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CURRENT, EFFECTIVENESS OF THERAPY AND OUTCOMES OF NEW CORONAVIRUS INFECTION: PRELIMINARY ANALYSIS

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◆ ***Relevance.*** Verification of a new coronavirus infection (COVID-19) requires clear algorithms for the diagnosis and treatment of patients, depending on clinical, laboratory and instrumental dates. Timely and informed decisions on optimizing management tactics and prescribing proactive anti-inflammatory therapy before development of a complete symptom complex life threatening conditions are needed in some cases.

Aim of the study. To analyze the course and outcomes of a new coronavirus infection, depending on the initial characteristics of the patients and treatment options.

Materials and methods. A preliminary analysis of the case histories of 129 people hospitalized in the center for treating patients with a new coronavirus infection at North-Western State Medical University n.a. I.I. Mechnikov was made by random sampling. Among the hospitalized patients there were 67 men (51.9%), the average age was 57.9 ± 16.4 years, 62 women (48.1%), and the average age was 60.2 ± 13.6 years. During hospitalization, all patients underwent standard clinical laboratory and instrumental examination, as well as determination of saturation (S_pO_2), markers of the cytokine storm (CRP, ferritin, AST, D-dimer, fibrinogen, lymphocytes), compute tomography (CT) of the lungs. The effectiveness and safety of therapy was evaluated by the outcome (recovery, death), as well as by the presence of adverse events in the background of the therapy. Statistical processing of the research results was carried out using the Statistica 12 for Windows application software package, the significance of differences between the two relative values was evaluated using the Student *t*-test ($t > 2$, $p < 0.05$).

Results. Fatal outcomes were significantly more frequently recorded among patients of older age groups and males. The presence of concomitant diseases such as obesity, diabetes mellitus, pathology of the cardiovascular system was accompanied by more frequent fatal outcomes. That allows considering comorbidity as a risk factor for severe course and poor prognosis of COVID-19. However, in general, in the presence of the indicated forms of concomitant diseases, it was not possible to establish significant differences with the outcomes of COVID-19, which may be due to an insufficient amount of patients. Predictors of fatal outcome was low values of saturation, the presence of respiratory failure, a significant amount of lung tissue damage (CT-3-4), as well as high values of CRP, ferritin, AST, D-dimer, neutrophilia, lymphopenia, thrombocytopenia. The use of anticytokine drugs (ACD) in complex therapy can be considered a favorable predictor of outcome, which indicates the advisability of wider use. The materials of the study allow not only a preliminary assessment of the course and effectiveness of complex therapy using anticytokine drugs with COVID-19 in patients with comorbid diseases, but also to develop therapeutic and diagnostic algorithms in patients of this category.

◆ **Keywords:** new coronavirus infection; SARS-CoV-2 (COVID-19); comorbidity; cytokine storm syndromes; data analysis; therapy.

КЛИНИЧЕСКОЕ ТЕЧЕНИЕ, ЭФФЕКТИВНОСТЬ ТЕРАПИИ И ИСХОДЫ НОВОЙ КОРОНАВИРУСНОЙ ИНФЕКЦИИ: ПРЕДВАРИТЕЛЬНЫЙ АНАЛИЗ

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◆ ***Актуальность.*** Для верификации новой коронавирусной инфекции (COVID-19) необходимо разработать четкие алгоритмы по диагностике и лечению пациентов в зависимости от клинико-лабораторных и инструментальных данных, а в ряде случаев принимать своевременные и обоснованные решения по оптимизации тактики ведения и назначению упреждающей противовоспалительной терапии до появления полной клинической картины жизнеугрожающих состояний.

Цель исследования — проанализировать течение и исходы новой коронавирусной инфекции в зависимости от первоначальных характеристик пациентов и вариантов лечения.

Материалы и методы. Методом случайной выборки проведен предварительный анализ историй болезней 129 человек, госпитализированных в центр по лечению больных новой коронавирусной инфекцией СЗГМУ им. И.И. Мечникова. Среди госпитализированных пациентов было 67 мужчин (51,9 %), средний возраст которых составил 57,9 ± 16,4 года, и 62 женщины (48,1 %), средний возраст которых был 60,2 ± 13,6 года. Всем пациентам при госпитализации проводили стандартное клинико-лабораторное и инструментальное обследование, а также определяли показатели сатурации (S_pO_2), содержание маркеров «цитокинового шторма» (С-реактивного белка, ферритина, аспартатаминотрансферазы, D-димера, фибриногена, лимфоцитов), выполняли компьютерную томографию легких. Эффективность и безопасность терапии оценивали по исходам (выздоровление, летальный), а также по наличию нежелательных явлений на фоне проведения терапии. Статистическую обработку результатов исследования выполняли с применением пакета прикладных программ Statistica 12 for Windows, достоверность различий двух относительных величин оценивали по *t*-критерию Стьюдента ($t > 2$, $p < 0{,}05$).

Результаты. Летальные исходы достоверно чаще регистрировали среди пациентов старших возрастных групп и лиц мужского пола. Наличие у пациентов, поступивших в стационар, таких сопутствующих заболеваний, как ожирение, сахарный диабет, патология сердечно-сосудистой системы, было ассоциировано с более частыми летальными исходами, что позволяет рассматривать коморбидность как фактор риска тяжелого течения и неблагоприятного прогноза COVID-19. Однако в целом не удалось установить достоверных отличий исходов у пациентов с COVID-19 и указанными формами сопутствующих заболеваний от исходов у пациентов без сопутствующих заболеваний, что, возможно, связано с недостаточной выборкой пациентов.

