FULL LENGTH ARTICLE

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 þ 2.1 months. High Cystatin C concentrations were associated to the occurrence of unfavourable outcomes and cardiovascular mortality during follow-up (1.19 þ 0.4 vs. 1.01 þ 0.35 mg/L, $p = 0.01$ and 1.21 þ 0.36 vs. 0.96 þ 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 receiveroperating 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.**

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

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

P.O. Box 2925 Riyadh – 11461KSA
Tel: +966 1 2520088 ext 40151
Fax: +966 1 2520718
Email: sha@sha.org.sa
URL: www.sha.org.sa

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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.

Abbreviations

CKD	Chronic kidney disease
HD	hemodialysis
LVFS	left ventricular fractional shortening
TDI	Tissue Doppler imaging
BSA	Body surface area
BNP	brain natriuretic peptide
BP	blood pressure
TTE	transthoracic echocardiography
LA	left atrial
IVST	interventricularseptal thickness
LVPWT	left ventricular posterior wall thickness
LVEDd	left ventricular end-diastolic dimension
LVESd	left ventricular end-systolic dimension
LVMi	left ventricular mass index
2D-LVEDVi	two-dimensional left ventricular end diastolic volume index
2D-LVESVi	two-dimensional left ventricular end systolic volume index
LVFS	left ventricular fractional shortening
LVEFs	left ventricular ejection fraction calculated by biplane Simpson method
3D-LVEDVi	three-dimensional left ventricular end diastolic volume index
3D-LVESVi	three-dimensional left ventricular end systolic volume index
3D-LAEDVi	three-dimensional left atrial end diastolic volume index
3D-LAESVi	three-dimensional left atrial end systolic volume index
3D-LVEF	three-dimensional left ventricular ejection fraction
3D-LAEF	three-dimensional left atrial ejection fraction
GLS	two-dimensional global longitudinal strain
GRS	two-dimensional global regional strain
GCS	two-dimensional global circumferential strain
LAS	left atrial strain
RVS	right ventricular strain
3D-GLS	three-dimensional global longitudinal strain

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 brunch 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 $\geqslant$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 hypoglycemic drug or insulin 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,

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)			
Age (y)	58 (11.65)	56.17 (13.6)	59.2 (10.5)	NS
Sex (M:F)	105:22	35:8	70:14	NS
BMI (kg/m^2)	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 (%)			
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

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 ejection infarction.

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 (53.5%)
CX	26 (31%)
RC	13 (15.5%)

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

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

	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)	

CAD = coronary artery disease; VD = vessel disease.
[a] All values are expressed as mean (standard deviation).

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): $186.3 \times (\text{serum creatinine}/88.4)^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female})$. 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 4. Cystatin C levels and severity of coronary artery disease in patients with NSTEMI (Group 1 = 43 patients).

	Cystatin C (mg/L)[a]	p
Vessels with significant lesions		
1-VD	0.96 (0.24)	0.003
2-VD	1.08 (0.49)	
3-VD	1.34 (0.60)	
CAD severity score		
Mild CAD (GENSINI score 1–20)	0.84 (0.21)	0.001
Severe CAD (GENSINI score >20)	1.10 (0.11)	

CAD = coronary artery disease; VD = vessel disease.
[a] All values are expressed as mean (standard deviation).

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

	Cystatin C (mg/L)[a]	p
Vessels with significant lesions		
1-VD	0.82 (0.16)	0.018
2-VD	0.93 (0.30)	
3-VD	1.11 (0.55)	
CAD severity score		
Mild CAD (GENSINI score 1–20)	0.89 (0.15)	<0.001
Severe CAD (GENSINI score >20)	1.18 (0.12)	
Initial TIMI flow		
TIMI 0	1.52 (0.21)	<0.001
TIMI 1	1.26 (0.24)	
TIMI 2	0.99 (0.26)	
TIMI 3	0.90 (0.27)	

CAD = coronary artery disease; TIMI flow = Thrombolysis In Myocardial Infarction flow; VD = vessel disease.
[a] All values are expressed as mean (standard deviation).

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 brunch 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 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.

Table 7. Association between laboratory parameters and major adverse cardiac events during follow-up.

Variable	MACE[a]		p
	Yes	No	
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

BNP = brain natriuretic peptide; MACE: =major adverse cardiovascular events.
[a] All values are expressed as mean (standard deviation).

($p < 0.001$) (Table 5). Cys C levels were also higher in patients having no-reflow after percutaneous coronary intervention but without significant difference (1.19 ± 0.16 and 1.12 ± 0.15, respectively).

