

## COURSE OF SEVERE CORONAVIRUS (COVID-19) IN A PATIENT AT RISK

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The article is devoted to the peculiarities of the clinical course of severe coronavirus infection in a 59-year-old woman at risk for comorbidities. Data on the pathogenesis of the severe form of COVID-19 are presented. Prognostic laboratory signs of an unfavorable outcome of coronavirus infection in people at risk are considered. The patient management tactics are described in accordance with the protocol for the treatment of new coronavirus infection. The assessment of patient management at the outpatient stage is given.

A new coronavirus infection in at-risk patients can quickly lead to a worsening of the condition, which is manifested by severe lung damage not only according to computed tomography data, but also by the clinical symptom of ARDS. The severity of the condition in this category of patients is due to severe viral aggression, the development of a cytokine storm. The use of the recommended protocol for the treatment of new coronavirus infection in patients at risk does not always give the expected positive result.

**Keywords:** COVID-19; severe form; prognostic laboratory signs; treatment protocol; negative experience.

## ТЕЧЕНИЕ ТЯЖЕЛОЙ КОРОНАВИРУСНОЙ ИНФЕКЦИИ (COVID-19) У ПАЦИЕНТА ГРУППЫ РИСКА

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Статья посвящена особенностям клинического течения тяжелой коронавирусной инфекции у женщины 59 лет, относящейся к группе риска по сопутствующей патологии. Приведены данные о патогенезе тяжелой формы COVID-19. Рассмотрены прогностические лабораторные признаки неблагоприятного исхода коронавирусной инфекции у лиц группы риска. Описана тактика ведения больной в соответствии с протоколом лечения новой коронавирусной инфекции. Приведена оценка ведения пациентки на амбулаторном этапе.

Новая коронавирусная инфекция у пациентов группы риска может быстро привести к ухудшению состояния, которое проявляется не только тяжелым поражением легких по данным компьютерной томографии, но и клиническими симптомами острого респираторного дистресс-синдрома. Тяжесть состояния у данной категории больных обусловлена выраженной вирусной агрессией, развитием цитокинового шторма. Использование рекомендуемой протоколом схемы лечения новой коронавирусной инфекции у пациентов группа риска не всегда дает ожидаемый положительный результат.

**Ключевые слова:** COVID-19; тяжелая форма; прогностические лабораторные признаки; протокол лечения; отрицательный опыт.

### Introduction

In late 2019 and early 2020, the world has learned about a new infectious disease caused by a different strain of human coronavirus, i.e., severe acute respiratory syndrome coronavirus 2

(SARS-CoV-2). The disease, i.e., 2019 coronavirus disease (COVID-19), is characterized by a varied clinical presentation, complete absence of any effective etiotropic therapy, and high mortality (from 0.5% to 15%) caused not only by the severe

course of the infection itself but also by a significant deterioration in the course of concomitant somatic pathology [1].

SARS-CoV-2 is a single-stranded ribonucleic acid virus. This virus is believed to be recombinant virus between the bat coronavirus and a coronavirus of unknown origin [2]. The entry portals of the infection caused by SARS-CoV-2 are epithelial cells of the upper respiratory tract and epithelial cells of the stomach and intestines, which possess type II angiotensin-converting enzyme (ACE2) receptors, but the main targets of the virus are type II alveolar cells of the lungs. If these cells are infected by the virus, pneumonia of varying severity developed. SARS-CoV-2 can infect epithelial cells of the stomach, small and large intestines, and other organs having ACE2 receptors [3].

