

PHENOTYPIC COMPOSITION OF PERIPHERAL BLOOD MONOCYTES IN YOUNG PATIENTS WITH COVID-19 AND ITS ASSOCIATION WITH THE RISK OF ACUTE MYOCARDIAL INFARCTION

Andrievskaya I.A.¹,
Shulga A.S.^{1,2},
Lyazgiyan K.S.¹

¹ Far Eastern Scientific Center of
Physiology and Pathology of Respiration
(Kalinin Str., 22, Blagoveshchensk 675000,
Russian Federation)

² Amur State Medical Academy
of the Ministry of Healthcare of the
Russian Federation (Gorky Str., 95,
Blagoveshchensk 675000, Russian
Federation)

Corresponding author:
Irina A. Andrievskaya
e-mail: irina-andrievskaja@rambler.ru

ABSTRACT

Background. COVID-19 is associated with systemic inflammation, endothelial dysfunction, and coagulopathy, significantly increasing the risk of thrombotic complications—including acute myocardial infarction (AMI) – including in young patients. The role of the monocyte–macrophage system in the pathogenesis of these complications remains insufficiently studied.

Aim. To investigate the phenotypic composition of peripheral blood monocytes in young patients with COVID-19 alone and in those with concomitant COVID-19 and AMI.

Methods. A comparative cross-sectional study included 223 male patients aged 36.4 (31.2; 41.6) years: 15 with moderate COVID-19 and AMI (main group), 179 with moderate COVID-19 without AMI (comparison group), and 29 healthy individuals (control group). Expression levels of CD14, HLA-DR, CD11b, CD206, CD32, TNFR1, TNFR2, CD68, TRAIL, and TGFβ1 on monocytes were assessed by flow cytometry.

Results. In patients with COVID-19, monocyte expression of CD14 and HLA-DR was significantly reduced compared to controls, while expression of TNFR2, TRAIL, TGFβ1, CD206, CD68, CD32, and CD11b was elevated. These alterations were more pronounced in patients with both COVID-19 and AMI, including increased TNFR1 expression relative to controls. Comparative analysis revealed significantly higher expression levels of TNFR1, TNFR2, TGFβ1, CD206, and TRAIL in the main group versus the comparison group. Significant correlations were found between monocyte marker expression (CD14, HLA-DR, CD206, TNFR1, TNFR2, TRAIL, TGFβ1) and the development of AMI in patients with COVID-19. ROC analysis confirmed the prognostic value of HLA-DR, CD206, TRAIL, and TGFβ1 as markers of high AMI risk in this population.

Conclusion. COVID-19 induces a phenotypic shift in monocytes toward an immunosuppressive, pro-inflammatory, and pro-fibrotic profile, thereby increasing the risk of AMI.

Keywords: COVID-19, acute myocardial infarction, monocytes, peripheral blood, phenotypic composition

Received: 08.05.2026
Accepted: 19.06.2026
Published: 23.07.2026

For citation: Andrievskaya I.A., Shulga A.S., Lyazgiyan K.S. Phenotypic composition of peripheral blood monocytes in young patients with COVID-19 and its association with the risk of acute myocardial infarction. *Acta biomedica scientifica*. 2026; 11(3): 19-26. doi: 10.29413/ABS.2026-11.3.3

ФЕНОТИПИЧЕСКИЙ СОСТАВ МОНОЦИТОВ КРОВИ У ПАЦИЕНТОВ МОЛОДОГО ВОЗРАСТА С COVID-19 И СОЧЕТАНИЕМ COVID-19 И ОСТРЫМ ИНФАРКТОМ МИОКАРДА

Андриевская И.А.¹,
Шульга А.С.^{1,2},
Лязгиян К.С.¹

¹ ФГБНУ «Дальневосточный научный центр физиологии и патологии дыхания» (675000, г. Благовещенск, ул. Калинина, 22, Россия)

