УДК 616.988:578.834.1-07
DOI: https://doi.org/10.17816/RFD635932

Клинико-лабораторная характеристика больных тяжелыми формами COVID-19 на фоне генно-инженерной терапии

А.В. Рогожкина[1], М.Н. Погромская[1, 2], Е.С. Романова[1, 2], Г.Ю. Старцева[1, 2], О.М. Филипович[1, 2], М.В. Клур[1], В.М. Антонов[1]

[1] Северо-Западный государственный медицинский университет им. И.И. Мечникова, Санкт-Петербург, Россия;
[2] Клиническая инфекционная больница им. С.П. Боткина, Санкт-Петербург, Россия

АННОТАЦИЯ

Обоснование. Одной из причин повышения риска смертельного исхода является развитие цитокинового шторма — гиперергического иммунного ответа, характеризующегося избытком цитокинов. Несмотря на использование биологической терапии, летальность от тяжелых форм COVID-19 по-прежнему остается довольно высокой.

Цель — проанализировать и оценить клинико-лабораторные показатели больных тяжелыми формами COVID-19, получавших биологическую терапию.

Материалы и методы. Для формирования выборки использован кластерный метод: в качестве кластеров выбраны тяжелое течение основного заболевания и терапия биологическими препаратами. В исследование включены 65 пациентов разделенных на две группы в зависимости от исхода заболевания: в группе 1 — 34 больных с благоприятным исходом основного заболевания, в группе 2 — 31 больной с летальным исходом.

Результаты. Группы значимо различались по возрасту ($p = 0,01$). У умерших пациентов отмечено большее количество сопутствующих заболеваний согласно индексу коморбидности Charlson ($p = 0,00009$) и шкале коморбидности (Cumulative Illness Rating Scale for Geriatrics, CIRS-G; $p = 0,000003$). По количеству дней с момента начала заболевания до назначения биологической терапии группы значимо различались ($p = 0,02$). На этапе терапии биологическими препаратами имело место ее более позднее начало в группе 2 (умерших пациентов), что способствовало сохранению высокой концентрации острофазовых белков.

Заключение. Решающими факторами эффективности терапии генно-инженерными препаратами тяжелых форм COVID-19, протекающих с цитокиновым штормом, являются возраст, наличие и выраженность сопутствующих заболеваний, сроки от начала болезни до госпитализации и биологической терапии.

Ключевые слова: COVID-19; тяжелое течение; биологическая терапия; генно-инженерная терапия; благоприятный исход; коморбидность.

Как цитировать
Рогожкина А.В., Погромская М.Н., Романова Е.С., Старцева Г.Ю., Филипович О.М., Клур М.В., Антонов В.М. Клинико-лабораторная характеристика больных тяжелыми формами COVID-19 на фоне генно-инженерной терапии // Российский семейный врач. 2024. Т. 28. № 4. С. 62–71. DOI: https://doi.org/10.17816/RFD635932

Рукопись получена: 11.09.2024 **Рукопись одобрена:** 27.09.2024 **Опубликована online:** 27.12.2024

DOI: https://doi.org/10.17816/RFD635932

Clinical and laboratory characteristics of patients with severe COVID-19 undergoing gene engineering therapy

Aleksandra V. Rogozhkina[1], Margarita N. Pogromskaya[1, 2], Elena S. Romanova[1, 2], Galina Yu. Startseva[1, 2], Olga M. Filipovich[1, 2], Margarita V. Klur[1], Vsevolod M. Antonov[1]

[1] North-Western State Medical University named after I.I. Mechnikov, Saint Petersburg, Russia;
[2] Clinical Infectious Diseases Hospital named after S.P. Botkin, Saint Petersburg, Russia

ABSTRACT

BACKGROUND: One of the primary factors contributing to an increased risk of fatal outcomes in severe COVID-19 cases is the development of a cytokine storm, a hyperimmune response characterized by excessive cytokine release. Despite using biologic therapies, mortality rates in severe COVID-19 cases remain significantly high.

AIM: To analyze and evaluate the clinical and laboratory parameters of patients with severe COVID-19 who received biologic therapy.

MATERIALS AND METHODS: A cluster sampling method was employed, with clusters selected based on the severity of the primary disease and biologic therapy. The study included 65 patients, divided into two groups based on disease outcomes: Group 1 comprised 34 patients with favorable outcomes, while Group 2 included 31 patients with fatal outcomes.

RESULTS: Significant differences were observed between the groups in terms of age ($p = 0.01$). Patients in Group 2 (with fatal outcomes) had a higher burden of comorbidities, as measured by the Charlson Comorbidity Index ($p = 0.00009$) and the Cumulative Illness Rating Scale for Geriatrics (CIRS-G; $p = 0.000003$). Additionally, the groups differed significantly in the number of days from disease onset to the initiation of biologic therapy ($p = 0.02$). In Group 2, delayed initiation of biologic therapy was associated with persistently high concentrations of acute-phase proteins.

CONCLUSIONS: Key factors influencing the efficacy of biologic therapy for severe COVID-19 with cytokine storm include patient age, the presence and severity of comorbidities, and the timing of hospitalization and initiation of biologic therapy.

Keywords: COVID-19; severe course; biological therapy; genetically engineered therapy; favorable outcome; comorbidity.

