

ORIGINAL ARTICLE

C-reactive Protein is a Predictor of Mortality in ST-segment Elevation Acute Myocardial Infarction

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Abstract

Background: Inflammation is a major component of the response to tissue injury caused by myocardial infarction. High-sensitivity C-reactive protein (hs-CRP) levels might be a simple marker of the severity of this inflammatory response, providing prognostic information.

Objective: To associate hs-CRP level on admission and other clinical characteristics with in-hospital mortality of patients with acute ST-segment elevation myocardial infarction (STEMI).

Methods: A retrospective cohort study of patients admitted with STEMI was carried out. Patients were analyzed regarding clinical characteristics, reperfusion therapy, hs-CRP on admission and outcomes. Continuous variables were analyzed by non-parametric Mann-Whitney U test and categorical variables by chi-square test. A p value of < 0.05 was considered statistically significant.

Results: Of the 118 patients analyzed, 20 died during hospitalization. Higher levels of hs-CRP ($p = 0.001$) and older ages ($p = 0.003$) were observed among those patients who died. Logistic regression showed that a one unit increase in hs-CRP increased the risk of death by 15% ($p = 0.0017$), after adjustment for established risk factors. Similarly, each one-year increase in age increases the risk of death by 6.6% ($p = 0.003$).

Conclusion: Our results demonstrate a strong association between hs-CRP obtained on admission and in-hospital mortality after STEMI. It suggests that hs-CRP can be a marker of inflammatory response to myocardial ischemia, providing prognostic information regarding the risk of death. (Int J Cardiovasc Sci. 2018; [online].ahead print, PP.0-0)

Keywords: Myocardial Infarction/mortality; C-Reactive Protein; Inflammation; Bionarkers; Hospital Mortality.

Introduction

Cardiovascular diseases are the leading cause of mortality and morbidity in the world.¹ Inflammation is thought to be the key mechanism in the pathogenesis of atherosclerosis and the value of assessing the levels of inflammatory biomarkers has risen.² Many prospective cohort studies have demonstrated that baseline levels of high-sensitivity C-reactive protein (hs-CRP) in apparently healthy men and women are highly predictive of future risk of heart attack.³

However, inflammation is important in all phases of heart disease, including in the short-term prognosis after acute myocardial infarction (AMI).³ In recent

years, many inflammatory biomarkers have been studied to determine whether increased levels of these molecules are related to a poor prognosis in patients who have had myocardial infarction. Several studies have shown an association between C-reactive protein (CRP) and recurrent coronary events in patients with acute coronary syndrome.^{3,4}

CRP is a plasma protein of the pentraxin family, widely used as a general inflammatory marker, since it is an acute phase protein synthesized by hepatocytes in response to proinflammatory cytokines, particularly interleukin-6. Currently, among systemic markers of inflammation, hs-CRP has been the most studied risk predictor in the clinical practice.^{1,5}

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One of the main components of the response to tissue injury caused by myocardial infarction is a robust inflammatory reaction.^{6,7} In the early phase of myocardial infarction, hs-CRP may be a simple marker of the magnitude of the inflammatory response to myocardial ischemia, potentially providing prognostic information regarding the risk of death.^{6,8,9}

We aimed to evaluate the association of hs-CRP levels on admission, and other clinical characteristics with occurrence of in-hospital death of patients with acute ST-segment elevation myocardial infarction (STEMI).

Methods

Study design

A retrospective cohort study of 136 patients admitted with acute STEMI to the emergency department or the coronary care unit during a one-year period was conducted. Eighteen patients were excluded from the study because of insufficient data, and thus 118 patients were analyzed. The following variables were evaluated – sex, age, diabetes mellitus, smoking habit, drinking habit, reperfusion therapy, arterial hypertension, hs-CRP on admission, and body mass index (BMI).

We identified a cohort of patients with a median age of 60 years old (interquartile range of 19.75 years), 69% of males. Table 1 shows clinical characteristics of the cohort.

ST-segment elevation was identified at first admission to the emergency department or the coronary care unit and myocardial infarction was diagnosed according to the Joint European Society of Cardiology / American College of Cardiology¹⁰ criteria.

