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Major predictive risk factors for cytokine storm in COVID-19 patients (Clinical trials)

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AIM: Searching for predictors of cytokine storm in patients with COVID-19 and creating a risk scale for this complication for practical implementation.

MATERIALS AND METHODS: The study included 458 patients with confirmed COVID-19 with signs of viral lung lesion according to computer tomography. The patients were divided into 2 groups: with a stable course of moderate severity (100 patients) and with progressive moderate, severe and extremely severe course (358 patients).

RESULTS: It has been established that the main risk factors for the development of cytokine storm in COVID-19 patients are interleukin-6 concentration >23 pg/ml, the dynamics of the index according to the NEWS scale ≥0, ferritin concentration >485 ng/ml, D-dimers >2,1, C-reactive protein >50 mg/l, the number of lymphocytes in the blood $<0{,}72 \cdot 10^9$/l, age ≥40 years. Cytokine storm incidence correlates with an increase in the number of risk factors. For practical use the scale is applied in 3 groups. In the patients of the first group (0-1 factor) almost no cytokine storm risk was detected, in the second group (2-3 factors) the probability of a storm was 55 % (increased by 35.5 times), in the third group (≥4 risk factors) reaches 96 % (increased by 718 times).

CONCLUSIONS: Diagnostic and monitoring criteria of cytokine storm in the patients with COVID-19 were established. The developed prognostic scale allows to identify patients at high risk of developing cytokine storm for early anti-inflammatory therapy.

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

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Основные прогностические факторы риска цитокинового шторма у пациентов с COVID-19 (клинические исследования)

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Цель — поиск предикторов цитокинового шторма у пациентов с COVID-19 и создание шкалы риска развития этого осложнения для практической работы.

Материалы и методы. В исследование вошли 458 пациентов с подтвержденной COVID-19 и признаками вирусного поражения легких при компьютерной томографии. Пациенты разделены на две группы: со стабильным течением средней тяжести (100 пациентов) и с прогрессирующим течением средней, тяжелой и крайне тяжелой степени (358 пациентов).

Результаты. Установлено, что основными факторами риска развития цитокинового шторма у пациентов с COVID-19 являются концентрация интерлейкина-6 >23 пг/мл, динамика индекса по шкале NEWS ≥0, концентрация ферритина >485 нг/мл, D-димера >2,1, С-реактивного белка >50 мг/л, количество лимфоцитов в крови $<0{,}72 \cdot 10^9$/л, возраст ≥40 лет. Частота случаев цитокинового шторма коррелирует с увеличением числа факторов риска. Для практического применения шкалы выделены три группы риска. У пациентов первой группы (0–1 фактор) риск цитокинового шторма практически отсутствует, во второй группе (2–3 фактора) вероятность составляет 55 % (увеличивается в 35,5 раза), в третьей группе (≥4 факторов риска) достигает 96 % (увеличивается в 718 раз).

Заключение. У пациентов с COVID-19 определены критерии диагностики и контроля цитокинового шторма. Разработанная прогностическая шкала позволяет выделить пациентов с высоким риском развития цитокинового шторма для раннего назначения противовоспалительной терапии.

Ключевые слова: COVID-19; цитокиновый шторм; ранняя диагностика и мониторинг.

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INTRODUCTION

COronaVIrus Disease 2019 (COVID-19), caused by the *severe acute respiratory syndrome coronavirus 2* (*SARS-CoV-2)*, remains as a global health problem. Most people infected with *SARS-CoV-2* have a mild disease course. In some patients, the immune response becomes unregulated that leads to severe lung damage manifested as acute respiratory distress syndrome with subsequent development of acute respiratory failure, extrapulmonary organ dysfunction, and high mortality. COVID-19, especially in severe cases, is commonly associated with increased levels of inflammatory biomarkers, cytokines, and chemokines. In addition, lymphocytopenia and neutrophilia with a significant decrease in CD8+ T-cells, CD4+ T-cells, and natural killer cells are common [6]. The mortality rate of hospitalized patients reaches 15–20% or higher in patients who required intensive care [12].

