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Clinical and Laboratory Parameters and Complication Rates In Patients With Myocardial Infarction Without Obstructive Coronary Artery Disease

Aim	To evaluate clinical, anamnestic and laboratory data and the incidence rate of complications in patients with myocardial infarction (MI) without obstructive coronary artery (CA) disease.
Material and methods	This study included 158 patients with MI without obstructive CA disease (main group), 150 patients with MI and obstructive CA disease (comparison group), and 55 patients without documented ischemic heart disease (IHD) (control group). Clinical and anamnestic data, carbohydrate and lipid metabolism, concentrations of high-sensitivity troponin and C-reactive protein (CRP) were evaluated, and electrocardiography, Holter electrocardiogram monitoring, echocardiography, and coronary angiography were performed for all patients.
Results	The incidence rate of MI without obstructive CA disease was 1.9%, which was in general consistent with international data. Patients with MI without obstructive CA disease were somewhat younger than patients of the comparison group. Traditional risk factors, such as arterial hypertension (AH), acute cerebrovascular disease, diabetes mellitus (DM), and obesity were more frequently observed in patients with MI and obstructive CA disease, but the body weight index was significantly higher in MI patients without obstructive CA disease. The multivariate regression analysis identified the most significant factors associated with the development of MI in the group without obstructive CA disease: lipid metabolism disorders, AH, DM, male gender, smoking, and family history of IHD. Patients with MI without obstructive CA disease had a lower troponin level but a higher CRP level. Patients with MI without obstructive CA disease had a higher left ventricular (LV) ejection fraction (EF); acute heart failure (AHF), acute LV aneurism, and arrhythmias were the most frequent complication in this group.
Conclusion	Patients with MI without obstructive CA disease had a higher LV EF, and their most frequent complications were AHF, acute LV aneurism, and arrhythmias.

Keywords	Myocardial infarction without obstructive coronary artery disease; risk factors for myocardial infarction; clinical and laboratory characteristics
For citation	Suspitsyna I.N., Sukmanova I.A., Safonova E.A. Clinical and Laboratory Parameters and Complication Rates In Patients With Myocardial Infarction Without Obstructive Coronary Artery Disease. Kardiologiia. 2023;63(7):16–22. [Russian: Суспицына И.Н., Сукманова И.А., Сафонова Е.А. Клинико-лабораторные показатели у пациентов с инфарктом миокарда без обструктивного поражения коронарных артерий. Кардиология. 2023;63(7):16–22].

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Introduction

Acute myocardial infarction (MI) is caused in most patients by a damage to the atherosclerotic plaque, atherothrombosis of obstructive coronary arteries; however, some patients with confirmed MI do not have no obstructive lesions of coronary arteries according to coronary artery angiography (CAG) (non-obstructive coronary arteries or less than 50% stenosis) [1]. The heterogeneity of the mechanisms of myocardial infarction with non-obstructive coronary arteries (MINOCA) also contributes to the variability of treatment approaches for such patients. According to Pasupathy et al., Niccoli et al., Yoo. et al., the prevalence of MINOCA ranges from 1% to 14% [2, 3–5]. In a large meta-analysis of 27 studies (176,502 patients), coronary artery obstruction was not detected by CAG in 6% of patients with MI [6]. According to the Russian registers, the incidence of MINOCA in different studies ranged from 4.1% to 14.5%. The variations in the prevalence of this disease may be due to the use of different definitions, for example, the inclusion of patients with takotsubo syndrome or myocarditis in this group [7–

