DOI: https://doi.org/10.17816/mechnikov61610

Prognostic value of cytokines in COVID-19 associated pneumonia

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BACKGROUND: Coronavirus disease 2019 (COVID-19) is often complicated by cytokine storm syndrome. Although many interleukins (IL) have predictive value, the sensitivity and specificity of a single marker is limited.

AIM: The purpose of the study is to develop an objective and informative cytokine storm scale for assessing the risk of developing a critical course in patients with COVID-19 associated pneumonia.

MATERIALS AND METHODS: A total of 226 cases of COVID-19 were investigated, 36 (16 %) of which were with poor outcomes. The cytokines IL-1b, IL-2, IL-6, IL-8, IL-10, IL-18, TNF-α, IFNα, IFN-γ were studied by enzyme immunoassay, commercial kits manufactured by Vector-Best, RF.

RESULTS: Since IL-6, IL-10, IL-18, and procalcitonin were associated with disease severity and death, these indicators were integrated into a 12-point scale called the cytokine storm scale. The patients who scored more than 6 points had a high risk of a poor outcome of the disease. According to ROC analysis, the area under the curve for the cytokine storm scale was larger than for each of the four markers separately [AUC 0.90 (95% CI 0.8455–0.9592), $p < 0.001$].

CONCLUSIONS: Thus, the cytokine storm scale system presents superior performance in determining patients with favorable and fatal outcomes to each individual cytokine.

Keywords: SARS-CoV-2 coronavirus; cytokine storm; interleukin 6; interleukin 18; interleukin 10; procalcitonin; cytokine storm scale.

To cite this article:
Tkachenko OYu, Pervakova MYu, Lapin SV, Mazing AV, Moshnikova AN, Kuznetsova DA, Kholopova IV, Blinova TV, Surkova EA, Kulikov AN, Vorobyev EA, Vorobyova SV, Stanevich OV, Polushin YuS, Afanasyev AA, Shlyk IV, Gavrilova EG, Titova ON, Volchkova EV, Potapenko VG, Khudonogova SV, Mazurov VI. Prognostic value of cytokines in COVID-19 associated pneumonia. *Herald of North-Western State Medical University named after I.I. Mechnikov.* 2021;13(1):59–69. DOI: https://doi.org/10.17816/mechnikov61610

Received: 12.03.2021 **Accepted:** 17.03.2021 **Published:** 31.03.2021

DOI: https://doi.org/10.17816/mechnikov61610

Прогностическая роль исследования цитокинов при COVID-19-ассоциированной пневмонии

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Введение. Коронавирусное заболевание 2019 г. (COVID-19) часто осложняется синдромом цитокинового шторма. Хотя многие интерлейкины обладают прогностической ценностью, чувствительность и специфичность одного маркера ограничена.

Цель исследования — разработать объективную и информативную шкалу цитокинового шторма для оценки риска развития критического течения у пациентов с COVID-19-ассоциированной пневмонией.

Материалы и методы. Было изучено 226 случаев COVID-19, 36 (16 %) из которых с неблагоприятным исходом. Исследованы цитокины — интерлейкин-1b, -2, -6, -8, -10, -18, фактор некроза опухоли-α, интерферон-α, интерферон-γ — методом иммуноферментного анализа с помощью коммерческих наборов производства Вектор-Бест (Россия).

Результаты. Поскольку уровни интерлейкинов-6, -10, -18 и прокальцитонина были связаны с тяжестью заболевания и летальным исходом, эти показатели были интегрированы в 12-балльную шкалу, названную шкалой цитокинового шторма. Пациенты, набравшие более 6 баллов, имеют высокий риск неблагоприятного исхода заболевания. Согласно ROC-анализу площадь под кривой для шкалы ЦШ оказалась больше, чем для каждого из четырех маркеров по отдельности [AUC 0,90 (95 % ДИ 0,8455–0,9592), $p < 0,001$].

Заключение. Таким образом, шкала цитокинового шторма обладает достаточно высокой информативностью в отношении риска неблагоприятного прогноза течения COVID-19.

Ключевые слова: коронавирус SARS-CoV-2; цитокиновый шторм; интерлейкин-6; интерлейкин-18; интерлейкин-10; прокальцитонин; шкала цитокинового шторма.