To cite this article
Rogozhkina AV, Pogromskaya MN, Romanova ES, Startseva GYu, Filipovich OM, Klur MV, Antonov VM. Clinical and laboratory characteristics of patients with severe COVID-19 undergoing gene engineering therapy. *Russian Family Doctor.* 2024;28(4):62–71. DOI: https://doi.org/10.17816/RFD635932

Received: 11.09.2024 **Accepted:** 27.09.2024 **Published online:** 27.12.2024

BACKGROUND

In March 2020, the global public health system faced of the infection caused by the SARS-CoV-2 virus spreading at unprecedented scale. After three years of the pandemic, over 675 million cases of infection were registered worldwide, including more than 6.8 million unfavorable outcomes. In Russia, the incidence exceeded 22 million cases, resulting in more than 388 thousand fatal outcomes. In St. Petersburg, the number of cases exceeded 1.1 million, with over 30,000 deaths.

A study conducted in China revealed that severe forms of the novel coronavirus develop in 5%–14% of cases [1].

The primary risk factors for a severe disease are old and senile age, as well as comorbidities (cardiovascular diseases, cancer, diabetes mellitus, obesity, and pulmonary diseases). Individuals at risk for severe COVID-19 are more likely to develop complications and have a higher probability of early death [2].

One of the causes of severe COVID-19 is a cytokine storm, which increases the risk of a fatal outcome [3]. A cytokine storm is defined as a hyperergic immune response that is characterized by an excess of cytokines (e.g., interleukin-1, -6 [IL-1, -6], tumor necrosis factor alpha [TNF-α], interferon, etc.). This excessive immune response leads to hyperinflammation and damage to vital organs and systems. The most significant pathogenic link is activation of alveolar macrophages, followed by release of proinflammatory cytokines. These cytokines stimulate migration of monocytes and neutrophils from the blood through the endothelium into the alveoli. This results in destabilization of intercellular interactions of endothelial cells, increased vascular permeability, changes in ventilation and perfusion, and fluid accumulation in the alveoli. Consequently, primary hypoxemia and ventilation dysfunction occur, creating a favorable environment for multiplication of anaerobic microflora and accession of secondary bacterial infection. Acute respiratory distress syndrome (ARDS), characterized by low oxygen saturation, is a primary cause of death in patients with COVID-19. Although the exact mechanism of ARDS in these patients is not fully clear, excessive production of proinflammatory cytokines is considered a significant contributing factor [4]. A study analyzing cytokine profiles in patients with COVID-19 demonstrated a direct correlation between a cytokine storm and lung damage, multiorgan failure, and an unfavorable prognosis in severe cases [5].

Proinflammatory cytokines were demonstrated to increase the life span of neutrophils and promote their migration through the walls of blood vessels, forming neutrophil extracellular traps that cause damage to internal organs [3]. Formation of neutrophil traps is accompanied by massive release of histones and serine proteases into the bloodstream, resulting in damage to the cells of blood vessels and other tissues [6]. This process, in turn, induces secretion of tissue thromboplastin and additional clotting factors, culminating in vascular thrombosis of affected tissues and organs. In cases of substantial damage, this may also provoke disseminated intravascular coagulation syndrome [3]. Consequently, activation of blood coagulation factors prompts stimulation of endothelial cells of blood vessels and circulating monocytes, leading to additional production of IL-6 [7]. Thus, hypercytokinemia becomes systemic and results in the development of multiorgan failure in the liver, kidneys, and heart [8].

It is still unclear whether a cytokine storm is the result of abnormal innate or adaptive immunity. One of the causes of hypercytokinemia is a genetic defect in the production and function of perforin in T cells, leading to excessive production of interferon gamma, which stimulates the release of IL-1, -6, -8, and TNF alpha by macrophages.

Additionally, according to some authors, major histocompatibility complex loci are determinants of genetic predisposition to infectious diseases [9]. Thus, carriers of some alleles can be classified as particularly vulnerable groups, prone to severe clinical manifestations of the disease [10].

Proinflammatory cytokines are known to be inducible, that is, not detectable in the blood under normal conditions. Therefore, determination of cytokine levels, early detection of a cytokine storm, and timely anti-inflammatory therapy are crucial for the COVID-19 outcome. Since increased IL-6 levels are associated with high mortality [3], IL-6 receptor antagonists and IL-6 receptor blockers are used to treat the severe forms of COVID-19.

Glucocorticoids and drugs to correct coagulopathy are used as pathogenetic therapy in addition to genetically engineered drugs. Antiviral drugs are used as etiotropic therapy to suppress SARS-CoV-2 replication.

Currently, hypercytokinemia occurs in 10%–15% of patients with severe forms of COVID-19. Despite the use of biological therapy targeting the main pathogenesis link, the mortality rate in severe forms of COVID-19 with a cytokine storm remains high.

The study aimed to analyze and evaluate the clinical and laboratory characteristics of patients with severe COVID-19 who received biological therapy.

MATERIALS AND METHODS

A retrospective study including patients diagnosed with COVID-19 (U07.1) was conducted at the Botkin Clinical Infectious Diseases Hospital. A cluster sampling method was employed, with clusters selected based on the severity of the underlying disease and biological therapy. A total of 65 patients were randomly selected from the general population of patients admitted for treatment in June 2021.

DOI: https://doi.org/10.17816/RFD635932

The diagnosis was confirmed by the detection of SARS-Cov-2 RNA in nasopharyngeal swabs by nucleic acid amplification in all patients.

Inclusion criteria: verification of SARS-Cov-2 virus, severe and extremely severe course of the underlying disease (COVID-19), and biological therapy with IL-6 receptor antagonists and IL-6 receptor blockers.