Предикторами неблагоприятного исхода являются низкие значения сатурации, дыхательная недостаточность, значительный объем поражения легочной ткани (КТ-3–4) при поступлении в стационар, а также высокие значения С-реактивного белка, ферритина, аспартатаминотрансферазы, D-димера, нейтрофилез, лимфопения, тромбоцитопения. Благоприятным предиктором исхода можно считать использование в комплексной терапии антицитокиновых препаратов. Материалы исследования позволяют не только предварительно оценить особенности течения и эффективность комплексной терапии с применением антицитокиновых препаратов при COVID-19 у пациентов с коморбидными заболеваниями, но и разработать лечебно-диагностические алгоритмы.

◆ **Ключевые слова:** новая коронавирусная инфекция; SARS-CoV-2; COVID-19; коморбидность; цитокиновый шторм; антицитокиновые препараты; эффективность терапии.

Introduction

The rapid spread of a new coronavirus infection (coronavirus disease 2019, COVID-19) is creating unprecedented challenges for public health worldwide. They are associated not only with the infection itself, but also with the need for emergency reorganization of the medical service, the lack of effective antiviral drugs, the need for timely use of drugs to stop the cytokine storm, and effective treatment of comorbidity.

In 2019, a local breakout of a coronavirus disease (COVID-19) in China caused by the new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) coronavirus has rapidly developed into a pandemic with more than 10 million infected (officially 7,941,791 people as of June 17, 2020), and billions of people are forced to apply special anti-epidemic measures. In some cases, COVID-19 infection is characterized by the development of various life-threatening conditions (pneumonia, severe acute respiratory distress syndrome [ARDS], sepsis) [1].

Coronaviridae is a family of ribonucleic acid (RNA)-containing viruses (riboviruses) that can cause both mild forms of acute respiratory infection and SARS. Four coronaviruses (HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1) are known to persist, which causes acute respiratory viral infections and mild and moderate upper respiratory tract damage. SARS-CoV-2 is a single-stranded RNA-containing virus, presumably a recombinant between a bat coronavirus and an unknown coronavirus [2].

SARS-CoV-2 enters through the epithelium of the upper respiratory tract and epithelial cells of the stomach and intestines, where the virus later penetrates into target cells of the respiratory system, heart, esophagus, kidneys, bladder, ileum, and central nervous system, which have angiotensin-converting enzyme type II receptors. COVID-19 is primarily a respiratory tract infection, and a mild form of acute respiratory viral infection occurs in 80% of cases. However, data indicate that this form of pathology should be considered as a systemic disease affecting the cardiovascular, respiratory, gastrointestinal, neurological, hematopoietic, and immune systems [3–5].

A significant proportion of patients with COVID-19 develop severe respiratory failure (RF), the main pathogenetic mechanism of which is inflammatory edema, leading to various degrees of lung atelectasis, resulting in impaired ventilation–perfusion and the formation of an intra-pulmonary shunt. In addition, lung microthrombi, which cause heart attacks and ineffective ventilation, can possibly develop [5, 6].

COVID-19 is also fatal because mortality from chronic somatic diseases increases significantly during the pandemic, especially in the group of comorbid patients. Elderly patients have the most severe forms with rapid progression of lower respiratory tract damage, pneumonia, acute RF, ARDS, sepsis, or septic shock [5–8]. For example, epidemiologists at the Centers for Disease Control and prevention analyzed 4226 cases of COVID-19 in the United States for significant outcomes, such as hospitalization, being in the intensive care unit, and death. A prominent effect of age (especially ≥60 years) on mortality has been shown [9].

Among cardiovascular diseases, arterial hypertension (approximately 15%), myocarditis (approximately 10%), and coronary heart disease (approximately 2.5%) are the most common. Patients with COVID-19 and cardiovascular disease have a high risk of developing severe ARDS and death [4, 7].

Diabetes mellitus (DM) is considered to be a risk factor for worsening the course and development of severe forms of COVID-19, as well as an increase in fatalities. The risk of developing severe forms, according to various sources, ranges from 9.2% to 16.2% and depends on the age (elderly patients have the highest risk), the presence of other diseases (patients with concomitant serious chronic heart and lung diseases), and control of glycemia (high risk with poor control, a long history of diabetes, vascular complications). The risk of nephritic and cardiac complications is increased, especially with vascular complications as a result of DM [5–7].

Typical signs of SARS-CoV-2 infection are fever and respiratory symptoms. However, many infected people also experience gastrointestinal disorders, such as diarrhea, vomiting, and abdominal pain. SARS-CoV-2 RNA is found in scrapings and smears from the rectum, as well as in fecal samples of some patients [6, 7].

In addition to gastrointestinal symptoms, patients with COVID-19 may seem to have cytolytic syndrome, which indicate liver damage. High activity of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) was recorded in

14%–53% of patients during the disease, whereas the bilirubin level slightly increased. The mechanism of liver damage is not fully understood, although the direct cytopathic effect of the SARS-CoV-2 virus on hepatocytes is considered because the virus can bind to cholangiocytes and hepatocytes via the angiotensin-converting enzyme of the type II receptor and lead to hepatocyte damage. In addition, the cause of liver damage may be immune inflammation or a systemic inflammatory reaction, especially in the case of a cytokine storm, as well as drug-induced liver damage [3, 8].