ISSN 0022-9040. Kardiologiia. 2023;63(7). DOI: 10.18087/cardio.2023.7.n1996

9]. According to the meta-analysis by Pasupathy et al. [2], MINOCA is more common in patients with acute non-ST-segment elevation coronary syndrome (67%) and in younger patients. It is known that there are more women among patients with MINOCA than among patients with MI with obstructive coronary arteries (43% and 24%, respectively; $p < 0.001$) [10–12]. There are no characteristic clinical features for MINOCA – more often patients complain of retrosternal pain and signs of heart failure. According to the literature, despite the presence of common clinical signs, traditional risk factors (RFs) for cardiovascular diseases are registered relatively less often in patients with MINOCA than in patients with classical MI [9]. The diagnosis criteria for MINOCA, which were first proposed by the European Society of Cardiology in 2017, include verified MI in the absence of coronary artery stenosis of ≥ 50% and the absence of other obvious causes of MI [13]. Prerequisites for the diagnosis of MINOCA are the exclusion of obvious extracardiac causes of increased levels of myocardial necrosis markers (for example, sepsis, pulmonary embolism (PE)); exclusion of lesions of small epicardial vessels (for example, complete occlusion of a small segment or the presence of significant stenosis of a distal coronary artery); and the exclusion of non-ischemic mechanisms of myocardial damage (myocarditis, takotsubo syndrome). Epicardial coronary artery disease (atherosclerotic plaque rupture, coronary artery dissection), thrombosis, or embolism in the absence of coronary artery wall lesions, endothelial dysfunction (large or small vessel spasm) are the main pathophysiological mechanisms of the development of MINOCA [14, 15]. Peculiarities of the development and course of MI, the incidence of complications in patients with MINOCA remain understudied and, thus, are a relevant issue of modern cardiology.

Objective

Evaluate clinical, anamnestic, and laboratory parameters, and the incidence of complications in patients with MINOCA.

Material and Methods

Retrospectively, 7,930 case records of patients with confirmed MI hospitalized in the Altai Regional Cardiology Dispensary were analyzed for the period from 2014 to 2018. It was found that, according to CAG, 158 (1.99%) patients with MI had normal coronary arteries or stenosis less than 50%. Among patients with MINOCA, 92 (58.2%) were male and 66 (41.8%) were female from 17 to 82 years old (mean age 55.2±1.1 years).

The inclusion criteria were the presence of MI confirmed by laboratory tests and clinical examinations and signed informed consent.

Exclusion criteria were acute or exacerbated chronic inflammatory diseases, sepsis, pulmonary embolism, pericarditis, myocarditis, and other causes of secondary myocardial damage, refusal of CAG, contraindications to CAG.

The comparison group consisted of 150 patients with MI and obstructive coronary arteries (more than 50% stenosis of one or more coronary arteries) from 43 to 78 years old (mean age 58.9±0.63 years), including 91 (60.7%) male and 59 (39.3%) female patients.

The control group consisted of patients who did not have documented coronary artery disease (CAD) (n=55), including 34 male and 21 female patients from 45 to 74 years old (mean age 59.1±1.2 years).

All patients underwent conventional laboratory tests and clinical examinations as well as the assessment of complaints, anamnesis, and physical examination. MI was diagnosed based of the Fourth Universal Definition of MI: combined data of the clinical picture, elevated levels of high-sensitivity troponin over time, documented myocardial ischemia, ECG data over time, echocardiogram, given the absence of coronary artery obstruction according to CAG [16]. The severity of acute heart failure (HF) was assessed using the Killip classification. Carbohydrate, lipid profile, C-reactive protein (CRP) were estimated in all patients of the main, comparison, and control groups; they also underwent echocardiography and CAG. High-sensitivity troponin test was performed at least 2 times at an interval of 3–6 hours. All patients underwent multiple 12-lead ECG exams, and 12-lead Holter monitoring was carried out for 24 hours.

All patients received standard drug therapy according to the current clinical guidelines: dual antiplatelet therapy, including acetylsalicylic acid and P2Y12 inhibitor, anticoagulants, statins, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, beta-blockers (if indicated and not contraindicated).

The study was approved by the ethics committee of the Altai Regional Cardiology Dispensary. All included patients signed the informed consent to participate in the study.

Statistical analysis

Excess and asymmetry characterizing the shape of the distribution curve were used in the statistical processing of the data obtained to assess the nature of distribution of the indicators. Continuous variables

are expressed as M±m, where M is a sample mean and SE is a standard error of mean. The means were compared using the Student t-test in case of a normal distribution and equality of variances. Nonparametric chi-square test was used to compare qualitative indicators. The significance threshold for the null hypothesis was p=0.05. The data obtained were processed in Statistica v.10.0.

