journal of clinical practice 2021 Том 12 №1

# MAJOR PREDICTIVE RISK FACTORS FOR A CYTOKINE STORM IN COVID-19 PATIENTS (A RETROSPECTIVE CLINICAL TRIALS)

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***Background:*** *According to WHO, as of March 31, 2021, 127 877 462 confirmed cases of the new COVID-19 coronavirus infection were registered in the world, including 2 796 561 deaths (WHO Coronavirus Disease). COVID-19 is characterized by a wide range of clinical manifestations, from asymptomatic to a rapid progression to severe and extremely severe. Predictive biomarkers for the early detection of high-risk individuals have become a matter of great medical urgency.* ***Aims:*** *Search for the predictors of a cytokine storm in patients with COVID-19 infection and creation of a risk scale of this complication for practical applications.* ***Methods:*** *The study included 458 patients with confirmed COVID-19 infection with signs of viral lung lesions according to the computer tomography data. The patients were divided into 2 groups: those with a stable course of moderate severity (100 patients) and those with progressive moderate, severe and extremely severe course (358 patients).* ***Results:*** *It has been established that the main risk factors for the development of a cytokine storm in COVID-19 patients are the following: interleukin-6 concentration >23 pg/ml, dynamics of the index on the NEWS scale ≥0, ferritin concentration >485 ng/ml, D-dimer concentration >2.1, C-reactive protein concentration >50 mg/l, number of lymphocytes in the blood <0.72×109/l, age ≥40 years. The cytokine storm incidence correlates with an increase in the number of risk factors. For the practical testing the scale was applied in 3 groups. In patients of the first group (0–1 factor) almost no cytokine storm risk was found, in the second group (2 -3 factors) the probability of the storm was 55% (increase by 35.5 times), in the third group (≥4 risk factors) it reached 96% (increase by 718 times).* ***Conclusion:*** *The diagnostic and monitoring criteria of a cytokine storm have been established in patients with COVID-19 infection. The developed prognostic scale allows identification of patients at high risk of developing a cytokine storm so that early anti-inflammatory therapy could be started.*

***Keywords:*** *COVID-19 infection; cytokine storm; early diagnosis and monitoring.*

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## BACKGROUND

The COVID-19 (COronaVIrus Disease 2019) infection caused by the SARS-CoV-2 coronavirus remains a global healthcare problem. Most people infected with SARS-CoV-2 have mild course of the disease. In some patients, the immune response becomes unregulated, which results in severe damage to the lungs and manifests itself as acute respiratory distress syndrome (ARDS) with the subsequent development of acute respiratory failure, dysfunction of extrapulmonary organs, and high mortality. COVID-19 disease is usually associated with elevated levels of inflammatory biomarkers, cytokines, and chemokines, especially in severe cases. In addition, lymphocytopenia and neutrophilia are registered frequently, with a significant decrease in the count of CD8+ T cells, CD4+ T cells, and natural killer (NK) cells [1]. The mortality rate of hospitalized patients ranges from 15 to 20% and even higher among those in need of intensive care [2].

Immune dysfunction with a pronounced uncontrolled generalized systemic inflammatory response due to increased production of inflammatory cytokines (cytokine storm, CS) is central in the COVID-19 pathophysiology. CS is accompanied by fever, cy-

topenia, hyperferritinemia, abnormal hepatic parameters, coagulopathy, and lung damage (including ARDS) [3]. In all these conditions, interleukins (IL) 1β, 18, 6 and interferon gamma (IFN-γ) are the main mediators of hyperinflammation. COVID-19-associated CS is a unique form of hyperinflammatory response that requires the development of criteria for its establishment [4].

**The study aimed** to search for biomarkers predictors of CS in patients with COVID-19 and to create a predictive scale for the risk of CS development on their basis for use in routine medical activities.

## METHODS

### Study design

Observational clinical study.

