Cystatin C as Prognostic Biomarker in ST-Segment Elevation Acute Myocardial Infarction

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Cystatin C is a marker of renal dysfunction, and preliminary studies have suggested it might have a role as a prognostic marker in patients with coronary artery disease. The aim of the present study was to evaluate the usefulness of cystatin C for risk stratification of patients with ST-segment elevation myocardial infarction, regarding in-hospital and long-term outcomes. We included 153 consecutive patients with ST-segment elevation myocardial infarction treated by primary angioplasty. The baseline cystatin C level was measured at coronary angiography. The in-hospital outcome was determined as progression to cardiogenic shock or in-hospital death, and the long-term outcome was assessed, considering the following end points: (1) death and (2) death or reinfarction. Of the 153 patients evaluated (age 61 ± 12 years; 75.6% men), 15 (14.4%) progressed to cardiogenic shock and 4 (2.7%) died during hospitalization. The patients who progressed to cardiogenic shock or died during hospitalization had significantly greater cystatin C levels (1.02 ± 0.44 vs 0.69 ± 0.24 mg/L; p = 0.001). Long-term follow-up was available for 130 patients (583 ± 163 days). Among them, 11 patients died and 7 had reinfarction. A high baseline cystatin C level was associated with an increased risk of death (hazard ratio 8.5; p = 0.009) and death or reinfarction (hazard ratio 3.89; p = 0.021). Furthermore, only high baseline cystatin C levels and left ventricular ejection fraction ≤40% were independent predictors of the long-term risk of death, with synergistic interaction between the 2. In conclusion, cystatin C is a new biomarker with significant added prognostic value for patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention, predicting both short- and long-term outcomes. **(Am J Cardiol 2012;109:1431–1438)**

The risk stratification of patients with coronary artery disease, particularly progression to death and acute heart failure, has been the subject of research in recent years. Several biomarkers have been identified over the years, and the search for new ones with better and more accurate profiles has been very intense. Cystatin C is a cysteine protease inhibitor that is produced at a constant rate in all nucleated cells and freely filtered by the glomerulus, without secretion or subsequent tubular reabsorption.[1] Several studies have shown that it is a good marker of renal dysfunction, particularly in patients with creatinine levels within normal limits.[2] Cystatin C is also physiologically expressed in cardiomyocytes, and its production increases in conditions of ischemia or hypoxia. Furthermore, by regulating protease activity, cystatin C modulates the inflammatory response, extracellular matrix degradation, and phagocytic activity.[3] That might explain its potential association with the progression of atherosclerosis and destabilization of the atheroma plaque.[4,5] Therefore, we postulated that cystatin C might be a useful biomarker for prognostic stratification in patients with myocardial infarction. The prognostic value of cystatin C has been documented in patients with acute coronary syndrome without ST-segment elevation, with respect to in-hospital outcomes and long-term prognosis.[6] However, its value in ST-segment elevation acute myocardial infarction (STEMI) remains unclear, probably because existing studies are of limited scope.[7] Therefore, the aim of the present study was to evaluate the prognostic value of cystatin C, regarding in-hospital and long-term outcomes in patients with STEMI.

Methods

This was a prospective observational study of patients consecutively admitted with the diagnosis of STEMI who underwent urgent coronary angiography from June 2008 to June 2009. All patients met the following criteria: age ≥18

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years; chest pain at rest lasting >30 minutes within the past 24 hours; ST-segment elevation of ≥1 mm in ≥2 consecutive leads that persisted for >30 minutes or was presumably new left bundle branch block; and admission to the hospital within the past 24 hours. Patients with chronic renal failure requiring dialysis were excluded from the analysis.

The hemodynamic status was evaluated on admission, including systemic blood pressure measurement and assessment of the Killip-Kimball class. At coronary angiography, a blood sample was taken for quantification of cystatin C (using automatic immunonephelometry methods), creatinine, glomerular filtration rate (GFR) (estimated using the Modification of Diet in Renal Disease formula), urea, uric acid, and N-terminal probrain natriuretic peptide (NT-proBNP). At 24 to 72 hours after revascularization, an echocardiographic study was performed, and the left ventricular ejection fraction (EF) was calculated using the biplane Simpson method. Significant left ventricular systolic dysfunction was defined as an EF of ≤40%. The maximum Killip-Kimball class during hospitalization was prospectively determined. During follow-up, the patients were evaluated in person at 12 months, and a structured questionnaire for the description of events was used. The circumstances of death were determined from the hospital records and/or interviews with the relatives. Participation in the study required informed consent. The study's protocol complied with the Declaration of Helsinki and was approved by the ethics committee of the North Lisbon Hospital Center.

