

Factors affecting the severity of COVID-19 and the development of complications

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Abstract. COVID-19 is a new unexplored disease about which nothing has been known so far. And therefore, the consequences of COVID-19 came as a complete surprise to doctors. Their forces were directed to the treatment of the acute stage of the disease, and they did not even suspect that in many patients the health problems would not end along with the end of the acute phase, which proceeds with fever and other vivid symptoms of viral inflammation. Information that COVID-19 does not end with a decrease in temperature and the disappearance of characteristic symptoms first appeared on social networks. And I must say that the medical community did not immediately take seriously the complaints of those who seemed to have recovered, but continued to complain of weakness, shortness of breath, memory impairment, etc. Only a few months later, when there were so many complaining that it was no longer possible to ignore doctors acknowledged the existence of a problem. In order to get an objective picture of how patients who have had COVID-19 actually feel, a number of studies have been conducted. For example, in the state of Michigan (USA), 1250 patients who were discharged from the hospital where they were treated for a new coronavirus infection were called. The survey showed that 6.7% of patients died during the study period, 32.6% of patients reported persistent symptoms, including 18.9% new or worsening symptoms. The most commonly reported were shortness of breath when climbing stairs (22.9%), less commonly cough (15.4%) and permanent loss of taste and/or smell (13.1%). Similar data were obtained in studies conducted in Europe.

1 Introduction

As a result of research and reflection on the results of numerous surveys of recovered patients, the terms “long-term COVID syndrome”, or “post-COVID-19”, or “post-covid syndrome” appeared in the medical literature [2]. Quite quickly it became clear that this condition develops regardless of the age of the patient and the severity of the disease. At first, doctors tried to explain such symptoms as stress and the usual post-viral asthenia, which is well known - it is experienced by many patients who have had a severe flu. However, facts gradually began to accumulate, indicating that the problem is much more complex and serious (Fig.1).

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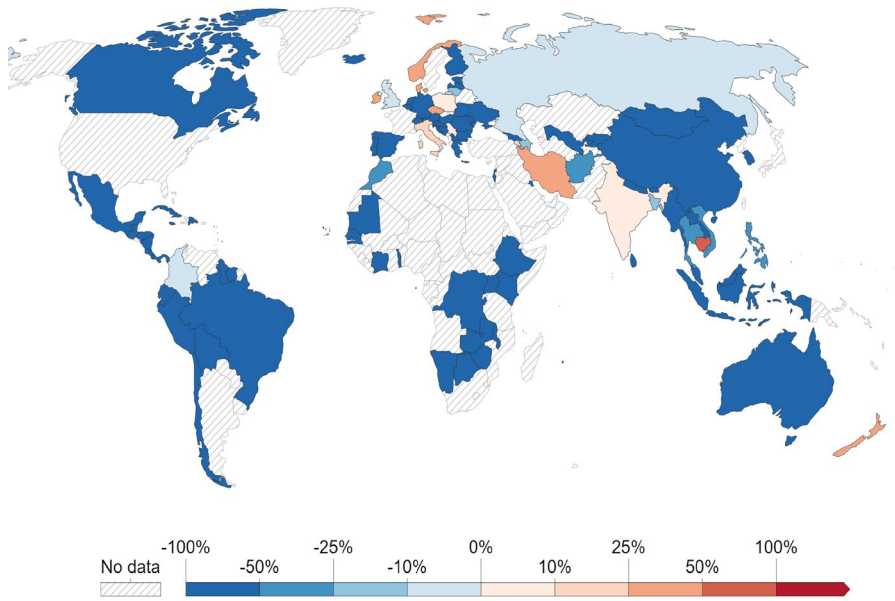