### Inclusion criteria

We analyzed 458 case histories of COVID-19 patients who were treated at the City Hospital No. 40 of St. Petersburg from 18.04.2020 to 21.11.2020, and who had a positive test result for the presence of SARS-CoV-2 RNA by the nucleic acid based amplification method in polymerase chain reaction (PCR); clinical manifestations and symptoms (fever, general asthenia and malaise, cough and dyspnea); viral pneumonia-type changes on the CT image of the lungs without intravenous contrast enhancement (predominantly in bilateral lower lobe, of peripheral, perivascular, multilobular nature; numerous peripheral ground glass opacity indurations of a rounded shape of various lengths; flattening of the crazy paving interlobular interstitium, areas of consolidation, an air bronchogram symptom, etc.) [5].

### Outcome registration methods

In all patients, anamnestic data was collected, specifying the characteristics of the course of the disease; a physical examination with an assessment of the parameters of hemodynamics, the respiratory system (respiratory rate, heart rate, blood pressure, degree of blood oxygen saturation, $SpO_2$; degree of respiratory failure); assessment on the scale of early detection of risk in patients with sudden acute illnesses (National Early Warning Score, NEWS), recommended for use in COVID-19 patients [6]; computed tomography (CT) of the chest organs with an assessment of the form of the disease on a four-unit scale (CT-1, CT-2, CT-3, CT-4); laboratory tests (clinical blood test; biochemical minimum; determination of levels of ferritin, C-reactive protein, IL-6, lactate dehydrogenase, and D-dimer), electrocardiography; additional instrumental techniques were used if necessary.

### Statistical analysis

The data obtained were evaluated by means of the STATISTICA for Windows system (version 10, license BXXR310F964808FA-V). Comparison of quantitative parameters (age, NEWS index, levels of D-dimer, CRP, IL-6, etc.), determination of the normal distribution of the sample in the groups of patients was performed using the Mann – Whitney, Kolmogorov – Smirnov tests, median $\chi^2$ and the ANOVA module, since the distribution of all indicators (with the exception of age) did not correspond to the norm. Frequency characteristics of qualitative indicators (gender, degree and form of pathological processes, complaints) were assessed using nonparametric methods $\chi^2$, Pearson's test, and Fisher's criterion.

Threshold levels for age, NEWS index, and laboratory data were determined using the method of constructing classification trees [7].

As for the relative risk of CS (odds ratio, OR), the ratio of the probability of a certain outcome in the comparison groups was studied by constructing a four-field contingency table with the calculation of the standard formula and the boundaries of the confidence interval. In case of the presence of zero values in the table, the Haldane correction was used for the calculation.

## RESULTS

### Subjects (participants) of the study

Demographic data, epidemiological history data, and comorbidities of patients in the study cohort are presented in Table 1.

### Key research findings

The prevalence of concomitant diseases in our patients exceeds significantly this indicator in adult patients with COVID-19 according to the literature (31% [8]). A high percentage of concomitant pathology in our patients is associated with a certain profilisation of our suite, namely, with the treatment of patients with severe and extremely severe disease. In the resuscitation and intensive care unit, 221 (48%) patients were transferred from other departments and hospitals due to the progressive course of COVID-19.

Upon admission, patients had fever (365; 80%), cough (329; 72%), dyspnea (265; 57.86%), muscle pain (43; 9.39%), general asthenia (344; 75.11%), headache (36; 7.86%), sore throat (29; 6.33%), runny nose, rhinorrhea (46; 10.04%), chest pain (51; 11.14% ), diarrhea


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journal of clinical practice 2021 Том 12 №1

