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Correlations between severity of coronary atherosclerosis and persistent elevation of circulating C-reactive protein levels 30 days after an acute myocardial infarction

Corelaţii între severitatea aterosclerozei coronariene şi persistenţa nivelelor serice crescute ale proteinei C reactive la 30 de zile după un infarct miocardic acut

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Abstract

***Introduction**: We aimed to assess the relationships between the persistence of elevated circulating levels of hs-CRP, a powerful inflammatory marker, determined at 30 days after an acute myocardial infarction (AMI), and the characteristics of the pre-existing coronary lesions. **Material and methods**: The study included 83 consecutive patients 30 days post AMI, who were subjected to coronary angiography and primary PCI. The patients were divided into two groups according to their hsCRP levels at 30 days after AMI: group 1 included 35 low-risk patients, with hsCRP levels <2 mg/l, and group 2 included 48 high-risk patients, with hsCRP levels >2 mg/l. **Results**: Angiographic analysis revealed the presence of a multivascular disease in 48.5% of the patients in group 1 versus 72.9% of the patients in group 2 (p=0.037). The Syntax scores for groups 1 and 2 were 22.2 +/- 6.6 and 27.07+/-0.94, respectively (p=0.001), and these values were significantly correlated with the hsCRP values (r=0.56, p<0.0001). LAD culprit lesions were found in 47.9% of the patients in group 1 and 20% of the patients in group 2 (p=0.01), and 42.8% of the group 1 patients and 83.3% of the group 2 patients had at least one significant stenosis in the LAD (p=0.0002). The ejection fraction at 30 days was significantly lower in the patients with elevated levels of hsCRP (52.91+/-4.03 vs 49.04+/-5.74, p=0.001), showing an inverse correlation with hsCRP levels (r=-0.52, p<0.0001). **Conclusions**: A more severe coronary artery disease was associated with am increased inflammatory status in the postinfarction phase, as evidenced by the high levels of circulating hsCRP. hsCRP can help for risk stratification in post AMI patients by identifying the subsets of patients who are at risk based on persistent elevated circulating levels of hsCRP at 30 days after infarction.*

***Key words:** hsCRP, inflammation, acute myocardial infarction*

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Rezumat

Introducere: *Scopul studiului a fost evaluarea corelaţiei dintre severitatea afectării coronariene şi persistenţa unor nivele serice crescute ale hs-CRP, un puternic marker inflamator, determinate la 30 de zile post Infarct Miocardic Acut (IMA).* ***Material şi metodă:*** *Studiul a inclus 83 pacienţi consecutivi cu IMA, la care s-a efectuat coronarografie şi angioplastie primară, împărţiţi în două grupuri în funcţie de nivelul hsCRP la 30 de zile postinfarct: grupa 1 – 35 pacienţi cu risc redus, cu nivele de hsCRP<2 mg/l, respectiv grupa 2 – 48 pacienţi cu risc înalt, cu nivele de hsCRP>2 mg/l.* ***Rezultate:*** *Analiza angiografică a relevat prezenţa unei afectări multivasculare la 48.5% din pacienţii grupei 1 versus 72.9% din pacienţii grupei 2 (p=0.037). Scorul Syntax a fost de 22.2 +/- 6.6 la grupa 1 vs 27.07+/-0.94 la grupa 2 (p=0.001), prezentând o corelaţie semnificativă cu valorile hsCRP (r=0.56, p<0.0001). Numărul mediu de coronare afectate a fost de 1.6+/- 0.69 vs 1.97+/-0.73 (p=0.019). Localizarea leziunilor ţintă la nivelul ADA a fost întâlnită la 47.9% din pacienţii grupei 1 vs 20% la grupa 2 (p=0.01) iar prezenţa de stenoze semnificative la nivelul ADA la 42.8% din pacienţii grupei 1 vs 83.3% din pacienţii grupei 2 (p=0.0002). Fracţia de ejecţie la 30 de zile a fost semnificativ mai mică la grupa 2 (52.91+/-4.03 vs 49.04+/-5.74, p=0.001), prezentând o corelaţie inversă cu nivelele hsCRP (r=-0.52, p<0.0001).* ***Concluzii****: Persistenţa unui status inflamator în faza postinfarct, evidenţiată de nivelele crescute ale hsCRPcirculant, se asociază cu o severitate mai crescută a afecţiunii coronariene şi o evoluţie mai severă. HsCRP poate contribui la stratificarea riscului postIMA, identificând subsetul de pacienţi la risc pe baza persistenţei nivelelor circulante crescute ale hsCRP la 30 de zile postinfarct.*

Cuvinte cheie: *hsCRP, inflamaţie, infarct miocardic acut*

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Introduction

Atherosclerosis is characterized nowadays as a generalized inflammatory disease that involves all vascular beds, most commonly localised at the level of the coronary, carotid and peripheral arteries (1). The most devastating manifestation of atherosclerosis is acute myocardial infarction (AMI), in which inflammation has been demonstrated to play a pivotal role; many studies have proven that an elevated inflammatory status is associated with the development of acute coronary syndromes (2).

In acute myocardial infarction, the rupture of an intracoronary plaque leads to the abrupt occlusion of the coronary artery and subsequent myocardial necrosis in the territory supplied by the occluded artery. Several days following the infarction, the myocardial healing process leads to the development of a scar at the site of necrosis. The inflammatory process is involved in different phases of acute myocardial infarction that include plaque formation, plaque rupture and also in the myocardial healing process that is followed by scar formation at the site of the damaged myocardium (3). During the postinfarction phase, myocardial ischaemia caused by coronary occlusion leads to a systemic humoral and a local cellular inflammatory response, which act as triggers of a myocardial inflammatory reaction that aims to promote myocardial healing. Simultaneously, the systemic activation of the humoral system following myocardial necrosis leads to an additional significant increase in the regional inflammatory response (4,5).