Fig. 1. Biweekly change in confirmed COVID-19

Based on the prevalence of various variants of the virus among the population and data on their biological properties (contagiousness, pathogenicity, relation to the neutralizing activity of antibodies), WHO identifies variants of concern (VOC - variant of concern), and variants under monitoring (variants that cause interest (VOI - variant of interest) is currently not highlighted) [1]. VOC - along with mutations, have biological properties that increase contagiousness, pathogenicity or reduce the neutralizing activity of antibodies. To date, only omicron (line PANGO B.1.1.529., first discovered in South Africa and Botswana in November 2021) is assigned to the VOC variant. The omicron variant, which carries multiple substitutions in the S-protein of the coronavirus, half of which are located in the receptor-binding domain, has the highest contagiousness among all SARS-CoV-2 variants. In the second half of 2022, a new strain of BQ1 ("Cerberus"), belonging to the BA.5 subvariant of the omicron variant, began to spread in many countries of the world. The BQ1 strain, as well as its genetically closely related strains (BQ.1.1, BQ.1.2 and others), does not have significant clinical features, but is characterized by a higher contagiousness compared to the BA.5 subvariant. The high pathogenicity of SARS-CoV, SARS-CoV-2 and MERS-CoV viruses allows them to be assigned to pathogenicity group II. At room temperature (20-25 °C), SARS-CoV-2 is able to remain viable on various environmental objects in a dried form for up to 3 days, in a liquid medium - up to 7 days. The virus remains stable over a wide pH range (up to 6 days at pH 5 to 9 and up to 2 days at pH 4.0 and pH 11.0). At a temperature of +4 °C, the stability of the virus persists for more than 14 days. When heated to 37 °C, complete inactivation of the virus occurs within 1 day, at 56 °C - within 45 minutes, at 70 °C - within 5 minutes. The virus is sensitive to ultraviolet irradiation with a dose of at least 25 mJ / cm² and to the action of various disinfectants in working concentrations [1].