Immune dysfunction with a pronounced uncontrolled generalized systemic inflammatory response due to increased production of inflammatory cytokine, i.e., cytokine storm (CS), takes a crucial place in the pathophysiology of COVID-19. CS is accompanied by fever, cytopenia, hyperferritinemia, coagulopathy, and lung damage (including acute respiratory distress syndrome), with abnormal levels of hepatic parameters [5]. In all these conditions, cytokines, namely, interleukin (IL)-1β, IL-18, interferon-γ, and IL-6, are the main mediators of hyperinflammation. COVID-19-associated CS is a unique form of hyperinflammatory response, so developing criteria for its diagnosis is necessary [13].

The aim of this study is to search for biomarkers that are predictors of CS in patients with COVID-19 and to create a predictive scale for the risk of CS development for use in daily medical work.

MATERIALS AND METHODS

This study follows an observational clinical design. The study analyzed case histories of 458 patients with COVID-19 who were treated at the City Hospital No. 40 of St. Petersburg from April 18, 2020, to November 21, 2020, with positive *SARS-CoV-2* RNA test results performed by nucleic acid amplification technique in the polymerase chain reaction. These patients presented with fever, general weakness and malaise, cough and dyspnea, and changes resembling those of viral pneumonia in non-contrasted computed tomography of the lungs (such as bilateral lower lobe, peripheral, perivascular, and multilobular changes; multiple peripheral indurations in the form of frosted glass with round shape and various sizes; flattening of the interlobular interstitium like a cobblestone; foci of consolidation; abnormal air bronchogram findings; among others) [1].

Anamnestic data were collected from all patients with specification of the characteristics of the disease course: an objective examination with assessment of hemodynamics and respiratory system parameters (including respiratory rate, heart rate, blood pressure, S_pO_2, and degree of respiratory failure), assessment according to the National Early Warning Score (NEWS) scale recommended for use in patients with COVID-19 [11], chest computed tomography scan with assessment of the disease form according to the 4-digit scale (CT-1, CT-2, CT-3, and CT-4), laboratory tests [clinical blood count, minimum biochemical blood assay, determination of ferritin, C-reactive protein (CRP), IL-6, and D-dimer levels, and lactate dehydrogenase (LDH) activity], electrocardiography, additional instrumental methods of diagnosis if necessary.

Statistical analysis. Data obtained were evaluated using Statistica for Windows (version 10, license BXXR310F-964808FA-V). Comparison of quantitative parameters (age, NEWS index, D-dimer, CRP, IL-6 levels, etc.) and determination of the normality of sample distribution in the patient groups was carried out using Mann–Whitney, Kolmogorov–Smirnov tests, median χ^2, and analysis of variance module in all parameters (excluding age) without normal distribution. Frequency characteristics of qualitative parameters (sex, pathological process degree and form, and complaints) were assessed using nonparametric methods, including χ^2, Pearson test, and Fisher test.

Threshold levels for age, NEWS index, and laboratory findings were determined using classification trees (CT) [3].

As regards the relative risk of CS, certain outcome probability ratio in the experimental groups was analyzed using fourfold contingency tabulation and calculation of the standard formula and confidence limits. If there were zero values in the table, the Haldane correction was used for calculation.

RESULTS AND DISCUSSION

Characteristics of patient groups at hospital admission. Demographic data, epidemiological history data, and comorbidities in the study cohort are presented in Table 1.

According to the literature, the prevalence of concomitant diseases in our patients significantly exceeds this parameter in adult patients with COVID-19 (31%) [7]. The high incidence of concomitant pathology in the examined patients is associated with a certain profile, that is, treatment of patients with severe and extremely severe disease course. Moreover, 221 (48%) patients were transferred to the intensive care unit from other departments and hospitals due to the progressive disease course.

