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# Epidemiology, Etiopathogenesis of Myocarditis Caused by COVID-19

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**Abstract**
The cardiovascular manifestation in COVID-19 is diverse: acute myocardial infarction, myocarditis, stress cardiomyopathy, non-ischemic cardiomyopathy, coronary spasm. A feature of coronavirus myocarditis is the presence of endotheliitis and destructive-productive vasculitis of small branches of the coronary arteries. In the pathogenesis of myocarditis in COVID-19, it should be considered that the introduction of coronavirus and its interaction with toll-like receptors induces an excessive, uncontrolled response of innate immunity with the release of an unbalanced amount of pro-inflammatory cytokines, which is called a cytokine storm, and causes tissue damage, including the lungs, heart and vessels.

## INTRODUCTION

On March 11, 2020, who announced a pandemic of coronavirus type 2 (SARS-CoV-2) severe acute respiratory syndrome (SARS), coining the term coronavirus disease 2019 (COVID-19) [31, 46]. The source of SARS-CoV-2 has not yet been accurately identified, although there are suggestions about the zoonotic nature of the infection [2].

Transmission from person to person occurs through close contact with an infected person through the ingestion of the pathogen by airborne droplets and dust into the respiratory tract; contact and fecal-oral transmission routes have also been described [1, 3]. The average age of patients is approximately 51 years, the most severe forms developed in patients 60 years and older. Among the patients, the following concomitant diseases were often noted: diabetes mellitus (20%), arterial hypertension (15%), and other cardiovascular diseases (15%). The clinical picture is characterized by fever, dry cough, shortness of breath, muscle pain, skin rash. Clinical variants of COVID-19 are classified as: acute respiratory viral infection (affecting only the upper respiratory tract); pneumonia without respiratory distress; pneumonia with acute respiratory failure (ARF); acute respiratory distress syndrome (ARDS); sepsis; septic (infectious toxic) shock. Hypoxemia develops in more than 30% of patients (decrease in SpO2 less than 88%). Distinguish between mild, moderate and severe forms of COVID-19. In 80% of patients, the disease is mild ARVI. A severe course of infection is characterized by the development of pneumonia, respiratory distress syndrome, kidney damage, central nervous system and other organs [4, 5].

SARS-CoV-2 is a single-stranded RNA virus [6]. The virus belongs to the genus Betacoronavirus of the Coronaviridae family. Currently, it is known about the circulation among the population of four types of coronaviruses that cause damage to the upper respiratory tract of mild to moderate severity. The virus is assigned to the II pathogenicity

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group, like some other members of this family (SARS-CoV virus, MERS-CoV). The entrance gate of the pathogen is the epithelium of the upper respiratory tract, the conjunctiva of the eye and the epithelial cells of the stomach and intestines. The SARS-CoV-2 genome, like other coronaviruses, encodes four structural proteins: proteins S (spike), E (envelope), M (membrane), and N (nucleocapsid). Protein S is responsible for the attachment and penetration of SARS-CoV-2 to the receptors of the host cell, which are probably the receptors for angiotensin converting enzyme 2 (ACE2) [7]. This receptor is expressed on cells of a number of organs and tissues, including the lung (bronchial epithelium, pneumocytes of the 1st and 2nd order), myocardium, renal epithelial cells, vascular endothelium, intestines, cells of the esophagus, urinary bladder, ileum , central nervous system. There was evidence that the S protein of this virus has a higher affinity for ACE2 receptors compared to the analogous protein of other related pathogens [8]. SARS-CoV-2 contains viral surface proteins, namely S-glycoprotein, which mediates interaction with ACE2 receptors. M- and E-glycoproteins are embedded in the lipid bilayer surrounding the helical nucleocapsid that contains viral RNA [9]. Cell Penetration and Replication SARS-CoV-2 Penetration of the coronavirus into the target cell is due to the binding of S-glycoprotein to the cellular receptor ACE2 [51] and CD147. Studies have shown that this SARS-CoV-2 protein exhibits 10–20 times higher affinity for this receptor in comparison with the analogous protein of the SARS-CoV virus [10]. Binding of the S-glycoprotein to the ACE2 receptor causes conformational changes in the former, leading to the fusion of the viral E-glycoprotein with the target cell membrane, followed by the penetration of the virus into it through the endosomal mechanism [11].
Further, the release of viral RNA takes place with its copying, followed by replication of the virus. Assembly of the virion occurs through the interaction of viral RNA and protein in the endoplasmic reticulum and the Golgi complex of the target cell. Subsequently, virions leave the cell through exocytosis.