The systemic inflammatory reaction in post acute myocardial infarction phase consists mainly in a humoral response that is represented by the release of cytokines and complement systems, and a cell-mediated response, represented by the migration and accumulation of inflammatory cells (i.e. neutrophils, monocytes/macrophages and mast cells) at the site of the ischaemic myocardium. Several inflammatory markers that can be easily measured in peripheral blood, have been proposed as indices of the

systemic inflammatory reaction that is associated with the development of an acute myocardial infarction. One such marker, *C-reactive protein* has been shown to be associated with increased early and late cardiovascular morbidity and mortality in patients with STsegment elevation myocardial infarction, and has been proposed to represent one of the most important markers for characterizing the systemic inflammatory process in post AMI patients (6,7).

The high-sensitivity C-reactive protein (hs-CRP) is currently considered to represent a marker of future cardiovascular events independent from the traditional cardiovascular risk factors such as elevated cholesterol, smoking, obesity or hypertension. Several studies have proven that high levels of hs-CRP are able to identify patients who are at risk for significant endothelial dysfunction and deleterious ventricular remodeling in the postinfarction phase (8,9).

However, all the studies published so far evaluated the correlation between high levels of hs-CRP collected upon hospital admission, during the acute phase of AMI, and cardiovascular events, without taking into consideration the risk associated with the persistence of high hsCRP levels in the postAMI phase.

In this angiographically-controlled study, we aimed to assess the relationships between the pre-existing coronary lesions (the angiographic severity of coronary artery diseases expressed by the Syntax scores, the locations of the culprit lesions, the involvement of different coronary arteries, the presence of multivascular disease and the total number of coronary arteries with significant stenosis) and the persistence of elevated circulating levels of hs-CRP as determined at 30 days after acute myocardial infarction.

Material and methods

The study included 83 consecutive patients who presented with acute myocardial infarction 30 days prior to the inclusion in the study and who were subjected to coronary angiography and primary PCI at the time of the infarction, performed within 12 hours of the onset of symptoms.

All patients received optimum medical therapy following the infarction, including aspirin (75 mg), clopidogrel (a 300 mg loading dose followed by 150 mg daily for 7 days, and then by 75 mg daily), ACE inhibitors and statins (80 mg atorvastatin for the first 30 days after the infarction as by local routine practice).

The demographic data, history and risk factors (i.e., age, gender, smoking status, presence of diabetes, hyperlipidemia, obesity, hypertension and blood tests) were recorded for every patient.

In all patients hs CRP levels were determined at 30 days postinfarction and the patients were divided into 2 groups according to their hsCRP levels: group 1 consisted in 35 low risk patients, with hsCRP levels below 2 mg/l, and group 2 consisted in 48 high risk patients, with hsCRP levels above 2 mg/l.

Measurements of hsCRP levels were performed utilizing lateral flow immunometric methodology, which enables hsCRP testing from fingerstick or venous whole blood using the Cholestech LDX System (Cholestech-LDX Analyzer, Biosite Incorporated, san Diego, CA, USA), which is a desk-top analyzer that utilizes dry chemistry cassettes and reflectance photometry to quantify substances in blood, based on the conversion of the reflectance reading (% R) to hs-CRP concentration in mg/L.

Retrospective assessment of coronary angiographies that were performed within the first 12 hours after the onset of the infarction included calculation of the Syntax score, the number of coronary arteries with significant stenoses, the number of coronary artery stenosis in each of the 3 major coronary arteries and the location of the culprit lesion. A significant stenosis was

defined as a stenosis >75% in a major epicardial coronary vessel. A culprit lesion was defined as a lesion that was responsible for an acute ischaemic event, as identified by ECG, echocardiography and angiography based on location in the coronary artery that supplied the myocardial territory with a contractility defect (as assessed with echocardiography) or with ST/T changes (as assessed by ECG), together with a correspondent angiographic picture (thrombus or unstable plaque).

Echocardiographic assessment included determination of the left ventricular end-diastolic and end-systolic volumes and calculation of left ventricular ejection at 30 day postinfarction. All echocardiographic acquisitions were made using a PhilipsSonos 7500 equipment. All acquired images were transferred to a workstation (QLab, Philips) for data processing, measurements and interpretation. Calculation of left ventricular ejection fraction was based on determination of left ventricular volumes on bi-dimensional assessment (in 4-chambers and 2-chambers apical views) using the modified Simpson technique.

All patients gave written informed consent for the study, and the study protocol was approved by the ethics committee of the medical center in which the study was conducted.

The primary objective of the study was to demonstrate the association between the severity of coronary atherosclerosis (as expressed by the Syntax score, the presence of multivascular disease and the total number of coronary arteries with significant stenoses) and increased levels of hsCRP 30 days after an acute myocardial infarction.

The secondary objectives of the study were to demonstrate the association between increased levels of hsCRP 30 days after an acute myocardial infarction and:

a. angiographic characteristics (i.e., location of the culprit lesion in different coronary arteries, the involvement of different coronary arteries in the atherosclerotic process, and postprocedural TIMI flow)
b. left ventricular function, as expressed by the ejection fraction immediate after intervention and at 30 days
c. other baseline characteristics that reflect metabolic status

We performed a multivariate analysis of factors that could predict a depressed ventricular function at 30 days postinfarction, including in this model the postprocedural TIMI flow, the total ischemic time, the immediate postprocedural left ventricular ejection fraction, the hsCRP values, the angiographic Syntax score, and the values of troponin I and CK-MB.

