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EPIDEMIOLOGICAL AND CLINICAL ASPECTS OF CARDIOVASCULAR DISEASES IN NOVEL CORONAVIRUS INFECTION

A review of the published data on the epidemiological and clinical aspects of cardiovascular diseases in the novel coronavirus infection is presented. Summarizing the results of studies by many authors, we state that the tropism of the new coronavirus infection to the cardiovascular system is manifested through ACE2 receptors, immune, cytokine inflammation, increased coagulation activity. These pathophysiological characteristics are especially evident in concomitant cardiovascular pathology, leading to decompensation of the existing pathology and often to a fatal outcome. Thus, cardiovascular disease is a dangerous risk factor for the development of fatal consequences in the current pandemic situation.

Keywords: SARS-CoV-2, COVID-19, cardiovascular disease, ACE2, arterial hypertension, myocarditis, arrhythmia.

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The novel coronavirus infection (SARS-CoV-2) was first reported in December 2019 in Wuhan, Hubei province, China. This viral infection quickly spread throughout the world at an alarming rate. The SARS-CoV-2 virus is characterized by high virulence and lethality. The World Health Organization declared COVID-19 a pandemic in March 2020. According to WHO, as of February 15, 2021, 108.2 million confirmed cases of COVID-19 were registered worldwide, with more than 2.3 million deaths [32]. In Russia, according to epidemiological data, as of February 15, 2021, more than 4 million cases and 82 thousand deaths were registered [1].

The standard clinical picture of the novel coronavirus infection was characterized as follows. The incubation period of the disease lasted from 3 to 7 days. The most common symptoms of the disease in patients with COVID-19 were fever (91.7%), cough (75.0%), fatigue (75.0%) and diarrhea (39.6%), and the most common comorbidity was hypertension (30.0%) and diabetes mellitus (12.1%) [54]. 80% of patients suffered from the disease in a mild and asymptomatic form, 15% - in severe and 5% - critical, requiring intensive therapy and mechanical ventilation [36]. One of the main diagnostic signs of the novel coronavirus infection is developing pneumonia with characteristic changes in the computed tomography of the chest - a "frosted glass" seal.

In a retrospective study by Navaratnam AV et al. [2] for the period from March 1 to May 31, 2020, out of 91,541 adult patients who were hospitalized in

England, 30.8% died in hospital, with the largest percentage of deaths occuring at the beginning of March 2020 - 52.2 % and up to 16.8% at the end of May 2020. The most susceptible to hospital mortality are the elderly, men and people of Asian or mixed ethnicity. The ratio of patients by race to Caucasians, Asians, and Blacks was 13.0:1.4:1.0. Asian ethnicity was associated with higher odds of death, although this differed between South Asian ethnicity (OR-1.246; 95% CI 1.152-1.48; n = 5117) and other Asian ethnicities (OR-1.108; 95% CI 0.973 -1.262; n = 2000). The higher hospital mortality among people of Asian or mixed ethnicity requires more detailed further study.

Despite the fact that the disease is mainly characterized by damage to the respiratory system, there is growing evidence of an increase in the number of COVID-19 patients with cardiovascular comorbidity, which has led to higher mortality among patients with COVID-19.

In the study of deaths from COVID-19 by age group 54 and under, 55 to 64, and 65 and over, across 6 weeks as of April 12, 2020 in 16 countries including Austria, Belgium, Brazil, Canada, China, France, Germany, India, Iran, Israel, Italy, the Netherlands, Portugal, Russia, South Korea, Spain, Sweden, Switzerland, Turkey, the United Kingdom and the United States - 178,568 deaths from COVID-19 were registered, with a total population of about 2.4 billion people [50]. The mortality rate was 8.1 times higher in patients older than 55 compared to people younger than 55 years old, and with the age of 65 years and older, the mortality rate was 62 times higher. In men, the mortality rate is 77% higher than in women. The United States has the highest number of COVID-19 deaths per week, followed by several Western European countries initially affected by COVID-19, followed by Canada and Brazil, then Germany and Austria. China and South Korea had the lowest death rates from COVID-19 among the countries in the sample. Comorbidities such as hypertension, diabetes mellitus and obesity are associated with higher mortality from COVID-19 [21]. Since the number of comorbid conditions increases with age, this logically explains the increased mortality in older patients. Although disease-related mortality is higher in the elderly and in patients with other conditions such as cardiovascular disease, changes associated with reduced immunity may explain the increased susceptibility to infection and high mortality due to novel coronavirus infection in the elderly [23].

