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Multifactor Predictive Model in Patients with Myocardial Infarction Based on Modern Biomarkers

Objective	To study the prognostic role of current serum biomarkers in patients with myocardial infarction (MI) by constructing a multifactorial model for prediction of cardiovascular complications (CVC) in remote MI. Acute coronary syndrome is a major cause of death and disability in the Russian Federation. Introduction of current biomarkers, such as N-terminal pro-brain natriuretic peptide, stimulating growth factor (ST2), and centraxin-2 (Pentraxin, Ptx-3), provides more possibilities for diagnostics and calculation of risk for CVC.
Materials and Methods	Concentrations of biomarkers were measured in 180 patients with MI (mean age, 61.4±1.7) upon admission. At one year, specific and composite endpoints were determined (MI, acute cerebrovascular disease, admission for CVD, and cardiovascular death). Based on this information, a prognostic model for subsequent events was developed.
Results	A mathematical model was created for computing the development of a composite endpoint. In this model, the biomarkers NT-proBNP, Ptx-3 and, to a lesser extent, ST2 demonstrated their prognostic significance in diagnosis of CVC with a sensitivity of 78.79% and specificity of 86.67% (area under the curve, AUC 0.73).
Conclusion	In patients with remote MI, the biomarkers NT-proBNP, ST2, and Ptx-3 improve prediction of CVC.
Keywords	Acute coronary syndrome; biomarkers; model of risk evaluation; cardiovascular complications
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About 12 million people die from cardiovascular disease (CVD) annually; most of these deaths are associated with coronary artery disease (CAD). Destabilization of CAD results in the development of acute coronary syndrome (ACS) and myocardial infarction (MI). In ACS, a significant challenge is to perform a timely risk assessment and determine a proper management plan to prevent possible severe complications. Therefore it is necessary to develop a model to assess the risk of complications such as repeated MI, cerebrovascular accident (CVA), hospitalization due to worsening of CAD, and death from CVD. Using cardiac-specific biomarkers in the model help improve risk stratification and outcome prognosis. Their concentration is correlated with event severity, and reflects the course of disease and the efficacy of treatment. In addition to common biomarkers, such as the myocardial band (MB) fraction of creatine phosphokinase (CPK-MB), aspartate aminotransferase (AST), and the well-established troponin, new biomarkers have recently been identified – N-terminal pro-brain natriuretic peptide (NT-proBNP), stimulating growth factor 2 (ST2), and pentraxin-related protein (Ptx-3).

ST2 is a member of the interleukin 1-receptor family. An increased concentration of ST2 circulating in the blood indicates a high risk of adverse outcomes (AO), hospitalizations, and even death not only for patients with chronic heart failure (CHF), but also for patients with CVD in the general population [1]. Ptx-3 is a member of the pentraxin superfamily. It has been shown that increased secretion of Ptx-3 is typical of patients with CAD and is associated with ACS, and that high plasma levels of Ptx-3 are predictors of AOs in patients with CHF. [2] Increased levels of Ptx-3 in peripheral blood are associated with the presence of diastolic

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dysfunction both in patients without signs of CHF and in CHF with preserved left ventricular ejection fraction (LVEF) [3].

NT-proBNP is a peptide hormone secreted by the heart in response to pressure or volume overload. Determination of NT-proBNP levels is a reliable screening test for the diagnosis, risk stratification, and prognosis of heart failure. Moreover, changes in NT-proBNP concentration can be used to judge the efficacy of treatment and adjust drug doses.NT-proBNP can serve as a prognostic factor indicating a risk of death and recurrence of MI, not only in patients with MI but also in patients with unstable angina in which myocyte necrosis is confirmed by an increase in troponin I. Numerous studies have shown that an increase in NT-proBNP levels is an independent predictor of death in CHF [4, 5].

The objective was to study a prognostic role of new serum biomarkers in patients with MI by constructing a multivariate model to predict long-term cardiovascular complications (CVCs) after myocardial infarction.

Materials and Methods

The study was carried out in the Cardiac Intensive Care Department of City Clinical Hospital No.21, Ufa, Russian Federation. It was performed under Good Clinical Practice standards and the principles of the Declaration of Helsinki and approved by the local ethics committee of Bashkir State Medical University and City Clinical Hospital No. 21, Ufa, Russian Federation (dated 09/12/2016). Before inclusion in the study, all subjects signed informed consent.

Inclusion criteria: more than 18 years old; ACS diagnosed at admission based on such evidence as the presence of retrosternal pain of anginal nature lasting 20 minutes or more; ST elevation by 0.1 mW in two or more contiguous leads and complete left bundle branch block in the electrocardiogram (ECG); troponin T level above 0.1 ng/mL; signed informed consent form to participate in the study.

