American Journal of Medicine and Medical Sciences 2022, 12(12): 1189-1194
DOI: 10.5923/j.ajmms.20221212.04

Features of the Clinical Course of COVID-19 in Patients with Chronic Diseases of the Cardiovascular and Pulmonary Systems

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Abstract The pandemic of the novel coronavirus infection COVID-19 has become a serious challenge to humanity. Prior to this period, cardiovascular diseases (CVS) were a major health problem in all countries, including hypertension (AH), which is a leading risk factor for vascular disasters; acute disorders of cerebral circulation, myocardial infarction. Hypertension makes a significant contribution to the structure of mortality and disability from cardiovascular diseases. The year 2020 changed the decades-old perception of diseases that pose a threat to health on a global scale. The leading clinical symptoms of COVID-19 in patients with background diseases CVS and hypertension are described. An important aspect of COVID-19 is the course of infection in patients with a burdened comorbid background, while the role of hypertension as a risk factor for severe forms is noted. The data obtained will serve to understand the systemic effects, including cardiovascular, that COVID-19 has, which will optimize the provision of timely comprehensive medical care to patients, develop an algorithm for the tactics of management and observation in different periods of the COVID-19 disease.

Keywords COVID-19, Cardiovascular diseases, Hypertension

1. Introduction

The most vulnerable categories of people affected by COVID-19 are patients with severe chronic diseases, such as heart and vascular diseases (coronary heart disease (CHD), heart failure, hypertension, cerebrovascular diseases), chronic obstructive pulmonary disease (COPD), chronic kidney disease and, of course, diabetes mellitus (DM). Analysis conducted by different groups of scientists from China, Italy and the United States showed different incidence of confirmed infection with SARS COV-2 in patients with diabetes. Thus, according to the Centers for Disease Prevention and Control, the incidence of diabetes among COVID-19 patients was 5.3% of the 20,892 patients in China [1,2], 10.9% of the 7162 patients in the United States [3] and 35.5% of the 355 patients in Italy [4]. In Russia, these data coming to the Federal Register of COVID-19 have yet to be analyzed.

Cardiac manifestations may be a primary phenomenon in COVID-19 (according to some researchers, this is the "cardiac phenotype" of the disease), but they can also be secondary to pulmonary damage (mixed pulmonary cardiac phenotype) [5]. It is important to note that the symptoms of CVD occur during any period of the patient's hospitalization, but as a rule, their risk increases from the 15th day from the onset of fever (or the appearance of other symptoms of a viral infection). The development of cardiovascular complications often develops after stabilization and / or improvement of the respiratory status of the patient [5]. There is no clear explanation for the variability of the cardiac manifestations of COVID-19 and it is not known why some patients are affected by CVS. Possible mechanisms of SARS-CoV-2-induced myocardial damage are correlated with increased expression of ACE2 in the heart and vascular endothelium [14].

Various pathophysiological phenomena of the development of cardiovascular complications in COVID-19 are discussed [7]:

- direct damaging effect of the SARSCoV-2 virus on pericytes (on their surface there is a high level of expression of ACE2), cardiomyocytes and fibroblasts [8];
- indirect effect of the SARS-CoV-2 virus on the myocardium under conditions of a "cytokine storm" (release of excessive amounts of inflammatory mediators and cytokines / chemokines) [8];
- direct damaging effect of the SARSCoV-2 virus on the vascular endothelium, leading to its dysfunction [9,10];

Received: Nov. 16, 2022; Accepted: Dec. 6, 2022; Published: Dec. 9, 2022
Published online at http://journal.sapub.org/ajmms

- hypercoagulation due to endothelial dysfunction, increased platelet activity and von Willebrand factor, increased production of a type 1 tissue plasminogen activator inhibitor and a decrease in the production of the tissue plasminogen activator that causes fibrinolysis, as a result of which blood flow is disturbed and micro- and macrothromboses are formed [9];

In severe hypoxemia, leading to increased anaerobic processes, intracellular acidosis and oxidative stress (discusses the direct effect of the virus on hemoglobin, leading to a decrease in the oxygen capacity of the blood) [9];