In pathogenesis, it should be considered that the introduction of coronavirus and its interaction with toll-like receptors induces an excessive, uncontrolled response of innate immunity with the release of an unbalanced amount of pro-inflammatory cytokines, which is called a cytokine storm, and causes tissue damage, including the lungs, heart and blood vessels. The serum of patients showed an increase in the content of pro-inflammatory cytokines, including IL-1β, IL-18, TNF-α, IL-6, IL-8 and IL-10, which are produced and regulated by various cells, including CD8 and CD4 T-lymphocytes ... As a result, the pathogenesis of organ damage in COVID-19 is due to three groups of interrelated factors that form a vicious pathological circle: the first factor is the cytopathic damaging effect of the virus on tropic cells; the second factor can be called a cytokine storm, which has a damaging effect on tissues and blood vessels and provides an inflammatory reaction and coagulopathy with the recruitment of leukocytes, macrophages, and lymphoid elements to the focus of damage; the third factor is clotting disorders due to damage to the vascular endothelium and liver cells, with the development of thrombosis and hemorrhage.

There is still little information about the nature and, moreover, the morphology of myocardial damage within the framework of the new coronavirus infection. First of all, clinicians drew attention to the infrequent, but natural involvement of the heart in a single pathological process in this disease. Thus, according to researchers from Wuhan, myocardial injury was diagnosed in 12% of cases (41 patients were studied in total), among 41 patients,

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myocardial injury was diagnosed in 5 cases [20]. According to global statistics, 19% of patients hospitalized with COVID-19 show signs of heart damage (chest pain, hypotension, arrhythmia, signs of heart failure). Sinus tachycardia is diagnosed in 16–72% of patients with COVID-19, in addition, there are cases of bradyarrhythmia, acute coronary syndrome (with an increase in troponin levels and characteristic changes on the electrocardiogram) and sudden cardiac death [21, 22, 23]. At the same time, severe patients with COVID-19 die from heart and pulmonary heart failure. The literature describes a variety of myocardial damage in COVID-19, which occurs by several pathogenetic mechanisms [24]: 1) direct myocardial damage associated with the effect of the virus on ACE-2 [22]; 2) the development of an acute systemic inflammatory response and cytokine storm with a high level of pro-inflammatory cytokines in the blood; 3) increased oxygen consumption by the myocardium due to systemic infection in combination with increasing hypoxia in the blood due to acute respiratory distress syndrome; 4) ischemic damage against the background of atherosclerotic changes in the coronary arteries (or coronaritis) and coagulopathy associated with COVID-19; 5) electrolyte imbalance (in particular, hypokalemia), which develops as a result of the effect of the virus on the renin-angiotensin-aldosterone system and contributes to the development of tachyarrhythmias; 6) toxic effects on the myocardium of antimalarial and antiviral drugs. The cardiovascular manifestation in COVID-19 is diverse: acute myocardial infarction, myocarditis, stress cardiomyopathy, non-ischemic cardiomyopathy, coronary spasm [25]. Moreover, to describe the symptoms and laboratory changes in the literature, a rather vague concept is often used - “acute myocardial injury” [26, 58].