At admission, the following signs were recorded: fever in 365 (80%), cough in 329 (72%), dyspnea in

Table 1. Demographic. epidemiological. and anamnestic data of the patients
Таблица 1. Демографические. эпидемиологические и анамнестические данные пациентов

Parameters	*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 patients having COVID-19	100 (22.22%)
Went out of the place of residence within the last14 days	45 (9.83%)
Presence of “cold” symptoms, such as fever, cough, and weakness, in close relatives	44 (9.61%)
History of diseases	
Essential hypertension	260 (56.77%)
Coronary artery disease	222 (48.47%)
Cerebrovascular disease	139 (30.35%)
Post-stroke status	97 (21.18%)
Post-acute myocardial infarction status	34 (7.42%)
Post-surgery status	89 (19.43%)
Rheumatoid arthritis and other autoimmune diseases	65 (14.19%)
Diabetes mellitus	63 (13.76%)
Chronic kidney disease (stages III–V)	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%)

265 (57.86%), muscle pain in 43 (9.39%), general weakness in 344 (75.11%), headache in 36 (7.86%), sore throat in 29 (6.33%), runny nose, rhinorrhea in 46 (10.04%), chest pain in 51 (11.14%), diarrhea in 34 (7.42%), nausea and vomiting in 13 (2.84%), and decreased sense of smell and taste in 40 (8.73%) patients. One or more disease symptoms were noted in 450 (98.25%) patients, and CT signs of pneumonia were found in 458 (100%) patients.

Patients were divided into two groups comparable in age. Group 1 consisted of 100 (21.8%) patients with clinical and radiological features specific for a stable course of moderate disease. Group 2 included 358 (78.2%) patients with progressive moderate, severe, and extremely severe disease course (Table 2). Treatment of COVID-19 and its complications in Group 1 included antibacterial and antiviral drugs, prevention of hypercoagulability and disseminated intravascular coagulation, symptomatic treatment, and oxygen therapy. In Group 2, in accordance with the severity of the condition for the prevention or treatment of CS, standard therapy was supplemented with the appointment of convalescent pathogen-reduced plasma, anticytokine drugs such as inhibitors of the IL-6 receptor (tocilizumab, olokizumab, and levilimab), IL-1 (canakinumab and RH104), janus kinases (tofacitinib, ruxolitinib, and baricitinib), tyrosine kinase Bcr – Abl (radotinib), and glucocorticoids (in some cases). According to the indications, patients received staged respiratory therapy, modified antibiotic therapy, extracorporeal membrane oxygenation, and treatment of sepsis and septic shock (extracorporeal detoxification, hemocorrection, etc.) [1].

At admission, patients in Group 1 were significantly more likely to have CT-1 disease form, while patients in Group 2 were more likely to have more severe forms (CT-2, CT-3, and CT-4). Despite the predominance in the second group of CT signs of moderate lung damage (CT-2) at admission, patients showed signs of progressive respiratory failure and fever (Table 3). A significant difference was found according to the NEWS scale. In Group 1, the NEWS index at admission averaged 2 points, and the average duration of hospitalization was 11 days. In Group 2, the NEWS index at admission averaged 4 points; it was 5 points at the beginning of therapy with an anticytokine drug, anti-COVID plasma, and hemosorption; and the average duration of hospitalization was 12 days. Patients in Group 2 with severe and extremely severe disease course had the highest mortality rate because of complications (28.8% in the group, 22.5% in the entire cohort). Such patients initially had an unfavorable disease prognosis due to age, comorbidity, clinical severity

Table 2. Characteristics of the disease severity in patient groups

Таблица 2. Характеристика тяжести течения заболевания в группах пациентов

Parameters	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 disease course						
average	100	100.00	153	42.74	253	0.000
severe and extremely severe	0	0.00	205	57.26	205	
Disease form according to CT-1–4 at 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	
Disease outcomes						
survivors	100	100.0	255	71.2	355	0.000
deceased	0	0.0	103	28.8	103	

Table 3. Comparison of patient groups according to the NEWS scale, admission time, and length of hospital stay

Таблица 3. Сравнение групп пациентов по шкале NEWS. срокам поступления в стационар и длительности госпитализации

