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Влияние коморбидных заболеваний на профили сигнальных биомаркеров (хемокина макрофагального происхождения, интерферон-γ-индуцируемого белка 10, растворимого CD40 лиганда и фактора роста сосудистого эндотелия) и тяжесть течения заболевания у пациентов с COVID-19: клинические исследования

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АННОТАЦИЯ

Обоснование. Анализ влияния коморбидных заболеваний на концентрацию биомаркеров поможет углубить понимание патогенетических механизмов воздействия коморбидных заболеваний на течение COVID-19 и помочь скорректировать прогностические модели ее терапии.

Цель исследования — изучить влияние коморбидных заболеваний на степень тяжести и исходы COVID-19, а также проанализировать уровни хемокина макрофагального происхождения, интерферон-γ-индуцируемого белка 10, растворимого CD40 лиганда и фактора роста сосудистого эндотелия у 472 пациентов с COVID-19 в зависимости от наличия различных форм коморбидной патологии.

Материалы и методы. В группе из 1648 пациентов с подтвержденной COVID 19 изучены концентрации биомаркеров. Оценены межгрупповые отличия (исход / тяжесть течения заболевания) в общей группе (1648 пациентов) и группе больных без коморбидной нагрузки (343 пациента) с индексом Charlson 2 балла и менее. Проанализированы 472 истории пациентов с COVID-19, определенными концентрациями исследуемых биомаркеров и коморбидной патологией, включенной в оценку по индексу Charlson. Для сравнения сформировано две выборки: опытная группа, состоящая из пациентов с COVID-19 и наличием определенного коморбидного заболевания, и контрольная группа, состоящая из пациентов, страдающих от COVID-19 без заданного коморбидного заболевания.

Результаты. Впервые получены данные, свидетельствующие о том, что при определенных коморбидных состояниях у больных COVID-19 уровни исследуемых биомаркеров значимым образом отличаются от показателей контрольной группы. Так, у пациентов с артериальной гипертензией (код I10–I15 по Международной классификации болезней 10-го пересмотра), хронической сердечной недостаточностью (I50.0), болезнями сосудистой системы (I70–I79), цереброваскулярными болезнями (I60–I69) и хронической болезнью почек (N17–N19) уровень хемокина макрофагального происхождения был достоверно ниже, чем у пациентов без данных заболеваний. При этом у больных COVID-19 с заболеваниями органов дыхания (J40–J47) уровни интерферон-γ-индуцируемого белка 10 и фактора роста сосудистого эндотелия были достоверно ниже, чем у пациентов без заболеваний легких.

Заключение. В результате исследования получены достоверные данные, подтверждающие роль сигнальных биомаркеров в развитии тяжелых форм и летального исхода у пациентов с COVID-19, а также показано значимое влияние коморбидной патологии на течение новой коронавирусной инфекции.

Ключевые слова: коморбидные заболевания; биомаркер; хемокин макрофагального происхождения; интерферон-γ-индуцируемый белок 10; растворимый CD40 лиганд; фактор роста сосудистого эндотелия; тяжелое течение COVID-19.

Как цитировать
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The influence of comorbid diseases on the profiles of signaling biomarkers (macrophage-derived chemokine, interferon-γ-induced protein 10 kD, soluble CD40 ligand, vascular endothelial growth factor) and severity in patients with COVID-19: clinical studies

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ABSTRACT

BACKGROUND: Analysis of the effect of comorbid diseases on the concentration of biomarkers will help to deepen the understanding of the pathogenetic mechanisms of the impact of comorbid diseases on the course of COVID-19 and adjust prognostic models for its therapy.

AIM: To study the impact of comorbid diseases on the severity and outcomes of COVID-19. In addition, an analysis of the levels of macrophage-derived chemokine, interferon-γ-induced protein 10 kD, soluble CD40 ligand, vascular endothelial growth factor has been carried out in 472 patients with COVID-19, depending on the presence of various forms of comorbid pathology.

MATERIALS AND METHODS: To study the concentration of biomarkers an analysis has been conducted in a group of 1648 patients with confirmed COVID-19. The study assessed intergroup differences (disease outcome/severity of disease) in the general group (1648 patients) and in the group of patients without comorbidity (343 patients) — Charlson index less than 2 points. 472 medical histories of patients with COVID-19 have been analyzed, including with certain concentrations of the studied biomarkers and comorbid pathology included in the Charlson Index. For comparison, two samples have been formed: an experimental group consisting of patients with COVID-19 and the presence of a certain comorbid disease and a control group consisting of patients suffering from COVID-19 without a specified comorbid disease.