Statistical analysis

All statistical analysis were performed using the InStat Graph Pad software. We used the Fisher's exact test (or the Student's *t*-test for age) to compare the baseline characteristics of patients between the low-risk and high-risk patient population. Continuous values are expressed as the mean and standard deviation, and statistical significance was determined using the Mann-Whitney test. Categorical variables are expressed as percentages. Linear regression was used to assess the correlation between EF and hsCRP values. Statistical significance was considered for a p value <0.05, and all p values were 2-sided.

Results

The clinical baseline characteristics of the study population showed no significant differences between the low-risk and the high-risk group in respect to age (p=0.6), gender (p=0.06), the presence of diabetes (p=0.5), hypertension (p=0.4), hyperlipidemia (p=1), obesity (p=0.7) or smoking status (p=0.4) (*Table I*). However, metabolic syndrome (defined as the presence

Table I. Baseline characteristics of study population.

	Group 1 -low risk, hsCRP<2 mg/l n=35 (42.16%)	Group 1 -high risk, hsCRP>2 mg/l n=48 (57.84%)	P value
Age, years	59.54 +/- 9.57	58.54 +/- 11.55	0.66
Gender, male	4 (11.4%)	14 (29.1%)	0.06
Diabetes	8 (22.8%)	8 (16.6%)	0.57
Hypertension	30 (85.7%)	44 (91.6%)	0.48
Hyperlipidemia	20 (57.1%)	27 (56.2%)	1
Obesity (BMS>25 km/m2)	5 (14.2%)	5 (10.4%)	0.73
Smoker *	13 (37.1%)	14 (29.1%)	0.48
Metabolic Syndrome	5 (14.2%)	18 (37.5%)	0.02

*past or present

of more than 3 parameters from the following: blood glucose>100 mg/dl, hypertension, triglycerides > 150 mg/dl, HDL cholesterol <40 mg/dl in males or <50 mg/dl in females, and central obesity) was present in a significantly greater proportion of the group of patients with high hs-CRP levels (p=0.02).

The hsCRP values were 1.42 +/- 0.52 mg/l in group 1, classified as low risk, and 5.59 +/-2.89 mg/l in group 2, classified as high risk. We recorded significantly higher values of trygliceride (166.25 +/- 32.02 versus 148.62 +/- 62.0 mg/dl, p=0.01) and troponin I (1.94 +/- 1.5 versus 1.25 +/- 0.13 µg/l, p=0.03). The other blood tests did not reveal a statistically significant difference between the groups, although these tests indicated a more expressed inflammatory reaction and greater lipidic metabolism alterations in the high hsCRP group (total cholesterol 195.02 +/- 64.1 versus 183.6 +/- 47.12 mg/dl, p=0.37, HDL-cholesterol 41.66 +/- 14.35 versus 47.02 +/- 11.8 mg/dl, p=0.07).

Severity of coronary atherosclerosis

Angiographic analysis indicated a significantly higher Syntax score in the high hsCRP group (27.07 +/- 0.94 versus 22.2 +/- 6.6, p=0.001), revealing a more diseased coronary artery tree in this group. Moreover, multivascular disease was present in 48.5% of patients from group 1 compared with 72.9% of patients from group 2 (p=0.037, OR = 2.85, 95% CI = 1.13- 7.14). The mean number of diseased coronary arteries was 1.6 +/- 0.69 in the low-risk group compared with 1.97 +/- 0.73 in the high risk group (p=0.019) (*Table II*).

Location of culprit lesion in different coronary arteries

Analysis of the culprit lesion location showed that in high-risk patients from group 2, the infarctions were more likely to be caused by obstructive diseases in the left anterior descending artery (LAD). Location of culprit lesions in LAD was encountered in 47.9% of patients from group 2 versus 20% of patients from group 1 (p=0.01, OR=3.68, 95% CI = 1.35-10.03), while location in any of the other two coronary arteries did not present a significant difference between the groups. The culprit lesions were located in the Circumflex artery (ACx) in 31.4% of cases from group 1 versus 18.7% from group 2 (p=0.2, oR = 0.5, 95% CI = 0.18-1.39), and in the right coronary artery (RCA) in 48.5% of cases from group 1 versus 33.3% from group 2 (p=0.1, OR = 0.52, 95%CI = 0.21-1.29) (*Table III*, *Figure 1*).

Table II. Comparison of blood tests, angiographic data and EF in patients with high versus low risk.

