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ORIGINAL RESEARCH

Association between Acute Inflammatory Response and Infarct Size in STEMI Patients Undergoing Primary PCI

Mirabela Morariu[1,2,3], Emese Márton[2,3], András Mester[1,2,3], Mihaela Rațiu[1,2], Imre Benedek[1,2,3]

[1] University of Medicine and Pharmacy, Tîrgu Mureș, Romania
[2] Center of Advanced Research in Multimodality Cardiac Imaging, Cardio Med Medical Center, Tîrgu Mureș, Romania
[3] Cardiac Critical Care Unit, Clinic of Cardiology, County Clinical Emergency Hospital, Tîrgu Mureș, Romania

ABSTRACT

Background: The inflammatory response of the immune system plays a major role in the period following an acute myocardial infarction (MI), as it coordinates the formation of the fibrous scar tissue that replaces the infarcted myocardial cells and ultimately leads to healing and remodeling of the affected zone. Along with other pro- and anti-inflammatory cytokines and acute phase proteins, interleukin-6 (IL-6) and C-reactive protein (CRP) are associated with the extent of the infarct size (IS) and may serve as predictors for remodeling and adverse left ventricular (LV) function. **Material and methods:** A single-center, non-randomized, observational prospective study was conducted, which included 75 patients with primary revascularized ST-elevation myocardial infarction (STEMI). High-sensitivity CRP (hs-CRP) serum levels were determined on day 1 and day 5 following the acute event. IL-6 was also determined on day 1. All patients underwent cardiac magnetic resonance imaging (CMR) at 1-month follow-up with determination of LV function and quantification of the scar tissue using late gadolinium enhancement imaging. The patients were divided into 2 groups based on baseline hs-CRP values. Results: Patients with higher baseline hs-CRP levels presented significantly higher infarct size ($p = 0.0003$), higher transmural extent ($p < 0.0001$), lower LV ejection fraction ($p = 0.0024$), end-systolic ($p = 0.0021$) and end-diastolic ($p = 0.0065$) volumes. Small IS (<10%) recorded the lowest levels of hs-CRP, while IS >20% presented the highest levels of hs-CRP, at baseline and day 5 ($p = 0.4$ and 0.001). IL-6 levels were also associated with the magnitude of infarct scar: 2.17 pg/mL for IS <10%, 15.52 pg/mL for IS between 10% and 20%, and 24.52 pg/mL for IS >20%, $p = 0.002$. Conclusion: hs-CRP and IL-6 serum levels following an MI are correlated with IS, transmurality extent of the scar tissue, as well as with altered systolic and diastolic LV function determined by CMR at 1-month follow-up.

Keywords: inflammation, STEMI, cardiac magnetic resonance, hs-CRP, primary PCI, LV function

ARTICLE HISTORY

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CORRESPONDENCE

Emese Márton
Str. Gheorghe Marinescu nr. 50
540136 Tîrgu Mureș, Romania
Tel: +40 265 212 111
E-mail: emese.marton92@gmail.com

Mirabela Morariu: Str. Gheorghe Marinescu nr. 38, 540139 Tîrgu Mureș, Romania. Tel: +40 265 215 551, E-mail: mirabela.morariu@yahoo.com
András Mester: Str. Gheorghe Marinescu nr. 38, 540139 Tîrgu Mureș, Romania. Tel: +40 265 215 551, E-mail: andras.mester@yahoo.com
Mihaela Rațiu: Str. Gheorghe Marinescu nr. 38, 540139 Tîrgu Mureș, Romania. Tel: +40 265 215 551, E-mail: d_a_mihaela@yahoo.com
Imre Benedek: Str. Gheorghe Marinescu nr. 38, 540139 Tîrgu Mureș, Romania. Tel: +40 265 215 551, E-mail: imrebenedek@yahoo.com

