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Interleukin-12 serum level has prognostic value in patients with ST-segment elevation myocardial infarction

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ABSTRACT

Objectives: The study aimed to evaluate whether serum inflammatory markers have prognostic value in patients with ST-segment elevation myocardial infarction (STEMI).
Background: The role of cytokine-driven inflammation in the development of postdischarge complications after STEMI is obscured.
Methods: We recruited 214 patients who were admitted within 24 h of STEMI onset to our Institute. IL-1α, -6, -8, -10, -12, TNF-α, and CRP serum levels were measured on the 10–14th day after STEMI onset.
Results: Serum levels of IL-12, TNF-α, and CRP were significantly higher in patients with 3 affected coronary arteries compared to those with 1 affected coronary artery. However, only Killip class II–IV at admission and IL-12 serum level ≥90.0 pg/mL were defined as statistically significant predictors of adverse outcome after 1 year of follow-up.
Conclusion: IL-12 serum level may be suggested as a candidate prognostic marker if measured 10–14 days after STEMI onset.

Introduction

According to World Health Organization statistics, coronary artery disease (CAD) is a leading cause of death worldwide.[1] An estimated 7.4 million people died from CAD in 2012, representing 11.2% of all global deaths.[1] In the Russian Federation alone, there were 597,921 deaths from CAD, which is the highest number among all countries included in analysis.[1] New versatile, highly sensitive, and specific prognostic markers of CAD are needed for efficient risk assessment.[2] It is known that both lipid deposition and inflammation play a major role in the development of atherosclerosis.[3,4] High levels of proinflammatory cytokines weaken the atherosclerotic plaque fibrous cap and activate prothrombotic factors.[3] Inflammation may further promote plaque rupture, atherothrombosis, and acute coronary syndrome.[5] However, the mechanisms through which cytokines affect the development of postdischarge complications after acute coronary syndrome have not been sufficiently studied. Furthermore, little is known about the associations of several cytokines with both coronary and peripheral atherosclerosis and its clinical manifestations. The aim of this study was to investigate the clinical and prognostic roles of certain innate immunity proteins in patients with ST-segment elevation myocardial infarction (STEMI).

Material and methods

To achieve the study aim, we planned to: (1) recruit the largest possible sample of patients with STEMI; (2) assess the severity of coronary and peripheral atherosclerosis; (3) measure the serum level of certain cytokines; and (4) investigate how these cytokine concentrations are associated with atherosclerosis and cardiovascular complications after 1 year of follow-up.

Abbreviations: CAD, coronary artery disease; STEMI, ST-segment elevation myocardial infarction; MI, myocardial infarction; PCI, percutaneous coronary intervention; ECA, extracranial arteries; LEA, lower extremity arteries; IMT, intima-media thickness; PVD, polyvascular disease; TLT, thrombolytic therapy; ACE, angiotensin-converting enzyme; IL, interleukin; TNF, tumor necrosis factor; CRP, C-reactive protein; NYHA, New York Heart Association; AUC, area under the ROC curve; MDRD, Modification of Diet in Renal Disease; Th1, type 1 helper T cells; Th2, type 2 helper T cells.

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Table 1
Clinicopathological features of patients with STEMI.

Feature	Number (%)
Demographics	
Males	164 (76.6%)
Cardiovascular features at admission	
Increase of creatine kinase-MB fraction >2-fold	99 (46.3%)
Killip class II–IV	32 (15.0%)
Systolic arterial pressure <100 mm Hg	9 (4.2%)
Heart rate ≥100 bpm	16 (7.5%)
Anterior myocardial infarction	85 (39.7%)
Cardiac history	
Early postinfarction angina	40 (18.6%)
Stable angina	98 (45.8%)
Congestive heart failure	13 (6.1%)
Left ventricular ejection fraction ≤40%	31 (14.5%)
Past medical history	
Myocardial infarction	42 (19.6%)
Percutaneous coronary intervention	21 (9.8%)
Coronary artery bypass graft surgery	3 (1.4%)
Stroke	15 (7.0%)
Comorbid conditions	
Polyvascular disease	201 (94.0%)
Arterial hypertension	182 (85.0%)
Diabetes mellitus	28 (13.1%)
Renal dysfunction (glomerular filtration rate <60 mL/min/1.73 m^2)	36 (16.8%)
Overweight or obesity (body mass index >25 kg/m^2)	157 (73.4%)
Hypercholesterolemia	24 (11.2%)
Smoking	104 (48.6%)

STEMI – ST-segment elevation myocardial infarction.

We recruited 214 patients who were admitted within 24 h of STEMI onset to Research Institute for Complex Issues of Cardiovascular Diseases (Kemerovo, Russian Federation) in 2013. The average age was 58 years (range of 32–79). The study was approved by the local ethical committee and all the participants provided written informed consent after receiving a full explanation of the study.

The criteria of inclusion into the study were (1) age >18 years; (2) diagnosis of STEMI according to the European Society of Cardiology Guidelines[6]; and (3) written informed consent to participate in the study. Criteria of exclusion were (1) age <18 years; (2) past medical history of cancer, concomitant autoimmune, and/or mental disorders; and (3) recurrent myocardial infarction (MI) after percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery. Clinicopathological features of the patients are presented in Table 1.