Multivariate binary logistic regression analysis was conducted to determine the risk factors. Statistical processing produced the parameters of the linear regression equation: $y=b0 + b1\times1 + b^2\times2+\ldots$, where y is the value of the logistic regression function; b0 is the absolute term of the equation; b1, b^2... are regression weight coefficients that reflect the contribution of each factor in the object classification. The results of Rosenbrook analysis and quasi-Newton analysis showed that the studied factors have a statistically significant collective effect (χ^2=46.1; p<0,001) on the classification results.

Results

The analysis revealed that the female-to-male ratio was almost equal in the study groups (58% of male versus 42% of female patients in the main group and 61% of male versus 39% of female patients in the comparison group; p = 0.439). Patients with MI and obstructive coronary arteries were older (Table 1) that patients with MINOCA (p=0.003). It was detected that 107 (67.7%) patients in the main group had normal coronary arteries, and 51 (32.3%) patients had a non-obstructive lesion with atherosclerotic plaques narrowing the lumen by less than 50%. ST-segment elevation myocardial infarction (STEMI) was diagnosed more often in patients with obstructive coronary arteries (p = 0.009). The evaluation of RFs revealed that patients with MI and obstructive coronary arteries were more likely to have family history of CAD (p=0.000; see Table 1). There were also statistically significantly more smoking patients in the comparison group (p=0.000). The analysis of concomitant pathology determined that arterial hypertension (AH) was determined in patients of both groups with almost similar high frequency (p=0.794). Significantly more patients with MI and obstructive coronary artery atherosclerosis had the history of type 2 diabetes mellitus (DM) (p=0.003). Atrial fibrillation and atrial flutter were more common in patients with MI and obstructive coronary artery atherosclerosis (p=0.000). There were no statistically significant differences in the incidence of obesity between the groups compared (p=0.127). However, mean body mass index (BMI) was 29.2 ± 0.4 kg/m² in the main group and 27.8 ± 0.4 kg/m² in the comparison group (p=0.018). There were no statistically significant differences in the number of patients with chronic heart failure (CHF) in the groups (p = 0.065). The history of cerebrovascular accident (CVA) was observed more often in patients with MI and obstructive coronary arteries (Table 1) in patients of the main group (p=0.011).

According to CAG, 112 (70.9%) patients with MINOCA did not have atherosclerotic plaques; 24 (15.2%), 4 (2.5%), 6 (3.8%), and 9 (5.7%) patients had hemodynamically insignificant (less than 50%) narrowing of the anterior interventricular artery, circumflex artery, right coronary artery, and two coronary arteries, respectively. In the comparison group, 81 (54%) patients multivessel CAD, and 17 (11.3%) patients had left main coronary artery lesion. Two-vessel CAD was diagnosed in 46 (30.7%) patients with

Table 1. Clinical and anamnestic characteristics of the patients of the main group and the comparison group

Parameter	Main group (n = 158), n (%)	Comparison group (n = 150), n (%)	p
Age, years	55.2 ± 1.1	58.9 ± 0.63	0.003
Family history of CAD	16 (10.1)	49 (32.6)	0.000
Smoking	73 (46.2)	99 (66)	0.000
DM type 2	24 (15.1)	40 (26.7)	0.003
AF/AFL	20 (12.6)	45 (30)	0.000
CHF	19 (12)	32 (21.3)	0.065
CVA	13 (8.2)	27 (18)	0.011
Obesity	56 (35.4)	68 (45.3)	0.127
AH	120 (76)	112 (74.7)	0.794
STEMI	96 (60.8)	112 (74.7)	0.009
Q-wave myocardial infarction	53 (33.5)	103 (68.7)	0.000

AF/AFL, atrial fibrillation/atrialflutter; CVA, cerebrovascular accident; STEMI, ST-segment elevation myocardial infarction.

