DOI: 10.17816/KMJ322039

The course of chronic heart failure in patients after COVID-19 against the background of active cytomegalovirus infection

S.N. Shilov[1]*, S.D. Mayanskaya[2], I.V. Pankova[1], N.S. Grigorieva[1], I.V. Govor[1]

[1]Novosibirsk State Medical University, Novosibirsk, Russia;
[2]Kazan State Medical University, Kazan, Russia

Abstract

Background. A new coronavirus infection may be complicated in the post-COVID period by the development of adverse cardiovascular events associated with chronic heart failure.

Aim. To study the features of the course of chronic heart failure in patients after COVID-19 infection against the background of active cytomegalovirus infection.

Material and methods. The study included 102 patients with chronic heart failure with reduced and intermediate left ventricular ejection fractions, who underwent COVID-19 in mild and moderate forms. The control group consisted of 61 patients with chronic heart failure and no COVID-19. Within 6 months after the infection with COVID-19, the features of the course of chronic heart failure were assessed. Quantitative determination of deoxyribonucleic acid (DNA) of cytomegalovirus in blood plasma was carried out by polymerase chain reaction. To assess the risk of adverse events, the odds ratio (OR) with a 95% confidence interval (95% CI) was calculated. Quantitative data were presented as median and interquartile range (25th and 75th percentiles).

Results. After coronavirus infection, the risk of an unfavorable course of chronic heart failure (OR=6.237; 95% CI=2.911–13.362; p=0.001), hospitalization due to decompensation of chronic heart failure (OR=5.9; 95% CI=1.313–26.504; p=0.033), an increase in the functional class of heart failure by 1 class or more (OR=4.19; 95% CI=1.636–10.736; p=0.009), development of atrial fibrillation paroxysms (OR=3.832; 95% CI=1.385–10.599, p=0.014), significantly increased. The number of copies of cytomegalovirus DNA in patients who underwent COVID-19 was significantly higher in the group of patients with an unfavorable course of chronic heart failure compared to the same group, in which patients did not tolerate COVID-19 — 2238.5 (1888.5; 2647.5) and 1411.5 (1112.5; 1684.5) copies/ml, respectively (p <0.001).

Conclusion. Patients with chronic heart failure after 6 months of COVID-19 infection are at high risk of developing adverse cardiovascular events against the background of active cytomegalovirus infection.

Keywords: COVID-19, cytomegalovirus, herpes virus, heart failure, prognosis.

For citation: Shilov SN, Mayanskaya SD, Pankova IV, Grigorieva NS, Govor IV. The course of chronic heart failure in patients after COVID-19 against the background of active cytomegalovirus infection. *Kazan Medical Journal.* 2023;104(3):332–340. DOI: 10.17816/KMJ322039.

Background

Acute infections can cause the release of proinflammatory cytokines, leading to a systemic inflammatory response that may damage organs and systems not initially affected by the virus [1]. Increased metabolic demand in the myocardium can lead to cardiac damage and the development of heart failure, which can be complicated by adverse cardiovascular events associated with chronic heart failure (CHF) [1, 2].

The term “long COVID” was first used to describe patients who continued to experience symptoms after the resolution of acute infection [2]. Currently, “long COVID” refers to clinical manifestations lasting between 4 weeks and 12 weeks from the onset of the disease, whereas “post-COVID syndrome” refers to symptoms persisting beyond 12 weeks [2].

The research community has taken an interest in investigating the long-term cardiovascular consequences of coronavirus infection because of the high mortality and myocardial damage observed during acute COVID-19 infection.

A study of 73,435 nonhospitalized patients with COVID-19, with a mean age of 61 years, indicated a high risk of death and cardiovascular events

*For correspondence: newsib54@gmail.com

Submitted 09.12.2022; accepted 01.03.2023; published 20.04.2023.

within 30 days of the acute phase of the disease [3]. A British study of 47,780 hospitalized patients with COVID-19, with a mean age of 65 years and 55% men, showed that the diagnosis of COVID-19 was associated with a threefold increase in the risk of serious adverse cardiovascular events within 4 months of diagnosis compared with nonhospitalized patients [4].

