Cystatin C: A prognostic marker after myocardial infarction in patients without chronic kidney disease

Leila Abid a,⇑, Salma Charfeddine a, Samir Kammoun a, Mouna Turki b, Fatma Ayedi b

a Cardiology Department, University Hédi Chaker Hospital, Sfax
b Biochemistry Laboratory, Habib Bourguiba University Hospital
a,b Tunisia

Aims: Cystatin C is an endogenous marker of renal function. It is a well established better marker of glomerular filtration rate than serum creatinine. There is also evidence that cystatin C is associated with atherosclerotic disease. The present prospective study evaluated the prognostic value of cystatin C after myocardial infarction in patients without chronic kidney disease.

Methods and results: A total of 127 patients who underwent coronary angiography after an acute coronary syndrome (ACS) were included. Cystatin C was associated with the severity of coronary artery disease (CAD). Cystatin C levels were significantly higher in patients with 3-vessels disease and severe CAD according to GENSINI score (p = 0.01 and p < 0.001 respectively). Among the patients admitted for ST elevation myocardial infarction, Cystatin C concentration was correlated with the initial TIMI flow in the culprit artery (p < 0.001). Mean duration of the follow-up period was 10.76 ± 2.1 months. High Cystatin C concentrations were associated to the occurrence of unfavourable outcomes and cardiovascular mortality during follow-up (1.19 ± 0.4 vs. 1.01 ± 0.35 mg/L, p = 0.01 and 1.21 ± 0.36 vs. 0.96 ± 0.27 mg/L, p = 0.03). Among different laboratory parameters, cystatin C was the best marker to predict the occurrence of major adverse cardiovascular events during the follow-up (Area under the receiver operating characteristic curve = 0.743).

Conclusion: High cystatin C levels are associated with the severity of coronary artery disease in patients presenting an acute coronary syndrome and a normal renal function. Cystatin C is also associated to unfavourable cardiovascular outcomes during follow-up and appears as a strong predictor for risk of cardiovascular events and death.

© 2015 The Authors. Production and hosting by Elsevier B.V. on behalf of King Saud University. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Keywords: Cystatin C, Myocardial infarction, Cardiovascular mortality, Coronary artery disease, Major adverse cardiovascular events

Disclosure: Authors have nothing to disclose with regard to commercial support.
Received 28 July 2015; revised 10 September 2015; accepted 1 October 2015.
Available online 9 October 2015

⇑ Corresponding author at: Cardiology Department, Hédi Chaker Hospital, Route Elain, Km 0.5, Sfax 3029, Tunisia.
E-mail addresses: leilaabid@yahoo.fr (L. Abid), mouna.turki@gmail.com (M. Turki), ayedifatma@yahoo.fr (F. Ayedi).
Introduction

The risk stratification of patients with coronary artery disease (CAD), especially death and acute heart failure, has been the subject of research in recent years [1–3]. Renal impairment is frequent in patients with cardiovascular disease and increases morbidity and mortality. The search for new biomarkers with better and accurate profiles has been very intense. Cystatin C (Cys C) is a novel marker for renal dysfunction and is better than serum creatinine, especially for mild renal impairment [4–6]. Cys C is a cysteine protease inhibitor produced in all nucleated cells at a constant rate and is freely filtrated by the glomeruli to be reabsorbed and degraded in the proximal tubules. Cys C is not affected by sex, age, and muscle mass. Recently, a close relationship has been established between Cys C and various subsets of atherosclerotic disease including CAD, stable CAD, as well as acute coronary syndromes (ACS). Therefore, Cys C might be a useful biomarker for prognostic stratification in patients with ACS [7–9].

The aim of the present study was to evaluate whether the concentration of Cys C could predict the severity of CAD after myocardial infarction in patients with normal or mildly impaired renal function estimated from the concentration of serum creatinine, and to determine the prognostic value of Cys C in predicting cardiovascular death during follow up.