Diabetes mellitus was defined as fasting plasma glucose ≥ 126 mg/dL, glycated hemoglobin $\geq 6.5\%$, or treatment with insulin or hypoglycemic agents. Patients with systolic/diastolic blood pressure $> 140/90$ mmHg or using any antihypertensive medication were defined as hypertensive. Drinking habit was defined as ingestion of alcoholic beverage in the last year, whereas cigarette smoking was defined as active smoking in the last six months.

Blood sampling and hs-CRP assay

Venous blood samples were obtained on admission and serum hs-CRP was determined by the turbidimetric method. This method assesses agglutination of latex particles coated with antibody against CRP by quantifying the absorbed light. The assay has a detection limit of 0.4 mg/dL

Statistical analysis

Data were analyzed by the computer software program R (R CORE TEAM, 2017), version 3.4.0. Descriptive characteristics were calculated for continuous variables (median and interquartile range, IQR) and

Table 1 - General characteristics of the cohort

Characteristic	n = 118
Gender	
Female	30.6%
Male	69.4%
Age	
< 60 years old	47.5%
≥ 60 years old	52.5%
Hypertension	
Yes	64.3%
No	35.7%
Drinking habit	
Yes	30.2%
No	69.8%
Smoking habit	
Yes	40.7%
No	39.8%
Ex	18.5%
Diabetes	
Yes	37.9%
No	62%
BMI	
< 27 kg/m ²	50.9%
≥ 27 kg/m ²	49.1%
hs-CRP (mg/dl)	
< 2.6 mg/dL	49.4%
≥ 2.6 mg/dL	50.6%
Any reperfusion therapy*	
Yes	70.5%
No	29.5%

*Thrombolytic therapy or primary angioplasty; hs-CRP: high-sensitivity C-reactive protein; BMI: body mass index.

for categorical variables (frequency/percentage). Our data followed a non-normal distribution. Continuous variables were analyzed by non-parametric Mann-Whitney U test, whereas categorical variables were analyzed using the chi-square test. Also, predictive factors were identified using binary logistic regression analysis after adjusting for age and hs-CRP. Multivariate analysis was performed expressing odds ratio per one unit increase in independent continuous variables. A p-value of <0.05 was considered statistically significant.

The institutional review committee on human research approved the study protocol.

Results

We studied 118 patients admitted with STEMI identified at first admission to the emergency department or the coronary care unit. Of the 118 patients, 98 survived (median 59 years [IQR 17]; M:F=69:29) and 20 died (median 73 years [IQR 22.75]; M:F=12:8) during hospitalization.

Clinical characteristics, hs-CRP levels at admission and use of reperfusion therapy of patients categorized by group, according to occurrence of in-hospital death, are

shown in table 2. There were no significant differences regarding reperfusion therapy between patients who died and those who survived. Body mass index did not significantly differ between the two groups. The prevalence of diabetes was higher in patients who died (40%) comparing with those who survived (32.65%), but the difference was not significant between the groups (p = 0.7089).

Smoking and drinking habits were not statistically associated with in-hospital death. Regarding sex distribution, the proportion of females was 40% among those who died and 29.6% among survivors. This difference was not statistically significant (p = 0.51).

Systemic arterial hypertension had no influence on in-hospital mortality in this group of patients with infarction even on univariate analysis.

In univariate analyses, we observed (Figure 1) significantly higher levels (p = 0.001) of hs-CRP in patients who died (median 10.47 [IQR 23.99]) compared to those who survived (median 2.13 [IQR 5.66]). Therefore, in patients with STEMI, an increase in the hs-CRP level at admission is associated with a poorer short-term prognosis and may represent an independent factor for death in the hospital.

A clear association between age and in-hospital death was also observed. Median age was significantly higher (p = 0.003) in patients who died (median 73 [IQR 22.75]) than in those who survived (median 59 [IQR 17]).

Multiple logistic regression analysis was performed to evaluate the independent contribution of hs-CRP levels to the risk of death. By binary logistic regression analysis (Figure 2), in-hospital death was associated with higher concentration of hs-CRP (odds ratio = 1.15 per unit increase; p = 0.0017) and older age (odds ratio = 1.066 per one year increment; p = 0.003). Therefore, a one unit increase in hs-CRP increased the risk of death by 15%, after adjustment for established risk factors. Similarly, a one year increase in age increased the risk of death by around 6.6% in patients with same hs-CRP levels.

