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Cardiovascular Complications in Patients with COVID-19 Complicated by Viral Pneumonia

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Abstract COVID-19 (Coronavirus Disease 2019) causes significant lung damage, including pneumonia and acute respiratory distress syndrome (ARDS). At the same time, researchers have observed many extrapulmonary manifestations of this formidable infectious disease. Accumulating clinical experience and emerging research suggest that in addition to the respiratory system, cardiovascular, hematological, renal, gastrointestinal and hepatobiliary, endocrinological, neurological, ophthalmic and dermatological systems may be affected. To identify the incidence of cardiovascular complications in patients with COVID-19 complicated by viral pneumonia, to compare the results obtained with the data of literature sources and to substantiate their pathogenetic occurrence. The object of the study was 70 patients with viral pneumonia caused by COVID-19, who received treatment in a COVID specialized center. The subject of the study is the blood and blood serum of patients with coronary artery disease for the quantitative determination of the main biochemical parameters (lipid spectrum). The novel coronavirus infection affects not only the respiratory system, but also has a significant impact on the state of the cardiovascular system, both due to the patient's immune response and due to the probable cytopathic effect of the virus. This is evidenced by the high incidence of CVS complications, the most common of which were valve regurgitation, including concomitant cardiac arrhythmias, of which supraventricular arrhythmias were the most common.

Keywords COVID-19, Arterial hypertension, Blood pressure, Comorbidity, Cardiovascular complications

1. Introduction

As you know, COVID-19 (Coronavirus Disease 2019) causes significant lung damage, including pneumonia and acute respiratory distress syndrome (ARDS). At the same time, researchers have observed many extrapulmonary manifestations of this formidable infectious disease. Accumulating clinical experience and emerging research suggest that in addition to the respiratory system, cardiovascular, hematological, renal [1], gastrointestinal and hepatobiliary [2,3], endocrinological, neurological [1], ophthalmic and dermatological systems may be affected. This pathology may reflect either extrapulmonary spread and replication of SARS-CoV-2, as observed for other zoonotic coronaviruses [22], or widespread immunopathological consequences of the disease. To give an idea of these extrapulmonary manifestations, including cardiovascular system (CVS), it is necessary to consider the crucial role of clinical and pathogenetic aspects of the development of multiple organ lesions in COVID-19 involving the cardiovascular system. In the early stages of COVID, the lungs are the main organ affected.

The COVID-19 pathogen, SARS-COV-2, uses the angiotensin-converting enzyme 2 (ACE2) receptor, which is abundant in the lower respiratory tract, to enter cells. Very importantly, ACE2 is also expressed in the heart, intestinal epithelium [3,4], vascular endothelium, and kidneys [1], making all these organs potential targets [9]. SARS-CoV-2 is a spherical particle with a diameter of approximately 120 nm containing a single-stranded RNA genome. It is classified as a beta coronavirus (β-CoV) [lineage B] and is the seventh coronavirus to infect humans, after 2 α-CoV (HCoV-229E and HKU-NL63) and 4 β CoV (HCoV-OC43 [lineage A), HCoV-HKU1 [lineage A], severe acute respiratory syndrome SARS-CoV [lineage B], and Middle East respiratory syndrome MERS-CoV [lineage C]) [12,13,18]. Structural proteins of SARSCoV-2 include S-proteins or "spike proteins", membrane protein, envelope protein, and nucleocapsid. The presence of spike-shaped S-proteins on electron microscopic imaging shows a "halo" or "crown" around the virus, which is why the virus was given the appropriate name. The S-protein plays an important role in the attachment, fusion and entry of the virus into cells, which allows it to be considered as a possible target to produce antibodies and vaccines. The angiotensin-converting enzyme 2 receptor (ACE2) is the main receptor for the spike-shaped S-protein of the virus and determines the infectivity of the pathogen