In the pathogenesis of the severe generalized form of coronavirus infection, great importance is given to damage to the microvasculature and disorders in the blood coagulation system. The major pathogenetic mechanism of COVID-19, which increases the probability of lethal outcome, is acute respiratory distress syndrome. The severity of COVID-19 is also dependent on vascular endothelium damage and increased thrombogenesis [4]. The degree of manifestation of general intoxication caused by COVID-19 is associated with an increase in the release of pro-inflammatory cytokines, in particular interleukin-6 (IL-6), and the development of a cytokine storm. Higher IL-6 levels were noted in patients with the most severe infection. In addition, studies have shown a relationship between the level of IL-6 and the frequency of lethal outcomes in patients with COVID-19 [5]. C-reactive protein (CRP), whose production is stimulated by IL-6, also serves as a biomarker for severe coronavirus infection. CRP is considered the primary laboratory marker of lung processes. The increase in CRP level has been proved to be proportional to the volume of lung tissue damage [6]. An unfavorable prognostic sign of the disease course in such patients is the emergence of coagulopathy. Laboratory signs of a hyperinflammatory reaction, or cytokine storm, include leukopenia; severe lymphopenia; a decrease in the number of monocytes, eosinophils, and blood basophils; high levels of IL-6 ( $>40$  pg/ml); CRP levels  $>75$  mg/l; an increase in ferritin level and activities of alanine aminotransferase, aspartate aminotransferase, and lactate dehydrogenase in blood serum; and a significant increase in the D-dimer level (4 times or higher than the reference value) [6].

Significant, both positive and negative, experiences have been accumulated so far in the management of patients with severe COVID-19. In St. Petersburg, by the order of the Health

Committee, at the City Organizational and Methodological Department of the Infectious Disease Service of the S.P. Botkin Clinical Infectious Diseases Hospital, a commission was established to analyze lethal outcomes from influenza and severe forms of other acute respiratory viral infections, including COVID-19, in the epidemic period from 2020 to 2021. This article presents one of such cases of a severe course of COVID-19 with a lethal outcome.

### Description of the clinical case

A 59-year-old female patient was admitted to the St. Petersburg S.P. Botkin Clinical Infectious Diseases Hospital on April 27, 2020. On admission, she complained of asthenia, sweating, cough with brownish sputum, and subfebrile body temperature. She considered herself ill from April 21, 2020, when asthenia, throat irritation, body pain, muscle pains, and cough appeared. Her body temperature was up to  $37.4^{\circ}\text{C}$ . On the same day, she sought medical attention. She took Arbidol and Grippferon intranasally in the form of drops. On day 2, the cough intensified, and she had a feeling of breath shortness in the supine position. Two days before admission, she noticed brownish sputum and therefore began to take Cifran. The past medical history showed that she had chronic pyelonephritis, hypertension stage II (she took Valsartan), and type 2 diabetes mellitus (the patient was on diet). Surgeries included hemithyroidectomy, appendectomy, and hysterectomy for fibroids in 2018.

Epidemiological history revealed that she had contact with individuals with COVID-19 at work from April 17, 2020.

On examination, she had clear consciousness and moderate severity of condition. Her skin color was normal, without rash, and the lymph nodes were not enlarged. She had slight edema of the lower legs. The patient had signs of obesity. Cyanosis did not occur, with unlabored breathing. Harsh breath sounds were heard in all lung fields. Dry rales were heard on the lower parts of the right lung. The respiration rate was 18 breaths per minute at rest, the  $S_pO_2$  was 93%, the pulse rate was 72 beats per minute and rhythmic, and the blood pressure was 140/80 mm Hg. Heart sounds were muffled, with systolic murmur at the apex. The tongue was moist, and there was minor hyperemia in the pharynx. The liver and spleen were not enlarged. Meningeal and focal symptoms were absent.

Taking into account the anamnestic and examination data, a preliminary diagnosis of acute respiratory viral infection, suspected pneumonia, contact with a patient with COVID-19, and possible infection was established. Concomitant di-

seases included hypertension stage II, obesity, and type 2 diabetes mellitus.

The condition severity was assessed according to the National Early Warning Score [7], and the patient had 5 points, indicating moderate severity.