Exclusion criteria: more than 3 days since the onset of ACS, congenital and acquired heart defects, cardiac conduction disorders (sick sinus syndrome, second- and third-degree atrioventricular block), chronic kidney disease stage 2a or more severe, pulmonary embolism, chronic obstructive pulmonary disease and other moderate-to-severe respiratory diseases, acute infectious diseases and exacerbation of chronic diseases at the time of inclusion, history of cancer, pregnancy, early postpartum period, lactation.

A total of 210 patients were screened, 180 of whom were included in the study based on these criteria. They were hospitalized with a provisional diagnosis of ACS. The mean age was 61.4±1.7 years.

Subsequently, a diagnosis of MI was verified according to the 2013 clinical guidelines of the European Society of Cardiology: elevated levels of troponin (>99th percentile of the normal reference values) and a regular trend in combination with the presence of clinical symptoms of myocardial ischemia; de novo ST-segment elevation by 0.1 mW in two or more contiguous leads or de novo left bundle branch block registered in ECG; the appearance of Q-wave in ECG; signs of new nonviable sites of the myocardium or new local contractility as shown by imaging techniques; and the presence of coronary artery thrombosis according to coronary angiography CA [6].

Blood samples were collected at admission to the hospital and were subsequently centrifuged and frozen. The concentrations of NT-proBNP, ST2, and Ptx-3 were determined by enzyme-linked immunosorbent assay (ELISA) using the Critical Diagnostics, Biomedica, and Hycult Biotech test systems, respectively.

Cardiac-specific markers (troponin I, CPK-MB) were identified, and biochemical blood analysis and determination of the blood lipid composition were carried out according to the standard algorithm in all patients during hospitalization. Among instrumental methods of examination, multiple ECG recording, echocardiography, Holter ECG monitoring (if indicated), chest X-ray, and computed tomography (CT) were used.

ECG analysis was performed both before and during hospitalization. Echocardiography was performed on days 4–5 of hospitalization: myocardial systolic and diastolic functions were estimated; the dimensions of the heart chambers and wall thicknesses were measured; the presence of sites of contractility disturbances and the condition of the valvular apparatus were assessed; and the pulmonary systolic pressure was measured. LVEF was assessed by the Simpson method. CA was carried out for the diagnosis and the emergency percutaneous coronary intervention (PCI).

At 12 months, the primary endpoints (MI, stroke, death, and hospitalizations for cardiovascular causes) were analyzed. The composite endpoint was also used, which included the following events: MI + stroke + death + hospitalization for CVD. Endpoints were determined by monitoring using the ProMed program, which contained data on death, strokes, MI, and hospitalizations for cardiovascular reasons, as well as data on patients' visits to the hospital, hospitalization outcomes, and death certificates.

Statistical processing of the study results was carried out using the Excel and Statistica software packages, and the R-Studio statistical modeling environment.

The normality of distribution of all signs was carried out using the Shapiro-Wilk test, in which the null hypothesis that a factor complies with the normal distribution law is rejected at the significance level of $p<0.05$.

The data are provided depending on the type of of variables distribution: as the mean±standard deviation ($m\pm\sigma$) in normal distribution, otherwise as the median Me and interquartile range $[Q_1, Q_3]$.

The models were based on various data mining algorithms: binary regression models (generalized linear model [GLM] family), deep learning neural network modeling with double-layer perceptron, and machine learning algorithms – gradient boosting and distributed random forest (DRF) algorithm. All of these algorithms are widely used in medicine for risk-score modeling. Thus, the use of GLM models is quite common in medicine. Song et al. [7] presented general principles and results of the operation of the GLM classifiers for prognosis purposes in various areas of medicine using the example of 20 data sets. Mogensen et al. [8] suggested a solution for the survival prognosis of patients hospitalized with MI using the random forest algorithm.

All prognosis algorithms were implemented in the R-Studio statistical modeling environment. Methods of data division into training and test samples at the ratio of 70:30 were used for the cross-validation of models and obtaining reliable results of CVC prognosis. The prognostic value of an indicator was estimated by the area under the ROC-curve (AUC) and calculated for all the algorithms used in the test samples. The optimal model for predicting the development of CVCs most accurately was selected based on the maximum AUC, as well as specificity (Sp) and sensitivity (Sen) with the probability cutoff criteria (0.5). Statistically significant factors influencing the outcome were selected with $p<0.05$.