- an imbalance between the need of the myocardium for oxygen and its delivery against the background of virus-induced inflammation, hypoxia, oxidative stress, endothelial damage and hypercoagulation, which causes acute myocardial damage, instability of the atheroma and its rupture with coronary artery thrombosis [11];
- activation of the sympathetic system with stress-induced release of catecholamines into the blood, leading to vasospasm, hypoperfusion / myocardial ischemia and life-threatening arrhythmias [12];
- electrolyte imbalance (in severe COVID-19), contributing to the development of tachyarrhythmia; the reason for the frequent development of hypokalemia is the interaction of SARS-CoV-2 with RAAS [44]. However, the exact mechanism for the development of acute myocardial injury in COVID-19 requires clarification. So, COVID-19 can provoke acute myocardial damage, worsening the prognosis of the patient's life. Of great importance is the timely diagnosis of acute myocardial damage at the time of hospitalization of the patient and during his stay in the hospital. Previously, according to autopsy data, it was established that cardiotropic viruses like SARS-CoV-1 can persist in myocardial tissues for several weeks and even months [13]. Based on information about the previous infection caused by the SARS-CoV-1 virus, patients who have had COVID-19 can expect an increase in cardiovascular complications in the future.

Patients with chronic CHD are at risk of severe COVID-19 and death, as well as exacerbations of the previously stable course of coronary artery disease [14]. Elderly patients with concomitant conditions are more likely to become infected with SARS-CoV-2, especially in the presence of hypertension, coronary artery disease and diabetes [15]. Currently, it remains unclear whether the risk of cardiovascular complications remains in the long term of the disease [16].

Clinical outcomes, including survival, for COVID-19 are less favorable in the elderly and patients with diabetes, cardiovascular disease, obesity, which formed the basis of a preventive strategy with the identification of high-risk groups who should limit social contact to prevent infection. Patients with chronic obstructive pulmonary disease (COPD) are included in these groups due to a predisposition to virus-induced exacerbations, initially impaired lung function, and a high prevalence of comorbidities [17].

Patients with AD have an increased susceptibility to SARS-CoV-2 infection and a tendency to have a more severe course of COVID-19 due to reduced antiviral immunity and the risk of virus-induced exacerbation [18]. However, it is interesting to suggest that cytokines that mediate inflammation of the second type (interleukins-4, -5 and -13), and eosinophilia in AD may protect against COVID-19. SARS-Cov-2, similar to SARS-Cov and other coronaviruses, uses angiotensin-reducing enzyme 2 (ACE2) to enter the cell [19]. Increased expression of ACE2 is thought to increase susceptibility to COVID-19. In patients with AD, respiratory epithelial cells have reduced expression of ACE2 receptor genes, which may provide protection against SARS-Cov-2 infection. However, in non-allergic AD, the expression of ACE2 receptor genes remains at the same level [19]. It was also found that inflammation of the second type is associated with an increased level of transmembrane serine protease 2 (TMPRSS2 - transmembrane Serine Protease 2), which provides effective binding of the virus to the cell membrane [20]. Perhaps the decrease in ACE2 gene expression by margin compensates for the minimal increase in TMPRSS2 expression, potentially allowing AD-related type II inflammation to be considered as a protective factor against COVID-19. In contrast, other authors have suggested that AD-related inflammation of the second type reduces the body's antiviral immunity [21,22]. In addition, lower airway obstruction in AD can exacerbate hypoxemia caused by diffuse alveolar damage in COVID-19 [23]. It was revealed that viral infections, including several types of coronaviruses, cause exacerbation of AD, contribute to inflammation of the respiratory tract and hypersecretion of mucus [24]. Nevertheless, it was found that the causative agents of SARS, as well as MERS (Middle East Respiratory Syndrome), similar types of coronaviruses, do not contribute to an increase in the risk of exacerbation of AD, whereas seasonal coronaviruses do increase it [50]. Grandbastien M. et al. determined that SARS-Cov-2 infection does not increase the frequency of severe exacerbations of AD [25]. However, it is assumed that, as in the case of other human coronaviruses (HcoV - Human CoronaVirus), SARS-Cov-2 contributes to the development of exacerbation of AD [44]. For these and other reasons, patients with AD are encouraged to continue maintenance therapy throughout the COVID-19 pandemic [26].

