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Research Paper

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.

Table 3
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), adjusted by age and gender.

Features	Number of affected coronary arteries						q–value
	One ($n = 74$)		Two ($n = 47$)		Three ($n = 66$)		
Age, years	56.20 (53.95–58.46)		56.78 (54.58–58.98)		57.97 (55.76–60.18)		$q > 0.05$
Gender	Males	Females	Males	Females	Males	Females	
Number (%)	**64 (87)**	**10 (14)**	**40 (85)**	**7 (15)**	**60 (90)**	**6 (10)**	$\boldsymbol{q = 0.03}$
TNF-α, pg/mL	**9.45 (8.41–10.48)**		11.04 (8.78–13.30)		**10.85 (9.72–11.97)**		$\boldsymbol{q_{1,3} = 0.03}$
IL-12, pg/mL	95.0 (70.57–119.43)		105.70 (84.82–126.59)		104.65 (83.85–125.45)		$q > 0.05$
IL-10, pg/mL	2.11 (1.66–2.56)		2.16 (1.71–2.60)		2.17 (1.58–2.75)		$q > 0.05$
IL-8, pg/mL	3.33 (2.84–4.81)		3.55 (2.81–5.28)		3.82 (2.08–5.56)		$q > 0.05$
IL-6, pg/mL	4.06 (2.48–5.65)		5.69 (3.07–8.32)		5.20 (1.58–8.82)		$q > 0.05$
IL-1β, pg/mL	1.19 (1.03–1.36)		1.09 (0.94–1.24)		1.20 (1.06–1.33)		$q > 0.05$
CRP, mg/L	**11.86 (9.76–13.95)**		13.89 (11.79–15.98)		**14.40 (12.25–16.54)**		$\boldsymbol{q_{1,3} = 0.041}$ $q_{1,2} > 0.05$

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

statistically significant. For multivariate analysis, we performed stepwise logistic regression with plotting a receiver operating characteristic (ROC) curve and further calculation of the area under the curve (AUC).

Results

Patients were divided into three groups (based on 1, 2, or 3 affected coronary arteries). The serum levels of TNF-α, IL-12, and CRP were significantly increased along with the number of affected coronary arteries (Table 2). However, only differences in serum levels of TNF-α and CRP remained statistically significant after adjustment by age and gender (Table 3). We then again divided patients into four groups (without PVD, with IMT ≥ 1 mm or <30% stenosis, with 30–50% stenosis, and with >50% stenosis). Statistically significant associations were found only for IL-12 (Table 4). These results remained statistically significant after adjustment by age and gender (Table 5).

We then performed stepwise logistic regression to determine independent factors affecting the severity of coronary atherosclerosis and PVD. According to our results, >50% coronary stenosis was significantly associated with age ≥53 years (OR = 1.4, $p < 0.01$) and IL-12 serum level ≥87.1 pg/mL (OR = 1.6, $p < 0.01$) with AUC = 0.71 (0.59–0.79). Likewise, >50% stenosis of ECA or LEA was significantly associated with age >65 years (OR = 3.3, $p < 0.01$) and IL-12 serum level ≥108.8 pg/mL (OR = 3.2, $p < 0.01$) with AUC = 0.73 (0.58–0.87). Therefore, IL-12 serum level was suggested as the most sensitive marker of atherosclerosis severity. However, there were no statistically significant associations of IL-12 serum level with left ventricular ejection fraction, MI localization, creatine kinase-MB fraction, total cholesterol, low- and high-density lipoprotein cholesterol, CAD duration before STEMI onset, diabetes mellitus, arterial hypertension, Killip class, early postinfarction angina, and urgent myocardial reperfusion.

Finally, we assessed independent predictors of adverse STEMI outcome after 1 year of follow-up. Data were collected from 178 (83.2%) patients, and adverse STEMI outcome was registered in 71 (39.9%) of them (Table 6). Again, we performed stepwise logistic regression to determine independent factors of yearly prognosis. Factors included into the regression were age; gender; body mass index; Killip class of acute heart failure at admission; past medical history of MI; past medical history of stroke; unstable and stable angina; smoking; diabetes mellitus; arterial hypertension; congestive heart failure; glomerular filtration rate (MDRD formula); blood glucose level; blood hemoglobin level; total cholesterol level; low- and high-density lipoprotein cholesterol level; creatine kinase-MB fraction; left ventricular ejection fraction; early postinfarction angina; cardiac arrhythmia; heart block; successful PCI; thrombolytic therapy; time from chest pain onset to myocardial revascularization; cytokine serum levels on the 10th–14th day

Table 4
Mean serum levels of innate immune proteins in patients with STEMI on the 10th–14th day from onset depending on the degree of ECA and LEA stenosis.

