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Increased High Sensitive C-reactive Protein is Associated with Major Adverse Cardiovascular Events after STEMI

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ABSTRACT

Objective: This study aims to investigate whether the high sensitive C-reactive protein (hsCRP) is associated with an ejection fraction of left ventricle (EFLV) in the early phase of ST-elevation myocardial infarction (STEMI), treated with the primary percutaneous intervention (pPCI), and to establish whether there exists a relationship between its values and the presence of major adverse cardiovascular events (MACE) within six months of pPCI.

Materials and Methods: In this prospective study, 357 patients who were diagnosed with STEMI and who underwent pPCI within 24 hours of pain onset were included. The following were monitored and recorded: 1) hsCRP values, which were measured between 24 and 48 hours of pPCI, 2) EFLV values, which were measured five days after the pPCI, and 3) MACE, which was established within six months of pPCI.

Results: The EFLV values measured five days after the pPCI were significantly lower with increasing hsCRP values (rho=-0.384, p<0.0001). There was a significant difference in hsCRP values between patients who had MACE and those without it (38.35 [98.10] vs. 12.97 [23.80], p=0.0001). In addition, hsCRP values were significantly increased in patients who died during the first six months after the pPCI compared with patients who survived (115.00 [202.80] vs. 15.84 [31.5], p=0.001).

Conclusion: The hsCRP values in patients with STEMI who were treated with the pPCI are related to systolic function in the early phase of STEMI, as well as MACE during the first six months of follow-up.

Keywords: C-reactive protein, myocardial infarction, prognosis

INTRODUCTION

Acute coronary syndrome (ACS) has been established to represent a consequence of atherosclerosis, with preventable and non-preventable risk factors that have been identified to lead to the onset of acute myocardial infarction (1, 2). Atherosclerosis is a chronic inflammatory process in the middle arterial intima for which the C-reactive protein (CRP), an acute-phase protein secreted during the inflammatory stimulus, has been shown to be an independent predictor of coronary artery disease (CAD) (3).

CRP is secreted by smooth muscle cells, macrophages, endothelial cells, lymphocytes, and adipocytes, and is formed in atherosclerotic plaque and endothelium (4). State-of-the-art laboratory techniques have enabled the detection of CRP in serum in the range of 0.01 to 10 mg/l, which is referred to as high-sensitive CRP (hsCRP) (5). Measurement of hsCRP is recommended for patients with medium risk for CAD since elevated levels of hsCRP indicate an increased risk for CAD, and require primary prevention of cardiovascular incident with a focus on lipid levels (3). Interleukin- 6 (IL-6) has been shown to be the most potent stimulator of the CRP secretion in the liver, and in association with IL-1, it is the most potent inflammatory stimulator during an acute myocardial infarction (6, 7). In addition, it has been shown that increased levels of hsCRP, leukocytes' count, and fibrinogen levels are associated with decreased left ventricular function and more pronounced myocardial damage at baseline and at four months after infarction (8). Furthermore, it has been demonstrated that high plasma CRP concentration at 24 hours after hospital admission of a patient with myocardial infarction indicates that left ventricular remodeling is taking place in patients after the first ST-elevation myocardial infarction (STEMI) treated with the primary percutaneous intervention (pPCI) (9). In another study, in patients with the STEMI, who underwent the pPCI, protein levels of hsCRP were shown to represent an independent predictor of a 30-day survival (10). In addition, increased plasma CRP concentration was found to associate with an adverse outcome in acute myocardial infarction and allowed clinicians to stratify patients for risk of death and heart failure (11). Moreover, increased CRP values in acute myocardial infarction were found to correlate with the presence and the degree of mitral regurgitation and diastolic dysfunction (12). Pharmacological therapy with statins and acetylsalicylic acid decreased hsCRP values, thus suggesting that hsCRP might represent a biomarker of an atherosclerotic process (13). Therefore, it was concluded that the analysis of inflammatory response biomarkers, as well as their kinetics, could provide an invaluable

