

## Research Article

<https://doi.org/10.23934/2223-9022-2023-12-4-577-583>

## Predicting the Development of Complications After Mitral Valve Repair Using Mathematical Analysis

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**AIM** To study the possibilities of using risk factors, data from instrumental research methods identified at the preoperative stage as independent variables for predicting the development of complications after mitral valve surgery.

**MATERIAL AND METHODS** The study included 103 patients, 46 men and 57 women, who underwent surgical correction of mitral valve defect and were treated at the Cardiac Surgery Department of Chelyabinsk Regional Clinical Hospital № 1 in the period from 2014 to 2019. Among those patients, the presence of anemia at the preoperative stage (blood hemoglobin level less than 100 g/l) was detected in 13 (12,6%) cases; obesity (BMI more than 30 kg/m<sup>2</sup>) – in 57 (55,3%) cases; transfusion of blood and its components in anamnesis – in 14 (13,6%) cases; type 2 diabetes mellitus – in 7 (6,8%) cases; stroke in anamnesis – in 9 (8,7%) cases; chronic Hepatitis C – in 6 (5,8%) cases; HIV infection – in 4 (3,9%) cases; antibiotic therapy before surgery was indicated in 21 (20,4%) cases; edema of the lower extremities was detected in 40 (38,8%) cases; an increase in body temperature before surgery – in 19 (18,4%) cases; the presence of atrial fibrillation before surgery – in 63 (61,2%) cases. The systematization of the source information was entered into a Microsoft Office Excel 2016 spreadsheet. Statistical analysis was carried out using the IBM SPSS Statistics v.26 program (developed by IBM Corporation). Binary logistic regression was used as a method of mathematical data analysis. Instrumental research methods: electrocardiography (ECG), echocardiography (ECHO-CG); coronary angiography was performed according to indications.

**RESULTS** The presence of risk factors such as anemia, obesity, as well as an increase in the size of the right atrium can be used as an independent variable to predict the development of complications. An increase in the diameter of the pulmonary artery trunk, and the presence of edema of the lower extremities reduces the risk of complications. The likelihood of developing complications after mitral valve surgery predicted by the logistic regression method was 53,4%. The resulting model predicts the absence of complications with the likelihood of 82,5%. The development of complications was correctly predicted in 93,3% of cases.

**CONCLUSION** This model can be used as an additional tool in predicting the development of complications after mitral valve surgery.

**Keywords:** mitral valve, logistic regression, anemia, obesity

**For citation** Matsuganov DA, Nuzhdin MD. Predicting the Development of Complications After Mitral Valve Repair Using Mathematical Analysis. *Russian Sklifosovsky Journal of Emergency Medical Care*. 2023;12(4):577–583. <https://doi.org/10.23934/2223-9022-2023-12-4-577-583> (in Russ.)

**Conflict of interest** Authors declare lack of the conflicts of interests

**Acknowledgments, sponsorship** The study has no sponsorship

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AF – atrial fibrillation

AKI – acute kidney injury

BMI – body mass index

CI – confidence interval

CHD – coronary heart disease

CRT – cardiac resynchronization therapy

CVD – cardiovascular diseases

EAT – epicardial adipose tissue

ECG – electrocardiography

ECHO-CG – echocardiography

HDL – high density lipoproteins

IAFT – intra-abdominal fat thickness

LE – lower extremities

OR – odds ratio

PA — pulmonary artery  
PFT — preperitoneal fat thickness  
RA — right atrium  
RF — risk factor

## INTRODUCTION

Predicting the development of a particular pathology is of great importance in primary prevention and early diagnosis of the disease, and also significantly affects its outcome. Knowledge of the main predictors influencing the development of complications can be used to prevent them by affecting risk factors (RFs). In cases where it is not possible to influence the factor, predicting the development of a complication provides an opportunity to take the necessary measures in a timely manner to prevent adverse outcomes of the disease, and improve the patient's quality of life.

One of the most accessible and promising methods for predicting the development of complications is the identification of risk factors in patients during initial contact with them, as well as the analysis of data from instrumental research methods.