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[32]. After initial infection, the development of acute disease can be divided into three distinct phases (early phase of infection, pulmonary phase, and hyperinflammatory phase) with significant overlap [7,14]. The hyperinflammatory stage is characterized by a cytokine storm leading to immune-mediated damage to distant organs [4]. Studies have demonstrated significant increases in inflammatory markers, including interleukin (IL)-6, -2, -7, tumor necrosis factor (TNF)-α, interferon-inducible protein (IP)-10, chemoattractant monocyte protein (MCP). -1, macrophage inflammatory protein (MIP)-1α, granulocyte colony stimulating factor (G-CSF), C-reactive protein (CRP), procalcitonin, and ferritin [25,60]. There are several mechanisms of cardiac damage, including direct myocardial damage by the virus itself, hypoxic damage mediated by respiratory failure, indirect cytokine-mediated damage secondary to the systemic inflammatory response, myocardial infarction (MI) due to plaque rupture secondary to systemic inflammation [62]. Direct damage to the heart mediated by the ACE2 receptor also remains a possibility. ACE2 receptors are expressed in cardiac pericytes and endothelial cells, and experimental data in animals suggest that their direct dysfunction secondary to viral infection or secondary inflammation may cause MI [16,64]. Increases in cardiac biomarkers, including troponin T, have been shown to be linearly correlated with inflammatory markers, indicating that myocardial damage is likely related to underlying inflammation [27].

Objective: to identify the incidence of cardiovascular complications in patients with COVID-19 complicated by viral pneumonia, to compare the results obtained with the data of literature sources and to substantiate their pathogenetic occurrence.

2. Materials and Methods of Research

70 patients with viral pneumonia caused by COVID-19. The comorbid background of patients, the data of routine methods of laboratory (complete blood count (CBC), troponin test: qualitative and quantitative) and instrumental (electrocardiography (ECG), echocardiography (echocardiography)) diagnostics were studied. Indicators of descriptive statistics were calculated: for indicators with a normal distribution, the results are presented in the form of an arithmetic mean, standard deviation, in other cases - in the form of median and interquartile range, categorical variables were presented in the form of quantity and percentage. The normality of the distribution was tested using the Shapiro-Wilk test. Statistical significance analyses were performed using the unpaired t-test and the Mann-Whitney U test for measures with a non-normal distribution. The critical value of the level of statistical significance was assumed to be $p \leq 0.05$. In the discussion, an analysis of the literature in the databases eLIBRARY.ru, PubMed, GoogleScholar, WebofScience for recent years, mainly for 2020-2021, was carried out to compare the results obtained.

3. Results and Discussion

A total of 70 patients with viral pneumonia were examined. Among them, 38 (54.3%) were men and 32 women (45.7%), the mean age was 54 years with an interquartile range from 49.75 to 71.25 (Fig. 1). The sample was dominated by patients over the age of 60 years among both men and women.

All patients were diagnosed with viral pneumonia caused by COVID-19, confirmed by the detection of SARS-CoV-2 virus RNA by molecular genetic method (PCR). The median body temperature measured at admission was 37.1 with an interquartile range of 36.8 to 37.6. One patient (1.4%) had a hyperpyretic temperature (above 41℃), two (2.85%) had a pyretic temperature (39℃ to 41℃). In all three cases of fever above 39℃, the patients were male. Most often, patients had respiratory failure (DI) of the first degree – in 31 (44.2%) patients, in the second degree – in 7 (10%) patients, Grade III was not detected, the absence of signs of DN was observed in 32 (45.7%) patients.

Viral pneumonia of moderate severity was predominantly observed in 65 (92.8%) patients. Severe viral pneumonia was observed in 5 (7.14%) male patients, two (2.8%) of whom were transferred to the Intensive Care Unit (ICU) due to the need to be connected to mechanical ventilation due to a decrease in oxygen saturation of less than 85%, which ended fatally.