Table 1

**Demographic, epidemiological, and anamnestic data of the patients**

| Indicator | *n* (%) |
|---|---|
| *Age, years* | |
| • ≤39 | 38 (8,30) |
| • 40–49 | 58 (12,66) |
| • 50–59 | 123 (26,86) |
| • 60–69 | 139 (30,35) |
| • ≥70 | 100 (21,83) |
| Contact with infectious patients | 100 (22,22) |
| Departure from the place of residence within the recent 14 days | 45 (9,83) |
| Cold symptoms in close relatives (fever, cough, asthenia) | 44 (9,61) |
| *History of diseases:* | |
| • hypertension | 260 (56,77) |
| • coronary heart disease | 222 (48,47) |
| • cerebrovascular diseases | 139 (30,35) |
| • condition after stroke | 97 (21,18) |
| • condition after acute myocardial infarction | 34 (7,42) |
| • condition after surgical treatment | 89 (19,43) |
| • rheumatoid arthritis and other autoimmune diseases | 65 (14,19) |
| • diabetes mellitus | 63 (13,76) |
| • chronic kidney disease of stages 3–5 | 32 (6,99) |
| • malignant neoplasms | 22 (4,80) |
| • chronic obstructive pulmonary disease | 20 (4,37) |
| • chronic bronchitis | 20 (4,37) |
| • bronchial asthma | 13 (2,84) |

(34; 7.42%), nausea and vomiting (13; 2.84%), anosmia and ageusia (40; 8.73%). The presence of one or more symptoms of the disease was noted in 450 (98.25%), CT signs of pneumonia were registered in 458 (100%) patients.

The patients were distributed into two groups comparable in age. The group 1 consisted of 100 (21.8%) patients with clinical and radiological aspects characterizing a stable course of the disease of moderate severity; the group 2 consisted of 358 (78.2%) patients with progressive moderate, severe, and extremely severe disease (Table 2).

Treatment of COVID-19 and its complications in group 1 included antibacterial and antiviral drugs, prevention of hypercoagulability and disseminated intravascular coagulation syndrome, symptomatic treatment, and oxygen therapy. In the group 2, in accordance with the severity of the condition, for the prevention or treatment of CS, standard therapy was supplemented with the prescription of convalescent pathogen-reduced plasma, anticytokine drugs, namely, inhibitors of receptors IL-6 (tocilizumab, olokizumab, levilimab), IL-1 (canakinumab, RH104), JAK-kinases (tofacitinib, ruxolitinib, baricitinib), tyrosine kinase Bcr-Abl (radotinib), and in some cases glucocorticoids. According to the indications, staged respiratory therapy, modified antibiotic therapy, extracorporeal membrane oxygenation, and treatment of sepsis and septic shock (extracorporeal detoxification and hemocorrection, etc.) were performed [5].

Upon admission, patients in group 1 were significantly more likely to have the CT-1 form of the disease, while patients in group 2 were hospitalized more often than patients in group 1 with more severe forms, namely CT-2, CT-3, and CT-4. Despite the predominance of CT signs of moderate lung lesions (CT-2) in group 2, the

Table 2

**Characteristics of the disease severity the in patient groups**

| Indicator | Group 1 | | Group 2 | | Total | p |
|---|---|---|---|---|---|---|
| | n | % | n | % | | |
| Women | 58 | 58,0 | 159 | 44,4 | 217 | 0,016 |
| Men | 42 | 42,0 | 199 | 55,6 | 241 | |
| *Severity of the disease course:* | | | | | | |
| • moderate | 100 | 100,00 | 153 | 42,74 | 253 | 0,000 |
| • severe, extremely severe | 0 | 0,00 | 205 | 57,26 | 205 | |
| *Form of the disease according to CT 1–4 upon admission:* | | | | | | |
| • CT-1 | 57 | 57,0 | 82 | 22,9 | 139 | 0,000 |
| • CT-2 | 43 | 43,0 | 223 | 62,3 | 263 | |
| • CT-3 | 0 | 0,0 | 44 | 12,3 | 47 | |
| • CT-4 | 0 | 0,0 | 9 | 2,5 | 9 | |
| *Outcomes of the disease:* | | | | | | |
| • survivors | 100 | 100,0 | 255 | 71,2 | 355 | 0,000 |
| • deceased | 0 | 0,0 | 103 | 28,8 | 103 | |

patients showed signs of progressive respiratory failure and fever upon admission (Table 3).