Regarding the in-hospital outcomes, the following end points were considered: (1) hemodynamic deterioration during hospitalization (defined as the occurrence of a final maximum Killip-Kimball class greater than that observed at urgent coronary angiography) and (2) progression to death or cardiogenic shock (composite end point). Regarding the long-term prognosis, the following composite end points were considered at any point after STEMI: death and death or reinfarction (composite end point).

Continuous variables are reported as the mean ± SD and were compared using *t* tests or the Wilcoxon rank sum test, as appropriate. Categorical variables are reported as the percentages of the cohort and were compared using Fisher's exact tests. The correlation of baseline cystatin C with NT-proBNP was determined using Pearson's coefficient. The accuracy for predicting each clinical end point was determined by the area under the receiver operating characteristic curve, for the significant continuous variables. Univariate and multivariate Cox regression analyses were conducted to identify and account for significant predictors of the clinical outcome. The quartile class associated with a greater risk on univariate analysis was considered as the testing class for continuous variables. Thus, the fourth quartile class was considered for laboratory variables, including cystatin C (cystatin C ≥0.84 mg/L [fourth quartile] is referred to as high cystatin C), and the first quartile class was considered for blood pressure, GFR, and EF (EF of ≤40%; first quartile; referred to as left ventricular global systolic compromise). To avoid overfitting, nonsignificant predictor variables were removed from the regression model in a stepwise fashion. Additional analyses included Kaplan-Meier representations for the time-to-event data. Statistical analysis was performed using the Statistical Package for Social Sciences, version 17.0 (SPSS, Chicago, Illinois). All tests of significance were 2-sided, with $p < 0.05$ considered statistically significant.

Table 1
Population characteristics

Cardiovascular Risk Factors	Patients (n)
Hypertension	91 (64%)
Hypercholesterolemia	78 (55%)
Diabetes mellitus type 2	35 (25%)
Smoker	66 (47%)
Former smoker (stopped ≥1 year previously)	12 (9%)

Table 2
Angiographic and procedural characteristics of the population

Characteristic	Patients (n)
Vessels with significant lesions	
1 Vessel	81 (53%)
2 Vessels	47 (31%)
3 Vessels	23 (15%)
Left main disease	2 (1%)
Infarct-related vessel	
Anterior descending artery	68 (45%)
Right coronary artery	67 (44%)
Circumflex artery	3 (2%)
Stent type	
Bare metal stent	83 (54%)
Drug-eluting stent	67 (44%)
Both	3 (2%)

Results

A total of 153 patients admitted with the diagnosis of STEMI and who underwent primary percutaneous coronary intervention were evaluated. Of these patients, 2 were excluded because of previous renal failure or dialysis. Of the remaining 151 patients, 115 were men (76.2%) and their mean age was 61 ± 12 years (range 36 to 91). Cardiovascular risk factors were very prevalent, but 11 patients (15.7%) had no identifiable conventional risk factors (Table 1). On admission, 98 patients (94.2%) were hemodynamically stable and showed no signs of heart failure (Killip-Kimball class I). The baseline cystatin C level (0.74 ± 0.29 mg/L, range 0.04 to 2.24) did not differ according to the hemodynamic parameters recorded on admission (ie, blood pressure or Killip-Kimball class) but correlated with NT-proBNP ($R = 0.41$; $p < 0.001$). The angiographic and procedural characteristics of the population are listed in Table 2. Of the 151 patients, 141 underwent successful percutaneous coronary intervention (final Thrombolysis In Myocardial Infarction flow grade III), 8 had no reflow, and 2 required major dissections of the culprit vessel.

