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RESEARCH ARTICLE

Increase of serum Cyclophilin C levels in the follow-up of coronary artery disease: A biomarker and possible clinical predictor

Aumento de niveles séricos de Ciclofilina C en el seguimiento de la enfermedad arterial coronaria: un biomarcador y posible predictor clínico

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Abstract

Objective: *This study is aimed at investigating the changes in serum CypC levels and their relationship with cardiovascular events at 12 months of follow-up in coronary artery disease (CAD) patients.* **Methods:** *The study included a total of 125 subjects (40 patients with acute CAD, 40 patients with chronic CAD, and 45 control volunteers) and we analyzed plasma CypC levels from baseline to 6 and 12 months for a better understanding of its behavior in atherosclerosis.* **Results:** *Serum CypC levels were shown to be gradually increased in CAD patients (30.63 pg/mL ± 3.77 at baseline, 38.70 pg/mL ± 6.41 at 6 months [p = 0.25], and 47.27 pg/mL ± 5.65 at 12 months [p = 0.007]). In addition, serum CypC levels during the follow-up were a significant predictor of CAD (c-statistic 0.76 at 6 months and 0.89 at 12 months; p < 0.001). Despite it, there was no significant association between CypC and cardiovascular events, but serum CypC levels tended to be higher in patients suffering cardiovascular events during the follow-up (29.02 pg/mL ± 6.39 vs. 79.96 pg/mL ± 22.18; p = 0.029). In this regard, plasma levels of high-sensitivity C-reactive protein (hsCRP) > 2.3 mg/L plus NT-proBNP > 300 pg/mL together were significant predictors of cardiovascular events during the follow-up in CAD patients with CypC levels >17.5 pg/mL (p = 0.048).* **Conclusions:** *Taken together, our results suggest that serum CypC levels increase during the follow-up in CAD patients and could be a novel biomarker with a possible prognostic value in combination with hsCRP and NT-proBNP.*

Keywords: *Coronary artery disease. Inflammation. Cyclophilin. Biomarkers.*

Resumen

Objetivo: *Este estudio tiene como objetivo investigar los cambios en los niveles séricos de CypC y su relación con eventos cardiovasculares a los 12 meses de seguimiento en pacientes con EAC.* **Método:** *El estudio incluyó un total de 125 sujetos (40 pacientes con EAC aguda, 40 pacientes con EAC crónica y 45 voluntarios de control) y se analizaron los niveles plasmáticos de CypC desde el inicio hasta los 6 y 12 meses para comprender mejor su comportamiento en la aterosclerosis.*

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Resultados: *Se demostró que los niveles séricos de CypC aumentaron gradualmente en pacientes con CAD [(30.63 pg/ml ± 3.77 al inicio del estudio, 38.70 pg/ml ± 6.41 a los 6 meses (p = 0.25) y 47.27 pg/ml ± 5.65 a los 12 meses (p = 0,007)]. Además, los niveles séricos de CypC durante el seguimiento fueron un predictor significativo de EAC (estadístico c 0.76 a los 6 meses y 0.89 a los 12 meses; p < 0.001). A pesar de ello, no hubo asociación significativa entre CypC y eventos cardiovasculares, pero los niveles séricos de CypC tendieron a ser más altos en los pacientes que sufrieron eventos cardiovasculares durante el seguimiento (29.02 pg/mL ± 6.39 vs. 79.96 pg/mL ± 22.18; p = 0.029). En este sentido, los niveles plasmáticos de hsCRP > 2.3 mg/L más NT-proBNP> 300 pg/ml juntos fueron predictores significativos de eventos cardiovasculares durante el seguimiento en pacientes con EAC con niveles de CypC > 17.5 pg/ml (p = 0.048).* **Conclusiones:** *Tomados en conjunto, nuestros resultados sugieren que los niveles séricos de CypC aumentan durante el seguimiento en pacientes con EAC y podría ser un nuevo biomarcador con un posible valor pronóstico en combinación con hsCRP y NT-proBNP.*

Palabras clave: *Enfermedad arterial coronaria. Inflamación. Ciclofilinas. Biomarcadores.*

Introduction

Traditional cardiovascular risk factors (CVRFs) are well known for their association with the presence and prognosis of coronary artery disease (CAD)[1]. Although multiple risk scores were developed to predict CAD with CVRF, new biomarkers play an important role in cardiovascular prognosis. It was reported that plasma levels of N-terminal pro-brain natriuretic peptide (NT-proBNP)[2] and high-sensitivity C-reactive protein (hsCRP)[3] are related to cardiovascular events. There is a link between these biomarkers and the inflammatory condition and atherosclerosis as the cornerstone of CAD is indeed an inflammatory disease[4].