	Group 1- low risk, hsCRP<2mg/l	Group 2- high hsCRP>2 mg/l	p value
BLOOD TESTS			
hsCRP (mg/l)			**<0.0001**
Mean +/- SD	1.428 +/- 0.529	5.59 +/- 2.89	
95% confidence interval	*1.24 – 1.61*	*4.75 – 6.44*	
Cholesterol (mg/dl)			**0.37**
Mean +/- SD	183.6 +/- 47.12	195.02 +/- 64.1	
95% confidence interval	*167.4 - 199.8*	*176.39 - 213.65*	
HDL-cholesterol (mg/dl)			**0.07**
Mean +/- SD	47.02 +/- 11.8	41.66 +/- 14.35	
95% confidence interval	*42.96 - 51.09*	*37.49 - 45.83*	
Triglyceride (mg/dl)			**0.01**
Mean +/- SD	148.62 +/- 62.0	166.25 +/- 32.02	
95% confidence interval	*139.17 - 158.09*	*156.94 - 175.56*	
WBC (*10^3)			**0.07**
Mean +/- SD	7.47 +/- 1.69	7.97 +/- 9.72	
95% confidence interval	*6.85 - 8.02*	*7.69 - 8.25*	
Thrombocyte count (*10^3)			**0.6**
Mean +/- SD	240.85 +/- 69.91	232.89 +/- 71.14	
95% confidence interval	*216.83 - 264.89*	*212.22 - 253.58*	
cTnI (µg/l)			**0.03**
Mean +/- SD	1.25 +/- 0.13	1.94 +/- 1.5	
95% confidence interval	*0.79 - 1.71*	*1.49 - 2.39*	
Peak CK-MB (µg/l)			**0.06**
Mean +/- SD	19.45 +/- 5.77	21.83 +/- 5.48	
95% confidence interval	*17.47 - 21.44*	*20.23 - 23.43*	
ANGIOGRAPHIC DATA			
Syntax score			**0.001**
Mean +/- SD	22.2 +/- 6.6	27.07 +/- 0.94	
95% confidence interval	19.93 - 24.47	25.13 - 28.94	
Number of diseased coronary arteries			**0.019**
Mean +/- SD	1.6 +/- 0.69	1.97 +/- 0.73	
95% confidence interval	*1.36 – 1.84*	*1.76 – 2.19*	
Ischemic time (min)			**0.9**
Mean +/- SD	304 +/- 132	301 +/- 109.59	
95% confidence interval	*258.74 - 349.61*	*269.15 - 332.85*	
Postprocedural TIMI flow			**0.3**
Mean +/- SD	*2.8 +/- 0.47*	*2.75 +/- 0.48*	
95% confidence interval	*2.63 - 2.96*	*2.6 - 2.89*	
EJECTION FRACTION			
Ejection fraction at baseline (%)			**0.07**
Mean +/- SD	47.74 +/- 3.8	45.79 +/- 5.45	
95% confidence interval	*46.43 - 49.05*	*44.2 - 47.37*	
Ejection fraction at 30 days (%)			**0.001**
Mean +/- SD	52.91 +/- 4.03	49.04 +/- 5.74	
95% confidence interval	*51.52 – 54.3*	*47.37 – 50.71*	

Table III. Angiographic characteristics of the study population.

	Group 1 -low risk, hsCRP<2 mg/l n=35 (42.16%)	Group 1 -high risk, hsCRP>2 mg/l n=48 (57.84%)	*P value*	*OR*	*95% CI*
Culprit lesion					
LAD	7 (20%)	23 (47.9%)	0.01	3.68	1.35 – 10.03
ACx	11 (31.4%)	9 (18.7%)	0.2	0.5	0.18 – 1.39
RCA	17 (48.5%)	16 (33.33%)	0.18	0.52	0.21 – 1.29
Presence of at least 1 significant stenosis					
LAD	15 (42.8%)	40 (83.3%)	0.0002	6.66	2.42 – 18.34
ACx	18 (51.4%)	18 (37.5%)	0.26	0.56	0.23 – 1.37
RCA	21 (60%)	37 (77.1%)	0.14	2.24	0.86 – 5.82
Multivascular disease	17 (48.5%)	35 (72.9%)	0.03	2.85	1.13 – 7.14

Involvement of different coronary arteries in the atherosclerotic process

The presence of at least one significant stenosis in the LAD was recorded in 42.8% of patients from group 1 compared with 83.3% of patients from group 2 (p=0.0002, OR=6.66, 95% CI = 2.42-18.34), while the presence of at least one significant stenosis in ACx or RCA did not present any statistically significant difference between the groups (51.4% versus 37.5%, p=0.2 for ACx, 60% versus 70.1%, p= 0.1 for RCA) (*Figure 2*).

Linear regression analysis indicated a good correlation between the levels of Syntax score and the values of hsCRP at 30 days postinfarction (r=0.56, p<0.0001) (*Figure 3*), indicating that a higher severity of coronary lesions correlates with higher values of inflammatory markers at 30 days postinfarction.

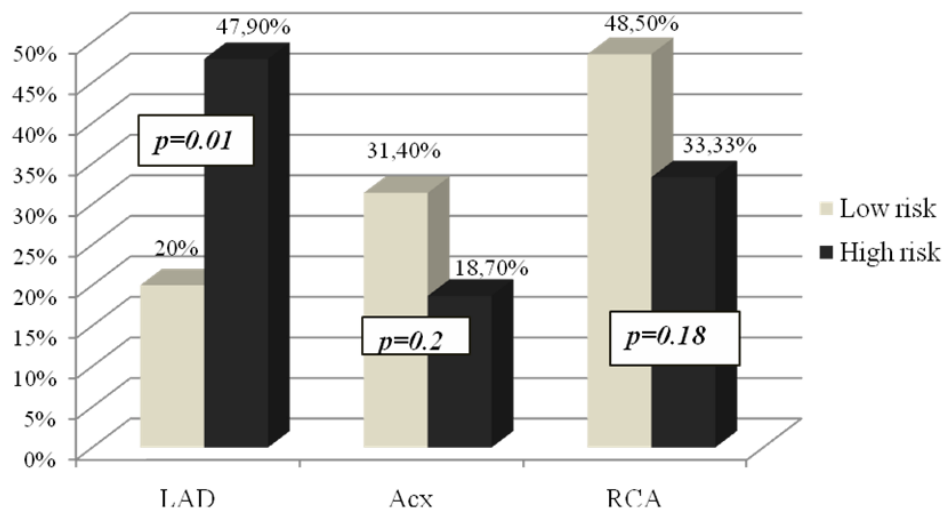

Figure 1. Location of culprit lesion in high versus low risk patients.