Elderly patients with severe comorbidities have the most severe progression of COVID-19, but young people without chronic diseases may also have potentially fatal complications, such as rapid myocarditis and disseminated intravascular coagulopathy (DIC) [8–10].

The proposed mechanisms of the development of a multiple organ failure are multifactorial and include hypercoagulation with the formation of blood clots in both micro- and macrocirculatory channels. The development of DIC is a serious predictor of death (occurring among 71.4% of patients with a fatal outcome and among 0.6% of survivors) [11, 12].

One of the main pathogenic features of COVID-19 is intense inflammation caused by severe ARDS with the development of an unregulated immune response (cytokine release syndrome, cytokine storm syndrome) in the most severe cases [13].

Thus, a pathological study of patients with COVID-19 infection complicated by acute RF revealed not only an activation of cytotoxic T-lymphocytes, but also an irritation of the humoral link of the immune system with hyperproduction of interleukin-6 (IL-6). In this regard, inhibition of IL-6, as well as the Janus kinase system, might be effective in the treatment of patients with severe COVID-19 infection. However, randomized studies are needed to confirm this assumption [14].

Currently, considering the data of real clinical practice, many questions arise about the features of the course of COVID-19, depending on sex and age, the presence of various concomitant diseases, and the choice of the most effective treatment methods, depending on clinical and laboratory data and computed tomography (CT) findings of lung damage. The search of the most informative predictive markers of COVID-19 for comorbid patients is equally important. In this regard, it is necessary to study the features of screening, prevention, diagnosis, clinical manifestations, and treatment of COVID-19.

This study aimed to analyze the course, effectiveness of therapy, and outcomes of a new coronavirus infection, depending on the characteristics of patients, clinical, laboratory and instrumental data, and treatment options.

Materials and methods

A random sample was used to perform a preliminary analysis of the medical history of patients with confirmed COVID-19 infection who were hospitalized in Covidcenter from May 5, 2020 to June 1, 2020. The mean age of the patients was 59.0 ± 15.1 years. The study included 67 men (51.9%) and 62 women (48.1%) with a mean age of 57.9 ± 16.4 and 60.2 ± 13.6 years, respectively (age differences are not reliable). All patients with COVID-19 infection were hospitalized at Peter the Great Clinic of the Mechnikov Northwestern State Medical University (264 beds were repurposed, including 24 intensive care units).

All patients underwent multispiral CT of the lungs during hospitalization. The severity (volume, area, extent) of lung damage of patients with suspected/known COVID-19-related pneumonia was assessed using an empirical visual scale by determining the approximate volume of compacted lung tissue in both lungs [15]:

— absence of characteristic appearances — CT-0;
— minimum volume/prevalence <25% of lung volume — CT-1;
— mean volume/prevalence of 25%–50% of lung volume — CT-2;
— significant volume/prevalence 50%–75% of lung volume — CT-3;
— subtotal volume/prevalence >75% of lung volume — CT-4.

All patients underwent pulse oximetry with S_pO_2 measurement to detect RF and evaluate the severity of hypoxemia. Patients with signs of acute RF (S_pO_2 <90% according to pulse oximetry data) were additionally examined for gas composition of arterial blood with the determination of p_aO_2 and p_aCO_2 [16, 17].

The standard clinical examination included a clinical blood test, a general urine test,

a blood test to determine the level of C-reactive protein (CRP), creatinine, urea, glucose, total protein, ferritin, troponin, D-dimer, AST activity, ALT with evaluation of the coagulogram, and electrocardiogram tracing.

The effectiveness of the therapy was evaluated by outcomes (recovery, death) and the presence of recorded adverse events during therapy.

The research results were statistically analyzed using Statistica 12 for Windows software package, with the evaluation of a coincidence of distributions of quantitative indicators to the normal law, determination of mean values, mean of a square deviation, variation range, and maximum and minimum values. The Pearson criterion χ^2 was applied to study the relationship between qualitative characteristics. The exact Fischer criterion was used if the assumption of expected frequencies is violated (if there is at least one value <10 in 2 × 2 tables and >25% of such values in multifield tables). Quantitative indicators with a distribution close to the normal law are represented as $M \pm \sigma$, where M is the mean value, and σ is the standard deviation. The reliability of the differences between the two relative values was evaluated using the Student t-criterion ($t > 2$, $p < 0.05$).

Results and discussion

Characteristics of patients: a clinical picture

The clinical picture was dominated by symptoms of intoxication and RF. At the time of hospitalization, 119 patients (92.2%) had fever. Most of the patients (76.5%) had high-grade fever, and 28 patients (23.5%) had low-grade fever. The mean duration of the fever during hospitalization was 7.7 ± 3.7 days.

Analysis of data on the presence and severity of RF at admission showed that 8 patients (6.3%) did not have RF, 41 patients (32%) had grade I RF, 36 patients (28.16%) had grade II RF, and 43 patients (33.6%) had grade III DN.

Sex differences in some clinical and laboratory indicators were shown. Thus, at admission, the saturation index (S_pO_2) was significantly lower for men (89.4 ± 7.6), than for women (91.8 ± 4.8) ($t = 2.14$, $p = 0.034$). Similar differences in the indicator remained at discharge ($t = 2.94$, $p = 0.004$). In addition, the ferritin level in men during hospitalization was significantly higher ($t = -2.87$, $p = 0.005$) than that in women.