During hospitalization, hemodynamic deterioration occurred in 15 patients (14.4%), the maximum Killip-Kimball class reached was II, III, and IV in 6 (4.1%), 7 (4.8%), and 15 patients (10.2%), respectively. The patients who progressed with deterioration of Killip-Kimball class had a greater baseline cystatin C (0.94 ± 0.45 vs 0.69 ± 0.24 mg/L, $p = 0.006$). Furthermore, the cystatin C levels were

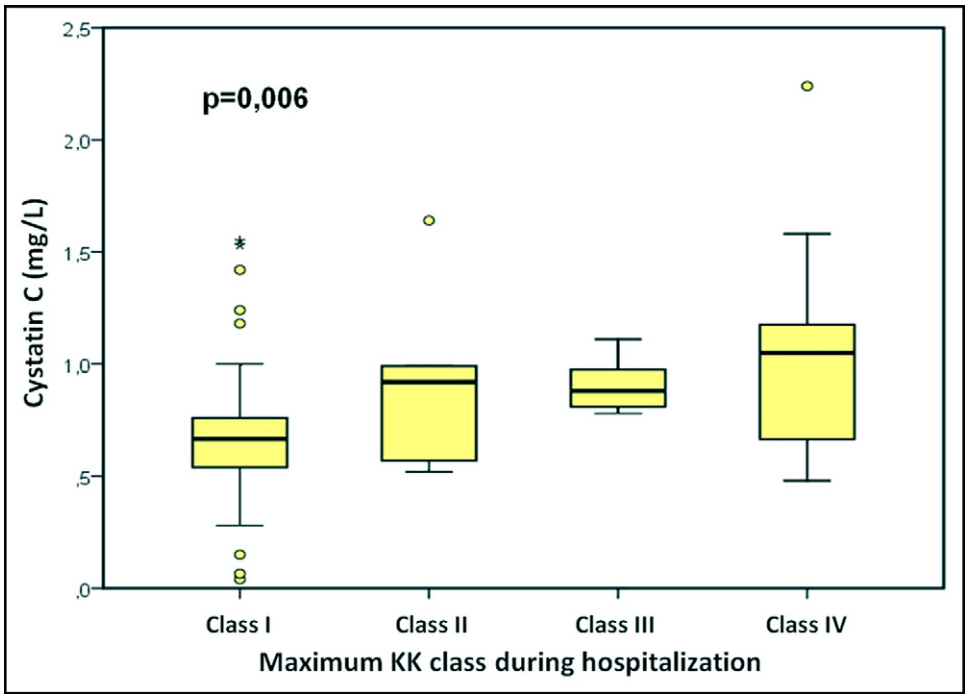

Figure 1. Serum concentration of cystatin C according to maximum Killip-Kimball class during hospitalization.

Table 3
Accuracy of baseline clinical and laboratory parameters in predicting death or cardiogenic shock during hospitalization

Variable	Receiver Operating Characteristic Curve			Univariate Analysis			
	Area	95% CI	p Value	Fourth Quartile	OR	95% CI	p Value
Systolic blood pressure (mm Hg)	0.75*	0.59–0.92	0.006	≤125.5†	4.40	1.22–15.84	0.026
Diastolic blood pressure (mm Hg)	0.72*	0.56–0.89	0.015	≤71.5†	4.40	1.22–15.84	0.026
Mean blood pressure (mm Hg)	0.76*	0.59–0.93	0.005	≤90.3†	5.78	1.47–22.44	0.013
Cystatin C (mg/L)	0.75	0.62–0.89	0.001	≥0.84	5.40	1.88–15.50	0.002
Creatinine (mg/dl)	0.79	0.76–0.92	<0.001	≥1.10	6.93	2.35–20.42	<0.001
Glomerular filtration rate (ml/min/1.73 m^2)	0.77*	0.64–0.89	0.001	≤71.1†	4.91	1.67–14.37	0.004
Urea (mg/dl)	0.71	0.61–0.81	0.005	≥52.25	1.72	0.59–5.05	NS
Uric acid (mg/dl)	0.77	0.67–0.87	<0.001	≥6.3	5.15	1.80–14.76	0.002
N-terminal probrain natriuretic peptide (pg/ml)	0.68	0.55–0.81	0.016	≥688.5	3.19	1.13–9.07	0.035
Ejection fraction (%)‡	0.72*	0.54–0.89	0.015	≤40%†	3.44	1.12–10.58	0.036

* Prediction of nonprogression to death or cardiogenic shock.
† First quartile.
‡ From 24 to 72 hours.