RESULTS: For the first time, data has been obtained indicating that patients with COVID-19 have comorbid conditions with the levels of the studied biomarkers differing significantly from the indicators of the control group. Thus, in patients with arterial hypertension (I10–I15 according to the International Classification of Diseases, 10th revision), chronic heart failure (I50.0), diseases of the vascular system (I70–I79), cerebrovascular diseases (I60–I69), chronic kidney disease (N17–N19), the level of the macrophage-derived chemokine biomarker was significantly lower than in the patients without these diseases. At the same time, in the COVID-19 patients with respiratory diseases (J40–J47), the levels of interferon-γ-induced protein 10 kD and vascular endothelial growth factor were significantly lower than in the patients who did not have lung diseases.

CONCLUSIONS: The study findings obtained have confirmed the role of signaling biomarkers in the development of severe forms and death in patients with COVID-19. Significant influence of comorbid pathology on the course of the new coronavirus infection has been shown.

Keywords: comorbid diseases; biomarker; macrophage-derived chemokine; interferon-γ-induced protein 10 kD; soluble CD40 ligand; vascular endothelial growth factor; severe COVID-19.

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BACKGROUND

The severity of COVID-19 significantly increases in the presence of certain comorbidities. Studies have shown that patients with complicated cardiovascular diseases, type 2 diabetes mellitus, metabolic syndrome, chronic kidney disease with advanced stages of chronic renal failure, and systemic autoimmune diseases [1–4] have an unfavorable prognosis when infected with COVID-19. Patients with COVID-19 admitted to the intensive care unit (ICU) are twice as likely to have comorbidities (72%) than patients who do not require intensive care (37%) [5, 6]. A meta-analysis of 42 studies involving 98,714 patients with COVID-19 showed that 61% of those with comorbidities required ICU hospitalization. Among the mortalities, 77% had multiple comorbidities. Multicenter studies from 2020 to 2021 have convincingly demonstrated that comorbid chronic diseases increase the mortality rate of patients with COVID-19 ($p < 0.001$) [7–8].

During COVID-19, the immune system becomes hyperactive, leading to a significant increase in proinflammatory cytokines. This phenomenon can result in a cytokine storm, causing systemic inflammation, hyperferritinemia, acute respiratory distress syndrome, impaired hemodynamics, thrombosis with disseminated intravascular coagulation, multiorgan failure, and a very poor prognosis. The literature suggests that vascular endothelial growth factor (VEGF), soluble CD40 ligand (sCD40L), interferon-γ-inducible protein 10 (IP-10 or CXCL10), fractalkine (CX3CL1), and macrophage-derived chemokine (MDC) are important biomarkers for characterizing the antiviral response, inflammation intensity, and thrombosis associated with SARS-CoV-2 infection.

VEGF exerts angiogenic and antiapoptotic effects on endothelial cells. Given that SARS-CoV-2 frequently causes endothelial dysfunction, acute respiratory distress syndrome, and systemic hypoxia, VEGF may play a significant role in the clinical manifestations of COVID-19 [11]. C.R.P. Moraes et al. confirmed that the destruction of the endothelial barrier is important in the pathogenesis of acute lung injury in COVID-19. The magnitude of this effect is proportional to disease severity and circulating VEGF levels [12].

Multiple studies have demonstrated a direct correlation between endothelial damage and platelet activation in patients with COVID-19. This phenomenon is due to the release of various bioactive molecules, including sCD40L, expressed by immune system cells, particularly activated $CD4^+$ T-lymphocytes and platelets [13, 14]. Low sCD40L levels indicate a slow and weak antiviral response [15]. Meanwhile, high sCD40L levels are associated with thrombosis and increased disease severity in patients with COVID-19 [16, 17]. These findings suggest that sCD40L plays a significant role in the COVID-19 pathogenesis, which is consistent with the discovery of A. Gupta et al. [2] that SARS-CoV-2 activates endothelial and platelet cells, leading to the progression of COVID-19 to a severe stage.

CXCL10 is secreted by T cells, neutrophils, monocytes, and endothelial cells and is involved in the SARS-CoV-2 clearance. This cytokine acts as an inflammatory mediator, promoting leukocyte recruitment to inflammatory foci and contributing to the inflammatory damage of various organs and tissues [18, 19]. The decline in the overall health of patients with COVID-19, leading to the development of acute respiratory distress syndrome, is frequently linked to a consistently high IP-10 level [20, 21]. Specifically, the IP-10 level is an independent predictor of mortality in patients admitted to the ICU [22].

CX3CL1 plays a crucial role in the recruitment and activation of inflammatory cells. Its overexpression leads to recruiting immune cells expressing CX3CR1, such as monocytes and cytotoxic T-lymphocytes, and initiating the inflammatory process in various organs and tissues [23]. In patients with COVID-19, a moderate increase in serum CX3CL1 levels is typically observed in mild cases. However, in severe cases, its production increases dramatically [24]. Fractalkine promotes vascular thrombosis through platelet activation [25].