Table 1. The hsCRP values obtained between 24 to 48 hours after hospital admission concerning the occurrence of MACE

Parameter	hsCRP (median and 25th–75th percentile)	p
Ejection fraction quartiles		
1st	38.35 (12.04–66.45)	0.001
2nd	15.82 (6.22–41.33)	
3rd	11.99 (6.39–24.94)	
4th	6.74 (3.17–11.49)	
MACE		
Yes	38.35 (14.38–112.50)	<0.001
No	12.97 (6.00–29.80)	

hsCRP: High sensitive C-reactive protein; MACE: Major adverse cardiovascular events

diagnostic tool as an estimate of extensiveness of injury, modality of treatment, as well as for the evaluation of the outcome itself (13).

The present study aims to investigate whether the levels of the hsCRP associate with left ventricular systolic function in the early phase of acute myocardial infarction treated using the pPCI. In addition, we aimed to examine whether there exists a relationship between hsCRP values and the occurrence of intra-hospital death, as well as the presence of MACE, events that include fatal outcome, stroke, reinfarction and re-revascularization, within six months of the pPCI.

MATERIALS and METHODS

This prospective study included 357 patients treated at the Clinic for Emergency and Internal Medicine, Military Medical Academy, University of Defense, Belgrade, Serbia, from January 2010 to September 2019. The criteria for inclusion in the study were: patients who were diagnosed with acute STEMI and who underwent the pPCI treatment within 24 hours of pain onset, patients with hsCRP levels measured between 24 and 48 hours of the pPCI, and an echocardiographically estimated ejection fraction of left ventricle (EFLV) on the fifth day after the pPCI. Exclusion criteria were as follows: all patients who had chest pain but no ST elevation on the electrocardiogram (ECG), and all patients diagnosed with acute STEMI who had not undergone the pPCI and with a cancer diagnosis. The following parameters were monitored and analyzed: hsCRP measured between 24 and 48 hours of the pPCI, EFLV five days after the pPCI (echocardiographically assessed using Simpson method), intra-hospital death, and MACE (fatal outcome, reinfarction, stroke, and re-revascularization) within six months of the pPCI intervention.

Statistical Analysis

The results were presented by case number, percentage, arithmetic mean, standard deviation, median with interquartile range, the area under the curve (AUC), sensitivity and specificity, and confidence intervals (CI). The distribution analysis was carried out using the Shapiro-Wilk test and, if the observed variables did not meet the criteria of the normal distribution, non-parametric tests (Mann-Whitney, Kruskal-Wallis, and Spearman's rank correlation coefficient) were used in the analysis. A receiver operating curve (ROC) was used to determine the sensitivity and specificity of the hsCRP. All results with the $p<0.05$ or 95% confidence level were considered statistically significant. The statistical analysis of the data was performed using the SPSS Windows software package (version 21.0, SPSS Inc, Chicago, Illinois, USA). This study was conducted in accordance with the basic principles of the Declaration of Helsinki (from 2013) describing the rights of patients involved in biomedical research. During the course of this study, the identity and all personal data of patients were protected in accordance with the regulations on the protection of identification data. For the protection of personal data, each patient was assigned a unique identification number, which was used during statistical data processing.

RESULTS

In this study, the mean age of subjects (N=357) was 60.93±12.011 years, while the mean values of hsCRP, measured between 24 to 48 hours following the pPCI, were 37.43 [34.80] mg/l. Median value of hsCRP was 16.05 [6.73–41.50] (25th-75th percentile).