² ФГБОУ ВО «Амурская государственная медицинская академия» Министерства здравоохранения Российской Федерации (675000, г. Благовещенск, ул. Горького, 95, Россия)

Автор, ответственный за переписку:
Андриевская Ирина
Анатольевна
e-mail: irina-andrievskaja@rambler.ru

РЕЗЮМЕ

Обоснование. COVID-19 ассоциирован с развитием системного воспаления, эндотелиальной дисфункцией и коагулопатией, что значительно повышает риск тромботических осложнений, включая острый инфаркт миокарда (ОИМ), в том числе у пациентов молодого возраста. Роль моноцитарно-макрофагального звена в механизмах развития данных осложнений остается недостаточно изученной.

Цель. Исследовать фенотипический состав моноцитов периферической крови у пациентов молодого возраста с COVID-19 и сочетанием COVID-19 и ОИМ.

Методы. Проведено сравнительное одномоментное исследование с участием 223 пациентов мужского пола в возрасте 36,4 (31,2; 41,6) лет, из них 15 пациентов со среднетяжелым течением COVID-19 и ОИМ (основная группа); 179 пациентов с COVID-19 средней степени тяжести без ОИМ (группа сравнения); 29 здоровых лиц (контрольная группа). Уровень экспрессии моноцитами CD14, HLA-DR, CD11b, CD206, CD32, TNFR1, TNFR2, CD68, TRAIL и TGFβ1 оценивали методом проточной цитометрии.

Результаты. У пациентов с COVID-19 выявлено достоверное снижение экспрессии моноцитами CD14 и HLA-DR относительно контрольной группы. Одновременно отмечено повышение уровней TNFR2, TRAIL, TGFβ1, CD206, CD68, CD32 и CD11b. При сочетании COVID-19 и ОИМ изменения были более выраженными, включая увеличение экспрессии TNFR1 по сравнению с контрольной группой. Сравнительный анализ показал, что у пациентов с COVID-19 и ОИМ уровни экспрессии TNFR1, TNFR2, TGFβ1, CD206 и TRAIL были значимо выше, чем у пациентов с COVID-19. При оценке взаимосвязи изменения параметров моноцитарного ответа с развитием ОИМ у пациентов с COVID-19 были выявлены значимые корреляции с CD14, HLA-DR, CD206, TNFR1, TNFR2, TRAIL и TGFβ1. ROC-анализ подтвердил прогностическую значимость HLA-DR, CD206, TRAIL и TGFβ1 как маркеров высокого риска ОИМ у пациентов с COVID-19.

Заключение. COVID-19 инициирует изменение фенотипа моноцитов, приводя к формированию субпопуляции с иммуносупрессивными, провоспалительными и профибротическими свойствами, что повышает риск развития ОИМ.

Ключевые слова: COVID-19, острый инфаркт миокарда, моноциты, периферическая кровь, фенотипический состав

Статья поступила: 08.05.2026
Статья принята: 19.06.2026
Статья опубликована: 23.07.2026

Для цитирования: Андриевская И.А., Шульга А.С., Лязгиян К.С. Фенотипический состав моноцитов крови у пациентов молодого возраста с COVID-19 и сочетанием COVID-19 и острым инфарктом миокарда. *Acta biomedica scientifica*. 2026; 11(3): 19-26. doi: 10.29413/ABS.2026-11.3.3

BACKGROUND

The novel coronavirus disease, COVID-19, caused by SARS-CoV-2, is recognized not only as a respiratory illness but also as a systemic disorder affecting multiple organs and systems, including the cardiovascular system [1]. Although the respiratory tract remains the main target of the virus, cardiovascular complications are increasingly being reported and contribute significantly to both morbidity and mortality, especially among patients with severe disease [2].