MDC/CCL22 [26] is expressed by monocytes and macrophages due to various pathogens, stimulating adaptive immune cells. Interaction with dendritic cells is necessary for the immunosuppressive function of regulatory T cells (Tregs). Decreased MDC-dependent interaction of dendritic cells with Tregs enhances inflammation [27]. The genetic deficiency of MDC creates conditions that decrease tolerance to infectious agents and increase the risk of immunoinflammatory diseases. MDC/CCL22 is considered a significant biomarker for predicting COVID-19 severity at early (up to 7 days) and late (8–12 days) disease stages. The MDC concentration in the blood of patients with severe and extremely severe COVID-19 is significantly lower than in those with mild COVID-19. In addition, its production decreases as the disease progresses, showing a significant negative correlation with changes in the IP-10 level [28–30].

The significance of this study lies in analyzing the effect of comorbidities on the COVID-19 course and the concentration of biomarkers involved in the formation of the inflammatory process. This analysis can expand existing knowledge about the mechanisms of their effect and aid in the development of informative prognostic markers for the course of COVID-19.

Herein, we **aimed** to investigate how comorbidities affect biomarker concentrations in patients with severe COVID-19.

MATERIALS AND METHODS

In this observational clinical trial, the researchers analyzed 1,648 case histories of patients with COVID-19 treated at City Hospital No. 40 in St. Petersburg between April 18, 2020 and November 21, 2020. The examined patients had a positive test result for the presence of SARS-CoV-2 RNA by nucleic-acid amplification polymerase chain reaction, as well as clinical manifestations and symptoms such as fever, general weakness and malaise, cough, and dyspnea. Changes in the viral pneumonia type were noted in patients during computed tomography (CT) of the lungs without intravenous contrast enhancement. The changes were predominantly bilateral in the lower lobe and peripheral and had a perivascular, multilobular characteristic. Numerous peripheral consolidations as rounded "frosted glass" and of different extents, flattening of the interdilol interstitium as "cobblestone sidewalk," areas of consolidation, and air bronchogram symptoms were observed.

All patients underwent the following:

- Anamnestic data collection with clarification of the peculiarities of the disease course
- Objective examination with the evaluation of hemodynamic and respiratory system parameters, including respiratory rate, heart rate, blood pressure, blood oxygen saturation, and degree of respiratory failure
- The National Early Warning Score, a scale recommended for use in patients with COVID-19 [32]
- Chest CT scan to evaluate the disease using a four-digit scale (CT-1, -2, -3, or -4)
- Laboratory tests (clinical blood analysis, biochemical minimum, and determination of ferritin, C-reactive protein, interleukin-6, D-dimer, and lactate dehydrogenase activity levels)
- Electrocardiography
- Additional instrumental techniques (if necessary)

All patients provided informed and voluntary consent to participate in the study, which was approved by the ethics review board of City Hospital No. 40 (Protocol No. 171 of May 18, 2020). The study objectives were fulfilled using biomaterials from the biobank collection of City Hospital No. 40.

The concentration of cytokines in the samples was determined using a customized panel (Merck, Millipore) and multiplex immunofluorescence analysis based on the xMap platform (Luminex). The quantification range of the method was 1–10,000 pg/mL. The panel consisted of sCD40L, MDC, fractalkine, IP-10, and VEGF. Frozen serum samples were used, and sample preparation and analysis were performed according to the manufacturer's instructions. Data on comorbidities were obtained from anamnesis.

The study analyzed the groups in several stages. The study evaluated intergroup differences among 1,648 patients and patients without comorbid burden, which consisted of 343 patients with a Charlson index score of <2 points. The study analyzed 472 patient histories of COVID-19, including the concentrations of the investigated biomarkers and comorbid pathology as defined by the Charlson index score. Two samples were compared: an experimental sample of patients with COVID-19 and a defined comorbidity and a control sample of patients with COVID-19 but without a defined comorbidity.

Statistical data processing

The normality of the sample distribution was assessed using the Shapiro–Wilk test. Differences between groups were identified using the Mann–Whitney U test. Regression models were constructed to differentiate the influence of comorbidities, age, and sex, with the presence/absence of the comorbidities under study, age, and sex as independent variables. Logistic regression was used to predict disease severity and outcome. The odds ratio was used for post hoc analysis. Akaike's information criterion was used to select the best model. Statistical tests deemed the difference between samples reliable at $p < 0.05$.

Data processing and visualization were performed using version 4.1.3 of the R programing language.

RESULTS

A total of 1,648 case histories of patients with COVID-19 with blood biosamples were analyzed. The demographic data of the study group, distributed by disease severity according to the criteria of the temporary methodological recommendations for the diagnosis and treatment of new coronavirus infection, are presented in Table 1.

Of the 1,648 patients, 343 had no significant comorbidity burden based on their Charlson comorbidity index score (excluding age) not exceeding 2. Table 2 presents the corresponding statistics on the sex and age composition of the groups.

