneous coronary intervention or thrombolytic therapy, frequencies of culprit coronary arteries or the number of obstructed arteries. Diabetes mellitus was more frequent in the high cystatin C group. Complication rates after AMI were similar in both the normal and high cystatin C groups on the 5th day and the 12th month. Mean age was higher in the high cystatin C group. ESR, low density lipoprotein (LDL) and total cholesterol were found to be significantly higher in the high cystatin C group. The optimum cut-off values for ESR, LDL and total cholesterol were 11, 88.6, and 161.5, respectively; diagnostic accuracies were adequate. Discussion: The results of the study showed that ESR, LDL and total cholesterol were higher in high cystatin C group, but complications were similar in both groups. We concluded that cystatin C was not a predictor for post-AMI complications at 12th month.

Keywords

Acute Myocardial Infarction; Cystatin C; Complication

DOI: 10.4328/JCAM.5853 Received: 03.04.2018 Accepted: 27.04.2018 Published Online: 28.04.2018 Printed: 01.01.2019 J Clin Anal Med 2019;10(1): 76-82
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Introduction

Atherosclerotic heart disease (ASHD) is one of the most important causes of morbidity and mortality worldwide. Data indicate that ASHD will have a ratio of 33% in all-cause mortality in 2020 [1, 2]. In Turkey, the TEKHARF study reported that the prevalence of coronary artery disease (CAD) was 14% in the 60 – 69 years age group [3]. Therefore, it is crucial to understand the physiopathology of ASHD.

In angiographic evaluation of patients before and after acute myocardial infarction (AMI), the lesions causing acute thrombosis and obstruction of the vessel lumen have been shown to be mostly a non-critical stenosis due to atheromatous plaques [4-7]. It is accepted that acute cardiovascular events result from the rupture of vulnerable plaques and contact of prothrombotic material in plaque with blood. New molecules have been detected that are involved in the formation of atheromatous plaques or the development of complications. These new molecules could be new therapeutic targets in the management of AMI and other acute cardiovascular events. One of these molecules is cystatin C [8,9]. Several studies have suggested that increased cystatin C is directly related to atherosclerosis [10].

A strong fibrous cap is an important factor contributing to the stability of atheromatous plaque. Unstable plaques are vulnerable to damage at the "shoulder" point. Inflammatory cells at this point secrete proteolytic enzymes destroying the collagenous matrix of the fibrous cap. Cathepsins are the inhibitors of these enzymes, and the most important of these is cystatin C. It has been thought that inflammatory cytokines stimulate the production of cathepsins, and therefore increased levels of cystatin C may indicate counterbalancing activity. Several studies have shown that decreased levels of cystatin C have been found in atheromatous plaques, although this association has not been well studied in patients with AMI [8,9,11]. The aim of this study was to investigate the plasma levels of cystatin C in patients with AMI and to evaluate the association of cystatin C levels with in-hospital and post-discharge cardiac complications.

Material and Method

Study Design

The study included a total of 85 patients referred to our clinics who were diagnosed with AMI. Both patients with ST elevation myocardial infarction (STEMI) and Non-ST elevation myocardial infarction (NSTEMI) undergoing primary percutaneous coronary intervention (PCI) or thrombolytic therapy were included in the study. Patients with STEMI were also sub-grouped as anterior or inferior AMI. Any patients with known cancer, active infection, aortic aneurysms or increased creatinine levels (>1.3mg/dL) were excluded from the study.

Demographic data, hematological and biochemical parameters were recorded and analyzed. Complete blood count was measured with an automated counter (Sysmex KX 21N andCobas Integra). Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and lipids were also measured. Due to the initial clinical table of AMI, troponin-I (TnI) and creatine kinase-MB (CK-MB) were measured in all patients. Ejection fraction of left ventricle (EF), left atrium diameter (LA), left ventricle end diastolic diameter (LVEDd), left ventricle end systolic diameter (LVESd), diameters of interventricular septum (IVS) and posterior wall (PW) were measured using echocardiographic evaluation.The patients were followed up for 12 months to observe complications. Complications were defined as mechanical complications, restenosis and death. Cystatin C levels >1.3mg/L were accepted as high.