The role of systemic inflammation and immune activation in the development and progression of heart failure, leading to poor prognosis and increased cardiovascular risk, has been proposed based on the current understanding of CHF pathogenesis [5]. Research has shown that proinflammatory cytokines are significant contributors to the progression of CHF. Proinflammatory cytokines primarily affect cardiac dysfunction and the intensity of myocardial and vascular remodeling processes by regulating cardiomyocyte apoptosis, which, in turn, is considered a fundamental mechanism in determining the development of contractile and possibly diastolic myocardial dysfunction [5].

Subclinical inflammation and immune response caused by viral infections, particularly COVID-19 and cytomegalovirus infection (CMVI), may be important factors in the development and progression of CHF. According to several studies, CMVI can induce the synthesis of proinflammatory cytokines, including tumor necrosis factor α and interleukin-1β [5].

Scientific publications have not extensively covered the role of CMVI in the development of CHF or the risk stratification of the progression and decompensation of this pathology. However, using an integrated approach to analyze the characteristics of CHF with active CMVI after COVID-19 can lead to improved prognosis and treatment optimization for heart failure. Therefore, this direction is a priority in modern cardiology.

This study aimed to examine the characteristics of CHF progression in patients with active CMVI after COVID-19.

Materials and methods

This study was conducted between February 2022 and October 2022 following the provisions of the Declaration of Helsinki and was approved by the local ethics committee of City Clinical Hospital No. 1 in the Novosibirsk Region (Protocol No. 200, dated January 31, 2019).

This study involved 102 patients with mild (n = 61, 59.8%) and moderate (n = 41, 40.2%) 6-month-old COVID-19 (Group 1). The patients had no prior history of a positive polymerase chain reaction result or a positive titer of Class G antibodies to SARS-CoV-2, confirming that this was their first time being infected with the new coronavirus.

Before COVID-19 infection, all patients were diagnosed with ischemic CHF with reduced and intermediate left ventricular ejection fraction (LVEF). The control group (Group 2) consisted of 61 patients with CHF who had no history of COVID-19 infection since the beginning of the pandemic period (Table 1). The observation groups were comparable in terms of clinical and demographic characteristics and current CHF therapy.

Exclusion criteria:

(1) Recent acute cardiovascular events (i.e., acute myocardial infarction, pulmonary embolism, and acute cerebrovascular disorder less than 6 months before COVID-19 disease);

(2) Active myocarditis;

(3) Presence of hemodynamically significant lesions in the heart valve apparatus: mitral regurgitation of more than Degree II, aortic stenosis with transaortic pressure gradient of more than 25 mm Hg, aortic insufficiency of more than Degree I, and tricuspid regurgitation of more than Degree II;

(4) Age >70 years;

(5) Acute or chronic liver disease;

(6) Glomerular filtration rate (<30 mL/min/1.73 m^2 according to CKD-EPI[1]);

(7) Severe bronchial asthma or chronic obstructive pulmonary disease;

(8) Autoimmune diseases;

(9) Pregnancy;

(10) Malignancies;

(11) Inability to sign an informed consent form.

During the 6-month follow-up of the cohort, the symptoms and signs of CHF and the echocardiographic parameters were evaluated. The indicators of the first observation point in Group 1 were obtained from outpatient records based on information on the dispensary follow-up of patients with CHF. These data were registered no more than 1 month before the confirmed diagnosis of COVID-19. In Group 2, comparable parameters were assessed at baseline and after the 6-month follow-up (Table 2). The functional class (FC) of CHF was determined based on the data from the 6-min walk test.

The combined endpoints of this study were defined as an increase in one or more classes in the FC of CHF (according to the NYHA[2]), hospitalization due to decompensation of CHF, registration of paroxysmal atrial fibrillation, and/or ventricular ectopias of high gradations (Ryan classes III–V)

[1] CKD-EPI — Chronic Kidney Disease Epidemiology Collaboration formula.

[2] NYHA — New York Heart Association.