Discussion

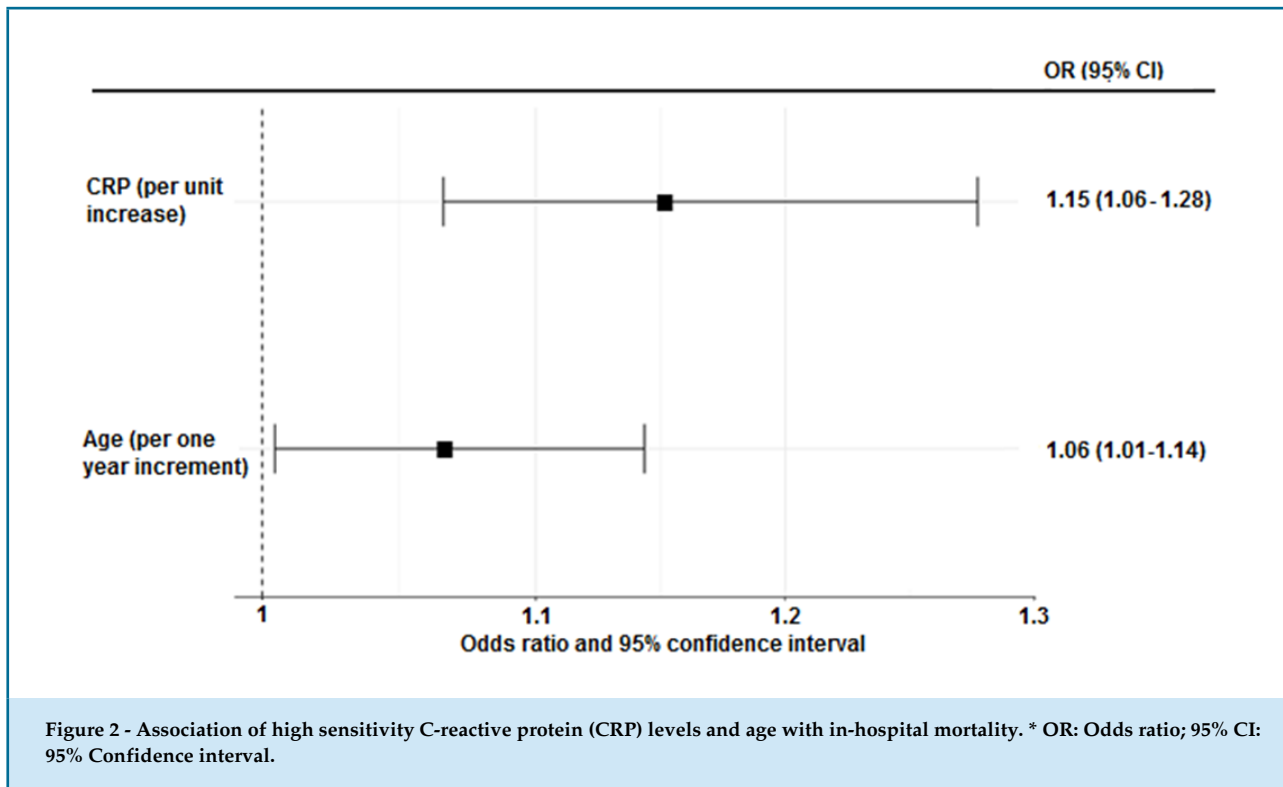
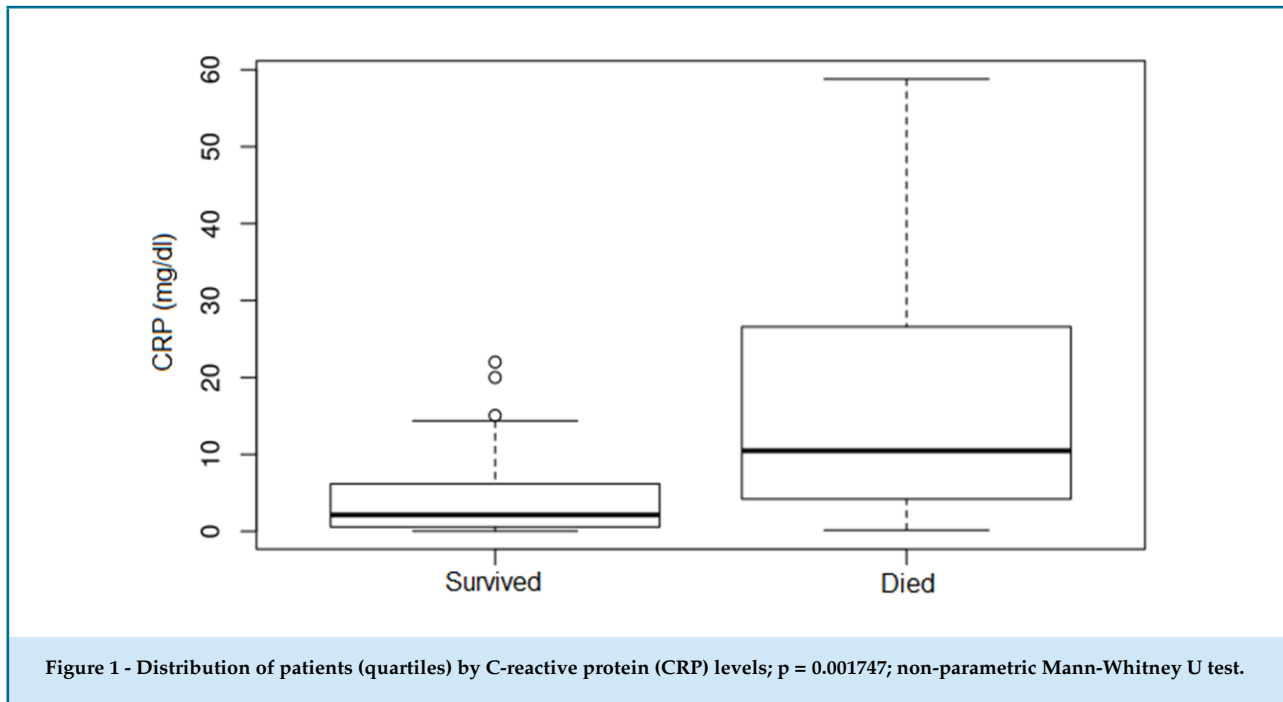
Our results demonstrated an important relationship between hs-CRP level on admission and in-hospital mortality after STEMI.