Cystatin C measurement

Blood samples were drawn before coronary angiography. The samples were collected in tubes withoutEDTA, and were frozen at -70°C after separation of the plasma. Plasma cystatin C was measured using the immunonephelometric method with a commercial kit (Dade Behiing N Latex Cystatin C assay) and the Behring BN ProSpec II device (Dade Behring Diagnostics). The immunonephelometric method for cystatin C is a fast, safe and automated method. The reliability of this method has been verified in several studies and the "Dade Behiing N Latex CystatinC assay" has been approved by the FDA [12-15].

In this method, polystyrene particles are coated with specific antibodies against human cystatin C. These polystyrene particles are then aggregated with a sample containing cystatin C. The light passing through these aggregates will distribute light bundles according to the cystatin C concentration. For this purpose, a suspension of polystyrene particles coated with anti-human cystatin C antibodies obtained from rabbits was used.

Statistical analysis

Data obtained in the study were analysed using SPSS 24.0 software (IBM Corparation, Armonk, New York, USA). The Shapiro-Wilk test was used to assess the conformity of the data with normal distribution. When comparing 2 independent groups according to quantitative data, the Independent-Samples T test was used with Bootstrap results, and the Mann-Whitney U test was used with Monte Carlo results. When comparing 2 dependent categorical variables, the McNemar test was used with the Monte Carlo simulation technique. In the comparison of categorical variables with each other, the Pearson Chi-Square, Fisher Exact and Fisher-Freeman-Holton tests were used with Exact and Monte Carlo simulation results. Odds Ratio was used to show that risk groups with a higher risk than the other subjects. ROC (Receiver Operating Curve), sensitivity and specificity levels analyzed the association between real classification and classification defined by cut-off levels calculated according to variables. Quantitative variables were defined as mean± standard deviation (SD), and median-range (maximum-minimum) in the tables. Categorical variables were shown as number (n) and percentage (%). Variables were analyzed at a 95% confidence level and a value of $p<0.05$ was accepted as statistically significant.

Results

There were no differences between the normal and high cystatin C groups in terms of gender, diagnosis, obesity, hypertension (HT), hyperlipidemia, or cigarette smoking. Diabetes mellitus (DM) was more frequent in the high cystatin C group (p=0.008, Odds Ratio=0.67, 95% confidence interval). No difference was determined between the groups according to the Killip classification (Table 1).

There were no differences between the normal and high cystatin C groups in terms of preference of primary PCI or thrombolytic

therapy. The frequencies of culprit coronary arteries were similar in both groups, as was the number of obstructed coronary arteries (Table 2).

No difference was determined between the normal and high cystatin C groups in respect of the presence of complications on both Day 5 and at the end of the 12thmonth (Table 3).

Mean age was observed to be higher in the high cystatin C group (60.02 ± 11.83 years vs 51.65 ± 14.21 years, p=0.026). Mean height, hematocrit, LVEDd, LVESd, IVS, PW and LA diameter values were similar in both groups (Table 4).

ESR, low density lipoprotein (LDL) and total cholesterol were found to be significantly higher in the high cystatin C group (p=0.037, p=0.017, p=0.010; respectively). Body weight, body mass index (BMI), systolic and diastolic blood pressure, pulse, white blood cell (WBC), platelet (PLT), CRP, blood urea nitrogen (BUN), creatinine (Cre), ALT, AST, CK-MB, TnI, high density lipoprotein (HDL), triglyceride (TG) and EF values were similar in both groups (Table 5).

The optimum cut-off values for ESR, LDL and total cholesterol were 11, 88.6, and 161.5, respectively, as identified by ROC. The area under the curve (AUC) with ESR used to detect high cystatin C was 0.685±0.075 (p=0.015; sensitivity 0.600, specificity 0.750) and diagnostic accuracy was adequate (Figure 1). The AUC with LDL used to detect high cystatin C was 0.683±0.072 (p=0.016; sensitivity 0.855, specificity 0.500) and diagnostic accuracy was adequate (Figure 2). The AUC with total cholesterol used to detect high cystatin C was 0.692±0.076 (p=0.011; sensitivity 0.873, specificity 0.500) and diagnostic accuracy was adequate (Figure 3) (Table 6).

Table 1. Demographic and clinical parameters of the patients.