Table 2. Laboratory indicators in the study groups

Parameter	Main group (n = 158)	Control group (n = 150)	p
Troponin, ng/mL			
• At admission (normal < 0.05 ng/mL)	0.88 ± 0.14	2.95 ± 0.36	0.000
• In 6 hours	5.67 ± 0.9	17.7 ± 1.6	0.000
TC, mmol/L	4.5 ± 0.1	4.6 ± 0.1	0.820
LDL cholesterol, mmol/L	2.6 ± 0.08	2.6 ± 0.1	0.820
HDL cholesterol, mmol/L	1.1 ± 0.03	1.0 ± 0.03	0.012
TG, mmol/L	1.8 ± 0.09	1.91 ± 0.08	0.258
CRP, mg/L	42.4 ± 6.9	26.2 ± 2.6	0.030

ISSN 0022-9040. Kardiologiia. 2023;63(7). DOI: 10.18087/cardio.2023.7.n1996

MI and obstructive coronary arteries, and 23 (15.3%) patients had single-vessel disease. Q-wave MI was diagnosed in the majority of patients with obstructive coronary arteries (n=103 (69%)), and MI resulted in the formation of a Q-wave only in 53 (33.5%) patients in the group with non-obstructive coronary atherosclerosis (p = 0.000).

Moreover, it should be noted that, in the main group, troponin I level (Table 2) was 0.88±0.14 ng/ml at admission and 5.67±0.9 ng/mL in 6 hours, which is statistically significantly less than those in the comparison group – 2.95±0.36 ng/mL (p=0.000) and 17.7±1.6 ng/mL (p=0.000), respectively. Results of lipid profile showed dyslipidemia in most patients in both groups, with a predominant frequency in the MINOCA group – 134 (84.8%) and 108 (72%), respectively (p=0.006). Total cholesterol was elevated in 104 (65.8%) patients of the main group and 98 (65.3%) patients of the comparison group (p=0.928). Low-density lipoprotein (LDL) cholesterol was elevated in 132 (83.5%) patients with MINOCA and 104 (69.3%) patients of the comparison group (p=0.003). Hypertriglyceridemia was established in 58 (36.7%) patients of the main group and 66 (44%) patients of the comparison group (p=0.192). Thus, despite the absence of statistically significant differences between the absolute values of most lipid profile indicators, it is possible to mention a larger number of patients with dyslipidemia, particularly elevated LDL cholesterol, in the main group, and relatively more patients with hypertriglyceridemia in the group with non-obstructive coronary arteries. This may be due to the frequency of lipid-lowering therapy. CRP level in patients with MINOCA was 42.4±6.9 ng/L, which was higher than in patients of the comparison group – 26.2±2.6 ng/L (p=0.030) (Table. 2).

The echocardiography results revealed that LVEF was within the normal range in the main group (61.1±0.8%); 14 (8.9%), 39 (24.7%), and 26 (16.4%) patients had 1, 2, and 3 zones of LV hypokinesia. LVEF was lower (56.2 ± 0.7%) in patients with obstructive coronary arteries than in the main group (p=0.000). In the comparison group, 25 (16.7%) and 43 (28.7%) patients had 1 and 2 zones of hypokinesia, respectively, and a statistically significant majority of patients with MI and obstructive coronary arteries (58 (38.7%)) had 3 or more zones of LV hypokinesia (p = 0.000).

The course of the disease was complicated by cardiac arrhythmias in 32 (20.3%) patients of the main group and 47 (31.3%; p = 0.026) patients of the comparison group. Life-threatening arrhythmias were diagnosed in a statistically significantly larger number of patients with obstructive coronary arteries compared to the main group – 18 (12%) and 7 (4.4%), respectively (p=0.015). Acute HF was diagnosed in 20 (12.7%) patients with MINOCA, and 57 (38%) patients had signs of acute HF of the comparison group (p<0.001). The comparison the acute HF incidence revealed that acute HF (Killip class II) was detected in 14 (9%) patients of the main group, acute HF (Killip class III) in 5 (3%) patients, and cardiogenic shock (acute HF Killip class IV) in 1 (0.6%) patient. In the comparison group, there were significantly more patients with acute HF: cardiogenic shock was detected in 8 (5.3%) patients (p=0.042), pulmonary edema (Killip class III) in 15 (10%) patients (p=0.037), and acute HF (Killip class II) in 34 (22.7%) patients (p=0.0003).