After examination, infusion therapy (Sterofundin solution 5% 500.0 ml + KCl 4%, 5.0 ml + MgSO<sub>2</sub> 25%, 5.0 ml administered intravenously) and antibiotic therapy (ceftriaxone at a dose of 2.0 g intravenously and azithromycin 500 mg) were given.

On the same day, chest computed tomography (CT) was performed, which revealed bilateral polysegmental viral pneumonia with a high probability of moderate COVID-19. Based on the CT findings, treatment was started in accordance with the temporary methodological recommendations "Prevention, diagnostics and treatment of new coronavirus infection (COVID-19), version 5 (08.04.2 020)" approved by the Ministry of Health of the Russian Federation. On April 28, 2020, hydroxychloroquine at a dose of 400 mg administered two times a day at a dose of 200 mg per day was added to the therapy, from April 29, 2020 to May 03, 2020. Even if the treatment was performed according to the protocol, the patient's condition continued to deteriorate from April 28, 2020. Respiratory failure worsened (shortness of breath up to 22 breaths per minute, in the presence of oxygen insufflation, saturation decreased to <90%). Under these circumstances, the patient was transferred to the intensive care unit on April 30, 2020. Due to the ineffective spontaneous breathing and critical indicators of gas exchange, the patient was shifted to artificial lung ventilation. In the intensive care unit, active multicomponent (infusion-corrective therapy, artificial lung ventilation, catecholamine support for cardiac activity, symptomatic therapy) and etiotropic therapy continued. In addition to hydroxychloroquine, lopinavir and ritonavir (Kaletra) 500 mg daily each was prescribed.

Laboratory data obtained in the first 2 days and in subsequent hospital days indicated a poor prognosis for the course of COVID-19 due to a severe viral process and development of a cytokine storm. Thus, the ferritin level ranged from 431 to 1806.5 µg/L (normal range, 15–150 µg/L), the IL-6 level ranged from 60.6 to 173 pq/ml (normal <10 pc/ml), the CRP level ranged from 482 to 576 mg/L (normal range, 0–5 mg/L), the D-dimer content was 1.85 µg/L (normal 0–0.5 µg/L). To suppress viral aggression, tocilizumab (a recombinant humanized monoclonal antibody to the human IL-6 receptor from the IgG1 immunoglobulin subclass) at a dose of 400 mg was twice administered intravenously. Two administrations of this drug did not decrease ferritin level and IL-6 indicators.

Despite intensive therapy, the patient's condition deteriorated progressively, and on day 10 of hospital stay (day 17 of illness), the patient died due to increasing multiple-organ and cardiovascular insufficiency.

### **Final clinical diagnosis**

The principal diagnosis was coronavirus infection, severe course of pneumonia caused by the COVID-19 virus, and the virus was identified by polymerase chain reaction performed on April 27, 2020.

### **Complications**

The complications included respiratory failure degree III, acute respiratory distress syndrome, and progressive acute cardiovascular failure (May 07, 2020).

### **Comorbidity**

Concomitant diseases were coronary heart disease, abdominal compartment syndrome, hypertension stage II, type 2 diabetes mellitus (decompensation), obesity degree III, and conditions after strumectomy and complete hysterectomy (2018).

The postmortem examination protocol was presented as follows:

As conclusion on the lethal outcome of a 59-year-old woman who died on May 07, 2020, at St. Petersburg S.P. Botkin Clinical Infectious Diseases Hospital, the postmortem autopsy was performed on May 08, 2020.

### *Postmortem diagnosis*

The underlying disease was COVID-19 (virological test by PCR: SARS-COV-2+). Bilateral total viral-bacterial pneumonia (growth of *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Enterococcus faecium*, and *Corynebacterium striatum*) was found.

### *Complications*

The patient had acute respiratory distress of the lungs, including acute respiratory failure (according to clinical data), affecting hyaline membranes. Tracheostomy was performed on April 30, 2020. The patient also had pulmonary edema, acute venous congestion of internal organs, and cerebral edema with dislocation of the brain stem.