Как цитировать:
Ткаченко О.Ю., Первакова М.Ю., Лапин С.В., Мазинг А.В., Мошникова А.Н., Кузнецова Д.А., Холопова И.В., Блинова Т.В., Суркова Е.А., Куликов А.Н., Воробьев Е.А., Воробьева С.В., Станевич О.В., Полушин Ю.С., Афанасьев А.А., Шлык И.В., Гаврилова Е.Г., Титова О.Н., Волчкова Е.В., Потапенко В.Г., Худоногова С.В., Мазуров В.А. Прогностическая роль исследования цитокинов при COVID-19-ассоциированной пневмонии // Вестник Северо-Западного государственного медицинского университета им. И.И. Мечникова. 2021. Т. 13. № 1. С. 59–69. DOI: https://doi.org/10.17816/mechnikov61610

Рукопись получена: 12.03.2021 **Рукопись одобрена:** 17.03.2021 **Опубликована:** 31.03.2021

INTRODUCTION

The new coronavirus infection caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [Coronavirus Disease 2019 (COVID-19)] virus was first reported in China in December 2019 and has since spread worldwide. Most patients with COVID-19 have asymptomatic or mild-to-moderate acute respiratory disease. However, in some patients, the infection can progress to interstitial pneumonia and acute respiratory distress syndrome, especially in elderly patients and patients with concomitant diseases [1, 2]. SARS-CoV-2 infection can affect the functions of the gastrointestinal tract, liver, and pancreas, and cause neurological manifestations (anosmia), damage the cardiovascular system, and contribute to kidney dysfunction. In patients with severe disease, functional limitations often persist for a long time.

Due to the genetic characteristics and virulence factors of the virus, a delayed synthesis of interferons occurs in the early stages of the disease, the clearance of SARS-CoV-2 is impaired, NETosis and pyroptosis increase creating a background for a severe disease course complicated by cytokine storm syndrome (CS) [3-5]. A distinctive feature of CS syndrome is an uncontrolled immune response, including constant activation of lymphocytes and macrophages. The massive synthesis of cytokines, namely interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-1β (IL-1β), interleukin-18 (IL-18), and tumor necrosis factor α (TNFα), causes apoptosis of lung epithelial and endothelial cells and damage to the microvascular and epithelial cell barriers leading to alveolar edema and hypoxia. Although the reason that CS develops in COVID-19 remains unclear, CS formation is closely related to disease pathogenesis, and its development is associated with a worse prognosis and severe viral pneumonia.

Although many cytokines have predictive value, the sensitivity and specificity of detecting a single marker are limited. Combining several biomarkers can improve the accuracy of laboratory assessments, and integrating cytokines into one diagnostic scale can improve the prediction of poor outcomes. This study assessed the role of various cytokines in the severe disease course and attempted to create a CS scale to assess the risk of developing a critical disease course in patients with COVID-19-associated pneumonia.

MATERIALS AND METHODS

During the "first wave" of the coronavirus infection epidemic in St. Petersburg from May 25, 2020, to July 25, 2020, 226 patients with COVID-19-associated pneumonia were examined. Of these, 36 (16%) had an unfavorable outcome. COVID-19 was confirmed in all patients by detecting SARS-CoV-2 nucleic acid by polymerase chain reaction using oropharyngeal and nasopharyngeal swabs during hospitalization. Data were collected on demographic characteristics, clinical manifestations, laboratory and radiological results, and the values of the SOFA and NEWS2 severity scales. The protocol for assessing the severity of the patient's condition NEWS2 contained indicators of respiratory rate per minute, oxygen saturation (%), the need for oxygen insufflation, data on body temperature, systolic blood pressure, heart rate, and changes in the level of consciousness. The SOFA scale included an assessment of respiratory function (p_aO_2/FiO_2 mmHg), coagulation (platelets, 10^3/μl), liver (bilirubin, μmol/l), cardiovascular system (hypotension), central nervous system (Glasgow coma scale), kidney (creatinine, mmol/l or diuresis). The control group included 30 healthy individuals (5 men, 25 women) aged 36 to 52 years.

Venous blood samples were collected in the morning on the first day after admission. The concentration of cytokines IL-1b, IL-2, IL-6, IL-8, IL-10, IL-18, TNFα, IFNα, and IFNγ was determined by enzyme immunoassay using commercial kits manufactured by Vector-Best (Russia).

Graphpad Prism 8.3 software was used for statistical analysis. Continuous and categorical variables are presented as median (interquartile range) and *n* (%), respectively. The Mann–Whitney *U*-test, χ^2 test, or Fisher's exact test were used to compare continuous and categorical variables. The predictive value of cytokine concentration and the CS scale were determined by measuring the area under the receiver operating characteristic curve (AUROC).