A retrospective analysis of patients' medical records was conducted to assess anamnestic data, including dates of hospitalization and disease duration. Comorbidities were evaluated using the Charlson Comorbidity Index (CCI) and the Cumulative Illness Rating Scale for Geriatrics (CIRS-G). The severity of patients' conditions was determined using the National Early Warning Score (NEWS). Laboratory tests, including complete blood count and blood chemistry and coagulation tests, as well as instrumental tests, such as chest X-rays and chest CT scans, were analyzed. Three test results were used as comparison points for laboratory parameters: upon admission, after biological therapy, and before discharge or death. An analysis was conducted on data upon admission to the intensive care unit (ICU) and the use of respiratory support, including oxygen insufflation, high-flow oxygen therapy, non-invasive ventilation, and mechanical ventilation. The enrolled patients were divided into two groups based on disease outcomes: 34 patients with favorable outcomes in Group 1, and 31 patients with fatal outcomes in Group 2.

The statistical analysis of data was performed using the Statistica 10.0 software. The quantitative data were presented as the mean, standard deviation, and median, whereas the qualitative data were presented as absolute and relative frequencies. The Student's *t*-test was used to compare parametric data, and the Mann–Whitney *U* test was used to compare nonparametric data.

RESULTS

Group 1 (patients with a favorable outcome) included 11 (32.4%) men and 23 (67.6%) women. Group 2 (patients with a fatal outcome) consisted of 18 (58.1%) men and 13 (41.9%) women. A statistically significant difference in age was observed between the two groups. The mean age in Group 1 was 49.8 ± 16.3, whereas in Group 2, it was 60.7 ± 17.9 ($p = 0.01$).

The disease duration in Group 1 was found to be 29.2 ± 9.3 days, with patients being hospitalized 6.3 ± 2.9 days after the disease onset, and their hospital stay being 22.9 ± 9.9 bed days. In Group 2, the disease duration was 23.19 ± 8.2 days, the patients were hospitalized 8.2 ± 4.9 days after the disease onset, and the hospitalization lasted 14.9 ± 8.8 bed days.

Of the entire sample, 21 (32.3%) patients had no comorbidities. Of these, 18 (52.9%) patients were in Group 1, while 3 (9.7%) patients were in Group 2. The other 44 (67.7%) patients had unfavorable premorbid background, with a predominance of cardiovascular diseases (such as hypertension, ischemic heart disease, and chronic heart failure), as well as type 2 diabetes mellitus and obesity. The prevalence of chronic obstructive pulmonary disease, chronic kidney disease, hepatobiliary system and gastrointestinal tract diseases were significantly less common. A higher prevalence of comorbidities was observed in the deceased patients, with a mean CCI of 1.4 ± 2.1 and 4.4 ± 3.5 in Groups 1 and 2, respectively ($p = 0.0000$). The mean sum of CIRS-G comorbidity scale scores was 4.6 ± 2.5 and 8.5 ± 3.6 in Groups 1 and 2, respectively ($p = 0.000003$).

The severity of patients' conditions upon admission was evaluated using the NEWS scale, which includes several physiological parameters such as respiratory rate, oxygen saturation, body temperature, systolic blood pressure, heart rate, and level of consciousness. This scale categorizes patients by the risk for developing critical conditions as low, medium, or high. In Group 1, 17 (50.0%), 10 (29.4%), and 7 (20.6%) patients were classified as having low, medium, or high risk, respectively. In Group 2, the distribution was as follows: 11 (35.5%) patients were classified as having a low risk, 9 (29.0%) patients were classified as having a moderate risk, and the remaining 11 (35.5%) patients were classified as having a high risk of developing severe disease.

The first point of comparison between the groups was laboratory tests upon admission. The results of the comparison of laboratory indicators in the groups are presented in Table 1.

Blood oxygen saturation levels upon admission were found to be less than 92% in 16 (47.0%) patients from Group 1 and 19 (61.3%) from Group 2. The 50% lung damage according to chest X-rays was found in 9 (26.5%) patients in Group 1 and 17 (54.8%) patients in Group 2.

Upon detection of clinical and laboratory characteristics of a cytokine storm, all patients were prescribed pathogenetic biological therapy with genetically engineered drugs. The distribution of genetically engineered drugs used in patients of Groups 1 and 2 is shown in Fig. 1.

As illustrated in Fig. 1, the majority of patients received treatment with IL-6 receptor antagonists (tocilizumab, levilimab), with a smaller proportion receiving IL-6 receptor blockers (olokizumab). The latter were prescribed based on abnormal changes in the lungs classified as CT1–CT4, in conjunction with two or more signs demonstrating the intensity of the inflammatory process, including elevated IL-6 levels.

In Group 1, the patients received biological therapy 8.9 ± 2.8 days after the disease onset, whereas in Group 2, it was administered 10.9 ± 3.9 days after the disease onset, that is, at a later disease stage.

Table 1. Laboratory indicators of patients at admission
Таблица 1. Лабораторные показатели пациентов при поступлении

Laboratory indicators	Group 1	Group 2	*p*-value
White blood cells, $\times 10^9$/L	6.8 ± 3.6	7.6 ± 4.0	$p > 0.05$
Absolute neutrophil count, $\times 10^9$/L	5.4 ± 3.5	6.3 ± 4.0	$p > 0.05$
Absolute lymphocyte count, $\times 10^6$/L	0.98 ± 0.4	0.8 ± 4.1	$p > 0.05$
Lactate dehydrogenase, U/L	349.6 ± 117.3	423.1 ± 152.3	$p = 0.035$
C-reactive protein, mg/L	79.8 ± 74.7	93.8 ± 73.4	$p > 0.05$
Ferritin, μg/L	431.6 ± 320.3	946.8 ± 674.6	$p = 0.002$
Interleukin-6, pg/mL	42.7 ± 59.6	56.1 ± 78.7	$p > 0.05$
D-dimer, ng/mL	0.78 ± 1.4	1.03 ± 1.5	$p = 0.014$

The second point of comparison was the laboratory tests after the biological therapy. A comparative analysis of the main indicators is given in Table 2.