Methods

Our study was prospective observational including Tunisian patients admitted to the department of cardiology of Hédi Chaker Hospital with the diagnosis of myocardial infarction who underwent urgent coronary angiography from May 2012 to December 2012. All patients have the following criteria: (1) chest pain at rest within the past 24 hours; (2) ST-segment elevation; (3) new presumed left bundle branch block; or (4) ST segment or T wave abnormalities with troponin Ic rise. All patients were admitted in the hospital within the past 24 hours. Patients were divided into two groups: Group 1 was defined by patients admitted with non-ST segment elevation myocardial infarction (NSTEMI) with troponin Ic rise and Group 2 included patients with ST-segment elevation myocardial infarction (STEMI). We excluded patients with chronic renal failure and those who had an estimated glomerular filtration rate (eGFR) <60 mL/min, calculated using the Modification of Diet in Renal Disease equation based on the level of serum creatinine from this study. Patients with significant valvular or structural heart disease were excluded. All the study participants provided their consent before entering the study. Patients with hypertension were defined by a blood pressure $\geq 140/90$ mmHg or having history of antihypertensive drug use. Diabetes mellitus was defined as fasting glucose level $>1.26$ g/L (7 mmol/L) or having history of antihypertensive drug use. Dyslipidemia was defined as a low density lipoprotein-cholesterol level $>1.4$ g/L (3.6 mmol/L) or if patients were taking a hypolipidemic drug. Smokers were defined as patients actively inhaling tobacco smoke. The hemodynamic status was evaluated at admission, including blood pressure measurement and the KILLIP class. For patients admitted with NSTEMI,
we have determined the GRACE risk score. Biochemical tests were collected at admission before coronary angiography. The serum concentration of Cys C was determined with a turbidimetric immunoassay (COBAS INTEGRA Cystatin C 400 Roche). Serum creatinine was determined using the Jaffe reaction. GFR was calculated using the Modification of Diet in Renal Disease study equation (mL/min): $186.3 / (\text{serum creatinine} / 88.4)^{1.154} \times \text{age}^{-0.203} \times (0.742$ if female).

An echocardiographic study was performed before discharge and during the follow-up. Left ventricular ejection fraction (LVEF) was calculated using the Simpson biplane method. Left ventricular systolic dysfunction was defined as an LVEF <50%. Coronary angiography was performed in all patients through radial or femoral access. The results of the coronary angiography were evaluated by at least three operators. Significant angiographic stenosis was defined as >50% in any of the major epicardial coronary arteries. Left anterior descending artery, left circumflex, and right coronary artery were examined to determine the number of stenotic arteries as 0–3-vessel disease. The involvement of the left main artery was evaluated as a 2-vessel disease. The severity of CAD was scored according to the number of stenotic arteries and the GENSINI score. The two CAD groups were determined according the GENsini score, mild CAD (score 0–20), and severe CAD (score >20). All patients were followed-up during 12 months. The follow-up was assessed by phone or clinical review. The circumstances of death were determined by interviews with relatives or hospital records. During follow up, the major

### Table 1. Baseline characteristics of the study population (127 patients).

| Variables | All patients (n = 127) | Group 1: NSTEMI (n = 43) | Group 2: STEMI (n = 84) | p |
|-----------|------------------------|--------------------------|------------------------|---|
| Quantitative variables | Mean (SD) | Mean (SD) | Mean (SD) | NS |
| Age (y) | 58 (11.65) | 56.17 (13.6) | 59.2 (10.5) | NS |
| Sex (M:F) | 108:22 | 35:8 | 70:14 | NS |
| BMI (kg/m²) | 29.56 (7.8) | 28.41 (9.6) | 30.18 (5.7) | NS |
| GRACE risk score | 123.12 (24.5) | 120.35 (17.5) | 143.42 (19.6) | 0.02 |
| eGFR (MDRD) (mL/min) | 98.8 (30.9) | 105.2 (25.8) | 89.6 (23.7) | 0.03 |
| Scr (µmol/L) | 92.9 (30.6) | 86.4 (24.6) | 98.5 (28.5) | 0.03 |
| Cystatin C (mg/L) | 1.04 (0.36) | 0.99 (0.28) | 1.13 (0.25) | 0.03 |
| BNP (pg/mL) | 275.2 (367.9) | 212.7 (258.1) | 376.4 (381.2) | 0.02 |
| LVEF (%) | 51.36 (10.8) | 54.5 (8.9) | 48.12 (9.6) | 0.04 |