The resolution of the ST segment on the ECG after the pPCI was analyzed, and it was established that the descent was greater than 50% in 33.9% of patients. Of the total number, 55.2% of patients did not have a Q wave on the ECG at admission, and of the total number of patients, 58.3% received one stent. The median and interquartile range for EFLV, estimated on the fifth day after the pPCI, was 47.00% [15]. Since there was no normal distribution of the sample, Spearman's rank correlation coefficient was used. The EFLV five days after the pPCI was significantly lower with increasing hsCRP values (rho=-0.384, $p<0.0001$). However, hsCRP values were different across the groups divided according to quartile of the ejection fraction (Kruskal Wallisanalysis of variance Chi-Square was 37.903, df=3, $p=0.001$). Median and 25th-75th percentile for the 1st, 2nd, 3rd and 4th quartiles were 38.35 (12.04–66.45), 15.82 (6.22–41.33), 11.99 (6.39–24.94) and 6.74 (3.17–11.49), respectively, decreasing from the first to the fourth quartile of the ejection fraction (Table 1). The Mann-Whitney non-parametric test showed that there was a significant difference in hsCRP values between patients who had MACE (fatal outcome, reinfarction, heart failure, and re-revascularization), within six months from the pPCI, and those who did not have MACE: 38.35 (14.38–112.50) and 12.97 (6.00–29.80), $p<0.001$ (Table 1).

Within the patients with MACE (N=69), 16 (23.2%) died, 7 (10.1%) had reinfarction, 46 (66.7%) had acute heart failure, and 17 (24.6%) re-revascularization. Taking into account all of the study's patients (N=357), the death rate was 4.5%, the reinfarction rate was 2.2%, the acute heart failure rate was 15.7%, and the rate of re-revascularization was 5.3%. When patients who died during the first six months after the pPCI were compared with those who survived the first six months after the pPCI, hsCRP values were significantly different (median and 25th-75th percentile): 83.20 (37.58–198.92) and 15.50 (6.55–34.35), $p=0.001$ (Table 2).

In our study, as shown by the ROC curve, the hsCRP had a moderate potential to predict MACE (Fig. 1). The area under the ROC curve (AUC) was 0.701±0.072 (95% CI), which is significantly different from the diagonal line ($p<0.001$). With the cut-off value of

Table 2. The hsCRP values obtained between 24 to 48 hours after hospital admission concerning the survival

	Died		Survived		
	Median	25th–75th percentile	Median	25th–75th percentile	p
hsCRP within 24 to 48 hours (mg/l) - fatal outcome	83.20	37.58–198.92	15.50	6.55–34.35	<0.001

hsCRP: High sensitive C-reactive protein; MACE: Major adverse cardiovascular events

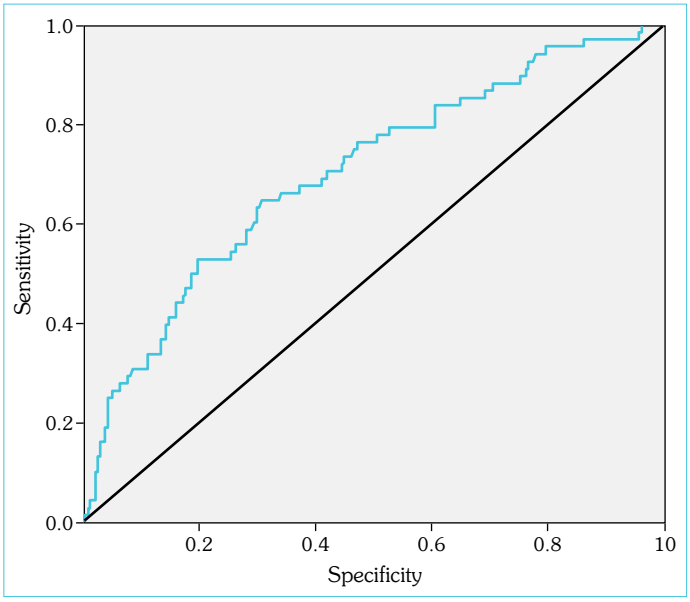

Figure 1. ROC curve showing the potential of hsCRP to predict MACE. The ROC curve was calculated to demonstrate the specificity and the sensitivity of the hsCRP values, measured in our cohort, to allow the prediction of MACE

24.15 mg/l (calculated using the Youden's index), the hsCRP may predict MACE with a sensitivity of 0.647 and specificity of 0.693.