RESULTS

The studied cohort included 138 (61%) men and 88 (39%) women, whose mean age was 56.82 ± 13.9 years (range, 23 to 87 years). The number of deaths of patients under 45 years old was 3 (7.31%), from 45 to 65 years – 12 (10.5%), whereas the largest number of deaths was observed in the group of patients aged 65 to 85 years (21%–58.3%). The body mass index (BMI) in 42% of patients exceeded 30 kg/m^2. The BMI in women was 33.0 ± 1.4 kg/m^2 and was significantly ($p < 0.01$) higher than the average BMI in men (29.3 ± 0.7 kg/m^2).

All patients examined had fever above 38°C, cough (158%–69.9%), and pain and compression in the chest (137%–31%). Diarrhea (11%–25%) and anosmia (18.5%–42%) were more common among patients with a favorable course of COVID-19 than in those with an unfavorable course.

The prevalence of concomitant pathology was 70%, while hypertension was noted in 57.8% (*n* = 130), coronary heart disease in 27% (*n* = 61), diabetes mellitus was detected in 16.2% (*n* = 36), and chronic heart failure was diagnosed in 8.6% (*n* = 19) patients. Also, 9.6% (*n* = 21)

Table 1. Demographic and clinical characteristics of patients with COVID-19

Таблица 1. Демографические и клинические характеристики пациентов с COVID-19

Characteristics	All patients (*n* = 226)	Recovery (*n* = 190)	Death (*n* = 36)	*p* (recovery vs. death)
		Demographics		
Age up to 45 years, % (*n*)	17.8 (41)	18.9 (36)	8.3 (3)	<0.05
Age 45–65, % (*n*)	50.4 (114)	52.6 (100)	30.5 (11)	<0.05
Age 65–85, % (*n*)	31.4 (71)	26.8 (51)	58.3 (21)	<0.05
Male, % (*n*)	61.0 (138)	60.5 (115)	63.8 (23)	n/a
Body mass index, kg/m^2	29.41 (25.9–33.8)	29.7 (26.2–34.2)	27.9 (24.9–31.96)	n/a
		Clinical manifestations		
Temperature, °C	38.9 (38.5–39)	39.0 (38.3–39.1)	38.8 (38.5–39.0)	n/a
Cough	69.9 (158)	70.5 (134)	66.6 (24)	<0.0001
Chest pain and tightness	137 (31)	13.1 (25)	16.6 (6)	<0.05
Diarrhea	11 (25)	12.1 (23)	5.55 (2)	<0.05
Anosmia	18.58 (42)	21.57 (41)	2.7 (1)	<0.05

Note. n/a – not statistically significant.

of patients had oncological diseases in the active stage, and 3.7% (*n* = 8) had chronic kidney disease of stage III or more. It should be noted that a high incidence of concomitant diseases was observed in critically ill patients and patients with fatal outcomes (Fig. 1). Chronic kidney disease, coronary heart disease, and cancer were directly correlated with deaths.

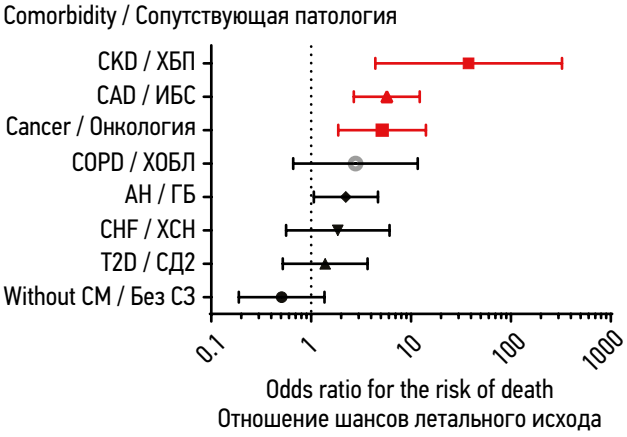

Fig. 1. Forest graph showing the relationship of various comorbidities with the risk of death. Groups of comorbidity with the highest odds ratios are highlighted in red. CKD — chronic kidney disease; CAD — coronary artery disease; COPD — chronic obstructive pulmonary disease; AH — arterial hypertension; CHF — congestive heart failure; T2D — type 2 diabetes; CM — comorbidity

Рис. 1. Форест-график, отражающий связь между наличием сопутствующих заболеваний и риском летального исхода. Красным выделены группы сопутствующей патологии с наибольшим значением отношения шансов. ХБП — хроническая болезнь почек; ИБС — ишемическая болезнь сердца; ХОБЛ — хроническая обструктивная болезнь легких; ГБ — гипертоническая болезнь; ХСН — хроническая сердечная недостаточность; СД2 — сахарный диабет 2-го типа; СЗ — сопутствующие заболевания