Objective: To study theclinical prevalence of COVID-19 in patients with chronic diseases of the cardiovascular and pulmonary systems.

2. Materials and Methods of Research

The study was conducted in the period from March 2020 to November 2021 in the departments of the Samarkand City Specialized Center for COVID-19. 221

patients receiving inpatient treatment were examined with a diagnosis of COVID-19 with concomitant diseases - main group, COVID-19 without comorbidities - comparison group. Of the 94 patients in main group, 45% were diagnosed with H II and 55% with H III. Comparison group included 91 patients with an average age of 64.1±1.2 years. Of these, 53% were men and 47% were women. Their average age was 64.8±1.2 years. All patients in the groups underwent a comprehensive examination, which included: history taking, physical examination, pulse oximetry, blood pressure and weight measurement, clinical blood test, coagulogram with D-dimer, chest X-ray and CT. The clinical trial was conducted on the basis of the following criteria and included: patient complaints and a history of life expectancy and risk factors for H, duration of fever common signs of catarrhal symptoms and all clinical signs of Covid-19 clinical development and outbreak during illness and comorbidities.

3. Results of the Study and Their Discussion

In our research, patients with comorbid conditions were hospitalized after 4.8±0.4 days from the onset of clinical manifestations of the disease, and in the group of patients without comorbid conditions after 5.7 ±0.2 days. The duration of hospitalization was 15.6±0.6 days in the main follow-up group and 12.9±0.3 days in the comparison group. When analyzing the frequency of hospitalization, a statistically significant difference was not obtained by group. However, the timing and duration of hospitalization in the main group were higher and differed statistically significantly. Patients predominantly indicated the suddenness of the onset of clinical symptoms of this disease. Sometimes there was a prodromal period with phenomena of general nonspecific malaise. Very typical in the clinical picture is the presence of fever. In the main group of patients, it was noted in 80.6%, in 17.3% of hyperthermia was not noted and in 2% the disease proceeded with hypothermia. At the same time, among febrile patients in the main group, most often the figures reached febrile values of -37.6%, subfebrile temperature was in 27.6% of patients and in 15.3% it reached hectic figures. The duration of the febrile period ranged from 1 to 30 days and most often was 7-14 days.

One of the distinguishing features of COVID-19 is the development of various olfactory disorders - dysosmia in the form of anosmia, parosmia, hyposmia and, especially painful, cacosmia. There were also violations of taste: ageusia, paragevsia. Clinical manifestations of a decrease in olfactory function are fundamentally different from similar observed symptoms in other acute respiratory infections. At the same time, often disorders of smell and taste were observed even without nasal congestion and rhinitis phenomena. In our study, a symptom such as anosmia in the main group of patients occurred in 58.1% of patients. In the comparison group, anosmia occurred in 50.5% of patients. On average, it appeared on 5-6 days, and olfactory disorders persisted from 3 to 120 days. In some patients, a year after suffering COVID-19, olfactory function has not been restored. Thus, in the present observation, anosmia was significantly more common in group A, especially pronounced in patients with hypertension.