	Normal Cystatin C	High Cystatin C	Total	P value
	(n=23)	(n=62)	(n=85)	
	n(%)	n(%)	n(%)	
Gender				
Female	1 (4.35)	13 (20.97)	14 (16.47)	0.099
Male	22 (95.65)	49 (79.03)	71 (83.53)	
Diagnosis				
NSTEMI	5 (21.74)	23 (37.10)	28 (32.94)	0.415
Inferior AMI	8 (34.78)	17 (27.42)	25 (29.41)	
Anterior AMI	10 (43.48)	22 (35.48)	32 (37.65)	
Obesity				
Absent	15 (65.22)	32 (51.61)	47 (55.29)	0.329
Present	8 (34.78)	30 (48.39)	38 (44.71)	
DM				
Absent	23 (100.00)	47 (75.81)	70 (82.35)	0.008
Present	0 (0.00)	15 (24.19)	15 (17.65)	0.67 (0.57-0.79)*
HT				
Absent	17 (73.91)	31 (50.00)	48 (56.47)	0.054
Present	6 (26.09)	31 (50.00)	37 (43.53)	
Hyperlipidemia				
Absent	20 (86.96)	49 (79.03)	69 (81.18)	0.540
Present	3 (13.04)	13 (20.97)	16 (18.82)	
Cigarette smoking				
Absent	5 (21.74)	25 (40.32)	30 (35.29)	0.132
Present	18 (78.26)	37 (59.68)	55 (64.71)	
Killip				
First degree	19 (82.61)	55 (88.71)	74 (87.06)	0.479
Second degree	4 (17.39)	7 (11.29)	11 (12.94)	

Fisher Exact Test (Exact) - Pearson Chi Square Test (Exact/Monte Carlo) / *:Odds Ratio (95% confidence interval)

Table 2. Distribution of primary therapy and culprit vessels in high and normal cystatin C groups.

	Normal cystatin C	High cystatin C	Total	P value
	(n=23)	(n=62)	(n=85)	
	n(%)	n(%)	n(%)	
Primary PCI				
Absent	15 (65.22)	42 (67.74)	57 (67.06)	1
Present	8 (34.78)	20 (32.26)	28 (32.94)	
Thrombolytic				
Absent	14 (60.87)	50 (80.65)	64 (75.29)	0.116
STK	8 (34.78)	9 (14.52)	17 (20.00)	
tPA	1 (4.35)	3 (4.84)	4 (4.71)	
Thrombolytic				
Absent	14 (60.87)	50 (80.65)	64 (75.29)	0.088
Present	9 (39.13)	12 (19.35)	21 (24.71)	
LMCA				
Absent	21 (100.00)	48 (96.00)	69 (97.18)	1
Present	0 (0.00)	2 (4.00)	2 (2.82)	
LAD				
Absent	4 (19.05)	10 (20.00)	14 (19.72)	1
Present	17 (80.95)	40 (80.00)	57 (80.28)	
Cx				
Absent	7 (33.33)	20 (40.00)	27 (38.03)	0.789
Present	14 (66.67)	30 (60.00)	44 (61.97)	
RCA				
Absent	7 (33.33)	11 (22.00)	18 (25.35)	0.375
Present	14 (66.67)	39 (78.00)	53 (74.65)	
Number of occluded vessels				
1	7 (33.33)	14 (28.00)	21 (29.58)	0.845
2	4 (19.05)	13 (26.00)	17 (23.94)	
3	10 (47.62)	23 (46.00)	33 (46.48)	

Fisher Freeman Halton (Monte Carlo) - Fisher Exact Test (Exact) - Pearson Chi Square Test (Exact/Monte Carlo). STK:streptokinaseA:tissue plasminogen activator LMCA:left main coronary artery LAD:left anterior descending Cx:circumflex artery RCA:right coronary artery

Table 3. Presence of complications in the patient groups.

	Normal cystatin C	High cystatin C	Total	P value
	(n=23)	(n=62)	(n=85)	
	n(%)	n(%)	n(%)	
Complication on the 5th day				
Absent	17 (73.91)	47 (75.81)	64 (75.29)	1
Present	6 (26.09)	15 (24.19)	21 (24.71)	
Complication at the end of the 12th month				
Absent	15 (65.22)	46 (74.19)	61 (71.76)	0.428
Present	8 (34.78)	16 (25.81)	24 (28.24)	
P value within the group	0.500	1	0.250	

Pearson Chi Square Test (Exact) - McNemar Test (Monte Carlo)