Laboratory data were analyzed to assess the prognosis of disease outcomes based on which significant differences were revealed between patients who died from COVID-19 and those who survived (Table 2). Thus, among patients with unfavorable disease outcomes, leukocytosis was significantly more frequent [26 patients (72%) versus 55 (28.9%); $p < 0.001$] and lymphopenia [25 (69.4%) patients versus 69 (36%); $p < 0.001$]. The average number of leukocytes and neutrophils in patients who died was significantly higher, and the average number of lymphocytes and platelets was significantly lower than in patients who recovered (Table 2). Also, there was a significant difference between the levels of several biochemical and coagulation parameters. Thus, it should be noted that in 16 (44%) of 36 deceased patients and 53 (27%) of 190 recovered patients, the D-dimer concentration was higher than 1000 ng/ml. The blood content of C-reactive protein and ferritin in deceased patients was significantly higher than in the recovered group (60 vs. 144 mg/l and 605 vs. 1243 μg/l, respectively).

Pro-inflammatory markers and cytokines

The concentrations of IL-2, IL-1b, and TNFα in patients with pneumonia were significantly higher than in healthy donors, but no differences were found between the deceased and surviving patients. In most patients with pneumonia, the concentrations of IFNγ and IFNα were undetectable. In deceased patients, increased blood concentrations of IL-6, IL-10, and IL-18 were more often observed than in recovered patients (Fig. 2*b–d*). At the same time, the level of IL-6 directly correlated with the degree of respiratory failure ($R = 0.49$, $p < 0.00001$), NEWS clinical scales ($R = 0.32$, $p < 0.001$), and SOFA ($R = 0.35$, $p < 0.0001$). In addition, the blood concentration of IL-18 was positively associated with the degree of respiratory failure ($R = 0.32$, $p < 0.001$), the

Table 2. Laboratory indicators of patients recovered from COVID-19 and patients with fatal outcomes

Таблица 2. Лабораторные показатели выздоровевших пациентов с COVID 19 и у больных с летальным исходом

Laboratory parameters	Recovery	Death	*p*
General clinical			
Platelets, $\times 10^9$/l (150–400)	257 (168–347)	215 (126.5–287.3)	<0.05
Leukocytes, $\times 10^9$/l (4.00–8.80)	7.16 (4.99–10.43)	12.89 (9.76–16.23)	<0.0001
Neutrophils, $\times 10^9$/l (2.20–4.80)	5.6 (3.32–8.87)	11.64 (7.45–14.11)	<0.0001
Lymphocytes, $\times 10^9$/l (1.2–2.5)	1.00 (0.8–1.6)	0.7 (0.42–1.4)	<0.05
Biochemical			
Glucose, mmol/l (3.90–6.10)	6.8 (6.05–8.05)	8.5 (6.85–11.85)	<0.0001
Lactate dehydrogenase, U/l (0.0–248.0)	351 (262–467)	591 (391–891)	<0.0001
Creatinine, μmol/l (53–115)	87 (76–102)	116 (82–226)	<0.0001
Creatine Glomerular filtration rate, ml/min/1.73 m^2 (>90)	72 (60–85)	34 (12.45–64.50)	<0.0001
Coagulation			
Prothrombin time, sec (11.5–14.5)	11.6 (11–12.65)	13 (12–14)	<0.001
Activated partial thromboplastin time, sec (27.0–37.0)	32 (28.4–36)	37 (30–53.6)	<0.001
D-dimer, ng/ml (<500)	812 (473–1451)	3096 (627.3–9422)	<0.001
C-reactive protein, mg/l (0.01–5.00)	60 (19.67–135.9)	144 (50.20–244)	<0.0005
Ferritin, μg/l (23.9–336.0)	605 (339.5–1074)	1243 (758–2113)	<0.0001