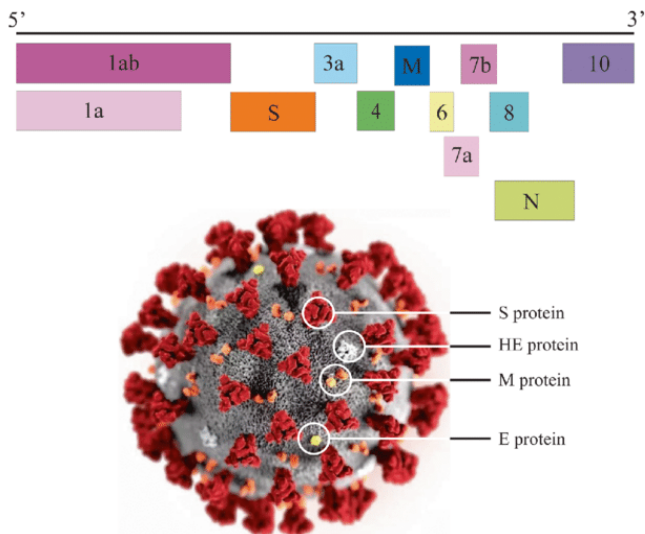


Fig. 2. SARS-Cov-2 genome organisation and structure

The original strain, isolated from samples from patients hospitalized in Wuhan in December 2019, is the reference genome for all subsequent sequences obtained by sequencing. The number of SARS-CoV-2 variants currently exceeds 1,000 different genetic lines. Most reported SARS-CoV-2 mutations have no functional significance. Only individual lines have a pronounced epidemiological significance. To analyze the epidemiological and clinical significance of virus variants and to facilitate the exchange of data on the emergence and spread of virus variants, WHO created a Working Group, which proposed to unify the designation of virus variant groups and designate them with Greek letters. Based on the prevalence of various variants of the virus among the population and data on their biological properties (contagiousness, pathogenicity, relation to the neutralizing activity of antibodies), WHO identifies variants of concern (VOC - variant of concern), and variants under monitoring (variants that cause interest (VOI - variant of interest) is currently not highlighted) [2]. VOC - along with mutations, have biological properties that increase contagiousness, pathogenicity or reduce the neutralizing activity of antibodies. To date, only omicron (line PANGO B.1.1.529., first discovered in South Africa and Botswana in November 2021) is assigned to the VOC variant. The omicron variant, which carries multiple substitutions in the S-protein of the coronavirus, half of which are located in the receptor-binding domain, has the highest contagiousness among all SARS-CoV-2 variants. In the second half of 2022, a new strain of BQ1 ("Cerberus"), belonging to the BA.5 subvariant of the omicron variant, began to spread in many countries of the world. The BQ1 strain, as well as its genetically closely related strains (BQ.1.1, BQ.1.2 and others), does not have significant clinical features, but is characterized by a higher contagiousness compared to the BA.5 subvariant. The high pathogenicity of SARS-CoV, SARS-CoV-2 and MERS-CoV viruses allows them to be assigned to pathogenicity group II. At room temperature (20-25 °C), SARS-CoV-2 is able to remain viable on various environmental objects in a dried form for up to 3 days, in a liquid medium - up to 7 days. The virus remains stable over a wide pH range (up to 6 days at pH 5 to 9 and up to 2 days at pH 4.0 and pH 11.0). At a temperature of +4 °C, the stability of the virus persists for more than 14 days. When heated to 37 °C, complete inactivation of the virus occurs within 1 day, at 56 °C - within 45 minutes, at 70 °C - within 5 minutes. The virus is sensitive to ultraviolet irradiation with a dose of at least 25 mJ / cm² and to the action of various disinfectants in working concentrations [3]. The entrance gate of the pathogen is the

epithelium of the upper respiratory tract and epithelial cells of the stomach and intestines. The initial stage of infection is the penetration of SARS-CoV-2 into target cells that have receptors for angiotensin-converting enzyme type II (ACE2) (fig.3).

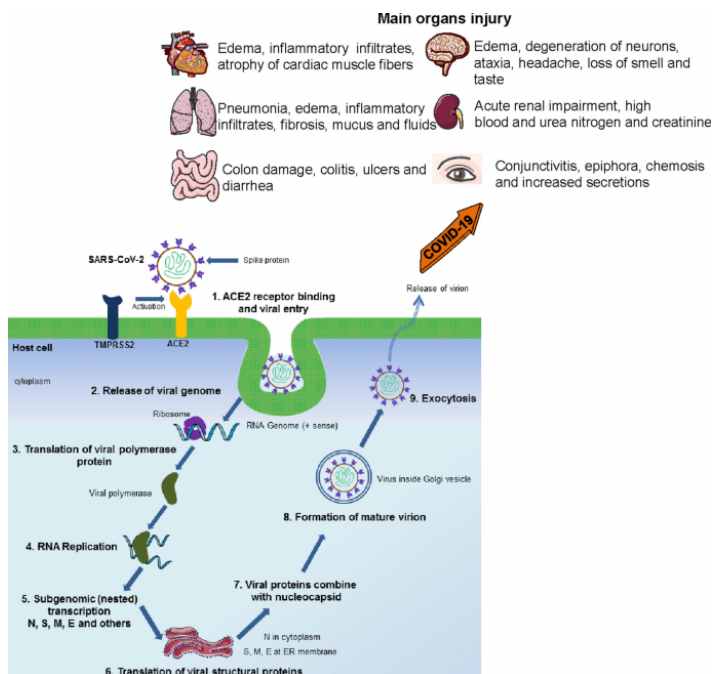


Fig. 3. ACE2: the molecular doorway to SARS-CoV-2

In addition to different sizes of hemorrhages, there are hemorrhagic infarctions obturating blood clots, mainly in the branches of the pulmonary veins [4]. Significant lesions of the trachea are not observed, detectable serous-purulent exudate and hyperemia of the mucous membrane in intubated patients are associated with nosocomial infection. In cases where COVID-19 joined another severe pathology, a combination of changes characteristic of different diseases is naturally observed. The nature of morphological changes in mild COVID-19 is unknown. Based on the analysis of clinical symptoms, we can assume the tropism of the virus to the epithelium of the larynx, ciliated epithelium of the respiratory tract throughout, alveolocytes I and II types [5]. Apparently, viral lesions in such patients do not lead to the development of pronounced exudative inflammation and, accordingly, catarrhal phenomena.

