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Biomarkers of inflammation in patients with myocardial infarction and heart failure with preserved and mid-range ejection fraction: 5-year prospective follow-up

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Aim. To evaluate the effect of biomarkers of inflammation on the long-term prognosis in patients with myocardial infarction (MI) and heart failure (HF) with preserved and mid-range ejection fraction according to a registry of percutaneous coronary interventions (PCI).

Material and methods. A total of 135 patients with MI included in the PCI registry in 2012-2013 were examined. Group 1 included 89 patients with HF with mid-range ejection fraction (HFmrEF) — 40-49%; group 2 included 46 patients with HF with preserved ejection fraction (HFpEF) — ⩾50%. Biomarkers of inflammation were determined at admission to the hospital, after 12 and 60 months.

Results. Eighteen people died during the follow-up period. The survival rate of patients in the compared groups after 60 months did not differ (group 1 — 85,0%; group 2 — 89,1%, p=0,492). Mortality predictors were the platelet count (HR, 1,011; 95% CI, 1,003-1,019; p=0,010), homocysteine level (HR 1,172; 95% CI, 1,008-1,364; p=0,040), MMP-9 >249 ng/ml (HR, 7,052; 95% CI, 1,346-36,950; p=0,021). In both groups there was a decrease in survival in patients with high levels of MMP-9 (>249 ng/ml). In group 1, mortality was higher among patients with platelet count >245*10^9/l. In both groups the levels of inflammatory markers exceeded the standard values for the entire period of follow-up. The dynamics of NT-proBNP, hs-CRP, TNF-α and homocysteine had a unidirectional pattern, in particular, a decrease in parameters after 12 months, followed by their increase after 60 months.

Conclusion. Levels of MMP-9, homocysteine, and platelets were the factors that influenced 5-year survival in the general group of patients after MI and PCI. In the group with HFmrEF, MMP-9 and platelets had a negative impact on the prognosis. In patients with HFpEF, reduced survival was associated only with high levels of MMP-9. The dynamics of markers of systemic inflammatory response and NT-proBNP indicates the prolonged inflammatory process in both groups of patients, persisting for 5 years after MI.

Keywords: myocardial infarction, heart failure, markers of inflammation, 5-year follow-up.

Relationships and Activities: none.

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Risk of cardiovascular events (CVE), especially death, remains high not only at the acute stage of myocardial infarction (MI) but also at later stages. Lately, the biochemical markers of system inflammation have been widely used when evaluating the forecast in acute coronary syndrome (ACS). They are of great importance in the pathologic physiology of the acute stage of MI.

Success in treating acute myocardial infarction (AMI) resulted in a growing number of patients with the signs of heart failure (HF) since in many of them MI is a starting point in developing HF with preserved ejection fraction (EF) ⩾50% (HFpEF) and reduced EF ⩽40% (HFrEF), which is associated with a high frequency of rehospitalizations and high death rate. Lately, in addition to distinguishing HFpEF and HFrEF, patients with mid-range EF (41-49%) (HFmrEF) have been differentiated. Patients with HFmrEF are so-called grey area, which is insufficiently known. Currently, there is no reliable method to stratify the risks of adverse events in HFpEF and HFmrEF [1]. The formation of left ventricular dysfunction takes place not only by involving neurohumoral systems but also with the participation of immune inflammation. It is assumed that myocardial injury with following remodeling, dilatation together with hypoxia results in the arousal of all main cytokine sources — cardiomyocytes, skeletal muscles, and immune competent cells. It is possible that the initial increase in cytokine secretion can be directly associated with the pathogenesis of diseases, conditioning HF, at the following stages of the course of which one or several specified mechanisms is engaged [2-4]. Consequently, determining biomarkers in this category of patients for assessing prognosis becomes increasingly significant.

The aim was to evaluate the effect of biomarkers of inflammation on the long-term prognosis in MI patients with HFpEF and HFmrEF according to a registry of percutaneous coronary interventions (PCI).

