COVID-19 AND CARDIOVASCULAR SYSTEM DAMAGES

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The outbreak of new coronavirus disease (COVID-19) caused by SARS-CoV-2 is the biggest medical problem of the 21st century. Although the virus primarily affects the lungs, and the clinical manifestations of the disease are dominated by respiratory symptoms, but it significantly affects the risk of the development and clinical course of cardiovascular disease. It should be noted that heart disease with COVID-19 can be observed in patients with chronic diseases of the cardiovascular system, as well as in patients who had no signs of heart disease before this infection. Concomitant cardiovascular disease is common in patients with COVID-19, and these patients have a higher risk of morbidity and mortality. The mechanisms underlying the damage to the cardiovascular system are direct invasion, inflammation, thrombosis, autoantibody synthesis and hypoxemia.

Purpose *– to analyze the data of the current literature of COVID-19 impact on the course of cardiovascular disease, mortality and prognosis.*

Conclusions. *Concomitant cardiovascular disease is common in patients with COVID-19, and these patients have a higher risk of morbidity and mortality. Cardiovascular manifestations of COVID-19 are acute coronary syndrome, arrhythmia, heart failure, thromboembolic complications. Patients on COVID-19 with cardiovascular events have a worse prognosis.*

КОРОНАВІРУСНА ХВОРОБА (COVID-19) ТА СЕРЦЕВО-СУДИННА СИСТЕМА

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Спалах нової коронавірусної хвороби (COVID-19), спричинений SARS-CoV-2, є найбільшою медичною проблемою XXI століття. Хоч вірус, у першу чергу, вражає легені, і в клінічних проявах захворювання переважають респіраторні симптоми, проте він суттєво впливає і на ризик розвитку та клінічний перебіг хвороб серця та судин. Слід зазначити, що ураження серця при COVID-19 можуть спостерігатися як у хворих із хронічними захворюваннями серцево-судинної системи, так і у пацієнтів, у яких до цієї інфекції не було ознак ураження серця. Коронавірус взаємодіє з серцево-судинною системою на багатьох рівнях, збільшуючи захворюваність пацієнтів із супутніми серцево-судинними захворюваннями та провокуючи ушкодження і дисфункцію міокарда.

Мета роботи *– проаналізувати дані сучасної літератури щодо впливу COVID-19 на перебіг серцево-судинних захворювань, смертність та прогноз.*

Висновки. *Супутні серцево-судинні захворювання часто зустрічаються у пацієнтів, хворих на COVID-19, і ці пацієнти мають більш високий ризик захворюваності та смертності. Серцево-судинними проявами COVID-19 є гострий коронарний синдром, аритмія, серцева недостатність, тромбоемболічні ускладнення. Пацієнти із серцево-судинними проявами, хворі на COVID-19, мають гірший прогноз.*

Introduction

The 21st century is a time for all scientists and physicians to reinterpret the role of coronaviruses in the development of human diseases and changes of approaches to understanding their epidemic potential.

Today, COVID-19 is a global pandemia. The first outbreak of pneumonia of unknown origin was detected in Wuhan, China, in Hubei Province, in December 2019 [1,3]. After the virus was identified, the causative agent of this pneumonia was originally called the new coronavirus of 2019 (2019-nCoV), but on January 30, 2020, the World Health Organization (WHO) officially named it coronavirus 2, which causes severe acute respiratory syndrome (SARS-CoV-2), and on 11 February 2020 approved the official name of the disease as «coronavirus disease 2019 (COVID-19)». Since December 2019, when the first case of COVID-19 was reported in China, the disease has spread worldwide. On March 11, 2020, the WHO declared COVID-19 as pandemia [2].

As of March 20, 2022, the coronavirus has spread to 192 countries, 470 million people worldwide have fallen ill, and more than 6 million have died. The impact of COVID-19 has global medical, psychological and socio-economic aspects. This is probably the biggest global threat in the 21st century [4].