According to the European consensus of 2018 [27], acute myocardial injury is diagnosed based on an increase in the level of biomarkers (troponin) in the absence of ischemia, morphological evidence of which is the death of cardiomyocytes. However, troponin can be increased both in myocardial pathology and in respiratory dysfunction and impaired renal function, which is present in the vast majority of patients and leads to troponin accumulation, which causes certain difficulties in diagnosing myocardial damage [28, 57]. Myocardial infarction develops as a result of direct exposure to SARS-CoV-2, a cytokine storm, or increasing hypoxia (due to thrombosis / thromboembolism of the coronary artery). In this case, one should also take into account the presence of comorbid pathology - atherosclerosis, hypertension and diabetes mellitus, which in some cases can be the main, and in some cases - combined diseases leading to the development of myocardial infarction. Severe systemic inflammation also increases the risk of atherosclerotic plaque rupture and myocardial infarction [29, 56]. Histologically, the site of myocardial necrosis with lysis and fragmentation of cardiomyocytes, the absence of nuclei, massive leukocyte infiltration and vascular plethora is determined. Groups of relatively intact cardiomyocytes with symptoms of atrophy and hypertrophy, accumulation of lipofuscin granules in the cytoplasm. Lymphocytic myocarditis is described in the literature extremely poorly. This is due to a certain commitment of European pathologists to mandatory morphological and immunohistochemical verification of myocarditis [30]. Only 2 cases of myocarditis have been reported [31, 32]. Our own histological and immunohistochemical study of myocardial preparations of patients with coronavirus infection suggests that not only the myocardium, but also the endo- and pericardium is involved in the inflammatory process. In the interstitial tissue of the myocardium, lymphoid infiltrates are found (in the amount of more than 14

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lymphocytes in the field of view and more than 7 CD3 T-lymphocytes per 1 mm 2 according to the international criteria of Dallas). In this case, the cardiomyocytes are unevenly hypertrophied, with lipofuscin granules, the nuclei are preserved. In some cardiomyocytes, nuclear lysis is observed. A feature of coronavirus myocarditis is the presence of endotheliitis and destructive-productive vasculitis of small branches of the coronary arteries. Almost all patients have a diffuse proliferation of mature connective tissue, including perivascular. In combination with COVID-19-associated lymphocytic myocarditis, lymphocytic pericarditis and endocarditis can develop. The endocardium is most often thickened, sclerosed, with residual symptoms of endocarditis (lymphoid infiltrates). Changes in the hemostasis system characteristic of COVID-19, such as an increase in the level of D-dimer, an increase in prothrombin time and aPTT, lead to the development of advanced thrombosis [9, 54, 55]. So, in most cases, there are parietal thrombi in the lumen of the heart chambers (most often in the right atrium and left ventricle) and fresh thrombotic masses in the branches of the coronary arteries. However, it is still unclear whether changes in hemostasis are a specific response to SARS-CoV-2 or a complication of the cytokine storm and systemic inflammatory response. Cardiomyopathy in COVID-19 has been described in a limited number of works and, according to the literature, occurs in 33% of cases [33, 34, 52], but these samples can hardly be called representative. Attention is drawn to the fact that in most patients at autopsy, an increase in the size and weight of the heart (400 g and more) is found, which is clinically manifested by increasing heart failure, which leads to the death of the patient. COVID-19 is associated with numerous cardiovascular pathologies, including myocarditis, acute myocardial infarction, endo- and pericarditis, small focal cardiosclerosis, and cardiomyopathy.

Competent drug support will help such patients reduce the risk of developing fatal arrhythmias and sudden cardiac death (Kogan E.A., 2020).

Thus, one should dwell on thanatogenesis in this disease and name the main causes of death: acute cardiopulmonary failure, acute renal failure, pulmonary embolism, shock and multiple organ failure, as well as sepsis.

Several clinical variants of heart damage have been reported: 1) aggravation of the course of chronic cardiovascular diseases (ischemic heart disease - IHD, heart failure, rhythm disturbances) [36, 50]; 2) the development of acute myocardial infarction (MI) due to thrombosis of both altered and unchanged coronary arteries [35, 49]; 3) the development of cardiogenic shock, acute heart failure in patients without previous heart disease [37]; 4) less severe manifestations - arrhythmias, changes in the electrocardiogram (ECG), echocardiography, etc. (not always clinically manifested) [48]; 5) an increase in the level of cardiospecific markers (troponin, NT-proBNP, etc.) in the blood, which is observed in 8% of patients and is not always accompanied by clinical deterioration [12, 47]. At the same time, to explain the symptoms and laboratory changes, such an unclear concept as "acute myocardial injury" is most often used. In accordance with the latest European consensus on MI [13, 46], acute myocardial injury can be diagnosed on the basis of an increase in the level of biomarkers (troponin) in the absence of ischemia, its morphological evidence is the death of cardiomyocytes. Obviously, this concept is too general; in particular, myocardial necrosis within severe (including viral) myocarditis also falls within this definition. At the same time, when describing patients with coronavirus infection, clinicians try to avoid the term