The present study showed a mortality rate after AMI of 16.9%, which is similar with those reported in previous studies (3.2-20.6%).^{11,12}

Table 2 - Statistical association of risk variables with in-hospital mortality

Variable	Median (IQR) or n (%)		p value
	Survived (n = 98)	Died (n = 20)	
Age (in years)	59 (17)	73 (22.75)	0.003506 ¹
Male gender	69 (70.4%)	12 (60%)	0.5158 ²
Diabetes	32 (32.65%)	8 (40%)	0.7089 ²
Smoking habit	40 (40.81%)	5 (25%)	0.2826 ²
Drinking habit	26 (26.53%)	3 (15%)	0.4199 ²
Any reperfusion therapy*	61 (62.24%)	8 (40%)	0.1116 ²
Hypertension	57 (58.16%)	10 (50%)	0.6716 ²
hs-CRP (mg/dl)	2.13 (5.66)	10.47 (23.99)	0.001 ¹
BMI	26.9 (6.51)	25.5 (6.2)	0.5592 ¹

1. Data analyzed by non-parametric Mann-Whitney U test. 2. Data analyzed using the chi-square test. * Thrombolytic therapy or primary angioplasty. IQR: Interquartile range; hs-CRP: high-sensitivity C-reactive protein; BMI: body mass index.



Our results also demonstrated that in-hospital mortality after STEMI was strongly associated with elderly patients. Previous studies have investigated the relationship between age and death in patients with

AMI and showed that age is an important predictor of mortality in these cases.¹³

In England, one third to half of the patients admitted to a hospital with acute myocardial infarction are

older than 70 years,¹⁴ whereas 74.4% of the deaths attributed to this condition occur in patients older than 70 years.¹⁵ There are many possible reasons for this. Elderly population has more severe coronary artery disease, receive less adequate treatment than younger individuals, and presents later at the hospital after the onset of infarction symptoms.¹⁶

Regarding sex distribution, our results demonstrate a higher proportion of females among those who died (40%) comparing to survivors (29.6%, $p = 0.51$). Several studies have already shown that female sex is independently associated with early mortality after STEMI.¹³

The present study also demonstrates a strong, positive association between hs-CRP obtained on admission and in-hospital mortality.