Parameter		Group 1		Group 2		*p*
		n	Value	*n*	Value	
NEWS index at admission	M ± SD min–max	100	2.4 ± 1.7 0–8	356	4.5 ± 2.7 0–14	<0.001
NEWS index at the start of cytokine storm therapy	M ± SD min–max	100	1.5 ± 1.6 0–6	357	5.68 ± 2.82 0–14	<0.001
NEWS index at discharge	M ± SD min–max	100	0.2 ± 1.02 0–9	349	3.29 ± 5.42 0–16	<0.001
Number of days from disease onset to hospitalization	M ± SD min–max	100	8.8 ± 5.9 0–37	356	6.63 ± 5.39 0–57	<0.001
Day of illness by the beginning of cytokine storm therapy (anticytokine drug, plasma, and hemosorption)	M ± SD min–max	100	9.0 ± 6.0 1–37	357	10.35 ± 5.98 1–59	<0.017
Length of hospitalization terms, bed-days	M ± SD min–max	100	11.8 ± 4.9 3.2–29.0	355	13.6 ± 6.7 0–44.1	<0.012

in terms of the degree of respiratory failure, NEWS index, prevalence, and subsequent negative dynamics of changes in lung tissues according to the CT data (Table 3).

The absolute lymphocyte count, LDH activity, and levels of CRP, ferritin, D-dimer, and IL-6 demonstrated an infectious process of viral etiology which resembles a CS (lymphopenia, hypercytokinemia, and hyperinflammation) [2, 8].

In a comparative analysis of the clinical, instrumental, and laboratory data in the selected groups of patients, the most important parameters characterizing the signs of the development of CS are indicated in Table 4.

The dynamics of the NEWS index was qualitatively different in patients of different groups. In Group 1, the index decreased [dynamics of –1 (–2; 0) points], and in Group 2 with a progressive disease course, the index increased [dynamics +1 (0; 2) score] ($p < 0.001$). Significant differences in laboratory parameters (absolute number of lymphocytes and levels of CRP, ferritin, D-dimer, and IL-6) were found between the groups, which are consistent with the dynamics of the patients' condition according to the NEWS scale from admission to the beginning of CS treatment.

CT method identified the threshold levels of risk factors for CS development (Table 5).

Exceeding the threshold values of the main predictors of CS was significantly more frequently observed in Group 2 (Table 6). Subsequently, a comprehensive

Table 4. Main parameters for diagnosing a cytokine storm at the beginning of proactive anti-inflammatory therapy

Таблица 4. Основные показатели, имеющие значение в диагностике цитокинового шторма, к началу упреждающей противовоспалительной терапии

Parameters	Group 1		Group 2		*p*
	n	M ± SD min–max	*n*	M ± SD min–max	
Age, years	100	57.53 ± 15.06 21–86	358	60.5 ± 13.37 24–89	0.05
Lymphocytes, 10^9/L	98	1.49 ± 0.59 0.46–3.2	349	1.28 ± 1.39 0.23–24.62	<0.01
Lactate dehydrogenase, U/L	27	357.78 ± 155.3 169–914	149	410.17 ± 191.24 134–1492	<0.1
C-reactive protein, mg/L	91	54.61 ± 64.92 0.5–274.9	346	106.71 ± 79.58 0.8–361.9	<0.001
Ferritin, ng/mL	20	328.57 ± 185.15 57.1–781.3	190	696.28 ± 792.88 0–7759.4	<0.01
D-dimer, μg/mL	29	1.26 ± 2.75 0.27–15.34	147	1.84 ± 2.79 0.15–18.69	<0.05
Interleukin-6, pg/mL	65	15.02 ± 23.64 0–127.2	318	161.26 ± 442.5 1.5–4894	<0.001
Dynamics of the NEWS index from admission to the start of treatment for cytokine storm	100	–0.96 ± 1.19 –4–4	356	1.24 ± 1.86 –3–11	<0.001

assessment of the CS risk was carried out with the ranking of parameters, which, in accordance with the rank of prognostic significance obtained by the CT method, by the beginning of CS therapy were as follows: dynamics of the index according to the NEWS scale, IL-6 level >23 pg/ml; CRP level ≥50 mg/l; absolute lymphocyte count $<0.72 \cdot 10^9$/l, positive result of SARS-CoV-2 RNA test, and age ≥40 years. These biomarkers can be used as criteria for assessing the risk of CS. Gender differences were not significant in the subsequent comprehensive assessment of the risk of CS development.

Fig. 1 shows the increase in the risk of CS depending on the value of the laboratory parameters.

An increase in the frequency of CS cases correlates with an increase in the number of risk factors (correlation coefficient Rg = +0.91, $p < 0.001$) (Table 6, Fig. 2). Any of the above factors, in combination with the largest number of other factors, increased the risk of developing CS.