Purpose of the study

To analyze the data of the current literature on the impact of COVID-19 on the course of cardiovascular disease, mortality and prognosis.

Main part

Patients with COVID-19 have a high prevalence of cardiovascular disease, and > 7 % of patients have myocardial lesions due to infection (22 % of patients are in critical condition). Pathological changes in the heart in coronavirus disease are due to various pathogenetic mechanisms associated with direct toxic effects of the virus, immunopathological disorders, inflammatory endothelial damage and the development of its dysfunction, increased coagulation and decreased fibrinolytic activity. The interaction of these factors leads to both inflammation and myocardial ischemia [5, 7].

Arrhythmias (atrial fibrillation, ventricular tachyarrhythmia, and ventricular fibrillation), heart disease, elevated levels of high-sensitivity troponin I (hs-cTnI) and creatinkinase (heart failure), myocarditis, disseminated intravascular coagulation (DIC) were found to be the most common complications in one of China's coronavirus hospitals.

Heart failure, cardiac arrhythmias and cardiac arrest were observed in 20-40 % of hospitalized patients [3, 6].

45 % of those, admitted to hospitals in Hubei Province with COVID-19, had concomitant cardiovascular disease (coronary heart disease, hypertension (10,5 %), atherosclerosis) and concomitant non-cardiovascular disease system – diabetes, lung disease, obesity [6].

The highest number of hospitalized COVID-19 patients was reported in New York City with common comorbidities: hypertension (57 %), obesity (42 %), and diabetes mellitus (34 %) [8].

Taking into consideration the heterogeneity of exposure, the inclusion of numerous pathogenetic mechanisms, differences in the severity of the infectious process and individual condition of the patient at the time of infection, it is advisable to dwell on the main provisions of coronavirus on the cardiovascular system and features of patients with certain diseases of the cardiovascular system.

Lesions of the cardiovascular system in patients with COVID-19. The surface of the SARS-CoV-2 shell contains protein S, which binds to the S1 subunit of angiotensin-converting enzyme type 2 (ACE2). ACE2 is expressed in human cells and initiates viral invasion. Then the virus with transmembrane serine protease enters the cell. ACE inhibitors and TMPRSS2 must be expressed in the same cell to initiate infection. Once in the host cell, viral mRNA is transmitted and produces viral proteins, which are then cleaved and collected to form new viruses. New viruses merge with the plasma membrane, enter the extracellular space and are ready to invade other cells [9, 10].

The affinity of SARS-CoV-2 for ACE inhibitors is stronger than that of SARS-CoV. ACE inhibitors are mainly expressed in the alveolar epithelium of the lungs type I and II, brain, liver, kidney, pericyte, cardiomyocytes, enterocytes of the small intestine and endothelial cells. The data confirm the theory of viral invasion of cardiomyocytes. Invasion can occur by spreading through the blood. More than 7.5 % of the myocardium expresses ACE, which contributes to direct heart damage [10].

However, damage to the cardiovascular system in COVID-19 is multifactorial. Invasion causes an immune response and inflammation, and ultimately myocardial necrosis. For several days, necrosis contributes to contractility and other clinical manifestations, which leads to increased levels of myocardial biomarkers, abnormalities in electrocardiography and tachocardiography [8, 10].

Inflammation causes the release of cytokines, especially interleukin-6, and damage to cardiomyocytes. Damage to the cardiovascular system in inflammation is more pronounced in hospitalized patients with severe or critical COVID-19. Excessive production of cytokines leads to an abnormal inflammatory response, called a cytokine storm, and is thought to be responsible for cardiovascular events in patients with COVID-19. Inflammation also increases the incidence of intravascular coagulopathy along with the risk of coronary thrombosis [7, 9].

On the other hand, autoantibodies are also involved in the pathogenesis of cardiovascular manifestations. There is molecular mimicry between the SARS-CoV-2 protein and the S2 regions of cardiac myosin. Invasion of SARS-CoV-2 also reduces the regulation of ACE2 expression, which acts as a protective agent against fibrosis in cardiomyocytes. Therefore, decreased ACE activity exacerbates cardiovascular disease [8].

