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COVID-19 Pandemic and Cardiovascular Diseases: Lessons and Prospects

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Abstract—This article is focused on the topicality of assessing complications and mortality from diseases of the circulatory system during the COVID-19 pandemic. The main variants of damage to the cardiovascular system, the mechanisms of their development, and risk factors are given. The long-term consequences of the new coronavirus infection for the heart and blood vessels are considered. In addition, the necessary measures to reduce the burden of disease after the pandemic are discussed.

Keywords: coronavirus infection, circulatory system diseases, myocarditis, chronic heart failure, heart transplantation

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Relationship between coronavirus infection and diseases of the circulatory system: The role of various factors. The COVID-19 pandemic, in addition to complications and deaths directly related to the infection, has significantly affected the system of care for cardiovascular diseases throughout the world and has led to an increase in mortality from diseases of the circulatory system [1]. This close relationship between infection and cardiovascular pathology is due to a number of factors.

In the first place, there is direct damage to the cardiovascular system caused by the virus, which can be manifested by myocarditis, the first manifestations of heart failure, rhythm disturbances, and other symptoms. Coronavirus infection in the acute period is often complicated by arterial and venous thrombosis, leading to fatal outcomes, and can also debut with myocardial infarction and stroke, which creates additional difficulties in patient routing and timely diagnosis. In addition, the infection can lead to a number of complications (they are combined into the so-called post-COVID syndrome), manifesting itself in an increased long-term tendency to thrombosis; aggravation of the course of previous diseases, including arterial hypertension and chronic heart failure; and the development of pulmonary hypertension in patients with pulmonary fibrosis. A certain role in heart damage can be played by the toxicity of antiviral drugs, particularly those affecting the duration of the QT interval, which was noted in the first wave of coronavirus infection, when these groups of drugs were widely used in treatment. According to the Almazov National Medical Research Center, among the 1412 patients who received hydroxychloroquine therapy in compliance with version 2 of the Interim Methodological Recommendations of the Russian Ministry of Health for the diagnosis and treatment of coronavirus infection [2], 14% experienced an increase in the QT interval to more than 500 ms, or more than 60 ms from the original.

The epidemic has had a very significant impact on the rates of mortality from diseases of the circulatory system because of the adjustments made to the process of organizing medical care. This is due not only and not so much to the shortage of beds and medical personnel as to changes in the behavior of the patients

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themselves, fear of infection and hospitals, and seeking medical help late [3]. In the context of the conversion of many hospitals to treat patients with coronavirus infection, the number of heart attacks and strokes did not increase during the epidemic and even decreased in many regions of the country. Most likely, this indicates that patients with mild symptoms did not consult a doctor in a timely manner (data from the Federal State Statistics Service (Rosstat) and monitoring of the decline in mortality from coronary heart disease conducted by the Russian Ministry of Health). In the long term, this problem may lead to an increase in the number of patients with chronic heart failure because of untimely emergency care or its absence in acute coronary pathology. Of course, the high burden on health care in all countries could not but affect the availability of medical care. At present, these drawbacks have partially been overcome thanks to telemedicine technologies and remote monitoring. However, the introduction of such services took time and required significant investments and training of staff and patients.

In Russia, in addition to the official register of patients with the new coronavirus infection, public associations and research centers have organized specialized registers, within the framework of which data were obtained on the prevalence of cardiovascular diseases as a comorbidity and on the prognosis of treatment for patients with coronavirus infection depending on the presence of diseases of the vascular system and complications. Thus, data from the ACTIV register have already been published, clearly demonstrating a relationship between cardiovascular pathology and mortality from coronavirus infection [4]. They are quite consistent with the data of the first study in China, in which diseases of the circulatory system were identified as the leading risk factors for severe and fatal COVID-19 [5]. In the ACTIV register, it was found that in the presence of arterial hypertension, the odds ratio for death was more than 3.0, and in the presence of chronic heart failure of functional classes III–IV, more than 6.0 [4]. Similar data were obtained in the registry of the Russian Society of Cardiology, according to which chronic heart failure was the most significant predictor of a poor prognosis not only immediate but also long-term [6], accounting for 55% of more than 100 cardiovascular complications of coronavirus infection and significantly surpassing rhythm disturbances (15.9%), acute coronary syndrome (9.9%), and myocarditis (7.9%) in terms of the registration frequency. Moreover, observation of patients for six months revealed that the presence of chronic heart failure significantly increased mortality (it exceeded 10% with a total of 2.4%) [7].

