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Phenotypes of the no-reflow phenomenon during percutaneous coronary interventions in myocardial infarction

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ABSTRACT

Aim. Using the cluster analysis, to determine and describe clinical and pathogenetic phenotypes of the coronary microvascular obstruction phenomenon (CMVO) that occurs during percutaneous coronary interventions (PCI) in patients with myocardial infarction (MI).

Materials and methods. The study included 190 patients with CMVO that occurred during PCI for type 1 MI: 137 (72%) men, 53 (28%) women, the median age was 64 [56; 70] years. The study was conducted in 2013–2020. CMVO criteria: blood flow < 3 points in the infarct-related artery (IRA) according to the TIMI flow grade (TFG); perfusion < 2 points according to the Myocardial Blush Grade; ST segment resolution < 70%. ST-elevation MI (STEMI) was found in 170 patients (89%). Primary PCI was noted in 127 (67%) cases. Nine patients (4.7%) died. Phenotyping was performed using the expectation – maximization (EM) algorithm.

Results. Three phenotypes were identified in a ratio of 56% (n = 106) / 27% (n = 52) / 17% (n = 32). The values of the parameters are the following, respectively: age 62 [54; 67] / 73 [67; 79] / 59 [50; 65] years; women 8 (8%) / 39 (77%) / 6 (19%); STEMI 102 (96%) / 43 (83%) / 25 (78%); thrombolysis 46 (43%) / 6 (12%) / 11 (34%); class 1 [1; 2] / 2 [1; 4] / 2 [2; 2] acute heart failure; platelet-to-lymphocyte ratio 110 [78; 153] / 106 [85; 132] / 132 [100; 182]; glucose at admission 8.0 [6.9; 9.6] / 11.1 [8.8; 15.2] / 7.5 [6.1; 8.1] mmol / l; total cholesterol 4.7 [4.2; 5.4] / 5.3 [3.7; 6.2] / 5.1 [4.5; 6.2] mmol / l; glomerular filtration rate according to CKD-EPI 77 [64; 88] / 58 [46; 74] / 81 [64; 88] ml /min / 1.73m^2; Syntax Score 15 [10; 21] / 20 [14; 26] / 8 [5; 10]; Syntax Score in the IRA 9 [8; 15] / 12 [7; 16] / 6 [3; 7]; coronary collaterals according to Rentrop: grade 0 [0; 1] / 0 [0; 1] / 0 [0; 0]; thrombosis of the IRA according to the TIMI thrombus grade 5 [5; 5] / 5 [3; 5] / 1 [0; 2]; TFG 0 [0; 0] / 0 [0; 1] / 2 [2; 3]; aspiration thrombectomy 30 (28%) / 7 (13%) / 4 (13%); IRA diameter 3.5 [3.0; 3.5] / 3.0 [2.8; 3.5] / 3.5 [3.0; 3.5] mm; balloon angioplasty 99 (93%) / 45 (87%) / 16 (50%); PCI of 2 or more arteries 0 (0%) / 4 (8%) / 3 (9%). Deaths – 2 (1.9%), 7 (13.5%), and 0 (0%) patients, respectively (p = 0.002, $\chi 2$ Pearson).

Conclusion. Three phenotypes were identified. Phenotype 1: severe IRA thrombosis, mostly men, moderate atherosclerotic lesions. Phenotype 2: mostly elderly women, high hyperglycemia, severe atherosclerotic lesions, severe AHF, impaired renal function, IRA thrombosis. Phenotype 3: mostly men, minor changes in the coronary arteries, absence of significant thrombosis and preserved blood flow in the IRA before PCI, elevated levels of inflammatory markers and total cholesterol.

Keywords: no-reflow phenomenon, myocardial infarction, percutaneous coronary intervention, cluster analysis, classification

Conflict of interest. The authors declare the absence of obvious and potential conflicts of interest related to the publication of this article.

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Conformity with the principles of ethics. All patients signed an informed consent to participate in the study. The study was approved by the local Ethics Committee at Privolzhsky Research Medical University (Protocol No. 5 of 08.04.2022).

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Фенотипы синдрома коронарной микрососудистой обструкции (no-reflow), развивающегося в ходе выполнения чрескожных коронарных вмешательств при инфаркте миокарда

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РЕЗЮМЕ

Цель: определить и охарактеризовать клинико-патогенетические фенотипы феномена коронарной микрососудистой обструкции (КМСО), возникающего при выполнении чрескожных коронарных вмешательств (ЧКВ) у пациентов с инфарктом миокарда (ИМ), используя метод кластеризации.

Материалы и методы. В исследование включены 190 больных с КМСО в ходе ЧКВ при ИМ I типа, в том числе 137 (72%) мужчин, 53 (28%) женщины. Медиана возраста – 64 [56; 70] года. Исследование проведено в 2013–2020 гг. Критерии КМСО: кровоток < 3 баллов в инфаркт-ответственной артерии (ИОА) по TIMI flowgrade (TFG); перфузия < 2 баллов по Myocardial blush grade; резолюция сегмента ST < 70%. ИМ с подъемом ST (ИМпST) у 170 больных (89%). Первичное ЧКВ наблюдалось в 127 (67%) случаях. Скончались 9 пациентов (4,7%). Фенотипирование осуществлялось с помощью алгоритма кластеризации (expectation-maximization – EM).