There is a significant difference according to the NEWS scale, as in the group 1, the NEWS index upon admission averaged 2 points, with the average duration of hospitalization of 11 days; while in the group 2, the NEWS index on admission averaged 4 points, by the start of therapy with an anti-cytokine drug, anti-COVID plasma, hemosorption, it averaged 5 points, and the average duration of hospitalization was 12 days. Patients of group 2 with severe and extremely severe course of the disease had the highest mortality rate from complications (28.8% in the group, 22.5% in the entire cohort). Such patients initially had poor prognosis of the disease due to age, comorbidity, clinical severity in terms of the degree of respiratory failure, the NEWS index value, prevalence and subsequent negative changes over time in the lung tissue according to CT data (Table 3).

Table 3

**Comparison of patient groups on the NEWS scale, hospitalization time, and duration of hospital stay**

| Indicator | Characteristics | Group 1 | | Group 2 | | p |
|---|---|---|---|---|---|---|
| | | n | Value | n | Value | |
| NEWS index upon admission | M±s.d | 100 | 2,4±1,7 | 356 | 4,5±2,7 | <0,001 |
| | Min–max | | 0–8 | | 0–14 | |
| NEWS index by the start of cytokine storm therapy | M±s.d | 100 | 1,5±1,6 | 357 | 5,68±2,82 | <0,001 |
| | Min–max | | 0–6 | | 0–14 | |
| NEWS index at discharge | M±s.d | 100 | 0,2±1,02 | 349 | 3,29±5,42 | <0,001 |
| | Min–max | | 0–9 | | 0–16 | |
| Number of days from the onset of the disease to hospitalization | M±s.d | 100 | 8,8±5,9 | 356 | 6,63±5,39 | <0,001 |
| | Min–max | | 0–37 | | 0–57 | |
| Day of illness by the start of cytokine storm therapy (anticytokine drug, plasma, hemosorption) | M±s.d | 100 | 9,0±6,0 | 357 | 10,35±5,98 | <0,017 |
| | Min–max | | 1–37 | | 1–59 | |
| Hospital stay duration (number of bed-days) | M±s.d | 100 | 11,8±4,9 | 355 | 13,6±6,7 | <0,012 |
| | Min–max | | 3,2–29,0 | | 0–44,1 | |


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journal of clinical practice 2021 Том 12 №1

Indicators of the absolute count of lymphocytes and levels of lactate dehydrogenase (LDH), CRP, ferritin, D-dimer, and IL-6 illustrate the presentation of the infectious process of viral etiology as developing CS (lymphopenia, hypercytokinemia, hyperinflammation) [9, 10].

In comparative analysis of clinical, instrumental, and laboratory data in the selected groups of patients, the most important indicators characterizing the signs of CS were indicated (Table 4).

The index changes of the NEWS scale over time are qualitatively different in patients of different groups, as in the group 1, the index decreases [dynamics –1 (–2; 0) points], and in patients of the group 2 with a progressive course of the disease, the index increases [dynamics +1 (0; 2) point] ($p < 0.001$). Significant differences in laboratory parameters (absolute lymphocyte count, CRP, ferritin, D-dimer, IL-6 levels) between the groups were revealed, which are consistent with the changes in the patients' condition according to the NEWS scale from the time of admission to the start of CS treatment.

The method of constructing classification trees identified the threshold levels of risk factors for the development of CS (Table 5).

Exceeding the threshold values of the main predictors of CS was significantly more often registered in patients of the group 2 (Table 6).

Subsequently, a comprehensive assessment of the CS risk was conducted with ranking of indicators, which, in accordance with the rank of prognostic significance obtained by the method of constructing classification trees, by the beginning of CS therapy, were the following:

1) changes over time in the index on the NEWS scale;
2) blood level of IL-6 higher than 23 pg/ml;
3) blood CRP level of 50 mg/l or higher;
4) absolute lymphocyte count less than 0.72 × $10^9$/l;
5) positive test result for coronavirus RNA (SARS-CoV-2);
6) the age of patients of 40 years and older.