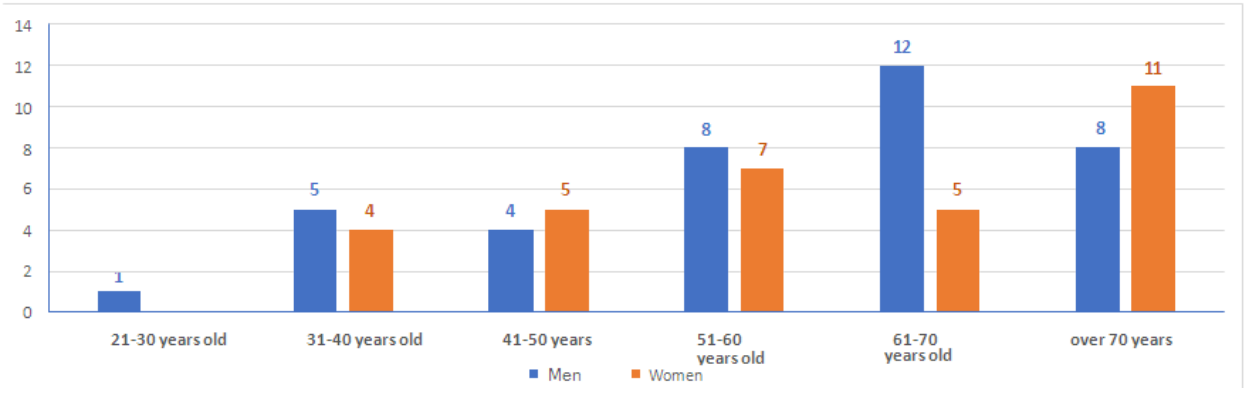

Figure 1. Distribution of patients according to gender and age

Hypertension (HA) prevailed in 31 (44%) patients, chronic heart failure (CHF) in 14 (20%) patients, CHD in 10 (14.2%) patients, diabetes mellitus (DM) in 8 (11.4%) patients, and obesity in 16 (22%) patients.

ECG analysis revealed conduction disorders in 19 patients (27%), sinoatrial node (SA) automatism disorders in 19 patients (27%), cardiac arrhythmias (HAR) – 25 (35.7%), T-wave and ST-segment changes – 19 (27%), infarction-like changes – 2 (2.8%).

Among LRS, supraventricular extrasystoles were predominantly observed in 5 (28%) of 7 patients with extrasystole and atrial fibrillation (AF) in 8 (32%) patients, and sinus tachycardias and bradycardias were also observed in some patients. At the same time, for the first time, the heart rhythm was disturbed in 21 (84%) patients out of the total number of patients with LDS. Among them, 2 (8%) patients had severe viral pneumonia, the rest had moderate pneumonia. QT prolongation was detected in 12 (17.14%) patients. It should be noted that 9 (75%) people took drugs in various dosages that prolong the QT interval (quinidine, amiodarone, sotalol, macrolides, fluoroquinolones, hydroxychloroquine, lopinavir/ritonavir).

According to echocardiography, the following changes were revealed: 40 patients with regurgitation on the heart valves – 40 (57.14%), among them: with regurgitation on the mitral valve – 32 (80%), with regurgitation on the tricuspid – 29 (72.5%), with regurgitation on the aortic valve – 17 (42.5%), with regurgitation on the pulmonary valve – 15 (37.5%).

There were 3 patients with regurgitation on one valve (7.5%), and 3 patients with regurgitation on all valves at the same time (7.5%). Simultaneous regurgitation on two valves was most common in 19 (47.5%) patients, among which regurgitation on the tricuspid and mitral valves was most common in 14 (35%) patients. Three-valve regurgitation was observed in 14 (35%) patients at the same time, and the most common combined regurgitation of the aortic, tricuspid, and mitral valves was observed in 8 (20%) patients.

Also, 19 (27.14%) patients with diastolic dysfunction, 3 patients (4.28%) with hypokinesis of certain segments, and 6 (8.6%) patients with signs of pulmonary hypertension were also identified. But no patients with systolic dysfunction were identified at all, which requires further study. Among individuals with pulmonary hypertension, 1 (16.7%) patient had chronic obstructive pulmonary disease, 3 (50%) patients had a history of persistent AF.