Результаты. Выявлены три кластера в соотношении 56% (n = 106) / 27% (n = 52) / 17% (n = 32). Значение параметров, соответственно: возраст 62 [54; 67] / 73 [67; 79] / 59 [50; 65] года; женщины 8 (8%) / 39 (77%) / 6 (19%); ИМпST 102 (96%) / 43 (83%) / 25 (78%); тромболитическая терапия 46 (43%) / 6 (12%) / 11 (34%); острая сердечная недостаточность 1 [1; 2] / 2 [1; 4] / 2 [2; 2] класса; отношение тромбоцитов к лимфоцитам 110 [78; 153] / 106 [85; 132] / 132 [100; 182]; глюкоза при поступлении 8,0 [6,9; 9,6] / 11,1 [8,8; 15,2] / 7,5 [6,1; 8,1] ммоль/л; общий холестерин 4,7 [4,2; 5,4] / 5,3 [3,7; 6,2] / 5,1 [4,5; 6,2] ммоль/л; скорость клубочковой фильтрации по CKD-EPI77 [64; 88] / 58 [46; 74] / 81 [64; 88] мл/мин/1,73 м^2; SyntaxScore 15 [10; 21] / 20 [14; 26] / 8 [5; 10] баллов; Syntax Score в ИОА 9 [8; 15] / 12 [7; 16] / 6 [3; 7] баллов; коллатерали по Rentrop 0 [0; 1] / 0 [0; 1] / 0 [0; 0] степени; тромбоз ИОА по TIMI thrombus grade 5 [5; 5] / 5 [3; 5] / 1 [0; 2] степени; TFG 0 [0; 0] / 0 [0; 1] / 2 [2; 3] степени; аспирационная тромбэктомия 30 (28%) / 7 (13%) / 4 (13%); баллонная ангиопластика 99 (93%) / 45 (87%) / 16 (50%); диаметр ИОА 3,5 [3,0; 3,5] / 3,0 [2,8; 3,5] / 3,5 [3,0; 3,5] мм; ЧКВ двух и более артерий 0 (0%) / 4 (8%) / 3 (9). Смертельные исходы – 2 (1,9%), 7 (13,5%) и 0 (0%) пациентов соответственно (p = 0,002; χ2-Пирсона).

Заключение. Определены три фенотипа. Фенотип 1: выраженный тромбоз ИОА, преимущественно мужчины, умеренное атеросклеротическое поражение. Фенотип 2: преимущественно женщины старческого возраста, высокая гипергликемия, выраженное атеросклеротическое поражение, тяжелая сердечная недостаточность, нарушенная функция почек, тромбоз ИОА. Фенотип 3: преимущественно мужчины, незначительные изменения коронарных артерий, отсутствие значимого тромбоза и сохраненный кровоток в ИОА до ЧКВ, повышенные уровни маркеров воспаления и общего холестерина.

Ключевые слова: инфаркт миокарда, коронарная микрососудистая обструкция, no-reflow, чрескожное коронарное вмешательство, кластеризация, фенотипирование, клинико-патогенетические фенотипы

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования: работа выполнена в рамках программы «Приоритет 2030».

Соответствие принципам этики. Все пациенты подписали информированное согласие на проведение исследования. Исследование одобрено локальным этическим комитетом ФГБОУ ВО «ПИМУ» Минздрава России (протокол № 5 от 08.04.2022).

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INTRODUCTION

Percutaneous coronary intervention (PCI) is the basic procedure for reperfusion in myocardial infarction (MI). In 5–10 % of cases, blood flow restoration in the infarct-related artery (IRA) does not lead to sufficient perfusion of the myocardium due to coronary microvascular obstruction (CMVO, no-reflow phenomenon) [1, 2]. CMVO is associated with increased in-hospital mortality and worse short-term and long-term survival rates [2].

It is worth noting that the data accumulated for the last years concerning risk factors and prognosis of CMVO evidence of advances in the medical science; however, the issue of developing new effective approaches to CMVO treatment is still unresolved. It is likely due to the multifactorial nature of the pathogenesis of this condition and clinical diversity of patient groups having this complication [3]. There are several mechanisms leading to CMVO; they can occur simultaneously and vary in different patients [4]. The existing data suggest that the risk of CMVO development is associated with the severity of IRA thrombosis, plaque features, severity and intensity of MI, systemic inflammations, carbohydrate metabolism disorders, and reperfusion features [5].