INTRODUCTION

Myocardial injury triggers an extensive inflammatory response, which plays a vital role in myocardial healing and remodeling following myocardial infarction (MI), as the human heart possesses minimal regenerative capacity.[1] Activation of immune cells with complement activation, secretion of cytokines, chemokines, enzymes, and extracellular matrix proliferation ultimately lead to scar formation in the infarcted area.[2] This post-infarction healing process can be divided into three different, but overlapping stages. The early stages are dominated by inflammation, activation of neutrophils, monocytes, and macrophages, and secretion of cytokines such as interleukin (IL)-1, -6,-8, and tumor necrosis factor alpha (TNF-α). IL-6 also serves as a stimulus for C-reactive protein (CRP) at the level of the liver.[3,4] This phase is followed by the proliferation of myofibroblasts, mediated by platelet-derived growth factor (PDGF), matrix metalloproteinase (MMP) family, and vascular endothelial growth factor (VEGF), leading to the final, maturation phase, when fibrous scar tissue replaces the infarcted area. These changes induce the structural and functional remodeling of the left ventricle (LV), leading to dilation, aneurysm formation, and alteration of the contractile function of the LV. The myocardial scar is also a substrate for re-entry circuits and slow conduction areas, which may lead to life-threatening arrhythmias, altering the prognosis of these patients.[5,6] Clinical studies investigated the role of IL-6 in myocardial scar formation and demonstrated positive correlations between infarct size (IS) and circulating IL-6 levels after MI, possibly serving as a predictive biomarker.[7,8] Animal studies also demonstrated positive correlations between IS and IL-6 levels, and furthermore, the blocking of IL-6 was associated with less neutrophil infiltration in the infarcted area.[9] Elevated CRP expression was also associated with altered LV function and unfavorable remodeling after MI, and it promotes cardiac fibrosis in animal models.[10,11] A recent clinical study demonstrated that high-sensitivity CRP (hs-CRP) is an independent predictor for mortality at 30 days after ST-elevation myocardial infarction (STEMI).[12]

The evaluation of LV function is one of the most important follow-up procedures in post-MI patients, with substantial prognostic value. Cardiac magnetic resonance (CMR) imaging is a noninvasive imaging method, which allows accurate functional and volumetric assessment of LV function with high reproducibility compared to transthoracic echocardiography. Furthermore, adding late gadolinium enhancement (LGE) imaging allows visualization of the infarcted myocardium, with quantification and characterization of the scar tissue, identification of microvascular obstruction and myocardial salvage.[13] LGE and elevated hs-CRP levels were associated with higher mortality and hospitalization rates in patients with dilated cardiomyopathy, possessing a negative prognostic value.[14] Recent studies demonstrated the prognostic value of these CMR parameters, adding additional predictive accuracy to classic left ventricular ejection fraction (LVEF) and clinical risk scores serving for better risk stratification of post-MI patients.[13]

This study aimed to investigate the correlation between the inflammatory response in the acute phase of myocardial infarction and the extension of the infarct scar at 1 month, in patients with STEMI undergoing primary revascularization.

MATERIAL AND METHODS

SUBJECTS

This was a single-center, non-randomized, observational prospective study, which included a total of 75 patients with acute myocardial infarction receiving urgent percutaneous revascularization (PCI) of the infarct-related artery in the County Clinical Emergency Hospital Tîrgu Mureș, Romania, between August 1, 2017 and July 1, 2018.

In all cases, PCI was carried out within the indicated timeframe of 12 hours, and CMR imaging was performed at 1 month post-infarction for assessment of the infarct size and of the transmurality index.

DATA COLLECTION AND BLOOD SAMPLE MEASUREMENTS

In all patients, baseline characteristics and medical history were recorded upon admission. Patient characteristics included age, gender, body mass index, comorbidities, and risk factors. Risk factors included smoking status, obesity, diabetes, dyslipidemia, and history of coronary artery disease, hypertension, stroke, or cerebrovascular disease.

Inflammatory status was assessed on the basis of serum levels of hs-CRP, a classic inflammation-associated biomarker, which were determined at baseline (day 1 after admission) and repeated after 5 days. hs-CRP serum levels were determined with nephelometry, using a BN ProSpec System (Siemens Healthcare Diagnostics, Marburg, Germany). At the same time, serum levels of IL-6,

an inflammation-related biomarker, was determined on day 1 using the Immulite equipment (Siemens, Erlangen, Germany) available at the Center for Advanced Medico-Pharmaceutical Research of the University of Medicine and Pharmacy, Tîrgu Mureș, Romania.

The 75 patients included in the analysis were divided into 2 groups, according to their hs-CRP levels at baseline: group 1 included 37 patients with low levels of baseline hs-CRP, and group 2 included 38 patients with high levels of baseline hs-CRP, with hs-CRP cut-off values established at 3.37 mg/L (the median value recorded in the study).