These biomarkers can be used as criteria for assessing the risk of CS. It should be noted that gender differences are insignificant in the further comprehensive assessment of the risk of CS.

The Fig. 1 illustrates the increase in the risk of CS (OR) depending on the value of laboratory parameters.

An increase in the frequency of CS cases correlates with an increase in the number of risk factors (correla-

Table 4

**The main indicators that are important in diagnostics of a cytokine storm by the start of preemptive anti-inflammatory therapy**

| Indicator | Group 1 | | Group 2 | | p |
|---|---|---|---|---|---|
| | n | M±s.d<br>Min–max | n | M±s.d<br>Min–max | |
| Age, years | 100 | 57,53±15,06<br>21–86 | 358 | 60,5 ± 13,37<br>24–89 | 0,05 |
| Blood lymphocytes, $10^9$/l | 98 | 1,49±0,59<br>0,46–3,2 | 349 | 1,28±1,39<br>0,23–24,62 | <0,01 |
| Blood lactate dehydrogenase, U/L | 27 | 357,78±155,3<br>169–914 | 149 | 410,17±191,24<br>134–1492 | <0,1 |
| Blood C-reactive protein, mg/l | 91 | 54,61±64,92<br>0,5–274,9 | 346 | 106,71±79,58<br>0,8–361,9 | <0,001 |
| Blood ferritin, ng/ml | 20 | 328,57±185,15<br>57,1–781,3 | 190 | 696,28±792,88<br>0–7759,4 | <0,01 |
| D-dimer, μg/ml | 29 | 1,26±2,75<br>0,27–15,34 | 147 | 1,84±2,79<br>0,15–18,69 | <0,05 |
| IL-6 blood, pg/ml | 65 | 15,02±23,64<br>0–127,2 | 318 | 161,26±442,5<br>1,5–4894 | <0,001 |
| Dynamics of the NEWS index from the moment of admission to the start of treatment for the cytokine storm | 100 | -0,96±1,19<br>-4–4 | 356 | 1,24±1,86<br>-3–11 | <0,001 |

Table 5

**Threshold values of cytokine storm predictors in groups 1 and 2 at the start of preemptive anti-inflammatory therapy**

| Indicator | Group 1 | | Group 2 | | Total | *p* |
|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | *n* | |
| *Blood lactate dehydrogenase, U/L* | | | | | | |
| • ≤390 | 20 | 19,80 | 81 | 80,20 | 101 | <0,1 |
| • >390 | 7 | 9,33 | 68 | 90,67 | 75 | |
| *Age, years* | | | | | | |
| • <40 years | 16 | 42,11 | 22 | 57,89 | 38 | <0,01 |
| • ≥40 years | 84 | 20,00 | 336 | 80,00 | 420 | |
| *SARS-CoV-2 RNA test* | | | | | | |
| • negative | 39 | 43,82 | 50 | 56,18 | 89 | <0,001 |
| • positive | 53 | 18,28 | 237 | 81,72 | 290 | |
| *Blood C-reactive protein, mg/l* | | | | | | |
| • <50 | 56 | 38,10 | 91 | 61,90 | 147 | <0,001 |
| • ≥50 | 35 | 12,07 | 255 | 87,93 | 290 | |
| *Blood lymphocytes, $10^9$/l* | | | | | | |
| • ≥0,72 | 94 | 25,47 | 275 | 74,53 | 369 | <0,001 |
| • <0,72 | 4 | 5,13 | 74 | 94,87 | 78 | |
| *D-dimer, μg/ml* | | | | | | |
| • ≥2,1 | 28 | 19,44 | 116 | 80,56 | 144 | <0,05 |
| • <2,1 | 1 | 3,13 | 31 | 96,88 | 32 | |
| *Blood ferritin, ng/ml* | | | | | | |
| • ≥485 | 18 | 15,93 | 95 | 84,07 | 113 | <0,01 |
| • <485 | 2 | 2,06 | 95 | 97,94 | 97 | |
| *NEWS scale index, score* | | | | | | |
| • <0 | 62 | 74,70 | 21 | 25,30 | 83 | <0,001 |
| • ≥0 | 38 | 10,19 | 335 | 89,81 | 373 | |
| *Blood IL-6, pg/ml* | | | | | | |
| • ≤23 | 54 | 52,94 | 48 | 47,06 | 102 | <0,001 |
| • >23 | 11 | 3,91 | 270 | 96,09 | 281 | |