DISCUSSION

The process of atherosclerosis underlies cardiovascular pathology. It is an inflammatory process for which CRP and hsCRP represent biomarkers that can monitor the extent of the atherosclerotic process (14). Both CRP and hsCRP have been assigned roles in a series of prediction scores for cardiovascular incidents (14, 15). Following the STEMI, there is an increase in the levels of inflammation markers, most notably CRP and hsCRP and their increase is in relation to the infarct size (16). Sustained release of hsCRP even after acute myocardial infarction carries a high risk of complications and mortality (16). An overall increase in inflammation adversely affects left ventricular remodeling in myocardial infarction, which results in accelerated cell apoptosis after myocardial infarction (15). Together, this leads to further damage to the cardiac muscle cells and impairs cardiac function.

In our study, the mean hsCRP value, measured between 24 to 48 hours of the pPCI, was 37.431±54.7815 mg/l. Our study showed that the ejection fraction was significantly lower with increasing hsCRP values and that increased hsCRP values were significantly associated with MACE and the onset of mortality within six months from the pPCI. When patients who died during the first six months after the pPCI were compared with those who survived six months, hsCRP values were significantly different (115±202.8 vs. 15.84±31.5, p=0.001). Our results suggest that the high value of hsCRP, in acute coronary syndrome, before the development of myocardial necrosis, may be an important indicator of poor prognosis of patients with cardiovascular comorbidities. Therefore, its assessment during the acute phase of STEMI may help stratify patients according to the risk of myocardial dysfunction.

One previous study has shown that, in STEMI, higher CRP levels predict worse patient outcomes (15). Stumpf et al. (15) reported that elevated hsCRP values represent a strong predictor of systolic dysfunction and cardiovascular mortality after more than a year from the pPCI. They showed that CRP levels reached a peak level 48 hours after the pPCI, while patients with STEMI and patients with signs of heart failure showed a significantly higher peak of CRP levels after the pPCI. In addition, they showed that in patients with peak CRP levels >47.5 mg/l, rates of one-year mortality and heart failure were higher than in patients with lower CRP levels (15). In a different study that examined 300 patients with STEMI treated with the pPCI, hsCRP levels were associated with 30-day mortality (10), a result which was confirmed by Schiele et al. (11). Furthermore, Swiatkiewicz et al. (9) observed that CRP concentration measured at 24 hours after hospital admission can predict post-infarct left ventricular remodeling after STEMI (CRP concentration at 24 hours after hospital admission was higher in patients with systolic dysfunction after six months from the pPCI). Bursi et al. (16) have demonstrated that CRP values at hospital admission were useful for predicting heart failure. In their study, there was a strong positive relationship between CRP levels and the risk of developing heart failure, as well as dying during the follow-up period of one year (16). De Servi et al. (17) demonstrated that patients with high levels of hsCRP who were diagnosed with ACS would have higher troponin I values. Moreover, Kavsak et al. (18) showed that high CRP titers, independent of age, sex, and troponin I concentration, predicted a long-term heart failure and mortality. Liu et al. (19) reported that both hsCRP and brain natriuretic peptide (BNP) levels, measured 30 days after an ACS, were independently associated with the risk of heart failure and cardiovascular mortality, with the highest risk occurring when both markers were simultaneously high. Al Aseri et al. (20) also established a correlation between elevated hsCRP values and the incidence of cardiac insufficiency. In a retrospective study of 7026 patients who underwent the pPCI procedure, Kalkman and colleagues estimated that 38% of patients who had hsCRP values ≥2 mg/l had a so-called persistent high residual inflammatory risk (RIR) which was associated with the highest all-cause mortality at one-year follow-up (2.6%) and the highest rate of myocardial infarction (7.5%) also at one-year follow-up (21). Therefore, the study by Kalkman et al. (21) suggests that inflammation may be associated