CMR IMAGING

All CMR examinations were performed with commercially available 1.5 T Siemens Magnetom Aera MRI equipment (Siemens, Erlangen, Germany). LV function was determined in long- and short-axis cine images. For determination of LV mass, LVEF, left ventricular end-diastolic volume (LVEDV, mL) and left ventricular end-systolic volume (LVESV, mL), short-axis volumetry was used. All MRI images were stored in a database, and image post-processing was performed with Medis QMass 8.1 software (Medis, Leiden, the Netherlands). For LGE image processing, delayed signal intensity (DSI) analysis was performed in 10–12 consecutive short-axis LGE images. For segmentation, full width at half maximum was used, with automated hyper-enhancement threshold. The transmurality threshold was set to 50%. Figure 1 shows a DSI analysis in short-axis. The following parameters were determined: LV myocardium volume (mL), myocardium mass (g), infarct size volume (mL), infarct size mass (g), infarct size percentage (%), high transmural extent (mL), high transmural extent (g), LVEDV (mL), LVESV (mL), and LVEF (%).

ETHICS

The study protocol has been approved by the ethics committee of the institution. All patients provided written informed consent, and all steps of the study were carried out in accordance with the code of ethics of the World Medical Association's Declaration of Helsinki.

STATISTICAL ANALYSIS

Data was analyzed using Graph Pad InStat 3.10 software (GraphPad Software, Inc., San Diego, USA). Continuous variables are presented as mean ± standard deviation, while categorical variables are expressed as numbers and percentages. We used unpaired Student`s t-test for normally distributed continuous variables and the Mann-Whitney test for non-normally distributed continuous variables. Fischer's exact test was used for comparison of categorical variables. The threshold for statistical significance was set at $p \leq 0.05$, and all statistical tests were 2-sided.

RESULTS

CHARACTERISTICS OF THE STUDY POPULATION

The clinical characteristics of the study population and the differences between the two groups are presented in Table 1. Male gender (p = 0.02), obesity (p = 0.02), and the presence of previous MI were significantly more frequent in the high hs-CRP group. There were no significant differ-

TABLE 1. Clinical characteristics of the study population

	All (n = 75)	Group 1 Low baseline hs-CRP (n = 37)	Group 2 High baseline hs-CRP (n = 38)	p value
Age, years	61.67 ± 10.98	61.86 ± 10.42	61.47 ± 11.64	0.7830
Gender, male, n (%)	64 (85.33%)	28 (75.67%)	36 (94.73%)	0.024
Obesity, BMI >25 km/m^2, n (%)	33 (44%)	11 (29.79%)	22 (57.89%)	0.020
Hypertension, n (%)	64 (45.33%)	31 (83.78%)	33 (86.84%)	0.7543
Dyslipidemia, n (%)	211.4 ± 61.79	200.6 ± 10.27	222.0 ± 9.743	0.1421
Diabetes, n (%)	23 (30.66%)	13 (35.13%)	10 (26.31%)	0.4596
Current smoking, n (%)	44 (58.66%)	20 (54.05%)	24 (63.15%)	0.48
Previous CAD, n (%)	12 (16%)	6 (16.21%)	6 (15.78%)	1.000
Previous myocardial infarction, n (%)	23 (30.66%)	5 (13.51%)	18 (47.36%)	0.002
Previous stroke, n (%)	28 (37.33%)	12 (32.43%)	16 (42.10%)	0.4760

TABLE 2. CMR data in the study population

	All (n = 75)	Group 1 Low baseline hs-CRP (n = 37)	Group 2 High baseline hs-CRP (n = 38)	p value
Myocardium volume (mL)	146.1 ± 38.00	142.8 ± 38.08	149.2 ± 38.16	0.2733
Left ventricle myocardium mass (g)	153.5 ± 40.04	150.3 ± 40.34	156.6 ± 40.03	0.2875
Infarct size volume (mL)	27.93 ± 20.63	21.12 ± 13.59	37.33 ± 25.02	0.0003
Infarct size mass (g)	29.33 ± 21.66	21.12 ± 13.59	37.33 ± 25.02	0.0003
Infarct size percentage (%)	18.23 ± 9.769	13.80 ± 7.523	22.54 ± 9.853	<0.0001
High transmural extent (mL)	21.07 ± 21.91	12.18 ± 12.96	29.72 ± 25.31	<0.0001
High transmural extent (g)	22.16 ± 23.13	12.79 ± 13.61	31.29 ± 26.77	<0.0001
Left ventricular end-diastolic volume (mL)	152.4 ± 52.96	138.1 ± 48.39	165.9 ± 54.14	0.0065
Left ventricular end-systolic volume (mL)	74.00 ± 42.83	59.39 ± 32.98	87.84 ± 46.75	0.0021
Left ventricular ejection fraction (LVEF)	54.31 ± 11.85	58.50 ± 10.08	50.34 ± 12.14	0.0024

ences between the low and high hs-CRP groups regarding smoking status (p = 0.48), history of ischemic cardiomyopathy (p = 1), hypertension (p = 0.75), diabetes (p = 0.45), and dyslipidemia (p = 0.14). CMR characteristics determined in the study population are presented in Table 2.