Pathogenetic aspects of damage to the cardiovascular system in COVID-19. Currently, several main mechanisms of myocardial damage in coronavirus infection are being considered [1, 8]. Hypoxemia contributes to myocardial dysfunction, especially in the development of acute respiratory distress syndrome. In addition, the activation of proinflammatory cytokines, systemic inflammation, and the development of immune inflammation in the heart muscle play a considerable role. Endothelial dysfunction, which inevitably develops against the background of infection, makes an additional contribution at the expense of hypercoagulability and systemic hypotension. Activation of the sympathetic nervous system can increase myocardial oxygen demand and further increase sensitivity to the damaging effects of hypoxia.

However, classical viral myocarditis does not develop as often as was believed. An analysis of 353 published articles showed that only 51 cases of coronavirus myocarditis were morphologically proven [9]. The following features are considered specific signs in the diagnosis of myocarditis: a significant increase in the D-dimer, ferritin, and C-reactive protein; a high level of troponin in the absence of other markers of myocardial necrosis; and an increased level of NT-proBNP. In addition, characteristic are the presence of global and/or regional disturbances of myocardial contractility; thickening of the wall of the left ventricle; and criteria for inflammation, detected using magnetic resonance imaging and data from an endomyocardial biopsy [10]. Today, many Russian researchers are actively studying the morphological changes in the heart of patients who have died of coronavirus infection. In particular, it has been shown by the Almazov Center that in most cases the death was caused by microthrombosis and endothelial damage, while signs of the presence of the virus itself in myocardial cells were not detected even in those patients who had been diagnosed with myocarditis during their lifetime on the basis of clinical and laboratory data. The pathogenesis of heart disease is still not quite clear and is being actively studied.

One of the factors contributing to a severe course of infection and heart damage may be vitamin D deficiency, which is widespread throughout the world; this circumstance initiated the search for relationships between the level of vitamin D supply and the pathology of the cardiovascular system as a whole. Work [11] was the first to point to a reduction in the risk of cardiovascular disease with a normal level of vitamin D supply, and the results of 24 population-based studies conducted in 15 countries demonstrated an increase in this risk in winter compared to summer [12].

Research at the Almazov Center revealed a 3.79-fold increase in the risk of a severe course and a 4.07-fold increase in mortality with COVID-19 in conditions of extreme vitamin D deficiency regardless of the presence of obesity, type 2 diabetes mellitus, and diseases of the cardiovascular system [13]. Considering the frequent development of hypokalemic syndrome in patients with COVID-19 and the significant contribution of electrolyte disturbances to an unfavorable outcome of the disease, we performed a number of studies

to assess the state of the renin–angiotensin–aldosterone system (RAAS)—a signaling pathway responsible in the body for the regulation of blood pressure [14]. Despite the presence of hypokalemia in a quarter of the patients examined, both in them and in patients with normokalemia, no activation of the RAAS was detected in the form of an increase in the level of plasma aldosterone and/or renin under vitamin D deficiency. There were also no significant differences in the degree of lung tissue damage, indicators characterizing the severity of systemic inflammation, the severity of COVID-19, the duration of hospitalization, and mortality among patients with and without electrolyte disorders [15].

The presence of myocardial damage in COVID-19 due to hypoxia, microthrombosis, cardiotoxic effects of drugs, severe systemic inflammation, and other pathogenetic factors leads to two main consequences, both in the acute and in the long-term period. As was already noted, coronavirus infection can initiate the occurrence of heart failure, as well as significantly worsen the condition of patients with its chronic form. The second most common complication against the background of COVID-19 and after it is the development of various kinds of atrial and ventricular arrhythmias, including an increased risk of sudden death [16]. The Almazov Center is dynamically monitoring patients with acute coronavirus infection using a multiday noninvasive ECG recorder. Observations over 21 days of hospitalization and 2 months after discharge from the hospital revealed cardiac arrhythmias in 50% of patients, including atrial fibrillation, and ventricular arrhythmias. In a number of cases, indications for the implantation of a cardioverter and resynchronizing devices have been noted, especially in patients with preexisting chronic heart failure.