Table 1. Clinical and demographic characteristics of the patients

Indicators	Group 1, COVID-19 survivors (*n* = 102)	Group 2, without a history of COVID-19 (*n* = 61)	p
Age, years	58,0 [51; 65]	59,0 (52; 65)	0,311
Men/women, *n* (%)	56 (54,9)/46 (45,1)	35 (57,4)/26 (42,6)	0,191
Body mass index, kg/m^2	28,1 [25,2; 31,6]	26,4 [24,6; 30,5]	0,426
CHF FC, *n* (%): FC I FC II FC III	 42 (41,2) 35 (34,3) 25 (24,5)	 26 (42,6) 19 (31,2) 16 (26,2)	 0,512 0,214 0,298
Postinfarction cardiosclerosis, *n* (%)	49 (48,0)	26 (42,6)	0,089
Atrial fibrillation, *n* (%)	23 (22,5)	17 (27,9)	0,091
Arterial hypertension, *n* (%)	89 (87,3)	57 (93,4)	0,072
Smoking, *n* (%)	23 (22,5)	21 (34,4)	0,043
COPD, *n* (%)	14 (13,7)	12 (19,7)	0,198
Total cholesterol, mmol/L	5,1 [4,4; 5,5]	5,0 [4,5; 5,6]	0,529
LDL, mmol/L	2,9 [2,3; 3,6]	2,8 [2,4; 3,2]	0,122
HDL, mmol/L	1,6 [1,5; 1,75]	1,6 [1,46; 1,7]	0,791
GFR, mL/min/m^2	52 [42; 58]	51 [42; 57]	0,314
Treatment, *n* (%): ACE inhibitors Valsartan/sacubitril β-Adrenoblockers MRAs Diuretics	 69 (67,6) 33 (32,4) 79 (77,5) 64 (62,7) 44 (43,1)	 44 (72,1) 17 (27,9) 47 (77,0) 35 (57,4) 28 (45,9)	 0,119 0,119 0,854 0,086 0,219

Note: FC, functional class; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; LDL, low-density lipoproteins; HDL, high-density lipoproteins; GFR, glomerular filtration rate; ACE, angiotensin-converting enzyme; MRAs, mineralocorticoid receptor antagonists.

Table 2. Dynamics of the echocardiographic parameters and 6-min walk test in the observation groups during the prospective follow-up (Me [Q_{25}; Q_{75}])

Indices	Baseline			After the 6-month follow-up		
	Group 1 (*n* = 102)	Group 2 (*n* = 61)	p	Group 1 (*n* = 102)	Group 2 (*n* = 61)	p
6MWT, m	407 [371; 447]	400 [369; 439]	0,829	371 [340; 408]	412 [372; 445]	0,041
LVEF, %	44 [40; 47]	43 [39; 47]	0,632	42 [39; 45]	46 [42; 50]	0,017
EDD, mm	48 [45; 52]	49 [45; 52]	0,562	50 [46; 54]	50 [47; 53]	0,229
ESD, mm	36 [33; 38]	36 [34; 38]	0,759	37 [34; 40]	36 [34; 39]	0,115
LVPWT, mm	11 [10; 12]	11 [10; 12]	0,995	11 [10; 12]	11 [10; 12]	0,943
LVST, mm	11 [11;12]	11 [11;12]	0,832	12 [11; 13]	11 [11;12]	0,038

Note: 6MWT, 6-min walk test; LVEF, left ventricular ejection fraction; EDD, end-diastolic dimension; ESD, end-systolic dimension; LVPWT, left ventricular posterior wall thickness; LVST, left ventricular septal thickness.

according to the data of the daily monitoring of electrocardiography, which was performed when clinical and/or electrocardiographic signs of arrhythmias were detected within 6 months after COVID-19 infection.

After the 6-month follow-up, the patients were examined for cytomegalovirus (CMV) deoxyribonucleic acid (DNA) levels in 1 mL of blood plasma using polymerase chain reaction with real-time hybridization–fluorescence detection of amplification products. The AmpliSens CMV-screen/monitor-FL reagent kit (Russia) and the Rotor-Gene Q Qiagen amplifier (Germany) were used for this purpose. The detection of CMV involved three steps: DNA extraction from blood, amplification of the DNA region of the microorganism, and hybridization–fluorescence detection. These steps are performed directly during the polymerase chain reaction. The quantification of CMV DNA was performed 6 months after COVID-19 infection.

Table 3. Characterization of the adverse course of chronic heart failure at 6 months after COVID-19, *n* (%)

Events	Group 1 (*n* = 102)	Group 2 (*n* = 61)	p
Unfavorable course of CHF	59 (57,8)	11 (18,0)	0,001
Decompensation of CHF	17 (16,7)	2 (3,3)	0,014
Increase in CHF FC by one class or more	32 (31,4)	6 (9,8)	0,001
Paroxysmal atrial fibrillation	26 (25,5)	5 (8,2)	0,001
High-grade ventricular ectopias	4 (3,9)	1 (1,6)	0,421

Note: CHF, chronic heart failure; FC, functional class.