In the early phase of AMI, CRP levels are probably a reaction to the inflammatory response following myocardial ischemia and not to chronic vascular inflammation.¹⁷⁻²⁰ It allows CRP levels to be a simple marker of the magnitude of the inflammatory response to myocardial ischemia, potentially providing prognostic information regarding the risk of death.^{8,9} Therefore, measurement of CRP can offer a strategy for risk stratification and management of patients at the highest risk for adverse outcomes.²¹⁻²³

Besides myocardial necrosis and ischemia, other kinds of tissue damage could cause CRP elevation in patients with AMI, such as atherosclerotic mass, underlying inflammatory process and circulating proinflammatory cytokines.²⁴

There have been several studies on the prognostic value of hs-CRP in AMI. High sensitivity CRP has been shown to be associated with hospital outcomes, such as death, myocardial infarction and angina,^{4,25-31} suggesting it to be a useful biomarker in risk assessment of patients with acute coronary syndrome.

Raposeiras-Roubín et al.,³² also evaluated the prognostic value of hs-CRP, showing that a higher level of hs-CRP is a predictor of in-hospital cardiac events in acute MI, independently of the GRACE (Global Registry of Acute Coronary Events) risk score.

Tanveer et al.,³³ analyzed 190 patients with STEMI to investigate the relationship between hs-CRP level and complications of myocardial infarction. However, there were no significant differences in hs-CRP values between patients who died and who survived during hospitalization.

Suleiman et al.,⁷ reported that patients with AMI with higher CRP levels on admission were older, had

higher baseline creatinine levels and were at increased risk of long-term development of heart failure. Schiele et al.,³⁴ showed an independent predictive role of CRP in patients with acute coronary syndrome; those in the highest quartile of CRP showed increased mortality rates at 30 days of follow-up.

In recent years, there has been an attempt to predict the risk of early adverse events in patients with STEMI. In order to stratify STEMI patients according to this risk, risk scores have been created with a strong prognostic capacity, such as the GRACE risk score. Inflammatory markers can add prognostic information to these scoring systems even in the current era of high-sensitivity cardiac troponin assays.³⁵

AMI is associated with an extensive myocardial inflammation, which leads to a systemic inflammatory response.^{6,36} Our results demonstrate that hs-CRP can measure inflammatory response to tissue injury after a STEMI, providing a means for assessing short-term prognosis and the risk of death.

The present study also has some limitations, because it is a retrospective study and it could not establish a cut-off point for CRP level in relation to mortality.

This study can help us better understand the prognostic significance of hs-CRP levels over the AMI spectrum, however further studies are needed to elucidate the inflammatory process due to myocardial ischemia.

Conclusions

Our results demonstrate a strong, positive association between high-sensitivity C-reactive protein obtained on admission and in-hospital mortality after STEMI. Moreover, in-hospital mortality is tightly associated with elderly patients.

These findings suggest that hs-CRP levels can measure inflammatory response to myocardial ischemia after STEMI, providing prognostic information regarding the risk of death. Therefore, CRP on admission of patients with STEMI is a strong univariate predictor of mortality.

Author contributions

Conception and design of the research: Milano SM, Lenci GL, Bordim A, Moura Junior OV. Acquisition of data: Milano SM, Bordim A, Moura Junior OV. Analysis and interpretation of the data: Milano SM, Lenci GL, Bordim A, Moura Junior OV. Writing of the manuscript:

Milano SM, Lenci GL. Critical revision of the manuscript for intellectual content: Lenci GL.

Potential conflict of interest

The authors have declared that no competing interests exist.