### *Comorbidity*

Comorbidities were type 2 diabetes mellitus, macroangiopathy, and hypertension stage III. Her heart weighed 370.0 g. There was myocardial hypertrophy of both ventricles. She also had arteriolosclerotic nephrosclerosis and obesity.

### *Results of histological examination*

**Trachea:** There was edema and plethora of the submucosal layer and subtotal desquamation of the epithelium.

**Lungs:** There was uneven airiness of the lung tissue and areas of disatelectasis. In most of the alveoli, there were many desquamated alveolocytes, with enlarged hyperchromic nuclei, macrophages with giant nuclei, symplasts, and siderophages. There were fields of airless alveoli due to eosinophilic masses, fibrin, and intense infiltration by neutrophilic leukocytes with focal melting of the interalveolar septa. In addition, erythrocyte and fibrin thrombi were found. There were excessive capillaries in the interalveolar septa, with stasis, sludge, and single erythrocyte thrombi. Hyaline membranes.

**Myocardium:** The stroma was sharply edematous, with a plethora of vessels. Around the vessels, there was proliferation of adipose and fibrous tissues. Cardiomyocytes were hypertrophied, and most of them were fragmented.

**Kidneys:** There were excessive arteriosclerotic nephrosclerosis, protein dystrophy, and necrosis of the convoluted tubule epithelium.

**Liver:** There was marked abundance of central veins with small focal hemorrhages around them. Hepatocytes showed signs of vacuolar degeneration.

**Spleen:** There was severe hyalinosis of the arterioles.

**Brain:** There was severe edema and neuroglia dystrophy.

**Conclusion:** A 59-year-old woman who had contact with patients with COVID-19 at work died on day 17 from disease onset and on day 10 of hospitalization from progressive cerebral edema with the development of dislocation syndrome

due to respiratory failure caused by bilateral total pneumonia, in the genesis of which the SARS-CoV-2 virus was significant. The novel coronavirus disease should be considered the underlying disease. Type 2 diabetes mellitus, stage III hypertension, and obesity represent unfavorable circumstances and were classified as concomitant diseases.

### Conclusion

The most severe forms of COVID-19 with a high mortality rate are registered in risk groups, which include patients with chronic comorbidities, such as type 2 diabetes mellitus, cardiovascular diseases, and obesity II or III. In these patients, a hyperinflammatory reaction, or a cytokine storm, occurs very quickly, and the lungs are the main target of viral aggression. Laboratory indicators of such an extremely severe condition are high levels of IL-6 and CRP. From the presented clinical case, all these factors were found and influenced the disease outcome. An aggravating factor that may have influenced the disease outcome was the underestimation of the patient's condition, as well as clinical and epidemiological data, by the polyclinic doctor. In the present case, the patient was suspected of COVID-19 during an outpatient examination, which was carried out in accordance with the temporary guidelines "Prevention, diagnostics and treatment of new coronavirus infection (COVID-19) version 5 (08.04.2020)." However, no pulse oximetry was performed, which could have helped identify incipient respiratory failure. These errors made at the outpatient stage resulted in late hospitalization (on day 8 of the disease) and delayed provision of adequate treatment.

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**For citation:** Kuznetsov NI, Vasiliev VV, Romanova ES, Startseva GYu. Course of severe coronavirus (COVID-19) in a patient at risk. *Russian Family Doctor*. 2020;24(3):21-26. <https://doi.org/10.17816/RFD46367>.

**Для цитирования:** Кузнецов Н.И., Васильев В.В., Романова Е.С., Старцева Г.Ю. Течение тяжелой коронавирусной инфекции (COVID-19) у пациента группы риска // Российский семейный врач. – 2020. – Т. 24. – № 3. – С. 21–26. <https://doi.org/10.17816/RFD46367>.

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