A rational approach to effective treatment of CMVO could be division of all patients with this complication into groups (clusters) with further identification of the leading pathogenetic mechanism in each group and determination of an appropriate therapy target. Currently only one pathogenetic classification of CMVO is known that distinguishes the following mechanisms: 1) microthromboembolism; 2) ischemic injury; 3) reperfusion injury; 4) individual susceptibility [3]. It should be noted that this classification was made up empirically and for the following 13 years, no effective therapeutic algorithm has been developed on its basis. The reason for such an ineffective empirical approach may be an impossibility to correlate scattered theoretical data concerning the pathogenesis of CMVO with clinically available markers.

To create an objective and practically-oriented classification, mathematical methods, including different clustering techniques, can be used. To date such approaches to resolving the issue of CMVO have not been used.

The aim of the study: using the cluster analysis, to determine and describe clinical and pathogenetic phenotypes of CMVO during PCIs for MI.

MATERIALS AND METHODS

A retrospective study was conducted. Out of 18,079 patients admitted to Regional City Clinical Hospital No. 13 of the Nizhny Novgorod Avtozavodskoy District with the diagnosis of acute coronary syndrome in 2013–2020, 7,456 patients with type 1 MI were selected; they underwent emergency PCI. Among patients with MI and PCI, 232 (3.1%) patients were identified who developed CMVO during the surgery. The patients with restricted coronary blood flow and myocardial perfusion due to other causes (initial cardiogenic shock, spasm or dissection of the coronary artery, etc.) were excluded from the study. The mortality rate in this group was 13.8% (32 in-hospital deaths). Since the absence of missing data in the analyzed dataset is a necessary condition for a cluster analysis, the inability to obtain necessary data for organizational reasons and due to the retrospective nature of the study (mostly due to the lack of certain laboratory tests) became an additional exclusion criterion. Thus, 190 patients with MI who developed CMVO during PCI and had a complete dataset for the analysis were selected for the study. The study was approved by the local Ethics Committee.

The diagnosis of type 1 MI was made based on clinical, electrocardiographic, and biochemical criteria according to the third and fourth universal definitions [6]. The severity of acute heart failure (AHF) was assessed using the Killip classification [1].

The term PCI was used to refer to stent implantation in the IRA, resulting in epicardial coronary artery patency restoration with residual stenosis of less than 50% and exclusion of complications, such as dissection, perforation, persistent spasm or severe thromboembolism of the coronary artery (CA). The following scales were used to describe the CA anatomy and characterize the results of PCI: 1) Thrombolysis in Myocardial Infarction (TIMI) flow grade (TFG) [3] for assessing coronary blood flow in the IRA before and after PCI; 2) TIMI thrombus grade (TTG) [1] for assessing the severity of thrombus burden in the IRA after PCI; 3) Myocardial Blush Grade (MBG) [3] for assessing myocardial perfusion after PCI; 4) Rentrop [5] for grading collaterals to the IRA; 5) Syntax Score (SS) [1] – for quantitative description of the severity of atherosclerotic lesion in the CA (evaluated on the whole and in the IRA).

The CMVO phenomenon was diagnosed according to the guidelines of the European Society of Cardiology [7]: 1) TFG score of less than 3; 2) MBG score of less than 2; 3) less than 70% resolution of ST-segment changes on the electrocardiogram (ECG) within 60–90 minutes after PCI.

The median age was 64 [56; 70] years. The study included 137 (72%) men and 53 (28%) women. Of the 190 patients included in the study, 57 (30%) people had a history of coronary artery disease (CAD), and 52 (27%) individuals had a history of diabetes mellitus; 170 (89%) patients were admitted with ST-segment elevation myocardial infarction (STEMI). Upon admission, 4 (2%) patients had class III AHF; cardiogenic shock was diagnosed in 17 (9%) patients.

The median total SS was 15 [9; 21] and SS in the IRA was 9 [7; 15]. The left main coronary artery or the left anterior descending artery were defined as the IRA in 81 (43%) patients. Initial severe thrombosis of the IRA (TTG score 4–5) was detected in 146 (77%) patients, CA occlusion was found in 150 (79%) patients, no visible collaterals to the IRA (Rentrop grade 0–1) were noted in 170 (90%) patients. CA ectasia, according to the definition by P.S. Swaye [8], was diagnosed in 13 (7%) patients.

Of the 190 patients included in the study, primary PCI was performed in 127 (67%) patients, and a pharmacoinvasive strategy (systemic thrombolytic therapy preceding PCI) was applied in 63 (33%) patients. The symptom-to-balloon time (from the onset of the status anginosus to the blood flow restoration by PCI) was 9.7 [4.8; 16.0] hours. Stenting was combined with balloon angioplasty in 160 (84%) cases. Vacuum aspiration thrombectomy was performed in 41 (22%) patients, concurrent PCI on multiple CAs was performed in 7 (4%) patients. The median number of stents implanted was 1 [1; 2], the median length of the implanted stents was 30 [26; 51] mm, and the median stent inflation pressure was 14 [12; 15] atm. The median diameter of the IRA was 3.5 [3.0; 3.5] mm.