greater in the patients who progressed to cardiogenic shock (Figure 1). Overall, the EF was 51 ± 12%. Despite percutaneous revascularization, left ventricular global systolic impairment persisted 24 to 72 hours after catheterization in 25 patients (17.1%). In those patients, a trend was seen for the baseline cystatin C levels to be greater (0.86 ± 0.41 vs 0.74 ± 0.30 mg/L; p = 0.08). A total of 19 patients (11.6%) progressed to death or cardiogenic shock during hospitalization (composite end point). Cystatin C and the associated parameters of renal function were significantly greater in these patients (cystatin C, 1.02 ± 0.44 vs 0.69 ± 0.24 mg/L, p = 0.001; creatinine, 1.25 ± 0.46 vs 0.91 ± 0.61 mg/dl, p <0.001; urea, 53 ± 14 vs 44 ± 15 mg/dl, p = 0.006; uric acid, 6.25 ± 1.36 vs 5.42 ± 3.4 mg/dl, p <0.001), with a lower GFR (67.8 ± 30.5 vs 98.0 ± 35.1 ml/min/1.73 m^2, p = 0.001). The accuracy of these parameters in predicting unfavorable in-hospital outcomes, evaluated using the area under the receiver operating characteristic curve, was only moderate (Table 3). In addition, patients belonging to the highest quartile (fourth quartile) of each parameter (except for urea) were a group at particularly high risk (Table 3). However, on multivariate analysis, only GFR of ≤71.1 ml/min/1.73 m^2 constituted an independent risk factor for death or cardiogenic shock (odds ratio [OR] 5.2, 95% confidence interval [CI] 1.27 to 21.37; p = 0.022). It should be highlighted that among patients with a baseline creatinine of <1.5 mg/dl, those with high cystatin C levels presented with a greater risk of subsequent hemodynamic deterioration (OR 3.96, 95% CI 1.19 to 13.20; p = 0.018) and progression to cardiogenic shock or death (OR 3.36, 95% CI 1.04 to 10.86; p = 0.034).

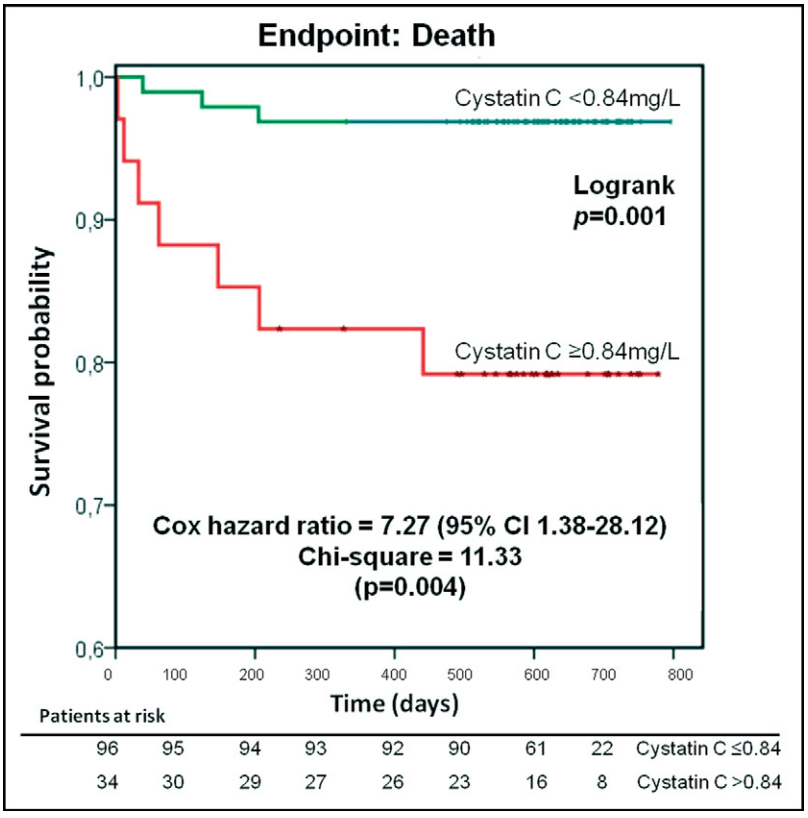

Figure 2. Prognostic stratification of occurrence of death in follow-up period according to cystatin C, evaluated using Kaplan-Meier survival curve.