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"myocarditis". This is primarily due to the strict adherence of European experts on myocardial diseases to the obligatory morphological and immunohistochemical verification of myocarditis [14]. One should be careful to talk about only two verified cases of a kind of myocarditis in COVID-19 [15, 45]. At the same time, clinical data (both individual cases and series of observations) indicate a high frequency of "acute myocardial injury". One of the most important mechanisms of such damage is thrombosis, including of large coronary arteries.

In the work of Kogan E.A. et al. (2020) demonstrated morphologically and immunohistochemically verified cases of acute lymphocytic myoendocarditis in a new coronavirus infection (COVID-19). The frequency of clinically diagnosed myocarditis is estimated by some authors at 4.8% [16, 41, 44]. One of the first convincing clinical descriptions of severe heart damage, regarded as myopericarditis, was presented by a group of doctors from Lombardy (Italy): a 53-year-old woman without previous heart disease developed severe systolic dysfunction a week after the onset of ARVI symptoms (decrease in ejection fraction to 35%), revealed signs of diffuse myocardial edema and pericardial effusion according to magnetic resonance imaging (MRI), increased levels of highly sensitive troponin (0.59 ng / ml) and NT-proBNP (8 465 pg / ml) in the blood [17, 42, 43]. Despite the absence of pneumonia, the diagnosis of COVID-19 was serologically confirmed. Myocardial biopsy was not performed, treatment with cardiotropic, antiviral drugs, steroids, and hydroxychloroquine had a distinct positive effect. Other cases of myocarditis diagnosed by MRI have also been described, including in young patients without pneumonia [19], which may indicate a particular tropism of this virus to the myocardium and requires the study of the specific mechanisms of its defeat.

Of greatest interest are, undoubtedly, the results of morphological examination of the myocardium in patients with clinical suspicion of myocarditis. More recently, a 17-year-old patient died from cardiac arrest followed by weakness, headache, nausea and vomiting in just 2 days. A positive result of a nasopharyngeal smear test for COVID-19 was obtained; no blood tests were performed, and autopsy showed no signs of pneumonia, but eosinophilic myocarditis was diagnosed [18]

Thrombosis of both large and small coronary vessels appears to be one of the key mechanisms of myocardial damage in COVID-19. Of the non-inflammatory changes in the myocardium, we also observed mild lymphocytic infiltration [38, 39], infiltration with a small number of monocytes and CD34-positive cells, and interstitial fibrosis (which is regarded as a sign of chronic myocardial damage) [40].

## CONCLUSION

In the pathogenesis of myocarditis in COVID-19, it should be considered that the introduction of coronavirus and its interaction with toll-like receptors induces an excessive, uncontrolled response of innate immunity with the release of an unbalanced amount of pro-inflammatory cytokines, which is called a cytokine storm, and causes tissue damage, including the lungs, heart and vessels. In the blood serum of patients, the content of pro-inflammatory cytokines, including IL-1β, IL-18, TNF-α, IL-6, IL-8, and IL-10, increases, which are produced and regulated by various cells, including CD8 and CD4 T-lymphocytes. As a result, the pathogenesis of organ damage in COVID-19 is due to three groups of

interrelated factors that form a vicious pathological circle: the first factor is the cytopathic damaging effect of the virus on tropic cells; the second factor can be called a cytokine storm, which has a damaging effect on tissues and blood vessels and provides an inflammatory reaction and coagulopathy with the recruitment of leukocytes, macrophages, and lymphoid elements to the focus of damage; the third factor is clotting disorders due to damage to the vascular endothelium and liver cells, with the development of thrombosis and hemorrhage. It is necessary to dwell on thanatogenesis in this disease and name the main causes of death: acute cardiopulmonary failure, acute renal failure, pulmonary embolism, shock and multiple organ failure, as well as sepsis.