INFARCT SIZE AND INFLAMMATORY BIOMARKERS

Baseline serum levels of hs-CRP were 1.88 ± 0.95 mg/L in group 1 and 24.55 ± 38.17 mg/L in group 2. Serum levels of hs-CRP determined at 5 days post-infarction were 7.14 ± 6.99 mg/L in group 1 and 49.82 ± 34.81 mg/L in group 2. There was a direct association between infarct size and hs-CRP levels on both day 1 and day 5. Patients with a small infarct size (<10%) presented the lowest levels of hs-CRP, while those with infarct size >20% presented the highest levels of hs-CRP, both at baseline and on day 5 post-infarction (p = 0.4 and p = 0.001, respectively) (Figure 2). Similarly, IL-6 levels were directly associated with the magnitude of infarct scar: 2.17 pg/mL for IS <10%, 15.52 pg/mL for IS between 10% and 20%, and 24.52 pg/mL for IS >20%, p = 0.002 (Figure 3).

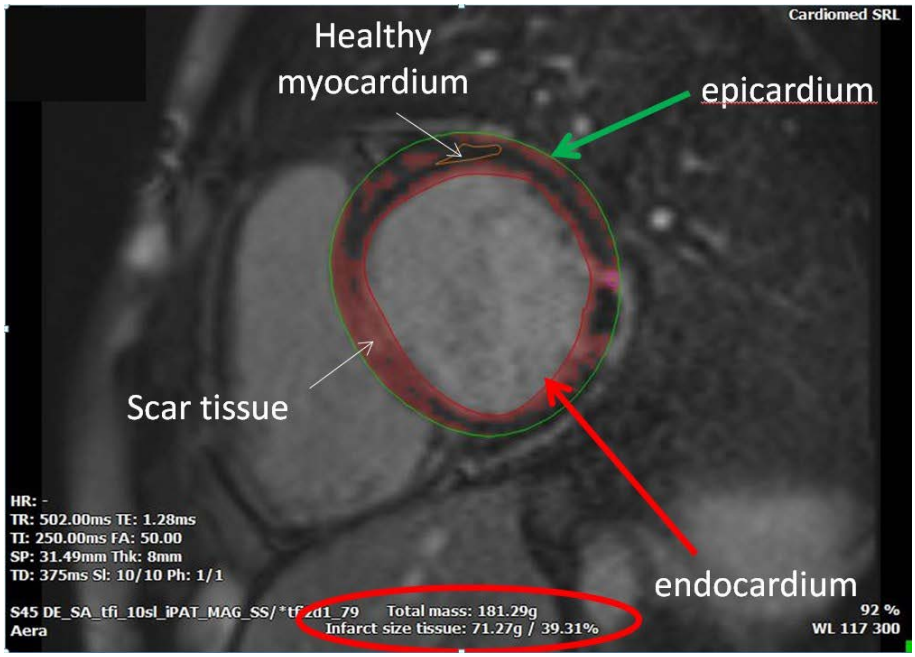

FIGURE 1. DSI analysis of the LV in LGE short-axis sequence after an extended anterolateral myocardial infarction, with a LV mass of 181.29 g and an infarct size of 71.27 g/39.31% (red circle)