Table 6

**Frequency of cytokine storm with different numbers of risk factors**

| Number of risk factors for cytokine storm | Group 1 | | Group 2 | | Total |
|---|---|---|---|---|---|
| | *n* | % | *n* | % | |
| No factors | 2 | 100,00 | 0 | 0,00 | 2 |
| 1 | 12 | 100,00 | 0 | 0,00 | 12 |
| 2 | 14 | 63,64 | 8 | 36,36 | 22 |
| 3 | 21 | 37,50 | 35 | 62,50 | 56 |
| 4 | 6 | 9,68 | 56 | 90,32 | 62 |
| 5 | 2 | 1,64 | 120 | 98,36 | 122 |
| 6 | 0 | 0,00 | 34 | 100,00 | 34 |
| Total | 57 | 18,39 | 253 | 81,61 | 310 |


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journal of clinical practice 2021 Том 12 №1

**Fig. 1.** Increased risk of cytokine storm (OR) with adverse values of indicators.

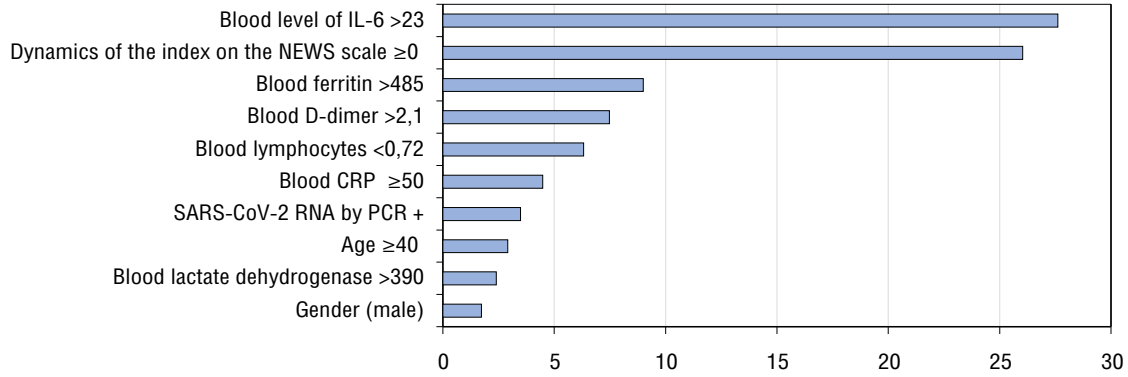
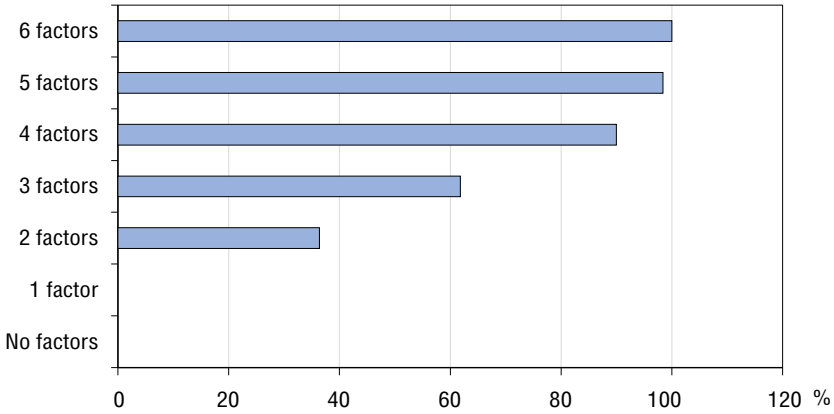



**Fig. 2.** The incidence of cytokine storm with a different number of risk factors.




tion coefficient Rg +0.91, $p < 0.001$) (Table 6; Fig. 2). Any of the factors presented, in combination with the largest number of others, increased the risk of CS.