Despite the administration of full pathogenetic therapy in patients of both groups, the severity of the disease course determined the need to continue treatment in the ICU.

In Group 1, 11/34 (32.4%) patients were transferred to the ICU, with an average delay of 2.5 ± 2.8 days. Notably, 4 (36.4%) patients required treatment in the ICU from the moment of admission to the hospital, with a median stay of 3.2 ± 1.7 bed days.

In Group 2, the predominant proportion of patients (28, 90.3%) received treatment in the ICU. The average time between the initiation of inpatient treatment and transfer was 6.4 ± 5.6 days. Notably, 4/28 (14.3%) patients were immediately admitted to the ICU upon admission.

When comparing the timing of biological therapy administration in patients treated in the ICU, it was found that genetically engineered drugs in Group 1 were administered on average three days earlier than in Group 2 (7.1 ± 2.8 and 10.7 ± 3.9 days after the disease onset, respectively).

The majority of patients were transferred to the ICU due to worsening of respiratory failure. Oxygen insufflation was indicated to the patients with a saturation level below 95%. In cases of respiratory failure worsening, high-flow nasal oxygenation (HFNO) was used or non-invasive ventilation if HFNO was ineffective. If this approach was also unsuccessful, mechanical ventilation was initiated. In Group 1, respiratory support was required in 4/11 (36.3%) patients. In Group 2, 24/28 (85.7%) patients were hospitalized in the ICU and died while on mechanical ventilation, whereas 4 (14.3%) patients died while on non-invasive ventilation.

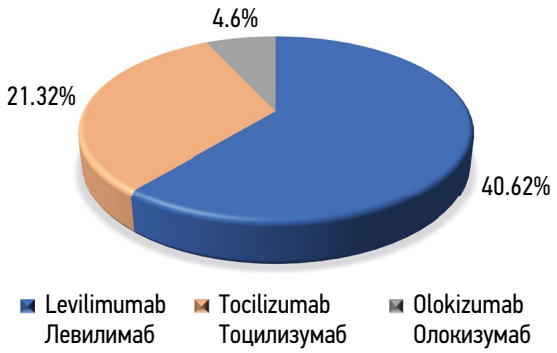

Fig. 1. Distribution of used genetically engineered drugs in patients of groups 1 and 2
Рис. 1. Распределение используемых генно-инженерных препаратов у больных групп 1 и 2

Table 2. Laboratory parameters of patients after biological therapy
Таблица 2. Лабораторные показатели пациентов после биологической терапии

Laboratory indicators	Group 1	Group 2	*p*-value
White blood cells, $\times 10^9$/L	10.8 ± 3.6	14.0 ± 7.2	$p = 0.03$
Absolute neutrophil count, $\times 10^9$/L	11.5 ± 15.5	12.1 ± 6.0	$p > 0.05$
Absolute lymphocyte count, $\times 10^6$/L	0.9 ± 0.4	0.7 ± 0.4	$p = 0.002$
Lactate dehydrogenase, U/L	484.0 ± 160.4	729.4 ± 292.9	$p = 0.001$
C-reactive protein, mg/L	67.5 ± 58.4	59.7 ± 43.5	$p > 0.05$
Ferritin, μg/L	853.4 ± 637.0	1353.6 ± 1079.5	$p > 0.05$
Interleukin-6, pg/mL	197.5 ± 179.3	224.1 ± 183.3	$p > 0.05$
D-dimer, ng/mL	1.3 ± 1.5	2.9 ± 3.7	$p = 0.02$

Table 3. Laboratory indicators of patients in the outcome of the disease
Таблица 3. Лабораторные показатели пациентов в исходе заболевания

Laboratory indicators	Group 1	Group 2	*p*-value
White blood cells, $\times 10^9$/L	9.6 ± 4.2	21.2 ± 14.4	$p = 0.000026$
Absolute neutrophil count, $\times 10^9$/L	6.8 ± 4.0	19.1 ± 13.8	$p = 0.000001$
Absolute lymphocyte count, $\times 10^6$/L	1.9 ± 0.8	0.9 ± 0.7	$p = 0.000002$
Lactate dehydrogenase, U/L	300.8 ± 139.3	1068.3 ± 560.0	$p = 0.000008$
C-reactive protein, mg/L	6.4 ± 13.1	78.8 ± 99.8	$p = 0.000000$
Ferritin, μg/L	650.2 ± 498.6	2376.3 ± 1748.7	$p = 0.008629$
Interleukin-6, pg/mL	128.3 ± 227.4	375.3 ± 292.5	$p > 0.05$
D-dimer, ng/mL	0.6 ± 1.0	3.55 ± 3.5	$p = 0.000001$

The primary end point of comparison was the results of blood count, biochemistry, and coagulation tests, which are presented in Table 3.

DISCUSSION

The findings obtained from the analysis of the sex and age structure, as well as the comorbidities of patients, are in accordance with the prevailing perspectives on the epidemiology of COVID-19. The predominance of male mortality was confirmed in several studies [11, 12]. Moreover, the advanced age and the presence of comorbidities was demonstrated to have a substantial effect on the severity of the disease's progression and the subsequent patient outcome [2].