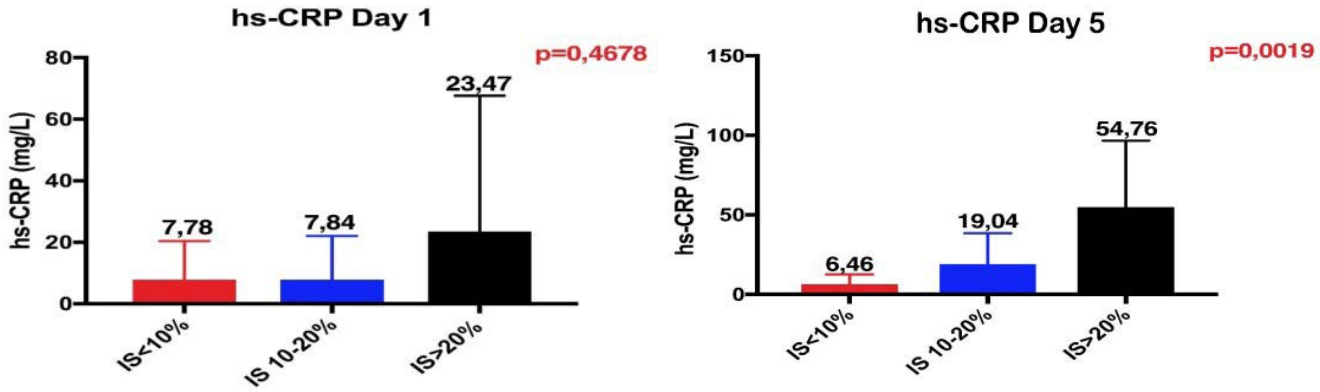

FIGURE 2. Association between infarct size and: **A** – baseline serum levels of hs-CRP on day 1 and **B** – levels of hs-CRP on day 5

HIGH TRANSMURALITY EXTENT AND HS-CRP LEVELS

Patients with high levels of baseline hs-CRP presented higher values of high transmurality indexes compared to those with low levels of baseline hs-CRP, however without reaching statistical significance (25.94 g vs. 18.78 g, p = 0.2). Moreover, when we compared the high transmurality extent index according to hs-CRP levels on day 5, we noticed that patients with high levels of hs-CRP on day 5 had a significantly higher index of high transmurality extent compared to those with lower levels of hs-CRP on day 5 (25.55 g vs. 10.48 g, p = 0.006), indicating that hs-CRP levels on day 5 present a better correlation with infarct size than the ones measured immediately post-infarction (Figure 4).

DISCUSSIONS

It is well established that chronic inflammation, and periodontal and systemic diseases are associated with marked atherosclerosis progression, development of vulnerable plaques, as well as increased myocardial infarction and higher adverse cardiovascular event rates.[15–18] The acute phase of a myocardial infarction is characterized by intense inflammatory response, which is associated with higher levels of circulating pro-inflammatory cytokines and acute phase proteins such as IL-6 and CRP. Some studies even indicated that elevated CRP levels were independent predictors for the development of heart failure.[19] The relation between myocardial infarct size, CRP and IL-6 levels has been widely researched and well elucidated, but the determination of the extent of the necrosis was mainly based on laboratory results (such as troponin levels) and echocardiographic findings. In our study, we used cine and LGE CMR imaging, as a gold standard for the evaluation of LV function and volumes, and a better characterization of infarct size. Karpinski *et al.* identified a positive correlation between elevated levels of IL-6 and CRP in the acute phase of primary revascularized STEMI patients and impaired LV systolic (OR = 1.27, p = 0.02; OR = 1.14, p = 0.05) and diastolic (OR = 1.14, p = 0.03; OR = 1.05, p = 0.01) function determined with echocardiography; moreover, elevated IL-6 and CRP levels were an independent predictor for LV dysfunction at 6 months following the event.[20] Our results support these findings, as the group of patients with high baseline hs-CRP values presented altered systolic and diastolic LV function, evidenced by significantly lower LVEF and LVESV, accompanied by significantly higher LVEDV. These findings may represent the signs of unfavorable remodeling in patients with more pronounced inflammatory response at 1-month CMR follow-up. In a study which included 1,028 STEMI patients treated with primary PCI, Ritschel *et al.* described positive correlations between circulating IL-6 and CRP levels and the extent of myocardial necrosis, evidenced by high peak troponin levels, as well as reduced LVEF at the 3-month echocardiographic follow-up in patients with high IL-6 and CRP levels at baseline.[21] Previous studies indicated that infarct

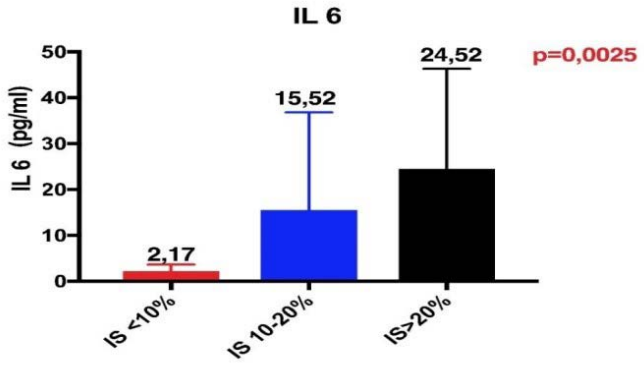

FIGURE 3. Association between infarct size serum levels of IL-6 on day 1 post-infarction