In addition to the emergence of life-threatening conditions, many chronic traditional high cardiovascular risk factors are exacerbated during and after COVID-19. Thus, the coronavirus infection itself, as well as many drugs used to treat it (steroid hormones, anticytokine drugs, Janus kinase inhibitors), contribute to an increase in blood pressure and, in some cases, to hyperlipidemia and the risk of diabetes mellitus. Often, after infection, a destabilization of the course of arterial hypertension is observed, as well as disturbances in the circadian rhythm of blood pressure (BP) regulation, an increase in the need for antihypertensive drugs, and an increase in BP variability [8]. This requires careful monitoring of this indicator during and after the disease. A certain negative role in the stability of blood pressure control on a population scale could be played by the fact that, at the beginning of the pandemic, the involvement of the renin–angiotensin–aldosterone system in the pathogenesis of the infection gave rise to concerns about taking drugs that block the renin–angiotensin system. Quite quickly, as early as May 2020, both European and Russian healthcare structures and scientific communities responded to these concerns in their recommendations [17, 18] by publishing scientific data and the expert position that the abandonment of angiotensin-converting enzyme inhibitors is not only unnecessary but also leads to negative consequences. Nevertheless, the abandonment of these drugs in a certain period was still observed, which could have led to a temporary violation of adherence to treatment in chronic pathology.

Coronavirus infection and heart transplantation. After heart transplantation, infectious complications are one of the leading causes of morbidity and mortality. Due to immunosuppression, recipients are characterized by a prolonged incubation period, atypical symptoms of infections, and initially altered results of laboratory and instrumental diagnostics, which hinder making a diagnosis. In patients after heart transplantation, the features of infection can be determined by the presence of initial leukopenia and lymphopenia during immunosuppressive therapy, which prevents an excessive response to lymphocyte infection and the expression of proinflammatory cytokines (IL-2, IL-3, IL-4, IFN-y, and TNF-a). In addition, glucocorticoids suppress the immune response by reducing the number of immunocytes and weakening the signal of T-cell receptors. At present, general recommendations have been formulated for the management of patients with COVID-19 after organ transplantation [19], but many questions remain unanswered regarding the management of patients with heart transplantation. Among those observed at the Almazov Center, 82 cases of infection were noted in 69 patients after heart transplantation. From the first day of the onset of clinical symptoms, part of the immunosuppressive therapy (mycophenolic acid/everolimus) was temporarily discontinued. Treatment at the outpatient stage was started from the first day and included antiviral therapy, mucolytics, vitamin C, and anticoagulants. If the disease began with a febrile fever, then, due to the high risk of mixed infection, empirical antibiotic therapy with levofloxacin was prescribed. There were no deaths. In 59 cases, patients were treated on an outpatient basis, in 23 they were hospitalized, but there was no severe course of the disease. We also showed that remote counseling of patients with a transplanted heart, compliance with the continuity of treatment at the place of residence, and account for the recommendations of supervising transplant doctors contributed to the timely diagnosis of infection, the rapid initiation of therapy, and the course of COVID-19 without complications. Reducing the use of immunosuppressive drugs (antiproliferative) for up to 14 days contributed to the fight against infection and was not accompanied by an acute crisis of rejection and/or a decrease in the function of the graft [20].

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If we talk about the forecast of the situation and what we should expect in the near future, then two mutually aggravating factors—the emergence of new cardiovascular diseases due to the infection and organizational problems in providing care to patients with diseases of the circulatory system during the pandemic—will certainly lead to an increase in the absolute number of patients requiring specialized cardiac care and rehabilitation. This makes it necessary to create and improve the existing infrastructure for the examination and treatment of such patients and additional education and advanced training of medical workers with account for the specifics of managing patients who have had coronavirus infection.

The main areas that will ensure the achievement of results in the short and long term include the following.

• Translational technologies, the fastest introduction of the latest scientific achievements and innovative methods into daily clinical practice.

• Value approach in health care and focus on the needs of patients.

• Coordination of care at the regional level based on the concept of a cardiovascular risk management system. Ensuring the continuity of care, interaction between hospitals and polyclinics, continuous monitoring of work efficiency using information systems at the regional level, registers.

Therefore, the epidemic of coronavirus infection has a significant and diverse impact, potentially contributing to an increase in mortality from diseases of the circulatory system. To understand their causes and the severity and duration of fluctuations in mortality rates in regions with different resilience of the healthcare system to the challenges of the pandemic, it is necessary to ensure careful monitoring of all levels of healthcare organization, targeted work with personnel, and further scientific research to provide reliable data and new approaches. It is also necessary to pay attention to drug provision, especially in high-risk groups; the formation of new criteria for the quality of medical care; and, finally, targeted work with the population, which should form correct public perceptions of the risks and necessary actions on the part of patients at the onset of the disease and after discharge from the hospital.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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