Table 4. Viral load in cytomegalovirus infection in the observation groups

Index	Group 1 (*n* = 102)		Group 2 (*n* = 61)	
	Favorable course of CHF	Unfavorable course of CHF	Favorable course of CHF	Unfavorable course of CHF
CMV DNA, copies/mL	1574 (1228; 1726)	2238,5*# (1888,5; 2647,5)	1243 (1012; 1489)	1411,5 (1112,5; 1684,5)

Note: CHF, chronic heart failure; DNA, deoxyribonucleic acid; CMV, cytomegalovirus; *p < 0.001 compared with Group 2; #p < 0.001 compared with the favorable course group who had COVID-19.

Statistical analysis was performed using the Statistica 10.0 and MedCalc 11.5.0.0 software packages. The Mann–Whitney test was used to compare the independent variables, whereas the Wilcoxon test and sign criterion were used to compare the dependent variables. For the qualitative features, conjugation tables were analyzed using Pearson's χ^2 criterion. The odds ratio (OR) with a 95% confidence interval (95% CI) was calculated to evaluate the risk of adverse cardiovascular events. Quantitative data are presented as the median (Me) and interquartile range (25th and 75th percentiles), whereas qualitative data are presented as the absolute values and percentages. Spearman's rank correlation coefficient (Spearman *R*) was used for the correlation analysis. The significance level for all analysis procedures was set at 0.05.

Results

The clinical and demographic characteristics of the observation groups were not significantly different (refer to Tables 1 and 2). After the 6-month follow-up, Group 1 exhibited a decrease in the distance traveled during the 6-min walk test and LVEF and an increase in the left ventricular end-diastolic and end-systolic dimensions. By contrast, Group 2 did not show any negative changes in these parameters (Table 2).

Of the patients with COVID-19, 57.8% (59) achieved the primary endpoint of the study within 6 months (Table 3). In the control group, 11 (18.0%) patients experienced adverse cardiovascular events during the 6-month follow-up period. Therefore, patients with CHF and reduced or intermediate LVEF who have had mild to moderate COVID-19 and received a negative result on a polymerase chain reaction test for the SARS-CoV-2 coronavirus within the past 6 months are at a significantly increased risk of adverse CHF outcomes (OR = 6.237; 95% CI = 2.911–13.362; p = 0.001). Among the major cardiovascular events, hospitalization due to decompensation of CHF (OR = 5.9; 95% CI = 1.313–26.504; p = 0.033), an increase in CHF Grade 1 or more (OR = 4.19; 95% CI = 1.636–10.736; p = 0.009), and the development of atrial fibrillation paroxysms (OR = 3.832; 95% CI = 1.385–10.599; p = 0.014) showed a significantly increased risk.

The concentration of CMV DNA in patients who had COVID-19 infection 6 months prior was higher than that in patients with CHF who had no history of COVID-19 infection. The determination of the CMVI viral load in 1 mL of blood plasma in the observation groups is presented in Table 4. Furthermore, the group of patients with COVID-19 and an unfavorable course of CHF had a significantly higher number of CMV DNA copies than the group of patients with CHF without COVID-19 (p < 0.001).

In Group 1, during an unfavorable course of CHF, the concentration of CMV DNA copies was significantly higher than that during a favorable course of the pathology (p < 0.001). In Group 2, no significant differences (p = 0.329) in the number of CMV DNA copies were detected depending on the nature of the course of CHF.

This study observed a significant correlation between CMV DNA levels and CHF class (r = 0.63, p = 0.007), 6-min walk test distance (r = −0.711, p = 0. 003), and echocardiographic parameters of left ventricular remodeling, including LVEF (r = −0.591, p = 0.014), left ventricular end-diastolic dimension (r = 0.482, p = 0.025), and left ventricular end-systolic dimension (r = 0.542, p = 0.002).

Discussion

Based on the results of this study, patients with CHF and reduced or intermediate LVEF who have had COVID-19 are 3.2 times more likely to experience serious adverse cardiovascular events. These events are characterized by an increased number of hospitalizations due to decompensation of CHF, a higher CHF grade, and the development of atrial fibrillation paroxysms within 6 months after discharge compared with patients with CHF who have not been infected with the new coronavirus.