with the cardiovascular prognosis in patients who have undergone the pPCI procedure and who have also developed high hsCRP levels. By examining 118 patients with STEMI, Milano et al. (22) also observed that higher levels of hsCRP at hospital admission were related to intra-hospital mortality. However, Tanveer et al. (23) did not show that levels of hsCRP have an effect on intra-hospital mortality.

Overall, many previous studies, as well as our own results, suggest that measuring hsCRP levels should become part of the mandatory laboratory diagnostics for patients diagnosed with STEMI as a predictor of disease prognosis in patients even after revascularization has been achieved. However, it should be emphasized that, in our study's cohort, patients with NSTEMI were not evaluated for the levels of hsCRP protein. The relationship between hsCRP levels and disease outcome should be examined in patients with NSTEMI as well although as shown by Habib et al. (24), high hsCRP values appear to be more related to STEMI than to NSTEMI patients. Furthermore, to better understand the role of hsCRP in STEMI, longitudinal monitoring of hsCRP values through time intervals and multiple hsCRP measurements would enable better connection with STEMI endpoints. If a larger number of patients were included, association with individual MACE features could be determined.

CONCLUSION

The hsCRP values in STEMI patients who were treated using pPCI are related to systolic function in the early phase of STEMI, as well as the occurrence of MACE during the six months of follow-up. Our results suggest that hsCRP could be valuable biomarker of a clinical status of the patients diagnosed with STEMI, as well as an important parameter that should be included in the development of MACE prediction scores.