Postinfarction angina pectoris was more often detected in patients with MI and patients with obstructive coronary arteries – 40 (26.7%) and 9 (5.7%), respectively (p<0.001). The course of the disease was complicated by acute LV aneurysm in 11 (7%) patients of the main group and in 28 (18.7%) patients with MI and obstructive coronary arteries (p = 0.002).

The analysis of the disease outcomes revealed no deaths in the group of patients with non-obstructive coronary arteries, all were discharged for further outpatient follow-up. In the comparison group (MI with obstructive coronary arteries), 2 patients died (one on day 9 of hospital stay, another one on day 11; ventricular fibrillation was the cause of death in both cases).

Multivariate binary logistic regression analysis was carried out to identify the RFs associated with the development of MI in the group of patients with non-obstructive coronary arteries. The strongest factors were selected, which were included in the final regression equation (Figure 1; Table 3).

The final linear regression equation was as follows:

$$y = -2.308 - 0.0258 \times Age + 0.0456 \times GFR + 2.763 \times TC + 0.3748 \times TG - 4.174 \times LDL - 0.1516 \times HDL + 0.1299 \times CRP - 0.0088 \times BMI + 0.3789 \times Male + 0.4272 \times Smoking + 0.6336 \times Heredity + 2.127 \times HHD + 0.620 \times DM$$

The adequacy analysis of the resulting regression model revealed its high sensitivity – 89.2% (Table 4).

The residual probabilities differ insignificantly on average from the expected normal deviation, which is indicative of the high quality of the regression model (Figure 1).

Our findings showed that disorders of lipid metabolism, male sex, smoking, family history of CAD, AH, and DM were the factors most associated with the development of MI in the group of patients with MINOCA.

Table 3. Logistic regression model

Regression equation parameters	Constant	Age	GFR	TC	TG	LDL cholesterol	HDL cholesterol	CRP	BMI	Sex	Smoking	Heredity	HHD	DM
Regression coefficient	–0.308	–0.0258	0.0456	2.763	0.3748	–4.147	–1,516	0.1299	–0.008	0.3789	0.4272	0.6336	2.127	0.620
Odds ratio	10.057	1.0262	0.9555	0.063	0.6874	64.9874	1.1637	0.8782	1.0088	1.4607	1.5329	1.8844	8.386	1.860

Table 4. Estimation of the adequacy of the classification model using the regression model

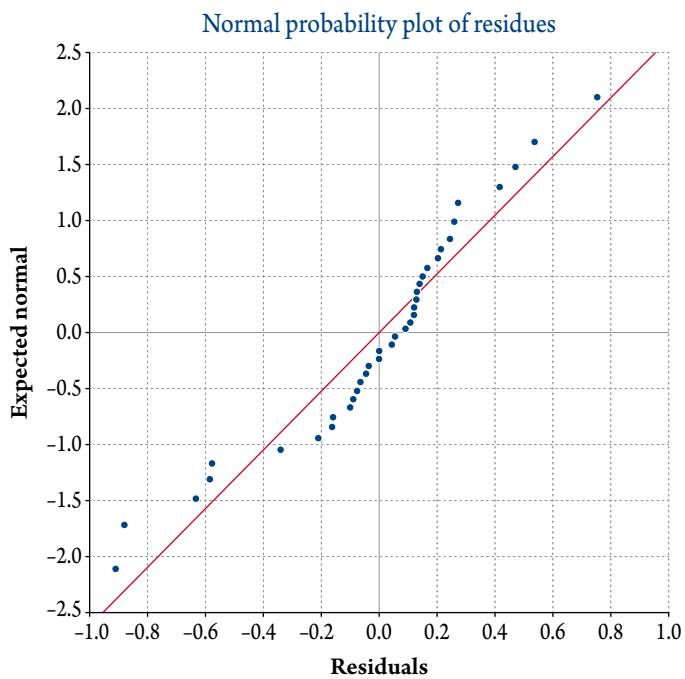
Observed result	Cardiovascular events	No cardiovascular events	Number of correct predictions, %	Total number of correct predictions, %	OR (95 %CI)
Cardiovascular events	58	7	89.2	80.2	11.3 (3.7–34.1)
Absence of cardiovascular events, n (%)	11	15	57.7		