The following strategies were used in the operating room to treat CMVO: intracoronary administration of isosorbide dinitrate in 80 (42%) patients; intracoronary administration of verapamil in 43 (23%) patients; intra-aortic balloon counterpulsation in 10 (5%) patients; and glycoprotein IIb / IIIa inhibitors in 6 (3%) patients.

The median values of the key laboratory parameters on admission were as follows: glucose – 8.3 [7.0; 10.5] mmol / l, platelet-to-lymphocyte ratio (PLR) – 111 [83; 149], total cholesterol (TC) – 4.9 [4.1; 5.7] mmol / l, glomerular filtration rate (GFR) according to the CKD-EPI equation 76 [57; 86] ml / min / 1.73m^2, leukocytes – 11.3 [8.7; 14.2] × 10^9 / l, neutrophils – 5.1 [4.0; 6.6] × 10^9 / l, troponin I – 0.76 [0.10; 6.35] ng / ml.

After PCI, the resolution of ST-segment changes on ECG was observed in 110 (58%) patients, Q-wave myocardial infarction developed in 172 (91%) patients. The median left ventricular ejection fraction (LVEF) calculated by the Simpson's method was 46 [41; 50] % on discharge. Nine patients (4.7%) died in the hospital. The causes of death were: cardiogenic shock in 5 (56%) cases, mechanical complications of MI in 2 (22%) cases, pulmonary edema in 1 (11%) patient, and thromboembolic complications in 1 (11%) patient.

To conduct clustering, we selected certain parameters that were predictors of CMVO development according to the current literature on the topic [5]. From the anamnestic and clinical parameters, the following were assessed: age, gender, medical history of CAD, admission with STEMI, AHF class, hemodynamic status, and systemic thrombolytic therapy. Out of the parameters characterizing CAs and performed PCI, the following were noted: the symptom-to-balloon time, total SS, SS in the IRA, presence of CA ectasia, lesion in the stem of the left coronary artery or left anterior descending artery, lesion in the right coronary

artery, collateral grading according to Rentrop, IRA diameter, TTG, TFG, size of the CA atherosclerotic lesion, balloon angioplasty (pre- and post-dilation) or vacuum aspiration thrombectomy, number, length, and implantation pressure of stents, concurrent stenting of multiple CAs. Laboratory tests performed on admission were the following: blood glucose level, leukocytes, lymphocytes, neutrophils, TC, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), cardiac troponin I, mean platelet volume, PLR, neutrophil-to-lymphocyte ratio (NLR), and estimated glomerular filtration rate (GFR). To evaluate the outcomes and severity of MI, in-hospital mortality, development of Q-wave MI, and LVEF were assessed.

Before conducting clustering, all quantitative variables were standardized to the mean and the standard deviation (*Mean* ± *SD*) [9]. Clustering was performed using the expectation – maximization (EM) algorithm, considering the type of distribution of the quantitative variables. The number of clusters was chosen using V-fold cross-validation [10].

In the statistical analysis, the Kolmogorov – Smirnov test was used to determine the nature of the distribution. Depending on the distribution, the Mann – Whitney and Kruskal – Wallis tests were used to evaluate the statistical significance of differences in the quantitative variables. The $\chi 2$ Pearson's test (including the Yates' correction) and the Fisher's exact test were used to evaluate the significance of differences in the categorical variables. The differences were considered statistically significant at $p < 0.05$. The Bonferroni correction was used for multiple comparisons (maximum number of compared groups – 3, p-value after correction < 0.018). The quantitative data were presented as the median and the interquartile range (*Me [Q_1; Q_3]*). The clustering and statistical analysis were performed using the Statistica 12.0 (StatSoft, USA) and MedCalc 11.5 (MedCalc Software, Belgium) software.

RESULTS

During clustering, a model consisting of three clusters was obtained based on 18 variables ($p <$ 0.05 for each parameter). The model included: age, gender, type of MI, AHF class, total SS, SS in the IRA, coronary collaterals by Rentrop, IRA diameter, TTG, TFG, PLR, GFR, TC, blood glucose level on admission, systemic thrombolytic therapy, vacuum aspiration thrombectomy, balloon angioplasty, and PCI in 2 or more CAs. The patients were distributed into the clusters as follows: cluster 1 included 106 (56%) patients, cluster 2 included 52 (27%) patients, cluster 3 encompassed 32 (17%) patients. The standardized mean values of the quantitative variables in the identified clusters are presented in Fig. 1, and the percentage of qualitative variables – in Fig. 2. For display convenience, ordinal parameters were transformed into binary ones (the threshold values were chosen based on clinical significance and are generally accepted) [5].