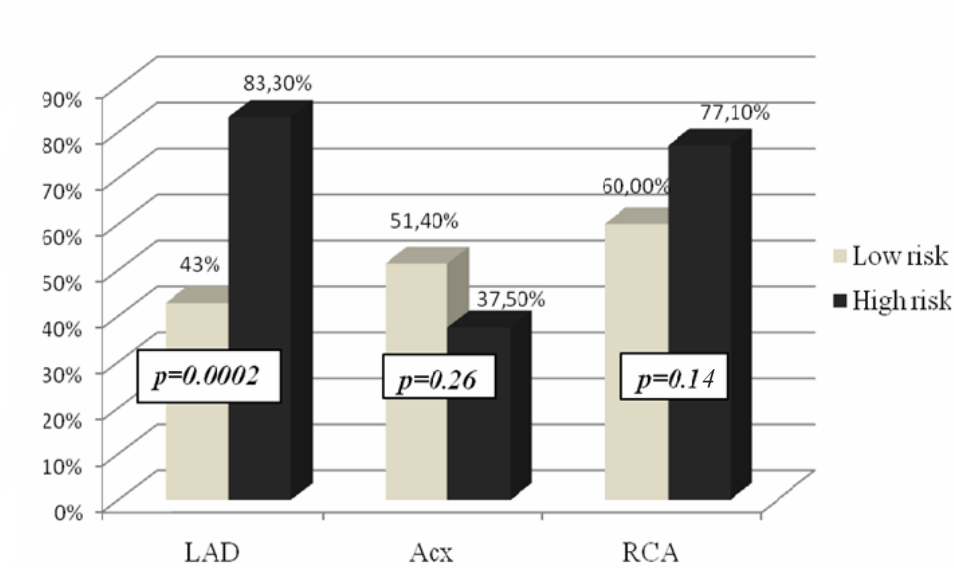

Figure 2. Involvement of main coronary arteries in high versus low risk patients.

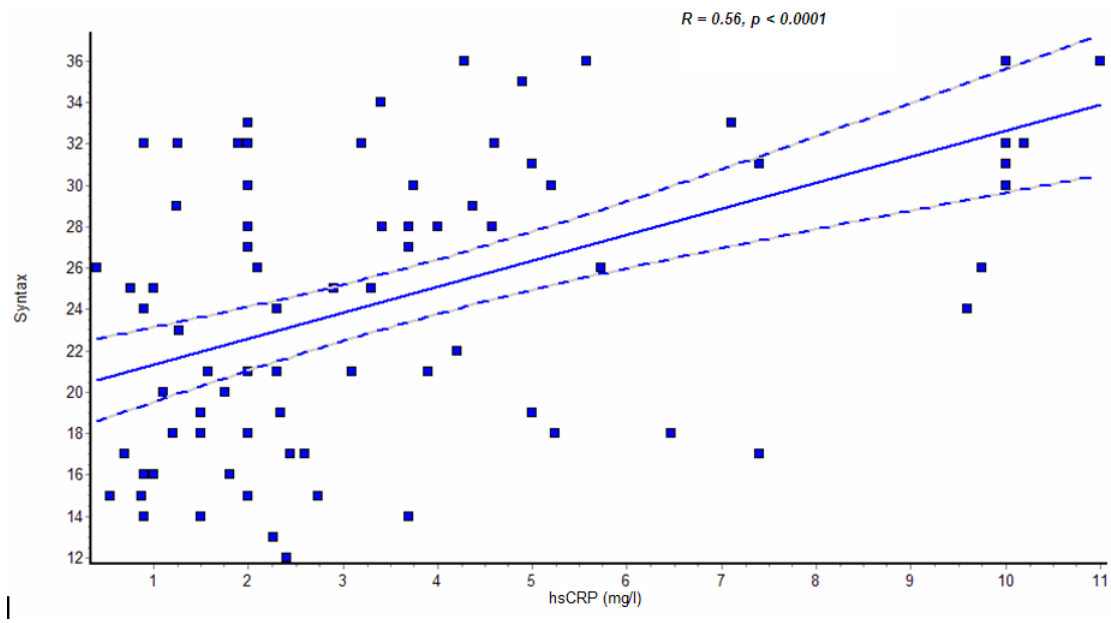

Figure 3. Correlation between Syntax score and hsCRP.

Ejection fraction and hsCRP values

The ejection fraction immediately after intervention did not show any statistically significant difference between the groups (47.74 +/- 3.8% vs 45.79 +/- 5.54%, p=0.07). However, as a result of revascularization and subsequent recovery of the viable myocardium, the ejection fraction increased slightly particularly in

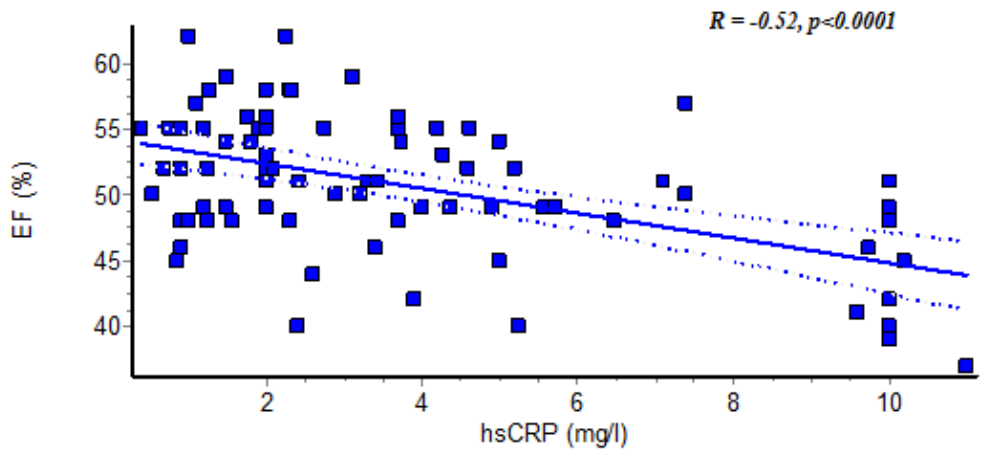

Figure 4. Correlation between ejection fraction and hsCRP.

the first group, and the difference between the groups became statistically significant at 30 days , when mean EF was 52.91 +/- 4.03, 95% CI 51.52 – 54.3 in group 1, and 49.04 +/- 5.74, 95% CI 47.37 – 50.71 in group 2, p=0.001. We also found a good correlation between the ejection fraction and the high levels of hsCRP (r=-0.52, p<0.0001) (*Figure 4*).