Results

Of all subjects, more patients were male (n=136). The mean age was 61.4±1.7 years. Table 1 shows the distribution of patients by age (normal distribution with p=0.29) and sex. Most subjects were patients of older age groups. The number of male patients significantly exceeded that of female patients (by almost three times), but the ratio decreased with increasing age.

The most common comorbidities were hypertension in 167 (92%) patients, MI in 42 (23%) patients, and diabetes mellitus (DM) in 31 (17%) patients (Table 2). The main risk factors (RFs) were smoking in 28 (16%), heart rate of more than 100 bpm in 32 (17.7%), and hypercholesterolemia in 73 (40.5%) patients. Most patients had preserved LVEF – 53.5% [49; 59]. PCI was carried out in 132 (73.3%) patients, PCI and thrombolytic therapy (TLT) in 30 (16.6%), and only TLT in 18 (10%) patients. According to CA, single-vessel disease was detected in 114 (86.4%), and multivessel disease in 18 (13.6%) patients.

At admission to the hospital, blood samples were collected from patients for biochemical and ELISA. Table 3 shows some of the laboratory test reults, which were used to determine significant disturbances of the lipid composition of blood at admission to the hospital.

Table 4 shows the median and interquartile ranges for specific biomarkers. The normal levels of NT-proBNP lie within the range of 0–200 pg/mL; an increase of more than 200 pg/mL is typical for CHF. The normal range of ST2 in male patients is 8.5–49.3 ng/mL; in female patients, 7.1–33.5 ng/mL. No references for Ptx-3 have been developed. The serum levels of NT-proBNP, ST2, and Ptx-3 were estimated at admission.

The standard therapy carried out throughout hospitalization according to the current guidelines for the treatment and management of patients with ACS included: angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, beta-blockers (if contraindicated, ivabradine), acetylsalicylic acid, thienopyridines (clopidogrel/ticagrelor), and statins. Drug therapy carried out in the hospital is presented in Table 5.

Clinical outcomes were analyzed 1 year (384.3±21.2 days) after MI: 22 patients died, recurrent MI occurred in 32 patients, CVA occurred in 5 patients, and 52 patients were hospitalized due to CVD.

The algorithms of data mining were used to predict CVCs taking into account various factors, such as generalized binary regression model (a general linear model [GLM]), neural network simulation (Deep Learning) with a two-layer perceptron and ReLu (rectified linear unit) activation function, a machine learning algorithm

Table 1. Sex and age of patients examined

Sex	Age, years					Total
	<30	31–40	41–50	51–60	>60	
Male	1	5	20	47	63	136
Female	–	–	2	6	36	44

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Table 2. Characteristics of patients in follow-up group (n=180)

Parameter	Value
History of MI, % (n)	42 (23.3)
History of CVA, % (n)	6 (3.3)
Smokers, n (%)	28 (16)
Diabetes mellitus, n (%)	31 (17)
Hypertension, n (%)	167 (92)
HR>100 bpm, n (%)	32 (17.7)
Hypercholesterolemia, n (%)	73 (40.5)
LVEF, %, Me [Q_1; Q_3]	53.5 [49; 59]
Pre-hospital TLT, %	18 (10)
Pre-hospital TLT and PCI, %	30 (16.6)
PCI, %	132 (73.3)
Affected artery, as shown by CA, n (%):	
• LAD	51 (38.6)
• LCX	12 (9.1)
• RCA	48 (36.4)
• LCA	1 (0.8)
• Marginal branch	2 (1.5)
• Multivessel disease	18 (13.6)

MI, myocardial infarction; CVA, cerebrovascular accident; HR, heart rate; LVEF, left ventricular ejection fraction; TLT, thrombolytic therapy; PCI, percutaneous coronary intervention; CA, coronary angiography; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; LCA, left coronary artery.

Table 3. Laboratory findings at admission to the hospital

Parameter	Values, Me [Q_1; Q_3]
TC, mmol/L	5.2 [4.5; 6.02]
LDL, mmol/L	3.2 [2.65; 3.93]
HDL, mmol/L	1.2 [1.0; 1.5]
Triglycerides, mmol/L	1.5 [1.1; 2]
Creatinine, μmol/L	90 [76; 106]
AST, mmol/L	61 [34; 114]
CPK-MB, mmol/L	74 [40; 142]
Troponin I, ng/mL	202 [10; 1613]

TC, total cholesterol; LDL, low-density lipoproteins; HDL, high-density lipoproteins; AST, aspartate aminotransferase; CPK-MB, MB fraction of creatine phosphokinase.