The data presented indicate significant heart damage during the acute phase of COVID-19, as well as subsequent metabolic disorders and provocation of chronic cardiovascular pathology. These facts direct us to a thorough assessment of the condition of patients with COVID-19 in the context of the diagnosis of cardiac diseases both during infection and in the long-term post-infection period. In addition, at the current stage of supervising patients with COVID-19, significant attention should be paid to cardioprotection and prevention of acute and chronic complications of CVD. Pulmonary myocarditis is one of the important nosological forms of acute lesions of the heart muscle in patients with COVID-19. It should be noted that coronavirus myocarditis predominantly develops in patients 10–15 days after the onset of the first symptoms of the disease, which more likely indicates its immunocomplex origin or the specifics of a delayed viral attack on cardiomyocytes.

## REFERENCES

[1] Aguiar D., Lobrinus J. A., Schibler M., Fracasso T., Lardi1 C. Inside the lungs of COVID-19 disease. International Journal of Legal Medicine. 2020;(134):1271–1274. https://doi.org/10.1007/s00414-020-02318-9

[2] Arentz M., Yim E., Klaff L., et al. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State. JAMA. 2020 [Epub ahead of print].

[3] Bangalore S, Sharma A, Slotwiner A, Yatskar L, Harari R, Shah B et al. ST-Segment Elevation in Patients with Covid-19 – A Case Series. New England Journal of Medicine. 2020;NEJMc2009020. [Epub ahead of print]. DOI: 10.1056/NEJMc2009020

[4] Bikdeli B., Madhavan M.V., Jimenez D., Chuich T., Dreyfus I., Driggin E., et al. COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-up. Journal of the American College of Cardiology. 2020. https://doi. org/10.1016/j.jacc.2020.04.031

[5] Caforio ALP, Pankuweit S, Arbustini E, Basso C, Gimeno-Blanes J, Felix SB et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. European Heart Journal. 2013;34(33):2636–48. DOI: 10.1093/eurheartj/eht210

[6] Chan J. F., Yuan S., Kok K. H., To K. K., Chu H., Yang J., et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a familycluster.Lancet.2020;395(10223):514523.https://doi.org/10.1016/ S0140-6736(20)30154-9 3. Ghinai I., McPherson T. D., H.

[7] Chen T., Wu D., Chen H., et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ. Mar 26 2020;368:m1091.
[8] Costabel U., du Bois R. M., Egan J. J. (eds.) Diffuse Parenchymal Lung Disease. Prog. Respir. Res. 2007;36:1–10. https://doi.org/10.1159/000102577
[9] Coutard B., Valle C., de Lamballerie X., Canard B., Seidah N. G., Decroly E. The spike glycoprotein of the new coronavirus 2019-nCoV contains a furin-like cleavage site absent in CoV of the same clade. Antivir. Res. 2020;176:104742. https://doi.org/10.1016/j.antiviral.2020.104742
[10] Craver R, Huber S, Sandomirsky M, McKenna D, Schieffelin J, Finger L. Fatal Eosinophilic Myocarditis in a Healthy 17-Year-Old Male with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2c). Fetal and Pediatric Pathology. 2020;1–6. [Epub ahead of print]. DOI: 10.1080/15513815.2020.1761491
[11] Craver R., Huber S., Sandomirsky M., McKenna D., Schieffelin J., Finger L. Fatal Eosinophilic Myocarditis in a Healthy 17-Year-Old Male with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2c). =Fetal Pediatr. Pathol. 2020:1–6. https://doi.org/10.1080/15513815.2020. 1761491. [Epub ahead of print].
[12] Самсонова М. В., Михалева Л. М., Черняев А. Л., Мишнев О. Д., Крупнов Н. М. Патологическая анатомия легких при COVID-19: Атлас; под ред. О. В. Зайратьянца. М.—Рязань: Издательство ГУП РО «Рязанская областная типография», 2020. [SamsonovaM. V., MikhalevaL. M., ChernyaevA. L., MishnevO. D., KrupnovN. M. PatologicheskayaanatomiyalegkihpriCOVID-19 Atlas. Ed. by O. V. Zayratyants. Moscow—Ryazan: Ryazanskayaoblastnayatipografiya, 2020. (In Russ.)]
[13] Dustbabaeva, N., Irsalieva, F., Kamalov, Z., Ziyadullaev, S., Akhmedov, K. Research of the association of IL-17A RS (2275913) gene polymorphism with allergic rhinitis associated with food co-sensitization. International Journal of Pharmaceutical Research, 2020, 12(2), стр. 758–762
[14] Eleonora, T., Shukhrat, Z., Zarina, N., ...Shokhruh, Y., Zaynitdin, K. Role of immuno-inflammatory reactions in the pathogenesis of clinical variants of coronary heart disease. Journal of Critical Reviews, 2020, 7(1), стр. 189–191
[15] Finlay B. B., See R. H., Brunham R. C. Rapid response research to emerging infectious diseases: lessons from SARS. Nat. Rev. Microbiol. 2004;2(7):602–607.
[16] Ghinai I., McPherson T. D., Hunter J. C., Kirking H. L., Christiansen D., et al. Illinois COVID-19 Investigation Team. First known person-to-person transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the USA. Lancet. 2020;S0140-6736(20)):30607–3. https://doi.org/10.1016/S0140-6736(20)30607-3
[17] Guzik T. J., et al. COVID-19 and the cardiovascular system implications for risk assessment, diagnosis, and treatment options. Cardiovascular Research. 2020. https:// doi.org/10.1093/cvr/cvaa106
[18] Hoffmann M., Kleine-Weber H., Schroeder S., Krüger N., Herrler T., Erichsen S., et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020;181:1–10. https://doi.org/10.1016/j.cell.2020.02.052