The mechanisms underlying the development of cardiovascular complications following acute viral illness remain poorly understood. One potential mechanism is a chronic inflammatory response induced by viral particles in the heart after acute infection. This response may be further exacerbated by secreted chemokines that worsen endothelial dysfunction through impaired endothelial nitric oxide synthase and reactive oxygen species synthesis [6]. These processes may cause irreversible tissue damage, leading to chronic myocardial fibrosis, which, in turn, results in impaired cardiac perfusion, increased myocardial stiffness, decreased contractility, and potential arrhythmias.

Lessons learned from previous coronavirus and influenza epidemics indicate that viral infections can worsen preexisting CHF. Multiple studies have shown an increased risk of rehospitalization during the influenza season [7]. With the more aggressive COVID-19 infection, patients with heart failure are at a significantly higher risk of developing complications. Several mechanisms may trigger and exacerbate this process [2].

Approximately one third of hospitalized patients with COVID-19 have a history of chronic cardiovascular disease. The presence of these conditions is typically associated with higher in-hospital mortality rates, thromboembolic risk, and septic shock incidence. Even in the subacute period, patients with a history of heart failure face a twofold to fourfold risk of decompensation and death [8]. The cardiometabolic profiles of COVID-19 and cardiovascular disease indicate that the novel coronavirus infection may destabilize chronic clinical conditions, such as coronary heart disease and heart failure [2].

The involvement of angiotensin-converting enzyme 2 receptors in SARS-CoV-2-related cardiac damage is well established [9]. Several mechanisms have been proposed to contribute to myocardial damage, including direct cytotoxic action, dysregulation of the renin–angiotensin–aldosterone system, endotheliitis, inflammation, and dysregulated immune response with cytokine release [9].

Cardiac troponin levels are frequently elevated in patients with COVID-19, indicating myocardial damage and/or ischemia [10]. In their study, Fox et al. (2021) [11] proposed a range of pathophysiological mechanisms that underlie myocardial damage in COVID-19. The authors proposed that hypoxia and pulmonary microvascular injury may lead to stress-induced cardiac injury and cardiomyocyte necrosis. The microvascular effects localized in the latter may be further enhanced by endotheliitis [12] associated with microthrombosis and impaired renin–angiotensin homeostasis [13]. Elevated cytokines, such as interleukin-1, interleukin-16, interleukin-17, interleukin-22, interferon γ, and tumor necrosis factor α, may also contribute to myocardial damage through endothelial dysfunction and platelet and neutrophil activation, ultimately causing a hypercoagulable state [1].

This study examined the potential negative impact of CMVI activation on the myocardium in the context of a new coronavirus infection. CMVI has been shown to induce a chronic immune inflammatory response, with latent infections periodically reactivating and stimulating chronic immune or inflammatory responses that can damage the vascular endothelium and inner membrane of endotheliocytes [5]. The formation of immune antibody complexes with the CMV antigen can also stimulate macrophages to synthesize and release interleukin-1, interleukin-6, interleukin-8, interleukin-10, interleukin-12, tumor necrosis factor α, and other inflammatory factors, which can, in turn, cause cellular and humoral immune responses in the myocardium, leading to an inflammatory chain reaction [5]. According to a previous study, periodic CMV activation increases the amount of p53 protein, which subsequently activates cell apoptosis. This process is considered one of the important links in the pathogenesis of CHF [14].

This study proposed a possible correlation between the parameters of the structural and functional states of the heart (including LVEF and left ventricular end-systolic and end-diastolic dimensions), CHF, 6-min walk test distance, and CMV DNA content. This correlation may indicate the influence of the infectious agent on the course of CHF.

CMVI activation in patients following coronavirus infection may prolong systemic inflammation and contribute to the progression of CHF, leading to adverse cardiovascular events. An imbalance in immune defense, which may result in an immunodeficient state, could be a possible cause of CMV activation after COVID-19 [10].

A limitation of this study is that it did not examine the state of the immune system of patients or the initial level of CMV DNA. To address this limitation, the dynamics of CMV DNA concentration during the acute period of COVID-19 and at dif-

ferent time points after obtaining a negative polymerase chain reaction result for SARS-CoV-2, in correlation with the peculiarities of the course of CHF, need to be investigated.