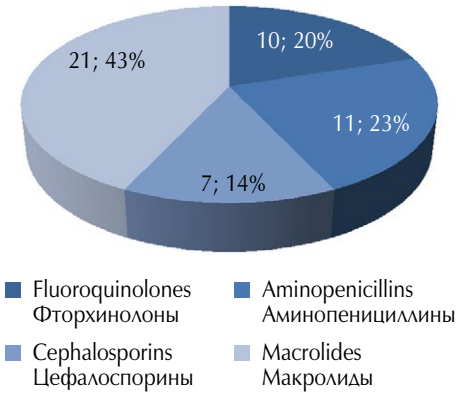

Fig. 1. Antibacterial drugs prescribed before hospitalization

Рис. 1. Антибактериальные препараты, назначенные на догоспитальном этапе

Before hospitalization, 52 patients (40.3%) received antibacterial therapy. The vast majority of patients (Fig. 1) were prescribed macrolides (43%), and the rest were prescribed aminopenicillins (23%), fluoroquinolones (20%) or cephalosporins (14%).

The analysis of the frequency of occurrence of comorbidity in the studied group of patients (Fig. 2) showed that 87 patients (67.4%) had pathology of the cardiovascular system, with ischemic heart disease, hypertension, and combination of ischemic heart disease and hypertension were found in 34 (26.4%), 86 (66.7%), and 33 patients (25.6%), respectively. Based on the literature, DM and obesity are risk factors for severe COVID-19 infection. In the study group, type 1 DM and obesity were noted in 30 patients (23.3%) and 44.2% of patients, whereas the first-, second-, and third-degree obesity was observed in 30 (23.2%), 15 (11.6%), and 12 patients (9.3%), respectively.

Based on CT data on the severity of lung damage, the patients were divided into four groups. Lung damage with CT-3 and CT-4 was observed in 58% of patients (Fig. 3).

Data on the presence of RF depending on the lung damage on CT are interesting (Fig. 4). Thus, only CT-1 or CT-2 lung damage was detected on CT in patients with no RF during hospitalization. Almost all patients (86.1%) with grade III RF had CT-3 or CT-4 (the volume of the lesion is >50%). However, the volume of lung lesion according to CT data may be CT-1 or CT-2 even in the absence of RF.