Myocardial injury in COVID-19 may arise through direct viral cytopathic effects or indirectly, via immune system hyperactivation, dysregulation of the renin-angiotensin system (RAS), endothelial dysfunction, and microvascular thrombosis [3]. SARS-CoV-2 enters cells, including cardiomyocytes and myocardial vascular cells, through the angiotensin-converting enzyme 2 (ACE2) receptor [4]. Following intracellular entry, the virus induces ACE2 internalization, leading to impaired regulatory function of ACE2 and a predominance of pro-oxidant, pro-inflammatory, and vasoconstrictive effects mediated by angiotensin II via the AT1 receptor [5].

A central role in the pathogenesis of cardiac complications is attributed to the systemic inflammatory response, characterized by excessive secretion of pro-inflammatory cytokines, including tumor necrosis factor- α (TNF- α), interleukin-2 (IL-2), IL-6, IL-7, and other inflammatory mediators [6]. This immune hyperreactivity initiates a cascade of pathological events, including cardiomyocyte apoptosis, microcirculatory dysfunction, and activation of the coagulation cascade. In this process, activated macrophages and monocytes release additional cytokines and procoagulant factors, contributing to atherosclerotic plaque destabilization, atherothrombosis, and ultimately acute myocardial infarction (AMI) [7]. In a significant subset of patients, AMI develops due to an imbalance between myocardial oxygen supply and demand, which can be precipitated by hypoxia, tachycardia, hypotension, or sepsis [8]. Meta-analyses indicate that signs of myocardial injury are detectable in 20–28 % of hospitalized COVID-19 patients and are associated with a significantly increased risk of mortality [9, 10].

Monocytes constitute a heterogeneous population of immune cells capable of polarization in response to the local microenvironment: pro-inflammatory M1 macrophages drive the inflammatory response, whereas anti-inflammatory M2 macrophages promote tissue remodeling and resolution of inflammation [11]. In severe COVID-19, a shift from M1 to M2 macrophage polarization has been observed [12], potentially leading to immune dysregulation and contributing to the development of cardiovascular complications.

The rising incidence of AMI among young adults aged 18–45 years [13] poses a serious clinical challenge and points to a prominent role played by pathogenetic mechanisms that are directly linked to viral-induced

inflammation and coagulation in COVID-19. Investigation of the phenotypic composition of circulating monocytes has particular scientific and clinical relevance in this context. Alterations in immune cell polarization underlie both pro-inflammatory and pro-fibrotic immune responses. Therefore, phenotypic analysis of peripheral blood monocytes in young patients with COVID-19, as well as in those with concomitant AMI, may not only deepen our understanding of the pathogenesis of cardiovascular complications but also identify potential targets for immunomodulatory therapeutic strategies.

AIM

To investigate the phenotypic composition of peripheral blood monocytes in young patients with COVID-19 alone and in those with concomitant COVID-19 and AMI.

MATERIALS AND METHODS

Study design and setting

A comparative cross-sectional case-control study was conducted involving 223 male patients, with a median age of 36.4 (31.2; 41.6) years. The main group consisted of 15 patients with moderate COVID-19 who developed AMI during hospitalization. The comparison group included 179 patients with moderate COVID-19 and no AMI, while the control group comprised 29 healthy individuals with no cardiovascular disease and with a negative PCR test for SARS-CoV-2.

Inclusion criteria were: age < 45 years, laboratory-confirmed COVID-19 (positive PCR for SARS-CoV-2 RNA), moderate disease severity, and newly diagnosed cardiovascular pathology during hospitalization.

Exclusion criteria were: history of coronary artery disease, prior AMI, coronary artery stents, chronic heart failure (NYHA functional class II–IV), malignancies, HIV infection, and severe COVID-19.

In addition, a retrospective review of medical records (Form No. 003/u) and inpatient charts was conducted. Laboratory analyses were performed at the research facilities of the Far Eastern Scientific Center of Physiology and Pathology of Respiration using equipment from the Shared Resource Center.

Ethical approval

The study was conducted in accordance with the Helsinki Declaration (World Medical Association, 2013) and it was approved by the local ethics committee of the Far Eastern Scientific Center of Physiology and Pathology of Respiration (Protocol No. 5, dated October 20, 2021). All participants provided written informed consent before participating in this study.