For the practical application of our predictive model, the following risk categories have been identified: first category (0–1 factor), there is practically no risk of CS; second category (2–3 factors), the risk of CS rises sharply to 55% and increases by 35.5 times in comparison with the first category; and third category (≥4 factors), the risk of CS reaches 96% and increases 718 times in comparison with the first category. The results of our study are consistent with the assessment of CS risk factors in COVID-19 in other studies [4, 10] and allow us to justify the choice of treatment strategies with early prescription of proactive anti-inflammatory therapy and anti-COVID plasma of convalescents for patients at high risk of CS development.

Since no convincing prognostic criteria for CS development in COVID-19 have been developed, we analyzed the predictive power of clinical, instrumental, and laboratory parameters available for the study using a sample of 458 patients with various disease courses to find coherent groups or clusters of those that are useful to formulate a forecast and establish their predictive power. To do this, we recorded clinical signs and symptoms at hospital admission and anamnesis demographic, epidemiological information, and clinical characteristics; assessed the severity of the condition using the NESW scale, severity of COVID-19, and comorbidity; and analyzed changes in the dynamics of lung tissue (frosted glass ± consolidation) on computed tomography images of the lungs according to the standard protocol without intravenous contrast enhancement [1] as well as values of laboratory blood parameters [9] within 24 h before or after the diagnosis of CS and during the next 7 days of hospitalization. Over the next 10 days, the results of the SARS-CoV-2 RNA test and duration of inpatient treatment and disease outcomes were evaluated. Comparative characteristics of patients with clinical and radiological signs

Table 5. Threshold values of predictors of cytokine storm development in groups 1 and 2 at the beginning of proactive anti-inflammatory therapy

Таблица 5. Пороговые значения предикторов развития цитокинового шторма в первой и во второй группах на момент начала упреждающей противовоспалительной терапии

Parameter	Group 1		Group 2		Total	*p*
	n	%	*n*	%	*n*	
Lactate dehydrogenase, U/L						
≤390	20	19.80	81	80.20	101	<0.1
>390	7	9.33	68	90.67	75	
Age						
<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	
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	
Ferritin, ng/mL						
≥485	18	15.93	95	84.07	113	<0.01
<485	2	2.06	95	97.94	97	
NEWS scale index, points						
<0	62	74.70	21	25.30	83	<0.001
≥0	38	10.19	335	89.81	373	
IL-6, pg/mL						
≤23	54	52.94	48	47.06	102	<0.001
>23	11	3.91	270	96.09	281	

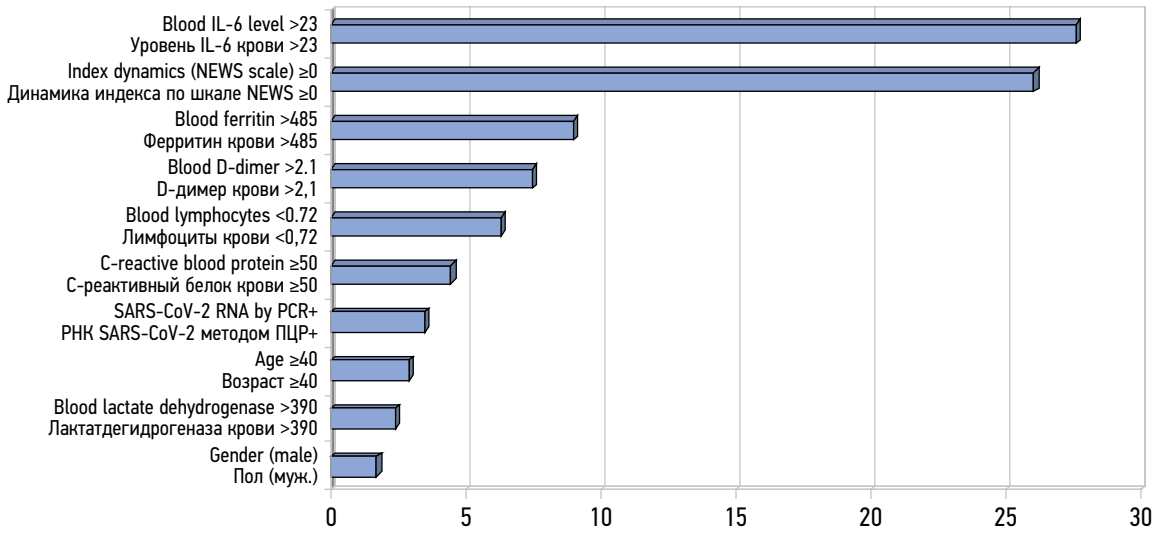

Fig. 1. Increased risk of developing a cytokine storm with unfavorable indicator values