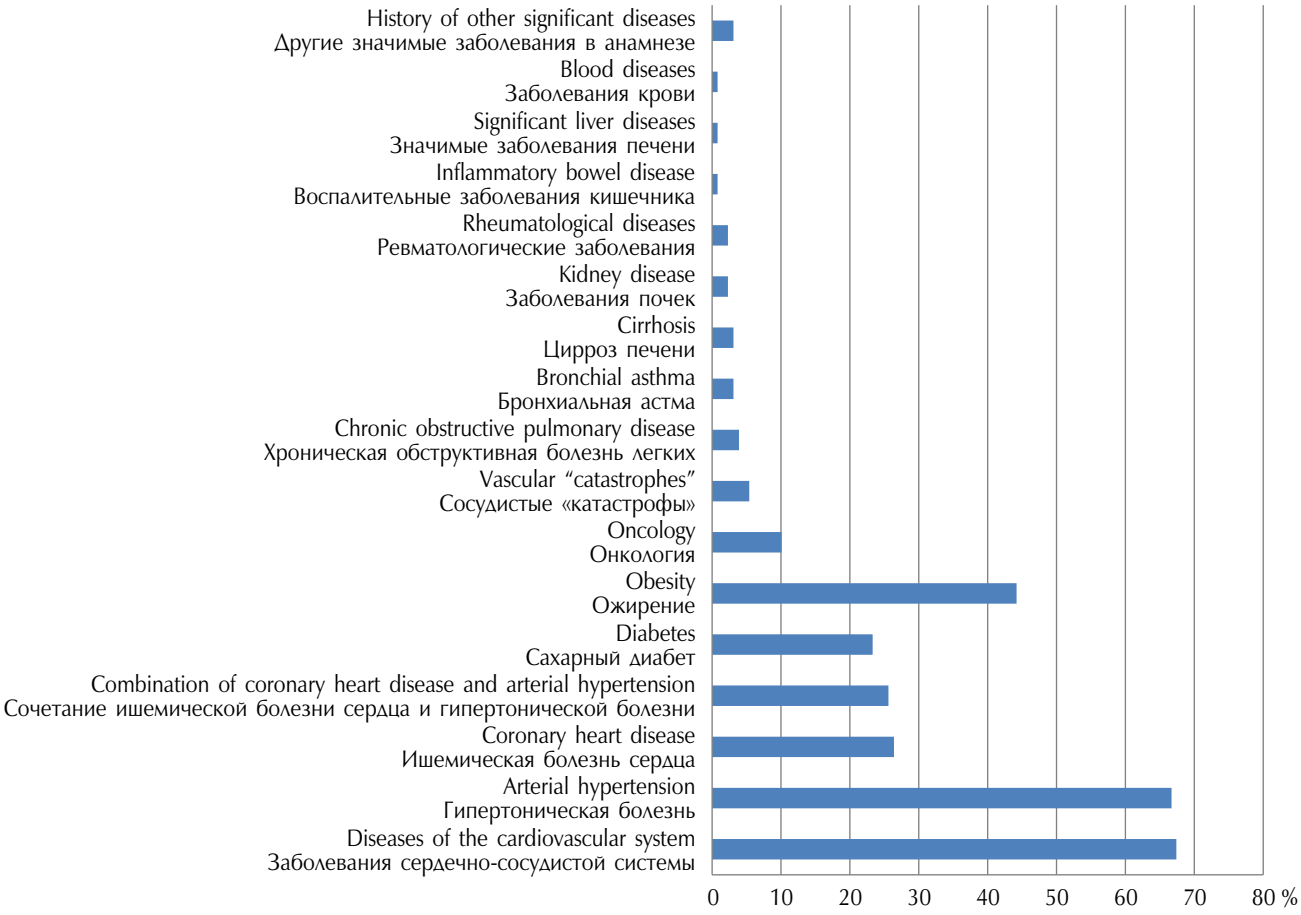

Fig. 2. The structure of concomitant pathology

Рис. 2. Структура сопутствующей патологии

Therapeutic approaches for COVID-19

All patients with a high risk for bacterial superinfection on the background of immunosuppressive therapy were treated with antibacterial therapy (respiratory fluoroquinolones, cephalosporins of III and IV generations, carbapenems, linezolid, etc.). The use of antibacterial therapy in hospital conditions in only 48.8% of patients is explained by the use of this type of therapy in the pre-hospital stage (40.3%, $n = 52$). The choice of the antibiotic and method of injection was based on the severity of the condition, the presence of concomitant diseases, and the results of microbiological diagnostics.

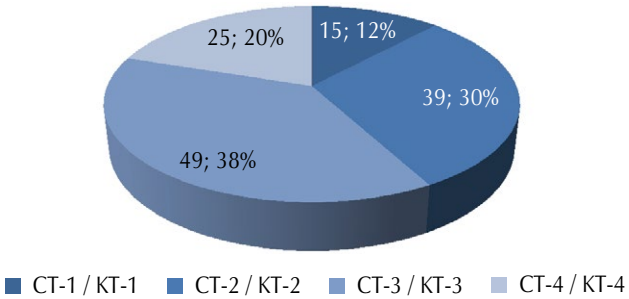

Fig. 3. Distribution of patients depending on the degree of lung involvement (CT)

Рис. 3. Распределение пациентов в зависимости от компьютерно-томографической картины поражения легких

Blood clotting disorders could develop because of severe life-threatening cytokine release syndrome.

The initial stages of the disease are characterized by hypercoagulation without signs of consumption and DIC, which was the basis for the prophylactic or therapeutic use of anticoagulants (low-molecular-weight heparins) in 100% of patients.

Fig. 5 shows the frequency of the use of various groups of drugs during treatment in a hospital.

When clinical and laboratory signs of a cytokine storm appeared, pathogenetic therapies were used, including anticytokine drugs (ADCS) — IL-6 receptor blockers and Janus kinase in-

hibitors, as well as glucocorticosteroids (GCS). Currently, clinical studies of the effectiveness and safety of ADCS and GCS in COVID-19 are ongoing. However, according to the temporary guidelines of the Ministry of Health of the Russian Federation, the appointment of GCS can be a means of blocking the synthesis of a wide range of proinflammatory mediators, an increase in the concentration of which is associated with the development of ARDS and sepsis. The regulatory documents specifically emphasize the inexpediency of prescribing GCS to all patients with COVID-19. The above factors were the basis for using GCS and ADCS in 45% and 38% of patients, respectively.

A sudden increase in clinical appearances after 1–2 weeks after the disease started (appearance or increase of RF, decline in saturation), the continuing or newly emerging febrile fever, severe lymphopenia in the blood test, a significant increase of D-dimer (>1500), or rapid growth and/or increased CRP levels >75 mg/l, and interstitial lung disease on CT were considered as signs of cytokine storm and ARDS [17]. The analysis of the main markers of cytokine storm showed that the CRP and ferritin levels and severity of lymphopenia increased with the increasing severity of lung damage on CT (Table 1), which allows predicting the volume of lung damage depending on the values of these laboratory parameters.

To suppress cytokine storm and as a preemptive anti-inflammatory therapy, ADCS were used: tocilizumab and sarilumab monoclonal antibodies to the IL-6 receptor, as well as reversible inhibitors of Janus kinases 1 and 2 (JAK1 and JAK2) — baricitinib and GCS [17]. In the absence of an effect from the Janus kinase inhibitor, the patient

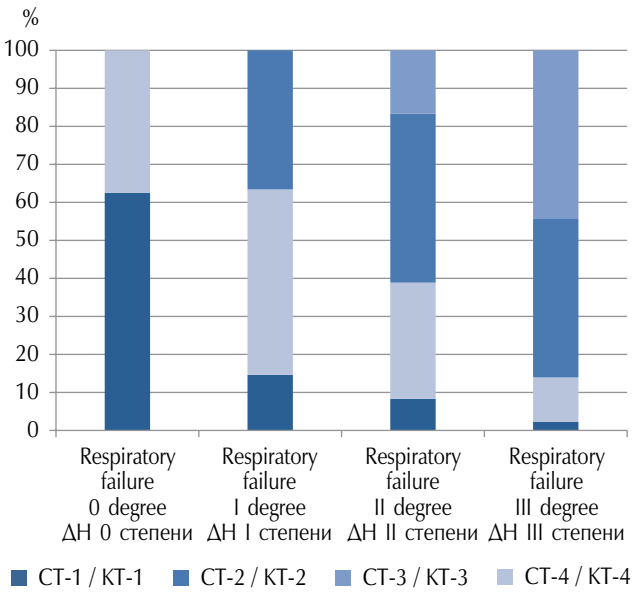

Fig. 4. The volume of lung damage according to CT data, depending on the degree of respiratory failure