Pulmonary dysfunction in COVID-19 causes hypoxemia and insufficient oxygen supply to many organs, including the heart. In addition, myocardial oxygen demand increases due to inflammation. This situation gives rise to ischemic myocardial damage and its consequences [5, 7].

Cardiovascular manifestations in patients with COVID-19. In 20-30 % of the hospitalized patients with coronavirus disease changes in the cardiovascular system were determined. In some patients there were only cardiovascular manifestations, despite the lack of respiratory symptoms [5, 6, 12].

Usually patients with cardiovascular disease had old age and other comorbidities, which significantly increased the risk of severe COVID-19. This can be caused by degenerative disorders of the immune system in the elderly in contrast to children who have stronger innate immunity, fewer comorbidities, differences in viral receptor maturation and previous exposure to other types of coronavirus, acute coronary syndrome (ACS) and arrhythmia [11].

Acute coronary syndrome is one of the initial cardiovascular manifestations of COVID-19, which is marked by elevation of the ST segment on the electrocardiogram. It is noted that ACS may be caused by plaque rupture, coronary vasospasm and microthrombus formation [5, 13].

Rhythm disorders are more noticeable in patients with pathologies of the structure and function of the heart. Arrhythmia in COVID-19 is due to direct myocardial infection and activated sympathetic nervous system. On the other hand, arrhythmia may be caused by side effects of drugs used in COVID-19. Arrhythmia is observed in 16.7 % of patients with COVID-19 and in 44 % of patients in the intensive care unit. Palpitations after arrhythmia were found in 7.3 % of patients on COVID-19. Types of arrhythmia include atrial and ventricular fibrillation,

ventricular tachycardia. Malignant arrhythmia is more common in patients with elevated cardiac troponin [13].

Heart failure is observed in 23 % of patients, while myocardial damage (myocarditis and myocardial infarction) is observed in 7.2-17 % of patients. Heart failure, myocarditis and myocardial infarction are the result of systemic inflammation and hypoxia. Coagulation disorders may increase the risk of thromboembolic complications [7, 12].

Ischemic heart disease and COVID-19. The versatility of the mechanisms of adverse effects of coronavirus disease on the heart and coronary arteries (induction of atherothrombosis, microvascular endothelial dysfunction, vasoconstriction against a background of high levels of angiotensin II and systemic hypertension, hypoxemia against a background of pulmonary artery thrombosis) form the basis of the diversity of myocardial infarction type 1, myocardial infarction type 2, myocardial infarction types 3 and 4a) [5, 11, 14]. The negative impact of coronary heart disease on atherosclerotic plaque (induction of inflammation and cytokine synthesis leads to damage of the integrity of the atherosclerotic plaque, vasoconstriction and thrombosis) contributes to atherothrombotic complications and the development of myocardial infarction type 1.

Coronary heart disease is in the case history of 5,8 % of patients with severe/critical symptoms compared with 1.8 % of patients with mild disease [14].

The results of numerous registries (Swedish, French, Northern California) covering millions of patients show that the structure of cardiovascular complications has changed somewhat during the pandemia – the incidence of myocardial infarction has decreased, but the disease has become more severe with increasing mortality [5, 6]. At the same time, the incidence of sudden cardiac death increased 27 % (possibly due to death in the early period of myocardial infarction – type 3), as well as the incidence of pulmonary embolism – 6 %. Myocardial infarction type 3 is known to be a myocardial infarction, not confirmed by biomarkers, when sudden death occurred in the prehospital stage.

The results of the registers analysis show that, despite the decrease in the incidence of myocardial infarction during the pandemic, their course became more severe, and mortality – higher, especially in patients with active coronavirus disease and STEMI – 23,1 %, compared with 5,7 % without COVID-19. Therefore, attention in the treatment of patients should be paid to antiplatelet therapy, as the incidence of stent thrombosis – type 4a myocardial infarction – has increased significantly [15].