Cyclophilins (Cyps), a subfamily of immunophilins of peptidyl-prolyl cis/trans isomerases, have been implicated in various cellular processes and involved in oxidative stress[5]. Some of them, such as CypA[6], CypB[7], and CypD[8], have been associated with atherosclerotic disease. It has been published that high serum CypC levels are a possible novel biomarker for diagnosing CAD, with a good correlation using a cutoff point of 17.5 pg/mL[9].

Serum CypA levels are significantly higher in patients with CAD in proportion to the severity of disease[10]. Moreover, CypA levels 1 month after acute myocardial infraction have an impact on the prognosis[11]. These findings suggest that Cyps play a continuous role in the CAD and they could be sensitive follow-up biomarkers. Since CypCs have been rarely studied in this field, we analyzed the serum CypC levels of CAD patients from baseline to 6 and 12 months for a better understanding of its behavior during the follow-up in atherosclerosis. This study is aimed at investigating the changes in serum CypC levels and assess if the cutoff point of 17.5 pg/mL keeps the ability to discriminate CAD throughout the 12-month follow-up.

Methods

Population study

The study included a total of 125 subjects (40 patients with acute CAD, 40 patients with chronic CAD, and 45 control volunteers) that were enrolled following the same protocol reported in our previous study[9]. Acute CAD was defined as unstable angina, non-ST-segment myocardial infarction (STEMI), or STEMI according to the current European Society of Cardiology (ESC) Practical Clinical Guidelines[12,13]. Chronic CAD was defined as a clinically stable syndrome without an increase in myocardial biomarkers, as defined in the ESC guidelines[14]. The institutional and regional ethics committee approved the study (Reference: 2016/508, Approval date: December 19, 2016) according to the principles outlined in the Helsinki Declaration. Informed oral and written consent was given by all the subjects participating in this study.

Blood sampling protocol and Cyps measurements

Peripheral blood was obtained from subjects and analyzed as previously described[9]. The blood was centrifuged (3000 rpm, 10 min at 4°C) and supernatants were collected and stored at −80°C until Cyps analysis. After thawed at room temperature, these supernatants were used to measure CypC levels using an ELISA kit. Absorbance measurements were taken using a microplate reader at 450 and 540 nm. Samples were always run in duplicate. The measurement range was 23.5-1.500 pg/mL for CypC. Serum levels below the lower limit of quantitation were undetectable and were therefore considered as 0 pg/mL for statistical analysis. The intra- and inter-assay coefficients of variation of the

ELISA kits were < 10%. No cross-reactivity was observed between Cyp antibodies. The human cyclophilin C ELISA kit (CSB-EL018473HU) was obtained from Cusabio.

Baseline measurements

The electronic medical history was reviewed to obtain all clinical data relative to patients. Clinical characteristics and laboratory values, including NT-proBNP and hsCRP, were collected.

Statistical analysis

SPSS 24 for Windows was used for the statistical analysis. Categorical variables were presented as percentages and continuous variables were presented as means ± SEM. Kolmogorov–Smirnov (with Lilliefors correction) was first performed as a normality test. Statistical significance in qualitative variables was calculated using the Chi-square test. Continuous variables with normal distribution were compared between two groups using the Student's t-test (including Levene's test); otherwise, the non-parametric Mann–Whitney U-test was used. Differences between three groups were calculated using the ANOVA test. Receiver operating characteristic (ROC) curves were generated to assess the sensitivity and specificity of CypC.