OR, odds ratio; CI, confidence interval.

Discussion

Thus, the incidence of MINOCA is 1.9%, which is consistent with the current literature data, although there are only few studies on this MI variant in our country. The study found that patients with MINOCA were younger than those with MI and atherosclerotic stenosis (p=0.003), STEMI was diagnosed less often in this group (p = 0.009). Traditional RFs, such as smoking (p = 0.000), family history of CAD (p=0.000), AH, obesity, history of CVA, and type 2 DM, were less common in patients with non-obstructive coronary arteries. Patients with MINOCA had lower levels of troponin, which is associated with a smaller area of myocardial damage and the predominance of non – Q-wave MI. Higher levels of CRP in this group of patients (p = 0.030) are indicative of the leading role of inflammatory and pro-inflammatory mechanisms in the development of the disease. Moreover, patients of the main group had higher LVEF (p=0.000), which is a manifestation of hemodynamically significant LV remodeling due to a larger area of myocardial ischemia in patients with obstructive coronary artery atherosclerosis. However, most frequent complications of MI in patients with MINOCA were acute HF (12.7%), acute LV aneurysm (6.69%), and cardiac arrhythmias (20.3%), although they were less common than in the group of patients with obstructive coronary arteries.

Figure 1. Graphical presentation of logistic analysis (plot of residuals)



The most significant factors associated with the development of MI in the group with non-obstructive coronary arteries were determined based on the results of multivariate regression analysis. Those were lipid metabolism disorders, AH, type 2 DM, male sex, smoking, and family history of CAD.

The data obtained during the study are of scientific interest for modern cardiology and will contribute to the continuation of further research in this area, particularly a detailed study of the mechanisms of development and features of the course of the disease in order to optimize approaches to the treatment of MINOCA. It is obvious that each patient with MINOCA requires an individual approach. The treatment of such patients should be based on the verified cause in each individual case, and secondary prevention programs should also be personalized.

Conclusions

1. The incidence of myocardial infarction with non-obstructive coronary arteries was 1.9%, which is generally consistent with the literature data.

ISSN 0022-9040. Kardiologiia. 2023;63(7). DOI: 10.18087/cardio.2023.7.n1996

2. Patients with myocardial infarction with non-obstructive coronary arteries were younger, fewer patients were smokers, had family history of coronary artery disease, atrial fibrillation, and diabetes mellitus. However, the incidence of obesity and arterial hypertension was comparable to that in the group of patients with obstructive coronary artery atherosclerosis.
3. Dyslipidemia, arterial hypertension, type 2 diabetes mellitus, male sex, smoking, and family history of coronary artery disease are the most significant factors associated with the development of myocardial infarction in patients with non-obstructive coronary arteries are.
4. Patients with myocardial infarction and non-obstructive coronary arteries had higher levels of C-reactive protein, which determines the leading role of inflammatory and pro-inflammatory mechanisms in the development of the disease.
5. Acute heart failure (12.7%), left ventricular aneurysm (6.69%), and cardiac arrhythmias (20.3%) were the most common complications in patients with myocardial infarction and non-obstructive coronary arteries.

Funding

No funding was received for this study.

No conflict of interest is reported.

The article was received on 20/02/2022

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ISSN 0022-9040. Kardiologiia. 2023;63(7). DOI: 10.18087/cardio.2023.7.n1996