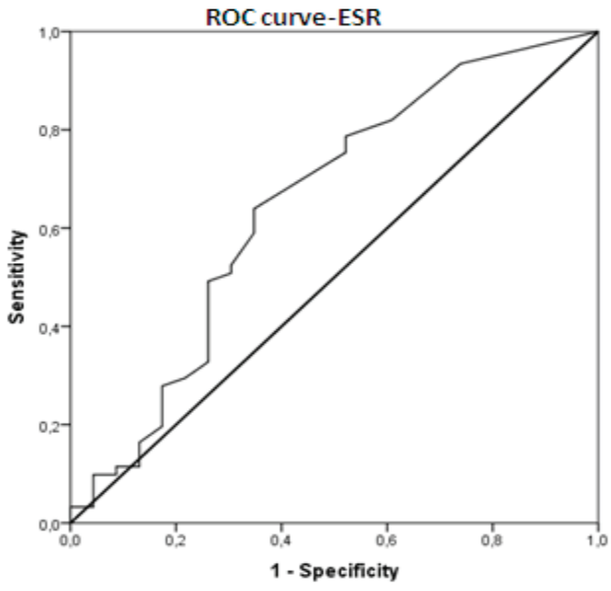

Figure 1. ROC curve for ESR.

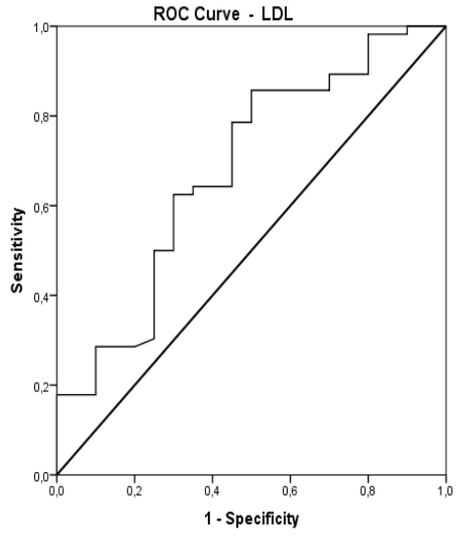

Figure 2. ROC curve for LDL.

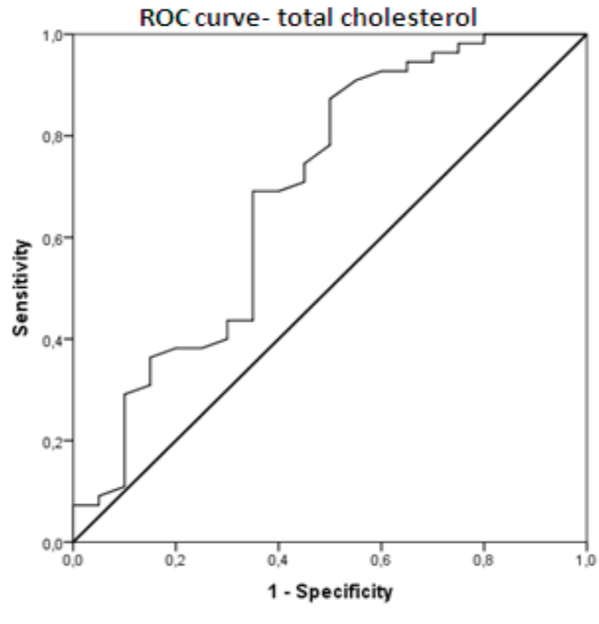

Figure 3. ROC curve for total cholesterol.

Table 4. Mean age, height, hematocrit and echocardiographic parameters in the patient groups.

	Normal cystatin C	High cystatin C	Total	P value
	mean±SD	mean±SD	mean±SD	
Age (years)	51.65 ± 14.21	60.02 ± 11.83	57.75 ± 12.98	0.026
Height (m)	1.69 ± 0.07	1.70 ± 0.07	1.70 ± 0.07	0.816
Hematocrit	42.57 ± 3.70	40.36 ± 5.02	40.96 ± 4.78	0.095
LVEDd	50.64 ± 5.27	50.95 ± 5.93	50.86 ± 5.73	0.719
LVESd	36.14 ± 5.04	35.82 ± 6.73	35.91 ± 6.27	0.775
IVS	10.91 ± 2.49	11.30 ± 2.02	11.19 ± 2.15	0.995
PW	10.16 ± 1.80	10.57 ± 1.71	10.46 ± 1.73	0.516
LA	34.63 ± 3.71	36.38 ± 4.26	35.93 ± 4.18	0.069

Independent t Test (Bootstrap) /SD:Standard deviation. LVEDd:left ventricle enddiastolic diameter LVESd:left ventricle endsystolic diameter IVS:interventricular septum PW:posterior wall LA:left atrium.