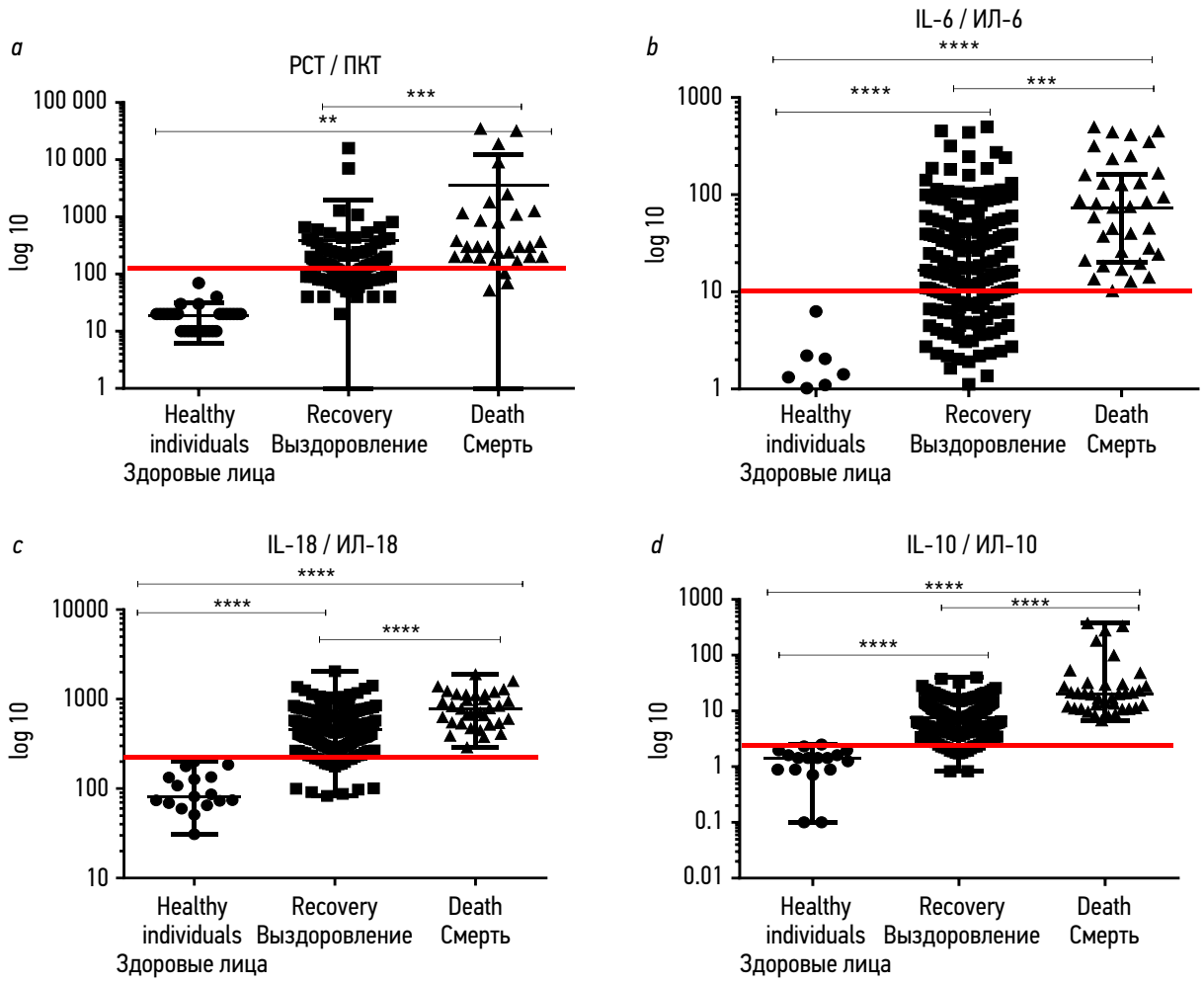

Fig. 2. Concentration of interleukin 6, interleukin 18, interleukin 10, procalcitonin in the healthy individuals, recovered and the deceased patients with COVID-19-associated pneumonia. IL-6 — interleukin 6, IL-18 — interleukin 18, IL-10 — interleukin 10, PCT — procalcitonin

Рис. 2. Концентрация интерлейкина-6, интерлейкина-18, интерлейкина-10, прокальцитонина у здоровых лиц, выздоровевших и умерших пациентов с COVID-19-ассоциированной пневмонией. ИЛ-6 — интерлейкин-6, ИЛ-18 — интерлейкин-18, ИЛ-10 — интерлейкин-10, ПКТ — прокальцитонин

Table 3. Cytokine storm scale

Таблица 3. Показатели шкалы цитокинового шторма

Serum biomarkers	0 points	1 point	2 point	3 point
	norm	threshold	threshold	threshold
IL-6, pg/ml	0–10	10–40	40–100	>100
IL-18, pg/ml	0–300	300–650	650–1000	>1000
IL-10, pg/ml	0–5	5–10	10–30	>30
PCT, ng/ml	0–0.25	0.25–0.99	1.0–2.0	>2.0

Note. IL-6 – interleukin-6; IL-18 – interleukin-18; IL-10 – interleukin-10; PCT – procalcitonin.