The following risk categories have been identified for the practical application of our predictive model:

- category 1 (0–1 factor) implies practically no risk of CS;
- category 2 (2–3 factors) implies sharp increase in the risk of CS to 55%, by 35.5 times compared with the category 1;
- category 3 (4 or more factors) indicates that the risk of CS reaches 96%, increases by 718 times compared to the category 1.

The results obtained are consistent with the assessment of CS risk factors in COVID-19 by other authors [11, 12] and enable to justify the choice of treatment approach with early prescription of preemptive anti-inflammatory therapy and anti-COVID plasma of convalescents for patients with a high risk of CS.

## DISCUSSION

Since no convincing prognostic criteria for the development of CS in COVID-19 have been developed, we analyzed the predictive power of clinical, instrumental, and laboratory parameters available for study using the example of 458 patients with different course of the disease, in attempts to reveal coherent groups or clusters of those that are useful for making a prognosis, and to establish their predictive power. For this purpose, we used the registration of clinical signs and symptoms upon admission to the hospital and in the anamnesis, as well as demographic, epidemiological information, clinical characteristics and assessment of the severity of the condition according to the NESW scale; the severity of COVID-19; comorbidity; analysis of changes in the lung tissue (ground glass opacity ± consolidation) on CT of the lungs according to the standard protocol without intravenous contrasting [5], as well as the values of laboratory blood parameters [13] within 24 hours before or after the diagnosis of CS and during subsequent 7 days of hospitalization. Over the next 10 days, the results of determining the SARS-CoV-2 RNA were evaluated, as well as the duration of inpatient treatment and disease outcomes. Comparative characteristics of patients with clinical and radiological signs of CS and patients without signs of CS revealed potential risk factors for the development of CS.

The increase in the NEWS scale index characterizes the clinical severity of the disease and the progression of hemodynamic disorders. Thus, in group 1, patients

upon admission had an index of no more than 4 points, which decreased during therapy by 1–2 points, while patients in group 2 had an increase in the number of points by 1.24 ± 1.86 with the initial higher value of the index. Significant differences between the groups 1 and 2 were registered when analyzing the levels of IL-6, CRP, ferritin, and the count of lymphocytes. Thus, with the progressive course of the disease, we detect the increasing indices of biomarkers that were involved in the implementation of the clinical presentation of CS in our patients.

## CONCLUSION

The main risk factors for the development of a cytokine storm in COVID-19 patients include male gender, age over 40 years old, positive test for SARS-CoV-2 RNA, lymphocyte count, levels of LDH, D-dimer, ferritin, and IL-6, NEWS scale index change. The laboratory criteria for diagnostics and follow-up of the course of the cytokine storm are the absolute lymphocyte count, levels of LDH, CRP, ferritin, D-dimer, and IL-6. The developed prognostic scale enables to identify a group of patients with a high risk of CS for early prescription of anti-inflammatory therapy.

## ADDITIONAL INFORMATION

**Author contribution.** A.Yu. Anisenkova, E.Yu. Garbuzov, D.N. Khobotnikov — treatment of patients; S.V. Apalko, Z.P. Asaulenko — laboratory studies of biological samples of patients; A.N. Bogdanov, D.A. Vologzhanin, O.A. Klitsenko — processing and discussion of the study results, manuscript writing; A.S. Golota, T.A. Kamilova — literature search and analysis, discussion of the study results, manuscript writing; O.S. Glotov — testing of biological samples of patients for SARS-CoV-2 coronavirus; E.M. Minina — radiological diagnostics; S.V. Mosenko — examination of patients; S.G. Shcherbak — management of the patient treatment and discussion of the study results.

The authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

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