In the same groups, the average leukocyte count and erythrocyte sedimentation rate (ESR) were compared. In the Tr>0.03 ng/mL group, the median leukocyte count was 11.58×109/L with an interquartile range of 8.81×109/L to 12.25×109/L, and in the Tr<0.03 ng/mL group, the median leukocyte count was 10.72×109/L with an interquartile range of 9.2×109/L to 14.4×109/L. The average ESR (M) was 31.17 mm/h, standard deviation (σ) – 13.33 mm/h in the first group and M = 31.18 mm/h, σ=16.10 mm/h in the second group, but no significant differences were revealed.

Maximum body temperature in the group with myocardial injury confirmed by Tr I assay was higher than in the group without evidence of myocardial injury ($p<0.05$). Also, there was no correlation between the increase in troponin levels and the degree of DN. Among patients with elevated Tr I levels, all patients had a chronological association with a previous infection with characteristic symptoms, including fever in 7 (58%) patients, leukocytosis in 8 (66.7%) patients. Large diagnostic criteria for myocarditis were revealed: rhythm and conduction disorders in 9 (75%) patients and the presence of heart failure in 4 (33%) patients. Therefore, out of the 70 case histories analyzed, myocarditis can be assumed in 12 (17.14%) patients according to large diagnostic criteria.

The incidence of concomitant CVDs (HB, CHF, CHD) in the sample we described is closer to the data of the New York study [3]. Among the concomitant diseases, obesity (22%) and diabetes (11.4%) were the most common. For comparison, here are the data on the prevalence of diseases in the general population in the Russian Federation before the COVID-19 pandemic: the prevalence of CHF is 7%, the prevalence of HA is 45%, CHD is 5-14%, obesity is 29%, and DM is 4.7% [4]. Diabetes mellitus and obesity are both cardiovascular risk factors and more severe COVID-19 risk factors. A more severe course of infections is due to an increased number of adipokines, lipokines, cytokines that attract immune cells and enhance the activation of the NLRP3 inflammasome, hyperglycemia enhances the replication of the SARS-CoV-2 virus in monocytes, increases the surface expression of ACE2, and enhances the pro-inflammatory cytokine response of exvivo monocytes [5]. The International Consortium on Severe Acute Respiratory and Emerging Infections (https://isaric.tghn.org/) presented 95,966 clinical cases of COVID-19, among which the prevalence of diabetes and obesity was 17.4% and 13.4%, respectively.

Among CVDs, hypertension was the most common – almost half of the patients in our hospital (44%). The answer to the question of the relationship between HA and the severity of COVID-19 remains ambiguous, as many studies do not consider the increase in the incidence of HA with age. In one of the largest epidemiological studies in England with the study of more than 17 million medical records have been found to have hypertension or reported blood pressure greater than 140/90 mmHg. taken together, they are not associated with in-hospital mortality from COVID-19 after full adjustment, which is consistent with our findings [6].

Among the cardiovascular complications of coronavirus infection, LDC was the most common – in 35.7% of patients, which is higher than the literature data. In a cohort study of patients hospitalized with COVID-19 in China, arrhythmias were reported in 17% of all hospital admissions and 44% of patients hospitalized in the ICU [7]. In a global study of arrhythmias associated with COVID-19, the prevalence of supraventricular arrhythmias, including AF, was reported, which correlates with our findings [8]. Also, according to studies conducted before the outbreak of the COVID-19 pandemic, the incidence of arrhythmias occurring in myocarditis of all others, except for viral myocarditis caused by the SARS-CoV-2 virus, is lower than in our sample, and the incidence of supraventricular arrhythmias is 13%, of

which AF is 11% [9].

The most common cause of ectopic foci in the atria during coronavirus infection, according to the literature, is hypoxia caused by damage to the lung tissue. Severe hypoxia due to a decrease in the adenosine triphosphate (ATP) pool leads to an increase in cytosolic calcium, which decreases the potential difference, making cardiomyocytes more excitable, which leads to the occurrence of early and late post-depolarization phenomena and the formation of ectopic foci. However, we did not observe a direct relationship between the degree of respiratory failure and the occurrence of arrhythmias, so we can assume that LDCs arose predominantly due to direct viral damage and the pro-inflammatory effect of cytokines. At the same time, there is a characteristic decrease in the expression of ACE-2, leading to the accumulation of angiotensin II, the high concentration of which triggers the remodeling of damaged/intact tissue with the formation of a fibrosis area with low conductivity. Another plausible mechanism is that angiotensin II activates NADPH oxidase. Activated NADPH oxidase increases the number of reactive oxygen species (ROS) that oxidize CaMKII (Ca++/calmodulindependentproteinkinase II) to ox-CaMKII. Ox-CaMKII, in turn, phosphorylates the ryanodine receptor 2 (RyR2), which leads to an increase in diastolic leakage of Ca++ from the sarcoplasmic reticulum to the cytosol, which leads to late and early post-depolarization phenomena [10].