Table 4. Parameters of ROC curve analysis

Таблица 4. Параметры результатов анализа ROC-кривой

Marker	Area under the curve	*p*	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Threshold value, pg/ml
PCT	0.8156 (0.6870–0.9441)	<0.0001	68.75 (41.34–88.98%)	89.22 (81.52–94.49%)	0.3250
IL-6	0.7248 (0.6338–0.8159)	<0.0001	51.35 (34.40–68.08%)	82.98 (76.83–88.06%)	71.31
IL-18	0.7806 (0.7016–0.8596)	<0.0001	64.71 (46.49– 80.25%)	78.19 (71.60–83.87%)	657.9
IL-10	0.8485 (0.7900–0.9070)	<0.0001	86.49 (71.23–95.46%)	70.2 (163.13–76.65%)	10.63
CS scale	0.9023 (0.8455–0.9592)	<0.0001	83.33 (62.62–95.26%)	84.82 (76.81–90.90%)	6

Note. IL-6 – interleukin-6; IL-18 – interleukin-18; IL-10 – interleukin-10; PCT – procalcitonin; CS scale – cytokine storm scale.

degree of lung damage according to the results of computed tomography ($R = 0.26$, $p < 0.001$), NEWS scale ($R = 0.28$, $p < 0.001$), and SOFA scale ($R = 0.35$, $p < 0.0001$). Also, IL-10 correlated with the SOFA scale ($R = 0.33$, $p < 0.001$).

Procalcitonin is also an inflammatory mediator closely related to cytokines. Procalcitonin levels exceeded normal values in 17 (47%) of 36 patients who died and in only 25 (13%) of 190 recovered patients (the norm is 0–0, 25 ng/ml, Fig. 2*a*). However, procalcitonin levels had a significant positive correlation with the degree of respiratory failure ($R = 0.45$; $p < 0.00001$).

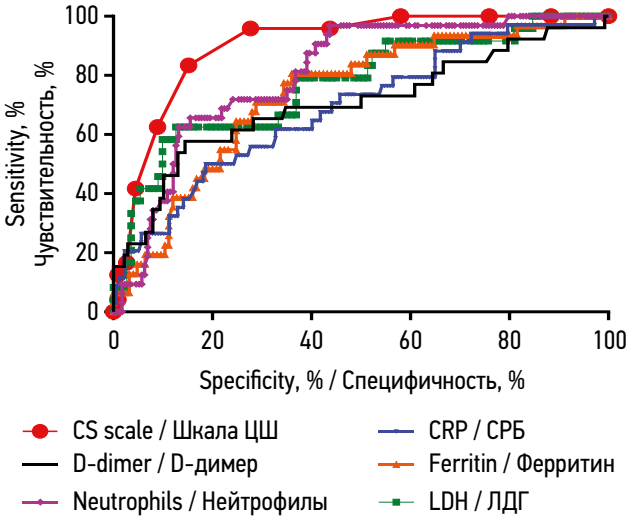

Fig. 3. ROC curves of the cytokine storm scale, C-reactive protein, lactate hydrogenase, ferritin, D-dimer, neutrophils for predicting the critical course of COVID-19. CS — cytokine storm; CRP — C-reactive protein; LDH — lactatdehydrogenase

Рис. 3. ROC-кривые шкалы цитокинового шторма, С-реактивного белка, лактатдегидрогеназы, ферритина, D-димера, нейтрофилов для прогнозирования критического течения COVID-19. ЦШ — цитокиновый шторм; СРБ — С-реактивный белок; ЛДГ — лактатдегидрогеназа

Cytokine storm scale

Since the indicators of IL-6, IL-10, IL-18, and procalcitonin were associated with the severity of the disease and death, they were integrated into a 12-point scale, the CS scale. The concentration ranges of IL-6, IL-18, IL-10, procalcitonin, and the corresponding points are presented in Table 3. The thresholds for these ranges were established based on ROC analysis. The cut-off values between low and medium levels were determined based on the studied laboratory parameter concentrations and characterized by a sensitivity of 60% and a specificity of 75%. In contrast, the values between the medium and high levels were characterized by a sensitivity of 40% and a specificity of 90%.

The CS scale is a 12-point scale that includes different levels of IL-6, IL-18, IL-10, and procalcitonin (Table 3). Scores from 1 to 3 correspond to normal, borderline, medium, and high levels of these biomarkers. Patients with scores of 6 or more have a high risk of an unfavorable disease outcome. According to ROC analysis, the area under the curve for the CS scale was greater than for each of the four markers separately [AUC 0.90 (95% confidence interval {CI} 0.8455–0.9592), $p < 0.001$] (Table 4). Other ROC analysis results include the area under the curve for IL-6, IL-10, IL-18, procalcitonin, sensitivity, specificity, and cut-off values (Table 4).