Table 4. Concentration of biomarkers and reference values

Parameter	Reference	Value
NT-proBNP, pg/mL	0–200	519 [54; 2130]
ST2, ng/mL	Male: 8.5–49.3 Female: 7.1–33.5	43.8 [24.8; 52.5]
Ptx-3, ng/mL	Absent	132 [111; 164]
Troponin I, ng/mL	Up to 0.1	202 [10; 1613]

The data are presented as the median and interquartile range — Me [Q_1; Q_3].

(gradient boosting [GBM]), and distributed random forest algorithm (DRF). We defined the following quality indicators of the models (Table 6) regarding the composite endpoint (MI + CVA + hospitalization due to CVD and death from CVD): AUC, the proportion of the maximum precision, mean squared error of the deviation of the estimated value from the actual value (MSE), specificity (Sp), and sensitivity (Sen). Probit regression based on normal distribution had the lowest value of the Akaike and Schwartz information criteria. For this reason, it was selected as the most effective binary regression model for further risk modeling. All attributes listed in Tables 2, 3, and 4 were used as risk predictors for all models. The significance of their effect on the risk of CVCs was calculated using the Wald test (GLM) and an algorithm for determining the attribute significance (GBM, DLN, DRF).

The probit regression model was interpreted using marginal effects, allowing the assessment of effects and ranking of factors studied according to their effect on the endpoints. Mathematical binary regression modeling revealed that biomarkers have an effect on CVCs: with increased ST2 levels, risk of stroke was higher by 1.4%; high levels of NT-proBNP increased risk of death by 1.52% ($p<0.01$); and elevated Ptx-3 levels increased risk of death by 1.18% ($p<0.05$). As for the composite endpoint (stroke + MI + hospitalization + death), the binary regression model made it possible to identify the following statistically significant ($p<0.05$) predictors of CVCs taking into account certain marginal effects (%):

1. Low diastolic blood pressure (BP) at admission to the hospital (2.2%)
2. Ventricular tachycardia at admission and during hospitalization as identified by ECG monitoring (2.03%)
3. NT-proBNP levels above normal (1.52%)
4. AST> 40 mmol/L (1.47%)
5. ST2 above normal (1.4%)
6. Age more than 65 years (1.35%)
7. DM type 2 (1.34%)
8. ST-elevation MI (1.3%)
9. High level of Ptx-3 (1.18%)

Following the comparative analysis of CVC prognosis models, it is suggested to use a generalized binary regression model (GLM) as a classifier for patients with ACS. The risk of the development of the composite endpoint can be determined by the following formula:

$$P(C_i)=\frac{1}{\sqrt{2\pi}}\times \int_0^{0,027x_1+0,76x_2+1,25x_3+0,008x_4+0,003x_5+0,001x_6+0,04x_7+0,003x_8+0,01x_9-2,437} e^{-z^2/2}dz,$$

where: P (Ci) is a risk of event development; x_1 is level of NT-proBNP; x_2 is the presence of ventricular

tachycardia; x_3 is diastolic BP; x_4 is the level of AST; x_5 is the patient's age; x_6 is the presence of ST elevation; x_7 is the level of ST2; x_8 is the presence of diabetes; and x_9 is the Ptx-3 level.

The ROC-curve (receiver operating characteristic curve) constructed for this logistic regression model with AUC=0.73 is represented in Figure 1. When the model was created, the ROC-analysis showed 78.79% sensitivity, 86.67% specificity, and 75% accuracy.

Discussion

We analyzed the prognostic value of the combination of pathophysiologically different biomarkers: NTproBNP (a marker of myocardial stress), ST2 (a marker of myocardial fibrosis and remodeling), and Ptx-3 (a marker of inflammation) in patients with MI at admission to the hospital to create a CVC prediction model.

A multimarker analysis with two or more biomarkers of various pathogenic classes provides additional prognostic information. It seems to be a rational and reliable modern strategy for risk stratification in patients with CVD who require more careful attention [9]. Most studies of multimarker approaches imply the value of adding promising new biomarkers to well-studied risk factors [10–12]. Ky et al. (2012) confirmed the role of ST2 as a reliable marker of risk in CHF and the improvement of prognosis when an established clinical risk score is used in combination with NT-proBNP. In the multicenter study, which included 1,141 outpatients with CHF, the risk of AOs with ST2≥36.3 ng/mL was higher than with ST2<22.3 ng/mL (adjusted odds ratio [OR] 1.9; 95% confidence interval [CI] 1.3 to 2.9; p=0.002) [13]. Bayes-Genis et al. (2015) showed in their study, which included 1,015 patients with CHF of predominantly ischemic origin and with reduced LVEF, that ST2 demonstrated a long-term risk stratification of patients with CHF at various serum concentrations of biomarkers of other pathogenic classes. Thus, the OR of death based on the concentrations of soluble ST2 was 1.22 (95% CI 1.08–1.37; p=0.001) in the upper tercile of NT-proBNP and 2.02 (95% CI 1.61–2.52; p=0.001) in the lower tercile of NT-proBNP [14]. Ptx-3 is a promising biomarker that has been shown to be effective in several studies in patients with CAD and MI, including those with preserved LVEF [3].