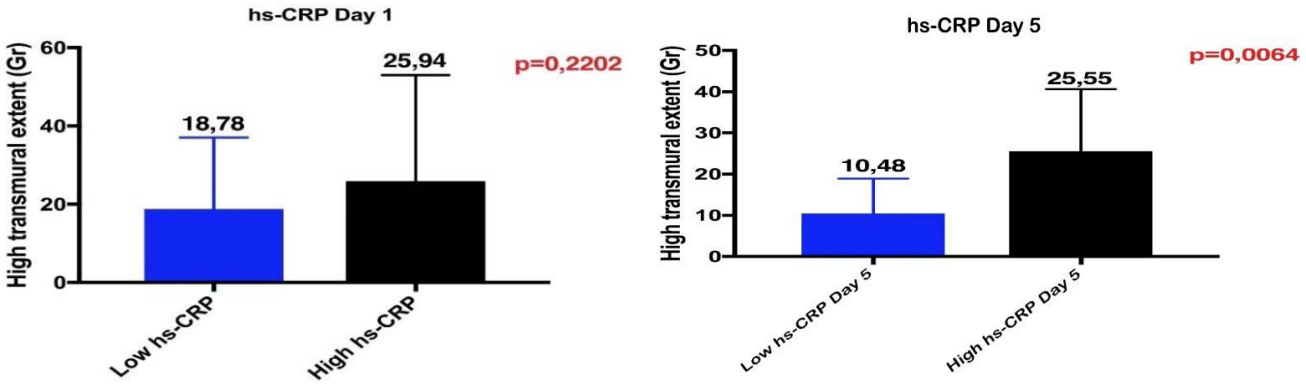

FIGURE 4. Association between high transmurality and: **A** – baseline serum levels of hs-CRP on day 1 and **B** – levels of hs-CRP on day 5

size determined by LGE CMR imaging is a good predictor for remodeling and long-term outcomes.[22–24] Numerous studies debated if the initial increase of inflammatory markers is a result of the general response of the immune system to the injury, or it is a marker of the magnitude of the affected myocardial tissue.[22] The systemic inflammatory response depends on many accompanying risk factors such as aging, hematological diseases, altered liver and renal function.[25,26] In our study, the group of patients with high baseline hs-CRP presented significantly higher infarct size and infarcted percentage of the LV. Larger infarct size (>20%) was associated with 3-fold higher levels of hs-CRP on day 1 compared to groups with smaller infarct size; however, there were no significant differences between the groups of smaller infarct size (<10% vs. 10–20%). These findings were even more expressed at 5 days, when the group of subjects with large infarct size (>20%) recorded almost 10-fold higher levels of hs-CRP compared to small infarct size (<10%) and 3-fold higher levels compared to the intermediary infarct size (10–20%) group. The transmurality of the myocardial scar was also higher in the group of subjects with higher baseline hs-CRP levels, but it only reached statistically significant differences on day 5. IL-6 (a powerful inducer of CRP) levels determined at baseline followed the same rule as hs-CRP levels and recorded significantly higher values in the group with larger infarct size compared to small or intermediary infarct size groups. These results suggest that the elevation of hs-CRP and IL-6 levels is closely related to the extent of the affected myocardial damage, rather than a general inflammatory response to the injury.

STUDY LIMITATIONS

Our study included a limited number of patients, and it needs validations on a larger cohort of subjects. Consecutive hs-CRP and IL-6 determinations would be needed to establish the best moment for blood sampling, which will most accurately describe the impact of myocardial infarction and might offer predictive value for remodeling or adverse events. A longer follow-up period is required to evaluate the final stage of myocardial healing and remodeling after myocardial infarction, with registration of adverse events that describe this period.

CONCLUSIONS

Higher baseline hs-CRP levels after an acute STEMI treated with primary PCI were associated with larger infarct size, transmural extent, and poorer LV systolic and diastolic function expressed by LVEF, LVESV, and LVEDV determined by CMR at 1-month follow-up. Baseline IL-6 levels were also correlated with the extent of myocardial scar tissue. CMR provides more accurate and detailed follow-up for patients who survived a myocardial infarction. Complex laboratory and imaging follow-up methods may predict the long-term outcomes of this vulnerable group of patients.

CONFLICT OF INTEREST

Nothing to declare.

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