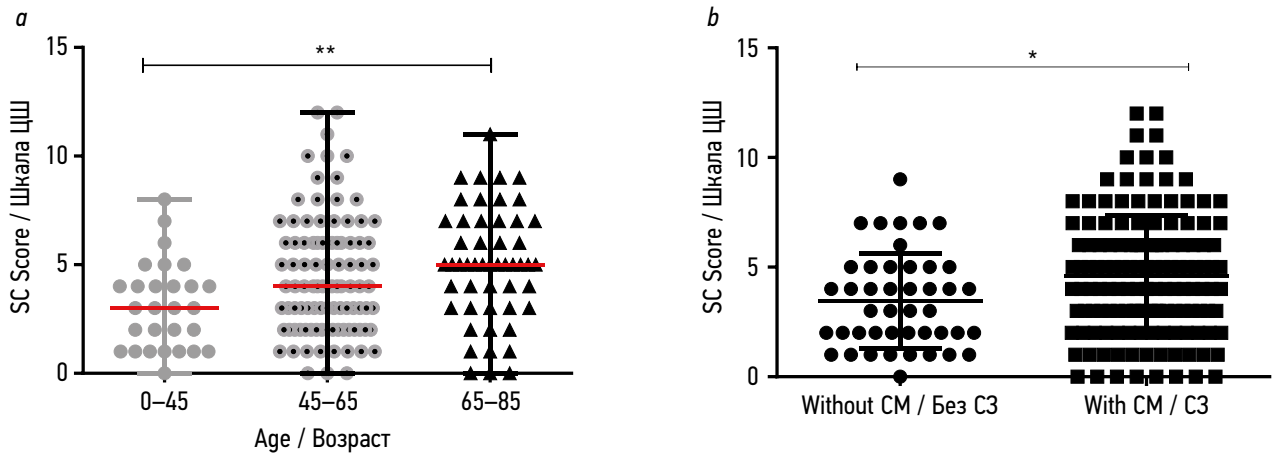

Fig. 4. Cytokine storm scale and age (*a*); Cytokine storm scale and comorbidity (*b*). CM — comorbitidies; CS — cytokine storm

Рис. 4. Индекс цитокинового шторма у пациентов различных возрастных групп (*a*); индекс цитокинового шторма у пациентов с сопутствующими заболеваниями и без таковых (*b*). С3 —сопутствующие заболевания; ЦШ — цитокиновый шторм

ROC curves of the levels of D-dimer, neutrophils, C-reactive protein, ferritin, and lactate dehydrogenase were constructed to compare the predictive value of the CS scale and other pro-inflammatory and general laboratory biomarkers (Fig. 3). The area under the curve was the largest for neutrophils and amounted to 0.8055 (0.7337–0.8772) with a sensitivity of 65.63% (range, 46.81% to 81.43%) and a specificity of 84.48% (range, 78.23% to 89.52%). For the diagnosis of critical COVID-19, the area under the curve for lactate dehydrogenase was 0.7712 (range. 0.6618 to 0.8806), for D-dimer – 0.7043 (range, 0.5793 to 0.8292). For such pro-inflammatory markers, such as C-reactive protein and ferritin, the area under the ROC curve was 0.6904 (0.5920 to 0.7889) and 0.739 (0.6456 to 0.8323), respectively.

For the CS index, a tendency to higher values was observed in persons of older age groups (Fig. 4*a*) and patients with concomitant diseases (Fig. 4*b*).

DISCUSSION

Predicting the course of COVID-19 infection is of fundamental importance for the timely and adequate distribution of efforts in the face of limited time and material resources caused by the massive admission of patients. A significant number of clinical algorithms and models have been proposed to solve this problem. Several studies have evaluated using previously developed clinical scales to assess the risk of developing a severe course, including the pneumonia severity index, scales for assessing the severity of pneumonia CURB-65 and CRB-65, A-DROP and SMART-COP, a scale for assessing the severity of the condition patient NEWS2, sequential assessment of organ failure qSOFA, and criteria for systemic inflammatory response syndrome [7]. Thus, the NEWS2 scale was superior to qSOFA and others in predicting the critical course of hospitalized patients [6]. New scales for assessing the severity of COVID-19 were also developed, based on demographic data, the presence of concomitant diseases, the results of instrumental studies, saturation data, and laboratory indicators [7]. A large-scale study of the informativeness of this approach was conducted in China. In this study, the area under the ROC curve of the clinical risk scale was 0.88 (95% CI, 0.85–0.91), with validation also 0.88 (95% CI 0.84–0.93). The American 10-point scale for assessing the severity of COVID-19, considering age, indicators of blood oxygen saturation, blood pressure, blood urea, C-reactive protein, and the value of the international normalized ratio, was characterized by similar prognostic indicators [8]. Despite the decisive role of cytokines and CS development, these data are not included in risk stratification algorithms because they are not performed as routine measurements in most clinical laboratories.