A statistical analysis of the first point of comparison in Group 2 revealed significant differences in the indicators reflecting the intensity of the inflammatory process. Lactate dehydrogenase (LDH), ferritin, and D-dimer were identified as prognostic markers of severe course and unfavorable prognosis in patients with COVID-19 [13]. Furthermore, the neutrophil to lymphocyte ratio (NLR), a measure of the patient's overall inflammatory status, exhibited a higher value in Group 2 patients (10.3, median 6.4) compared to Group 1 patients (7.3, median 4.3). According to studies conducted in Italy, an increase in NLR is associated with an escalation of the disease severity and is a risk factor for a fatal outcome in COVID-19 [14].

At the second comparison point, a significant difference was observed in the prognostic markers of severe disease and unfavorable outcome. An increase in white blood cell and neutrophil levels compared to levels at admission is generally considered as an indirect sign of secondary infection (including as a side effect of genetically engineered drugs). However, complications in the form of bacterial infection were included in the diagnosis in only 3 (4.6%) patients. Nevertheless, the NLR coefficient was high: 7.5 (median 4.1) and 22.1 (median 14.5) in Groups 1 and 2, respectively. These findings indicate that higher NLR coefficient values are associated with an unfavorable prognosis in Group 2 patients at the stage of biological therapy. Furthermore, the findings revealed regularities consistent with the progression of coronavirus infection following treatment with genetically engineered biological drugs. These regularities manifested as a substantial decrease in the serum level of C-reactive protein in patients across both groups compared to their initial values upon admission.

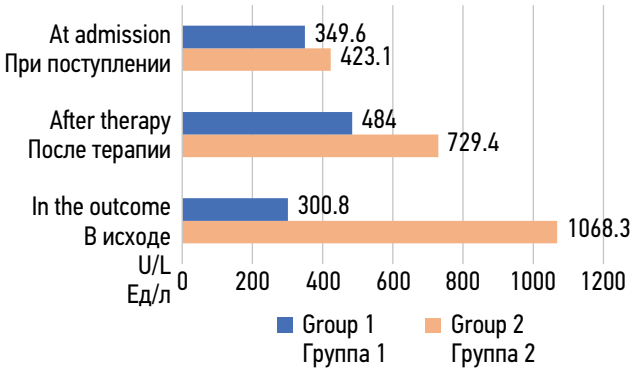

Fig. 2. Dynamics of changes in lactate dehydrogenase levels in patients from groups 1 and 2
Рис. 2. Динамика изменения уровня лактатдегидрогеназы у пациентов из групп 1 и 2

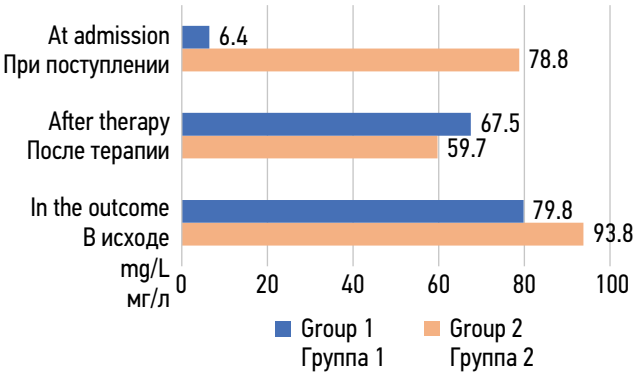

Fig. 3. Dynamics of changes in the level of C-reactive protein in patients from groups 1 and 2
Рис. 3. Динамика изменения уровня С-реактивного белка у пациентов из групп 1 и 2

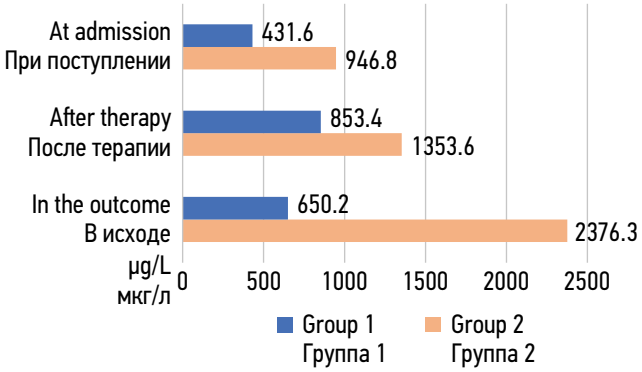

Fig. 4. Dynamics of changes in the level of ferritin in patients from groups 1 and 2
Рис. 4. Динамика изменения уровня ферритина у пациентов из групп 1 и 2

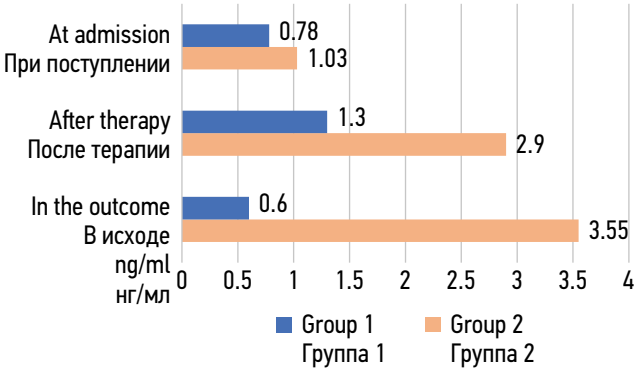

Fig. 5. Dynamics of changes in the level of D-dimer in patients from groups 1 and 2
Рис. 5. Динамика изменения уровня Д-димера у пациентов из групп 1 и 2

Elevated D-dimer levels are indicative of the development of thromboemboli (immune-inflammatory thrombosis), which is a direct pathogenic consequence of hypercytokinemia. In hypercytokinemia, immunothrombosis leads to intensification of inflammation [3]. Given the significantly higher levels of IL-6 observed in both groups compared to those recorded upon admission, it can be assumed that the elevated D-dimer levels are a consequence of prolonged hypercytokinemia.