In modern literature, there are a large number of scientific articles on predicting the development of complications in the postoperative period. Thus, in patients with acute kidney injury (AKI) after cardiac surgery, new biomarkers (urinary liver-type fatty acid-binding protein (L-FABP), neutrophil gelatinase-associated lipocalin (NGAL), serum L-FABP, heart-type FABP, kidney injury molecule-1 (KIM-1), and interleukin-18) were identified and recognized as reliable indicators for diagnosis, prediction of poor outcome, and even death from postoperative AKI. Therefore, it was concluded that to achieve a promising prognosis, renal replacement therapy should be started as early as possible [1].

There is also evidence of the development of atrial fibrillation (AF) in the postoperative period of heart surgery. It was shown, that it is associated with subsequent cardiac and renal failure, systemic embolism, and increased hospital days and mortality. AF in the postoperative period of cardiac surgery usually appears in the first 48 hours after surgery. Also, the following concomitant risk factors were identified: older age, chronic obstructive

TCH — total cholesterol  
TG — triglycerides  
WFI — abdominal wall fat index

pulmonary disease, chronic kidney disease, valve surgery, reduced left ventricular ejection fraction (less than 40%), and withdrawal of beta blockers. Prophylactic treatment with  $\beta$ -blockers and amiodarone was shown to be associated with a reduction in the occurrence of AF after surgery [2].

**Aim:** To study the possibilities of using risk factors identified at the preoperative stage to predict the development of complications after mitral valve repair.

## MATERIAL AND METHODS

The research was performed in accordance with the standards of Good Clinical Practice and the principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of the Chelyabinsk Regional Clinical Hospital. Before inclusion in the research, written informed consent was obtained from all the participants.

The study included 103 patients (46 males and 57 females) who were treated in the Cardiac Surgery Department of the Chelyabinsk Regional Clinical Hospital No. 1 from 2014 to 2019 and underwent surgical correction of mitral valve disease.

Among those patients, the presence of anemia at the preoperative stage (blood hemoglobin level less than 100 g/l) was detected in 13 cases (12.6%); obesity (BMI more than 30 kg/m<sup>2</sup>) - in 57 (55.3%); blood transfusion and its components in the anamnesis - in 14 (13.6%); type 2 diabetes mellitus - in 7 (6.8%); acute cerebrovascular accident (ACVA) in the anamnesis - in 9 (8.7%); chronic hepatitis C - in 6 (5.8%); HIV infection - in 4 cases (3.9%); antibiotic therapy before surgery was indicated in 21 cases (20.4%); edema of the lower extremities (LE) was detected in 40 cases (38.8%); increased body temperature before surgery - in 19 (18.4%); and the presence of AF before surgery - in 63 (61.2%) cases. The patients participating in the research underwent a clinical and instrumental examination, including electrocardiography (ECG), echocardiography (ECHO-CG), and coronary angiography if indicated.

**Statistical processing.** The systematization of the source information was entered into a Microsoft Office Excel 2016 spreadsheet. Statistical analysis was carried out using IBM SPSS Statistics v. 26 (developed by IBM Corporation).

The normality of the distribution of quantitative indicators was determined using the Shapiro–Wilk test. If the distribution of values was normal, the mean and standard deviation were used; and the Student's *t* test was used to assess statistical significance. If the distribution of values did not correspond to normal, the median and quartiles were used. To determine the significance of differences in pairwise comparisons, the Mann–Whitney *U* test was used. When assessing qualitative indicators, descriptive statistics are presented in absolute numbers and percentages. The statistical significance of differences in qualitative indicators was assessed using the  $\chi^2$  test or Fisher's exact test (with expected frequencies lower than 10). Binary logistic regression was used as a method of mathematical data analysis. The building of the logistic regression model was carried out by the method of step-by-step inclusion of prognostic factors with the determination of the minimum set of predictors by assessing the value of the Nagelkerke's coefficient of determination  $R^2$ , showing the share of influence of all the model predictors on the variance of the dependent variable. The statistical significance of the model was checked using the  $\chi^2$  test. If the *p* value was less than 0.05, the hypothesis of statistical insignificance of the model was rejected. The fit of the model to the data used was assessed using the Hosmer and Lemeshow goodness-of-fit test. When *p* is more than 0.05, the hypothesis of model consistency was accepted. The interpretation of the logistic regression parameters was based on the exp (*B*) value: if the coefficient *B* is positive, then exp (*B*) is greater than 1, and the chances that the predicted event occurs increase; a negative value of the coefficient *B* indicates a decrease in the odds (exp(*B*)<1). The sensitivity and specificity of the predictors were assessed using ROC analysis.