Predictors for low EF at 30 days postinfarction

Multivariate analysis identified the following parameters as significant predictors of low ejection fraction at 30 days postinfarction: postprocedural TIMI flow (Odds Ratio 3.06, p=0.05), low (<45%) immediate postprocedural ejection fraction (Odds Ratio 3.9, p=0.006) and angiographic Syntax score (Odds Ratio 3.9, p=0.01) (*Table IV*).

Discussion

The excessive release of inflammation mediators during the acute phase of a myocardial infarction may lead to the exacerbation of tissue damage and the development of severe complications (10). During the acute phase of AMI, serum C-reactive protein has been suggested to represent not only a sensible inflammatory marker, but also a direct inflammatory promoter (11) with pro-atherogenic (12) and pro-thrombotic properties (13). According to a study published by Bonvini et al, inflammatory response following an acute myocardial infarction should

Table IV. Multivariate predictors of 30-days EF.

	Odds Ratio (95% CI)	***p value***
Ischemic time	2.35 (0.88 - 6.29)	0.1
Post-procedural TIMI flow (<3)	3.06 (1.02 - 9.16)	0.05
Immediate post-procedural Left Ventricular Ejection Fraction (<45%)	3.9 (1.46 - 10.55)	0.006
High hs-CRP value (>2 mg/dl)	2.4 (0.8 - 6.6)	0.09
Angiographic Syntax score	3.9 (1.29 - 11.9)	0.01
TnI	1.6 (0.65 - 3.96)	0.3
CK-MB	1.24 (0.51 - 3.03)	0.65

represent a new therapeutic target for postinfarction patients (5).

CRP is an acute-phase protein synthetized by hepatocytes under the control of inflammatory cytokines and particular intrerleukin 6, and is released into the circulation in response to inflammation and tissue damage. Given that the circulating level of CRP, considered currently considered to represent a "golden marker for inflammation", reflects the severity of inflammatory response and plays a significant role in the development of atherosclerosis, many studies have attempted to predict the future cardiovascular events and the response to therapy based on CRP-based risk classification (14,15). It has been proved that high levels of circulating CRP upon admission correlates with the extent of the infarction, the development of postinfarction heart failure and the presence of severe lesion by angiography, while in patients undergoing primary PCI, high CRP level before the procedure predicted the rate of early complications (16,17). In a previous study of *Pietila et al*, high serum C-reactive protein concentrations in acute myocardial infarction patients were found to predict an increased mortality up to 6 months following the infarction (18). Moreover, *Cagh et al* recently demonstrated that hs-CRP is an independent predictor of ST resolution following primary PCI for AMI, showing also that a level of hs-CRP higher than 0.88 mg/dl predicted poor myocardial blush following PCI with 73% sensitivity and 31% specificity (19).

While all these studies have focused on the levels of CRP or hsCRP upon admission, during the acute phase of the infarction, our study evaluated the correlation between the persistence of the inflammatory response, as expressed by persistent elevation o the hsCRP levels at 30 days postinfarction, the clinical and angiographic characteristics and the evolution of these patients.

Furthermore, this is the first study to correlate the high levels of hsCRP with the severity of the coronary artery disease and the location of the culprit lesion, lesion that is responsible for the acute myocardial infarction in patients with multiple coronary lesions. As the site of the culprit lesion indicates the location of infarction (in the territory supplied by the coronary artery in which culprit lesion is located), our study indicates that there is an association between high hsCRP levels and certain locations of infarction. We found that an anterior infarction, produced by a culprit lesion in the LAD, is associated with higher levels of inflammation than infarctions located in other coronary territories.

Our study found that culprit lesions located in LAD are more likely to trigger an exacerbated inflammatory response, as the LAD was the infarct related artery in a significantly higher extent in the high-risk group patients than in the low-risk group patients (47.9% from the patients in the high risk group having the culprit lesion located in the LAD, compared with 20% from patients in the low-risk group, p=0.01), while for ACx and RCA there were no statistically significant differences between the groups. Interestingly, the involvement of the LAD in the atherosclerotic process was also associated with higher hsCRP levels (83.3% in the high hsCRP group compared with 42.8% in the low hsCRP group), independent of the nature of LAD lesions (culprit or non-culprit). Therefore, we can postulate that stenoses in the LAD, whether acute (culprit) or chronic (non-culprit) are associated with higher levels of hsCRP and therefore these stenoses represent higher risk lesions than those in the ACx and RCA. A possible explanation for this observation is that LAD, compared to the other arteries, irrigates a larger portion of the left ventricle, represented by the anterior wall, the septum and the apex. Therefore, occlusions of the LAD usually result in larger myocardial infarction, with larger areas of myocardial ne-

crosis and more marked systemic inflammatory responses.