Features	Degree of ECA and LEA stenosis								q–value
	IMT <1 mm, no stenosis ($n = 13$)		IMT ≥1 mm, <30% stenosis ($n = 113$)		30–50% stenosis ($n = 42$)		>50% stenosis ($n = 46$)		
Age, years	**45.54 (40.08–51.0)**		**57.20 (55.59–58.82)**		**58.76 (56.34–61.19)**		**62.63 (60.36–64.90)**		$\boldsymbol{q_{1,2} = 0.001}$ $\boldsymbol{q_{1,3} = 0.001}$ $\boldsymbol{q_{1,4} = 0.001}$ $\boldsymbol{q_{2,4} = 0.001}$
Gender	Males	Females	Males	Females	Males	Females	Males	Females	$q > 0.05$
Number (%)	10 (77)	3 (23)	89 (79)	24 (21)	31 (74)	11 (26)	34 (74)	12 (26)	
TNF-α, pg/mL	9.39 (7.30–11.49)		10.34 (9.17–11.51)		10.0 (8.37–11.63)		10.66 (9.38–11.94)		$q > 0.05$
IL-12, pg/mL	**69.78 (34.58–104.97)**		**103.74 (86.27–121.21)**		**102.59 (80.39–124.79)**		**128.44 (93.17–163.71)**		$\boldsymbol{q_{1,4} = 0.02}$ $\boldsymbol{q_{2,4} = 0.03}$ $\boldsymbol{q_{3,4} = 0.03}$
IL-10, pg/mL	2.47 (1.05–3.89)		2.05 (1.71–2.39)		2.01 (1.34–2.69)		2.22 (1.67–2.76)		$q > 0.05$
IL-8, pg/mL	6.31 (1.20–11.42)		3.83 (2.89–4.78)		3.90 (2.39–5.41)		5.82 (3.26–8.37)		$q > 0.05$
IL-6, pg/mL	6.98 (1.69–15.65)		4.42 (3.13–5.72)		4.19 (1.85–6.52)		7.41 (2.04–12.78)		$q > 0.05$
IL-1β, pg/mL	0.93 (0.59–1.26)		1.16 (1.05–1.28)		1.14 (0.99–1.29)		1.13 (0.93–1.32)		$q > 0.05$
CRP, mg/L	11.19 (5.04–17.35)		13.91 (12.29–15.53)		12.80 (10.21–15.39)		13.31 (10.88–15.74)		$q_{1,4} > 0.05$

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

Table 5
Mean serum levels of innate immune proteins in patients with STEMI on the 10th–14th day from onset depending on the degree of ECA and LEA stenosis, adjusted by age and gender.

Features	Degree of ECA and LEA stenosis						q–value
	IMT ≥1 mm, <30% stenosis ($n = 83$)		30–50% stenosis ($n = 36$)		>50% stenosis ($n = 46$)		
Age, years	61.04 (59.60–62.47)		60.72 (58.51–62.93)		62.63 (60.36–64.90)		$q > 0.05$
Gender	Males	Females	Males	Females	Males	Females	
Number (%)	61 (73)	22 (27)	27 (75)	9 (25)	34 (74)	12 (26)	$q > 0.05$
TNF-α, pg/mL	10.58 (9.03–12.13)		10.09 (8.19–12.00)		10.66 (9.38–11.94)		$q > 0.05$
IL-12, pg/mL	**109.47 (89.32–129.63)**		106.37 (79.40–133.34)		**128.44 (93.17–163.71)**		$\boldsymbol{q_{1,3} = 0.027}$
IL-10, pg/mL	2.14 (1.73–2.56)		2.05 (1.22–2.88)		2.22 (1.67–2.76)		$q > 0.05$
IL-8, pg/mL	3.70 (2.54–4.86)		3.91 (2.31–5.51)		5.82 (3.26–8.37)		$q > 0.05$
IL-6, pg/mL	4.43 (2.81–6.05)		4.28 (1.66–6.90)		7.41 (2.04–12.78)		$q > 0.05$
IL-1β, pg/mL	1.19 (1.05–1.34)		1.14 (0.97–1.32)		1.13 (0.93–1.32)		$q > 0.05$
CRP, mg/L	13.70 (11.75–15.65)		13.86 (11.01–16.72)		13.31 (10.88–15.74)		$q > 0.05$

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

after MI; and regular use of aspirin, beta-blockers, ACE inhibitors, and statins during the whole year. However, only Killip class of acute heart failure at admission and IL-12 serum level were defined as statistically significant predictors of adverse STEMI outcome after 1 year of follow-up with AUC = 0.89 (0.80–0.98). Therefore, we suggested a new prognostic scale (Killip class II–IV at admission can be counted as 1 point, IL-12 serum level from 90.0 to 129.9 pg/mL as 2 points, and IL-12 serum level ≥130.0 pg/mL as 3 points).