Long-term follow-up data were available for 130 patients (62 ± 12 years; 74% men). During the follow-up period (583 ± 163 days), 11 patients (8%) died and 7 (5%) experienced reinfarction. The patients who died were older (73 ± 7 vs 60 ± 12 years; p = 0.002) and had greater baseline cystatin C (0.94 ± 0.23 vs 0.71 ± 0.29 mg/L, p = 0.002), creatinine (1.11 ± 0.34 vs 0.89 ± 0.29 mg/dl, p = 0.034), urea (55 ± 19 vs 44 ± 14 mg/dl, p = 0.032), and NT-proBNP (2,207 ± 3,668 vs 814 ± 1,954 pg/ml, p = 0.008) levels and lower EF (39 ± 11% vs 52 ± 11%, p = 0.008). The prognostic accuracy of these parameters in predicting death during follow-up, evaluated by the area under the receiver operating characteristic curve, was moderate (cystatin C, OR 0.77, 95% CI 0.63 to 0.92, p = 0.003; creatinine, OR 0.89, 95% CI 0.52 to 0.85, p = 0.042; urea, OR 0.69, 95% CI 0.52 to 0.87, p = 0.034; NT-proBNP, OR 0.74, 95% CI 0.63 to 0.85, p = 0.008; EF, OR 0.80, 95% CI 0.64 to 0.97, p = 0.008). On univariate analysis, cystatin C, urea, and EF were predictors of long-term mortality. However, only the presence of elevated cystatin C and impaired EF were independent predictors, increasing the risk of death by 8 times (hazard ratio [HR] 8.5, 95% CI 1.71 to 42.15, p = 0.009) and 4 times (HR 4.73, 95% CI 1.18 to 19.0, p = 0.028), respectively. Thus, the cumulative survival of patients with high cystatin C levels was significantly lower in the long term (p = 0.001; Figure 2). In addition, to evaluate the interaction of the 2 risk factors, the Kaplan-Meier survival curve was determined for cystatin C, with stratification for EF. The risk of death was significantly greater in patients presenting with both elevated cystatin C levels and impaired EF (p = 0.003). Remarkably, the risk of death tended to be greater in patients with elevated cystatin C and EF >40% than in those with impaired EF and nonelevated cystatin C, although statistical significance was not reached (Figure 3).

During follow-up, 15 patients (8.5%) progressed to death or reinfarction. These patients had higher cystatin C and creatinine levels and a lower EF (Table 4). The prognostic accuracy of these parameters in predicting the progression to death or reinfarction was moderate (Table 4). On univariate analysis, elevated cystatin C and an EF of ≤40% correlated with the risk of death or reinfarction, and both constituted independent predictors of this outcome (Table 5). Thus, the risk of death or reinfarction more than tripled for patients with elevated cystatin C levels (Figure 4).

Discussion

The results of the present study have demonstrated the prognostic value of cystatin C in the short- and long-term outcomes of patients with STEMI who have undergone primary percutaneous coronary intervention. Despite numerous technical advances regarding early diagnosis and treatment, patients with STEMI still have a high risk of death, particularly if progression to cardiogenic shock occurs. Therefore, risk stratification assumes special significance to identify those patients who will require more aggressive therapy and intensive monitoring. In recent years, the prognostic potential of several biomarkers has been investigated. Special attention has recently been given to biomarkers of renal dysfunction.[8,9] It is now