Quantitative interpretation of the results was performed using ROC curves with an assessment of the AUC indicator (Area under the ROC curve).

## RESULTS

The logistic regression model can be represented mathematically as a dependence of the logarithm of the chance of the predicted event occurs (logit) on a linear combination of factor variables. Accordingly, the probability of the predicted event can be expressed through the following equation:

$$p = 1 / (1 + e^{-z}) \cdot 100\%, \\ z = a_0 + a_1 \cdot X_1 + \dots + a_n \cdot X_n,$$

where, *p* is the probability of the predicted event (%), *e* is a mathematical constant of 2.72, *z* is the degree of the exponential function, *a*<sub>0</sub> is the model constant, *a*<sub>1</sub> is the coefficient of the independent variable *X*<sub>1</sub>, showing the change in logarithmic odds caused by a single change in the variable, and *n* is the serial number of the predictor included into the equation.

Logistic regression models were built with each predictor included in turn, resulting in a statistically significant regression model. The values of the model coefficients are presented in Table 1.

As can be seen from the table, all coefficients are statistically significant and have an impact on the dependent variable. Thus, the probability of developing complications after mitral valve surgery can be represented by the following equation (1):

$$P = 1 / (1 + e^{-z}) \cdot 100\%, \\ z = -5,53 + 4,6 \cdot X_{ANEM} + 4,04 \cdot X_{OBES} - 2,25 \cdot X_{EDLE} + \\ + 1,66 \cdot X_{RA} - 2,43 \cdot X_{PA} \quad (1),$$

where, *P* is the probability of developing complications (%); *X*<sub>ANEM</sub> is the anemia before surgery (blood hemoglobin level less than 100 g/ml; 0 – absence, 1 – presence); *X*<sub>OBES</sub> is the obesity before surgery (BMI>30 kg/m<sup>2</sup>; 0 – absence, 1 – presence); *X*<sub>EDLE</sub> is the edema of the lower extremities (LE) before surgery (0 – absence, 1 – presence); *X*<sub>RA</sub> is the size of the right atrium (RA) (cm); *X*<sub>PA</sub> is the diameter of the pulmonary artery (PA) trunk (cm).

Table 1

**Summary data on the regression model for the development of complications after mitral valve surgery at the ninth step**

	B	Mean square error	Values	Exp (B)	95% CI for Exp (B)	
					Lower	Upper
Anemia	4.597	1.485	0.002	99.226	5.408	1820.751
Obesity	4.042	1.587	0.011	56.926	2.539	1276.338
Edema of the lower extremities	-2.253	1.108	0.042	0.105	0.012	0.922
Pulmonary artery	-2.435	0.933	0.009	0.088	0.014	0.545
Right atrium	1.665	0.700	0.017	5.287	1.341	20.849
Constant	-5.532	3.707	0.136	0.004		

Notes: CI – confidence interval, B – coefficient in the equation, Exp (B) shows how many times the chance of the occurrence of the event under study will change if the value of one of the predictors changes by one with fixed values of the other predictors

Based on the values of regression coefficients, the presence of anemia, obesity, and the size of the RA have a direct relationship with the likelihood of developing a complication. However, the influence of edema of the LE and the diameter of the PA trunk have an inverse relationship with the likelihood of developing complications. Anemia before surgery increases the chances of developing a complication by 99.2 times (95% CI (confidence interval): [5.41–1820.75]); obesity before surgery increases the chances of developing a complication by 56.92 times (95% CI: [ 2.54–1276.34]); an increase in the size of the RA by 1 cm increases the chances of developing a complication by 5.29 times (95% CI: [1.34–20.85]).

However, the presence of edema of the LE before surgery reduces the chances of developing a complication by 9.52 times (1/0.105) (95% CI: [0.012–0.92]); an increase in the diameter of the PA trunk by 1 cm reduced the chances of developing a complication by 11.36 times (1/0.088) (95% CI:[0.014–0.545]).