Table 3 presents data on the concentrations of the investigated biomarkers for patient groups categorized by the severity of COVID-19, in addition to significant differences in MDC, sCD40L, and IP-10 concentrations between the severe and other groups. The p-value for the difference in MDC and IP-10 concentrations was very high ($p < 0.0001$), whereas the difference in sCD40L levels was also significant but to a lesser extent ($p = 0.0003$) than the former. In patients with a Charlson comorbidity index score of ⩽2, the difference in sCD40L levels disappeared ($p = 0.9$). However, the difference persisted for IP-10 ($p < 0.0001$); the difference in MDC levels disappeared but remained close to the level of statistical significance ($p = 0.07$).

Table 4 presents the data on the concentrations of biomarkers in groups distinguished by disease outcomes.

The biomarker concentrations showed similar differences between groups of disease severity for different disease outcomes. In the main group, MDC, sCD40L, and IP-10 concentrations exhibited significant differences between surviving and deceased patients ($p < 0.0001$). The same differences, except for sCD40L data, were observed in patients with a Charlson comorbidity index score of ⩽2. The study analyzed the medical records of 472 patients with COVID-19, including their biomarker concentrations and comorbidities measured by the Charlson index score.

Table 5 presents the demographic data and distribution by severity of the COVID-19 course in the study cohort. The data

Table 1. Demographic data of patients with COVID-19 distributed by disease severity

Таблица 1. Демографические данные пациентов с COVID-19 с распределением по степени тяжести течения заболевания

Group	Total, *n*	Men, *n*	Women, *n*	Age (total), M ± SD, years	Age (men), M ± SD, years	Age (women), M ± SD, years
Distribution of cases by disease outcome						
Deceased	302	154	147	74.7 ± 11.3	73 ± 11.2	76.4 ± 11.2
Survivors	1346	652	693	61.8 ± 15.4	59.4 ± 14.7	64.1 ± 15.6
Distribution of disease severity						
Mild	33	21	12	52.2 ± 16.6	54.3 ± 16.6	48.7 ± 16.6
Moderate	868	395	473	61.1 ± 15.8	58.5 ± 15.1	63.3 ± 16
Severe	746	391	355	68.3 ± 14	65.8 ± 14.1	70.9 ± 13.6

Note. M ± SD indicates the mean and standard deviation.

Table 2. Demographic data of patients with COVID-19 classified by outcomes and disease severity in a subgroup of patients with Charlson comorbidity index of ⩽2 points

Таблица 2. Демографические данные пациентов с COVID-19, выделенных по исходам и тяжести течения заболевания, в подгруппе пациентов с индексом коморбидности Charlson 2 балла и менее

Group	Total, *n*	Men, *n*	Women, *n*	Age (total), M ± SD, years	Age (men), M ± SD, years	Age (women), M ± SD, years
Distribution of cases by disease outcome						
Deceased	23	15	8	68.2 ± 13.4	67.3 ± 14.9	70 ± 10.6
Survivors	320	137	183	56.2 ± 14.8	53.7 ± 13.7	58.1 ± 15.4
Distribution of disease severity						
Mild	12	6	6	50.8 ± 15.9	51.5 ± 13.6	50.2 ± 19.2
Moderate	237	96	141	56.7 ± 15.3	54.6 ± 14.2	58.1 ± 15.9
Severe	94	50	44	58.8 ± 14.2	56.3 ± 14.9	61.6 ± 12.9

Note. M ± SD indicates the mean and standard deviation.

Table 3. Concentrations of the studied biomarkers in patients categorized by COVID-19 severity

Таблица 3. Концентрации исследуемых биомаркеров в группах пациентов, выделенных по тяжести течения COVID-19

Biomarkers	Sample	Mild severity	Moderate severity	Severe course	*p*
Fractalkine, pg/mL	Total	0 (0–95.6)	0 (0–49.9)	11.4 (0–57.3)	0.16
	Noncomorbid	6.7 (0–118.1)	0 (0–41.2)	0 (0–32.1)	$p = 1$
MDC, pg/mL	Total	652.4 (566.6–863.6)	594.4 (404.2–883.8)	457.6 (292.5–710.7)	$p < 0.001$
	Noncomorbid	568 (489.5–637.7)	536 (345.8–791.9)	447.8 (292.8–726.3)	$p < 0.001$
sCD40L, pg/mL	Total	5809.4 (3414–9432)	5694 (3114.7–9635.1)	4901.7 (2255.5–8096.7)	$p < 0.003$
	Noncomorbid	5038.4 (3038.9–8433.1)	5104.4 (3002.5–10,000)	5599.7 (3137.9–8756.2)	$p = 0.27$
IP-10, pg/mL	Total	728.9 (282.8–2157)	1151.8 (456.7–2226)	1887.7 (640.5–3419)	$p < 0.001$
	Noncomorbid	1543.4 (416.9–2383.8)	1292.4 (489.9–2524.2)	2481.2 (1220–3771.3)	$p < 0.001$
VEGF, pg/mL	Total	99 (29.5–217.8)	128.8 (52.3–270.5)	131.7 (48–277.3)	$p = 0.32$
	Noncomorbid	131.5 (30.8–315.6)	113.9 (34.2–249.1)	98.5 (35.4–233)	$p = 0.35$

Note. Data are presented as the median with the interquartile range. IP-10, interferon-γ-inducible protein 10; MDC, macrophage-derived chemokine; sCD40L, soluble CD40 ligand; VEGF, vascular endothelial growth factor.