The withdrawal of drug therapy aimed at treating CHF during the acute phase of COVID-19 is one reason for the increased incidence of heart failure decompensation after discharge [15]. Therefore, successfully resuming and optimizing heart failure therapies to prevent adverse cardiovascular events after acute COVID-19 may be of great importance.

Heart failure may develop as a variant of the clinical course of COVID-19, particularly in severe forms of pathology, or occur in patients with preexisting myocardial dysfunction [2, 8]. Therefore, understanding the impact of SARS-CoV-2 and CMV on the course of CHF is crucial to optimize patient management. A multidisciplinary approach involving the heart failure team and infectious disease specialists may lead to optimal understanding and management of patients with this pathology.

Conclusions

1. Patients with CHF and reduced or intermediate LVEF are at a significantly increased risk of adverse outcomes within 6 months of receiving a negative result for SARS-CoV-2 coronavirus. These outcomes include increased hospitalizations due to decompensation of CHF, higher FC, development of atrial fibrillation paroxysms, and increased CMVI activity. Notably, COVID-19 disease in mild and moderate forms may exacerbate these risks. Therefore, close monitoring and management of CHF in these patients is crucial.

2. One possible factor that may negatively impact the course of CHF after coronavirus infection is CMVI activation, which correlates with the parameters of the structural and functional states of the heart, the FC of CHF, and the distance walked by patients during the 6-min walk test.

Authors' contribution. S.N.S. and S.D.M., supervising the work; I.V.P., conducting the study; and N.S.G. and I.V.G., collecting and analyzing the results.

Funding source. The study received no sponsorship support.

Conflict of interest. The authors declare no conflict of interest for the submitted article.

REFERENCES

1. Tufan A, Avanoğlu Güler A, Matucci-Cerinic M. COVID-19, immune system response, hyperinflammation and repurposing antirheumatic drugs. *Turk J Med Sci.* 2020;50(SI-1):620–632. DOI: 10.3906/sag-2004-168.

2. Arutyunov AG, Seferovic P, Bakulin IG, Bakulina NV, Batyushin MM, Boldina MV, Krstacic G, Macut D, Salukhov VV, Shimosawa T, Shustov VV, Tarlovskaya EI, Vrtovec B, Wanner C, Aisanov ZR, Arutyunov GP, Avdeev SN, Babin AP, Cattaneo M, Chesnikova AI, Ezhov MV, Kamilova UK, Koziolova NA, Lopatin YuM, Mitkovskaya NP, Morais J, Galstyan GR, Sarybaev ASh, Sugraliev AB, Yavelov IS, Essaian AM, Zolotovskaya IA, Zhangelova ShB, Zyryanov SK, Melnikov ES, Bashkinov RA, Shlyakhto EV. Rehabilitation after COVID-19. Resolution of the International Expert Council of the Eurasian Association of Therapists and the Russian Society of Cardiology. *Russian Journal of Cardiology.* 2021;26(9):4694. (In Russ.) DOI: 10.15829/1560-4071-2021-4694.

3. Al-Aly Z, Xie Y, Bowe B. High-dimensional characterization of post-acute sequelae of COVID-19. *Nature.* 2021;594:259–264. DOI: 10.1038/s41586-021-03553-9.

4. Ayoubkhani D, Khunti K, Nafilyan V, Maddox T, Humberstone B, Diamond I, Banerjee A. Post-COVID syndrome in individuals admitted to hospital with COVID-19: Retrospective cohort study. *BMJ.* 31;372:n693. DOI: 10.1136/bmj.n693.

5. Jeong SJ, Ku NS, Han SH, Choi JY, Kim CO, Song YG, Kim JM. Anti-cytomegalovirus antibody levels are associated with carotid atherosclerosis and inflammatory cytokine production in elderly Koreans. *Clin Chim Acta.* 2015;445:65–69. DOI: 10.1016/j.cca.2015.03.015.

6. Kim HW, de Chantemèle EB, Weintraub NL. Perivascular adipocytes in vascular disease. *Arterioscler Thromb Vasc Biol.* 2019;39:2220–2227. DOI: 10.1161/ATVBAHA.119.312304.