Figure 1 compares the values of the adjusted odds ratio with 95% CI for the studied factors included in the model (1).

The threshold value of the logistic function P was determined using the ROC curve analysis method. The resulting curve is shown in Figure 2.

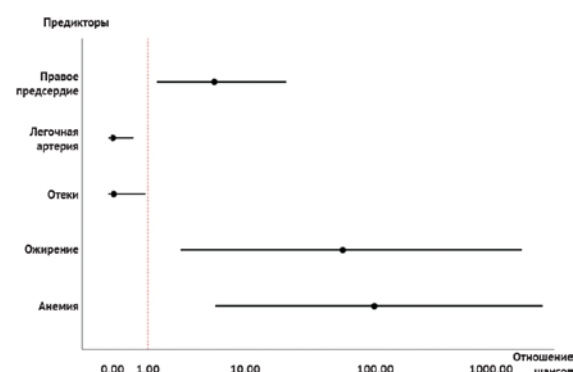


Fig. 1. Estimates of odds ratios with 95% confidence intervals for the studied predictors of detection of complications after surgery

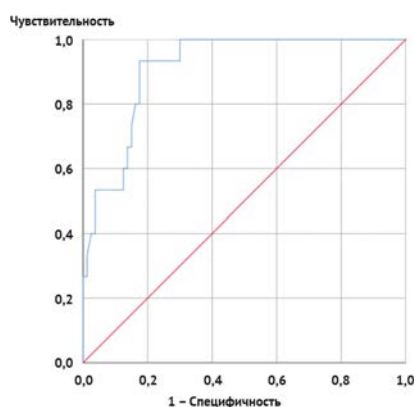


Fig. 2. ROC curve characterizing the dependence of the likelihood of developing complications on the values of the prognostic function (1)

As can be seen from Fig. 2, the area under the ROC curve was  $0.91 \pm 0.03$  (95% CI: [0.85–0.97]). The value of the logistic function (1) at the cut-off point was 17.2%. P values  $>17.2\%$  were defined as a high risk of complications, and P values less than 17.2% were defined as a low risk of complications. The sensitivity and specificity of the model (1) at this threshold were 93.3% and 82.5%, respectively.

The probability of developing a complication resulting from the influence of these signs is 53.4%.

The resulting model predicts the absence of complications with a probability of 82.5%. The development of complications was correctly predicted in 93.3% of cases.

This model can be used as an additional tool in predicting the development of complications after mitral valve repair. In particular, risk factors for the development of complications are the presence of anemia, obesity, an increase in the size of the RA; and an increase in the diameter of the PA trunk and the presence of edema of the LE are protective factors.

## DISCUSSION

Detection of risk factors for the development of complications in patients with cardiovascular pathology is possible during initial contact with them. In a literature review assessing obesity as a risk factor for cardiovascular disease (CVD), with an emphasis on ultrasound [3], intra-abdominal fat thickness (IAFT) was identified as a parameter. The relationship of IAFT with cardiovascular risk factors has been studied by several researchers [4]. Thus, they found a positive correlation of IAFT with total cholesterol (TCH) and blood levels of glucose [5], insulin, high-density lipoprotein (HDL), and triglycerides (TG) [6, 7]. IAFT was also associated with carotid intima-media thickness [8]. In general, most authors agree that IAFT is better suited for assessing regional obesity, and shows good predictive value for identifying CVD risk [9]. The next indicator was the abdominal wall fat index (WFI). It was shown that it decreased with increasing BMI, and positively correlated with blood levels of TG ( $r=0.37$ ,  $p<0.01$ ) and uric acid ( $r=0.40$ ,  $p<0.001$ ) in the 1st quartile of BMI (30.2–36.4); and negatively correlated with the level of HDL ( $r=-0.32$ ,