Table 5. Distribution of body weight, BMI, blood pressure, and basic hematological and biochemical parameters in the patient groups.

	Normal cystatin C	High cystatin C	Total	p value
	Median(Min./Max)	Median(Min./Max)	Median(Min./Max)	
Body weight (kg)	75 (54/114)	75 (55/113)	75 (54/114)	0.650
BMI	25.39 (21.63/37.80)	25.95 (20.76/45.78)	25.91 (20.76/45.78)	0.643
sBP	110 (65/140)	110 (80/140)	110 (65/140)	0.319
dBP	75.50 (45/88)	69.50 (50/120)	70 (45/120)	0.457
Pulse	74.50 (41/100)	76 (48/136)	76 (41/136)	0.420
WBC	12.40 (7.40/25)	11.10 (5.80/21)	11.50 (5.80/25)	0.192
PLT	238 (136/504)	226.50 (150/513)	231 (136/513)	0.421
CRP	12.10 (3/96.30)	15 (3/102)	15 (3/102)	0.627
ESR	10 (2/62)	16 (2/104)	14 (2/104)	0.037
BUN	15 (10/43.40)	16.45 (7.20/60)	16 (7.20/60)	0.145
Cre	0.85 (0.63/1.40)	0.90 (0.60/1.55)	0.90 (0.60/1.55)	0.245
AST	29 (12/350)	51 (15/504)	50.50 (12/504)	0.329
ALT	24 (7.60/199)	23.70 (9.70/347)	23.85 (7.60/347)	0.892
Peak CPK	1.268 (69/5.186)	1.256 (83/7.113)	1.256 (69/7.113)	0.760
Peak CKMB-mass	105 (1.50/500)	126 (5/569)	123 (1.50/569)	0.838
Tn I	65 (0.20/100)	41.45 (0.20/100)	52 (0.20/100)	0.652
LDL	92 (31.20/156)	116.75 (57/331)	113.40 (31.20/331)	0.017
HDL	43.50 (26/69)	41 (25/67)	41.40 (25/69)	0.416
Total cholesterol	165 (37/263)	187 (128/382)	184 (37/382)	0.010
TG	98 (21/256)	137 (18/441)	128 (18/441)	0.095
EF(teichoz)	58 (36/67)	54.50 (30/80)	56.50 (30/80)	0.229

Mann Whitney U Test (Monte Carlo) / Min.:Minumum - Max.:MaximumsBP:systolic blood pressure dBP:diastolic blood pressure

Discussion

The mean age of the patients was observed to be higher in the high cystatin C group. Height and body weight did not differ between the groups. The distributions of gender, type of myocardial infarction, frequency of obesity, hyperlipidemia, hypertension

Table 6. ROC analysis of age, sedimentation, LDL and total cholesterol.

Cystatin C High-Normal	AUC ± SE	Cut-off value	Sensitivity	Specificity	p value
Age (years)	0.633 ± 0.077	>54.5	0.673	0.600	0.079
ESR	0.685 ± 0.075	>11	0.600	0.750	0.015
LDL	0.683 ± 0.072	>88.6	0.855	0.500	0.016
Total cholesterol	0.692 ± 0.076	>161.5	0.873	0.500	0.011

Roc(Receiver Operating Curve) Analysis (Honley&Mc Nell - Youden index J)
AUC: Area under the ROC curve SE: Standard error

and cigarette smoking were similar in both groups. No differences were found between the groups in terms of the number of patients in different Killip classes. The frequency of DM was found to be higher in the high cystatin C group. No differences were found between the groups in terms of type or number of vessels occluded, application of fibrinolytic or primary PCI therapy. Echocardiographic results were similar in both groups. Complications, both on the 5thday and at the end of the 12th month were determined at similar frequencies in both groups. ESR, LDL and total cholesterol values were significantly higher in the high cystatin C group. There were no differences between the groups in respect of hematological and biochemical parameters.