Material and methods

The paper presents data available from the PCI registry conducted within the period of 2012-2013 at the Tyumen Cardiology Center (branch of the Tomsk National Research Medical Center). The study was conducted in accordance with Good Clinical Practice standards and the Declaration of Helsinki. The study was approved by the local Ethics Committee. Before inclusion, a written informed consent was obtained from every participant. Based on 2007 Russian Society of Cardiology and 2011 European Society of Cardiology/American Heart Association guidelines, ACS was diagnosed in 359 people who entered the register. After coronary angiography, all patients were made PCI with stenting using X-ray system Philips Integris Allura (Holland). The study group included 135 people with ST-segment elevation (45,9%) and non-ST-segment elevation (54,1%) MI. Group 1 (n=89) and group 2 (n=46) consisted of patients with HFmrEF and HFpEF, respectively. Patients in the groups were of the same age (60,8±9,8 years and 59,2±9,3, p=0,468, respectively), sex and have the same comorbidities as hypertension, diabetes, chronic kidney disease, and obesity. The optimal medication therapy included the antiplatelet agents, beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin-2 receptor antagonists, statins, as well as nitrates and diuretics when necessary. After 12±3,1 and then 60±4,3 months, we contacted with patients for medical examination.

Venous blood was collected at admission, after 12 and 60 months. Neutrophils, lymphocytes, platelets were determined using Mindray BC-5800 5-diff auto hematology analyzer (China). The following parameters were also determined: high-sensitivity C-reactive protein (hs-CRP, reference range, 0-3,0 mg/l) — by immunoturbidimetry with C-reactive protein hs kit (BioSystem, Spain) using Semi-automatic biochemical analyzer Clima MC-15 (Spain); interleukin-1β (IL-1β, reference range, 0-5,0 pg/ml), interleukin-6 (IL-6), IL-8, tumor necrosis factor-α (TNF-α, reference range 0-8,11 pg/ml) — sandwich form and homocysteine (HYC, reference range, 5,0-15,0 umol/l), N-terminal pro-brain natriuretic peptide (NT-proBNP) — solid-phase competition enzyme-linked immunosorbent assay using the IMMULITE 2000 System (Siemens Diagnostics, US); matrix metalloproteinase-9 (MMP-9, reference range, 20,3-77,2 ng/ml) — Bender MedSystems an eBioscience company, Austria; tissue inhibitor of metalloproteinase-1 (TIMP-1, reference range, 92-116 ng/ml) — Human TIMP-1 Elisa K.t Invitrogen (USA) using the Personal Lab analyzer (Italy).

Table 1

The impact on laboratory inflammatory markers on the five-year death rate in the general group of patients

Laboratory parameters	HR	95% CI	p
Platelets, 10^9/l	1,011	1,003-1,019	0,010
Homocysteine, μmol/l	1,172	1,008-1,364	0,040
MMP-9 >249 ng/ml	7,052	1,346-36,950	0,021

Abbreviations: CI — confidence interval, MMP-9 — matrix metalloproteinase-9, HR — hazards ratio.

Table 2

Comparative characteristics of laboratory parameters during follow-up

Parameters	Group 1 (n=89), (Me [25%; 75%])			Group 2 (n=46), (Me [25%; 75%])		
	Initially	After 12 months	After 60 months	Initially	After 12 months	After 60 months
NT-proBNP, pg/ml	976,74 [121,00; 736,50]	396,48 [100,62; 401,50]*	759,92 [84,90; 573,00]	558,86 [96,90; 489,00]	236,72 [64,90; 224,50]§	356,55 [70,30; 302,50]†§
IL-1β, pg/ml	3,87 [2,70; 4,55]	3,88 [3,13; 4,40]	2,53 [1,93; 2,76]††	3,64 [2,83; 4,43]	3,65 [2,78; 4,33]	2,34 [1,80; 2,52]††
IL-6, pg/ml	3,87 [1,55; 4,10]	2,03 [1,35; 2,52]	2,32 [1,79; 2,83]††	3,40 [1,47; 3,79]	2,55 [1,39; 2,37]*	2,24 [1,51; 2,82]†
IL-8, pg/ml	13,49 [8,55; 16,40]	15,63 [9,36; 19,50]	11,94 [7,92; 14,90]††	17,87 [10,30; 18,20]	15,88 [9,37; 18,70]	10,96 [7,82; 13,80]††
TNF-α, pg/ml	6,18 [4,65; 7,49]	4,89 [3,15; 5,97]	6,41 [4,64; 7,55]†	6,24 [4,37; 8,49]	4,70 [3,55; 6,12]	5,86 [4,61; 7,39]†
Homocysteine, umol/l	14,80 [12,25; 18,20]	12,23 [8,16; 15,45]*	16,05 [8,16; 15,45]†	13,45 [10,30; 15,90]	11,36 [8,32; 14,75]**	14,31 [10,92; 15,85]††
MMP-9, ng/ml	237,62 [140,25; 303,05]	179,11 [144,47; 211,49]	133,53 [92,80; 184,45]†	202,43 [139,40; 230,40]	190,89 [139,25; 217,05]	160,40 [100,50; 207,45]
TIMP-1, ng/ml	250,54 [187,90; 318,20]	252,25 [204,77; 313,40]	284,58 [204,77; 313,40]	249,27 [193,80; 294,05]	255,28 [203,22; 282,75]	255,33 [198,75; 310,65]
hs-CRP, mg/l	4,80 [1,54; 8,21]	2,14 [0,54; 2,12]**	4,34 [0,54; 2,12]	4,41 [0,76; 6,02]	2,30 [0,50; 2,64]*	4,13 [1,43; 4,82]