| Qualitative variables | N (%) | N (%) | N (%) | NS |
| HT | 52 (40.9) | 17 (39.5) | 35 (41.6) | NS |
| DM | 58 (45.6) | 19 (44.1) | 39 (46.4) | NS |
| DL | 33 (26) | 10 (23.2) | 23 (27.3) | NS |
| Smokers | 81 (63.8) | 27 (62.7) | 54 (64.2) | NS |
| CF | 11 (8.7) | 3 (6.9) | 8 (9.5) | 0.04 |

### Table 2. Angiographic characteristics of the study population.

| Characteristic | Patients [n (%)] |
|----------------|-----------------|
| Vessels with significant lesions | |
| 1 vessel | 46 (36.2%) |
| 2 vessels | 45 (35.4%) |
| 3 vessels | 36 (28.3%) |
| Left main disease | 14 (11%) |
| CAD severity score | |
| Mild CAD (GENSINI score 1–20) | 55 (43.3%) |
| Severe CAD (GENSINI score >20) | 72 (56.7%) |
| Infarct-related vessel (STEMI) | |
| LAD | 45 (35.5%) |
| CX | 26 (31%) |
| RC | 13 (15.5%) |

### Table 3. Cystatin C levels and severity of coronary artery disease in the study population (127 patients).

| Characteristic | Cystatin C (mg/L)a | p |
|----------------|-------------------|---|
| Vessels with significant lesions | |
| 1-VD | 0.93 (0.24) | 0.01 |
| 2-VD | 1.04 (0.34) | |
| 3-VD | 1.17 (0.47) | |
| CAD severity score | |
| Mild CAD (GENSINI score 1–20) | 0.87 (0.19) | <0.001 |
| Severe CAD (GENSINI score >20) | 1.12 (0.24) | |

### Notes:

- BMI = body mass index; BNP = brain natriuretic peptide; CF = family history of premature ischemic heart disease; DL = dyslipidaemia; DM = diabetes mellitus; eGFR (MDRD) = estimated glomerular filtration rate by Modification of Diet in Renal Disease formula; HT = hypertension; LVEF = left ventricular ejection fraction; NS = not significant; NSTEMI = non ST-elevation myocardial infarction; Scr = serum creatinine; SD = standard deviation; STEMI = ST-elevation myocardial infarction.

- All values are expressed as mean (standard deviation).

- CAD = coronary artery disease; CX = circumflex artery; LAD = left anterior descending artery; RC = right coronary artery; STEMI = ST-elevation myocardial infarction.

- All patients were followed-up during 12 months. The follow-up was assessed by phone or clinical review. The circumstances of death were determined by interviews with relatives or hospital records. During follow up, the major...
adverse cardiovascular events (MACE) were recorded. The MACE included cardiovascular death, reinfarction, ACS, or acute heart failure requiring rehospitalization.

Statistical analysis

Statistical analysis was performed using PSS version 18.0 (Chicago, IL, USA). Laboratory parameters were presented as the mean (standard deviation). Correlations between continuous variables were assessed using Pearson’s or Spearman’s correlation analysis. The Student t test was used to compare means between groups, and the Chi-square test was used to compare proportion between groups. Analysis of variance was used for multigroup comparison. A receiver-operating characteristic curve analysis was used to identify the optimal cut-off points of Cys C for predicting CAD. A value of \( p < 0.05 \) was considered as statistically significant. Survival analysis included Kaplan-Meier representations for the time to event data.