Study duration and methods

Sample collection was performed between 2021 and 2023 at the Infectious Diseases Department

of the Blagoveshchensk City Clinical Hospital (Blagoveshchensk, Amur Region). Peripheral venous blood was collected in the morning after an overnight fast within the first 72 hours of hospitalization into vacuum tubes containing EDTA (China). Mononuclear cells were isolated by density gradient centrifugation on Ficoll-Paque medium (density 1.077 g/mL; Cytiva, Sweden). Monocyte surface marker expression was assessed by flow cytometry using a BD FACS Canto II cytometer (Becton Dickinson, USA) with fluorochrome-conjugated monoclonal antibodies (BioLegend, USA) against CD14, HLA-DR, CD11b, CD206, CD68, CD32, TNFR1, TNFR2, TRAIL, and TGFβ1. Data were analyzed using BD FACSDiva™ v8.0 software (Becton Dickinson, USA).

Statistical analysis

Statistical processing was performed using IBM SPSS Statistics v.23.0 (IBM Corp., USA). Quantitative variables are expressed as median (Me) and interquartile range (Q1; Q3). Normality was assessed using the Kolmogorov – Smirnov and Shapiro – Wilk tests. Between-group comparisons of non-normally distributed continuous

variables were performed using the Mann – Whitney U test. A p -value < 0.05 was considered statistically significant.

RESULTS

Phenotypic analysis of peripheral blood monocytes in young patients with moderate COVID-19 revealed statistically significant alterations in cell surface antigen expression, associated both with SARS-CoV-2 infection itself and with the development of AMI in the context of infection (Table 1).

In the COVID-19 group, compared to the control group, there was a decrease in the number of monocytes expressing CD14 – by 1.25 times ($p < 0.001$) and HLA-DR antigen – by 1.18 times ($p < 0.001$). TNFR2 expression levels increased by 3.03 times ($p < 0.001$), TRAIL – by 3.96 times ($p < 0.001$), and TGFβ1 – by 3.08 times ($p < 0.001$). At the same time, an increase in CD206 expression by 1.80 times ($p < 0.01$), CD68 – by 2.29 times ($p < 0.001$), CD32 – by 1.04 times ($p < 0.05$),

TABLE 1

PHENOTYPIC COMPOSITION OF PERIPHERAL BLOOD MONOCYTES IN THE STUDY GROUPS (%)

Parameters	COVID-19 <i>n</i> =179	COVID-19 + AMI <i>n</i> =15	Control group <i>n</i> =29	<i>p</i>
CD14	75.2 (73.9; 76.4)	76.7 (74.3; 79.9)	93.9 (91.5; 94.6)	$p_{1,2}<0.001$ $p_3>0.05$
HLA-DR	79.0 (76.0; 83.7)	80.6 (77.0; 83.1)	93.4 (90.9; 96.6)	$p_{1,2}<0.001$ $p_3>0.05$
CD11b	80.4 (72.4; 82.0)	82.3 (73.3; 83.5)	75.9 (73.6; 77.9)	$p_1<0.001$ $p_{2,3}<0.05$
CD206	7.9 (7.1; 8.7)	10.7 (10.0; 11.5)	4.4 (4.1; 5.5)	$p_{1-3}<0.001$
CD32	93.6 (92.4; 94.5)	94.4 (93.8; 95.1)	89.8 (89.2; 90.7)	$p_{1,2}<0.05$ $p_3>0.05$
TNFR2	41.8 (37.0; 45.7)	65.8 (61.7; 69.3)	13.8 (10.5; 15.1)	$p_{1-3}<0.001$
TNFR1	62.3 (56.0; 64.2)	78.6 (74.7; 84.1)	62.3 (56.7; 64.9)	$p_1>0.05$ $p_{2,3}<0.001$
CD68	50.4 (46.8; 64.6)	48.7 (46.0; 52.4)	22.0 (18.0; 24.4)	$p_{1,2}<0.001$ $p_3>0.05$
TRAIL	55.5 (53.2; 57.3)	59.0 (57.8; 61.9)	14.0 (11.7; 14.6)	$p_{1,2}<0.001$ $p_3>0.05$
TGFβ1	11.4 (9.3; 12.6)	17.9 (14.8; 19.8)	3.7 (3.0; 5.2)	$p_{1-3}<0.001$