Our study included 180 patients with a history of MI with mainly preserved LVEF who underwent PCI and TLT. The long-term analysis of endpoints after year 1 was performed using several mathematical and statistical tools to create an optimal prediction model. The GLM turned out to be the most accurate. This

Figure 1. ROC-curve of the probit regression model for all cardiovascular endpoints

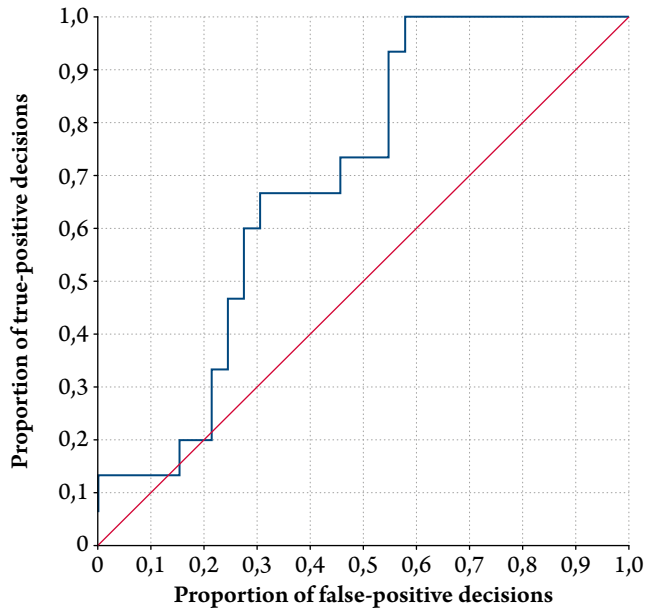

Table 5. Drug therapy in the hospital

Parameter	Number of patients	
	Abs.	%
ACE inhibitors/ARB	170	94.4
Beta-blockers	168	93.3
Ivabradine	14	7.8
Statins	169	93.8
ASA	170	94.4
Thienopyridines	169	93.8
Calcium-channel blockers	8	4.4
Diuretics	58	32.2
NOACs	8	4.4

ACE, angiotensin-converting enzyme;
ARB, angiotensin II receptors blockers;
ASA, acetylsalicylic acid; NOACs, new oral anticoagulants.

Table 6. Comparative indicators of quality of model classification

Model	GLM	GBM	DRF	DLN
AUC	0.7313	0.6949	0.6676	0.6282
Maximum accuracy	0.75	0.7292	0.7083	0.7292
MSE	0.1886	0.2267	0.2006	0.2429
Sp	0.7879	0.7273	0.8667	0.7879
Sen	0.8667	0.7333	0.697	0.6

GLM, a generalized probit regression model;
GBM, a gradient boosting model; DLN, deep learning neural network modeling with double-layer perceptron and ReLu activation function; DRF, distributed random forest algorithm;
AUC, area under the ROC-curve.

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model describes the development of the composite endpoint (MI + stroke + hospitalization for CVD and death from CVD) with a sensitivity of 78.79% and a specificity of 86.67% (AUC=0.73). The AUC was higher than that of each biomarker, which confirms the efficacy of the multimarker score in the analysis of endpoint [15–17].

Moreover, each marker was analyzed in terms of impact on the endpoints of CVD, and the obtained results were used to create a mathematical model for the prognosis of AOs. The regression analysis showed that high levels of ST2 increase the risk of stroke by 1.4%, and the risk of MI was reduced by 1.3% ($p<0.05$ in both cases). At the same time, high levels of NT-proBNP and Ptx-3 ($p<0.05$) increased the risk of death in 1 year. Besides these factors, the RFs of the development of CVD were lower diastolic BP, ventricular tachycardia at admission to the hospital, high levels of AST, and other parameters confirmed in the literature [18].

Thus, elevated serum concentrations of NT-proBNP and Ptx-3, and to a lesser extent ST2, in combination with conventional RFs, improved CVD risk stratification in post-MI patients based on a 1-year follow-up period. A corresponding mathematical model that determines the risk of CVD with high sensitivity and specificity was created.

No conflict of interest is reported.

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