2 Research Methodology

The study of the influence factors of Covid-19 on the human body and the development of complications includes a wide range of methods. Here are some of them:

1. Epidemiological research: Analysis of the spread of the disease in different populations, identification of distribution features and relationships with various factors such as age, gender, place of residence, etc.

2. Clinical studies: Study of the clinical manifestations of the disease in patients of varying severity, analysis of symptoms, nature of the course and long-term consequences.

3. Molecular biological research: Analysis of the genetic structure of the virus, its mutations, mechanisms of interaction with body cells. Study of the immune response to the virus and its effect on the body.

4. Immunological studies: Study of the reaction of the immune system to the virus, antibodies, cytokines, study of the immune status of patients and its influence on the development of complications.

5. Radiological studies: The use of radiography, computed tomography and magnetic resonance imaging to study changes in the lungs and other organs.

6. Blood coagulation studies: Analysis of platelets, blood coagulation and thrombosis risk studies in patients with Covid-19.

7. Biochemical studies: The study of biochemical parameters of the blood and organs in order to assess the function of various body systems in a disease.

8. Genetic studies: The study of genetic predispositions to develop severe forms of the disease or complications.

9. Microbiome studies: Study of the influence of the composition of the microbiome of the body on the course of the disease and the possible effect on the immune response.

10. Social research: Analysis of the influence of social and economic factors on the spread of the disease and access to medical care.

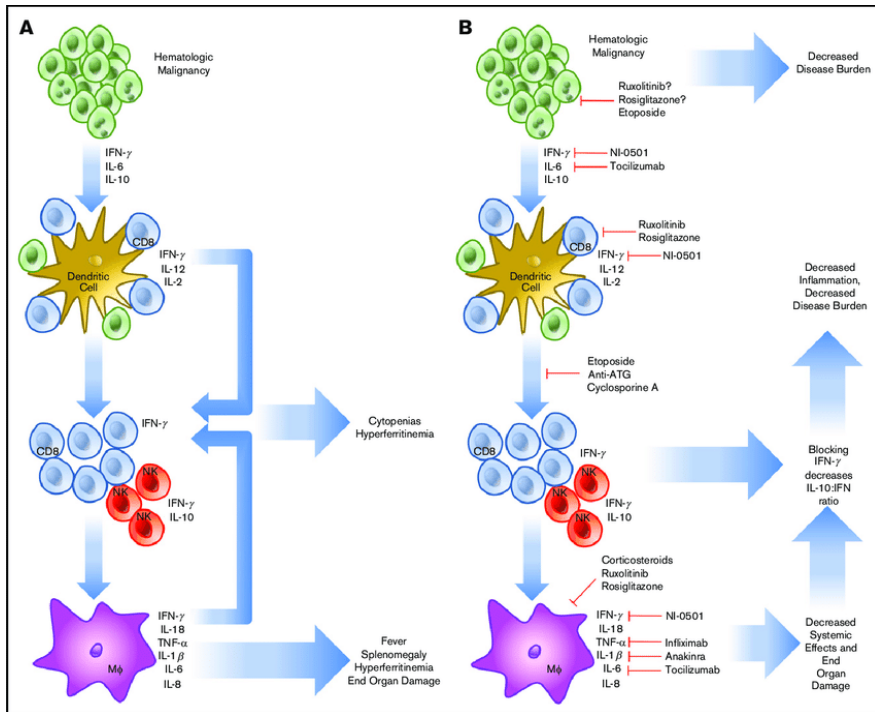
These methods help expand our understanding of the impact of Covid-19 on the human body and the factors that influence the development of complications.