7. Kytömaa S, Hegde S, Claggett B, Udell JA, Rosamond W, Temte J, Nichol K, Wright JD, Solomon SD, Vardeny O. Association of influenza-like illness activity with hospitalizations for heart failure: The atherosclerosis risk in communities study. *JAMA Cardiol.* 2019;4(4):363–369. DOI: 10.1001/jamacardio.2019.0549.

8. Chatrath N, Kaza N, Pabari PA, Fox K, Mayet J, Barton C, Cole GD, Plymen CM. The effect of concomitant COVID-19 infection on outcomes in patients hospitalized with heart failure. *ESC Heart Fail.* 2020;7(6):4443–4447. DOI: 10.1002/ehf2.13059.

9. Lechner-Scott J, Levy M, Hawkes C, Yeh A, Giovannoni G. Long COVID or post COVID-19 syndrome. *Mult Scler Relat Disord.* 2021;55:103268. DOI: 10.1016/j.msard.2021.103268.

10. Bieber S, Kraechan A, Hellmuth JC, Muenchhoff M, Scherer C, Schroeder I, Irlbeck M, Kaeaeb S, Massberg S, Hausleiter J, Grabmaier U, Orban M, Weckbach LT. Left and right ventricular dysfunction in patients with COVID-19-associated myocardial injury. *Infection.* 2021;49(3):491–500. DOI: 10.1007/s15010-020-01572-8.

11. Fox SE, Vander Heide RS. COVID-19: the heart of the matter-pathological changes and a proposed mechanism. *J Cardiovasc Pharmacol Ther.* 2021;26:217–224. DOI: 10.1177/1074248421995356.

12. Vrints CJM, Krychtiuk KA, Van Craenenbroeck EM, Segers VF, Price S, Heidbuchel H. Endothelialitis plays a central role in the pathophysiology of severe COVID-19 and its cardiovascular complications. *Acta Cardiol.* 2021;76:109–124. DOI: 10.1080/00015385.2020.1846921.

13. Robinson FA, Mihealsick RP, Wagener BM, Hanna P, Poston MD, Efimov IR, Shivkumar K, Hoover DB. Role of angiotensin-converting enzyme 2 and pericytes in cardiac complications of COVID-19 infection. *Am J Physiol Heart Circ Physiol.* 2020;319:H1059–H1068. DOI: 10.1152/ajpheart.00681.2020.

14. Speir E, Modali R, Huang ES, Leon MB, Shawl F, Finkel T, Epstein SE. Potential role of human cytomegalovirus and p53 interaction in coronary restenosis. *Science.* 1994;265:391–394. DOI: 10.1126/science.8023160.

15. Rey JR, Caro-Codón J, Rosillo SO, Iniesta ÁM, Castrejón-Castrejón S, Marco-Clement I, Martín-Polo L, Merino-Argos C, Rodríguez-Sotelo L, García-Veas JM, Martínez-Marín LA, Martínez-Cossiani M, Buño A, Gonzalez-Valle L, Herrero A, López-Sendón JL, Merino JL Heart failure in COVID-19 patients: Prevalence, incidence and prognostic implications. *Eur J Heart Fail.* 2020;22:2205–2215. DOI: 10.1002/ejhf.1990.

Author details

Sergey N. Shilov, M.D., D. Sci. (Med.), Prof., Depart. of Pathological Physiology and Clinical Pathophysiology, Novosibirsk State Medical University, Novosibirsk, Russia; newsib54@gmail.com; ORCID: http://orcid.org/0000-0002-7777-6419

Svetlana D. Mayanskaya, M.D., D. Sci. (Med.), Prof., Depart. of Hospital Therapy, Kazan State Medical University, Kazan, Russia; smayanskaya@mail.ru; ORCID: http://orcid.org/0000-0001-6701-5395

Irina V. Pankova, Assistant, Depart. of Pathological Physiology and Clinical Pathophysiology, Novosibirsk State Medical University, Novosibirsk, Russia; pankovairin@mail.ru; ORCID: http://orcid.org/0000-0001-7864-3194

Natalya S. Grigoreva, Stud., Novosibirsk State Medical University, Novosibirsk, Russia; natasha_grigoreva_99@mail.ru; ORCID: http://orcid.org/0000-0002-7361-6143

Inna V. Govor, Stud., Novosibirsk State Medical University, Novosibirsk, Russia; i.v.govor@gmail.com; ORCID: http://orcid.org/0000-0002-3032-8686