Notes. p_1 – statistical significance of differences between the COVID-19 group and the control group; p_2 – statistical significance of differences between the COVID-19 + AMI group and the control group; p_3 – statistical significance of differences between the COVID-19 group and the COVID-19 + AMI group.

and CD11b – by 1.06 times ($p < 0.05$) was noted. TNFR1 expression levels in the COVID-19 group did not differ significantly from those in the control group ($p > 0.05$).

In patients with COVID-19 and AMI, compared to the control group, there was a decrease in CD14 expression – by 1.22 times ($p < 0.001$) and HLA-DR – by 1.16 times ($p < 0.001$). TNFR1 expression levels increased by 1.26 times ($p < 0.001$), TNFR2 – by 4.77 times ($p < 0.001$), TRAIL – by 4.21 times ($p < 0.001$), TGF β 1 – by 4.84 times ($p < 0.001$), CD206 – by 2.43 times ($p < 0.001$), CD68 – by 2.21 times ($p < 0.001$), CD32 – by 1.05 times ($p < 0.05$), and CD11b – by 1.08 times ($p < 0.05$).

Further comparative analysis showed that TNFR1 expression levels in the COVID-19 + AMI group were higher than in the COVID-19 group, differing by 1.26 times ($p < 0.001$), TNFR2 – by 1.57 times ($p < 0.001$), TGF β 1 – by 1.57 times ($p < 0.001$), CD206 – by 1.35 times ($p < 0.001$), and TRAIL – by 1.06 times ($p < 0.05$). No significant differences in CD14, HLA-DR, CD32, or CD68 expression were found between these groups ($p > 0.05$).

When assessing the correlation between changes in monocyte response parameters and AMI development in COVID-19 patients, correlations were identified with CD14 ($p = -0.43$, $p < 0.05$), HLA-DR ($p = -0.71$, $p < 0.01$), CD206 ($p = 0.74$, $p < 0.01$), TNFR1 ($p = 0.34$, $p < 0.05$), TNFR2 ($p = 0.43$, $p < 0.05$), TRAIL ($p = 0.75$, $p < 0.01$), and TGF β 1 ($p = 0.77$, $p < 0.01$).

In a further integrated assessment of the contribution of monocyte CD markers to AMI development in COVID-19 patients, ROC analysis was performed (Fig.). Decreased monocyte HLA-DR expression (AUC = 0.713, $p = 0.002$) and increased CD206 (AUC = 0.849, $p < 0.001$), TRAIL (AUC = 0.752, $p < 0.001$), and TGF β 1 (AUC = 0.836, $p < 0.001$) levels are prognostically significant risk factors for AMI in COVID-19 patients (Table 2).

DISCUSSION

The identified changes in the phenotypic composition of peripheral blood monocytes in young patients with COVID-19 and with the combination of COVID-19 and AMI reflect complex immune response processes, where phases of hyperinflammation, functional “exhaustion” of immune cells, and tissue remodeling alternate sequentially. The decreased monocyte expression of CD14 and HLA-DR observed in patients with COVID-19 and COVID-19 + AMI compared to the control group may indicate the formation of a functionally “exhausted” cell pool – CD14⁺HLA-DR^{neg/low}, previously described in sepsis and cancer [13], and in later studies – in severe SARS-CoV-2 infection [14]. Moreover, in the COVID-19 + AMI group, the decrease in HLA-DR expression was more pronounced than in the COVID-19 group. Our results are consistent with those of Fraccarollo D. et al., who reported an increase in CD14⁺HLA-DR^{neg/low} monocyte