$p<0.001$ ) in the 3rd quartile of BMI (40.6–45.1) (statistically significant in all the cases) [10, 11]. This may indicate an ambiguous effect of this indicator on the risk factors for CVD in individuals with different body weights. Additionally, preperitoneal fat thickness (PFT) is associated with the degree of coronary artery stenosis and lipid abnormalities in nonobese men. When studying patients with the presence of coronary artery disease (CAD), but without obesity, a positive relationship was found between PFT and the severity of coronary artery stenosis ( $r=0.246$ ,  $p<0.05$ ). Moreover, PFT correlated positively with TCH ( $r=0.259$ ,  $p<0.01$ ), TG ( $r=0.205$ ,  $p<0.05$ ) and HDL ( $r=0.205$ ,  $p<0.05$ ), and negatively – with serum HDL level ( $r=-0.261$ ,  $p<0.01$ ) (statistically significant in all the cases). Thus, PFT showed a positive association with the severity of coronary artery stenosis and dyslipidemia. This fact allows this indicator to be used as one of the markers of poor prognosis in men with CAD [10, 11]. The thickness of the epicardial adipose tissue (EAT), when it increases due to the anatomical proximity to the coronary arteries, actively contributes to the development and progression of coronary atherosclerosis. EAT thickness has endocrine, paracrine, vasocrine and inflammatory effects and is associated with metabolic syndrome, insulin resistance, CAD and hypertension. Consequently, measurement of EAT thickness has become important for identifying risks of CVD progression [12–14].

In modern literature, the identification of cardiac biomarkers plays an important role in predicting complications. Thus, in a study on determining the role of markers for ischemia and reperfusion injuries in patients with ST-segment elevation acute coronary syndrome (ST-ACS), it was proven that more informative indicators in assessing the risk of developing microvascular damage phenomena are the initial blood value of N-terminal pro-brain natriuretic peptide (NT-proBNP), as well as levels of cardiac troponin I (eTnI), high-sensitivity C-reactive protein (hsCRP), soluble stimulating growth factor (sST2) after percutaneous coronary intervention [15]. These findings are supported by an expert panel review on

CVD risk stratification published in 2021, which suggested complementing the scores with biomarkers that have the ability to predict CVD risk. One such biomarker is troponin I (TnI) [16].

Besides laboratory markers, there are a number of studies on predicting complications based on data from instrumental research methods. Thus, for the first time, in a research on predicting reverse remodeling against the background of cardiac resynchronization therapy (CRT), the diagnostic value of a longer duration of the QRS complex, changes in the direction of the interventricular septum vector, slow transseptal conduction, a U-shaped activation pattern and changes in the direction of repolarization of the left ventricle, identified by ECG data, were established. A mathematical model was proposed for predicting reverse remodeling during CRT based only on ECG signs [17].

In the present study, the prognostic model was built to determine the likelihood of complications after mitral valve surgery. RFs, as well as data from instrumental research methods that may increase the chances of developing an unfavorable outcome were identified. This mathematical model can be used to determine the probability of a complication occurring with a sensitivity of 93.3% and specificity of 82.5%.

## CONCLUSION

The presence of risk factors such as anemia, obesity, and an increase in the size of the right atrium can be used as an independent variable to predict the development of complications. An

increase in the diameter of the pulmonary artery trunk and the presence of edema of the lower extremities reduce the risk of complications. The probability of developing complications after mitral valve surgery, predicted by the logistic regression, was 53.4%.

## FINDINGS

Based on the results of our study, it was determined that the presence of anemia, obesity, and RA size have a direct relationship with the likelihood of developing complications. However, the influence of LE edema and the diameter of the PA trunk have an inverse relationship with the likelihood of developing complications. Anemia before surgery increases the chances of developing a complication by 99.2 times (95% CI (confidence interval): [5.41–1820.75]), obesity before surgery increases the chances of developing a complication by 56.92 times (95% CI: [ 2.54–1276.34]), an increase in the RA size by 1 cm increases the chances of developing a complication by 5.29 times (95% CI: [1.34–20.85]).

But, the presence of LE edema before surgery reduces the chances of developing a complication by 9.52 times (1/0.105) (95% CI: [0.012–0.92]), an increase in the diameter of the PA trunk by 1 cm reduced the chances of developing a complication by 11.36 times (1/0.088) (95% CI:[0.014–0.545]). The resulting model predicts the absence of complications with a probability of 82.5%. The development of complications was correctly predicted in 93.3% of cases.

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**Received on 06/01/2022**

**Review completed on 08/02/2022**

**Accepted on 26/09/2023**