Results

The study included 125 subjects (40 patients with acute CAD, 40 patients with chronic CAD, and 45 control volunteers) with a mean age 57.8 ± 14.5 years and 72.8% were male. Patients with CAD had more CVRF as compared to the controls. In the results of the laboratory tests, white blood cells, neutrophils, monocytes, hemoglobin, and glucose were significantly increased in CAD patients. Comparing acute to chronic CAD, a significant difference was seen in only CVRF (active smoker 37.5% vs. 17.5%; p = 0.045). The clinical characteristics of the sample are given in table 1. CypC levels (mean ± SD) were analyzed at baseline, at 6 months, and at 12 months (Fig. 1). The mean follow-up was 64.76 ± 22.16 months. NT-proBNP and hsCRP were measured in 74 CAD patients (37 chronic CAD and 37 acute CAD), with a mean of 463 ± 1699 pg/mL for NT-proBNP and 3.20 ± 6.46 mg/L for hsCRP, and no significant differences between the two groups.

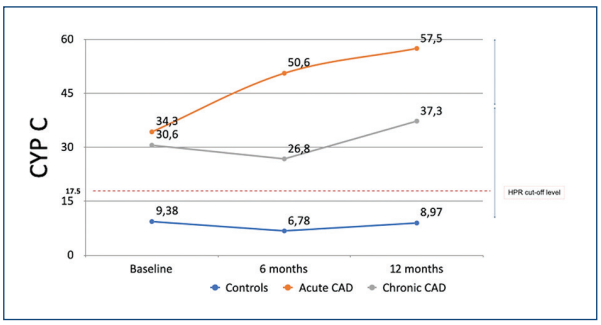

Figure 1. Serum CypC values (mean) along 6- and 12-month follow-up. CypC: cyclophilin C; CAD: coronary artery disease.

CypC levels were significantly higher in CAD patients than in the controls: 32.42 pg/mL ± 3.71 versus 9.38 pg/mL ± 1.51 (p < 0.001), but there were no differences between the acute and chronic CAD groups (34.28 pg/mL ± 5.77 vs. 30.56 pg/mL ± 4.73; p = 0.620). CypC ≥ 17.5 pg/mL was present in 72.5% of acute CAD cases, 57.5% of chronic CAD cases, albeit only in 11.1% of controls. We assessed several differences in the clinical characteristics and CVRF in CAD patients between CypC < 17.5 pg/mL and CypC ≥ 17.5 pg/mL. CypC ≥ 17.5 pg/mL was associated with an older age (64.0 ± 1.6 vs. 52.8 ± 1.8 years; p < 0.001), hypertension (48.2% vs. 27.5%; p = 0.017), dyslipidemia (69.6% vs. 36.2%; p < 0.001), and a higher number of coronary arteries with significant stenosis (91.1% vs. 42%; p < 0.001).

We collected the CypC levels from all patients, except 2 patients (1.6%) at 6 months and 7 patients (5.6%) at 12 months. A significant predictive value of serum CypC levels was found during the 6- and 12-month follow-up. The area under the curve (AUC) (c-statistic) calculated was 0.85, with a significant value (p < 0.001) of CypC as a predictor of CAD at baseline. The AUC was 0.76 at 6 months and 0.89 at 12 months, persisting as a good predictor of CAD (p < 0.001) (Fig. 2).

The analysis of CypC levels during the period evidenced that it gradually increased in the CAD group (30.63 pg/mL ± 3.77 at baseline, 38.70 pg/mL ± 6.41 at 6 months [p = 0.25], and 47.27 pg/mL ± 5.65 at 12 months [p = 0.007]). CypC did not rise in the control group over 12 months (9.4 pg/mL ± 1.5 baseline vs. 9.0 pg/mL ± 1.1; p = ns).

Seventeen of the 80 patients with CAD were admitted with acute coronary syndrome (ACS), 11 patients in the first 12 months, and 6 after that. Four patients were admitted for heart failure, three of them in the first 12 months of follow-up. Patients who experienced a cardiovascular event in the follow-up had 3 times higher