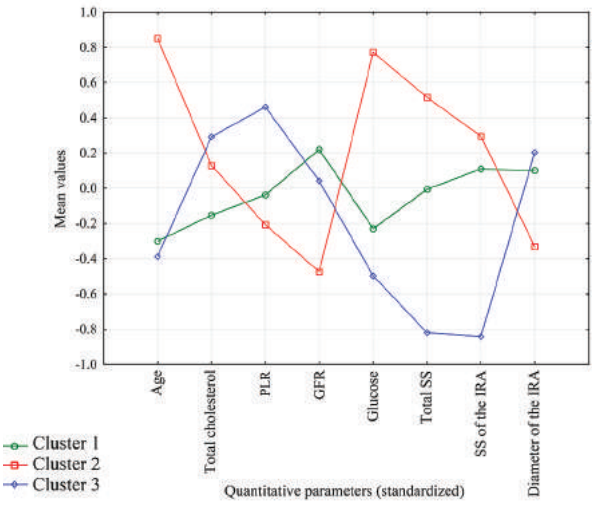

Fig. 1. Standardized mean values of quantitative variables in the clusters: IRA – infarct-related artery, GFR – glomerular filtration rate, PLR – platelet-to-lymphocyte ratio, SS – Syntax Score

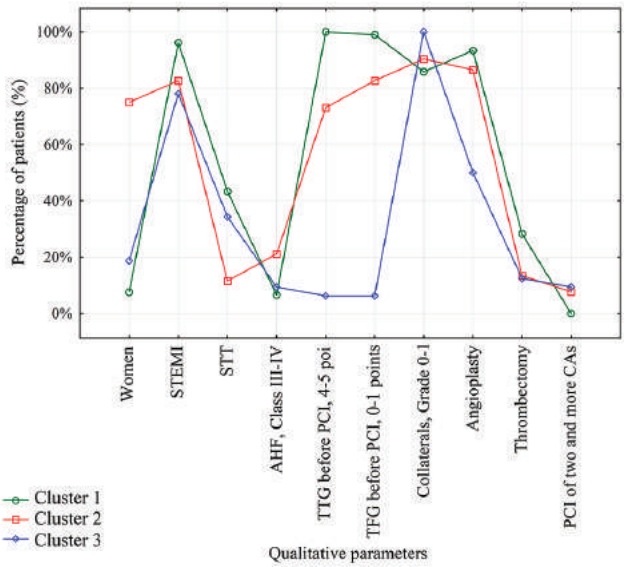

Fig. 2. Percentage of qualitative variables in the clusters: STEMI – ST-segment elevation myocardial infarction, CA – coronary artery, AHF – acute heart failure, PCI – percutaneous coronary intervention, TIMI – Thrombolysis in Myocardial Infarction, TFG – TIMI flow grade, TTG – TIMI thrombus grade

Table compares the groups by the parameters included in the clustering model (multiple and pairwise comparisons of the clusters adjusted to the number of tests). The clusters differed significantly in hospital outcomes "death" and "left ventricular ejection fraction" (Fig. 3). No differences in the frequency of Q-wave MI were found: cluster 1 – 99 (93%) patients, cluster 2 – 47 (90%) patients, cluster 3 – 26 (81%) patients, $p = 0.12$.

Table

Comparison of the clusters by the parameters included in the clustering model

Parameter	Cluster 1, n = 106	Cluster 2, n = 52	Cluster 3, n = 32	p-value
Age, years, *Me* [Q_1; Q_3]	62 [54; 67][2]	73 [67; 79][1, 3]	59 [50; 65][2]	<0.001
Female / male, n (%)	8 (8) / 98 (92)[2]	39 (75) / 13 (25)[1, 3]	6 (19) / 26 (81)[2]	<0.001
Admitted with STEMI, n (%)	102 (96)[2, 3]	43 (83)[1]	25 (78)[1]	0.002
Systemic thrombolytic therapy, n (%)	46 (43)[2]	6 (12)[1, 3]	11 (34)[2]	<0.001
AHF, class, *Me* [Q_1; Q_3]	1 [1; 2][2]	2 [1; 4][1]	2 [1; 2]	<0.001
Blood glucose level, mmol / l, *Me* [Q_1; Q_3]	8.0 [6.9; 9.6][2]	11.1 [8.8; 15.2] [1, 3]	7.5 [6.1; 8.1] [2]	<0.001
PLR, *Me* [Q_1; Q_3]	110 [78; 153] [3]	106 [85; 132][3]	132 [100; 182][1, 2]	0.04
Total cholesterol, mmol / l, *Me* [Q_1; Q_3]	4.7 [4.2; 5.4][2, 3]	5.3 [3.7; 6.2][1]	5.1 [4.5; 6.2][1]	0.047
GFR, ml / min / 1.73 m^2, *Me* [Q_1; Q_3]	77 [64; 88][2]	58 [46; 74] [1, 3]	81 [64; 88] [2]	<0.001
Total Syntax Score, points, *Me* [Q_1; Q_3]	15 [10; 21][2, 3]	20 [14; 26][1, 3]	8 [5; 10] [1, 2]	<0.001
Syntax Score in the IRA, points, *Me* [Q_1; Q_3]	9 [8; 15] [3]	12 [7; 16] [3]	6 [3; 7] [1, 2]	<0.001
Collateral grading, grade, *Me* [Q_1; Q_3]	0 [0; 1] [3]	0 [0; 1] [3]	0 [0; 0] [1, 2]	0.01
TIMI thrombus grade, grade, *Me* [Q_1; Q_3]	5 [5; 5][2, 3]	5 [3; 5][1, 3]	1 [0; 2] [1, 2]	<0.001
TIMI flow grade, grade, *Me* [Q_1; Q_3]	0 [0; 0][2, 3]	0 [0; 1][1, 3]	2 [2; 3] [1, 2]	<0.001
Vacuum aspiration thrombectomy, n (%)	30 (28)[2, 3]	7 (13)[1]	4 (13)[1]	0.04
Balloon angioplasty, n (%)	99 (93)[3]	45 (87)[3]	16 (50)[1, 2]	<0.001
IRA diameter, mm, *Me* [Q_1; Q_3]	3.5 [3.0; 3.5][2]	3.0 [2.8; 3.5] [1, 3]	3.5 [3.0; 3.5] [2]	0.02
PCI in 2 or more CAs, n (%)	0 (0)[2, 3]	4 (8)[1]	3 (9)[1]	0.009