Statins, which are widely used in primary and secondary cardioprophylaxis and are the standard of care for patients with myocardial infarction, have been shown to reduce the risk of COVID-19, improve course and affect mortality by almost 2-fold. There is evidence that the use of statins is associated with a decrease in the incidence of sudden cardiac death during a pandemic [14, 15]. Statins are included in the international and Ukrainian protocols for the treatment of patients with COVID-19.

COVID-19 and arterial hypertension. Since the beginning of the coronavirus pandemic, there has been evidence that patients with hypertension (AH) have a more severe course of coronavirus, and it has been suggested that this association may be due to the use of certain antihypertensive medications (AHM). Since then, numerous studies and meta-analyzes have been performed to understand better the role of AH and AHM in patients [9, 16].

In February 2020, the epidemiological team responding to the new coronavirus pneumonia emergency published an analysis of a large sample from China. The overall mortality rate (CFR) was 2,3 % (1023 out of 44672 confirmed cases) versus 6,0 % in patients with hypertension. However, this analysis did not take into account the age of the patients. It is known that CFR COVID-19 and the prevalence of hypertension increase with age, reaching 8,0 % and more than 50 %, respectively, for the age group 70-79 years.

In the OpenSAFELY study, which included > 17 million people in the UK, the presence of hypertension after age and other related factors was associated with a 7 % increase in in-hospital mortality from COVID-19 [8, 16].

As of early 2021, the U. S. Centers for Disease Control and Prevention considers hypertension to be a factor that may increase the risk of severe coronavirus disease (unlike, for example, coronary heart disease, heart failure, type 2 diabetes, and obesity, which increase this risk) [17]. In contrast, the World Health Organization, the British Heart Foundation and the Executive Health Service of Ireland consider hypertension to be a significant risk factor for severe COVID-19 and prioritize patients with hypertension as a priority vaccine against coronavirus [9, 17].

Heart failure and coronavirus disease. It is important for each physician to make a differential diagnosis between decompensated heart failure, often complicated by pulmonary infection, and COVID-19 infection. Moreover, computed tomography (CT) scans of patients with decompensated heart failure are very similar to those of COVID-19 infection. An extraordinary increase in natriuretic peptide levels has also been reported in deaths related to heart failure and cardiac arrest.

In a large cohort from China, heart failure was reported in 23 % of infected patients, and the prevalence was significantly higher among survivors (52 % vs. 12 %) [14].

It is clear that a patient with previous heart failure will have complicated lung disease of any kind. However, during the COVID-19 pandemic, fulminant myocarditis or cardiomyopathy is observed. It has been hypothesized that major structural heart disease in the early stages (such as fractional ejection heart failure) develops in the context of pulmonary complications and later in the form of acute systolic heart failure in response to the cytokine phase COVID-19 [15].

Left ventricular hypertrophy, diastolic dysfunction, or systolic dysfunction may occur in elderly patients with heart failure. These patients are prone to increased pulmonary vascular pressure according to the typical scenario of fluid overload to maintain blood pressure, as well as the use of parenteral drugs [7, 11]. The use of nonsteroidal anti-inflammatory drugs, the use of

secretagogues, in the presence of diabetes, alters the salt and water balance and may impair respiratory and cardiac function, including pulmonary edema.

Atrial fibrillation and COVID-19. According to the Danish National Register, the incidence of atrial fibrillation, which occurred for the first time, depends on quarantine and decreased 47 % in the first three weeks of national lockdown, compared to the same period last year. However, does this reflect the true situation, or is it the result of patients not turning to medical facilities, even if they develop arrhythmias for fear of infection during a lockdown? This fact indirectly confirms the increase in the incidence of ischemic stroke against a background of a new case of atrial fibrillation during a pandemic [16].