Table 1. Demographic and clinical characteristics

Variables	Controls (n = 45)	Coronary artery disease		p	
		Chronic (n = 40)	Acute (n = 40)	Between three groups	Chronic CAD versus acute CAD
Gender (male)	51.1% (23)	82.5% (33)	87.5% (35)	< 0.001	0.531
Age	45.6 ± 1.5	65.2 ± 1.8	64.2 ± 1.9	< 0.001	0.713
LVEF (%)	--	54.2 ± 10.3	55.6 ± 8.7	--	0.528
Cardiovascular risk factors					
Hypertension	6.7% (3)	60.0% (24)	47.5% (19)	< 0.001	0.262
Dyslipidemia	13.3% (6)	77.5% (31)	67.5% (27)	< 0.001	0.317
Active smoker	4,5% (2)	17.5% (7)	37.5% (15)	0.001	0.045
Diabetes	2.2% (1)	35% (14)	20% (8)	< 0.001	0.248
Family history of CAD	4.4% (2)	12.5% (5)	17.5% (7)	0.768	0.531
Medications					
ASA	0% (0)	77.5% (31)	15% (6)	< 0.001	< 0.001
Clopidogrel	0% (0)	12.5% (12)	7.5% (3)	0.04	0.712
Statins	11.1% (5)	75% (30)	42.5% (17)	< 0.001	0.003
Number of coronary artery vessels with significant stenosis					
0	0 (0%)	2.5% (1) *	0% (0)	< 0.001	0.219
1	0 (0%)	35% (14)	47.5% (19)		
2	0 (0%)	22.5% (9)	30% (12)		
3	0 (0%)	40.5 (16)	22.5% (9)		
Type of coronary artery revascularization					
None	100% (45)	7.5% (3)	2.5% (1)	< 0.001	0.405
PCI	0% (0)	82.5% (33)	92.5% (37)		
CABG	0% (0)	10% (4)	5% (2)		
Complete coronary artery revascularization					
Yes	0% (0)	40% (16)	70% (28)	< 0.001	0.007
Laboratory parameters					
Total cholesterol (mg/dL)	201.14 ± 26.98	149.7 ± 33.06	177.05 ± 41.55	< 0.001	0.006
LDL (mg/dL)	120.77 ± 24.44	81.85 ± 26.32	108.0 ± 34.17	< 0.001	0.001
HDL (mg/dL)	57.77 ± 15.28	41.15 ± 7.91	36.53 ± 7.95	< 0.001	0.024
TG (mg/dL)	107.17 ± 40.16	133.78 ± 45.91	164.0 ± 69.69	<0.001	0.053
CRP (mg/dL)	0.49 ± 0.5	8.33 ± 11.64	43.45 ± 45.31	0.001	0.050
ALT (U/L)	22.06 ± 2.38	33.14 ± 19.47	33.32 ± 22.75	0.029	0.973
WBC (number/µL)	6632.35 ± 320.45	7305,25 ± 1958.07	10383.50 ± 4732.36	< 0.001	< 0.001
Lymphocytes (number/µL)	2139.39 ± 113.98	2030.75 ± 788.78	1982.50 ± 1167.70	0.806	0.829
Neutrophils (number/µL)	3757.58 ± 293.36	4347.5 ± 1543.06	7462.50 ± 4238.39	< 0.001	< 0.001
Monocytes (number/µL)	548.48 ± 23.08	641.75 ± 222.98	730.00 ± 315.58	0.010	0.153
Hemoglobin (g/dL)	13.88±1.30	14.33 ± 1.54	14.65 ± 1.54	0.068	0,326
Platelet	229147±52606	188250.0 ± 55290.72	221925.0 ± 77988.62	0.013	0.029
Glucose (mg/dL)	90.5±32.4	120.28 ± 48.55	110.8 ± 19.97	0.002	0.259

ALT: alanine aminotransferase; ASA: acetylsalicylic; BNP: brain natriuretic peptic; CABG: coronary artery bypass graft; CAD: coronary artery disease; CRP: C-reactive protein; HDL: high-density lipoprotein; LDL: low-density lipoprotein; LVEF: left ventricular ejection fraction; n/p: not apply; PCI: percutaneous coronary intervention; TG: triglyceride; WBC: white blood cell.

CypC levels than those who did not (29.02 pg/mL ± 6.39 vs. 79.96 pg/mL ± 22.18; p = 0.029). Furthermore, in CAD patients, CypC increased more in those who had a second cardiovascular event during the 12-month follow-up, although this was not significant probably due to the lack of events (CypC 23.0 pg/mL ± 6.6 baseline vs. CypC 83.5 pg/mL ± 24.1; p = ns). The CypC cutoff of 17.5 pg/mL did not prove effective in predicting