Рис. 4. Объем поражения легких (по данным компьютерной томографии — КТ) в зависимости от степени дыхательной недостаточности (ДН)

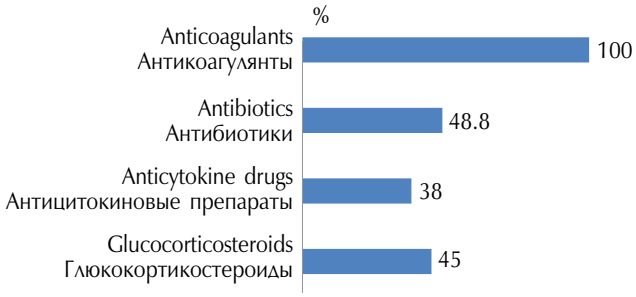

Fig. 5. The use of different classes of drugs at the hospital stage

Рис. 5. Применение лекарственных препаратов (по классам) в стационаре

Table 1 / Таблица 1

Laboratory markers of cytokine storm depending on lung CT data
Лабораторные маркеры цитокинового шторма в зависимости от данных компьютерной томографии легких

Parameter	Degree of lung damage based on computed tomography	Mean	Mean root mean square error
Ferritin	3	921.5	149.2
	4	1092.8	149.8
C-reactive protein	3	99.1	7.8
	4	145.9	19.1
Lymphocytes	3	1.6	0.3
	4	0.9	0.09

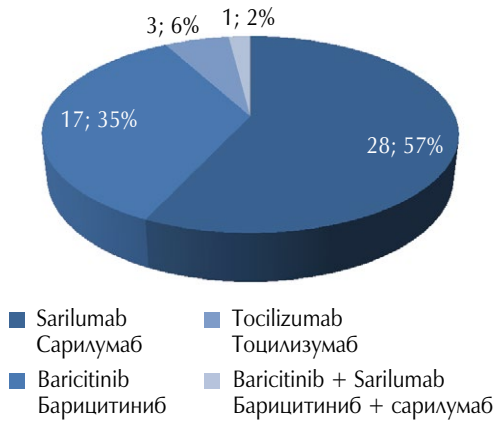

Fig. 6. Frequency of use of various anti-cytokine drugs

Рис. 6. Частота использования различных антицитокиновых препаратов

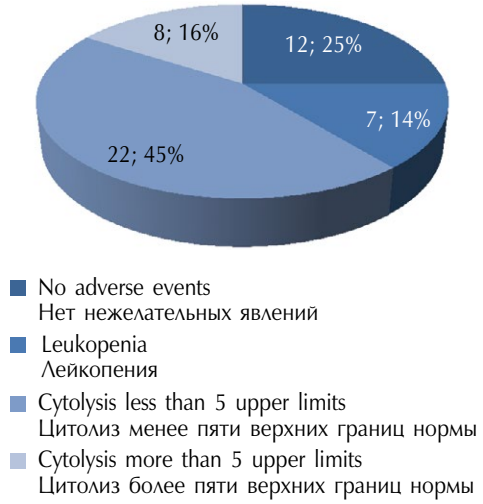

Fig. 7. The frequency and structure of adverse events in the use of anticytokine drugs

Рис. 7. Частота и структура нежелательных явлений при применении антицитокиновых препаратов

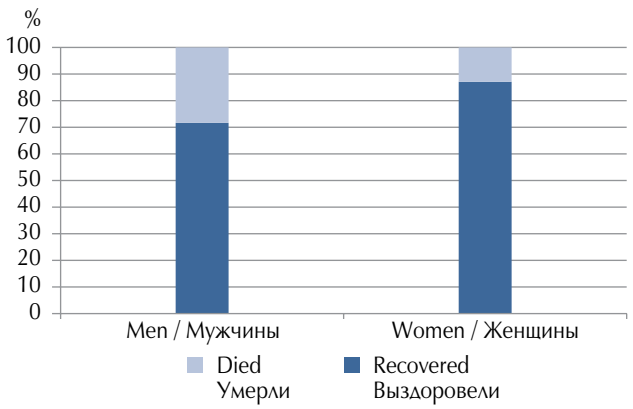

Fig. 8. Outcomes of the disease depending on gender

Рис. 8. Исходы заболевания в зависимости от пола

was transferred to monoclonal antibodies to the IL-6 receptor.

ADCS were administered in 49 patients (38.0%), and sarilumab was prescribed most frequently (in 57% of cases) (Fig. 6).

The development of adverse events was evaluated using ADCS. The frequency and structure of the most frequent laboratory adverse events are shown in Fig. 7. Cytolytic syndrome was considered the most frequent laboratory adverse event, which was detected in 61% of patients (30 patients), whereas in most cases (73.3%), cytolysis was <5 upper limits of the norm.

Disease outcome

The outcomes of the disease (recovery, death), depending on age, sex, characteristics, presence of concomitant diseases, and clinical and laboratory indicators, were analyzed.

The mean age of the patients who recovered and those who died was 56.5 ± 14.6 and 67.6 ± 13.2 years, respectively ($t = -3.56$, $p = 0.00005$).