Table 4. Concentrations of the studied biomarkers in patient groups categorized by disease outcomes

Таблица 4. Концентрации исследуемых биомаркеров в группах пациентов, выделенных по исходам заболевания

Biomarkers	Sample	Survivors	Deceased	*p*
Fractalkine, pg/mL	Total	0 (0–54.5)	9.8 (0.0–56.1)	$p = 0.5$
	Noncomorbid	0 (0.0–31.9)	0 (0.0–34.9)	$p = 0.73$
MDC, pg/mL	Total	578.6 (381.3–856.9)	367.9 (238.5–547.3)	$p < 0.001$
	Noncomorbid	527.9 (334.9–780.3)	308.7 (223.3–383.3)	$p < 0.001$
sCD40L, pg/mL	Total	5622.9 (2988.1–9147.9)	4112.2 (1807.9–7257.8)	$p < 0.001$
	Noncomorbid	5352.3 (2802.5–7988.0)	6673.5 (3381.5–10,000.0)	$p = 0.25$
IP-10, pg/mL	Total	1293.7 (484.8–2497.5)	2278.6 (747.1–4229.2)	$p < 0.001$
	Noncomorbid	2271.1 (1098.7–3444.9)	3497.7 (1948.7–4754.3)	$p = 0.06$
VEGF, pg/mL	Total	128.9 (49.5–267.6)	132.4 (47.2–282.2)	$p = 0.72$
	Noncomorbid	87 (30.5–215)	175.3 (49.0–382.2)	$p = 0.13$

Note. Data are presented as the median with the interquartile range. IP-10, interferon-γ-inducible protein 10; MDC, macrophage-derived chemokine; sCD40L, soluble CD40 ligand; VEGF, vascular endothelial growth factor.

Table 5. Demographic data and distribution by COVID-19 severity in the studied cohort

Таблица 5. Взаимосвязи между гендерными различиями и степенями тяжести течения заболевания у пациентов с COVID-19

Patient group	Total, *n*	Men, *n*	Women, *n*	Mean age, M ± SD, years
Moderate severity	170	90	80	54.8 ± 14.0
Severe course	255	164	91	53.2 ± 12.5

Note. M ± SD indicates the mean and standard deviation.

Table 6. Demographic data and outcomes of COVID-19 in the studied cohort

Таблица 6. Гендерные различия и исходы COVID-19 у исследуемой когорты пациентов

Outcome	Total, *n*	Men, *n*	Women, *n*	Mean age, M ± SD, years
Survivors	279	178	101	54.3 ± 12.9
Deceased	75	47	28	61.0 ± 12.4

Note. M ± SD indicates the mean and standard deviation.

Table 7. Demographic data and comorbidities of patients in the studied cohort

Таблица 7. Демографические данные и коморбидные заболевания пациентов исследуемой когорты

Disease	Total, *n* (%)	Men, *n*	Women, *n*	Age (total), M ± SD, years	Age (men), M ± SD, years	Age (women), M ± SD, years
Hypertension	170 (36)	100	70	59.9 ± 9.6	58 ± 10.3	62.7 ± 8
Myocardial infarction	37 (8)	29	8	67.5 ± 9.1	67.3 ± 9.6	68.1 ± 7.1
Congestive heart failure	108 (23)	70	38	65.1 ± 9.2	65.2 ± 9.8	64.9 ± 8.2
Peripheral arterial disease*	59 (12)	37	22	64.7 ± 8.9	64.4 ± 10.3	65.2 ± 6
Cerebrovascular disease	113 (24)	69	44	66.3 ± 9.2	66.1 ± 10.2	66.6 ± 7.5
Dementia	3 (0.6)	3	0	72.7 ± 7.4	72.7 ± 7.4	–
Chronic pulmonary disease	36 (8)	21	15	58.8 ± 12.4	58.5 ± 11.7	59.1 ± 13.7
Connective tissue disease	21 (5)	6	15	60 ± 8.6	61.2 ± 6.9	59.5 ± 9.3
Peptic ulcer	24 (5)	15	9	61.4 ± 10.6	61.8 ± 11.1	60.7 ± 10.3
Diabetes mellitus	61 (13)	34	27	60.6 ± 9.9	59 ± 10.6	62.7 ± 8.7
Chronic kidney disease	36 (8)	24	12	62.4 ± 12	62 ± 13.3	63.1 ± 9.3
Malignant neoplasm	14 (3)	5	9	70.6 ± 7	73.4 ± 6.9	69 ± 7

*Intermittent claudication or bypass surgery for chronic arterial insufficiency, history of gangrene or acute arterial insufficiency, or untreated thoracic or abdominal aneurysm of ≥6 cm.

suggest that severe COVID-19 was more prevalent in men (n = 164) than in women (n = 91), despite no significant difference in mean age between the study groups (54.8 and 53.2 years in patients with moderate and severe COVID-19, respectively).