Color duplex screening of the extracranial arteries (ECA) and lower extremity arteries (LEA) was performed on the 5th–7th day of hospitalization in all patients using the cardiovascular ultrasound system Vivid 7 Dimension (General Electric Healthcare), with a 5.7-MHz linear array transducer (for ECA), a 2.5–3-MHz curved array transducer, and a 5-MHz linear array transducer (for LEA). The extent of arterial stenosis was assessed in B regimen and by dopplerography (visualizing the local hemodynamics in the stenosis zone). Common and internal carotid arteries, vertebral arteries, and subclavian arteries were visualized from both sides during the ECA screening; common and deep femoral arteries, popliteal arteries, and anterior and posterior tibial arteries were visualized from both sides during the LEA screening. The intima-media thickness (IMT) of the common carotid artery was measured in automatic mode (a value up to 1 mm was considered normal). Polyvascular disease (PVD) was defined as IMT increase ≥1 mm or ECA and/or LEA stenosis. Selective coronary angiography was performed in the first hours after admission using GE Healthcare Innova 3100 Cardiac Angiography System (General Electric Healthcare). Luminal stenosis ≥50% was defined as significant coronary stenosis.[7] The preferable methods of myocardial reperfusion were defined in the shortest terms and included PCI (74.1% of patients) and systemic thrombolytic therapy (TLT) (4.8% of patients). Myocardial revascularization was not conducted when technical problems occurred or in patients with complex coronary anatomy or contraindications to TLT or PCI. All patients received the standard therapy of unfractionated heparin, aspirin, clopidogrel, angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, and statins.

On the 10th–14th day after STEMI onset, we measured interleukin (IL)-1β, -6, -8, -10, -12, tumor necrosis factor (TNF)-α, and C-reactive protein (CRP) serum level by enzyme-linked immunosorbent assay using BIOSOURCE and BIOMERICA reagents. After 1 year of follow-up, we assessed the status (presence or absence) of cardiovascular complications (cardiac death, recurrent MI, stroke, acute decompensated heart failure, unstable angina, progression of chronic stable angina, or chronic heart failure) to (New York Heart Association (NYHA) functional class III–IV). The presence of any of these complications was considered as an adverse outcome. Follow-up was conducted by a telephone-based interview.

Statistical analysis was performed using MedCalc Software (MedCalc). A sampling distribution was assessed by the D'Agostino-Pearson test. Regarding descriptive statistics, data were represented by the median, the interquartile range (25th and 75th percentiles), the mean, and the confidence intervals (CIs) for both the median and mean. Two independent groups were compared by the Mann–Whitney *U*-test. Independent groups numbering three or more were compared using the Kruskal–Wallis test, with pairs further compared by the Mann–Whitney *U*-test if statistically significant differences were revealed by the Kruskal–Wallis test. An adjustment for multiple comparisons was performed using false discovery rate (FDR). *p*-values of ≤0.05, or *q*-values if FDR was applied (*q*-values are the name given to the adjusted *p*-values found using an optimized FDR approach), were regarded as

Table 2
Mean serum levels of innate immune proteins in patients with STEMI on the 10th–14th day from onset depending on the number of affected coronary arteries (>50% stenosis).

Features	Number of affected coronary arteries						*q*–value
	One ($n = 74$)		Two ($n = 58$)		Three ($n = 82$)		
Age, years	56.20 (53.95–58.46)		58.31 (56.16–60.46)		59.32 (57.35–61.28)		$q > 0.05$
Gender	Males	Females	Males	Females	Males	Females	
Number (%)	**64 (87)**	**10 (13)**	**40 (69)**	**18 (31)**	**60 (73)**	**22 (27)**	$\boldsymbol{q = 0.04}$
TNF-α, pg/mL	**9.45 (8.41–10.48)**		10.88 (8.81–12.96)		**10.61 (9.68–11.55)**		$\boldsymbol{q_{1,3} = 0.03}$
IL-12, pg/mL	**95.0 (70.57–119.43)**		107.16 (87.96–126.36)		**112.19 (92.33–132.05)**		$\boldsymbol{q_{1,3} = 0.041}$
IL-10, pg/mL	2.11 (1.66–2.56)		2.16 (1.74–2.58)		2.08 (1.61–2.56)		$q > 0.05$
IL-8, pg/mL	3.33 (2.84–4.81)		4.55 (2.99–6.12)		3.61 (2.28–4.95)		$q > 0.05$
IL-6, pg/mL	4.06 (2.48–5.65)		6.35 (3.81–8.89)		5.16 (2.23–8.09)		$q > 0.05$
IL-1β, pg/mL	1.19 (1.03–1.36)		1.07 (0.92–1.22)		1.14 (1.02–1.26)		$q > 0.05$
CRP, mg/L	**11.86 (9.76–13.95)**		14.40 (12.41–16.39)		**14.06 (12.15–15.97)**		$\boldsymbol{q_{1\text{-}3} = 0.03}$

STEMI – ST-segment elevation myocardial infarction, TNF – tumor necrosis factor, IL – interleukin, CRP – C-reactive protein. Bold font indicates statistically significant differences.