Discussion

Here we identified that elevated serum level of IL-12 is significantly associated with a higher severity of coronary and peripheral atherosclerosis along with adverse STEMI outcome after 1 year of follow-up. It may reflect the possible significance of this cytokine in the development of STEMI; moreover, IL-12 might be suggested as a prognostic marker for clinical use.

The pathologic role of IL-12 in MI may be due to its participation in several inflammatory pathways.[8] Previously, increased activity of type 1 helper (Th1) cells due to imbalance of the Th1/Th2 system was found to possibly lead to the development of atherosclerosis, particularly unstable plaques.[9] It is worth noting that IL-12 is one of the key regulators of Th1 cell response.[9] On the contrary, Th2 cell response may perform antiatherogenic activity.[10] Moreover, it was shown that mice with predominant Th2 cell response can be rather tolerant to atherosclerosis.[11] Davenport and Tipping[12] and Lee et al[13] demonstrated that IL-12 is able to independently induce early development and rapid progression of atherosclerosis in mouse models. Functional blockade of endogenous IL-12 during 6 weeks led to a significant decrease of low-density lipoprotein cholesterol level, degree of carotid stenosis, and IMT.[14] In addition, IL-12 is able to induce T cell recruitment into the atherosclerotic plaque, promoting local inflammation.[15] In combination with IL-18, IL-12 may significantly induce the production of IFN-γ and TNF-α, enhancing atherosclerosis progression.[16]

Table 6
Independent predictors of adverse STEMI outcome after 1 year of follow-up.

Adverse outcome	Number (%)
Cardiac death	8 (4.5%)
Recurrent myocardial infarction	16 (9.0%)
Stroke	3 (1.7%)
Acute decompensated heart failure	3 (1.7%)
Unstable angina	19 (10.7%)
Stable CCS class III-IV angina	8 (4.5%)
NYHA class III-IV chronic heart failure	14 (7.9%)
Combined adverse outcome	71 (39.9%)

CCS – Canadian Cardiovascular Society, NYHA – New York Heart Association.

According to the epidemiological studies,[17] IL-12 can be associated with arterial stiffness in healthy individuals. It was reported that serum and plasma IL-12 level is significantly higher in patients with acute MI within 24 h after onset compare to healthy subjects.[18–20] In addition, Sheu et al[21] revealed that IL-12 is over expressed in the infarct and peri-infarct areas 3 weeks after MI in mini-pig models. Moreover, IL-6 and CRP baseline plasma levels were independent predictors of atherosclerosis progression after 12 years of follow-up.[22] Therefore, persisting inflammatory response after STEMI may reflect the severity of the process and define adverse outcome. It can be particularly significant regarding IL-12-mediated immune response, since IL-12 serum level is still high even 2 weeks after STEMI onset while serum levels of IL-1β, -6, -8, -10, TNF-α, and CRP are low or gradually decrease after 2 days from STEMI onset.[23–28]

In our investigation, elevated IL-12 serum level measured 10–14 days after STEMI onset was significantly associated with an increased number of affected coronary arteries, PVD, coronary, ECA or LEA stenosis >50%, and adverse STEMI outcome after 1 year of follow-up. Nevertheless, our research has certain limitations: (1) a relatively small sample size; (2) inability to collect follow-up data from all patients due to technical difficulties.

Our study may have certain implications for research and clinical practice. To the best of our knowledge, this is the first study showing the possible prognostic value of IL-12 serum level measured 10–14 days after STEMI onset. Our sample size was not large enough for making a clear conclusion about IL-12 as a prognostic marker or to recommend the routine use of IL-12 as a post-STEMI risk indicator. However, our investigation provides a rationale for a larger cohort study or studies of using anti-IL-12 antibodies for the prevention of STEMI-related long-term adverse outcomes. In addition, further basic studies are required for defining the role of IL-12 in the development of atherosclerosis and MI.

Conclusions

IL-12 serum level measured 10–14 days after STEMI onset may be useful in predicting adverse STEMI outcomes after 1 year of follow-up. In addition, the IL-12 serum level may be also suggested as a clinical marker of PVD and coronary atherosclerosis severity. Further large cohort studies and studies of anti-IL-12 therapeutics are needed to uncover the role of IL-12 in atherosclerosis.

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