[1], [2], [3] the value of the parameter is statistically significant ($p < 0.018$, with the Bonferroni correction) and differs from the identical parameter in cluster 1, 2 or 3, respectively.

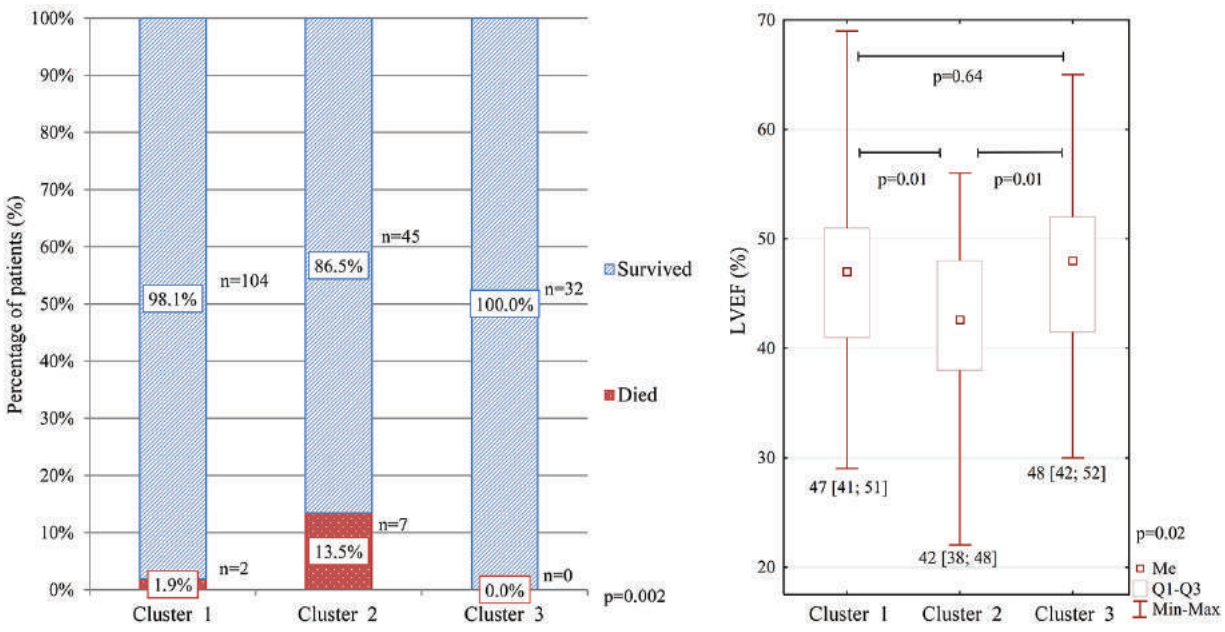

Fig. 3. Comparison of the clusters by the outcomes "death" and "LVEF": Min – Max – minimum and maximum values

DISCUSSION

The goal of the cluster analysis is to divide a sample into groups (clusters) in such a way that each cluster consists of similar objects, while objects from different clusters differ significantly from one other. The researcher's task in the cluster analysis is to knowledgeably select input parameters based on the relevant data on the research topic. Since clustering is a type of unsupervised machine learning (the "correct" division is not known in advance), the resulting classification is generally objective and is more a product of mathematical analysis rather than personal empirical choice [9, 10]. The researcher's ultimate task in this case is to analyze and explain the obtained results.

It should be noted that in some situations, the values of the parameters from different clusters may overlap, which is considered to be acceptable, since any parameter used for the classification is characterized by a certain proportion of false positive and false negative results. The evidence of statistically significant differences in the parameters between the clusters and, accordingly, the correctness of the obtained model is a p value of less than 0.05 for all parameters. It should be noted that in the cluster analysis, the original sample is divided by a combination of many features, even though individual parameters in the clusters may match [9, 10].