Most publications on the analysis of the course and clinical outcomes of COVID-19 relate to middle-aged and elderly patients. However, due to the rapid spread of the SARS-CoV-2 virus, it is important to note the course of the disease and the risk of adverse events and death in young patients. In a study by Cunningham JW. et al. [13] for the period from 01.04. to 30.06.2020, 3222 patients with COVID-19 aged 18 to 34 years were hospitalized in 419 US hospitals, their average age being 28.3 ± 4.4 years, 57% of which were of the Negroid race and Hispanics. In the study group, comorbid pathology was widespread: obesity (36.8%), arterial hypertension (16.1%), diabetes mellitus (18.2%). The mortality rate was 2.7%, which is lower than in the older age group, but twice as high as the mortality rate in young patients with acute myocardial infarction without COVID-19. Patients with multiple risk factors (obesity, arterial hypertension and / or diabetes mellitus) were characterized by a comparable risk of adverse outcomes to patients with COVID-19 in the 35-64 age group without the listed cardiovascular risk factors.

Given the rising incidence of COVID-19, the study's findings highlight the importance of COVID-19 prevention measures across all age groups. The high prevalence of comorbid pathology and the associated increase in mortality even in the subgroup of young patients with COVID-19 determine the need to promote healthy lifestyles and correct modifiable risk factors such as hypertension and obesity.

Previous outbreaks of the novel coronavirus infection, such as Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS), have had cardiovascular complications as well as cardiovascular comorbidities [14,57]. The most frequent complications were hypotension, myocarditis, arrhythmias and sudden cardiac death [49,52]. The novel coronavirus infection also has similar complications from CVS.

In China, in a large retrospective analysis of 72,314 patient histories, of which 44,672 (61.8%) had confirmed cases of COVID-19, 16,186 (22.4%) were suspected of having it, and 889 (1.2%) had asymptomatic cases [15]. Among the confirmed cases, 12.8% had hypertension, 5.3% - diabetes and 4.2% - cardiovascular disease [15]. Interestingly, these figures are lower than the prevalence of cardiovascular risk factors in a typical Chinese population, but it is important to mention that they are not age-standardized and that there was no data on comorbidities in 53% of cases [56].

A study of 5700 patients with COVID-19 from New York, Long Island and Westchester County (USA) showed that 56.6% of them had hypertension, obesity - 41.7%, diabetes - 33.8%, coronary heart disease - 11.1% and congestive heart failure 6.9%, which were the most common comorbidities [35]. For comparison, according to the US Centers for Disease Control and Prevention in 2017, the prevalence of hypertension, obesity and diabetes was 45%, 42.4% and 10.5%, respectively [7,8,9].

In an early retrospective analysis of 138 patients in Wuhan, China, approximately 50% of patients with COVID-19 had one or more comorbidities. Moreover, in patients admitted with severe COVID-19, this proportion reached 72% [48]. It remains unclear whether diabetes, hypertension and other cardiovascular diseases are causally related or age-related. However, it is important to note that patients with a severe form of the disease are more likely to have comorbidities, including cardiovascular disease.

In a study by Li S. et al. in patients with a severe form of the disease, there was a high expression of inflammatory cytokines (IL-2, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1A and TNF-α), the so-called "cytokine release syndrome" or "cytokine storm "[29]. Many researchers argue that the level of serum interleukin-6 is a biomarker for the severe, highly-lethal form of the disease [12,18,31,44,47]. In the meta-analysis of 6212 patients [45], IL-6 and IL-10 were biomarkers of the severe, more lethal form of COVID-19; these biomarkers were significantly higher in severe patients compared to non-severe patients (OR - 18.63, 95% CI 10.91 - 26.35, P <0.00001; OR - 2.61, 95% CI 2.00-2.32, P <0.00001; respectively), it was also higher in patients with fatal outcomes compared to survivors (OR - 57.82, 95% CI 10.04 -105.59, p=0.02; OR - 4.94, 95% CI 3.89 - 6.00, p <0.00001; respectively).

In patients with pre-existing heart failure, there was an increased expression of angiotensin converting enzyme 2 (ACE2) both at the mRNA level and at the protein level, causing dysfunction of capillary endothelial cells, thereby affecting small vessels. This means that when infected with the SARS-CoV-2 virus, these patients have a higher risk of heart attack and severe form of the disease. The results of this study explain the high rate of severe cases among COVID-19 patients with cardiovascular disease [10]. The PURE study [41], which included 10,753 participants from 14 countries of 5 continents of the world, where the effect

of ACE2 level on the risk of death from CVD, an increase in heart failure (OR - 1.27; 95% CI 1.10-1.46), myocardial infarction (OR - 1.23; 95% CI 1.13-1.33), stroke (OR - 1.21; 95% CI 1.10-1.32) and diabetes (OR - 1.44 ; 95% CI 1.36-1.52) was researched. The results were not influenced by gender, age, nationality, and traditional risk factors. Compared to other risk factors, such as smoking, hypertension, diabetes, dyslipidemia, obesity, the ACE2 level was the most informative predictor of death from heart failure, stroke and myocardial infarction. Thus, an increased concentration of ACE2 is closely associated with the risk of death, cardiovascular complications and diabetes. It was also noted that ACE2 levels were higher in men, the elderly, people who had a history of smoking, had diabetes, had a higher BMI, high blood pressure, and higher blood lipid concentrations.