Results

A total of 127 patients were admitted in our cardiology department with the diagnosis of ACS. The demographic and clinical features for the study population are summarized in Table 1.

On admission, 105 patients (82.6%) were hemodynamically stable with no signs of heart failure (KILLIP class I). The angiographic characteristics of the study population are listed in Table 2. Among the 127 patients, 94 underwent successful percutaneous coronary intervention (final Thrombolysis in Myocardial Infarction flow III) and three had no reflow. A total of 11 patients underwent coronary artery bypass surgery and 19 had medical treatment only.

Among the 43 patients admitted with NSTEMI, Cys C levels were significantly higher in patients with ST-segment depression (1.47 ± 0.35 and 1.08 ± 0.23 respectively, \( p = 0.01 \)) and in patients presenting a left bundle branch block (1.64 ± 0.38 and 1.10 ± 0.19 respectively, \( p = 0.006 \)). Cystatin C concentration was also higher in patients with elevated GRACE risk score >140 (1.37 ± 0.21 and 1.01 ± 0.24 respectively, \( p = 0.04 \)). Cys C levels were significantly higher in patients with 3-vessels disease and severe CAD according to GENSINI score compared with the other groups (Tables 3–5). Among the patients admitted for STEMI, Cys C concentration was correlated with the initial Thrombolysis in Myocardial Infarction flow in the culprit artery.

Table 4. Cystatin C levels and severity of coronary artery disease in patients with NSTEMI (Group 1 = 43 patients).

| Vessels with significant lesions | Cystatin C (mg/L) | P  |
|---------------------------------|-------------------|----|
| 1-VD                            | 0.96 (0.24)       | 0.003 |
| 2-VD                            | 1.08 (0.49)       | 0.018 |
| 3-VD                            | 1.34 (0.60)       | 0.018 |

CAD severity score

| Mild CAD (GENSINI score 1–20) | 0.89 (0.15)       | <0.001 |
| Severe CAD (GENSINI score >20) | 1.18 (0.12)       | <0.001 |

CAD = coronary artery disease; VD = vessel disease.

Statistical analysis included Kaplan-Meier representations for the time to event data.

Table 5. Cystatin C levels and severity of coronary artery disease in patients with STEMI (Group 2 = 84 patients).

| Vessels with significant lesions | Cystatin C (mg/L) | P  |
|---------------------------------|-------------------|----|
| 1-VD                            | 0.82 (0.16)       | 0.18 |
| 2-VD                            | 0.93 (0.30)       | 0.018 |
| 3-VD                            | 1.11 (0.55)       | 0.018 |

CAD severity score

| Mild CAD (GENSINI score 1–20) | 0.89 (0.15)       | <0.001 |
| Severe CAD (GENSINI score >20) | 1.18 (0.12)       | <0.001 |

Initial TIMI flow

| TIMI 0                          | 1.52 (0.21)       | <0.001 |
| TIMI 1                          | 1.26 (0.24)       | <0.001 |
| TIMI 2                          | 0.99 (0.26)       | <0.001 |
| TIMI 3                          | 0.90 (0.27)       | <0.001 |

CAD = coronary artery disease; TIMI flow = Thrombolysis In Myocardial Infarction flow; VD = vessel disease.

Table 6. Major adverse cardiac events in the study population.

| MACE                          | All patients n = 127 | Group 1 n = 43 | Group 2 n = 84 | P  |
|-------------------------------|----------------------|----------------|----------------|----|
| Death                         | 6 (4.7%)             | 1 (2.3%)       | 5 (9.2%)       | 0.01 |
| Myocardial reinfarction       | 6 (4.7%)             | 2 (4.6%)       | 4 (4.7%)       | NS  |
| NSTEMI                        | 13 (10.3%)           | 8 (18.6%)      | 5 (5.9%)       | 0.02 |
| Heart failure                 | 7 (5.5%)             | 3 (6.9%)       | 4 (4.7%)       | NS  |

MACE = major adverse cardiovascular events; NS = not significant; NSTEMI = nonST-elevation myocardial infarction.
coronary intervention but without significant difference (1.19 ± 0.16 and 1.12 ± 0.15, respectively).