Inflammatory cells secrete proteolytic enzymes which destroy the collagenous matrix of the fibrous cap. Cystatin C is one of the most important inhibitors of proteolytic enzymes. Hence, it regulates inflammatory activity and contributes to the formation of balance between production and destruction of the extracellular collagenous matrix [16]. Cystatin C is produced by all nucleated cellssuch as cardiomyocytes. Ischemia promotes the production of cystatin C, and cystatin C modulates vascular inflammatory activity. Therefore, it might be associated with the natural course of atheromatous plaque [17]. Gu et al showed that cystatin C was higher in patients with acute coronary syndrome than in those with stable angina pectoris, in a study using intravascular ultrasonography [18]. It was also reported that cystatin C was correlated with plaque area.

Akgul et al. investigated the association of cystatin C with in-hospital and post-discharge complications in 475 patients with STEMI who had undergone primary PCI [19]. In that study, similar to the current study findings and another study by Ristiniemi, the mean age was higher in the high cystatin C group [20]. Older patients with coronary artery disease can be assumed to have an increased inflammatory burden, DM associated with increased age, and increased malnutrition. The increased inflammatory state may explain the increased mean age in the high cystatin C group. As renal function decreases with increasing age [21], this could also explain the older age in the high cystatin C groups.

In a study by Akgul et al. a history of DM was found to be more prevalent in the high cystatin C group similar to the current study. DM is known to be an accepted traditional risk factor for coronary artery disease, so these results were anticipated. Some studies have shown that cystatin C level was related not only to cardiovascular disease but also to type 2 DM [22]. However, in some studies, the frequency of DM was similar in both groups [20]. In one study, 660 very elderly patients (>80 years) undergoing coronary angiography for acute coronary syndrome were investigated to detect the prognostic impact of cystatin C [23]. Patients were separated into two groups according to the presence of DM. Over a mean follow-up period of 28 months, Cystatin C was found to be significantly higher in the diabetic group. Survival was significantly lower in diabetics and mortality was higher. Plasma cystatin C concentration was reported to be an independent predictor for adverse cardiac events in the diabetic group, with a cut-off value for mortality in diabetics of 1.605.

In the current study, LDL and total cholesterol were found to be higher in the high cystatin C group, and creatinine and hemoglobin were similar in both groups. However, in another study, creatinine was higher, and hemoglobin and LDL were lower in high cystatin C groups, while other lipids were similar [19]. Elevated creatinine may be a confounder for cystatin C to be a predictor. In the same study, the distribution of culprit coronary arteries and the number of obstructed vessels were not different between the 2 groups, which was a similar finding to the current study. In that previous study, both in-hospital and 1-month major adverse cardiac events, both in-hospital and 1-month advanced heart failure, cardiogenic shock, resuscitation, intra-aortic balloon pump use, atrial fibrillation, transient pacemaker use, gastrointestinal hemorrhage were detected at higher rates in the high cystatin C group. The in-hospital and 1-month cardiovascular mortality rates were found to be increased in patients with higher cystatin C compared to low cystatin C (9.4% vs 1.6%, p<0.001; 14.5% vs 2.2%, p<0.001; respectively). High cystatin C was found to be a strong predictor for mortality (OR=5.3, p=0.02). In contrast to the current study, Killip scoring and history of HT were higher in the high cystatin C group. This difference could have resulted from the inclusion of patients with STEMI only, in that study. A Killip score >1 was also determined as an independent predictor of mortality in that study. Similarly, in a study by Ristiniemi, mortality risk increased with increasing cystatin C levels, with a hazard ratio of cystatin C for mortality of 2.19 [20]. Two other studies also investigated the predictive role of cystatin C in patients with STEMI [24,25]. Ichimoto et al found that high cystatin C was associated with hospitalization for heart failure, and Silva et al showed that patients who developed cardiogenic shock had higher cystatin C levels.

Ristiniemi et al included 245 patients with NSTEMI and followed up them 1 year. Increased serum cystatin C was found to be an independent predictor of all-cause mortality and AMI after adjustments for other factors. Creatinine was not an independent factor for adverse outcomes and it can be concluded that cystatin C may not be affected by multiple confounders [20]. In the current study, cardiac biomarkers were found to be similar in the high and normal cystatin C groups. In a study by Ristiniemi, again TnI levels were found to be similar in both groups [20]. Due to the nature of the patient groups included in the current study, the similarity was expected. In a previous study investigating major adverse cardiac events, 160 patients with acute coronary syndrome were evaluated. Cardiac events were determined at a higher rate in the high cystatin C group, and cystatin C was found to be the most important parameter associated with major cardiac events [26]. Taglieri et al. evaluated 525 patients with NSTEMI in the “Systemic Inflammation Evaluation in patients with NSTE-ACS” (SIESTA) study [27]. Patients were subgrouped according to the cystatin C levels. The higher cystatin C groups were associated with cardiac events at 1-year follow-up,

although serum creatinine was not a predictor for end point. In a study including 726 patients with NSTEMI, cystatin C was again found to be independently associated with mortality but not with the risk of subsequent AMI [28].