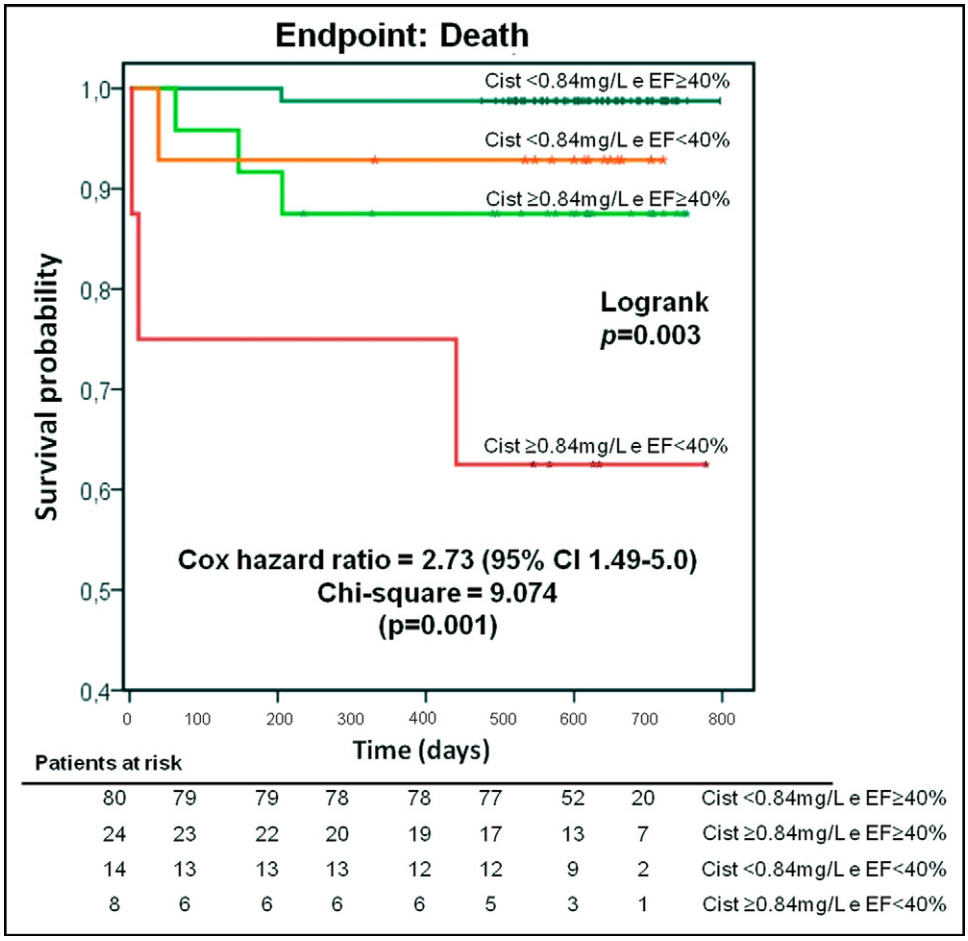

Figure 3. Prognostic stratification of occurrence of death in follow-up period according to cystatin C level and EF, evaluated using Kaplan-Meier survival curve.

Table 4
Comparison of clinical and laboratory characteristics according to occurrence of death or reinfarction during follow-up period

Admission	Favorable Outcome	Death or Reinfarction	p Value	Receiver Operating Characteristic Curve		
				Area	95% CI	p Value
Systolic blood pressure (mm Hg)	139 ± 31	141 ± 22	NS	—	—	NS
Diastolic blood pressure (mm Hg)	81 ± 19	80 ± 15	NS	—	—	NS
Mean blood pressure (mm Hg)	102 ± 21	104 ± 16	NS	—	—	NS
Cystatin C (mg/L)	0.73 ± 0.30	0.86 ± 0.23	0.016	0.69	0.56–0.82	0.016
Creatinine (mg/dL)	0.89 ± 0.30	1.05 ± 0.31	0.042	0.66	0.52–0.79	0.044
Glomerular filtration rate (ml/min/1.73 m^2)	96.9 ± 37.1	80.9 ± 25.3	NS	—	—	NS
Urea (mg/dl)	44 ± 14	50 ± 19	NS	—	—	NS
Uric acid (mg/dl)	5.64 ± 3.55	5.69 ± 1.64	NS	—	—	NS
N-terminal probrain natriuretic peptide (pg/ml)	865 ± 2,019	1,691 ± 3,228	NS	—	—	NS
Ejection fraction (%)*	53 ± 11	41 ± 10	0.003	0.77†	0.65–0.89	0.003

* From 24 to 72 hours.
† Prediction of nonprogression to death or reinfarction.

recognized that there is an intense and close interaction between the kidney and heart.[4,10,11] Thus, the concept of a cardio-renal syndrome was introduced to describe the 2-way interaction of acute and/or chronic dysfunction of these organ systems.[10,12]

The plasma concentration of creatinine is commonly used to estimate renal function. Thus, it was shown to correlate with the risk of unfavorable in-hospital evolution in patients with acute heart failure (including in the setting of STEMI).[10,13,14] We observed that the baseline concentration of creatinine is the strongest predictor of short-term unfavorable outcomes, with the risk of death or progression to cardiogenic shock 7 times greater for patients with a baseline creatinine ≥1.1 mg/dl. However,

Table 5
Association of baseline clinical and laboratory characteristics with risk of death or reinfarction during follow-up