During hospitalization, the maximum of KILLIP class reached was II in 11 patients (8.6%), III in three patients (2.3%), and 23 patients (18.1%) presented hemodynamic deterioration. These patients had greater Cys C concentration (0.96 ± 0.24 vs. 0.78 ± 0.19, p < 0.001). Furthermore, Cys C levels were higher in patients presenting global systolic left ejection fraction impairment (1.04 ± 0.2 vs. 1.02 ± 0.4, p = 0.3).

Long-term follow-up data were available for all patients. The follow-up period was 10.76 ± 2.1 months. During this period, 32 patients (25.2%) presented at least one MACE and six

| Table 7. Association between laboratory parameters and major adverse cardiac events during follow-up. |
| Variable | MACE<sup>a</sup> | p |
|----------|-----------------|---|
| Cystatin C (mg/L) | 1.19 (0.4) | 1.01 (0.35) | 0.01 |
| Creatinine (μmol/L) | 101.26 (32.5) | 90.31 (29.7) | 0.08 |
| Urea (mmol/L) | 7.34 (2.74) | 6.6 (2.57) | 0.16 |
| Uric acid (μmol/L) | 371.50 (115.9) | 322.10 (108.4) | 0.03 |
| BNP (pg/mL) | 315.80 (224.5) | 232.46 (210.0) | 0.05 |

<sup>a</sup> All values are expressed as mean (standard deviation).

<sup>BNP</sup> = brain natriuretic peptide; MACE: =major adverse cardiovascular events.

Table 8. Comparison of clinical and laboratory characteristics according to occurrence of death during the follow-up period in the study population.

| Variables | Favourable outcome<sup>a</sup> | Death<sup>a</sup> | p |
|-----------|-----------------|-----------------|---|
| Mean blood pressure (mmHg) | 103 (19) | 107 (21) | NS |
| Cystatin C (mg/L) | 0.96 (0.27) | 1.21 (0.36) | 0.03 |
| Creatinine (μmol/L) | 91.65 (29.8) | 117.09 (37.2) | 0.04 |
| Urea (mmol/L) | 6.67 (2.58) | 8.69 (2.33) | NS |
| Uric Acid (μmol/L) | 360.45 (113.6) | 381.21 (108.7) | NS |
| BNP (pg/mL) | 247.05 (325.7) | 536.97 (605.7) | 0.04 |
| Ejection fraction (%) | 54 (17) | 39 (12) | 0.03 |

<sup>a</sup> All values are expressed as mean (standard deviation).

<sup>BNP</sup> = brain natriuretic peptide; NS = not significant.

Figure 1. Receiver-operating characteristic curves analyses for cystatin C, creatinine, uric acid, and brain natriuretic peptide in predicting occurrence of major adverse cardiovascular events during the follow-up period in the study population. BNP = brain natriuretic peptide.
patients (4.7%) died. The group of patients with STEMI had a poor prognosis and presented more myocardial reinfarction and heart failure during the follow-up than the patients who presented with NSTEMI (Table 6).

Cys C and uric acid were associated with the occurrence of unfavorable outcomes during follow-up (Table 7). The accuracy of these parameters in predicting MACE, evaluated using the area under the receiver-operating characteristic curve, was moderate. Among these parameters, Cys C was the best marker to predict occurrence of MACE during the follow-up (Fig. 1). For a cutoff value of 0.97 mg/L, Cys C had a sensitivity of 84% and a specificity of 66% for prediction MACE.