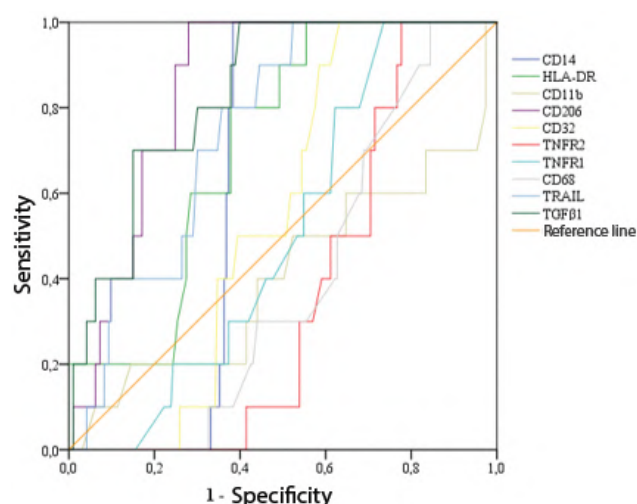


FIG.

Roc curve illustrates the discriminatory ability of monocyte response parameters in predicting the risk of AMI in patients with COVID-19

TABLE 2

ROC CURVE PARAMETERS IN THE GROUP OF PATIENTS WITH COVID-19 AND AMI

Parameters	AUC	95% CI	p
CD14	0.634	0.567–0.701	0.038
HLA-DR	0.713	0.624–0.802	0.002
CD11b	0.406	0.259–0.553	0.051
CD206	0.849	0.794–0.904	<0.001
CD32	0.549	0.469–0.630	0.467
TNFR2	0.365	0.289–0.441	0.047
TNFR1	0.505	0.411–0.600	0.038
CD68	0.392	0.302–0.481	0.111
TRAIL	0.752	0.670–0.833	<0.001
TGF β 1	0.836	0.766–0.906	<0.001

expression in the blood of patients with AMI was reported [15]. HLA-DR is one of three class II major histocompatibility complex (MHC) glycoproteins expressed on antigen-presenting cells, functioning to present antigens internalized by the cell to T-cell receptors (TCR), leading to T-cell activation. Decreased HLA-DR expression on CD14⁺ cells may indicate a suppression of monocyte antigen-presenting capacity to T cells

[11]. *In vitro* studies have shown that culturing monocytes with cytokines such as TGFβ1 leads to decreased HLA-DR surface expression [16]. Similar changes, involving alveolar macrophages, were described by Bühling F. et al. [17]. The authors demonstrated an inverse correlation between high TGFβ1 concentration and HLA-DR expression, and a direct correlation with CD11b levels in alveolar macrophages of patients with pneumonia. CD11b is one of the α-chains of β2 integrins and is a receptor for iC3b, ICAM-1,2,4, fibrinogen, and CD14. It plays an important role in macrophage interaction with endothelial cells or extracellular matrix proteins [17]. The study suggested that microbial antigens are the primary regulators of CD11b expression. We found that CD11b levels in patients with COVID-19 and COVID-19 + AMI were elevated compared to the control group but did not differ between the groups, which further supports the influence of infection on antigen expression. Similar changes were observed in other CD markers, such as CD32 and CD68.