According to the same register, 5,3 % suffered an ischemic stroke with a new AF, and 2,7 % died, which is more than in the period before the pandemic (4,3 % and 1,3 %, respectively, in 2019).

These results probably reflect the fact that most patients with the first symptoms of AF delayed seeking help or refused it [14]. They may have feared contact with medical services due to the pandemic, thus delaying the onset of anticoagulation and increasing the risk of thromboembolic complications. It is very likely that only those who had a cardioembolic stroke as a complication were eventually hospitalized.

There are no specific reports of AF during SARS-CoV-2 infection. Based on the available literature, AF was detected in 19-21 % of all patients with COVID-19; one study reported a prevalence of up to 36 % in patients with cardiovascular disease, with AF observed in 42 % of survivors [7, 16].

Thus, among patients with COVID-19 AF is registered 2-4 times more often than in the general population. Every 3-4 patients out of 10 who have COVID-19 have AF.

COVID-19 is an acute disease with an incubation period of an average of five to six days, in some cases up to 14 days. This relatively short period of time is insufficient to increase the risk of AF, for example, causing fibrosis, which usually takes weeks or months to develop. Although structural remodeling of the atria is important to provide a substrate that supports AF, the onset of AF and its paroxysms are often temporarily associated with acute SARS-CoV-2 infection [20]. It should be noted that patients with COVID-19 who developed AF were older, and most had at least one pre-existing risk factor, including hypertension. Some patients have not previously had any cardiovascular disease.

Thus, the group of patients with AF and coronavirus is quite heterogeneous – some patients on COVID-19 with newly diagnosed AF may have a pre-existing substrate for AF, and acute SARS-CoV-2 infection may be a trigger to initiate AF consistent with the temporal relationship between the new episode of AF and COVID-19.

Thromboembolism in patients with COVID-19. To date, a high risk of thromboembolic complications in patients with COVID-19 has been proven. There are several meta-analyzes that have estimated the incidence of venothrombotic events in hospitalized patients, while the incidence of thrombosis in outpatients is unknown.

In 33 studies (n = 4009 patients) with heterogeneous thrombotic risk factors, the incidence of venous thrombosis was 9 % overall and 21 % for patients admitted to intensive care. The incidence of proximal lower extremity thrombosis was 3 % and 8 %, respectively, and the incidence of pulmonary embolism was 8 % and 17 %, respectively [18]. The lack of anticoagulants in the treatment was accompanied by a higher frequency of thromboembolism.

If we mention the classical Virchow triad as a guarantee of thrombosis, conditions of pathological thrombosis, the lesions in COVID-19 can be a classic illustrative material, where there is a violation of blood flow and changes in vascular wall with inflammation, and coagulation and fibrinolysis, and platelet function and neutrophils.

The results of autopsy of patients with COVID-19 indicate systemic endothelial dysfunction [19].

An additional activator of thrombosis in COVID-19 is hypoxia, which occurs in moderate and severe COVID-19 and therefore may lead to worsening endothelial dysfunction and hypercoagulation. Activation of endothelial P-selectin and adhesion molecules in hypoxia leads to adhesion of platelets and leukocytes. Monocytes adhere to activated endothelial cells through the glycoprotein P-selectin ligand-1, and additionally secrete prothrombotic factors. Hypoxia promotes thrombosis by increasing the release of PAI-1 endothelium and inflammatory cytokines (eg, TNF, interleukin (IL) –2), while reducing thrombomodulin regulation. In addition, increased activity of prothrombotic factors may initiate immune disorders, activation and local adhesion of macrophages, stimulating the release of proinflammatory cytokines, including IL-6 and TNF-α [18].

The main aspects of diagnosis and treatment. The diagnosis of COVID-19 requires the collection of samples from the upper or lower respiratory tract to conduct a polymerase chain reaction (preferably samples for PCR are a nasopharyngeal swab). A confirmatory assessment showed a decrease in the total number of leukocytes and lymphocytes with an increase in the ratio of neutrophilic granulocytes and lymphocytes. SARS-CoV-2 specific antibodies can confirm the diagnosis. IgM and IgG are detected 2-4 days after the onset of symptoms. Antibodies gradually increase during the first 3 weeks from the onset of the disease [3, 12].