Variable	Fisher's Exact Test With Risk Estimate			Univariate Cox Regression			Multivariate Cox regression		
	OR	95% CI	p Value	HR	95% CI	p Value	HR	95% CI	p Value
Cystatin C ≥0.84 mg/L	4.33	1.48–12.72	0.013	3.40	1.23–9.39	0.018	3.89	1.23–12.31	0.021
Creatinine ≥1.10 mg/dl	1.84	0.62–5.51	NS	—	—	NS	—	—	NS
GFR ≤71.1 ml/min/1.73 m^2*	1.55	0.49–0.93	NS		—	NS	—	—	NS
Urea ≥52.25 mg/dl	2.5	0.85–7.33	NS	—	—	NS	—	—	NS
Uric acid ≥6.3 mg/dl	2.28	0.78–6.66	NS	—	—	NS			NS
N-terminal probrain natriuretic peptide ≥688.5 pg/ml	2.28	0.64–7.01	NS	—	—	NS	—	—	NS
Ejection fraction ≤40%*	4.37	1.37–14.17	0.018	3.32	1.09–10.16	0.035	3.46	1.09–10.96	0.035

* First quartile.

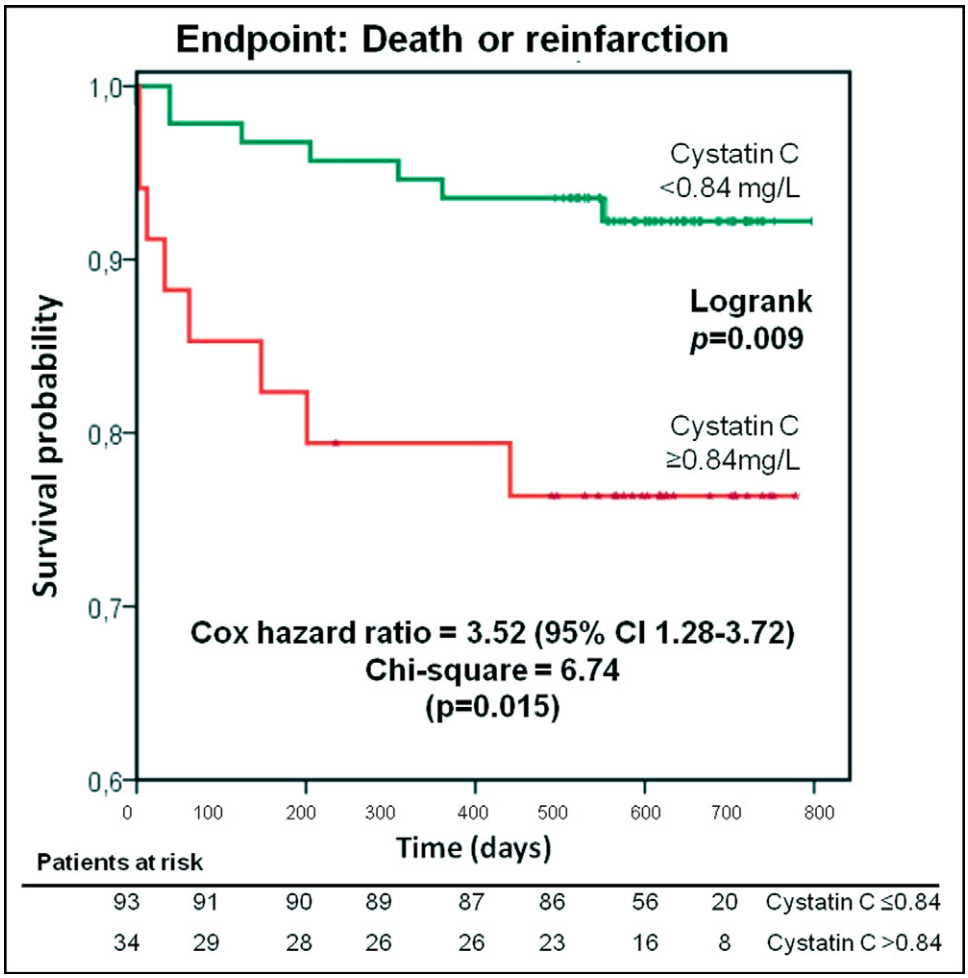

Figure 4. Prognostic stratification of occurrence of death or reinfarction in follow-up period according to cystatin C level, evaluated using Kaplan-Meier survival curve.