It should be noted that monocytes with reduced HLA-DR levels in patients with COVID-19 and COVID-19 + AMI do not exhibit pronounced immunosuppressive activity. This is confirmed by increased monocyte expression of immunoregulatory molecules and inflammatory markers, such as CD206, TNFR1, TNFR2, TRAIL, and TGFβ1, which are most pronounced in the COVID-19 + AMI group compared to the COVID-19 group. These results may support the role of monocytes with low HLA-DR levels in the mechanisms of AMI development. *In vitro* experiments have shown that macrophages derived from CD14⁺HLA-DR^{neg/low} monocytes from AMI patients, upon IFN-γ stimulation, produce large amounts of inflammatory cytokines TNF-α, IL-6, and IL-1β compared to macrophages with high HLA-DR expression [15]. Increased cellular expression of TNFR1, TNFR2, and TRAIL is a marker for systemic inflammation and endothelial dysfunction [18]. The authors demonstrated that activation of the TNF-α/TNFR1 complex induces the release of extracellular vesicles from endothelial cells, which are involved in vascular injury and promote apoptosis, and inflammatory damage to endothelial cells. TNFR2 initiates the recruitment of TRAF2 and TRAF5 proteins, activating the NF-κB and MAPK signaling pathways to sustain inflammation and lead to the production of pro-inflammatory cytokines (IL-6 and IL-8) [2]. In recent years, there has been a significant increase in interest in the role of TRAIL in the pathogenesis of cardiovascular pathology. According to Goncalves I. et al., TRAIL induces the apoptosis of macrophages, vascular smooth muscle cells, and endothelial cells, and maintains the inflammatory activity of atherosclerotic plaques, leading to their instability and increasing the risk of thrombosis and AMI development [19]. Alonso-Herranz L. et al. showed that TGFβ1 hyperactivation in macrophages after ischemic myocardial injury promotes local

endothelial-to-mesenchymal transition of cells and formation of myofibroblasts involved in cardiac fibrosis and remodeling [20]. A review by Budnevsky A.V. et al. confirmed the role of post-COVID syndrome in TGFβ1 overexpression, leading to prolonged immunosuppression and fibrosis [21].

The above literature data are supported by our studies, in which ROC analysis demonstrated that changes in monocyte expression of HLA-DR, CD206, TRAIL, and TGFβ1 can serve as biomarkers for high AMI risk in patients with COVID-19.

This study has several limitations. First, the sample size was relatively small, which may reduce the statistical power of the analysis and limit the generalizability of the results to a broader population. Second, the study design was single-center, potentially introducing bias related to patient selection and treatment protocols specific to a single institution. Third, the absence of longitudinal patient follow-up precludes assessment of long-term cardiovascular outcomes and dynamics of monocyte phenotypic composition in the post-hospital period. Despite these limitations, the data obtained are valuable for understanding the early immunopathogenetic mechanisms of cardiovascular complications in patients who have recovered from COVID-19.

CONCLUSION

COVID-19 induces changes in monocyte phenotype, leading to the formation of a subpopulation with immunosuppressive, pro-inflammatory, and pro-fibrotic characteristics, which increases the risk of AMI development.

Funding

The study was funded by the federal budget as part of a state assignment for fundamental scientific research (State Registration No. 122021800166-9).

Conflict of interest

The authors declare no conflict of interest.

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Information about the authors

Irina A. Andrievskaya – Dr. Sc. (Biol.), Head of the Laboratory of mechanisms of etiopathogenesis and recovery processes of the respiratory system in nonspecific lung diseases, Far Eastern Scientific Centre of Physiology and Pathology of Respiration; e-mail: irina-andrievskaja@rambler.ru, <https://orcid.org/0000-0003-0212-0201>

Andrey S. Shulga – cardiovascular surgeon of Cardiac Surgery Clinic, Amur State Medical Academy; applicant for the degree of Candidate of Science, Laboratory of Mechanisms of Etiopathogenesis and Recovery Processes of the Respiratory System at Non-Specific Lung Diseases, Far Eastern Scientific Center of Physiology and Pathology of Respiration; e-mail: mig2994@mail.ru, <https://orcid.org/0000-0003-0854-2990>

Karen S. Lyazgyan –junior research officer at the Laboratory of Mechanisms of Etiopathogenesis and Recovery Processes of the Respiratory System in Nonspecific Lung Diseases, Far Eastern Scientific Centre of Physiology and Pathology of Respiration; e-mail: lyazgiyankaren@mail.ru, <https://orcid.org/0000-0002-8329-3237>