The analysis revealed significant heterogeneity in the group of patients with CMVO, resulting in the formation of 3 clusters with statistically significant differences (Table). The first cluster was the largest: 106 (56%) patients out of 190. It mainly included relatively young (62 [54; 67] years old) men (92%) with moderate atherosclerotic lesions of the CA (SS 15 [10; 21]). The prevailing predictors of the CMVO development in this cluster included high thrombus burden of the IRA (TTG 5 [5; 5]) and the associated sharp decrease in the baseline coronary blood flow (TFG 0 [0; 0]).

The association of CMVO in the group with intracoronary thrombosis is confirmed by the highest proportion of patients with STEMI – 95%, p = 0.02 (the development of STEMI is usually due to thrombotic occlusion of the IRA) [7, 11] and the most frequent use of balloon angioplasty (93%, $p < 0.001$) and vacuum aspiration thrombectomy (28%, $p = 0.04$) (also explained by the initially high thrombus burden of the IRA) [7, 11]. Thus, it would be reasonable to define the first cluster as a "microthromboembolic" phenotype, thereby underlining the most likely part of the pathogenesis – distal microembolism with thrombus debris fragmentation by PCI [2, 5, 11].

The second cluster (27% of the included patients) was characterized by the predominance of elderly women (75%) (73 [67; 79] years old) with high hyperglycemia (glucose 11.1 [8.8; 15.2] mmol / l, diabetes mellitus in 60% of the patients), severe atherosclerotic lesions of the CAs (SS 20 [14; 26]), the smallest diameter of the IRA (3.0 [2.8; 3.5] mm), reduced kidney function (GFR 58 [46; 74] ml / min / 1.73m^2), and hospitalization with severe AHF (class 2 [1; 4]). It should be noted that patients in this group also had high thrombus burden (TTG 5 [3; 5]) and reduced coronary blood flow (TFG 0 [0; 1]).

On the one hand, it is obvious that the trigger for the CMVO development in this group was also distal peripheral microembolism caused by intracoronary thrombus debris during PCI. On the other hand, it is known that the presence of severe persistent endothelial dysfunction, which is a predictor of the CMVO development [1, 5, 11], is characteristic of patients with the aforementioned clinical profile (especially those with diabetes). Apparently, the clustering algorithm correctly identified the most vulnerable and severe group of elderly patients. It is the age that was the factor that largely determined the clinical profile in this group: severe ischemic heart disease, severe atherosclerosis of the CAs, and comorbidity (diabetes, renal failure) [1, 5, 11]. Therefore, this cluster should be referred to as an "age-associated" phenotype. It should be noted that the rare use of thrombolytic therapy among patients in this cluster (12%, $p < 0.001$) was also likely due to their advanced age and associated hemorrhagic risk.

The third cluster (17% of the included patients) was mainly represented by relatively young (59 [50; 65] years old) men (81%) with minor atherosclerotic lesions of the CAs (SS 8 [5; 10]), almost no intracoronary thrombosis (TTG 1 [0; 2]), preserved blood flow (TFG 2 [2; 3]) in the IRA, and no visible coronary collaterals (Grade 0 [0; 0]). At the same time, this group had a relatively high level of TC (5.1 [4.5; 6.2] mmol / l) and the highest value of PLR (132 [100; 182]) – a parameter reflecting the severity of inflammation and a reliable predictor of the CMVO development [12].

The absence of severe IRA thrombosis in combination with dyslipidemia and severe inflammation suggests that the CMVO development in the patients of this group was caused by the rupture of a large, lipid-rich

atherosclerotic plaque with subsequent microembolism of the distal bed with its debris [1, 5, 11]. The relationship between the risk of developing CMVO and the lipid composition of the plaque, evaluated using modern methods of intravascular visualization, has been demonstrated in many studies in recent years [14, 15]. The cause of rupture and fragmentation of the plaque was intense mechanical stress during PCI [11], as indicated by the frequent use of multivessel stenting (9%, $p = 0.009$) in this group. Inflammation, on the other hand, apparently contributed to the development and destabilization of the atheroma [13, 16] and was a component of the pathogenetic cascade that exacerbated obstruction of the microvascular bed and led to the CMVO development [17]. Given the above, this cluster can be accurately referred to as an "atheroembolic" phenotype.

The above analysis of data and current literature allows us to assert that the described clusters can be considered as clinical and pathogenetic phenotypes of CMVO in MI. It should be stressed that the proposed names of the phenotypes were suggested to simplify the perception. These names are descriptive and reflect the leading, but not always the only factor in the CMVO development in the phenotype. In order to simplify the classification of patients with CMVO into a specific phenotype, we suggest using the algorithm presented in Fig. 4.