The patients who died had greater Cys C, creatinine, and brain natriuretic peptide levels and lower LVEF (Table 8). The risk of cardiovascular death was multiplied by 4.8 for patients with elevated Cys C levels >1.2 mg/L (p = 0.01). The cumulative survival of patients with high Cys C concentration was significantly lower during the follow-up (Fig. 2). Furthermore, combined GRACE score and Cys C levels showed that the risk of cardiovascular death in patients with NSTEMI and GRACE score >140 was 2.5 times higher if Cys C concentration was >1.2 mg/L (p = 0.02).

Discussion

It is well known that chronic kidney dysfunction in patients with CAD is common and increases morbidity and mortality. Heart and kidney functions are strongly associated and it is known that the dysfunction of one of these organs necessarily damages the other [10,11]. Thus, even mild renal impairment is associated with high cardiovascular risk. Cys C, a cysteine protease inhibitor, is a novel marker for renal function. It has been shown that Cys C is more sensitive and specific for GFR estimation than creatinine. In fact, Cys C is less influenced by sex, age, and muscle mass and is a better marker for detection of mild renal impairment [12].

Cys C is produced by all nucleated cells. Ischemia and hypoxia increases Cys C production by the cardiomyocytes. By its cysteine protease activity, Cys C regulates the inflammatory response, the phagocytic activity, and participates in the balance of production and degradation of extracellular matrix [13]. Therefore, this marker could be associated with the development and progression of atheroma plaque [14,15] and it might be a good prognostic biomarker in patients with myocardial infarction.
In this present prospective study of 127 patients with normal GFR (eGFR >60 mL/min) who underwent coronary angiography, we demonstrated that higher Cys C levels were correlated to the severity of CAD attested by the number of stenotic arteries and GENSINI score. This was consistent with the findings of previous study. In fact, some studies have shown that Cys C is closely related to CAD, both in stable CAD as well as in patients presenting ACS (STEMI and NSTEMI). Koenig et al. [7], Wang et al. [16], and Koc et al. [17] have previously demonstrated that higher Cys C levels were associated with CAD and that among different renal parameters; Cys C was the best predictor of coronary angiographic severity. However, in another study, Niccoli et al. [18] had found that Cys C was proportional to the number of stenotic arteries but did not predict lesion complexity or CAD severity in patients admitted for ACS.

Furthermore, the results of our study showed the prognostic value of Cys C. Higher concentrations of Cys C were associated with worse clinical outcomes and cardiovascular death during the follow-up period. Among other renal parameters, Cys C was the best predictor of death and MACE. The risk of death was 4.8 times greater for patients with Cys C levels >1.2 mg/L. Therefore, the prognostic value of this biomarker had been investigated in several studies. Indeed, previous studies demonstrated that Cys C was associated to greater cardiovascular risk and mortality. Silva et al. [19] suggested that patients admitted for STEMI and who presented elevated Cys C levels (≥0.84 mg/L) on admission, had greater risk of progression to cardiogenic shock or death during hospitalization. In this same study, only Cys C levels ≥0.84 mg/L and impaired LVEF <40% were predictors of the risk of death during the follow-up. Ichimoto et al. [20], in a population of 71 patients with STEMI, had also suggested the prognostic value of Cys C, high concentrations of this marker were associated with greater frequency of rehospitalization and acute heart failure episodes. Association of Cys C with greater mortality rate during follow-up was also observed in other studies in patients admitted with NSTEMI [21,22]. A recent study [23] on 660 patients with diabetes and ACS suggested that Cys C was the best renal marker for predicting death at long-term. A Cys C value of 1.6 mg/L predicted mortality during follow-up with sensitivity around 72% and specificity of 71%. Manzaro et al. [24] had demonstrated that GRACE score combined to Cys C levels improved risk stratification in NSTEMI (hazard ratio 2.25; confidence interval 95%; 1.61–3.15; p < 0.001).