[19] Huang C., Wang Y., Li X., Ren L, Zhao J., Hu Y., et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497–506. https://doi.org/10.1016/S0140-6736(20)30183-5

[20] Inciardi RM, Lupi L, Zaccone G, Italia L, Raffo M, Tomasoni D et al. Cardiac Involvement in a Patient With Coronavirus Disease 2019 (COVID-19). JAMA Cardiology. 2020; [Epub ahead of print]. DOI: 10.1001/jamacardio.2020.1096

[21] Jain A. COVID-19 and lung pathology. Indian J. Pathol. Microbiol. 2020;63:171–172.

[22] Katzenstein F.-L. Diagnostic atlas of non-neoplastic lung disease. A practical guide for surgical pathologist. New York, NY: Demos Medical Publishing, 2016.

[23] Kim I-C, Kim JY, Kim HA, Han S. COVID-19-related myocarditis in a 21-year-old female patient. European Heart Journal. 2020;41(19):1859–1859. DOI: 10.1093/eurheartj/ehaa288

[24] Kochi A. N., Tagliari A. P., Forleo G. B., Fassini G. M., Tondo C. Cardiac and arrhythmic complications in patients with COVID-19. J CardiovascElectrophysiol. 2020;31:1003–1008. https://doi.org/10.1111/jce.14479

[25] Liu P. P., Blet A., Smyth D., Li H. The Science Underlying COVID-19: Implications for the Cardiovascular System. Circulation. 2020 Apr 15. https://doi.org/10.1161/CIRCULATIONAHA.120.047549. [Epub ahead of print].

[26] Liu PP, Blet A, Smyth D, Li H. The Science Underlying COVID-19: Implications for the Cardiovascular System. Circulation. 2020;CIRCULATIONAHA.120.047549. [Epub ahead of print]. DOI: 10.1161/CIRCULATIONAHA.120.047549

[27] Long B., Brady W. J., Koyfman A., et al. Cardiovascular complications in COVID-19. American Journal of Emergency Medicine. https://doi.org/10.1016/j. ajem.2020.04.048

[28] Mahmud E., Dauerman H. L., Welt F. G., Messenger J. C., Rao S. V., Grines C., et al. Management of Acute Myocardial Infarction During the COVID-19 Pandemic. Journal of the American College of Cardiology. 2020. https://doi. org/10.1016/j.jacc.2020.04.039

[29] Manish Bansal. Cardiovascular disease and COVID-19. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2020;14:247–250. https://doi.org/10.1016/j.dsx.2020.03.013

[30] Negmatovna, T.E., Khudayberdievich, Z.S., Sayfutdinovich, K.Z., ...Shukhratovna, K.F., Abdullaevna, A.G. Urate regulation gene polymorphisms are correlated with clinical forms of coronary heart disease. International Journal of Pharmaceutical Research, 2019, 11(3), стр. 198–202