Table 6 summarizes the sex differences in COVID-19 outcomes among the study cohort. The mean age of the survivor and deceased groups differed significantly (53.3 and 61.2 years in the survivor and deceased groups, respectively; Welch's t-test of 4.1; p = 0.000072). Table 7 presents the demographic data and comorbidities of the patients in the study cohort.

Table 7 shows the prevalence of comorbidities in patients with COVID-19, with hypertension being the most common (36%), followed by cerebrovascular disease (24%), congestive heart failure (23%), and diabetes mellitus (13%). The proportion of patients with ongoing myocardial infarction (8%) may be related to the focus of the COVID-19 diagnostic and treatment service on providing emergency care, including high-tech care, to patients with myocardial infarction and a positive test result for the presence of SARS-CoV-2 RNA by polymerase chain reaction.

The study group had a mean Charlson comorbidity index score of >3 points (range 1–5 points), indicating a high frequency of comorbidities (Fig. 1).

Table 8 shows the codes of the studied comorbidities according to the international classification of diseases, 10th revision.

Table 9 shows the laboratory and clinical data on the concentrations of the investigated biomarkers in the study and control groups of patients with COVID-19.

Table 9 presents only the results that show significant differences or trends toward significance. The study group in this table comprised patients with comorbidities,

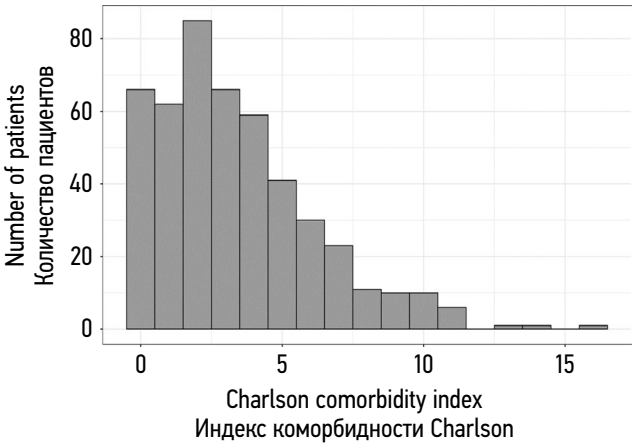

Fig. 1. Charlson Index indicators in the studied group
Рис. 1. Показатели индекса Charlson в исследуемой группе

whereas the control group consisted of patients without these comorbidities. The presented data show that patients with comorbidities, such as hypertension, cerebrovascular disease, peripheral arterial disease, and congestive heart failure, had significantly lower concentrations of MDC (306 vs. 504 pg/mL; $p < 0.0001$, 304 vs. 389 pg/mL; $p = 0.0002$, 287 vs. 373 pg/mL; $p < 0.0008$, and 308 vs. 378 pg/mL; $p = 0.0045$, respectively). In addition, MDC levels tended to be higher in the control group of patients with chronic kidney disease ($p = 0.086$).

Figure 2 shows the MDC level spread diagram of patients in the study groups with and without cerebrovascular disease.

Significant differences were observed in the IP-10 levels ($p < 0.0386$) between the study and control groups. In addition, VEGF levels tended to be high in the control group ($p < 0.0558$) of patients with COVID-19 and chronic pulmonary disease. Patients with chronic pulmonary disease

Table 8. International classification of diseases, 10th revision codes for comorbid conditions
Таблица 8. Коды коморбидных заболеваний по Международной классификации болезней 10-го пересмотра

Group	Name	Code
Hypertension	Diseases characterized by high blood pressure	I10–I15
Myocardial infarction	Ischemic heart disease	I20–I25
Congestive heart failure	Congestive heart failure	I50.0
Peripheral arterial disease	Diseases affecting the arteries, arterioles, and capillaries	I70–I79
Cerebrovascular disease	Cerebrovascular diseases	I60–I69
Dementia	Dementia in Alzheimer's disease Dementia in other diseases classified under other headings	F00, F02
Chronic pulmonary disease	Chronic diseases of the lower respiratory tract	J40–J47
Connective tissue disease	Systemic lesions of the connective tissue	M30–M36
Peptic ulcer	Diseases of the esophagus, stomach, and duodenum	K20–K31
Diabetes mellitus	Diabetes mellitus	E10–E14
Chronic kidney disease	Renal failure	N17–N19
Malignant neoplasm	Malignant neoplasms	C00–C97

Table 9. Concentrations of biomarkers in the experimental and control groups of patients with COVID-19 categorized by the presence or absence of comorbidities

Таблица 9. Концентрации биомаркеров в опытной и контрольной группах пациентов с COVID-19, выделенных по наличию или отсутствию коморбидного заболевания