cystatin C was also found to be of use in detecting patients with a risk of hemodynamic deterioration when the creatinine levels were within the normal limits. Furthermore, the affect of impaired renal function in patients with STEMI manifests itself mainly in the in-hospital period. Neither creatinine on admission nor the GFR have distinguished the long-term prognosis of patients who survived hospitalization. It is accepted that the accuracy of creatinine in prognostic stratification is compromised because its concentration is influenced by a range of other factors, including age, gender, muscle mass, physical activity, diet, and medication.[15]

Cystatin C is a sensitive endogenous marker of renal function, and it has been demonstrated that it detects a reduced GFR even in patients with normal creatinine levels.[7] However, it has also been observed that cystatin

C elevation can occur without impairment of renal function. Very importantly, a number of studies suggested that patients with elevated cystatin C have greater cardiovascular risk and a greater risk of mortality.[7–9,12,15,16] Cystatin C has, therefore, been proposed to be not only a marker of renal dysfunction but also a biomarker of atherosclerosis and cardiovascular risk.[12] Some experiments using animal models have suggested that cystatin C might interact with the inflammatory response, leading to activation of cathepsins and resulting in the degradation of collagen in the atheroma plaque, with an increased risk of rupture.[4]

The results of our study, which included a homogeneous population of 153 patients with STEMI undergoing primary angioplasty, suggest that patients with elevated initial levels of cystatin C (≥0.84 mg/L) have an approximately 5 times greater risk of progression to cardiogenic shock or death during hospitalization. However, its greatest utility lies in its capacity to identify patients at risk of death in the long term. Its strong correlation with the risk of death (HR 8.5) appears to have played an important role in its correlation with the composite end point of death or reinfarction (HR 3.89). Also, of all the variables studied, only cystatin C levels of ≥0.84 mg/L and impaired EF were independent predictors of the risk of death. Furthermore, the effect of elevated cystatin C levels on the risk of death was twice as strong as EF impairment. Our results also suggest that an interaction exists between these 2 variables in their prognostic potential. The presence of elevated cystatin C identified the subgroup of patients with impaired EF at a greater risk of death. Although statistical significance was not achieved, we note the trend toward a greater risk of unfavorable evolution among patients with cystatin C of ≥0.84 mg/L and normal EF compared to those with impaired global systolic function but nonelevated cystatin C.

A previous study by Ichimoto et al[7] had already suggested the potential value of cystatin C in the prognostic stratification of patients with STEMI. However, a smaller population was studied (n = 71), with a shorter follow-up period (5.6 ± 2.8 months). In an observational study by Jernberg et al[6] of patients with myocardial infarction without ST-segment elevation, greater long-term mortality was observed among patients with elevated cystatin C levels—the cumulative probability of death during an average follow-up of 40 months was 12 times greater for patients with cystatin C >1.25 mg/L.[17] A similar association was observed by Kilic et al[18] in a heterogeneous population of 160 patients with acute coronary syndrome. To our knowledge, ours is the largest prospective observational study of patients with STEMI to evaluate the short- and long-term prognostic value of this new biomarker. A limitation of the present study was that we measured the biomarker at a single point.

In a study of this nature, it is not possible to fully identify the pathophysiologic mechanisms underlying the prognostic significance of cystatin C after STEMI. However, a number of possibilities can be considered. The results suggest that a part of the prognostic significance of cystatin C derives from its correlation with the severity of left ventricular systolic function impairment, but the demonstration of the synergic interaction between an elevated cystatin C level and impaired EF suggests that other mechanisms are also relevant. Cystatin C identifies mild renal dysfunction (not detected by the analysis of serum creatinine), and in these circumstances, there is increased activation of the renin-angiotensin-aldosterone system with potentially deleterious effects. However, no evidence has been shown to support such powerful prognostic significance of the overactivation of this neurohumoral system after infarction. Also not to be ignored is the possibility that cystatin C is a biologically active mediator in the setting of the local and systemic inflammatory response that accompanies STEMI.[4] It has been suggested that cystatin C might modulate the vascular inflammatory response at a local and systemic level. This would affect the stability of the atheroma plaques, progression of atherosclerotic disease, and, potentially, the electrophysiologic properties of cardiomyocytes.[4] This could explain why the long-term prognostic significance of cystatin C exceeds that of the conventional parameters of renal function.

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