**Conclusion**

Cys C is a novel sensitive marker of mild renal impairment (not detected by creatinine). Its role in the development of atherosclerosis and CAD may be due to its cysteine protease activity, modulating the vascular inflammatory response. The results of our study suggest that high Cys C levels indicate the severity of CAD in patients with ACS and normal renal function. Cys C is also a strong predictor for risk of cardiovascular events and death. Therefore, it can be a good prognostic marker for risk stratification after ACS.

**References**

[1] Shlipak MG, Sarnak MJ, Katz R, Fried LF, Seliger SL, Newman AB, et al. Cystatin C and the risk of death and cardiovascular events among elderly persons. N Engl J Med 2005;352:2049–60.
[2] Go AS, Chertow GM, Fan D, McCulloch CE, Hsu C. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004;351:1296–305.
[3] Weiner DE, Tighiouart H, Amin MG, Stark PC, MacLeod J, Cathcart D, et al. Serum cystatin C as a new marker for noninvasive estimation of glomerular filtration rate and as a marker for early renal impairment. Am J Kidney Dis 2000;36:28–34.
[4] Coll E, Botey A, Alvarez L, Poch E, Quinto L, Saurina A, et al. Serum cystatin C: a new renal marker for risk stratification after ACS. J Saudi Heart Assoc 2016;28:144–151.
[5] Lange J, Price CP, Scott MG. Cystatin C: an improved estimator of glomerular filtration rate? Clin Chem 2002;48:699–707.
chain reaction directly for in situ and northern blot hybridizations. J Histochem Cytochem 1993;41:1863–7.

[16] Wang J, Sim AS, Wang XL, Salonikas C, Moriatis M, Naidoo D, et al. Relations between markers of renal function, coronary risk factors and the occurrence and severity of coronary artery disease. Atherosclerosis 2008;197:853–9.

[17] Koc M, Batur MK, Karaarslan O, Abali G. Clinical utility of serum cystatin C in predicting coronary artery disease. Cardiol J 2010;17:374–80.

[18] Niccoli G, Conte M, Della Bona R, Altamura L, Siviglia M, Dato I, et al. Cystatin C is associated with an increased coronary atherosclerotic burden and a stable plaque phenotype in patients with ischemic heart disease and normal glomerular filtration rate. Atherosclerosis 2008;198:373–80.

[19] Silva D, Cortez-Dias N, Jorge C, Marques JS, Carrilho-Ferreira P, Magalhães A, et al. Cystatin C as prognostic biomarker in ST-segment elevation acute myocardial infarction. Am J Cardiol 2012;109:1431–8.

[20] Ichimoto E, Jo K, Kobayashi Y, Inoue T, Nakamura Y, Kuroda N, et al. Prognostic significance of cystatin C in patients with ST-elevation myocardial infarction. Circ J 2009;73:1669–73.

[21] Jernberg T, Lindahl B, James S, Larsson A, Hansson L-O, Wallentin L. Cystatin C: a novel predictor of outcome in suspected or confirmed non-ST-elevation acute coronary syndrome. Circulation 2004;110:2342–8.

[22] Kilic T, Oner G, Ural E, Yumuk Z, Sahin T, Bildirici U, et al. Comparison of the long-term prognostic value of cystatin C to other indicators of renal function, markers of inflammation and systolic dysfunction among patients with acute coronary syndrome. Atherosclerosis 2009;207:552–8.

[23] Fu Z, Xue H, Guo J, Chen L, Dong W, Gai L, et al. Long-term prognostic impact of cystatin C on acute coronary syndrome octogenarians with diabetes mellitus. Cardiovasc Diabetol 2013;12:157.

[24] Manzano-Fernández S, López-Cuenca A, Januzzi JL, Parra-Pallares S, Mateo-Martínez A, Sánchez-Martínez M, et al. Usefulness of β-trace protein and cystatin C for the prediction of mortality in non ST segment elevation acute coronary syndromes. Am J Cardiol 2012;110:1240–8.