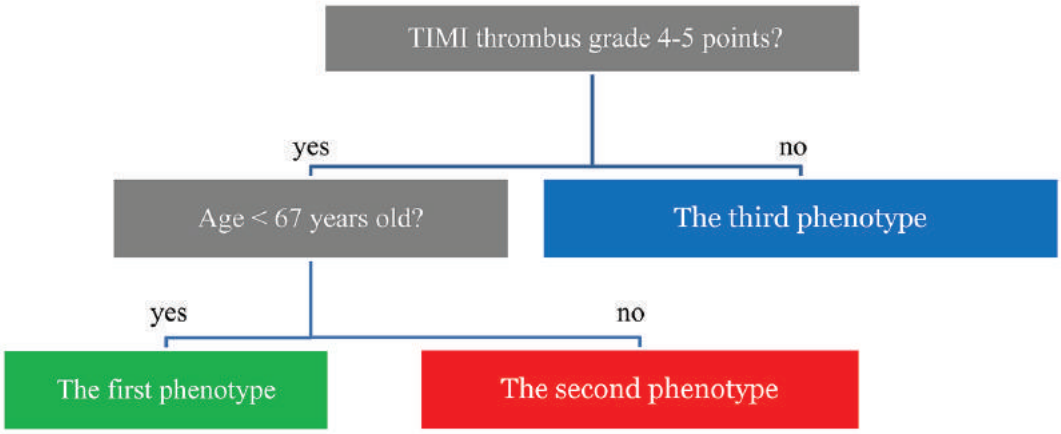

Fig. 4. Algorithm for attributing patients with CMVO to a specific phenotype.

It is worth noting that all identified phenotypes were mainly associated with different variants of distal peripheral microembolism after PCI. However, an important predictor of CMVO, the symptom-to-balloon time, was not included in the cluster model, although it is known that a delay in reperfusion is associated with severe ischemic damage [5, 11]. This can be explained by the fact that the time parameter is more associated with transportation and logistics. The delay in reperfusion definitely aggravates ischemic damage and contributes to the CMVO development, but it is not related to the patient's clinical profile [1, 4].

The identified phenotypes differed in the severity of hospital outcomes. The worst prognosis was observed in patients with the second phenotype (in-hospital mortality 13.5%, $p = 0.002$, LVEF at discharge – 42 [38; 48] %, $p = 0.01$, the Bonferroni correction threshold – 0.018), which was associated with severe MI, old age, severe atherosclerotic lesions of the CAs, frequent presence of AHF, and comorbidity.

These findings allow us to identify potential aims for targeted prevention and treatment of CMVO. In the case of the "microthromboembolic" phenotype, the most effective methods may be aimed at eliminating intracoronary thrombus: vacuum aspiration thrombectomy and the use of glycoprotein IIb/IIIa inhibitors [1, 3]. In CMVO with the "age-associated" phenotype, in addition to combating intracoronary thrombosis, effective methods may include perioperative correction of hyperglycemia, timely recognition of incipient cardiogenic shock, and the use of mechanical circulatory support [4, 18]. For patients with the "atheroembolic" phenotype, it is advisable to use minimally invasive interventions: performing PCI only in the IRA, performing post-dilation of the stent only if necessary, implanting the stent at moderate pressure, and using a deferred stenting strategy in selected patients [4, 19]. Early use of high-dose statins and anti-inflammatory drugs may also be effective in patients in this group [1, 20]. The

algorithm for such a selective approach is yet to be developed and tested in a prospective study.

LIMITATIONS OF THE STUDY

The presented study has several limitations, mainly related to the retrospective nature of the study. It is likely that some patients with moderate CMVO were not included in the study due to the retrospective inclusion of patients based on hospital database information, with subsequent verification of CMVO by angiography and ECG findings (as CMVO was not recorded in the primary documentation). The second limitation was that some laboratory tests associated with CMVO were not performed within the first day of hospitalization. Since the cluster analysis does not allow any missing data, a number of patients with CMVO who did not undergo the necessary tests had to be excluded from the study. Another factor that may have affected hospital outcomes in the studied group of patients was rare use of glycoprotein IIb/IIIa inhibitors.

CONCLUSION

Three phenotypes of CVMO were identified following the cluster analysis. The first phenotype is associated with severe thrombosis of the IRA and includes mostly men with moderate atherosclerotic lesions. The second phenotype is characterized by prevalence of elderly women with high hyperglycemia, advanced atherosclerotic lesions, severe AHF, impaired renal function, and thrombosis of the IRA. The third phenotype includes mostly men with mild atherosclerotic lesions, absence of severe thrombus burden, and preserved blood flow in the IRA before PCI, but with high levels of inflammatory markers and TC. The highest mortality rate and reduced LVEF were observed in patients of the second phenotype.

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Authors' contribution

Frolov A.A. – conception and design, analysis and interpretation of the data, justification of the manuscript, critical revision of the manuscript for important intellectual content. Frolov I.A. – conception and design, analysis and interpretation of the data. Ulanova N.D., Kuzmichev K.V. – analysis and interpretation of the data. Pochinka I.G. – analysis and interpretation of the data, justification of the manuscript, critical revision of the manuscript for important intellectual content, final approval of the manuscript for publication. Mukhin A.S., Sharabrin E.G. – justification of the manuscript, critical revision of the manuscript for important intellectual content, final approval of the manuscript for publication.

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