[31] Park W. B., Kwon N. J., Choi S.J., Kang C. K., Choe P. G., Kim J. Y., et al. Virus isolation from the first patient with SARS-CoV-2 in Korea. J. Korean Med. Sci. 2020;35(7):e84. https://doi.org/10.3346/jkms.2020.35.e84

[32] Paul J-F, Charles P, Richaud C, Caussin C, Diakov C. Myocarditis revealing COVID-19 infection in a young patient. European Heart Journal - Cardiovascular Imaging. 2020;jeaa107. [Epub ahead of print]. DOI: 10.1093/ehjci/jeaa107

[33] Perrella A., Trama U., Bernardi F. F., Russo G., Monastra L., Fragranza F., et al. Editorial — COVID-19, more than a viral pneumonia. European Review for Medical and Pharmacological Sciences. 2020;24:5183–5185.

[34] Pomara C., Volti G. L., Cappello F. COVID-19 Deaths: Are We Sure It Is Pneumonia? Please, Autopsy, Autopsy, Autopsy! J. Clin. Med. 2020;9:1259. https://doi.org/10.3390/ jcm9051259

[35] Rey JR, Jiménez Valero S, PovedaPinedo D, Merino JL, LópezSendón JL, Caro-Codón J. COVID-19 y trombosissimultáneaen dos arteriascoronarias. Revista Española de Cardiología. 2020; [Epub ahead of print]. DOI: 10.1016/j.recesp.2020.05.004

[36] Rizaev J.A. Influence of fluoride affected drinking water to occurrence of dental diseases among the population // EurAsian Journal of BioMedicine, Japan, Vol. 4, Issue 5, P.1-5.

[37] Rizaev J.A., Khazratov A.I. Carcinogenic effect of 1,2 - dimethylhydrazine on organism as a whole // Problems of biology and medicine, 2020. № 1. Vol. 116. C. 269.

[38] Rizaev J.A., Khazratov A.I., Lisnichuk N.E., Olimjonov K.J., Reimnazarova G.J. Pathomorphological changes in the oral mucosa in patients with colon cancer // European Journal of Molecular & Clinical Medicine, vol.7, Issue 7, P.666-672.

[39] Sala S, Peretto G, Gramegna M, Palmisano A, Villatore A, Vignale D et al. Acute myocarditis presenting as a reverse Tako-Tsubo syndrome in a patient with SARS-CoV-2 respiratory infection. EuropeanHeartJournal. 2020;41(19):1861–2. DOI: 10.1093/eurheartj/ehaa286

[40] Sala S., Peretto G., Gramegna M., Palmisano A., Villatore A., Vignale D., et al. Acute Myocarditis Presenting as a Reverse Tako-Tsubo Syndrome in a Patient With SARS-CoV-2 Respiratory Infection. Eur. Heart J. 2020;41(19):1861–1862. https://doi.org/10.1093/eurheartj/ehaa286

[41] Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA et al. Fourth universal definition of myocardial infarction (2018). European Heart Journal. 2019;40(3):237–69. DOI: 10.1093/eurheartj/ehy462

[42] Thygesen K., Alpert J. S., Jaffe A.S., Chaitman B. R., Bax J. J., Morrow D. A., et al. ESC Scientific Document Group. Fourth universal definition of myocardial infarction (2018). Eur Heart J. 2019;40(3):237–269. https://doi. org/10.1093/eurheartj/ehy462

[43] Wallace A.H., Simpson J., Hirani N. Spencer's pathology of the lung. Vol. 1. Ed. Ph. Hasleton, D.B. Frieder. Acute lung injury. Cambridge: Cambridge University Press. 2013;1:342–365.

[44] Walls A. C., Park Y. J., Tortorici M. A., Wall A., McGuire A. T., Veesler D. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. Cell. 2020;180:1–12. https://doi.org/10.1016/j.cell.2020.02.058

[45] Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus – Infected Pneumonia in Wuhan, China. JAMA. 2020;323(11):1061–9. DOI: 10.1001/jama.2020.1585.