Table 2. CypC cutoff of 17.5 pg/mL and cardiovascular events during follow-up

Events	Acute CAD			Chronic CAD		
	CypC ≥ 17.5	BNP > 300	PCR > 2.3	CypC ≥ 17.5	BNP > 300	PCR > 2.3
ACS						
Yes	17.9% (5)	10.0% (1)	0%	26.1% (6)	27.3% (3)	60.0% (10)
No	82.1% (23)	90.0% (9)	100% (11)	73.9% (17)	72.7% (8)	40.0% (4)
HF						
Yes	7.1% (2)	20.0% (2)	18.2% (2)	4.3% (1)	9.1% (1)	10.0% (1)
No	92.9% (26)	80.0% (8)	81.8% (9)	95.7% (22)	90.9% (11)	90.0% (9)

ACS: acute coronary syndrome; BNP: brain natriuretic peptide; CAD: coronary artery disease; CypC: cyclophilin C; CRP: C-reactive protein; HF: heart failure.

events in patients with CAD (Table 2). Only when considering ACS or HF together did we observe 23.2% (13 patients) in the CypC ≥ 17.5 pg/mL group versus 10.1% (7 patients) in the CypC < 17.5 pg/mL group (p = 0.047). Nevertheless, CypC persisted as a good diagnostic tool to discriminate between patients with and without CAD during the follow-up.

Considering CypC as a predictor of any cardiovascular event (ACS and/or HF) in the follow-up, we did not observe any statistical significance, but there was a tendency to difference.

Kaplan–Meier curves showed significant differences in the cardiovascular event prediction during the follow-up using a hsCRP cutoff point of 2.3 mg/L and a NT-proBNP cutoff point of 300 pg/mL. In this regard, plasma levels of hsCRP > 2.3 mg/L plus NT-proBNP > 300 pg/mL combined were significant predictors of cardiovascular events during the follow-up in CAD patients with levels of CypC > 17.5 pg/mL (p = 0.048) (Fig. 3).

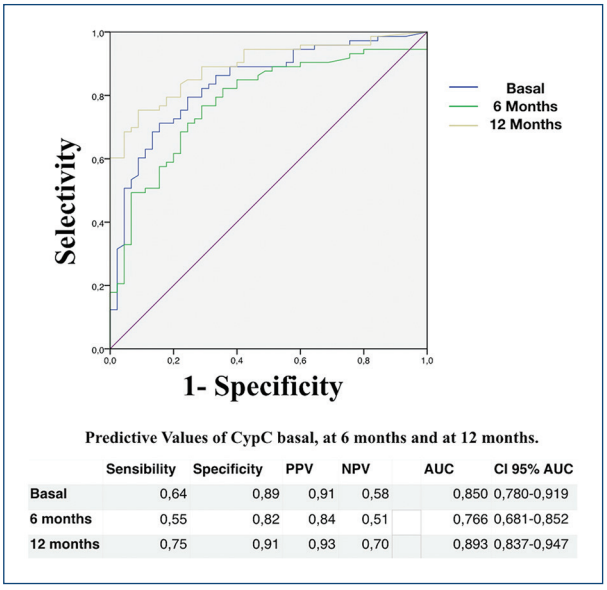

Figure 2. Area under the curve of CypC ≥ 17.5 pg/mL at baseline, at 6 months, and at 12 months. AUC-COR: area under the curve; 95% CI AUC: 95% confidence interval area under the curve; NPV: negative predictive value; PPV: positive predictive value.

Discussion

The major findings of our study are that serum CypC levels were a good biomarker of CAD as have been published[9] and that this correlation persisted over the 12-month follow-up. The previous studies correlated higher plasma CypA levels with CAD and it had a prognostic impact to predict mortality, readmission, and the need for coronary artery revascularization[11] CypA is secreted from vascular smooth cells in response to oxidative stress[15] and it has been reported that CypA may also be secreted from macrophages, lymphocytes, and platelets[16,17]. As it has been shown that CypA levels are increased proportionally to CAD severity[10], there is no information about serum CypC levels and their role in CAD overtime.