The statistical difference in the timing of administration of genetically engineered drugs (with patients in Group 1 receiving therapy on average three days earlier than those in Group 2) indicates that the earlier initiation of pathogenetic biological therapy is a crucial factor in predicting the outcome in patients with COVID-19. According to a Japanese study, in the absence of immediate and adequate therapeutic intervention, patients develop ARDS as a result of acute lung damage, which subsequently leads to multiorgan failure and death [15]. The delayed initiation of biological therapy in Group 2 was likely to contribute to the development of critical conditions in a significant number of patients, necessitating transfer to the ICU.

Presumably, the most important factor influencing the development of complications is the severity of comorbidities. However, a comparison of the comorbid status of patients in both groups, treated and untreated in the ICU, using the CCI and CIRS-G scales, revealed no statistically significant difference in the sum of the scores. This does not exclude the presence of other factors that exacerbate the course of COVID-19.

At the third comparison point, positive laboratory changes over time were observed in the surviving patients (Group 1). Figures 2–5 illustrate the change in acute-phase C-reactive protein and adverse outcome markers related to COVID-19 in patients of both groups during hospitalization.

The level of ferritin, considered as an acute-phase protein together with C-reactive protein, may indicate the destruction of organ tissues [16]. In addition, some authors admit that mechanisms of ferritin-cytokine interaction may exist. These mechanisms involve the ability of cytokines to induce ferritin expression, and vice versa, with ferritin having the ability to regulate the expression of pro- and anti-inflammatory cytokines [17]. The high concentration of D-dimer suggests that thromboembolism is irreversible. Studies showed that ARDS is the primary cause of mortality among patients [18]. According to autopsy results, ARDS was listed as the cause of death in 22 (70.9%) patients in Group 2.

CONCLUSION

The study found that even in the outpatient setting, patients in the fatal outcome group (Group 2) had higher levels of LDH, ferritin, and D-dimer (early markers of a high risk of unfavorable outcomes) than patients in Group 1, which may be due to significant age differences and more severe comorbidities. In addition to the above factors, later treatment may have influenced the unfavorable outcome. At the stage of biological therapy, treatment in patients from the group with the fatal outcome was initiated on a later date. This contributed to the persistence of high concentrations of acute-phase proteins and markers of poor prognosis. Furthermore, the NLR, which reflects the inflammatory status of patients, increased. Due to the progression of pathogenetic mechanisms, patients developed conditions that required respiratory support. Consequently, a higher proportion of patients in the fatal outcome group required transfer to the ICU compared to the patients in the survival group. The laboratory data obtained during the disease course fully reflected the pathogenetically determined conditions in the form of vascular thrombosis, the development of bacterial complications, prolonged hypercytokinemia, and the further increase in systemic organ damage. These conditions were manifested by high levels of LDH, C-reactive protein, ferritin, and neutrophils. Therefore, age, comorbidities, time to hospitalization, and initiation of biological therapy may be critical factors in the efficacy of genetically engineered therapies for successful treatment

of severe cases of COVID-19 with a cytokine storm. Obviously, these factors are not the cause of hypercytokinemia; rather, they are critical in predicting outcomes.

In conclusion, a severe and extremely severe course of COVID-19 accompanied by a cytokine storm was also observed in young and middle-aged patients without comorbidities, which should be further investigated.

ADDITIONAL INFORMATION

Funding source. This study was not supported by any external sources of funding.

Competing interests. The authors declare that they have no competing interests.

Author contribution. All the authors have made a significant contribution to the development of the concept, research, and preparation of the article as well as read and approved the final version before its publication.

Personal contribution of the authors: *A.V. Rogozhkina* — concept and plan of the study, collection and mathematical analysis of data, text writing; *M.N. Pogromskaya* — concept and plan of the study, collection and mathematical analysis of data; *O.M. Filipovich* — collection and mathematical analysis of data; *A.V. Rogozhkina, E.S. Romanova, G.Yu. Startseva, M.V. Klur, V.M. Antonov* — text writing.

Ethics approval. The present study protocol was approved by the local Ethics Committee of the North-Western State Medical University named after I.I. Mechnikov (No. 2 dated 18.10.2021).

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Наибольший вклад распределен следующим образом: *А.В. Рогожкина* — концепция и план исследования, сбор и математический анализ данных, написание текста; *М.Н. Погромская* — концепция и план исследования, сбор и математический анализ данных; *О.М. Филипович* — сбор и математический анализ данных; *Е.С. Романова, Г.Ю. Старцева, М.В. Клур, В.М. Антонов* — написание текста.

Этический комитет. Протокол исследования был одобрен локальным этическим комитетом СЗГМУ им. И.И. Мечникова (№ 2 от 18.10.2021).