Note: * — p<0,05 difference between the initial indicators and after 12 months, ** — p<0,01 difference between the initial indicators and after 12 months, † — p<0,05 difference between the initial indicators and after 12 and 60 months, †† — p<0,01 difference between the initial indicators and after 12 and 60 months, § — p<0,05 difference between the indicators in compared groups.

Abbreviations: hs-CRP — High-sensitivity C-reactive protein, IL-1β — interleukin-1β, IL-6 — interleukin-6, IL-8 — interleukin-8, MMP-9 — matrix metalloproteinase-9, TIMP-1 — tissue inhibitor of metalloproteinase -1, TNF-α — tumor necrosis factor-alpha, NT-proBNP — N-terminal pro-brain natriuretic peptide.

The distribution was assessed using the Kolmogorov-Smirnov test. Normally distributed continuous variables are presented as the arithmetic mean and standard deviation (M±SD); non-normally distributed variables — as a median, lower and upper quartiles (Me [25%; 75%]). Depending on the distribution, Student's t-test or Mann-Whitney test was used when comparing 2 independent groups and Friedman's test adjusted for multiple comparisons to assess the significance of differences. Qualitative variables are presented as relative frequencies (n, %). Comparison of these variables in 2 groups was performed using the chi-squared test or Fisher's exact test. Kaplan-Meier survival analysis was used to assess 5-year survival in patients with MI and PCI. To compare the survival rate for the entire follow-up period in the two groups, a log-rank test was used. To assess the influence of independent factors on survival and to predict the risk of an event, the Cox regression model was used.

Results

When discharged from the hospital, optimal medication therapy was recommended to all patients. In 1 year only three-quarters of patients continued to take β-blockers and statins, which continued in 5 years of follow-up. The number of patients without anti-thrombotic therapy increased from 19,9% in 12 months to 29,7% in 60 months. The therapy conducted within 60 months didn't result in achieving the target values of lipid profile in any of the groups.

In the course of follow-up, we compared findings dividing the patients into groups with HF-mrEF and HFpEF. During the follow-up, 18 people died (mean age of deceased — 60,9±13,5 years; alive — 60,0±8,9 years). The survival rate in 60 months was 86,7%. Differences in compared groups were not detected (85,0% and 89,1%, respectively, p=0,492).

The blood test data in 12 and 60 months are shown in Table 1. We observed increased values of hs-CRP, MMP-9 and TIMP-1 in both groups of patients, with a downward trend of MMP-9 in the point of 12 and 60 months of follow-up. As for hs-CRP, TNF-α and homocysteine, with a decreasing trend at the second observation point, the trend towards increase at 60 months was recorded. Interleukins had the general trend towards decrease by the 3 observation point as compared to initial data in both groups. Thus, the comparative characteristics of biomarkers in the groups did not differ in the majority of studied parameters. Consistently, the levels of NT-proBNP were higher in the group 1 than in group 2 in 12 and 60 months of follow-up. Moreover, the one-directional changes of NT-proBNP in 12 and 60 months in both groups similar to the dynamics of such inflammatory markers as hs-CRP, TNF-α, homocysteine are notable.

Such laboratory parameters as platelets, homocysteine and increased MMP-9 >249 ng/ml became the independent risk factors of mortality over the follow-up period in the general group of patients. With increase in platelets by $1*10^9$/l, the risk of fatal outcome increases by 1,1%; with increase in homocysteine by 1 μmol/l — by 17,2%; with increase in MMP-9 >249 ng/ml, the risk increases 7 times (Table 2). In 5 years a decrease in the survival rate in patients with a high level of MMP-9 (>249 ng/ml) was recorded. In the 1 group, the death rate was higher among the patients with a platelet count $>245*10^9$/l (Table 3).