Serum hsCRP and uric acid levels have been correlated with complex CAD, mainly with the Syntax score[18]. Furthermore, serum hsCRP levels on admission in patients with ACS could predict the severity and complexity of coronary atherosclerosis together with multivessel CAD, left ventricular ejection fraction, and troponin levels[19]. A retrospective analysis of 2.867 consecutive patients who underwent percutaneous coronary intervention for stable CAD evaluated the association between baseline hsCRP and both all-cause and cancer deaths, concluding that elevated baseline hsCRP was significantly associated with cancer mortality in patients with stable CAD[20]. A recent

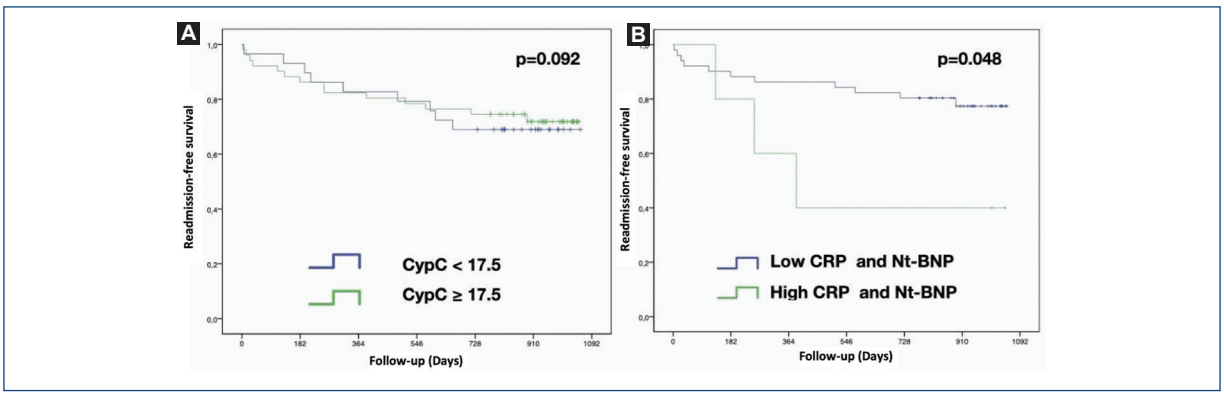

Figure 3. A and B: Kaplan–Meier curves differences in the cardiovascular events prediction during the follow-up using a high-sensitivity C-reactive protein cutoff point of 2.3 mg/L and a NT-proBNP cutoff point of 300 pg/mL.

meta-analysis concluded that, comparing high to low serum levels of hsCRP in the general population, the relative risk was significantly higher (1.25 for cancer-related mortality, 2.03 for cardiovascular mortality, and 1.75 for all-cause mortality) in the highest level group[21].

Other meta-analyses showed that elevated circulating interleukin-6 levels were independently associated with a risk of cardiovascular and all-cause mortality in the general elderly population, considered as over 60s[22]. Several biomarkers, such as hsCRP and NT-proBNP, have been correlated with increased global mortality in the general population and they are strong predictors of cardiovascular events in patients with stable CAD[20,23,24].

However, CypC, as an endoplasmic reticulum cyclophilin, plays a major role in the inflammation and cellular oxidation status by the regulation of redox homeostasis in the endoplasmic reticulum[25]. These findings may be related to atherosclerotic disease, promoting macrophage release of pro-inflammatory cytokines in the vascular wall and endothelial dysfunction. Cyps have not been adequately studied in chronic CAD scenarios. We considered that CypC could play a key role in CAD, from the acute phase of the disease to the last phases in the follow-up of these patients.

We highlighted that serum CypC levels were high in patients with CAD and they remained high over the 12-month follow-up and could be a novel biomarker in these patients. There was no significant association with cardiovascular events, because of the small number of patients, but serum CypC levels were generally higher in patients suffering cardiovascular events during this time. In addition, the combination of different cardiovascular risk biomarkers in CAD patients could be a good option for monitoring the risk during the follow-up. In our study, the combination of high levels of CypC > 17 pg/mL, added to high levels of hsCRP > 2.3 mg/L plus NT-proBNP > 300 pg/mL, was significant predictors of cardiovascular events at 12 months in these CAD patients.

However, our study has limitations related to the small sample size, so further studies with a larger sample size are needed to support the results obtained in the current study.

Conclusions

Our data demonstrated that serum CypC levels increase during the follow-up in CAD patients. CypC could have a role as a novel biomarker in CAD patients, with a possible prognostic value in combination with other biomarkers (hsCRP and NT-proBNP). Thus, further analyses with more patients may show the possible prognostic value of CypC in CAD patients.

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Conflicts of interest

The authors do not present conflicts of interest regarding the present work.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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