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REFERENCES

1. Bahall M, Seemungal T, Legall G. Risk factors for first-time acute myocardial infarction patients in Trinidad. BMC Public Health 2018; 18(1): 161. [CrossRef]
2. Kiani F, Hesabi N, Arbabisarjou A. Assessment of Risk Factors in Patients With Myocardial Infarction. Glob J Health Sci 2015; 8(1): 255–62. [CrossRef]
3. Kamath DY, Xavier D, Sigamani A, Pais P. High sensitivity C-reactive protein (hsCRP) & cardiovascular disease: An Indian perspective. Indian J Med Res 2015; 142(3): 261–8. [CrossRef]
4. Roberts WL; CDC; AHA. CDC/AHA Workshop on Markers of Inflammation and Cardiovascular Disease: Application to Clinical and Public Health Practice: laboratory tests available to assess inflammation--performance and standardization: a background paper. Circulation 2004; 110(25): e572–6. [CrossRef]
5. Sproston NR, Ashworth JJ. Role of C-Reactive Protein at Sites of Inflammation and Infection. Front Immunol 2018; 9: 754. [CrossRef]
6. Tanaka T, Kishimoto T. The biology and medical implications of interleukin-6. Cancer Immunol Res 2014; 2(4): 288–94. [CrossRef]
7. Ritschel VN, Seljeflot I, Arnesen H, Halvorsen S, Weiss T, Eritsland J, et al. IL-6 signalling in patients with acute ST-elevation myocardial infarction. Results Immunol 2013; 4: 8–13. [CrossRef]
8. Reindl M, Reinstadler SJ, Feistritzer HJ, Theurl M, Basic D, Eigler C, et al. Relation of Low-Density Lipoprotein Cholesterol With Microvascular Injury and Clinical Outcome in Revascularized ST-Elevation Myocardial Infarction. J Am Heart Assoc 2017; 6(10): e006957. [CrossRef]
9. Swiatkiewicz I, Kozinski M, Magielski P, Fabiszak T, Sukiennik A, Navarese EP, et al. Value of C-reactive protein in predicting left ventricular remodelling in patients with a first ST-segment elevation myocardial infarction. Mediators Inflamm 2012; 2012: 250867. [CrossRef]
10. Ribeiro DR, Ramos AM, Vieira PL, Menti E, Bordin OL Jr, Souza PA, et al. High-sensitivity C-reactive protein as a predictor of cardiovascular events after ST-elevation myocardial infarction. Arq Bras Cardiol 2014; 103(1): 69-75. [CrossRef]
11. Schiele F, Meneveau N, Seronde MF, Chopard R, Descotes-Genon V, Dutheil J, et al; Reseau de Cardiologie de Franche Comte. C-reactive protein improves risk prediction in patients with acute coronary syndromes. Eur Heart J 2010; 31(3): 290–7. [CrossRef]
12. Arruda-Olson AM, Reeder GS, Bell MR, Weston SA, Roger VL. Neutrophilia predicts death and heart failure after myocardial infarction: a community-based study. Circ Cardiovasc Qual Outcomes 2009; 2(6): 656–62. [CrossRef]
13. Frangogiannis NG, Smith CW, Entman ML. The inflammatory response in myocardial infarction. Cardiovasc Res 2002; 53(1): 31–47.
14. Canale ML, Stroppa S, Caravelli P, Petronio AS, Mariotti R, Mariani M, et al. Admission C-reactive protein serum levels and survival in patients with acute myocardial infarction with persistent ST elevation. Coron Artery Dis 2006; 17(8): 693–8. [CrossRef]
15. Stumpf C, Sheriff A, Zimmermann S, Schaefauer L, Schlundt C, Raaz D, et al. C-reactive protein levels predict systolic heart failure and outcome in patients with first ST-elevation myocardial infarction treated with coronary angioplasty. Arch Med Sci 2017; 13(5): 1086–93. [CrossRef]
16. Bursi F, Weston SA, Killian JM, Gabriel SE, Jacobsen SJ, Roger VL. C-reactive protein and heart failure after myocardial infarction in the community. Am J Med 2007; 120(7): 616–22. [CrossRef]
17. De Servi S, Mariani M, Mariani G, Mazzone A. C-reactive protein increase in unstable coronary disease cause or effect?. J Am Coll Cardiol 2005; 46(8): 1496–502. [CrossRef]
18. Kavsak PA, MacRae AR, Newman AM, Lustig V, Palomaki GE, Ko DT, et al. Elevated C-reactive protein in acute coronary syndrome presentation is an independent predictor of long-term mortality and heart failure. Clin Biochem 2007; 40(5-6): 326–9. [CrossRef]
19. Liu D, Qi X, Li Q, Jia W, Wei L, Huang A, et al. Increased complements and high-sensitivity C-reactive protein predict heart failure in acute myocardial infarction. Biomed Rep 2016; 5(6): 761–5. [CrossRef]

20. Al Aseri ZA, Habib SS, Marzouk A. Predictive value of high sensitivity C-reactive protein on progression to heart failure occurring after the first myocardial infarction. Vasc Health Risk Manag 2019; 15: 221–7. [CrossRef]
21. Kalkman DN, Aquino M, Claessen BE, Baber U, Guedeney P, Sorrentino S, et al. Residual inflammatory risk and the impact on clinical outcomes in patients after percutaneous coronary interventions. Eur Heart J 2018; 39(46): 4101–8. [CrossRef]
22. Milano SS, de Moura Júnior OV, Bordin SAA, Marques GL. C-reactive Protein is a Predictor of Mortality in ST-segment Elevation Acute Myocardial Infarction. Int J Cardiovasc Sci 2019; 32(2): 118–24. [CrossRef]
23. 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. [CrossRef]
24. Habib SS, Kurdi MI, Al Aseri Z, Suriya MO. CRP levels are higher in patients with ST elevation than non-ST elevation acute coronary syndrome. Arq Bras Cardiol 2011; 96(1): 13–7. [CrossRef]