Table 3

The impact of laboratory inflammatory markers on the patient survival rate in compared groups

Laboratory parameters	Five-year survival rate	p
Group 1 (HFmrEF)		
MMP-9 >249 ng/ml	75,0%	0,026
MMP-9 <249 ng/ml	96,6%	
Platelets $>245*10^9$/l	74,3%	0,015
Platelets $<245*10^9$/l	93,3%	
Group 2 (HFpEF)		
MMP-9 >249 ng/ml	55,6%	0,000
MMP-9 <249 ng/ml	97,1%	

Abbreviations: MMP-9 — matrix metalloproteinase-9, HFmrEF — heart failure with mid-range ejection fraction.

Discussion

The recorded patterns of changes of vascular inflammatory response parameters and NT-proBNP suggest the need for an association of detected blood changes with a recorded stable decrease in taking medications. We didn't reveal the NT-proBNP effect on survival, however, the meta-analysis of 19 studies showed a prognostic significance of BNP on the relative death risk increase [5]. In both groups of patients, the recorded increased levels of vascular inflammation markers (hs-CRP, MMP-9, TIMP-1, homocysteine, NT-proBNP) suggest the presence of prolonged inflammatory potential for possible cardiovascular event development.

It is considered that increased MMP-9 level is an independent predictor of a cardiovascular event in patients with different types of coronary artery disease, which has a prognostic significance for restenosis development and correlates to a high level of post-infarction LV remodeling due to increased degradation of extracellular matrix proteins and myosin heavy chains, as well as contributes to poor prognosis related to the LV dysfunction [6, 7]. These data are reflected in our research too.

Numerous studies have confirmed that hyperhomocysteinemia is one of the significant and independent risk factors for early and rapid progression of atherosclerosis, endothelial damage, systemic inflammatory response, activation of hemostasis with a poor prognosis in MI patients and is also a predictor of all-cause mortality and cardiovascular events [8, 9]. In our study, this theory was confirmed. The level of homocysteine significantly increased by the 3rd follow-up point in both groups, irrespective of the initial LVEF and was associated with other inflammatory markers and five-year survival in the general group.

In addition to their leading role in atherothrombosis initiation, platelets have important functions in modulating inflammation. They can adhere to intact endothelial cells and promote local vascular inflammation by involving leukocytes through direct interactions or by secreting inflammatory mediators such as chemokines [10]. One of the causes for the increased activity of platelets may be the acceleration of their production and turnover [11]. When thrombocytopoiesis is stimulated, large and reticular "young" platelets appear in the bloodstream, which are not only markers, but also predictors of atherothrombotic events, and, first of all, ACS. An increase in the number of such platelets in patients receiving antiplatelet drugs may be associated with a decrease in the effectiveness of their antiplatelet action [12]. According to our study, an increase in the number of platelets, although to a lesser extent than other biomarkers, affects the mortality rates in patients after MI and PCI during 5-year follow-up, mainly due to patients with HFmrEF, which may be explained by platelet dysfunction due to neurohumoral activation in HF [13].

Thus, today biomarkers are a reliable, safe and objective tool of diagnostics, control of dynamics and risk stratification of adverse events, complementing clinical and instrumental data reflecting the features of the pathophysiological mechanisms of cardiovascular diseases [14]. In general, it should be noted that a multimarker strategy for the management of patients with coronary artery disease and HF may become a promising approach that significantly changes the traditional views on diagnosis and risk stratification.

The key factor for such a biomarker dynamic may lie in the pathogenesis of vascular inflammation course, which depends on the severity of the underlying and comorbid conditions, and on the patients' medical adherence. This multifaceted problem makes it necessary to continue the search for new associations of clinical manifestations and biomarkers in order to reduce the risk of CVDs, including mortality.

Study limitations. During studying the effect of platelet levels on long-term prognosis, we did not study the aggregative activity of platelets, which, undoubtedly, could explain the presented results.

Conclusion

In this study, we identified biomarkers, which make it possible to forecast the risk of 5-year adverse outcomes in patients after MI and PCI. Levels of MMP-9, homocysteine, and platelets were the factors that influenced 5-year survival in the general group of patients after MI and PCI. In the group with HFmrEF, MMP-9 and platelets had a negative impact on the prognosis. In patients with HFpEF, reduced survival was associated only with high levels of MMP-9. The dynamics of markers of systemic inflammatory response and NT-proBNP indicates the prolonged inflammatory process in both groups of patients, persisting for 5 years after MI.

Relationships and Activities: none.

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