Comorbidity	Biomarker, unit of measurement	Control group	Study group	*p*
Hypertension	MDC, pg/mL	504 (236–673)	306 (172–486)	$p < 0.0001$
Congestive heart failure	MDC, pg/mL	378 (198–600)	308 (174–430)	$p = 0.0045$
Peripheral arterial disease	MDC, pg/mL	373 (200–593)	287 (122–400)	$p = 0.0008$
Cerebrovascular disease	MDC, pg/mL	389 (201–619)	304 (164–414)	$p = 0.0002$
Renal failure	MDC, pg/mL	366 (201–563)	319 (126–413)	$p = 0.086$
Chronic pulmonary disease	IP-10, pg/mL	23,800 (1350–40,000)	3760 (620–40,000)	$p = 0.0386$
Chronic pulmonary disease	VEGF, pg/mL	277 (62.7–557)	121 (28–367)	$p = 0.0558$

Note. Data are presented as the median with the interquartile range. IP-10, interferon-γ-inducible protein 10; MDC, macrophage-derived chemokine; VEGF, vascular endothelial growth factor.

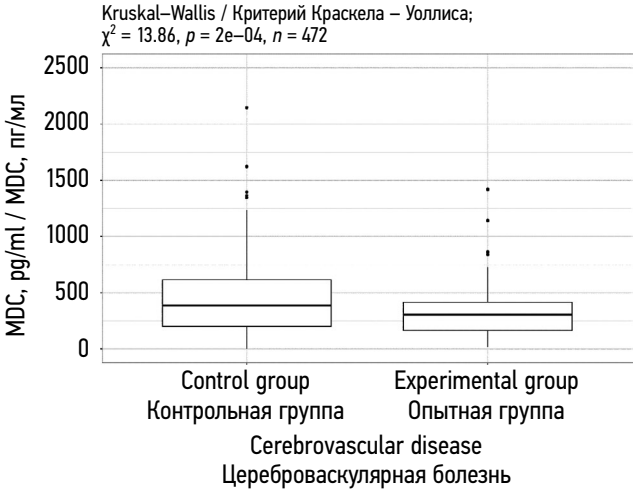

Fig. 2. Boxplot of macrophage-derived chemokine concentration in the studied groups (absence/presence of cerebrovascular disease history); *p*-value obtained using Mann–Whitney *U* test. MDC, macrophage-derived chemokine levels

Рис. 2. Диаграмма размаха уровня хемокина макрофагального происхождения в исследуемых группах с отсутствием/наличием цереброваскулярной болезни в анамнезе; значение *p* получено с использованием критерия Манна – Уитни. MDC — уровень хемокина макрофагального происхождения

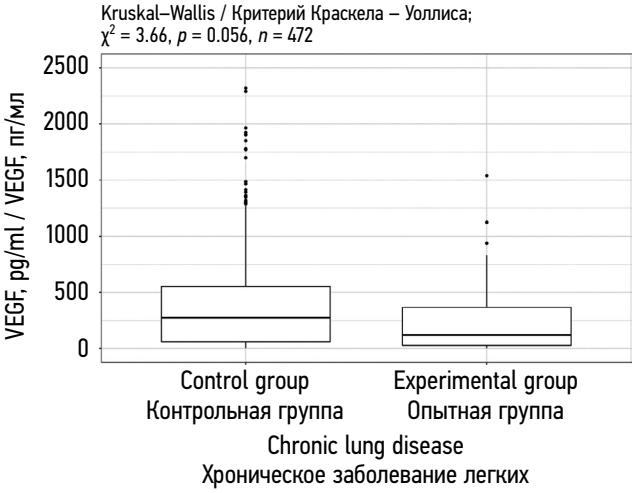

Fig. 3. Boxplot of vascular endothelial growth factor concentration levels expressed in picograms per milliliter in the studied groups (absence/presence of chronic unspecific lung disease history); *p*-value obtained using Mann–Whitney *U* test. VEGF, vascular endothelial growth factor level

Рис. 3. Диаграмма размаха уровня фактора роста сосудистого эндотелия в исследуемых группах с отсутствием/наличием хронического неспецифического заболевания легких в анамнезе; значение *p* получено с использованием критерия Манна – Уитни. VEGF — уровень фактора роста сосудистого эндотелия

had a significantly lower concentration of interferon-γ induced (3,760 pg/mL) than those without this comorbidity (23,800 pg/mL).

Figure 3 demonstrates the VEGF levels in patients with chronic pulmonary disease compared with controls (121 vs. 277 pg/mL; $p = 0.055$).

DISCUSSION

The association of comorbidities with the severe course and outcomes of COVID-19 has been observed since the onset of the COVID-19 pandemic. This study analyzed the influence of comorbidities on the profiles of signaling biomarkers in patients with different COVID-19 severities.