Рис. 1. Увеличение риска развития цитокинового шторма при неблагоприятных значениях показателей

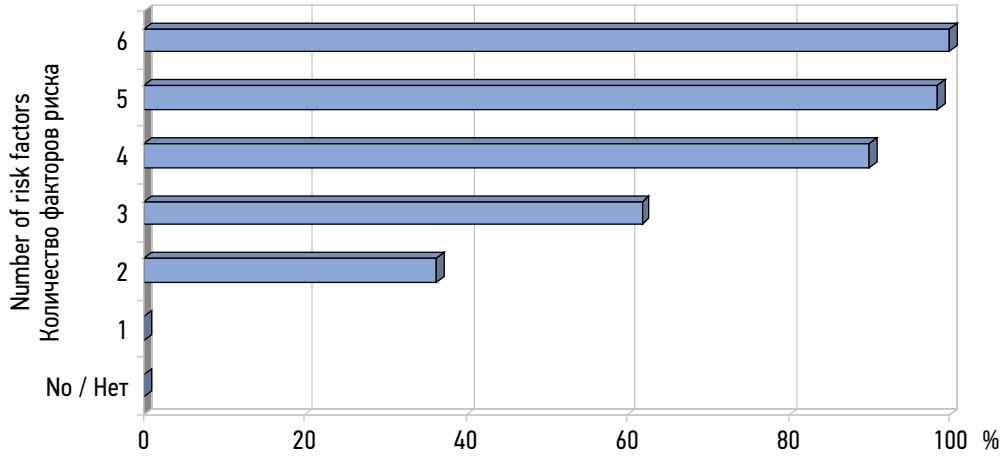

Fig. 2. The incidence of cytokine storms with different number of risk factors

Рис. 2. Частота случаев цитокинового шторма при различном количестве факторов риска

Table 6. The incidence of cytokine storms with different number of risk factors

Таблица 6. Частота случаев цитокинового шторма при различном числе факторов риска

Number of risk factors for cytokine storm	Group 1		Group 2		Total
	n	%	*n*	%	
No	2	100.00	0	0.00	2
One	12	100.00	0	0.00	12
Two	14	63.64	8	36.36	22
Three	21	37.50	35	62.50	56
Four	6	9.68	56	90.32	62
Five	2	1.64	120	98.36	122
Six	0	0.00	34	100.00	34
Total	57	18.39	253	81.61	310

of CS and patients without signs of CS revealed potential risk factors for the development of CS.

The increase in the NEWS index characterizes the clinical severity of the disease and progression of hemodynamic disorders. Thus, at admission, patients in Group 1 had NEWS index no more than 4 points, which decreased during therapy by 1–2 points, whereas patients in Group 2 had NEWS index increased by 1.24 ± 1.86 points with an initial overly high index. Significant differences between Groups 1 and 2 were obtained when analyzing the levels of IL-6, CRP, and ferritin and number of lymphocytes.

Thus, with the progressive disease course, there is an increase in the indices of biomarkers involved in the implementation our prognostic scale of CS.

CONCLUSIONS

1. The main risk factors for the development of a CS in patients with COVID-19 include male sex, LDH activity, age >40 years, positive result for SARS-CoV-2 RNA test, lymphocyte count, D-dimer levels, ferritin levels, NEWS index dynamics, and IL-6 concentration.
2. The laboratory criteria for diagnosis and dynamic control over the course of a CS are the absolute number of lymphocytes, LDH activity, and CRP, ferritin, D-dimer, and IL-6 levels.
3. The developed prognostic scale makes it possible to identify patients with a high risk of developing a CS for early implementation of an anti-inflammatory therapy.

Conflict of interest. There is no conflict of interest.

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