A link was found (Fig. 8) between sex and disease outcome (Fisher exact criterion, $p = 0.02530$; Pearson χ^2, $p = 0.03110$). Thus, 48 of 67 men (71.6%) were discharged, and 19 (28.4%) had a fatal outcome. Of 62 women, 54 (87.1%) were discharged, and 8 (12.9%) had a fatal outcome.

A number of authors point to the high fatality and more severe course of COVID-19 in the presence of comorbidity in patients, particularly DM, obesity, etc. No reliable link was found between coronary heart disease, DM, and fatal outcomes in our study (Fig. 9 and Table 2)

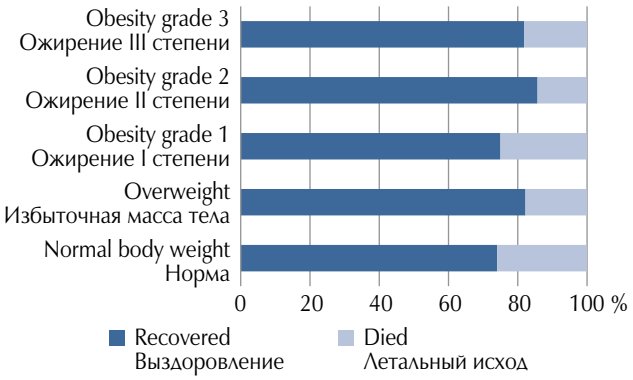

Fig. 9. Outcomes of the disease depending on body mass index

Рис. 9. Исходы заболевания в зависимости от индекса массы тела

Table 2 / Таблица 2

Analysis of the outcomes of hospitalization of patients with COVID-19 depending on the comorbidity
Анализ исходов госпитализации в связи с COVID-19 в зависимости от сопутствующей патологии

Comorbidity		Recovery	Fatality	Existence of a link
CHD	No	83.2%	16.8%	χ^2 Pearson, $p = 0.05641$; FET, $p = 0.05124$
	Yes	67.7%	32.3%	
HBP	No	83.7%	16.3%	χ^2 Pearson, $p = 0.35850$; FET, $p = 0.24840$
	Yes	76.7%	23.3%	
DM	No	80.8%	19.2%	χ^2 Pearson, $p = 0.37798$; FET, $p = 0.26075$
	Yes	73.3%	26.7%	

N o t e. CHD, coronary heart disease; HBP, high blood pressure; DM, diabetes mellitus; FET, Fisher exact test.

Table 3 / Таблица 3

Significance of differences in laboratory test results depending on hospitalization outcomes
Результаты лабораторных параметров, достоверно различающиеся в зависимости от исходов госпитализации

Index	Mean value (recovery)	Mean value (fatal outcome)	*t*-indication	*p*
C-reactive protein	68.78 ± 52.85	150.3 ± 90.0	–6.03488	0.000000
Ferritin	873.48 ± 844.70	1438.5 ± 1101.3	–2.55339	0.012194
Aspartate aminotransferase	62.13 ± 41.78	88.0 ± 83.3	–2.01792	0.046450
Neutrophils	5.02 ± 5.83	7.9 ± 5.0	–2.30741	0.022663
Lymphocytes	1.54 ± 1.70	0.9 ± 0.9	1.99522	0.048176
Platelets	248.53 ± 87.21	206.6 ± 118.3	2.04770	0.042667
D-dimer	0.85 ± 1.51	4.0 ± 3.2	–6.62573	0.000000

Table 4 / Таблица 4

Average S_pO_2 values for different hospitalization outcomes
Средние значения S_pO_2 при различных исходах госпитализации

S_pO_2	Mean value (recovery)	Mean value (fatal outcome)	*t*-indication	*p*
Admission	92.05 ± 4.84	85.1 ± 8.8	5.46293	0.000000
Discharge	97.39 ± 1.87	82.4 ± 11.7	12.33664	0.000000

($p = 0.378$). However, it drew attention to the fact that in patients with the above-mentioned concomitant pathology, fatal outcomes were recorded more often, which allowed us to consider this comorbidity as a risk factor for severe disease and an unfavorable prognosis.

In cases of fatal outcome in our study, the mean values of indicators, such as CRP, ferritin, AST, D-dimer, and neutrophils, were significantly higher than normal, and lymphocyte and platelet counts were significantly lower than normal values (Table 3). Thus, these indicators can be considered as predictors of an adverse outcome.

Based on the results of pulse oximetry (S_pO_2), patients with an unfavorable outcome had significantly lower S_pO_2 values at admission compared with those who recovered (Table 4); thus, this indicator can also be used as a predictor of an unfavorable outcome.

A relationship was found between severity of pulmonary involvement based on CT and disease outcome (Pearson χ^2; $p = 0.00007$). Thus, all patients with minimal lung changes on CT (CT-1) recovered, but the proportion of patients with an adverse outcome progressively increased as the volume and prevalence of lung

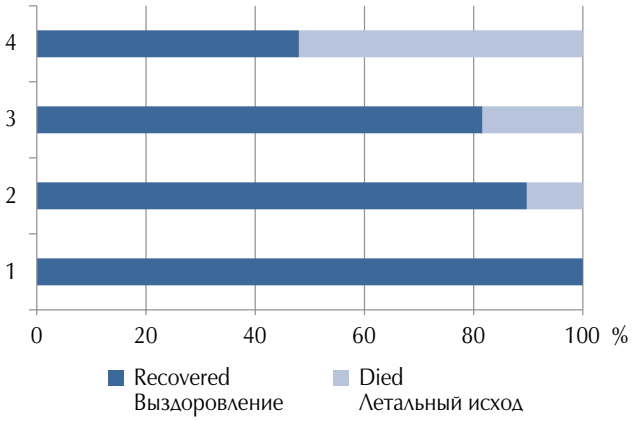

Fig. 10. Outcomes of the disease depending on the volume of lung damage (according to CT)

Рис. 10. Исходы заболевания в зависимости от объема поражения легких (по компьютерно-томографическим данным)

damage increased, and the mortality rate was 52% in cases of subtotal lung damage (CT-4). The results obtained (Fig. 10) suggest that the severity of lung damage based on CT is the most important predictor of adverse outcome of COVID-19.