Cystatin C is eliminated mainly by glomerular filtration, neither secreted nor reabsorbed by tubules [29]. The cystatin C level is not influenced by age, muscle mass, exercise, sex or diet [30, 31]. It has been shown to be superior in evaluating renal function compared to creatinine [32-35]. Several studies have shown the inverse relationship between decreased renal function and cardiovascular outcomes [36-38]. Cystatin C has also been shown to be a superior marker in the prediction of preclinical kidney disease compared to creatinine [32]. When investigating the role of cystatin C in cardiovascular mortality in patients with AMI, the results should be adjusted for potential confounders such as increased creatinine level. After adjustment for creatinine, Akgul et al and Silva et al found cystatin C to be an independent factor in the development of cardiovascular mortality after AMI [19, 25]. Especially in the elderly, cystatin C shows higher sensitivity and detects minor impairments compared to creatinine and it increases more steeply than creatinine [39, 40]. Minor renal dysfunction may also be of important clinical significance. From this aspect, the association of cystatin C with mortality can be expected to be more prominent compared to creatinine, as has been shown in a previous study [41]. Sanchis et al. investigated the predictors of frailty in 342 patients suffering from acute coronary syndrome, and cystatin C >1.2mg/L was detected as one of the biomarkers predicting frailty [42].

To eliminate the confounding effect of creatinine, some studies have been designed to include a number of patients with glomerular filtration rate >60mL/min [43]. Abid et al. investigated 127 patients without chronic kidney disease, undergoing coronary angiography for acute coronary syndrome [43]. Cystatin C was found to be associated with the severity of coronary artery disease both according to the number of culprit vessels and the Gensini score. The patients were followed up for an average of 10 months, and cystatin C was associated with both unfavorable outcomes and cardiovascular mortality.

Sun et al. investigated 605 patients with acute coronary syndrome undergoing successful PCI [44]. Patients were separated into groups according to cystatin C levels. In afollow-up period of at least 12 months, mortality, non-fatal myocardial infarction, revascularization, and heart failure rates were determined to be higher in the high cystatin C groups. Cystatin C elevation was shown as an independent predictor of major adverse cardiac events, and survival was lower in higher cystatin C groups. EF was lower in patients with major adverse cardiac events, and was a predictor for cardiac events. In that study, elevated cystatin C was found to be a predictor for cardiac events in contrast to the current study results. Sun et al. followed up patients for at least 12 months and the predictive value of cystatin C even in the 12th month indicated cystatin C as a long-term marker in patients with acute coronary syndrome. The current study follow-up was relatively shorter. In addition, the patients included in that previous study were patients with both AMI and unstable angina pectoris, who underwent only successful PCI defined as TIMI (thrombolysis in myocardial infarction) III flow after intervention. In the current study, patients with unstable angina pectoris were not included, although patients undergoing both PCI and thrombolytic therapy were included. In the above-mentioned study, an unsuccessful procedure was found to be an independent predictor for cardiac events [19]. Therefore, inclusion of both patients with successful and unsuccessful interventions may cause a confounding effect, but provide exact results.

One of the limitations of the current study was the small study population. More patients with acute coronary syndrome could have been included. Furthermore, other than for cystatin C, the patients could not be separated into subgroups as those with STEMI or NSTEMI. The results were analyzed of patients undergoing thrombolytic therapy and primary PCI. Further subgrouping according to the therapy applied could have been useful but would have required a larger sample. Patients were followed up for 12 months. Several studies analyzing long-term complications post AMI have been published in literature.

In conclusion, the results of this study showed that post-AMI complications both at the 5th and 12th month were found at similar frequencies in both the high and normal cystatin C groups. ESR, LDL and total cholesterol values were significantly higher in the high cystatin C group. Further investigations are necessary to show the association of these parameters with cystatin C.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

Funding: None

Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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How to cite this article:
Tascanov MB, Yılmaz O. May cystatin-c be associated with post-myocardial infarction complications? J Clin Anal Med 2019;10(1): 76-82.