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Study association

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Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

References

- Shrivastava AK, Singh HV, Raizada A, Singhd SK. C-reactive protein, inflammation and coronary heart disease. *Egypt Heart J*. 2015;67(2):89-97.
- Yousuf O, Bibhu D, Mohanty BD, Martin SS, Joshi PH, Blaha MJ, et al. High-sensitivity C-reactive protein and cardiovascular disease. A resolute belief or an elusive link? *J Am Coll Cardiol*. 2013;62(5):397-408.
- Ridker PM. C-Reactive Protein: A Simple Test to Help Predict Risk of Heart Attack and Stroke. *Circulation*. 2003;108(12):e81-e85.
- Correia LC, Esteves JP. C-Reactive protein and outcomes in acute coronary syndromes: a systematic review and meta-analysis. *Arq Bras Cardiol*. 2011;97(1):76-85.
- Ridker PM. A test in context: high-sensitivity C-Reactive protein. *J Am Coll Cardiol*. 2016;67(6):712-23.
- Swiatkiewicz I, Taub PR. The usefulness of C-reactive protein for the prediction of post-infarct left ventricular systolic dysfunction and heart failure. *Kardiol Pol*. 2018;76(5):821-9.
- Suleiman M, Khatib R, Agmon Y, Mahamid R, Boulos M, Kapeliovich M, et al. Early inflammation and risk of long-term development of heart failure and mortality in survivors of acute myocardial infarction. *J Am Coll Cardiol*. 2006;47(5):962-8.
- Biasucci LM, Koenig W, Mair J, Mueller C, Plebani M, Lindahl B, et al. Study Group on Biomarkers in Cardiology of the Acute Cardiovascular Care Association of the European Society of Cardiology. How to use C-reactive protein in acute coronary care. *Eur Heart J*. 2013;34(48):3687-90.
- Berton G, Cordiano R, Palmieri R, Pianca S, Pagliara V, Palatini P. C-reactive protein in acute myocardial infarction: association with heart failure. *Am Heart J*. 2003;145(6):1094-101.
- Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *J Am Coll Cardiol*. 2000;36(3):959-69.
- Piva e Mattos LA, Berwanger O, Santos ES, Reis HJ, Romano ER, Petriz JL, et al. Clinical outcomes at 30 days in the Brazilian Registry of Acute Coronary Syndromes (ACCEPT). *Arq Bras Cardiol*. 2013;100(1):6-13.
- Escosteguy CC, Portela MC, Medronho RA, de Vasconcellos MT. Acute myocardial infarction: clinical and epidemiological profile and factors associated with in-hospital death in the municipality of Rio de Janeiro. *Arq Bras Cardiol*. 2003;80(6):600-6,593-9.
- Conrotto F, D'Ascenzo F, Humphries KH, Webb JG, Scacciarella P, Grasso C, et al. A meta-analysis of sex-related differences in outcomes after primary percutaneous intervention for ST-segment elevation myocardial infarction. *J Interv Cardiol*. 2015;28(2):132-40.
- McMechan SR, Adgey AA. Age related outcome in acute myocardial infarction: elderly people benefit from thrombolysis and should be included in trials. *BMJ*. 1998;317(7169):1334-5.
- Marcus FI, Friday K, McCans J, Moon T, Hahn E, Cobb L, et al. Age-related prognosis after acute myocardial infarction (The Multicenter Diltiazem Post-Infarction Trial). *Am J Cardiol*. 1990;65(9):559-66.
- Barakat K, Wilkinson P, Deane A, Fluck D, Ranjadayalan K, Timmis A. How should age affect management of acute myocardial infarction? A Prospective Cohort Study. *Lancet*. 1999;353(9157):955-9.
- Ribeiro DR, Ramos AM, Vieira PL, Menti E, Bordin Jr OL, Souza PAL. Proteína C-Reativa prediz eventos cardiovasculares após infarto do miocárdio com elevação do ST? *Arq Bras Cardiol*. 2014;103(1):69-75.
- Izumiya Y, Hanatani S, Kimura Y, Takashio S, Yamamoto E, Kusaka H, et al. Growth differentiation factor-15 is a useful prognostic marker in patients with heart failure with preserved ejection fraction. *Can J Cardiol*. 2014;30(3):338-44.
- Makrygiannis SS, Ampartzidou OS, Zairis MN, Patsourakos NG, Pitsavos C, Tousoulis D, et al. Prognostic usefulness of serial C-reactive protein measurements in ST-elevation acute myocardial infarction. *Am J Cardiol*. 2013;111(1):26-30.
- James S, Oldgren J, Lindback J, Johnston N, Siegbahn A, Wallentin. An acute inflammatory reaction induced by myocardial damage is superimposed on a chronic inflammation in unstable coronary artery disease. *Am Heart J*. 2005;149(4):619-26.
- Anzai T. Post-infarction inflammation and left ventricular remodeling: a double-edged sword. *Circ J*. 2013;77(3):580-7.
- Seropian IM, Sonnino C, Van Tassel BW, Biasucci LM, Abbate A. Inflammatory markers in ST-elevation acute myocardial infarction. *Eur Heart J Acute Cardiovasc Care*. 2016;5(4):382-95.
- Minamisawa M, Motoki H, Izawa A, Kashima Y, Hioki H, Abe N, et al. Comparison of inflammatory biomarkers in outpatients with prior myocardial infarction. *Int Heart J*. 2016;57(1):11-7.
- Schoenhagen M. Current developments in atherosclerosis research. New York: Nova Biomedical Books; 2005.