In patients on echocardiography, the following changes were detected. In patients of the main group, the diastolic size of the left ventricle on average decreased from 6.8±0.1 cm to 6.0±0.1 cm, the last systolic size, in turn, decreased from 5.4±0.1 cm to 4.7±0.1 cm and the fraction of blood ejection into the left ventricle increased from 36.5±4. With a high significant increase of 44.5±1.2%, the final diastolic volume changed positively from 218.5±5.9 ml to 190.4±9.0 ml, and the final systolic volume -from 139.1±4.9 ml to 104.4±5.6 ml. In the comparison group, the final diastolic index decreased from 6.0±0.09 cm to 5.8±0.08 cm, and the final systolic index decreased from 5.0±0.1 cm to 4.6±0.1 cm, while the blood ejection fraction in the comparison group was 35.9±1.2% to 39.0±1.04%, the late diastolic volume changed from 210.9±4.8 ml to 194.4±4.9 ml, and the late systolic volume changed from 146.9±5.0 ml to 134.8±5.1 ml. In patients of the comparison group, the final diastolic size of the left ventricle is from 6.2±0.1 cm to 5.9±0.1 cm, the final systolic size is from 4.9±0.1 cm to 4.6±0.2 cm ($R<0.05$), the blood ejection fraction is from 42.9±1.2% to 46.9±1.3%, the last diastolic volume changed from 186.8±11.2 ml to 179.6±11.2 ml, and the last systolic volume changed from 112.0±8.6 ml to 104.7±8.5 ml. While the indicators of transmittal Doppler Blood flow underlying treatment had no statistically significant changes in patients of the comparison group, early diastolic filling in patients of the main group ranged from 0.47±0.02 to 0.55±0.03 ($p<0.05$), and the ratio of E/ A was from 0.66±0.04 to 0.85±0.04 an increase was found.

Using a test with a 6-minute walk, we determined how well patients withstand physical exertion. This method of research is considered the simplest and at the same time the most common method of assessing the performance of all patients with GB and CVD. The indicator of patients' resistance to physical exertion in the study was assessed based on the results of the test with 6-minute walking. The results in the initial case in patients with FC II in the control group, this indicator was 346.8±11.46 meters. In patients with FC II who had COVID-19 based on hypertension in the main group and the comparison group, it was 328.6±12.54 and 334.6±13.54 meters, respectively. It was found that the indicator of resistance to physical activity in the control group in patients of the main group and the comparison group decreased by 5.3% and 4.2%, respectively. After the prescribed treatment, it was revealed that the patients' level of exercise tolerance in both groups changed positively with an increase in the average distance in the test with 6-minute walking.

If we compare the data on the prevalence of COVID-19 in China and the United States (5.3% and 10.9%, respectively) with the total prevalence of diabetes in these countries

(10.9% and 13.3%, respectively) [27], it becomes obvious that the number of infected patients with diabetes does not exceed the total prevalence of diabetes in these countries. This means that the risks of contracting this disease in patients with diabetes do not exceed those risks in the general population. However, if a person with diabetes is already infected with the new coronavirus SARS COV-2, then the disease in him flows much more severely than in patients without diabetes, and the frequency of deaths in patients with diabetes is significantly higher. This fact is confirmed in several studies of Chinese colleagues, the experience of which is summarized in the review [28]. According to the studies cited in the review, the frequency of severe COVID-19 was 1.3–3.9 times higher, and the mortality rate was 1.5–4.4 times higher in people with diabetes compared to people without diabetes [29]. A just-published meta-analysis of 30 studies describing the outcomes of COVID-19 pneumonia confirms that diabetes patients have significantly higher risks of severe disease (RR=2.45; 95% CI 1.79–3.35; p<0.001), more frequent development of acute respiratory distress syndrome (RR=4.64; 95% CI 1.86–11.58; p=0.001), and higher mortality (RR=2.12; 95% CI 1.44–3.11; p<0.001), than in persons without diabetes [30].

With the mortality in a subgroup of patients with comorbidities COPD assessed with 10 patients with COPD, of whom 6 died [31]. In a larger cohort study that included 1,13 COVID-19 patients seeking emergency care, the presence of COPD was associated with an increased risk of hospitalization (OR 1.77; 95% CI 1.67-1.87) and a tendency to increase mortality (OR 1.08; 95% CI 0.88-1.33) [32]. Similar results were obtained in the Italian cohort study with a total of 1,113 hospitalized COVID-19 patients, among whom COPD patients had a significantly high risk of developing severe respiratory failure (OR 1.17; 95% CI 1.09–1.27) [33]. In a Spanish longitudinal cohort study, the presence of COPD in COVID-19 patients was associated with a 70% increased risk of death (OR 1.69; 95% CI 1.23–2.32) [34]. The prevalence of COPD is higher among patients suffering from more severe forms of COVID-19. Thus, among 257 patients hospitalized with COVID-19 in the intensive care unit of a hospital in New York, the prevalence of COPD was 9%, and former smokers and smokers - 33% [35]. In addition, the presence of COPD was associated with a significantly higher risk of death (HR 3.15; 95% CI 1.84–5.39). According to the Italian registry of 3,032 patients, COPD as a comorbidity occurred in 16.4% of patients who died due to COVID-19. This corresponded to a COPD prevalence of 17.2% among patients aged ≥ 65 years and 11.1% among younger patients. In a retrospective study conducted in 60 regions of the Russian Federation, Avdeev S. N. et al. determined the prevalence of COPD at 3.1% among 1,307 patients with pneumonia caused by SARS-CoV-2 hospitalized in intensive care units. COPD patients have shown a tendency towards a more severe course of COVID-19, including a greater incidence of shock and the need for non-invasive ventilation [11].