In a study by Shi S. et al. [39] of 416 patients, 57 were fatal. Among the deceased, heart damage accounted for 19.7%, coronary heart disease - 10.6%, heart failure - 4.1%, and 5.3% - cerebrovascular diseases.

It is noted that more than 7% of patients have had cardiovascular complications in the form of myocardial damage [24,51]. Cardiac manifestations in COVID-19 patients included myocardial infarction (MI), cardiac arrhythmias, cardiac arrest, heart failure, and blood clotting disorders ranging from 7.2% to 33%. Heart damage in patients with COVID-19 is caused both by direct damage to myocardial cells, mediated by ACE2 receptors, as suggested by some studies, and systemic inflammation, which causes indirect damage to myocytes [16]. The risk of morbidity and mortality from COVID-19 is higher in patients with CVD. An increase in ACE2, and in response, an increase in angiotensin II associated with the renin-angiotensin-aldosterone system, are key mechanisms for the development of hypertension, atherosclerosis, and heart failure [5,17]. In a study of 187 patients infected with SARS-CoV-2, 35% had a history of cardiovascular disease. The mortality rate from COVID-19 was 10.5% higher in patients with concomitant CVS pathology, and 52% higher in patients with heart failure. In patients with CVD, an elevated cardiomarker troponin T was detected (up to 55%) [40].

Myocardial damage of non-ischemic origin can manifest itself in the form of myocarditis, cardiomyopathy. Acute myocardial injury can be accompanied by increased levels of lactate and other inflammatory markers, including C-reactive protein, procalcitonin, cardiac enzymes such as troponin I, troponin T, and N-terminal-pro hormone BNP (NT-proBNP). ProBNP and BNP levels are usually elevated in myocarditis due to acute myocardial injury and possible ventricular dilatation [20,25,37,53]. Although a negative troponin result does not exclude myocarditis, especially for atypical forms or for chronic patients, in patients with COVID-19, the level of cardiac troponins and NT-proBNP may increase due to myocardial stress, a possible complication of severe respiratory illness, indicating an unfavorable course [22]. But one cannot exclude the development of type 1 myocardial infarction due to rupture, thrombosis of atherosclerotic plaques as a result of hypercoagulation. A history of concomitant ischemic heart disease should be especially taken into account. This requires selective coronary angiography in these patients. Also, the development of myocardial ischemia due to sepsis, leading to increased myocardial oxygen demand, is not excluded [11]. Myocardial ischemia in this case may be aggravated by the development of type 2 myocardial infarction.

It is believed that the pathophysiology of myocarditis is associated with the direct damaging effect of the virus on the myocardium and damage due to the immune response of the human body caused by a cytokine storm [28]. The cytokine storm triggers the activation of T-lymphocytes and further release of inflammatory cytokines that stimulate more T-lymphocytes, resulting in a positive feedback loop of immune activation and myocardial damage. It is believed that the sensitivity of T-lymphocytes to cardiomyocytes results from the interaction between the heart-produced hepatocyte growth factor (HGF) and the HGF receptor on naive T-lymphocytes (c-Met) [27].