Several studies of cytokines in COVID-19 demonstrated that in patients with severe COVID-19 and those who died from this infection, the levels of cytokines, such as IL-1β, IL-2 and its soluble receptor, IL-6, IL-8, IL-17, IL-18, TNFα, chemoattractant protein of monocytes 1 (MCP1 or CCL2), inflammatory protein of macrophages 1-alpha (MIP-1α or CCL3), and anti-inflammatory cytokine IL-10, were significantly higher than in the group of patients with slighter forms of COVID-19 [1, 9]. At the same time, the blood levels of IL-2, IL-1b, TNFα, and IL-8 in patients with COVID-19-associated pneumonia were significantly higher than in healthy donors. However, no significant differences were found between deceased and surviving patients.

In COVID-19, the rapid expression of IFN type 1 is inhibited since many SARS-CoV2 proteins act as IFN antagonists. Antagonism of the interferon response promotes viral replication, which leads to an increase in the release of pyroptosis products, which can further induce aberrant inflammatory responses. It should be noted that the majority of patients in the study cohort had undetectable concentrations of IFNγ and IFNα, consistent with the data of other studies [21, 22].

The pro-inflammatory cytokine IL-6 is synthesized by T-lymphocytes, fibroblasts, endothelial cells, and monocytes. IL-6 is an essential mediator during the acute phase response in sepsis and other infections [10]. The level of this cytokine is increased in both severe and mild cases of COVID-19. In contrast, it is directly correlated with the volume of the affected lung tissue in patients with acute respiratory distress syndrome. Giofoni et al. (2020) showed that the predictive value of an IL-6 level of 25 pg/ml in the blood is an independent risk factor for the progression of severe COVID-19 [11]. In another study, IL-6 levels >80 pg/ml were associated with the need for mechanical ventilation [12]. In our study, the IL-6 level >71 pg/ml was an unfavorable factor regarding the risk of death.

Several studies found that the concentration of IL-18 in the blood significantly correlates with the severity of COVID-19 and damage to the vital organs [13]. It is noteworthy that the increase in blood levels of IL-18 due to the activation of NLRP3/inflammasome is characteristic of both COVID-19 and autoinflammatory diseases. In the cohort we studied, the concentration of IL-18 in deceased patients was significantly higher than in survivors. At the same time, the levels of IL-18 correlated with the severity of respiratory failure, the degree of lung damage according to computed tomography data, and indicators according to the NEWS and SOFA scales.

A unique feature of COVID-19 is an increase in IL-10 in patients with severe disease [15-17]. IL-10 is also one of the key cytokines in sepsis and systemic inflammatory processes. On the one hand, the induction of IL-10 synthesis at the initial stage of COVID-19 inhibits cellular immunity. On the other hand, as the production of endogenous IL-10 increases, it can stimulate the production of other CS mediators. In endotoxemia and sepsis, IL-10 can enhance the hyperinflammatory response [19]. According to the ROC analysis, our study results indicate that IL-10 is a more informative indicator of a poor prognosis in patients with COVID-19-associated pneumonia compared with other biomarkers.

Many studies have shown that elevated procalcitonin levels are significantly associated with the severity of COVID-19 [20-22]. It is assumed that the cascade of inflammatory reactions triggered by the coronavirus through the release of pro-inflammatory cytokines, such as IL-1b and IL-6, can induce the release of procalcitonin in patients even without bacterial coinfection. In the studied cohort, a procalcitonin level of 0.32 ng/ml or higher was recorded in almost half of the patients who died, confirming its high predictive value.

Among the limitations of this study, it is necessary to note the insufficient representativeness of the sample, which included only inpatients, the lack of validation of the CS index on an independent sample of COVID-19 patients, including the lack of direct comparisons with indicators on other risk assessment scales. Nevertheless, it seems important that our model confirms the role of excessive cytokine activation in the unfavorable course of COVID-19.

CONCLUSION

Thus, the CS scale has a reasonably high information content regarding the risk of an unfavorable prognosis of the COVID-19 course. The combination of the predictive capabilities of IL-6, IL-18, IL-10, and procalcitonin facilitates predicting mortality in COVID-19-associated pneumonia compared with isolated markers. In contrast, they are directly correlated with risk factors, such as age and the presence of comorbidities.

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