As mentioned above, 9 patients with viral pneumonia took drugs that prolong the QT interval hydroxychloroquine and azithromycin, which are included in the first interim guidelines for the treatment of COVID-19. These drugs inhibit a certain class of voltage-gated K+ channels belonging to humanether-a-go-go (hERG-K+), which is responsible for the initiation of repolarization. Its inhibition lengthens the plateau phase, which leads to a prolongation of the QT interval [11]. The absence of a history of QT-prolonging drugs in 3 patients is explained by the fact that tumor necrosis factor-alpha (TNF-alpha), interleukin-1 (IL-1), and interleukin-6 (IL-6), which increase during the cytokine storm in coronavirus infection, significantly prolongs the action potential of ventricular myocardial cells by modulating the expression or function of K+ channels [12]. It is likely that drugs that prolong the QT interval may act synergistically with these cytokines.

The incidence of specific valve involvement has not been reported in the literature. The predominance of patients with mitral and tricuspid valve regurgitation is probably due to a history of HA. However, the obtained immunofluorescence and Western blot data show that ACE-2 is widely expressed in the stromal fibroblasts of the heart valves, especially the aortic valves. In addition, reverse transcriptase PCR (RT-PCR) results suggest that ACE-2 expression is suppressed in stenotic valves. Inhibition of the ACE-2/angiotensin (1-7)/Mas receptor axis in SARS-CoV-2 valve endothelial lesions may increase inflammation, fibrosis, and valvular sclerosis. At the same time, the increased regulation of the angiotensin II-angiotensin II receptor type 1 (AngII-AT1R) axis, as mentioned above, induces the production of inflammatory cytokines, such as TNP-alpha and IL-6, which additionally contributes to the synthesis of pro-inflammatory cytokines and which creates a positive feedback loop of inflammation in the area of valve lesions [13].

According to the literature, 8% of patients with viral pneumonia due to COVID-19 have pulmonary hypertension, which was confirmed by our data [14]. The main mechanisms leading to the development of pulmonary hypertension associated with the novel coronavirus infection are extensive lung damage, as well as changes in the pulmonary vasculature (caused by thrombotic processes, endothelial damage, and hypoxic vasoconstriction) [15].

The incidence of myocardial injury (as reflected by elevated Tr I levels) among hospitalized patients with COVID-19 was 7% and 22% among patients hospitalized in the ICU [16]. For comparison, according to the consensus of the European Association of Cardiovascular Pathology from 2011 before the onset of the coronavirus pandemic, inflammatory myocardial lesions detected by endomyocardial biopsy were detected in 3–5% of all postmortem examinations [17]. It is assumed that the pathogenesis of myocarditis associated with COVID-19 is based on a combination of direct viral damage and myocardial damage due to the host immune response. During the cytokine storm, T lymphocytes are activated, further releasing pro-inflammatory cytokines that attract even more T lymphocytes. Cardiotropism of T lymphocytes occurs as a result of the interaction of the heart-produced hepatocyte growth factor (HGF) and the HGF receptor on naïve T lymphocytes (c-Met) [18].

4. Conclusions

The novel coronavirus infection affects not only the respiratory system, but also has a significant impact on the state of the cardiovascular system, both due to the patient's immune response and due to the probable cytopathic effect of the virus. This is evidenced by the high incidence of CVS complications, the most common of which were valve regurgitation, including concomitant cardiac arrhythmias, of which supraventricular arrhythmias were the most common.

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