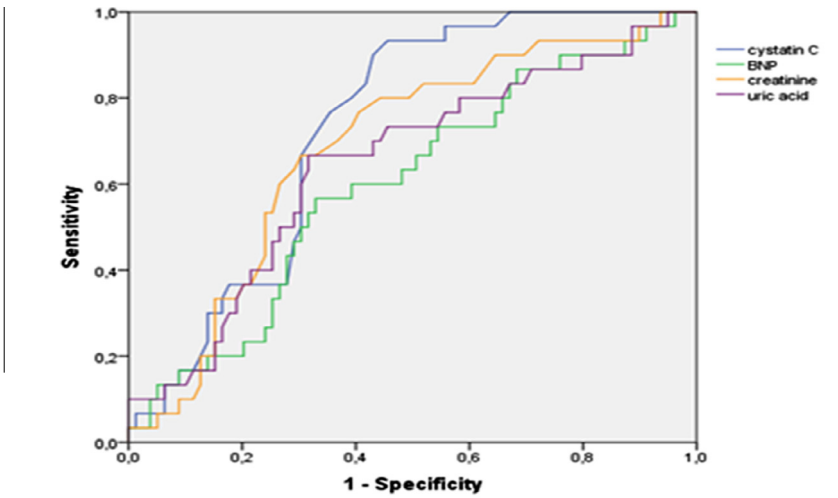
During hospitalization, the maximum of KILLIP class reached was II in 11 patients (8.6%), III in three patients (2.3%), and 23 patients (18.1%) presented hemodynamic deterioration. These patients had greater Cys C concentration (0.96 ± 0.24 vs. 0.78 ± 0.19, $p < 0.001$). Furthermore, Cys C levels were 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 8. Comparison of clinical and laboratory characteristics according to occurrence of death during the follow-up period in the study population.

Variables	Favourable outcome[a]	Death[a]	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

BNP = brain natriuretic peptide; NS = not significant.
[a] All values are expressed as mean (standard deviation).



Variables	Area under curve	Cut-off	Sensitivity	Specificity
Cystatin C	0.743	0.97 mg/L	84%	66%
Creatinine	0.682	80.5 µmol/L	78%	52%
Uric Acid	0.617	340.7 µmol/L	74%	50%
BNP	0.607	135.6 pg/mL	72%	48%

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.

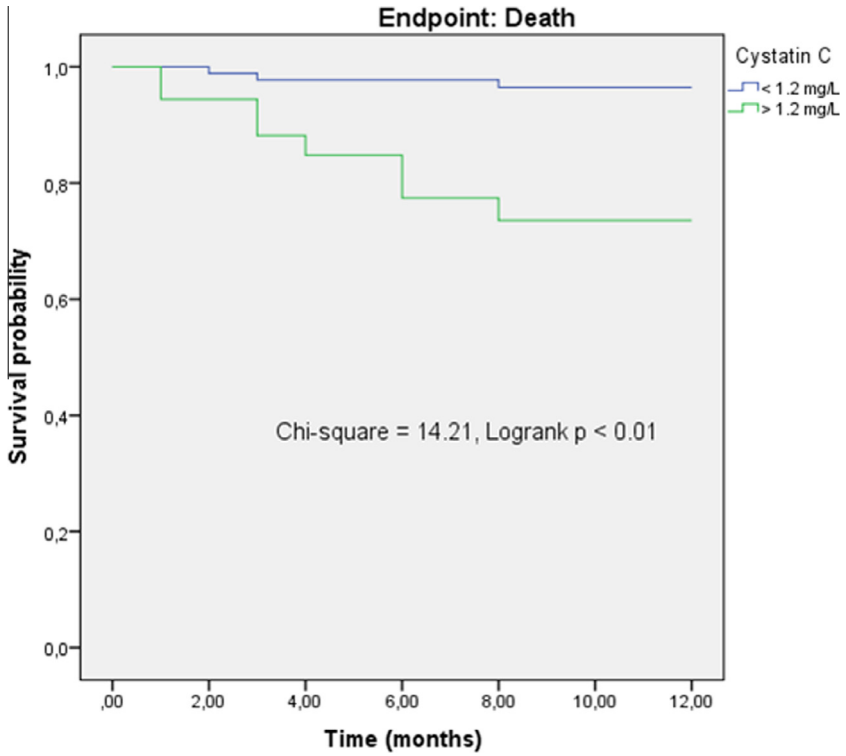


Figure 2. Occurrence of death during the follow-up period according to cystatin C, evaluated with Kaplan-Meier survival curve.

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 cut-off 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 ($\geqslant$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 $\geqslant$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.

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