3 Results and Discussions

The difference between COVID-19-induced secondary HLH and other virus-induced cytokine storms is that the target organ of this cytokine storm is the lung, which is related to the targeting of lung tissue by coronaviruses and the more gradual increase in serum ferritin levels in COVID-19. The enhanced immune response in COVID-19 is often limited to the lung parenchyma, adjacent bronchioles, and alveolar lymphoid tissue and is associated with the development of ARDS [6]. In the early period of COVID-19 pneumonia, normal levels of blood fibrinogen, regional fibrinolysis, and a high level of D-dimer are observed, which is not a sign of the development of acute macrophage activation syndrome. This process can be regarded as a CAM-like intrapulmonary inflammation that enhances the severity of local vascular dysfunction, including microthrombosis and hemorrhage, which leads to the development of pulmonary intravascular coagulopathy to a greater extent than disseminated intravascular coagulation. Clinical and pathological changes are difficult to differentiate from multiple organ thrombosis that develops with DIC and thrombotic microangiopathy (TMA). COVID-19 Cytokine storms commonly cause ARDS, multiorgan failure, and can be fatal [7]. Microscopic examination Intraalveolar edema with admixture of erythrocytes, macrophages, detached alveolar cells, single neutrophils, lymphocytes, and plasma cells in the edematous fluid; hyaluronic acid membrane within the alveoli, sometimes extending to the inner surface of the bronchioles; alveolar epithelium (as single cells and their layers) and bronchioles epithelial detachment; appearance of large type II alveolar cells of irregular shape with rough chromatin and enlarged nuclei with clear nucleoli (some of them have a halo around the nucleus, and in the cytoplasm - round basophilic and eosinophilic inclusion bodies, characteristic of viral cell damage); proliferation of type II alveolar cells, their formation of zymoplasts. Moderate perivascular and peribronchial infiltration with lymphocytes and macrophages, as well as infiltration of alveolar spaces and walls of small vessels by different populations of lymphocytes and macrophages is characteristic. CD3+ T lymphocytes predominate, including CD2+, CD5+, CD8+ T cells. B-lymphocytes (CD20+, CD80+) are relatively few, natural killers (CD16+/CD56+) are practically absent.

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mucous membrane in intubated patients are associated with nosocomial infection. In cases where COVID-19 joined another severe pathology, a combination of changes characteristic of different diseases is naturally observed [8]. The nature of morphological changes in mild COVID-19 is unknown. Based on the analysis of clinical symptoms, we can assume the tropism of the virus to the epithelium of the larynx, ciliated epithelium of the respiratory tract throughout, alveolocytes I and II types. Apparently, viral lesions in such patients do not lead to the development of pronounced exudative inflammation and, accordingly, catarrhal phenomena.



Patients with a critical course of COVID-19 develop vascular endothelial dysfunction, coagulopathy, thrombosis with the presence of antibodies to phospholipids, with a clinical picture resembling catastrophic antiphospholipid syndrome. Clinical and pathological changes are difficult to differentiate from multiple organ thrombosis that develops with DIC and thrombotic microangiopathy (TMA). The cytokine storm in COVID-19 typically leads to ARDS, multiple organ failure, and can be fatal. At microscopic examination, attention is drawn to: intraalveolar edema with an admixture of erythrocytes, macrophages, desquamated alveocytes, single neutrophils, lymphocytes and plasmocytes in the edematous fluid; intraalveolar hyaline membranes, sometimes extending to the inner surface of the bronchioles; desquamation of the alveolar (in the form of individual cells and their layers) and bronchiolar epithelium; the appearance of large, irregularly shaped type II alveocytes, with enlarged nuclei with coarse-grained chromatin and distinct nucleoli (in some of them, a halo is visible around the nucleus, and in the cytoplasm there are rounded basophilic and eosinophilic inclusions characteristic of viral cell damage); proliferation of type II alveocytes, the formation of their symplasts. Mild perivascular and peribronchial lymphoid and macrophage infiltration is characteristic, as well as infiltration of the interalveolar septa and walls of small vessels, represented by various populations of lymphocytes and macrophages. CD3+ T lymphocytes predominate, including CD2+, CD5+, CD8+ T cells. B-lymphocytes (CD20+, CD80+) are relatively few, natural killers