4. Conclusions and Recommendations

It has been established that in patients with comorbid conditions with COVID-19, there is a significantly more frequent fluctuation in blood pressure figures in one direction or another compared to patients whose history is not burdened with comorbid conditions. Identified changes in the course of hypertension require changes in the therapy; dose reduction and cancellation are less often required, more often - increased therapy in the form of increasing doses and prescribing combinations of groups of antihypertensive drugs with the progression or start of hypertension. Thus, based on the data obtained during the study and analyzing the information available earlier, it is advisable to single out hypertension as an independent risk factor that determines the severity of the course of COVID-19. There is no doubt that this group of patients is shown monitoring of blood pressure and dose adjustment of drug therapy. The information obtained creates the need for a screening examination of patients in order to determine the degree of risk of possible complications and develop management tactics. The foregoing necessitates preventive measures, differentiated in each specific clinical group.

Exposure to the SARS-CoV-2 virus and other pathogenic factors with toxic, pro-inflammatory and procoagulant effects can lead to decompensation of concomitant CVD and increase hospital mortality. The new role of ACE2 as a receptor for the SARS-CoV-2 virus to some extent explains the pathophysiological link between viral infection, the immune system, and CVD. A new coronavirus infection can provoke acute myocardial damage and other new cardiac complications. Since a number of drugs used in COVID-19 have a cardiotoxic effect, constant monitoring of hemodynamic parameters, ECG and EchoCARD (according to indications) is necessary. The association of taking RAAS blockers (ACE inhibitors and ARBs) with an increased risk of infection of patients and a worsening of the course of COVID-19 at the present stage has not been confirmed, so patients with CVD should continue to take them. Survivors of COVID-19 should be involved in medical rehabilitation programs to restore the functions of various systems (primarily respiratory and cardiovascular), improve the quality of life and reduce the risk of disability more quickly and qualitatively.

Risk factors for adverse COVID-19 outcomes include age, concomitant cardiovascular disease. COPD is a disease that occurs in adulthood and is associated with a variety of comorbidities, including cardiovascular diseases. In addition to age-related risk and comorbidities, COPD itself is associated with adverse outcomes. The reasons for this may lie in increased susceptibility to viral infection (due to a decrease in antiviral protection or an increase in the expression of ACE2) or impaired lung function in patients with COPD. The heterogeneity of COPD patients should also be considered, especially in the severity of manifestations and the frequency of exacerbations. The

long-term effect of patient social isolation (to prevent SARS-CoV-2 infection) on the course of COPD is unclear. It can lead to a reduction in viral infections in the short term but have an undesirable effect on the overall physical and psychosocial health of these patients. As a result, reduced physical activity can deprive patients of the positive effects of comprehensive pulmonary rehabilitation programs, including improving quality of life, reducing symptoms of the disease, and increasing the risk of COPD exacerbations. Thrombosis and coagulopathies are common in patients with COPD and often occur in severe COVID-19. It is unclear whether predisposing endothelial dysfunction in COPD patients to vascular complications of COVID-19. Evidence of the long-term effects of COVID-19 in COPD patients does not yet exist. New data obtained from the examination of COVID-19 convalescents without previous respiratory diseases show a decrease in lung function and changes on computed tomography within 3 months. after clinical recovery.

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