As the areas supplied by the LAD are the most important contributors to left ventricular contractility, it is not surprising that in this study, the left ventricular function was significantly depressed in patients with elevated hsCRP levels at 30 days postinfarction, as indicated by the inverse correlation between EF and hsCRP values and also by the significantly lower EFs in the group with high hsCRP levels (49.04 +/-5.74 versus 52.91 +/- 4.03 in group 1, p=0.001).

In a study published by *Swiatkiewicz et al*, multivariate analysis demonstrated CRP concentration at discharge to be an independent marker of early postinfarction left ventricular dysfunction (odds ratio of 1.38, 95 % confidence interval 1.01–1.87; $p < 0.04$), which proves that higher levels of CRP upon admission identifies patients with worse outcomes and suggests that high hsCRP levels may identify patients who will have poorer results after reperfusion, or may be more likely to have ventricular remodeling and enlargement after hospital discharge (20). Similarly, in a recently published study by *Perlas et al,* high levels of hsCRP upon admission were found to correlate with an increase in cardiovascular risk on short term (21). Our study goes a step forward and shows that persistence of inflammation at 30 days postinfarction was also associated with a poorer outcome as reflected by the lower ejection fraction in patients with persistently elevated hsCRP levels. This finding may be due to mydriad factors that contribute to the impairment of left ventricular function, including the severity of the coronary artery disease, the postintervention TIMI flow and ejection fraction, the involvement of the LAD, the anterior location of the infarction, the presence of a multivascular disease with coexisting significant stenoses in other coronary territories, and also the marked elevation in the inflammatory status, which classifies these patients at high-risk for future cardiovascular events.

Another parameter which significantly correlated with higher hsCRP values was the presence of a multivascular coronary artery disease, which was defined as the involvement of at least two coronary arteries in the atheromatous process. In our study, the presence of a significant stenosis in at least 2 coronary arteries was associated with higher hsCRP levels compared to the presence of a significant stenosis in only one main coronary artery (multivascular disease in 48.5% of patients from group 1 compared with 72.9% of patients from group 2, p=0.03). As the presence of multiple stenoses is a marker of a more generalized inflammation, it is reasonable that the presence of a multivascular disease reflects a more expressed inflammatory status than a disease localized in only one vessel. Therefore the increased levels of hsCRP in patients with multivascular disease may be attributable to such elevation in the global inflammatory status. As this status was evaluated at 30 days postinfarction, it is reasonable to believe that it represents not only an infarct-related overexpression of the inflammatory response related to infarction, persisting at 30 days postinfarction, but also a factor involved in the pathophysiology of the acute coronary syndrome. However, the exact contribution of these two mechanisms to the marked inflammation persistent at 30 days postinfarction remains to be established.

Multivariate analysis showed that a postprocedural TIMI flow <2, a low (<45%) immediate postprocedural ejection fraction, an angiographic Syntax score higher than 22 and persistence of high levels of hsCRP were the strongest predictors of low ejection fraction at 30 days postinfarction.

In comparison with other studies, we extended the time window for assessing the hsCRP values to 30 days postinfarction, which allowed

us to identify the patients with persistence of inflammatory response, who are more exposed to cardiovascular risk than those with normal values of inflammatory markers. Our study indicates that the persistent elevated serum hsCRP levels at 30 days postinfarction indicates a more severe coronary artery disease and should classify the patient as being at risk for future cardiovascular events, triggering the initiation of appropriate therapeutic strategies in these patients.

Conclusions

Our study showed that the severity of the coronary artery disease is correlated with a marked inflammation at 30 days postinfarction, particularly in patients with coronary artery disease that involves the LAD or with culprit lesions that are located within the LAD. However, multivariate analysis indicated that the most powerful contributors to a low ejection fraction postinfarction were the postprocedural TIMI flow, the immediate postprocedural ejection fraction and the severity of coronary artery disease as expressed by the Syntax score. Moreover, patients with persistently high levels of hsCRP at 30 days postinfarction exhibited poorer outcome as reflected by lower ejection fraction following the infarction. Therefore, hsCRP is an inflammatory marker which can aid the risk stratification in post myocardial infarction patients, identifying subsets of patients at risk based on persistently elevated levels of circulating hsCRP at 30 days postinfarction.

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List of abbreviations

ACx – Circumflex artery
AMI – Acute Myocardial Infarction
CRP – C-Reactive Protein
hs-CRP – High Sensitivity C- Reactive Protein
LAD – Left Anterior Descending Artery
EF – Ejection Fraction
RCA – Right coronary artery

Disclosures

There are no disclosures related to this manuscript.

References

1. Frangogiannis NG, Smith CW, Entman ML. The inflammatory response in myocardial infarction.Cardiovasc Res. 2002 Jan;53(1):31-47. DOI: 10.1016/S0008-6363(01)00434-5
2. Lindahl B, Toss H, Siegbahn A, Venge P, Wallentin L. Markers of myocardial damage and inflammation in relation to long-term mortality in unstable coronary artery disease. FRISC Study Group. Fragmin during Instability in Coronary Artery Disease. N Engl J Med. 2000 Oct;343(16):1139-47. DOI: 10.1056/NEJM200010193431602
3. Anzai T, Yoshikawa T, Shiraki H, Asakura Y, Akaishi M, Mitamura H, et al. C-reactive protein as a predictor of infarct expansion and cardiac rupture after a first Q-wave acute myocardial infarction. Circulation. 1997 Aug;96(3):778-84. DOI: 10.1161/01.CIR.96.3.778
4. Ridker PM, Thuren T, Zalewski A, Libby P.Interleukin-1β inhibition and the prevention of recurrent cardiovascular events: rationale and design of the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS).Am Heart J. 2011 Oct;162(4):597-605. DOI: 10.1016/j.ahj.2011.06.012
5. Bonvini RF, Hendiri T, Camenzind E. Inflammatory response post-myocardial infarction and reperfusion: a new therapeutic target? Eur Heart J Suppl.2005 Oct;7(-suppl I):I27-I36. DOI: 10.1093/eurheartj/sui077
6. Nian M, Lee P, Khaper N, Liu P. Inflammatory cytokines and postmyocardial infarction remodeling. CircRes. 2004 Jun;94(12):1543-53. DOI: 10.1161/01.RES.0000130526.20854.fa
7. Rioufol G, Zeller M, Dentan G, Laurent Y, L'Huillier I, Ravisy J, et al. Predictors and prognosis for complex coronary lesions in patients with acute myocardial infarction: data from RICO survey. Am Heart J. 2007