At the next stage of the study, the disease outcomes were analyzed depending on the antibacterial therapy (Table 5). The number of deaths was significantly higher in the group of patients administered with levofloxacin ($p = 0.03192$). However, for confirmation, a more detailed study should be conducted on the influence of risk factors, such as age, cardiovascular pathology, DM, etc., on mortality in this group of patients.

Based on the ADC variant used, ADC therapy was significantly accompanied by a decrease in mortality. Thus, all 17 patients prescribed with baricitinib recovered, although the introduction of a powerful IL-6 inhibitor, such as sarilumab, had a fatal outcome in 14.29% of the examined patients (Table 6).

Table 7 shows the statistics of the use of different types of ADC for different volumes of lung damage. Baricitinib was used in milder cases (CT-1–3), 71.5% of patients with CT-3–4 were prescribed sarilumab.

Table 5 / Таблица 5

Analysis of hospitalization outcomes depending on antibiotic therapy
Анализ исходов госпитализации в зависимости от антибактериальной терапии

Antibacterial therapy		Recovery	Fatal outcome	The existence of a link
Azithromycin	Not prescribed	77.5%	22.5%	χ^2 Pearson, $p = 0.65550$; FET, $p = 0.41167$
	Prescribed	80.7%	19.3%	
Amoxiclav	Not prescribed	83.6%	16.4%	χ^2 Pearson, $p = 0.17416$; FET, $p = 0.12672$
	Prescribed	83.6%	16.4%	
Levofloxacin	Not prescribed	83.6%	16.4%	χ^2 Pearson, $p = 0.03192$; FET, $p = 0.03350$
	Prescribed	73.8%	26.2%	

N o t e. FET, Fisher exact test.

Table 6 / Таблица 6

Analysis of hospitalization outcomes depending on the anticytokine drug
Анализ исходов госпитализации в зависимости от примененных антицитокиновых препаратов

Anticytokine drugs		Recovery	Fatal outcome	The existence of a link
ACD	Not prescribed	72.50%	27.50%	χ^2 Pearson, $p = 0.01909$; FET, $p = 0.01464$
	Prescribed	89.80%	10.20%	
Baricitinib	Not prescribed	75.89%	24.11%	χ^2 Pearson, $p = 0.02281$; FET, $p = 0.01355$
	Prescribed	100.00%	0.00%	
Sarilumab	Not prescribed	77.23%	22.77%	χ^2 Pearson, $p = 0.954$; FET, $p = 0.435$
	Prescribed	85.71%	14.29%	

N o t e. ACD, anticytokine drugs; FET, Fisher exact test.

Table 7 / Таблица 7

The number of cases of prescribing an anticytokine drug depending on the severity of the disease according to CT data
Количество случаев назначения антицитокиновых препаратов в зависимости от тяжести заболевания по компьютерно-томографическим данным

Anticytokine drugs		Volume of the lesion on computed tomography				Total
		1	2	3	4	
Baricitinib	Quantity	1	6	10	0	17
	Part in ADC, %	5.9	35.3	58.8	0.0	100.0
Sarilumab	Quantity	1	7	12	8	28
	Part in ADC, %	3.6	25.0	42.9	28.6	100.0

N o t e. ACD, anticytokine drugs.

However, further research is needed on the effectiveness of various ADC depending on the timing of the disease, duration of signs of cytokine storm, initial characteristics of the somatic status of patients, and the choice of doses and ADC prescribing schemes.

Conclusion

The results obtained allowed us to draw a number of conclusions that can be considered preliminary.

First, fatalities were significantly more frequent among older age groups and in men.

Second, the mortality rate increased in patients with COVID-19 who had comorbidities (coronary heart disease, hypertension, DM, and obesity), which makes it possible to consider comorbidity as a risk factor for a severe course and unfavorable prognosis of COVID-19. At the same time, the considered comorbidities in the general group of examined patients did not significantly affect the outcomes of COVID-19, which may be due to a small sample of patients included in the analysis.

Third, the predictors of an adverse outcome are low values of saturation, presence of RF, a large volume of lung tissue damage based on CT (CT-3–4) at admission, high levels of CRP, ferritin, AST, D-dimer, neutrophilosis, lymphopenia, and thrombocytopenia. A favorable predictor of the outcome of the disease are use of ADC that indicates the possibility of wider use of anticytokine therapy in the complex treatment of pneumonia caused by COVID-19 of medium and moderate severity.

This study allowed us not only to pre-evaluate the features of the course and effectiveness of complex therapy for COVID-19 for patients with comorbid diseases, but also to open up prospects for a more detailed search for effective predictors of the course and outcomes, the development of therapeutic and diagnostic algorithms, and for the rational use of existing and innovative ACD for patients in this category.

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