25. Oemrawsingh RM, Cheng JM, Akkerhuis KM, Kardys I, Degertekin M, van Geuns RJ, et al. High-sensitivity C-reactive protein predicts 10-year cardiovascular outcome after percutaneous coronary intervention. *EuroIntervention*. 2016;12(3):345-51.
26. Klingenberg R, Aghlmandi S, Räber L, Gencer B, Nanchen D, Heg D, et al. Improved risk stratification of patients with acute coronary syndromes using a combination of hsTnT, NT-proBNP and hsCRP with the GRACE score. *Eur Heart J Acute Cardiovasc Care*. 2018;7(2):129-38.
27. Yanishi K, Nakamura T, Nakanishi N, Yokota I, Zen K, Yamano T, et al. A Simple risk stratification model for ST-Elevation Myocardial Infarction (STEMI) from the combination of blood examination variables: acute myocardial infarction-Kyoto Multi-Center Risk Study Group. *PLoS ONE*. 2016;11(11):e0166391.
28. Correia LC, Vasconcelos I, Garcia G, Kalil F, Ferreira F, Silva A, et al. Does C-reactive protein add prognostic value to GRACE score in acute coronary syndromes? *Arq Bras Cardiol*. 2014;102(5):449-55.
29. Ahmed K, Jeong MH, Chakraborty R, Cho KH, Sim DS, Hong YJ, et al. Prognostic impact of baseline high-sensitivity C-reactive protein in patients with acute myocardial infarction undergoing percutaneous coronary intervention based on body mass index. *Korean Circ J*. 2012;42(3):164-72.
30. Vrsalovic M, Pintaric H, Babic Z, Pavlov M, Presecki AV, Getaldic B, et al. Impact of admission anemia, C-reactive protein and mean platelet volume on short term mortality in patients with acute ST-elevation myocardial infarction treated with primary angioplasty. *Clin Biochem*. 2012;45(16-17):1506-9.
31. Mouridsen MR, Intzilakis T, Binici Z, Nielsen OW, Sajadieh A. Prognostic value of high sensitive C-reactive protein in subjects with silent myocardial ischemia. *J Electrocardiol*. 2012;45(3):260-4.
32. Raposeiras-Roubín S, Pardal CB, Janeiro BR, Abu-Assi E, García-Acuña JM, González-Juanatey JR. High-sensitivity C-reactive protein is a predictor of in-hospital cardiac events in acute myocardial infarction independently of GRACE risk score. *Angiology*. 2012;63(1):30-4.
33. Tanveer S, Banu S, Jabir NR, Khan MS, Ashraf GM, Manjunath NC, et al. Clinical and angiographic correlation of high-sensitivity C-reactive protein with acute ST elevation myocardial infarction. *Exp Ther Med*. 2016;12(6):4089-98.
34. Schiele F, Meneveau N, Seronde MF, Chopard R, Descotes-Genon V, Dutheil J et al. C-reactive protein improves risk prediction in patients with acute coronary syndromes. *Eur Heart J*. 2010;31(3):290-7.
35. Widera C, Pencina MJ, Bobadilla M, Reimann I, Guba-Quint A, Marquardt I, et al. Incremental prognostic value of biomarkers beyond the GRACE (Global Registry of Acute Coronary Events) score and high-sensitivity cardiac troponin T in non-ST-elevation acute coronary syndrome. *Clin Chem*. 2013;59(10):1497-505.
36. Teixeira DA, Sousa CFP, Pereira GLH, Maia LFL, Teixeira FH, Lisita CLF. C-reactive protein: association between inflammation and complication after acute myocardial infarction in the elderly. *Rev Bras Clin Med*. 2009;7:24-26.