Aug;154(2):330-5. DOI: 10.1016/j.ahj.2007.04.013
8. 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 Jan 1;111(1):26-30. DOI: 10.1016/j.amjcard.2012.08.041
9. Raposeiras-Roubín S, Barreiro Pardal C, Rodi-o Janeiro B, Abu-Assi E, García-Acu-a 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 Jan;63(1):30-4. DOI: 10.1177/0003319711406502
10. Ridker PM. Moving beyond JUPITER: will inhibiting inflammation reduce vascular event rates? CurrAtheroscler Rep. 2013 Jan;15(1):295. DOI: 10.1007/s11883-012-0295-3
11. Brodie BR, Stuckey TD, Hansen C, VerSteeg DS, Muncy DB, Moore S, et al. Relation between electrocardiographic ST-segment resolution and early and late outcomes after primary percutaneous coronary intervention for acute myocardial infarction. Am J Cardiol. 2005 Feb;95(3):343-8. DOI: 10.1016/j.amjcard.2004.09.031
12. Gibson CM, Cannon CP, Murphy SA, Marble SJ, Barron HV, Braunwald E, et al. Relationship of the TIMI myocardial perfusion grades, flow grades, frame count, and percutaneous coronary intervention to long-term outcomes after thrombolytic administration in acute myocardial infarction. Circulation. 2002 Apr;105(16):1909-13. DOI: 10.1161/01.CIR.0000014683.52177.B5
13. Gibson CM, Kirtane AJ, Morrow DA, Palabrica TM, Murphy SA, Stone PH, et al. Association between thrombolysis in myocardial infarction myocardial perfusion grade, biomarkers, and clinical outcomes among patients with moderate- to high-risk acute coronary syndromes: observations from the randomized trial to evaluate the relative PROTECTion against post-PCI microvascular dysfunction and post-PCI ischemia among antiplatelet and antithrombotic agents-Thrombolysis In Myocardial Infarction 30 (PROTECT-TIMI 30). Am Heart J. 2006 Oct;152(4):756-61. DOI: 10.1016/j.ahj.2006.04.016
14. Raposeiras Roubín S, Barreiro Pardal C, Roubín-Cami-a F, Ocaranza Sanchez R, Alvarez Castro E, ParadelaDobarro B, et al. High-sensitivity C-reactive protein predicts adverse outcomes after non-ST-segment elevation acute coronary syndrome regardless of GRACE risk score, but not after ST-segment elevation myocardial infarction.Rev Port Cardiol. 2013 Feb;32(2):117-22. DOI: 10.1016/j.repc.2012.05.026
15. Suleiman M, Khatib R, Agmon Y, Mahamid R, Boulos M, Kapeliovich M, et al. Early inflammation and risk of longterm development of heart failure and mortality in survivors of acute myocardial infarction predictive role of C-reactive protein. J Am CollCardiol. 2006 Mar;47(5):962-8. DOI: 10.1016/j.jacc.2005.10.055
16. Herrmann J, Lennon RJ, Barsness GW, Sandhu GS, Gulati R, Best PJ, et al. High sensitivity C-reactive protein and outcomes following percutaneous coronary intervention in contemporary practice. CircCardiovascInterv. 2012 Dec;5(6):783-90. DOI: 10.1161/CIRCINTERVENTIONS.112.972182
17. Magadle R, Hertz I, Merlon H, Weiner P, Mohammedi I, Robert D. The relation between preprocedural C-reactive protein levels and early and late complications in patients with acute myocardial infarction undergoing interventional coronary angioplasty.ClinCardiol. 2004 Mar;27(3):163-8. DOI: 10.1002/clc.4960270314
18. Pietilä KO, Harmoinen AP, Jokiniitty J, Pasternack AI. Serum - C-reactive protein concentration in acute myocardial infarction and its relationship to mortality during 24 months of follow-up in patients under thrombolytic treatment. Eur Heart J. 1996 Sep;17(9):1345-9. DOI: 10.1093/oxfordjournals.eurheartj.a015068
19. Cağli KE, Topaloğlu S, Aras D, Günel EN, Ozlü MF, Uygur B, et al. The significance of admission hs-CRP in patients undergoing primary percutaneous intervention for acute myocardial infarction. Turk KardiyolDernArs. 2009 Jan;37(1):19-25.
20. Swiatkiewicz I, Kozinski M, MagielskiP. Usefulness of C-reactive protein as a marker of early post-infarct left ventricular systolic dysfunction. Inflamm Res.2012 July;61(7):725–734. DOI: 10.1007/s00011-012-0466-2
21. Perlas TR., Te CG, Punzalan FE., Uy CC., Medldrick G. High Sensitivity CRP and Short-Term Cardiovascular Risk among Patients with Acute Myocardial Infarction: A Two-center Study. ActaMedPhilipp. 2012;46(3):64-68.