REFERENCES

1. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. *JAMA.* 2020;323(13):1239–1242. doi: 10.1001/jama.2020.2648

2. Shherbak SG, Kamilova TA, Golota AS, Vologzhanin DA. Risk factors for severe course and lethal outcome of COVID-19. *Physical and Rehabilitation Medicine, Medical Rehabilitation.* 2022;4(1):14–36. EDN: IWIVWC doi: 10.36425/rehab104997

3. Potapnev MP. Cytokine storm: causes and consequences. *Immunologiya.* 2021;42(2):175–188. EDN: KTUDQQ doi: 10.33029/0206-4952-2021-42-2-175-188

4. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* 2020;395:497–506. doi: 10.1016/S0140-6736(20)30183-5

5. Ruan Q, Yang K, Wang W, et al. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med.* 2020;46:1294–1297. doi: 10.1007/s00134-020-05991-x

6. Morris G, Bortolasci C, Puri BK, et al. Preventing the development of severe COVID-19 by modifying immunothrombosis. *Life Sci.* 2021;264:118617. doi: 10.1016/j.lfs.2020.118617

7. Jayarangaiah A, Kariyanna PT, Chen X, et al. COVID-19-associated coagulopathy: an exacerbated immunothrombosis response. *Clin Appl Thromb Hemost.* 2020;26:1–11. doi: 10.1177/1076029620943293

8. Chernyh ER, Leplina OJu, Tihonova MA, et al. Cytokine balance in the pathogenesis of systemic inflammatory response: a new target for immunotherapeutic interventions in the treatment of sepsis. *Medical Immunology.* 2001;3(3):415–429. (In Russ.). EDN: JUARZX

9. Shi Y, Wang Y, Shao C, et al. COVID-19 infection: the perspectives on immune responses. *Cell Death Differ.* 2020;27(5):1451–1454. doi: 10.1038/s41418-020-0530-3

10. Nguyen A, David JK, Maden SK, et al. Human leukocyte antigen susceptibility map for SARS-CoV-2. *J Virol.* 2020;94(13):1–12. doi: 10.1128/JVI.00510-20

11. Williamson E, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature.* 2020;584(7821):430–436. doi: 10.1038/s41586-020-2521-4

12. Zhang J, Wang X, Jia X, et al. Risk factors for disease severity, unimprovement, and mortality in COVID-19 patients in Wuhan, China. *Clin Microbiol Infect.* 2020;26(6):767–772. doi: 10.1016/j.cmi.2020.04.012

13. Vorob'eva NA, Vorob'eva AI. Predictive value of D-dimer in COVID-19. *Health care Standardization Problems.* 2021;5(6):36–42. EDN: AYAAXX doi: 10.26347/1607-2502202105-06036-042

14. Ponti G, Maccaferri M, Ruini C, et al. Biomarkers associated with COVID-19 disease progression. *Crit Rev Clin Lab Sci.* 2020;57(6):389–399. doi: 10.1080/10408363.2020.1770685

15. Ishikawa T. Clinical preparedness for cytokine storm induced by the highly pathogenic H5N1 influenza virus. *J Pharmacogenom Pharmacoproteomics.* 2012;3(6):1000e131. doi: 10.4172/2153-0645.1000e131

16. Polushin JuS, Shlyk IV, Gavrilova EG, et al. The role of ferritin in assessing COVID-19 severity. *Bulletin of anesthesiology and resuscitation.* 2021;18(4):20–28. EDN: VGUGSZ doi: 10.21292/2078-5658-2021-18-4-20-28

17. Kuznecov IA, Potievskaja VI, Kachanov IV, Kuraleva OO. Ferritin's role in biological circles of the person. *Modern problems of science and education.* 2017;(5):206. EDN: ZQNIGV

18. Antoshkin ON, Vorotnikova TV. Analysis of complications from coronavirus infection COVID-19 according to pathoanatomical studies. *Journal of Volgograd state medical university.* 2021;78(2):156–159. EDN: FTGALT doi: 10.19163/1994-9480-2021-2(78)-156-159

СПИСОК ЛИТЕРАТУРЫ

1. Wu Z., McGoogan J.M. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention // JAMA. 2020. Vol. 323, N 13. P. 1239–1242. doi: 10.1001/jama.2020.2648

2. Щербак С.Г., Камилова Т.А., Голота А.С., Вологжанин Д.А. Факторы риска тяжелого течения и летального исхода COVID-19 // Физическая и реабилитационная медицина, медицинская реабилитация. 2022. Т. 4, № 1. С. 14–36. EDN: IWIVWC doi: 10.36425/rehab104997

3. Потапнев М.П. Цитокиновый шторм: причины и последствия // Иммунология. 2021. Т. 42, № 2. С. 175–188. EDN: KTUDQQ doi: 10.33029/0206-4952-2021-42-2-175-188

4. Huang C., Wang Y., Li X., et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China // Lancet. 2020. Vol. 395. P. 497–506. doi: 10.1016/S0140-6736(20)30183-5

5. Ruan Q., Yang K., Wang W., et al. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China // Intensive Care Med. 2020. Vol. 46. P. 1294–1297. doi: 10.1007/s00134-020-05991-x

6. Morris G., Bortolasci C., Puri B.K., et al. Preventing the development of severe COVID-19 by modifying immunothrombosis // Life Sci. 2021. Vol. 264. P. 118617. doi: 10.1016/j.lfs.2020.118617

7. Jayarangaiah A., Kariyanna P.T., Chen X., et al. COVID-19-associated coagulopathy: an exacerbated immunothrombosis response // Clin Appl Thromb Hemost. 2020. Vol. 26. P. 1–11. doi: 10.1177/1076029620943293

8. Черных Е.Р., Леплина О.Ю., Тихонова М.А., и др. Цитокиновый баланс в патогенезе системного воспалительного ответа: новая мишень иммунотерапевтических воздействий при лечении сепсиса // Медицинская иммунология. 2001. Т. 3, № 3. С. 415–429. EDN: JUARZX

9. Shi Y., Wang Y., Shao C., et al. COVID-19 infection: the perspectives on immune responses // Cell Death Differ. 2020. Vol. 27, N 5. P. 1451–1454. doi: 10.1038/s41418-020-0530-3