[46] World Health Organization Coronavirus disease 2019 (COVID-19) situation report—51. World Health Organization, 2020. https://www.who.int/docs/defaultsource/coronaviruse/situationreports/20200311-sitrep-51-covid-19.pdf?sfvrsnj1ba62e57_10

[47] Wrapp D., Wang N., Corbett K. S., Goldsmith J. A., Hsieh C. L., Abiona O. et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science. 2020;367(6483):1260–1263. https://doi.org/10.1126/ science.abb2507

[48] Xiong T. Y., Redwood S., Prendergast B., Chen M. Coronaviruses and the cardiovascular system: acute and longterm implications. European Heart Journal. 2020;0:1–3. https://doi.org/10.1093/eurheartj/ehaa231

[49] Xiong Y., Sun D., Liu Y., Fan Y., Zhao L., Li X., Zhu W. Clinical and high-resolution CT features of the COVID-19 infection: comparison of the initial and follow-up changes. Investig. Radiol. 2020. https://doi.org/10.1097/ RLI.0000000000000674.

[50] Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. The Lancet Respiratory Medicine. 2020;8(4):420–2. DOI: 10.1016/S2213-2600(20)30076-X

[51] Yao XH, Li TY, He ZC, Ping YF, Liu HW, Yu SC et al. A pathological report of three COVID-19 cases by minimal invasive autopsies. Chinese Journal of Pathology. 2020;49(5):411–7. DOI: 10.3760/ cma.j.cn112151-20200312-00193

[52] Yusufovna, K. N., Ziyadullaev, S. K., Agababyan, I. R., & Ismailov, J. A. (2021). Pharmacogenetics-A New Word in the Treatment of Rheumatoid Arthritis. Annals of the Romanian Society for Cell Biology, 259-265.

[53] Zhao D., Yao F., Wang L., Zheng L., Gao Y., Ye J., et al. A comparative study on the clinical features of COVID-19 pneumonia to other pneumonias. Clin. Infect. Dis. 2020;ciaa247. https://doi.org/10.1093/cid/ciaa24

[54] Zheng Y.-Y., Yi M.-T., Zhang J. -Y., Xie X. COVID-19 and the cardiovascular system. Nature reviews. 2020;17:259–260.

[55] Zheng Y-Y, Ma Y-T, Zhang J-Y, Xie X. COVID-19 and the cardiovascular system. Nature Reviews Cardiology. 2020;17(5):259–60. DOI: 10.1038/s41569-020-0360-5

[56] Ziyadullaev, S., Alimdjanovich, J.R., Rubenovna, I.A., Abduraimovich, J.I., Jiyanboyevich, S.Y. The effect of budesonide on the quality of life in patients with bronchial asthma. European Journal of Molecular and Clinical Medicine, 2020, 7(2), стр. 1760–1766

[57] Е. А. Коган, Ю. С. Березовский, Д. Д. Проценко, Т. Р. Багдасарян , Е. М. Грецов , С. А. Демура , Г. А. Демяшкин , Д. В. Калинин , А. Д. Куклева , Э. В. Курилина , Т. П. Некрасова , Н. Б. Парамонова, А. Б. Пономарев , С. Г. Раденска-Лоповок , Л. А. Семенова , А. С. Тертычный.ПАТОЛОГИЧЕСКАЯ АНАТОМИЯ ИНФЕКЦИИ, ВЫЗВАННОЙ SARS-COV-2 .СУДЕБНАЯМЕДИЦИНАRussianJournalofForensicMedicine • ISSN: 2411-8729 Том 6 | № 2 | 2020 Vol. 6 | Issue 2 | 2020.С.8-30.

[58] Коган Е.А. ,Березовский Ю.С. , Благова О.В. , Куклева А.Д., Богачева Г.А., Курилина Э.В., Калинин Д.В. , Багдасарян Т.Р., Семенова Л.А., Грецов Е.М., Эргешов А.Э. 2, Фомин В.В. Миокардиту пациентовс COVID-19, подтвержденный результатами иммуногистохимического исследования. ISSN 0022-9040. Кардиология. 2020;60(7). DOI: 10.18087/cardio.2020.7.n1209 С.4-10.