The clinical picture of SARS-CoV-2 myocarditis varies depending on the severity. Some patients may have relatively mild symptoms such as fatigue and shortness of breath [20,25], while others may have chest pain or tightness during exertion [37,53]. The condition of many patients with deterioration of the condition is manifested by symptoms of tachycardia and acute heart failure up to cardiogenic shock [20,25,53]. Mild cases of myocarditis often remain undetermined. It may manifest on an electrocardiogram (ECG) and in an increase in cardiomarkers (troponins I and T). In myocarditis, ECG changes similar to those in pericarditis, such as elevation or depression of the ST segment, can be observed, however, these data are not sensitive in detecting the disease, and their absence is no exception [6]. With myocarditis, other ECG changes can also be observed, including new-onset bundle branch block, lengthening of the QT interval, ventricular premature beats and bradyarrhythmia with the development of atrioventricular block, pseudoinfarction. For a more accurate diagnosis of myocarditis, imaging methods such as echocardiography (ECHOKG), magnetic resonance imaging (MRI) or computed tomography (CT) of the heart with enhanced contrast, which exclude damage to the coronary arteries, are used, since many patients have concomitant cardiovascular pathology. Echocardiography is easier to deploy under time constraints, portable, affordable, easy to quickly disinfect and monitor. Signs of myocarditis on echocardiography may include an increase in wall thickness, dilatation of the heart chambers, and pericardial effusion in the presence of systolic ventricular dysfunction [26]. More informative methods are MRI and CT of the heart with enhanced contrast, allowing differentiation from other cardiac pathology. But these methods require more thorough deep disinfection after use, given the high infectivity of the new coronavirus infection. For definitive diagnosis, some researchers recommend endomyocardial biopsy [6,26]. The difficulties in carrying out this study lie in the lack of proper experience and false negative results. Biopsy specimens should be immunohistochemically tested for inflammatory changes and RNA / DNA isolation to check for viral genomes [55]. This method involves the identification of biomarkers for the development of a diagnostic test for SARS-CoV-2 myocarditis.

The mechanism of heart rhythm disturbances has not yet been clarified and remains controversial, although manifestations of arrhythmia are also not uncommon. Arrhythmia was one of the possible clinical characteristics of cardiovascular complications in patients with COVID-19. In one observational study in Hubei Province of China, 137 COVID-19 patients had heart palpitations and they accounted for 7.3% of the clinical manifestations [30]. Wang D. et al. [48] in their study reported that 16.7% of 138 patients had arrhythmias, manifested in severe cases of the disease, characterized in the form of paroxysms of atrial fibrillation. The nature of the development of arrhythmia remains unexplored, the real figures are unknown due to the small sample size. Perhaps the arrhythmias were the result of electrolyte imbalance or the occurrence of pre-existing arrhythmias, or as a result of the development of myocardi-

tis. Peretto G. et al. reported that 78.7% of patients with myocarditis had ventricular arrhythmias that depended on the stage of myocardial injury. Monomorphic ventricular tachycardia and regular ventricular arrhythmias were more common in patients with cured than with acute myocarditis [33]. The pathophysiology of arrhythmias includes, in addition to direct damage to cardiomyocytes, possible infection of pericytes, causing myocardial ischemia as a result of multivessel disease [10,34]. The influence of pro-inflammatory cytokines on the occurrence of arrhythmias is not excluded.

Research by Arentz M. et al. showed that 67% of critically ill COVID-19 patients needed vasopressors, and 33% developed cardiomyopathy [3]. This study does not exclude sepsis-associated cardiomyopathy characterized by reversible myocardial dysfunction. Previous studies have shown that myocardial damage occurs due to increased production of nitric oxide, which suppresses the response of cardiomyocytes to calcium and β1-adrenergic receptors [38]. The main signs of sepsis-associated cardiomyopathy were left ventricular dilatation, impaired ejection fraction, and recovery in 7-10 days. Difficulties arise in the differential diagnosis of stress-induced cardiomyopathy, sepsis-induced cardiomyopathy, and acute coronary syndrome.

The novel coronavirus infection with concomitant CVS pathology can also be complicated by heart failure. In a study carried out in Israel, which included 100 patients with COVID-19, whose average age was 66 years, in 90% of cases - ejection fraction was intact, and the most frequent pathological findings were right ventricular dilatation (39%) and left ventricular diastolic dysfunction (16%) [42]. Similar results were obtained in New York in a study of 105 patients of similar age [4].

Dwelling on the treatment of the novel coronavirus infection and associated cardiovascular diseases is not the purpose of this literature review. Vaccination is at the forefront of stopping the spread of this viral infection around the world. Given that there are new variants of SARS-CoV-2 501Y.V1 (B.1.1.7) in the UK [46] and 501Y.V2 (B.1.351) in South Africa [43], the end of the pandemic is possible only when vaccines effective against circulating variants will be evenly distributed around the world.

Conclusion. In conclusion, we state the tropism of the novel coronavirus infection to the cardiovascular system, exerting an effect through the ACE2 receptors, immune, cytokine inflammation, increased coagulation activity, etc. These pathophysiological characteristics are especially evident in concomitant cardiovascular pathology, leading to decompensation of the existing pathology and often to a fatal outcome. Thus, cardiovascular disease is a dangerous risk factor for the development of fatal consequences in the current pandemic situation.

The COVID-19 pandemic has proven the need for a more thorough study of the effect of SARS-CoV-2 on cardiovascular pathology, both during the period of illness and in the long-term, as well as making adjustments to many pathogenetic mechanisms and clinical features of the consequences of the disease for the cardiovascular system, to further develop the latest guidelines for curation of such patients.

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