(CD16+/CD56+) are practically absent. The SARS-CoV-2 virus is detected in the ciliated cells of the bronchi, bronchiole epithelium, in alveolocytes and macrophages, as well as in the vascular endothelium using nucleic acid amplification methods (NAAT), immunohistochemical, ultrastructural studies [9]. Specific viral and cytokine storm-induced (and later, possibly autoimmune) damage to the endothelium, called SARS CoV 2-associated endothelial dysfunction and even endothelitis, and hypercoagulation syndrome are the basis of thrombotic microangiopathy, predominantly of the lungs, characteristic of COVID-19, less often - other organs (myocardium, brain, kidneys, etc.), and thrombosis of large arteries and veins (often with thromboembolism). Do not exclude the possibility of platelet activation by antibodies to SARS-CoV-2 as an important cause of the development of hypercoagulation syndrome. In single observations, local pulmonary or systemic productive-destructive thrombovascular disease develops, possibly as a result of superinfection [10]. There is evidence of a connection of some of the observations of post-covid syndrome, along with other pathological processes, with prolonged thrombotic microangiopathy and persistent hypercoagulation syndrome.

4 Conclusions

Complications of Covid-19 are varied and affect different body systems. Here are some of the common complications that patients may experience:

1. **Pneumonia:** One of the most common complications of Covid-19 is pneumonia, an inflammation of the lungs. Pneumonia can lead to short-term or long-term airway dysfunction.

2. **ARDS (Acute Respiratory Distress Syndrome):** This is a serious complication in which the lungs are unable to carry out sufficient gas exchange, resulting in dysfunction of other organs.

3. **Thrombosis:** Covid-19 can promote thrombosis (formation of blood clots) by increasing blood clotting. This can lead to thrombosis of the lungs, heart, brain and other organs.

4. **Cardiac complications:** The virus can infect the heart muscle, causing myocarditis and acute myocardial injury. This can lead to irregular heart rhythm and heart function.

5. **Kidney complications:** Covid-19 can cause kidney damage leading to acute kidney failure.

6. **Neurological complications:** Neurological consequences are possible, including inflammation of the brain (encephalitis) and impaired sense of smell and taste.

7. **Skin complications:** After contact with the virus, redness, swelling or rash may occur.

8. **Vascular complications:** Covid-19 can affect the blood vessels, causing inflammation of the vessel walls and increasing the risk of blood clots.

9. **Eye complications:** Although rare, the virus can cause conjunctivitis and other eye conditions.

10. **Long-term effects ("eye effects"):** Some patients appear to be cured, but symptoms such as fatigue, difficulty breathing, and memory loss persist.

These complications can occur in patients with varying degrees of severity and may require specialized treatment and supervision by healthcare professionals.

There are several methods and approaches to diagnosing complications of Covid-19, which can be used to identify changes in the body resulting from exposure to the virus. Some of these methods are described below:

1. **Clinical blood test:** measurement of protein, white blood cells and platelets allows you to determine the presence of inflammation or other abnormalities associated with complications.

2. X-ray studies: X-rays or computed tomography of the lungs help to identify pneumonia, bronchiectasis, fibrosis, and other organ damage.
3. Lung function tests: Spirometry and lung diffusion tests evaluate lung function and detect breathing problems.
4. Coagulation tests: evaluation of coagulation parameters and clotting time helps to determine the risk of thrombosis.
5. Biochemical tests: analysis of biochemical parameters can detect damage to organs such as the liver, kidneys and heart.
6. Immunological tests: Determination of the level of antibodies, cytokines and other immune markers helps to understand the response of the immune system to the virus and its effect on the body.
7. Cardiac monitoring: Electrocardiograms and echocardiograms can detect cardiac abnormalities caused by complications of Covid-19. Magnetic resonance imaging (MRI): allows you to examine the internal organs and tissues in more detail.
8. Blood oxygen monitoring: Continuous monitoring of blood oxygen levels is important for patients with serious complications.
9. Bacteriological testing: For patients with complications such as pneumonia, testing of bacteria in sputum and other specimens may be required.
10. Diagnosing complications of Covid-19 usually requires the full cooperation of various specialists, including infectious disease specialists, respiratory specialists and cardiologists.

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