Patients with severe COVID-19 exhibited the lowest MDC levels. A direct correlation between low MDC levels and fatal outcomes was observed, consistent with the findings of other studies [28–30]. In addition, patients with COVID-19 and comorbidities such as arterial hypertension, chronic heart failure, cerebrovascular disease, peripheral arterial disease, and chronic kidney disease had significantly lower MDC levels than the control group. The existing literature does not contain any results from such studies. Patients with preexisting chronic hypercytokinemia and increased levels

of angiotensin II probably experience more pronounced dysregulation of the immune system during the primary activation of antiviral immunity and the subsequent development of immunosuppression, accompanied by persistent lymphopenia and signs of systemic inflammatory response. The differences in MDC levels between patients with and without comorbidities confirm the significant role of cardiovascular disease, type 2 diabetes mellitus, chronic kidney disease, and cerebrovascular disease in the development of severe forms and fatal outcomes of COVID-19.

IP-10 (CXCL10) is a potent inflammation mediator that affects T cells, natural killer cells, the monocyte/macrophage system, and dendritic cells. It attracts leukocytes to inflammatory foci, supports the formation of systemic inflammatory responses, and plays a key role in inflammatory tissue damage [18, 19].

The results showed that patients with severe COVID-19 exhibited significantly high IP-10 levels, consistent with previous literature findings [19, 20]. IP-10 is associated with immune depletion in COVID-19 and pulmonary epithelial damage [31, 32]. However, in this study, patients with chronic pulmonary disease had lower IP-10 levels than patients without lung pathology. However, patients with COVID-19 had higher relative odds of a severe disease course (odds ratio, 1.30; 95% confidence interval, 0.57–3.00) and risk of mortality (odds ratio, 1.87; 95% confidence interval, 0.60–4.87) than the control group. This finding is consistent with those of studies conducted by the University of Oxford investigating the effect of asthma on biomarker levels in the peripheral blood [33].

Reportedly, patients hospitalized for severe COVID-19 have significantly higher VEGF levels than patients with mild or moderate COVID-19 and healthy individuals [11]. Herein, the levels of this cytokine did not differ significantly among patients with different COVID-19 severities or fatal outcomes. This finding is subject to further investigation.

Low sCD40L levels are characteristic of a slow and weak antiviral response [15]. Meanwhile, high sCD40L levels are associated with thrombosis and increased severity of COVID-19 [16]. The present data indicate that patients with severe COVID-19 and lethal outcomes had low sCD40L levels. This finding reflects the depth of immunogenesis disorders that contribute to the development of septic complications. No significant differences in sCD40L levels were found between patients with COVID-19 with and without comorbidities.

The CX3CL1 level did not show significant differences between patients in the comparison groups. However, its direct association with thrombosis in infectious diseases and cancer suggests the need for further investigations of its role in patients with COVID-19 with various comorbidities [25].

This study confirms the significant role of signaling biomarkers in the development of severe and lethal outcomes of COVID-19 in patients with comorbidities. Further research on the role of signaling biomarkers in patients with COVID-19 having different comorbidities will help develop personalized approaches for managing this patient population.

CONCLUSIONS

1. SARS-CoV-2 triggers the production of several signaling biomarkers crucial for developing COVID-19 in patients with comorbidities.
2. A direct correlation between low MDC biomarker levels and disease course was established in patients with arterial hypertension, chronic heart failure, vascular disease, cerebrovascular disease, and chronic kidney disease. Patients with respiratory pathology exhibited significantly reduced production of CXCL-10 and VEGF compared with the index in patients without respiratory diseases.
3. In patients with comorbidities, MDC and sCD40L levels may serve as additional prognostic biomarkers for the COVID-19 course and outcome.

ADDITIONAL INFORMATION

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Author contributions. Thereby, all the authors confirm that their authorship complies with the international ICMJE criteria (all the authors have made a significant contribution to the development of the concept, research, and preparation of the article as well as read and approved the final version before its publication).

Personal contribution of the authors: *O.S. Popov, O.P. Mamaeva, S.V. Mosenko* — collecting and processing the material, writing the text; *A.Yu. Anisenkova, S.V. Apalko, N.N. Sushentseva* — literature review, collecting and processing the material, writing the text; *V.I. Mazurov, A.M. Sarana, S.G. Shcherbak* — concept and design of the study, collecting and processing the material, writing and editing the main part of the text.

Ethics approval. The study has been approved by the local Ethics Committee of the City Hospital No. 40 Recreation Administrative District of Saint Petersburg (protocol No. 171 of 18.05.2020).

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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

Вклад авторов. Все авторы подтверждают соответствие своего авторства международным критериям ICMJE (все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией).

Наибольший вклад распределен следующим образом: *С.В. Мосенко, О.С. Попов, О.П. Мамаева* — сбор и обработка материала, написание текста; *С.В. Апалько, Н.Н. Сушенцева* — обзор литературы, сбор и обработка материала, написание текста; *А.Ю. Анисенкова, С.Г. Щербак, А.М. Сарана, В.И. Мазуров* — концепция и дизайн исследования, сбор и обработка материала, написание и редактирование текста.

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