10. Nguyen A., David J.K., Maden S.K., et al. Human leukocyte antigen susceptibility map for SARS-CoV-2. // J Virol. 2020. Vol. 94, N 13. P. 1–12. doi: 10.1128/JVI.00510-20

11. Williamson E., Walker A.J., Bhaskaran K., et al. Factors associated with COVID-19-related death using OpenSAFELY // Nature. 2020. Vol. 584, N 7821. P. 430–436. doi: 10.1038/s41586-020-2521-4

12. Zhang J., Wang X., Jia X., et al. Risk factors for disease severity, unimprovement, and mortality in COVID-19 patients in Wuhan, China // Clin Microbiol Infect. 2020. Vol. 26. N 6. P. 767–772. doi: 10.1016/j.cmi.2020.04.012

13. Воробьева Н.А., Воробьева А.И. Прогностическая значимость Д-димера при COVID-19 // Проблемы стандартизации в здравоохранении. 2021. Т. 5, № 6. С. 36–42. EDN: AYAAXX doi: 10.26347/1607-2502202105-06036-042

14. Ponti G., Maccaferri M., Ruini C., et al. Biomarkers associated with COVID-19 disease progression // Crit Rev Clin Lab Sci. 2020. Vol. 57, N 6. P. 389–399. doi: 10.1080/10408363.2020.1770685

15. Ishikawa T. Clinical preparedness for cytokine storm induced by the highly pathogenic H5N1 influenza virus // J Pharmacogenom Pharmacoproteomics. 2012. Vol. 3, N 6. P. 1000e131. doi: 10.4172/2153-0645.1000e131

16. Полушин Ю.С., Шлык И.В., Гаврилова Е.Г., и др. Роль ферритина в оценке тяжести COVID-19 // Вестник анестезиологии и реаниматологии. 2021. Т. 18, № 4. С. 20–28. EDN: VGUGSZ doi: 10.21292/2078-5658-2021-18-4-20-28

17. Кузнецов И.А., Потиевская В.И., Качанов И.В., Куралева О.О. Роль ферритина в биологических средах человека // Современные проблемы науки и образования. 2017. № 5. С. 206. EDN: ZQNIGV

18. Антошкин О.Н., Воротникова Т.В. Анализ осложнений от коронавирусной инфекции COVID-19 по данным патологоанатомических исследований // Вестник ВолгГМУ. 2021. Т. 78, № 2. С. 156–159. EDN: FTGALT doi: 10.19163/1994-9480-2021-2(78)-156-159

AUTHORS INFO

*** Aleksandra V. Rogozhkina**, MD;
address: 41 Kirochnaya St., Saint Petersburg, 191015, Russia;
ORCID: 0000-0003-4423-7408;
eLibrary SPIN: 4984-6618;
e-mail: gostevaaleksandra@gmail.com

Margarita N. Pogromskaya,
MD, Cand. Sci. (Medicine), Assistant Professor;
ORCID: 0000-0001-8072-6589;
e-mail: M.Pogromskaya@szgmu.ru

Elena S. Romanova, MD, Cand. Sci. (Medicine), Assistant Professor;
ORCID: 0000-0002-9887-8561;
eLibrary SPIN: 9435-6838;
e-mail: E.Romanova@szgmu.ru

ОБ АВТОРАХ

*** Александра Витальевна Рогожкина**;
адрес: Россия, 191015, Санкт-Петербург, Кирочная ул., д. 41;
ORCID: 0000-0003-4423-7408;
eLibrary SPIN: 4984-6618;
e-mail: gostevaaleksandra@gmail.com

Маргарита Николаевна Погромская,
канд. мед. наук, доцент;
ORCID: 0000-0001-8072-6589;
e-mail: M.Pogromskaya@szgmu.ru

Елена Сергеевна Романова, канд. мед. наук, доцент;
ORCID: 0000-0002-9887-8561;
eLibrary SPIN: 9435-6838;
e-mail: E.Romanova@szgmu.ru

* Corresponding author / Автор, ответственный за переписку

AUTHORS INFO

Galina Yu. Startseva,
MD, Cand. Sci. (Medicine), Assistant Professor;
ORCID: 0000-0002-3660-2666;
eLibrary SPIN: 8392-2950;
e-mail: star661@rambler.ru

Olga M. Filipovich, MD;
ORCID: 0000-0001-9569-6941;
eLibrary SPIN: 3667-8214;
e-mail: filipowitch.olga@yandex.ru

Margarita V. Klur, MD, Cand. Sci. (Medicine), Assistant Professor;
ORCID: 0009-0006-6222-2452;
e-mail: rita-med@mail.ru

Vsevolod M. Antonov,
MD, Cand. Sci. (Medicine), Assistant Professor;
ORCID: 0009-0002-3172-7926;
eLibrary SPIN: 9925-2139;
e-mail: Vsevolod.Antonov@szgmu.ru

ОБ АВТОРАХ

Галина Юрьевна Старцева,
канд. мед. наук, доцент;
ORCID: 0000-0002-3660-2666;
eLibrary SPIN: 8392-2950;
e-mail: star661@rambler.ru

Ольга Михайловна Филипович;
ORCID: 0000-0001-9569-6941;
eLibrary SPIN: 3667-8214;
e-mail: filipowitch.olga@yandex.ru

Маргарита Вилленовна Клур, канд. мед. наук, доцент;
ORCID: 0009-0006-6222-2452;
e-mail: rita-med@mail.ru

Всеволод Михайлович Антонов,
канд. мед. наук, доцент;
ORCID: 0009-0002-3172-7926;
eLibrary SPIN: 9925-2139;
e-mail: Vsevolod.Antonov@szgmu.ru