Myocardial damage can be detected by electrocardiographic changes, X-rays, and levels of biomarkers such as troponin, creatine kinase, lactate dehydrogenase, and MB creatine kinase isoenzyme. A meta-analysis showed that cardiac troponin I levels were abnormal in 8-12 % of hospitalized patients on COVID-19 [11]. Echocardiography, angiography and other cardiac examinations are not performed in patients with hemodynamically stable and moderately elevated troponin levels. All studies should be weighed against the risks and benefits to patients.

Cardiac biopsy was performed to demonstrate infiltration of inflammatory cells, moderate pericardial effusion with light yellow and clear fluid, and mild edema, indicating involvement of pericardial inflammation in cardiovascular disorders [19]. However, this test is too invasive, so non-invasive and cardiac biomarker studies should be used as much as possible to diagnose

cardiovascular disease in patients on COVID-19. Enhanced thrombogenesis is characterized by elevated levels of D-dimer [11].

Preventing the effects of SARS-CoV-2 is a major effort to reduce the spread of COVID-19. Vaccination is becoming the most promising approach to combating this pandemic.

Treatment of COVID-19 patients with cardiovascular disease is predominantly supportive and depends on the patient's condition and heart disease.

In particular, the use of antiviral drugs should be monitored. In a study of 138 patients on COVID-19, 89.9 % received antiviral drugs. However, many antiviral drugs can cause heart failure, arrhythmia, or other cardiovascular disorders [20]. Therefore, the risk of cardiac toxicity should be closely monitored during the treatment of patients with COVID-19, especially with antiviral agents.

Immunosuppressants are an option for the treatment of myocarditis, but its use in COVID-19 requires further research. Tocilizumab belongs to this class of drugs [21]. Based on several studies, hydroxychloroquine has shown a positive effect in COVID-19. It acts by preventing endosomal oxidation, viral internalization and modulates the immune system. Unfortunately, hydroxychloroquine and antiviral drugs increase the risk of QT prolongation [22].

Azithromycin is also used in patients on COVID-19. It has a positive effect as an antiviral and anti-inflammatory agent. This drug can also cause a prolongation of the QT interval.

Extracorporeal membrane oxygenation supports the patient's cardiopulmonary function during the critical period of the disease.

The role of pharmacological blockade of the renin-angiotensin-aldosterone system in patients with cardiovascular disease and COVID-19 infection requires further investigation, as the relationship appears to be very complex. To date, professional cardiac societies do not recommend discontinuing angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists for all patients taking these drugs for other indications [23]. There is no evidence of an increased risk of infection or worsening of the clinical course in patients taking these drugs. But there is a warning that stopping drugs that have been shown to reduce mortality in patients with cardiovascular disease can lead to excessive mortality from cardiovascular causes.

In patients with heart failure, excessive fluid intake and medications that may alter the salt and water balance, such as nonsteroidal anti-inflammatory drugs, should be avoided.

Patients with ischemic heart disease and COVID-19 infection are suggested to use atherosclerotic plaque stabilizing agents (aspirin, statins, beta-blockers and angiotensin-converting enzyme inhibitors) as a possible therapeutic strategy [24].

Particular care should be taken with regard to the potential cardiovascular side effects of the various therapies used to treat viral infections: antivirals, hydrochloroquine, azithromycin, and the like. When using them, it is recommended to perform daily electrocardiographic monitoring of the QT interval.

Conclusions

1. Concomitant cardiovascular disease is common in patients with COVID-19, and these patients have a higher risk of morbidity and mortality.

2. Cardiovascular manifestations of COVID-19 are acute coronary syndrome, arrhythmia, heart failure, thromboembolic complications.

3. Patients on COVID-19 with cardiovascular events have a worse prognosis.

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